

WRN INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Appl. No. 63/507,014, filed June 8, 2023; U.S. Provisional Appl. No. 63/519,746, filed August 15, 2023; U.S. Provisional Appl. No. 63/586,952, filed September 29, 2023; U.S. Provisional Appl. No. 63/613,647, filed December 21, 2023; U.S. Provisional Appl. No. 63/566,038, filed March 15, 2024; and U.S. Provisional Appl. No. 63/639,457, filed April 26, 2024; the entirety of each of which is herein incorporated by reference.

FIELD OF INVENTION

[0002] The invention provides bicyclic compounds and compositions, the use thereof and methods using the compounds, for inhibiting Werner Syndrome RecQ DNA helicase (WRN) and methods of treating disease using said compounds, in particular the use in treating cancer, and in particular the treatment of cancer characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), including colorectal, gastric and endometrial cancer. The invention also provides the use of said compounds as research chemicals, intermediate compounds, combinations, processes and formulations.

SEQUENCE LISTING

[0003] This application contains a Sequence Listing which has been submitted in .xml format via EFS and is hereby incorporated by reference. The ST.26 copy, created on June 8, 2023, is named 407274-78WRP5_ST26.xml and is 8,751 bytes in size.

BACKGROUND

[0004] Loss of DNA mismatch repair is a common initiating event in cancer development occurring in 10-30% of colorectal, endometrial, ovarian and gastric cancers (Aaltonen, L. A. et al. Clues to the pathogenesis of familial colorectal cancer, Science 260, 812-816 (1993), Bonneville R et al., Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precis Oncol. 1: PO.17.00073 (2017)). Cancers that are deficient in mismatch repair (dMMR) have a high mutational burden, and frequent deletion and insertion events in repetitive DNA tracts, a phenotype known as microsatellite instability (MSI). While progress has been made in the treatment of

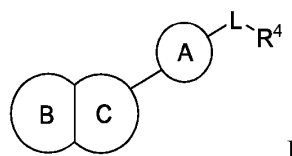
microsatellite instability high (MSI-H) cancers, and the demonstration that pembrolizumab (anti-PD1) treatment led to significantly longer progression-free survival than chemotherapy when received as first-line therapy for MSI-H-dMMR metastatic colorectal cancer (CRC) which resulted in the recent approval of pembrolizumab as first-line treatment of these cancers, there is still a significant unmet medical need in CRC and other MSI-H indications (André T., et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *N Engl J Med* 383(23):2207-2218 (2020)). Several large-scale functional genomics screens across large panels of cell lines, including Novartis with 398 cell lines from the Cancer Cell Line Encyclopedia (CCLE) (McDonald E.R. et al., Project DRIVE: A Compendium of Cancer Dependencies and Synthetic Lethal Relationships Uncovered by Large-Scale, Deep RNAi Screening. *Cell* 170(3):577-592 (2017)), have identified the Werner Syndrome RecQ helicase (WRN) as being selectively required for the survival of cell lines with defective mismatch repair that have become MSI-H (Behan, F. M. et al. Prioritization of cancer therapeutic targets using CRISPR—Cas9 screens. *Nature* 568, 511-516 (2019), Chan, E. M. et al. WRN helicase is a synthetic lethal target in microsatellite unstable cancers. *Nature* 568, 551-556 (2019). Kategaya, L., Perumal, S. K., Hager, J. H. & Belmont, L. D. Werner syndrome helicase is required for the survival of cancer cells with microsatellite instability. *iScience* 13, 488-497 (2019), Lieb, S. et al. Werner syndrome helicase is a selective vulnerability of microsatellite instability-high tumor cells. *eLife* 8, e43333 (2019)). WRN is synthetically lethal with MSI cancers. Depletion of WRN leads to anti-proliferative effects and results in activation of multiple DNA damage signaling markers, induction of cell cycle arrest and apoptosis in MSI-H cancer models but not cancer cells with an intact MMR pathway (otherwise known as microsatellite stable or MSS). The anti-proliferative effects of WRN depletion could not be rescued with a helicase deficient WRN construct, demonstrating that helicase activity of WRN is required for MSI-H viability. These findings indicate that WRN helicase provides a DNA repair and maintenance function that is essential for cell survival in MSI cancers. Recently, the mechanism of WRN dependence has been elucidated. It has been shown that dinucleotide TA repeats are selectively unstable in MSI cells and undergo large scale expansions. These expanded TA repeats form secondary DNA structures that require the WRN helicase for unwinding (van Wietmarschen, N. et al. Repeat expansions confer WRN dependence in microsatellite-unstable cancers. *Nature* 586, 292-298, 2020). In the absence of WRN (or upon WRN helicase inhibition), expanded TA repeats in MSI cells are subject to nuclease cleavage and

chromosome breakage. Thus, inhibiting the WRN helicase is an attractive strategy for the treatment of MSI-H cancers.

SUMMARY

[0005] There remains a need for new treatments and therapies for the treatment of cancer, and in particular cancers characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), including colorectal, gastric or endometrial cancer. The invention provides compounds, pharmaceutically acceptable salts thereof, pharmaceutical compositions thereof and combinations thereof, said compounds being inhibitors of Werner Syndrome RecQ DNA Helicase (WRN). The invention further provides methods of treating, preventing, or ameliorating a disease or condition, comprising administering to a subject in need thereof an effective amount of a WRN inhibitor. The invention also provides compounds, pharmaceutically acceptable salts thereof, pharmaceutical compositions thereof and combinations thereof, said compounds being useful for the treatment of cancer, in particular cancers characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). Also provided are compounds that bind to, and/or inhibit WRN, and are therefore useful as research chemicals, e.g., as a chemical probe, and as tool compounds. Various embodiments of the invention are described herein.

[0006] In one aspect, the disclosure provides a compound of Formula I, or a pharmaceutically acceptable salt thereof:



wherein bicyclic Ring BC, linker L, R^4 , and Ring A are as described and defined herein.

[0007] In another aspect, the invention provides a pharmaceutical composition comprising a compound of Formula I of the present invention and one or more pharmaceutically acceptable carriers.

[0008] In another aspect, the invention provides a combination, in particular a pharmaceutical combination, comprising a compound of Formula I of the present invention and one or more therapeutically active agents.

[0009] In another aspect, the invention provides a compound of Formula I of the present invention for use as a medicament, in particular for the treatment of a disorder or disease which can be treated by WRN inhibition.

[0010] In another aspect, the invention provides a compound of Formula I of the present invention for use in the treatment of cancer, particularly wherein the cancer is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

[0011] In another aspect, the invention provides a method of treating a disorder or disease which can be treated by WRN inhibition in a subject, comprising administering to the subject a therapeutically effective amount of a compound of Formula I of the present invention.

[0012] In another aspect, the invention provides a method of treating cancer in a subject, more particularly wherein the cancer is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), comprising administering to the subject a therapeutically effective amount of a compound of Formula I of the present invention.

[0013] In another aspect, the invention provides the use of a compound of Formula I of the present invention in the manufacture of a medicament for the treatment of a disorder or disease which can be treated by WRN inhibition.

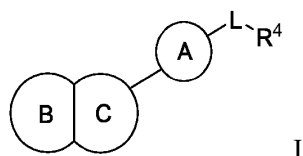
[0014] In another aspect, the invention provides a compound of Formula I of the present invention for use as a research chemical, for example as a chemical probe or as a tool compound.

[0015] In another aspect, the invention provides a solid form, process or intermediate as described herein.

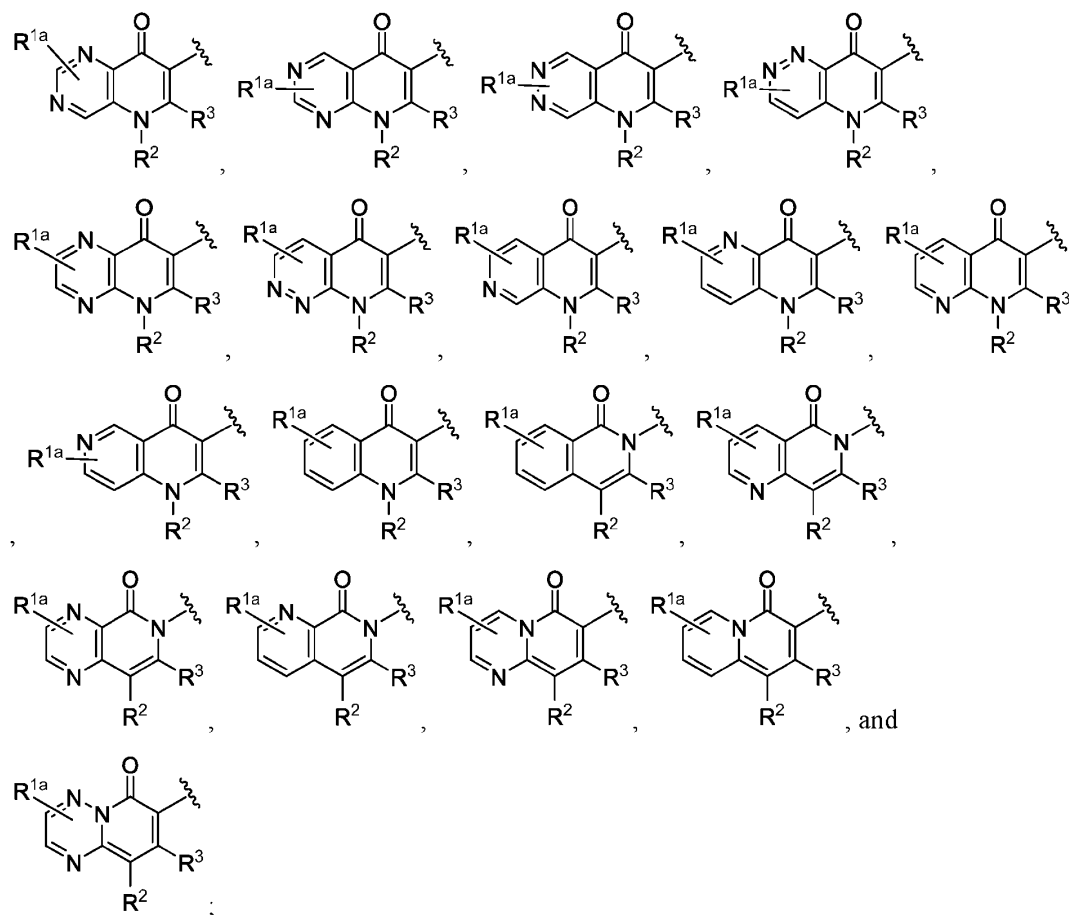
DETAILED DESCRIPTION

1. General Description of Certain Embodiments of the Invention:

[0016] In one aspect, the disclosure provides a compound of Formula I, or a pharmaceutically acceptable salt thereof:



wherein bicyclic Ring BC is selected from one of the following:



wherein denotes the point of attachment to Ring A;

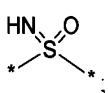
and wherein Ring B may be further optionally substituted with 1 or 2 R^{1b} groups independently selected from H, halogen, CN, OH, C_1 - C_6 aliphatic, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, C_1 - C_6 alkylene-O- C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, halo C_1 - C_6 alkoxy, and C_3 - C_6 cycloalkoxy, wherein said C_1 - C_6 aliphatic, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, C_1 - C_6 alkylene-O- C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, halo C_1 - C_6 alkoxy, and C_3 - C_6 cycloalkoxy are each independently and optionally substituted with 1-5 halogen, OH, CN, C_1 - C_6 alkyl, or C_3 - C_6 cycloalkyl groups;

Ring A is:

a 4-7 membered saturated or partially unsaturated bivalent monocyclic carbocyclylene or 4-7 membered saturated or partially unsaturated bivalent heterocyclylene ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 0 or 1 nitrogen atoms in addition to the 1-4 heteroatoms); or

a 4-12 membered saturated or partially unsaturated bivalent bicyclic ring system that is fused, bridged, or spirocyclic selected from carbocyclylene or heterocyclylene (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

wherein Ring A is substituted with 0-4 independently selected R^B substituents;

-L- is a linker selected from -C(O)-, -S(O)-, -S(O)₂-, and ;

R^{1a} is selected from:

a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with 1-3 groups independently selected from halogen, C₁-C₆aliphatic, C₃-C₆cycloalkyl, haloC₁-C₆alkyl, C₁-C₆alkoxy, and C₃-C₆cycloalkoxy, wherein said 5-6 membered heteroaryl is further substituted with 0-3 independently selected R^B ;

a 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted with 1 or 2 groups independently selected from C₁-C₆aliphatic, C₃-C₆cycloalkyl, C₁-C₆alkoxy, C₃-C₆cycloalkoxy, and -OR, wherein said 4-7 membered saturated or partially unsaturated heterocyclyl is further substituted with 0-3 independently selected R^B ;

a 4-12 membered saturated or partially unsaturated bicyclic ring system that is fused, bridged, or spirocyclic selected from carbocyclyl or heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein said carbocyclyl or heterocyclyl is substituted with 0-3 independently selected R^B ; and

H, halogen, C₁-C₆aliphatic, C₃-C₇cycloalkyl, C₁-C₆alkylene-O-C₁-C₆alkyl, CN, -OR, -OR¹⁰, -NR¹⁰R¹¹, -C(O)NR¹⁰R¹¹, -CH₂NR¹⁰R¹¹, or -SO₂R¹², wherein said C₁-C₆aliphatic, C₃-C₇cycloalkyl, or C₁-C₆alkylene-O-C₁-C₆alkyl is substituted with 0-5 independently selected R^B ;

or R^{1a} and one R^{1b} on adjacent atoms of Ring B, taken together with the adjacent Ring B atoms to which they are attached, form a cyclic group fused to Ring B selected from phenyl, a 5-6 membered heteroaryl (having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur), a 4-7 membered saturated or partially unsaturated carbocyclyl, or a 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur), wherein said cyclic group fused to Ring B is substituted with 0-3 independently selected R^B;

R² is C(R^C)₂C(O)N(R)R^{2A};

R^{2A} is phenyl or pyridyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C₁-C₄aliphatic, haloC₁-C₄alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, -OH, -CN, C₁-C₄alkoxy, haloC₁-C₄alkoxy, and -SF₅, and wherein two substituents on adjacent atoms of the phenyl or pyridyl, together with said adjacent atoms, form a 4-7 membered carbocyclyl fused to the phenyl or pyridyl, and wherein two substituents on adjacent atoms of the phenyl or pyridyl together with said adjacent atoms form a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) fused to the phenyl or pyridyl, wherein said fused 4-7 membered carbocyclyl or fused 4-7 membered heterocyclyl is substituted with 0-5 independently selected halogen; or

R^{2A} is 2-benzimidazolyl, 2-naphthyl, or 3-quinolinyl, each of which is optionally substituted with 1, 2 or 3 substituents independently selected from halogen, C₁-4alkyl, and -OH;

R³ is hydrogen, C₁-C₄aliphatic, C₃-C₅cycloalkyl, C₁-C₄alkoxy, -NHR^{3A}, -N(R^{3A})₂, or C₁-C₄alkylthio, each of which, besides hydrogen, is optionally substituted with -OH, 1-5 independently selected halogen, OR, -C(O)NR¹⁰R¹¹, or N(R)C(O)R;

each R^{3A} is independently selected from C₁-C₄alkyl;

R⁴ is phenyl or a first 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) wherein said phenyl or first 5-6 membered heteroaryl is substituted with 0-5 R^B; and optionally two adjacent atoms of said phenyl or first 5-6 membered heteroaryl have two substituents that together with said adjacent atoms form a cyclic group fused to the phenyl or first 5-6 membered heteroaryl selected from a 4-7 membered carbocyclyl, a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen,

and sulfur), or second a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said fused cyclic group is substituted with 0-3 independently selected R^B; or

R⁴ is a C₁-C₄aliphatic, C₁-C₄alkoxy, or C₃-C₆cycloalkyl, each of which is substituted with 0-3 groups independently selected from halogen, -CN, -OH, C₁-C₄alkyl, C₁-C₄alkoxy, optionally substituted 5-6 membered heterocyclyl, and optionally substituted 5-6 membered heterocycloxy;

R¹⁰ is H, C₁-C₆aliphatic, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, -C(O)C₁-C₆alkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R¹⁰ except H being optionally substituted with 1 or 2 independently selected R^B;

R¹¹ is H, C₁-C₆aliphatic, or C₃-C₆cycloalkyl, or R¹⁰ and R¹¹ are taken together with the nitrogen atom to which they are attached to form a 5-6 membered ring optionally substituted with 1, 2, or 3 substituents independently selected from halogen, -OH, -CN, C₁-C₄alkoxy, and haloC₁-C₄alkoxy;

R¹² is C₁-C₆aliphatic, C₃-C₆cycloalkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R¹² optionally substituted with 1 or 2 groups independently selected from halogen, C₁-C₆aliphatic, haloC₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, and C₃-C₆cycloalkoxy;

R^B is independently selected at each occurrence from the group consisting of optionally substituted phenyl, optionally substituted 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), halogen, optionally substituted C₁-C₆aliphatic, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, C₁-C₆alkoxy, haloC₁-C₆alkoxy, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy, C₁-C₆alkylene-O-C₁-C₆alkyl, -CN, -NO₂, oxo, -OR, -SR, NR₂, S(O)₂R, S(O)₂NR₂, S(O)R, S(O)NR₂, C(O)R, C(O)OR, -C(O)NR₂, C(O)N(R)OR, OC(O)R, OC(O)NR₂, -N(R)C(O)OR, N(R)C(O)R, N(R)C(O)NR₂, N(R)C(NR)NR₂, N(R)S(O)₂NR₂, and -N(R)S(O)₂R;

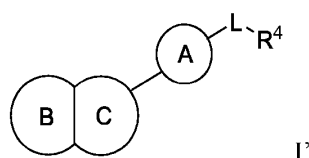
R^C is independently selected at each occurrence from hydrogen, -CH₃, or -CH₂CH₃, or two R^C taken together with the carbon to which they are attached form a cyclopropyl ring;

each R is independently hydrogen, or an optionally substituted C₁₋₆aliphatic group, an optionally substituted phenyl, an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or an optionally substituted 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); or

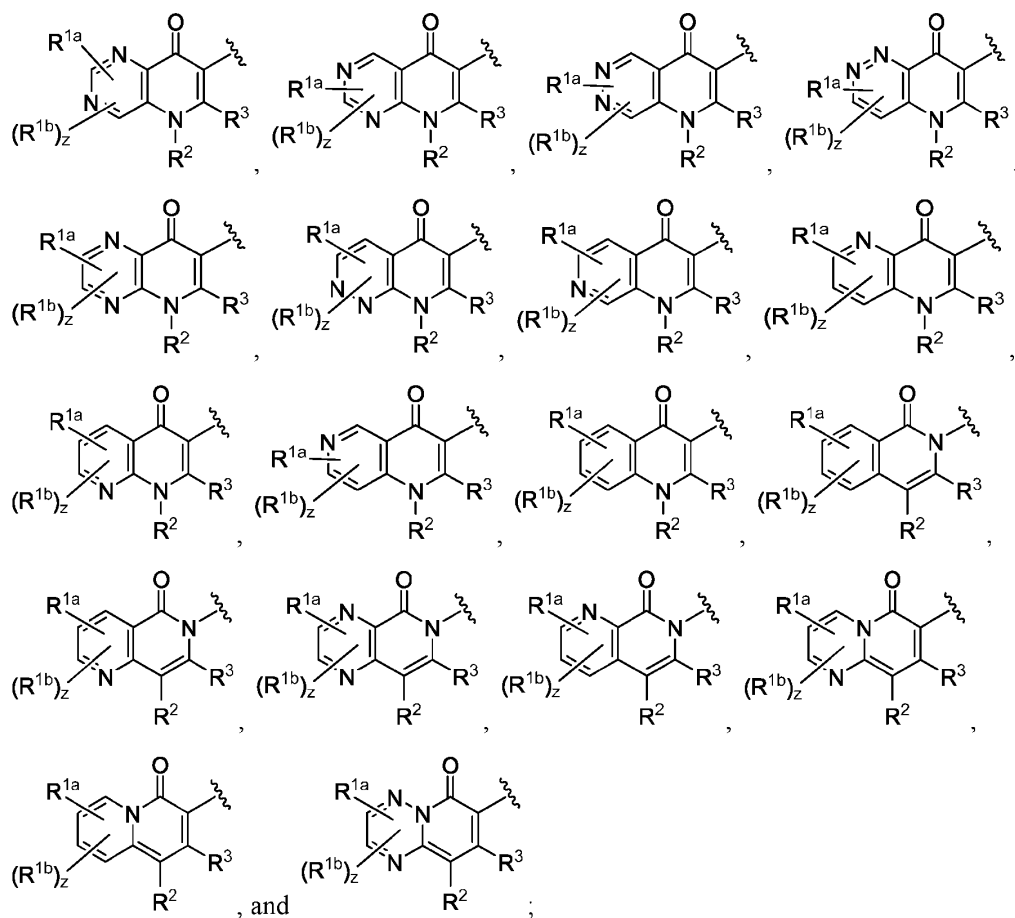
two R groups on the same atom are taken together with the same atom to form a cyclic group selected from an optionally substituted 4-7 membered saturated ring, a 4-7 membered partially unsaturated ring, or a 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said cyclic group has 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

[0017] In another aspect, the invention provides a method of treating a disorder or disease which can be treated by WRN inhibition in a subject, comprising administering to the subject a therapeutically effective amount of a compound of Formula I of the present invention, or a pharmaceutically acceptable salt thereof.

[0018] In one aspect, the disclosure provides a compound of Formula I', or a pharmaceutically acceptable salt thereof:



wherein bicyclic Ring BC is selected from one of the following:



wherein $\sim$ denotes the point of attachment to Ring A;

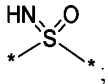
and each R^{1b} group is independently selected from H, halogen, CN, OH, C_1 - C_6 aliphatic, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, C_1 - C_6 alkylene-O- C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, halo C_1 - C_6 alkoxy, and C_3 - C_6 cycloalkoxy, wherein said C_1 - C_6 aliphatic, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, C_1 - C_6 alkylene-O- C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, halo C_1 - C_6 alkoxy, and C_3 - C_6 cycloalkoxy are each independently and optionally substituted with 1-5 halogen, OH, CN, C_1 - C_6 alkyl, or C_3 - C_6 cycloalkyl groups; wherein z is 0, 1, or 2;

Ring A is:

a 4-7 membered saturated or partially unsaturated bivalent monocyclic carbocyclylene or 4-7 membered saturated or partially unsaturated bivalent heterocyclylene ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 0 or 1 nitrogen atoms in addition to the 1-4 heteroatoms); or

a 4-12 membered saturated or partially unsaturated bivalent bicyclic ring system that is fused, bridged, or spirocyclic selected from carbocyclylene or heterocyclylene (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

wherein Ring A is substituted with 0-4 independently selected R^B substituents;

-L- is a linker selected from -C(O)-, -S(O)-, -S(O)₂-, and ;

R^{1a} is selected from:

a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with 1-3 groups independently selected from halogen, C₁-C₆aliphatic, C₃-C₆cycloalkyl, haloC₁-C₆alkyl, C₁-C₆alkoxy, and C₃-C₆cycloalkoxy, wherein said 5-6 membered heteroaryl is further substituted with 0-3 independently selected R^B ;

a 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted with 1 or 2 groups independently selected from C₁-C₆aliphatic, C₃-C₆cycloalkyl, C₁-C₆alkoxy, C₃-C₆cycloalkoxy, and -OR, wherein said 4-7 membered saturated or partially unsaturated heterocyclyl is further substituted with 0-3 independently selected R^B ;

a 4-12 membered saturated or partially unsaturated bicyclic ring system that is fused, bridged, or spirocyclic selected from carbocyclyl or heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein said carbocyclyl or heterocyclyl is substituted with 0-3 independently selected R^B ; and

H, halogen, C₁-C₆aliphatic, C₃-C₇cycloalkyl, C₁-C₆alkylene-O-C₁-C₆alkyl, CN, -OR, -OR¹⁰, -NR¹⁰R¹¹, -C(O)NR¹⁰R¹¹, -CH₂NR¹⁰R¹¹, or -SO₂R¹², wherein said C₁-C₆aliphatic, C₃-C₇cycloalkyl, or C₁-C₆alkylene-O-C₁-C₆alkyl is substituted with 0-5 independently selected R^B ;

or R^{1a} and one R^{1b} on adjacent atoms of Ring B, taken together with the adjacent Ring B atoms to which they are attached, form a cyclic group fused to Ring B selected from phenyl, a 5-6 membered heteroaryl (having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur), a 4-7 membered saturated or partially unsaturated carbocyclyl, or a 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur), wherein said cyclic group fused to Ring B is substituted with 0-3 independently selected R^B,

R² is selected from C(R^C)₂C(O)N(R)R^{2A}, C(R^C)₂C(R^C)₂C(O)N(R)R^{2A}, C(R^C)₂C(R^C)₂N(R)C(O)N(R)R^{2A}, and C(R^C)₂C(R^C)₂N(R)C(O)R^{2A},

R^{2A} is phenyl, pyridyl, cubanyl, a saturated or partially unsaturated 4-8 membered monocyclic ring, a saturated or partially unsaturated bridged, fused, or spirocyclic 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered ring, wherein said saturated or partially unsaturated monocyclic ring, or saturated or partially unsaturated bridged, fused, or spirocyclic ring contains 0, 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and wherein said phenyl, pyridyl, cubanyl, saturated or partially unsaturated monocyclic ring, or saturated or partially unsaturated bridged, fused, or spirocyclic ring are each optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C₁-C₄aliphatic, haloC₁-C₄alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, -OH, -CN, C₁-C₄alkoxy, haloC₁-C₄alkoxy, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy and -SF₅, and wherein two substituents on adjacent atoms of the phenyl or pyridyl, together with said adjacent atoms, optionally form a 4-7 membered carbocyclyl fused to the phenyl or pyridyl, and wherein two substituents on adjacent atoms of the phenyl or pyridyl together with said adjacent atoms optionally form a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) fused to the phenyl or pyridyl, wherein said fused 4-7 membered carbocyclyl or fused 4-7 membered heterocyclyl is substituted with 0-5 independently selected halogen, and wherein two substituents on the same atom of said saturated or partially unsaturated monocyclic ring, or saturated or partially unsaturated bridged, fused, or spirocyclic ring optionally form a cyclic group selected from:

- an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclyl, and

- an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

R^{2A} is 2-benzimidazolyl, 2-naphthyl, or 3-quinoliny, each of which is optionally substituted with 1, 2 or 3 substituents independently selected from halogen, C₁-4alkyl, and -OH;

R³ is hydrogen, C₁-C₄aliphatic, C₃-C₅cycloalkyl, C₁-C₄alkoxy, -NHR^{3A}, -N(R^{3A})₂, or C₁-C₄alkylthio, each of which, besides hydrogen, is optionally substituted with -OH, 1-5 independently selected halogen, OR, -C(O)NR¹⁰R¹¹, or N(R)C(O)R;

each R^{3A} is independently selected from C₁-C₄alkyl;

R⁴ is phenyl or a first 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) wherein said phenyl or first 5-6 membered heteroaryl is substituted with 0-5 R^B; and optionally two adjacent atoms of said phenyl or first 5-6 membered heteroaryl have two substituents that together with said adjacent atoms form a cyclic group fused to the phenyl or first 5-6 membered heteroaryl selected from a 4-7 membered carbocyclyl, a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or a second 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said fused cyclic group is substituted with 0-3 independently selected R^B; or

R⁴ is a C₁-C₄aliphatic, C₁-C₄alkoxy, or C₃-C₆cycloalkyl, each of which is substituted with 0-3 groups independently selected from halogen, -CN, -OH, C₁-C₄alkyl, C₁-C₄alkoxy, optionally substituted 5-6 membered heterocyclyl, and optionally substituted 5-6 membered heterocyclloxy;

R¹⁰ is H, C₁-C₆aliphatic, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, -C(O)C₁-C₆alkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R¹⁰ except H being optionally substituted with 1 or 2 independently selected R^B;

R¹¹ is H, C₁-C₆aliphatic, or C₃-C₆cycloalkyl, or R¹⁰ and R¹¹ are taken together with the nitrogen atom to which they are attached to form a 5-6 membered ring optionally substituted with 1, 2, or 3 substituents independently selected from halogen, -OH, -CN, C₁-C₄alkoxy, and haloC₁-C₄alkoxy;

R¹² is C₁-C₆aliphatic, C₃-C₆cycloalkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R¹² optionally substituted with 1 or 2 groups independently selected from halogen, C₁-C₆aliphatic, haloC₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, and C₃-C₆cycloalkoxy;

R^B is independently selected at each occurrence from the group consisting of optionally substituted phenyl, optionally substituted 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), halogen, optionally substituted C₁-C₆aliphatic, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, C₁-C₆alkoxy, haloC₁-C₆alkoxy, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy, C₁-C₆alkylene-O-C₁-C₆alkyl, -CN, -NO₂, oxo, -OR, -SR, NR₂, S(O)₂R, S(O)₂NR₂, S(O)R, S(O)NR₂, C(O)R, C(O)OR, -C(O)NR₂, C(O)N(R)OR, OC(O)R, OC(O)NR₂, -N(R)C(O)OR, N(R)C(O)R, N(R)C(O)NR₂, N(R)C(NR)NR₂, N(R)S(O)₂NR₂, and -N(R)S(O)₂R;

R^C is independently selected at each occurrence from hydrogen, -CH₃, or -CH₂CH₃, or two R^C taken together with the carbon to which they are attached form a cyclopropyl ring;

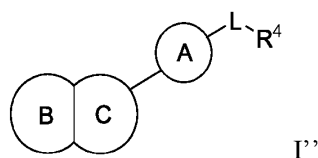
each R is independently hydrogen, or an optionally substituted C₁-C₆aliphatic group, an optionally substituted phenyl, an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or an optionally substituted 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); or

two R groups on the same atom are taken together with the same atom to form a cyclic group selected from an optionally substituted 4-7 membered saturated ring, a 4-7 membered partially unsaturated ring, or a 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said cyclic group has 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

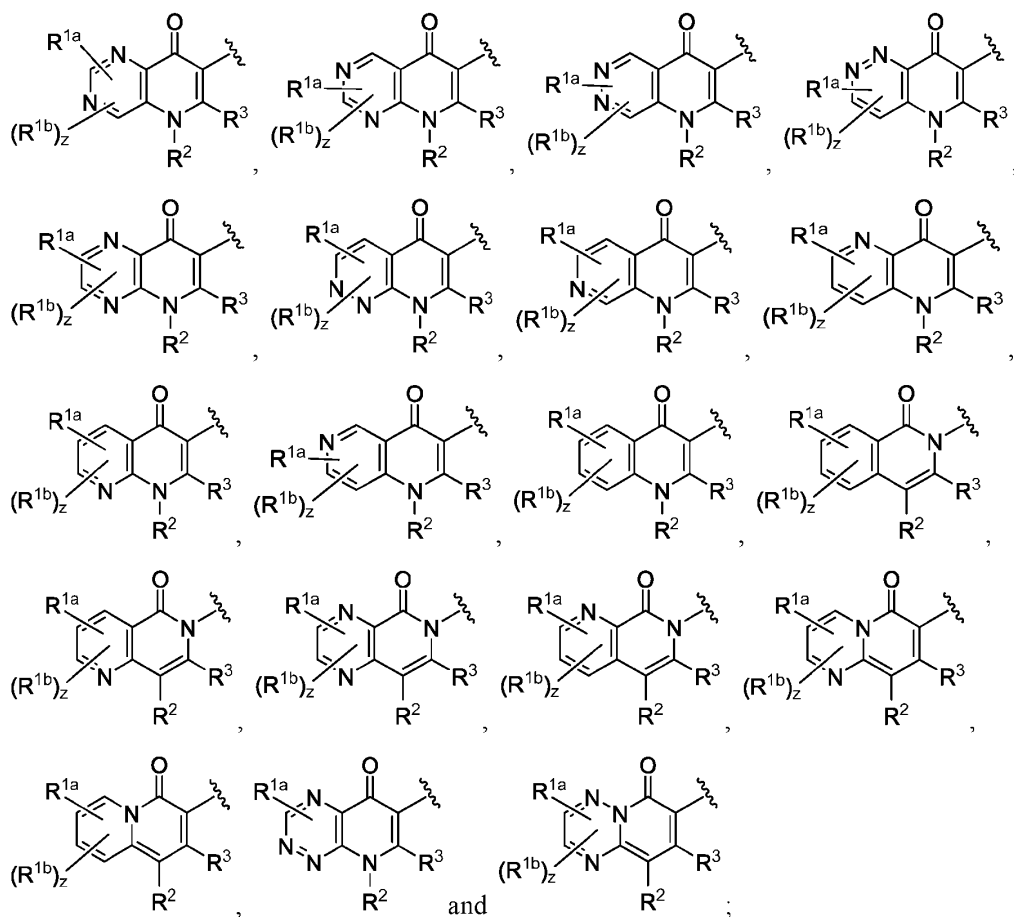
[0019] In another aspect, the invention provides a method of treating a disorder or disease which can be treated by WRN inhibition in a subject, comprising administering to the subject a

therapeutically effective amount of a compound of Formula I' of the present invention, or a pharmaceutically acceptable salt thereof.

[0020] In one aspect, the disclosure provides a compound of Formula I'', or a pharmaceutically acceptable salt thereof:



wherein bicyclic Ring BC is selected from one of the following:



wherein denotes the point of attachment to Ring A;

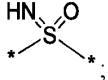
and each R^{1b} group is independently selected from H, halogen, CN, OH, C₁-C₆aliphatic, C₁-C₆alkoxy, C₃-C₆cycloalkyl, C₁-C₆alkylene-O-C₁-C₆alkyl, haloC₁-C₆alkyl, haloC₁-C₆alkoxy, and C₃-C₆cycloalkoxy, wherein said C₁-C₆aliphatic, C₁-C₆alkoxy, C₃-C₆cycloalkyl, C₁-C₆alkylene-O-C₁-C₆alkyl, haloC₁-C₆alkyl, haloC₁-C₆alkoxy, and C₃-C₆cycloalkoxy are each independently and optionally substituted with 1-5 halogen, OH, CN, C₁-C₆alkyl, or C₃-C₆cycloalkyl groups; wherein z is 0, 1, or 2;

Ring A is:

a 4-7 membered saturated or partially unsaturated bivalent monocyclic carbocyclylene or 4-7 membered saturated or partially unsaturated bivalent heterocyclylene ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 0 or 1 nitrogen atoms in addition to the 1-4 heteroatoms); or

a 4-12 membered saturated or partially unsaturated bivalent bicyclic ring system that is fused, bridged, or spirocyclic selected from carbocyclylene or heterocyclylene (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

wherein Ring A is substituted with 0-4 independently selected R^B substituents;

-L- is a linker selected from -C(O)-, -S(O)-, -S(O)₂-, and ;

R^{1a} is selected from:

a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with 1-3 groups independently selected from halogen, C₁-C₆aliphatic, C₃-C₆cycloalkyl, haloC₁-C₆alkyl, C₁-C₆alkoxy, and C₃-C₆cycloalkoxy, wherein said 5-6 membered heteroaryl is further substituted with 0-3 independently selected R^B;

a 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted with 1 or 2 groups independently selected from C₁-C₆aliphatic, C₃-C₆cycloalkyl, C₁-C₆alkoxy, C₃-C₆cycloalkoxy, and -OR, wherein said 4-7 membered saturated or partially unsaturated heterocyclyl is further substituted with 0-3 independently selected R^B;

a 4-12 membered saturated or partially unsaturated bicyclic ring system that is fused, bridged, or spirocyclic selected from carbocyclyl or heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein said carbocyclyl or heterocyclyl is substituted with 0-3 independently selected R^B ; and

H, halogen, C_1 - C_6 aliphatic, C_3 - C_7 cycloalkyl, C_1 - C_6 alkylene-O- C_1 - C_6 alkyl, CN, -OR, -OR¹⁰, -NR¹⁰R¹¹, -C(O)NR¹⁰R¹¹, -CH₂NR¹⁰R¹¹, or -SO₂R¹², wherein said C_1 - C_6 aliphatic, C_3 - C_7 cycloalkyl, or C_1 - C_6 alkylene-O- C_1 - C_6 alkyl is substituted with 0-5 independently selected R^B ;

or R^{1a} and one R^{1b} on adjacent atoms of Ring B, taken together with the adjacent Ring B atoms to which they are attached, form a cyclic group fused to Ring B selected from phenyl, a 5-6 membered heteroaryl (having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur), a 4-7 membered saturated or partially unsaturated carbocyclyl, or a 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur), wherein said cyclic group fused to Ring B is substituted with 0-3 independently selected R^B ;

R² is selected from C(R^C)₂C(O)N(R)R^{2A}, C(R^C)₂C(R^C)₂C(O)N(R)R^{2A}, C(R^C)₂C(R^C)₂N(R)C(O)N(R)R^{2A}, and C(R^C)₂C(R^C)₂N(R)C(O)R^{2A};

R^{2A} is phenyl, pyridyl, cubanyl, a saturated or partially unsaturated 4-8 membered monocyclic ring, a saturated or partially unsaturated bridged, fused, or spirocyclic 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered ring, wherein said saturated or partially unsaturated monocyclic ring, or saturated or partially unsaturated bridged, fused, or spirocyclic ring contains 0, 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and wherein said phenyl, pyridyl, cubanyl, saturated or partially unsaturated monocyclic ring, or saturated or partially unsaturated bridged, fused, or spirocyclic ring are each optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1 - C_4 aliphatic, halo C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, halo C_3 - C_6 cycloalkyl, -OH, -CN, C_1 - C_4 alkoxy, halo C_1 - C_4 alkoxy, C_3 - C_6 cycloalkoxy, halo C_3 - C_6 cycloalkoxy and -SF₅, and wherein two substituents on adjacent atoms of the phenyl or pyridyl, together with said adjacent atoms, optionally form a 4-7 membered carbocyclyl fused to the phenyl or pyridyl, and wherein two substituents on adjacent atoms of the phenyl or pyridyl together with said adjacent atoms optionally form a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) fused to the phenyl or pyridyl, wherein

said fused 4-7 membered carbocyclyl or fused 4-7 membered heterocyclyl is substituted with 0-5 independently selected halogen, and wherein two substituents on the same atom of said saturated or partially unsaturated monocyclic ring, or saturated or partially unsaturated bridged, fused, or spirocyclic ring optionally form a cyclic group selected from:

- an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclyl, and
- an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

R^{2A} is 2-benzimidazolyl, 2-naphthyl, or 3-quinoliny, each of which is optionally substituted with 1, 2 or 3 substituents independently selected from halogen, C₁₋₄alkyl, and -OH;

R³ is hydrogen, C₁₋₄aliphatic, C₃₋₅cycloalkyl, C₁₋₄alkoxy, -NHR^{3A}, -N(R^{3A})₂, or C₁₋₄alkylthio, each of which, besides hydrogen, is optionally substituted with -OH, 1-5 independently selected halogen, OR, -C(O)NR¹⁰R¹¹, or N(R)C(O)R;

each R^{3A} is independently selected from C₁₋₄alkyl;

R⁴ is phenyl or a first 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) wherein said phenyl or first 5-6 membered heteroaryl is substituted with 0-5 R^B; and optionally two adjacent atoms of said phenyl or first 5-6 membered heteroaryl have two substituents that together with said adjacent atoms form a cyclic group fused to the phenyl or first 5-6 membered heteroaryl selected from a 4-7 membered carbocyclyl, a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or a second 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said fused cyclic group is substituted with 0-3 independently selected R^B; or

R⁴ is a C₁₋₄aliphatic, C₁₋₄alkoxy, or C₃₋₆cycloalkyl, each of which is substituted with 0-3 groups independently selected from halogen, -CN, -OH, C₁₋₄alkyl, C₁₋₄alkoxy, optionally substituted 5-6 membered heterocyclyl, and optionally substituted 5-6 membered heterocycloxy;

R¹⁰ is H, C₁₋₆aliphatic, haloC₁₋₆alkyl, C₃₋₆cycloalkyl, haloC₃₋₆cycloalkyl, -C(O)C₁₋₆alkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from

nitrogen, oxygen, and sulfur); each R^{10} except H being optionally substituted with 1 or 2 independently selected R^B ;

R^{11} is H, C_1 - C_6 aliphatic, or C_3 - C_6 cycloalkyl, or R^{10} and R^{11} are taken together with the nitrogen atom to which they are attached to form a 5-6 membered ring optionally substituted with 1, 2, or 3 substituents independently selected from halogen, -OH, -CN, C_1 - C_4 alkoxy, and halo C_1 - C_4 alkoxy;

R^{12} is C_1 - C_6 aliphatic, C_3 - C_6 cycloalkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R^{12} optionally substituted with 1 or 2 groups independently selected from halogen, C_1 - C_6 aliphatic, halo C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, and C_3 - C_6 cycloalkoxy;

R^B is independently selected at each occurrence from the group consisting of optionally substituted phenyl, optionally substituted 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), halogen, optionally substituted C_1 - C_6 aliphatic, halo C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo C_3 - C_6 cycloalkyl, C_1 - C_6 alkoxy, halo C_1 - C_6 alkoxy, C_3 - C_6 cycloalkoxy, halo C_3 - C_6 cycloalkoxy, C_1 - C_6 alkylene-O- C_1 - C_6 alkyl, -CN, -NO₂, oxo, -OR, -SR, NR₂, S(O)₂R, S(O)₂NR₂, S(O)R, S(O)NR₂, C(O)R, C(O)OR, -C(O)NR₂, C(O)N(R)OR, OC(O)R, OC(O)NR₂, -N(R)C(O)OR, N(R)C(O)R, N(R)C(O)NR₂, N(R)C(NR)NR₂, N(R)S(O)₂NR₂, and -N(R)S(O)₂R;

R^C is independently selected at each occurrence from hydrogen, -CH₃, or -CH₂CH₃, or two R^C taken together with the carbon to which they are attached form a cyclopropyl ring;

each R is independently hydrogen, or an optionally substituted C_1 - C_6 aliphatic group, an optionally substituted phenyl, an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or an optionally substituted 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); or

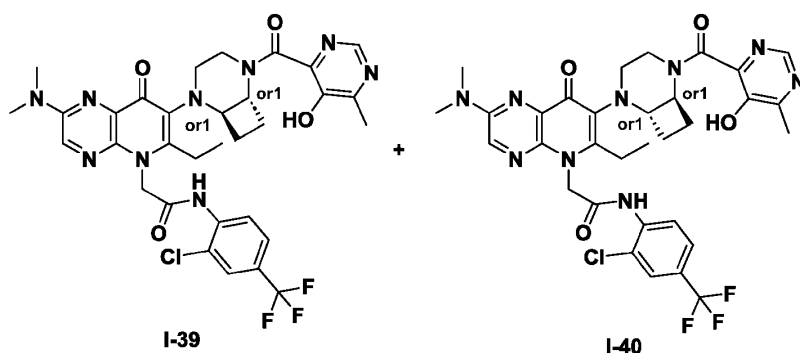
two R groups on the same atom are taken together with the same atom to form a cyclic group selected from an optionally substituted 4-7 membered saturated ring, a 4-7 membered partially unsaturated ring, or a 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said cyclic group has 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

[0021] In another aspect, the invention provides a method of treating a disorder or disease which can be treated by WRN inhibition in a subject, comprising administering to the subject a therapeutically effective amount of a compound of Formula I' of the present invention, or a pharmaceutically acceptable salt thereof.

2. Compounds and Definitions:

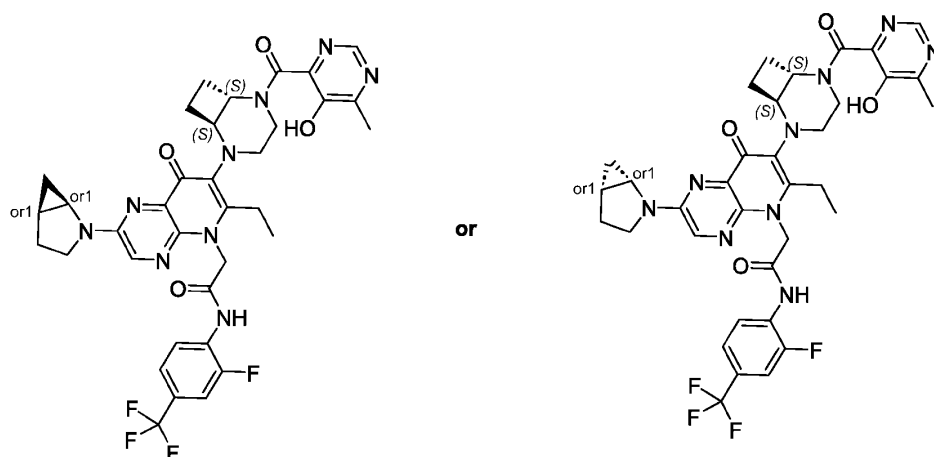
[0022] Compounds of the present invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry," Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry," 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001.

[0023] Compound structures shown throughout the present specification and in the examples or claims contain designations at certain stereocenters which indicate the following: "or1" and is intended to cover stereochemically pure compounds wherein the stereochemistry at the stereocenter marked with "or1" is either the stereochemistry shown in the diagram or wherein the marked stereocenter has a configuration opposite to what is shown in the diagram. In structures with stereocenters with the same label such as "or1" the relative stereochemistry between two stereocenters with said label is as drawn, as in Example I-39 and I-40.



Stereocenters marked with “abs” intend to cover material wherein the marked stereocenter is of the stereochemistry shown in the diagram. Stereocenters marked with “&1” or “and1” indicate that the compound material has a mixture of *R* and *S*-configured stereoisomers with respect to the marked stereocenter and is in the same relative configuration to each other if they share the same label such as “and1” or “&1” as in Example I-34.

[0024] Compound structures shown throughout the present specification and in the examples or claims which contain designations at certain stereocenters which indicate “or1” and contain other designations at certain stereocenters which are absolute and indicate “S” is intended to cover mixtures of stereochemically pure compounds wherein the stereochemistry at the stereocenter marked with “or1” is either the stereochemistry shown in the diagram or wherein the marked “or1” stereocenter has a configuration opposite to what is shown in the diagram and the stereocenters marked “S” are absolute and are as indicated as in Example (I-122): 2-(2-((1R*,5S*)-2-azabicyclo[3.1.0]hexan-2-yl)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide.



[0025] The term “aliphatic” or “aliphatic group,” as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as “carbocycle,” “cycloaliphatic” or “cycloalkyl”), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, “cycloaliphatic” (or “carbocycle” or “cycloalkyl”) refers to a monocyclic C₃-C₆ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0026] As used herein, the term “bridged bicyclic” refers to any bicyclic ring system, i.e., carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one bridge. As defined by IUPAC, a “bridge” is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a “bridgehead” is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some embodiments, a bridged

bicyclic group has 5-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. The term “alkyl” refers to a C₁₋₁₂ straight or branched saturated aliphatic group. In certain instances, alkyl refers to a C₁₋₈ straight or branched saturated aliphatic group or a C₁₋₆ straight or branched saturated aliphatic group. The term “lower alkyl” refers to a C₁₋₄ straight or branched alkyl group.

[0027] Exemplary lower alkyl groups are methyl (-CH₃), ethyl (-CH₂CH₃), propyl, isopropyl (also referred to interchangeably herein as 2-propyl, iPr, ⁱPr and i-Pr), butyl, isobutyl (also referred to interchangeably herein as 2-butyl, iBu, ⁱBu and i-Bu) and tert-butyl (also referred to interchangeably herein as 2-methyl-2-butyl, tBu, ^tBu and t-Bu).

[0028] The term “alkenyl” refers to a C₂₋₁₂ straight or branched partially unsaturated aliphatic group comprising at least one unsaturated carbon carbon double bond. In certain instances, alkenyl refers to a C₂₋₈ or a C₂₋₆ straight or branched partially unsaturated aliphatic group comprising at least one unsaturated carbon carbon double bond. The term “lower alkenyl” refers to a C₂₋₄ straight or branched partially unsaturated aliphatic group comprising at least one unsaturated carbon carbon double bond. Alkenyl groups include both cis (Z) and trans (E) regioisomers. Exemplary lower alkenyl groups are vinyl, allyl, 2-propenyl, and butenyl isomers (-CH₂CH₂CH=CH₂, -CH₂CH=CHCH₃ and -CH=CHCH₂CH₃).

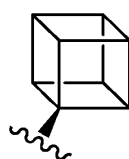
[0029] The term “alkynyl” refers to a C₂₋₁₂ straight or branched partially unsaturated aliphatic group comprising at least one unsaturated carbon carbon triple bond. In certain instances, alkynyl refers to a C₂₋₈ or a C₂₋₆ straight or branched partially unsaturated aliphatic group comprising at least one unsaturated carbon carbon triple bond. The term “lower alkynyl” refers to a C₂₋₄ straight or branched partially unsaturated aliphatic group comprising at least one unsaturated carbon carbon triple bond. Exemplary lower alkynyl groups are ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, and 3-butynyl.

[0030] The term “haloalkyl” refers to a straight or branched alkyl group that is substituted with one or more halogen atoms. The term “lower haloalkyl” refers to a C₁₋₄ straight or branched alkyl group that is substituted with one or more halogen atoms.

[0031] The term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR⁻ (as in N-substituted pyrrolidinyl).

[0032] The term “unsaturated,” as used herein, means that a moiety has one or more units of unsaturation.

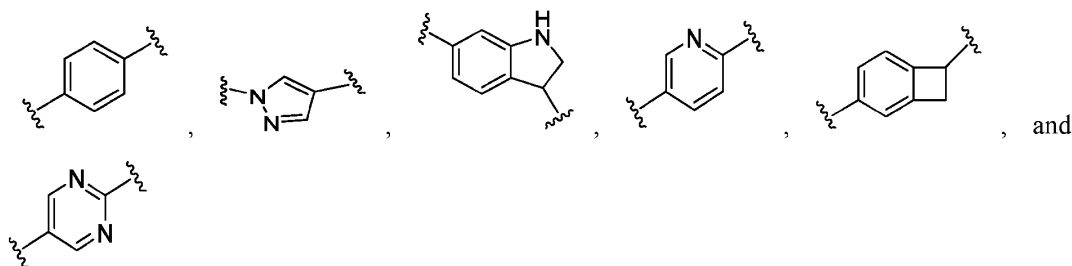
[0033] The term “cubanyl” refers to a substituent of cubane as shown below.



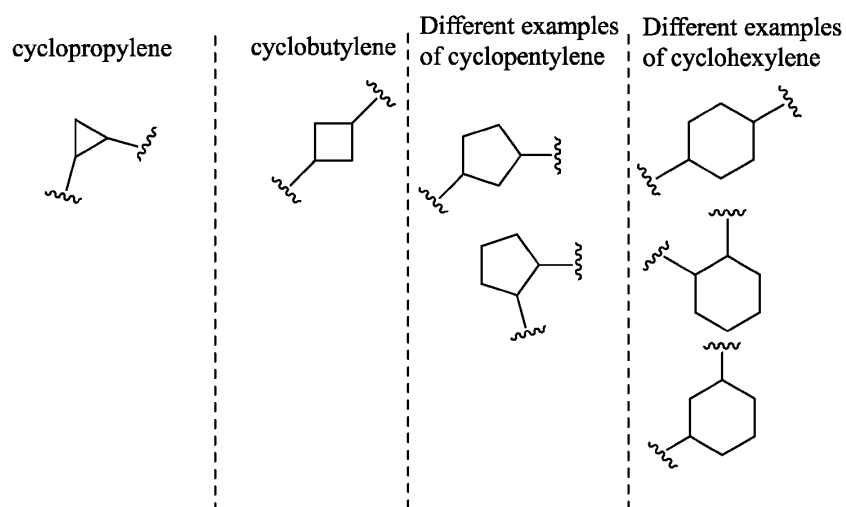
[0034] The substituent -Me, as used herein refers to a methyl group, -CH₃.

[0035] As used herein, the term “bivalent C₁₋₈ (or C₁₋₆ i.e., C₁-C₆) saturated or unsaturated, straight or branched, hydrocarbon chain,” refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

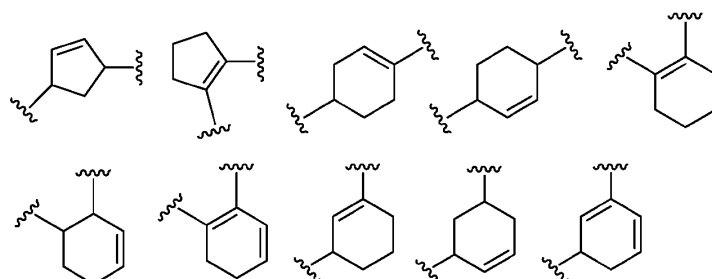
[0036] As used herein, the term “bivalent,” to describe a cyclic (and noncyclic) group refers to, for example, bivalent carbocyclylene, phenylene, heterocyclylene, and heteroarylene that are bivalent moieties of carbocycles, phenyls, heterocycles, and heteroaryls described herein. Non-limiting examples include



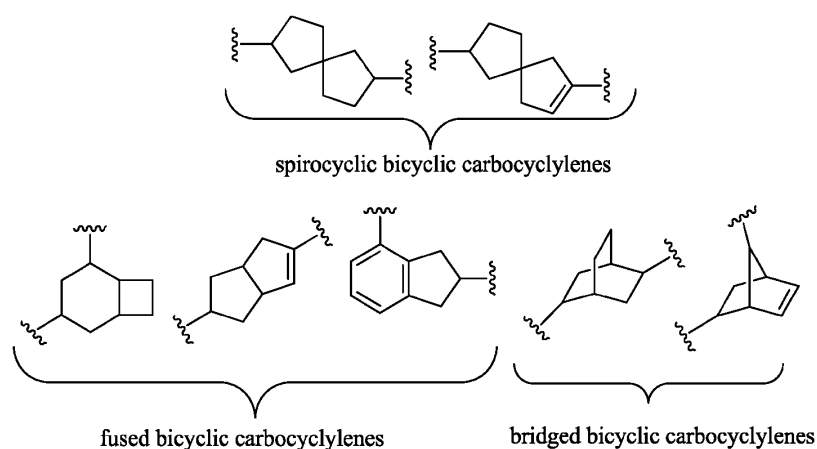
[0037] “Carbocyclylene” as used herein refers to a carbocyclic or cycloalkyl moiety that is bivalent as described above (i.e., attached at two different points to the rest of the compound). Non-limiting examples include cyclopropylene, cyclobutylene, cyclopentylene, or cyclohexylene as shown below.



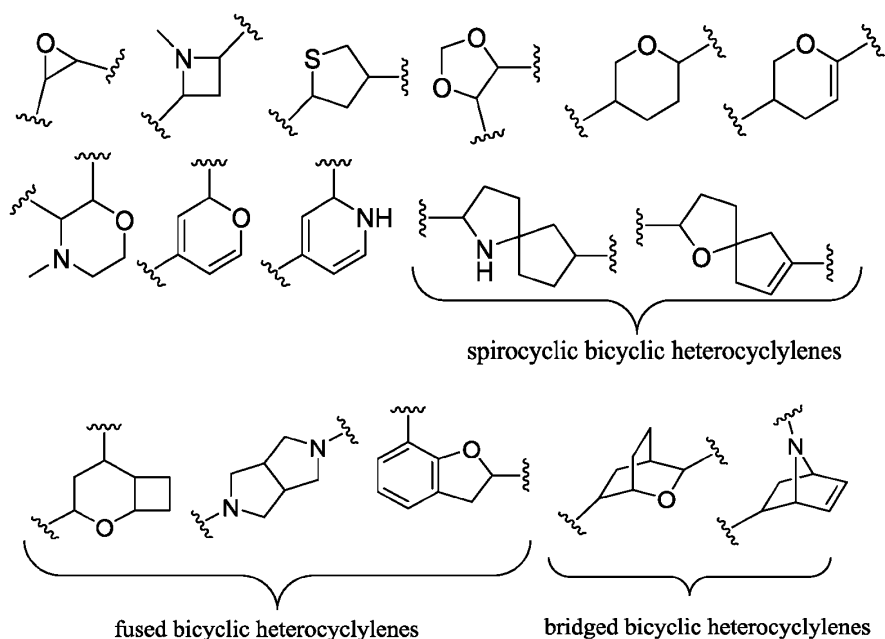
[0038] A carbocyclylene may be saturated as in the examples shown above or partially unsaturated as in the examples shown below.



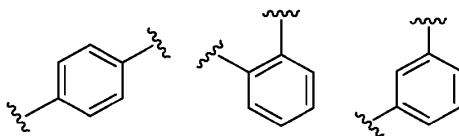
[0039] A carbocyclylene may be multi-cyclic, for example, bicyclic or tricyclic. Such multi-cyclic carbocyclylene systems may be saturated or partially unsaturated (while one ring of the bicyclic system may be aromatic it is to be understood that multi-cyclic ring systems that are not in their entirety aromatic may also fall under the definition of carbocyclylene). The rings may form bridged, fused, or spiro systems. Non-limiting examples are shown below.



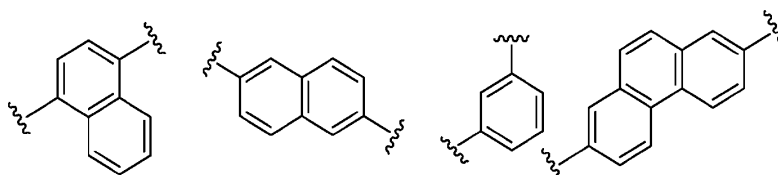
[0040] “Heterocyclylene” as used herein refers to a heterocyclic or heterocyclyl moiety that is bivalent as described above (i.e., attached at two different points to the rest of the compound) and may also be saturated or partially unsaturated. Non-limiting examples include those shown below. Heterocyclylene is understood to include bicyclic heterocyclylene systems. Non-limiting examples of bicyclic heterocyclylene moieties are also shown below and said bicyclic systems may be spirocyclic, fused, or bridged and may be saturated or partially unsaturated.



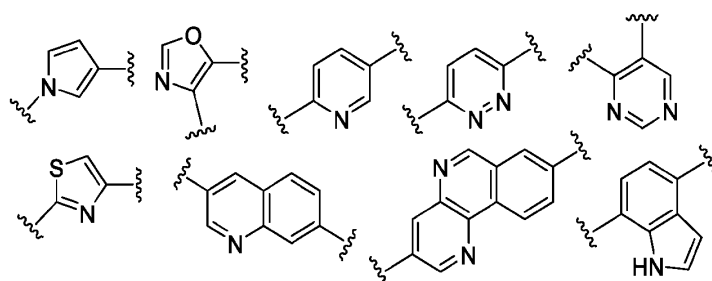
[0041] “Phenylene” as used herein refers to a phenyl moiety that is bivalent as described above (i.e., attached at two different points to the rest of the compound). Examples are shown below.



[0042] “Arylene” as used herein refers to a mono or multi-cyclic aryl (i.e., phenyl or a multi-cyclic aryl) moiety that is bivalent as described above (i.e., attached at two different points to the rest of the compound), wherein the arylene group contains no heteroatoms. Examples are shown below.

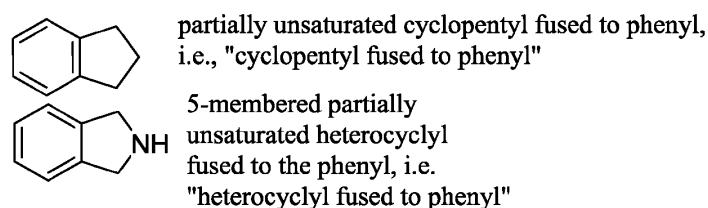


[0043] “Heteroarylene,” as used herein refers to a mono or multi-cyclic aryl ring system that contains at least one heteroatom wherein the ring system is bivalent as described above (i.e., attached at two different points to the rest of the compound). Examples are shown below.

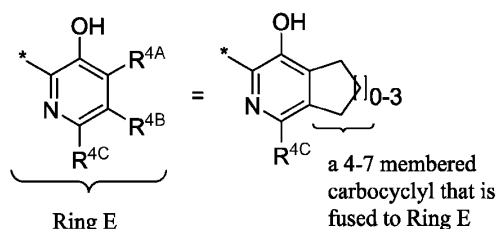


[0044] The term “alkylene” refers to a bivalent alkyl group. An “alkylene chain” is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0045] “Carbocyclyl (or heterocyclyl, aryl, phenyl, or heteroaryl) fused to” another phenyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl, for example, a “phenyl or pyridyl” as used herein, may be referred to as “partially unsaturated” without said “carbocyclyl (or heterocyclyl, aryl, phenyl, or heteroaryl) fused to” the other ring requiring further unsaturation besides the carbon carbon bond which it shares with the ring to which it is fused (i.e., the “phenyl or pyridyl”). This is illustrated below.



[0046] A further example below shows a carbocyclyl moiety fused to a Ring E as defined in the embodiments herein. Said carbocyclyl does not explicitly require a descriptor of “partially unsaturated” to describe said carbocyclyl because it shares two carbons with the aromatic pyridine to which it is fused. Such language is used herein to describe such systems, for example, “ R^{4A} and R^{4B} , along with their intervening atoms, join to form 4-7 membered carbocyclyl that is fused to Ring E” as shown in the image below. As such, “Ring E” may refer to a monocyclic ring (i.e., the pyridine shown below and its substituents which do not form a fused ring), without any further fused rings created by its substituents (i.e., R^{4A} and R^{4B}). Any further fused ring created by the substituents of Ring E is described as being “fused to Ring E.” Likewise, R^{4A} and R^{4B} , along with their intervening atoms, join to form 4-7 membered carbocyclyl or heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) that is fused to Ring E (not pictured), is subject to the same interpretation.



[0047] The term “alkenylene” refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

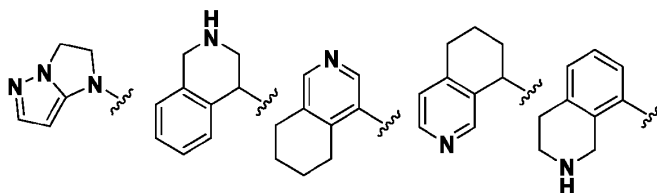
[0048] The term “halogen” means F, Cl, Br, or I.

[0049] The term “aryl” used alone or as part of a larger moiety as in “aralkyl,” “aralkoxy,” or “aryloxyalkyl,” refers to monocyclic or bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term “aryl” may be used interchangeably with the term “aryl ring.” In certain embodiments of the present invention, “aryl” refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term “aryl,” as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[0050] The terms “heteroaryl” and “heteroar-,” used alone or as part of a larger moiety, e.g., “heteroaralkyl,” or “heteroaralkoxy,” refer to groups having 5 to 10 ring atoms, preferably 5, 6, 9 or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term “heteroatom” refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, triazinyl, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl (i.e., 1,2,3-triazolyl), 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, indoliziny, purinyl, naphthyridinyl, and pteridinyl. The terms “heteroaryl” and “heteroar-,” as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where unless otherwise specified, the radical or point of attachment is on the heteroaromatic ring or on one of the rings to which the heteroaromatic ring is fused. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, indoliziny, isoindolin-1-onyl, 1,2-dihydro-3H-pyrrolo[3,4-c]pyridin-3-onyl, 2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-onyl, imidazo[1,2-

a]pyridyl, imidazo[1,5-a]pyridyl, pyrazolo[1,5-a]pyridyl, pyrrolo[1,2-b]pyridazinyl, pyrrolo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinoliziny, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolyl, and tetrahydroisoquinolyl. A heteroaryl group may be mono- or bicyclic. The term “heteroaryl” may be used interchangeably with the terms “heteroaryl ring,” “heteroaryl group,” or “heteroaromatic,” any of which terms include rings that are optionally substituted. The term “heteroaralkyl” refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0051] As used herein, the terms “heterocycle,” “heterocyclyl,” “heterocyclic radical,” and “heterocyclic ring” are used interchangeably and refer to a stable 5- to 7-membered monocyclic or 7-10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. Said 7-10-membered bicyclic heterocyclic moiety that is partially unsaturated may include an aryl or heteroaryl ring fused to a non-aromatic ring. For example, said 7-10-membered bicyclic heterocyclic moiety may include a bicyclic heterocyclyl as shown below:



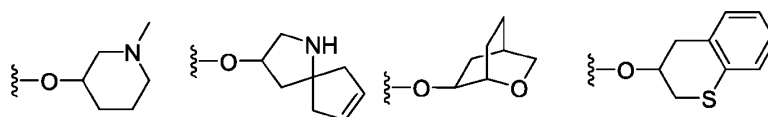
When used in reference to a ring atom of a heterocycle, the term “nitrogen” includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl), or ⁺NR (as in *N*-substituted pyrrolidinyl).

[0052] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, oxetanyl, azetidiny, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, oxazolidinyl,

piperaziny, dioxanyl, dioxolanyl, diazepiny, oxazepiny, thiazepiny, morpholiny, 2-oxa-6-azaspiro[3.3]heptane, and quinuclidiny. The terms “heterocycle,” “heterocyclyl,” “heterocyclyl ring,” “heterocyclic group,” “heterocyclic moiety,” and “heterocyclic radical,” are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indoliny, 3*H*-indolyl, chromanyl, phenanthridiny, or tetrahydroquinoliny. A heterocyclyl group may be mono- or bicyclic. The term “heterocyclylalkyl” refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0053] “Arylene” or “heteroarylene,” as used herein (i.e., phenylene), refers to any bivalent aryl or heterocyclyl described herein, that is a bisradical substituted at each of two substitutable positions of the ring system as described in detail *supra*.

[0054] “Heterocyclyloxy,” as used herein, refers to an -OR group wherein the R is a heterocyclyl. Nonlimiting examples are shown below.



[0055] As used herein, the term “partially unsaturated” refers to a ring moiety that includes at least one double or triple bond. The term “partially unsaturated” is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0056] As described herein, compounds of the invention may contain “optionally substituted” moieties. In general, the term “substituted,” whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain

embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0057] Suitable monovalent substituents on a substitutable carbon atom of an “optionally substituted” group are independently halogen; $-(CH_2)_{0-4}B(OR^\circ)_2$; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$; $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R° ; $-CH=CHPh$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}pyridyl$ which may be substituted with R° ; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)C(NR^\circ)N(R^\circ)_2$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-(CH_2)_{0-4}P(O)_2R^\circ$; $-(CH_2)_{0-4}P(O)R^\circ_2$; $-(CH_2)_{0-4}OP(O)R^\circ_2$; $-(CH_2)_{0-4}OP(O)(OR^\circ)_2$; $-SiR^\circ_3$; $-(C_{1-4}$ straight or branched alkylene) $O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene) $C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-SO_2-C_{1-4}$ aliphatic (i.e., $-SO_2CH_3$), $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$ -(5-6 membered heteroaryl ring), or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R° , taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0058] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$, $-O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched

alkylene)C(O)OR[•], or –SSR[•] wherein each R[•] is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently selected from C₁₋₆ aliphatic, –CH₂Ph, –O(CH₂)₀₋₁Ph, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R[°] include =O and =S.

[0059] Suitable divalent substituents on a saturated carbon atom of an “optionally substituted” group, which includes instances of R[°] (or the ring formed by taking two independent occurrences of R[°] together with their intervening atoms), include the following: =O, =S, =NNR^{*}₂, =NNHC(O)R^{*}, =NNHC(O)OR^{*}, =NNHS(O)₂R^{*}, =NR^{*}, =NOR^{*}, –O(C(R^{*})₂)₂₋₃O–, or –S(C(R^{*})₂)₂₋₃S–, wherein each independent occurrence of R^{*} is selected from hydrogen, C₁₋₆aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an “optionally substituted” group include: –O(CR^{*})₂₋₃O–, wherein each independent occurrence of R^{*} is selected from hydrogen, C₁₋₆aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0060] Suitable substituents on the aliphatic group of R^{*} include halogen, –R[•], –(haloR[•]), –OH, –OR[•], –O(haloR[•]), –CN, –C(O)OH, –C(O)OR[•], –NH₂, –NHR[•], –NR[•]₂, or –NO₂, wherein each R[•] is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C₁₋₄aliphatic, –CH₂Ph, –O(CH₂)₀₋₁Ph, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0061] Suitable substituents on a substitutable nitrogen of an “optionally substituted” group include –R[†], –NR[†]₂, –C(O)R[†], –C(O)OR[†], –C(O)C(O)R[†], –C(O)CH₂C(O)R[†], –S(O)₂R[†], –S(O)₂NR[†]₂, –C(S)NR[†]₂, –C(NH)NR[†]₂, or –N(R[†])S(O)₂R[†]; wherein each R[†] is independently hydrogen, C₁₋₆aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R[†], taken together with their intervening atom(s)

form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0062] Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, $-R^{\bullet}$, $-(\text{halo}R^{\bullet})$, $-\text{OH}$, $-\text{OR}^{\bullet}$, $-\text{O}(\text{halo}R^{\bullet})$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^{\bullet}$, $-\text{NH}_2$, $-\text{NHR}^{\bullet}$, $-\text{NR}^{\bullet}_2$, or $-\text{NO}_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0063] As used herein, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1–19. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like.

[0064] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $\text{N}^+(\text{C}_{1-4}\text{alkyl})_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically

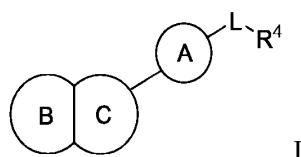
acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0065] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, Z and E conformational isomers and R_a (or M) and S_a (or P) atropisomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention. In certain embodiments, Ring A of a provided compound may be substituted with one or more deuterium atoms.

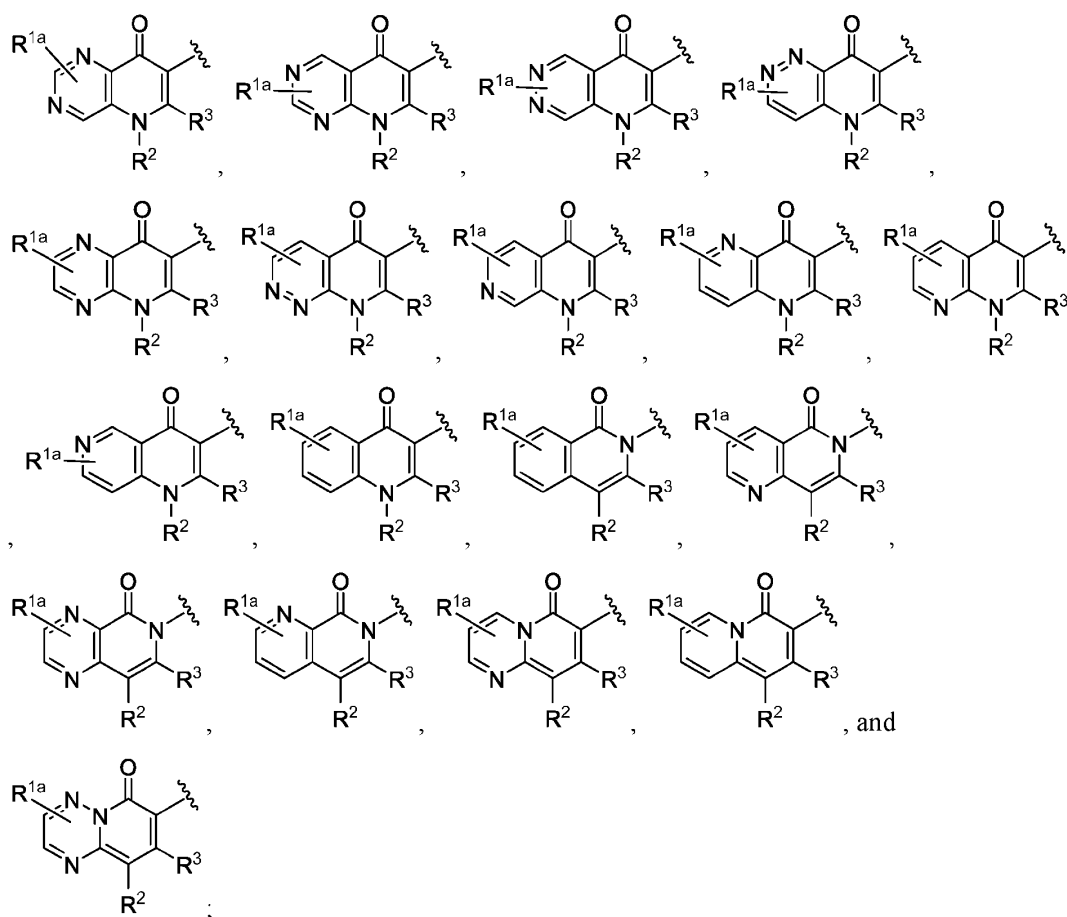
[0066] The structures as drawn represent relative configurations, unless labeled as absolute configurations. The invention contemplates individual enantiomers and racemic mixtures.

3. Description of Exemplary Embodiments:

[0067] In one aspect, the disclosure provides a compound of Formula I, or a pharmaceutically acceptable salt thereof:



wherein bicyclic Ring BC is selected from one of the following:



wherein  denotes the point of attachment to Ring A;

and wherein Ring B may be further optionally substituted with 1 or 2 R^{1b} groups independently selected from H, halogen, CN, OH, C₁-C₆aliphatic, C₁-C₆alkoxy, C₃-C₆cycloalkyl, C₁-C₆alkylene-O-C₁-C₆alkyl, haloC₁-C₆alkyl, haloC₁-C₆alkoxy, and C₃-C₆cycloalkoxy, wherein said C₁-C₆aliphatic, C₁-C₆alkoxy, C₃-C₆cycloalkyl, C₁-C₆alkylene-O-C₁-C₆alkyl, haloC₁-C₆alkyl, haloC₁-C₆alkoxy, and C₃-C₆cycloalkoxy are each independently and optionally substituted with 1-5 halogen, OH, CN, C₁-C₆alkyl, or C₃-C₆cycloalkyl groups;

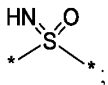
Ring A is:

a 4-7 membered saturated or partially unsaturated bivalent monocyclic carbocyclylene or 4-7 membered saturated or partially unsaturated bivalent heterocyclylene ring (having 1-4 heteroatoms

independently selected from nitrogen, oxygen, and sulfur, and 0 or 1 nitrogen atoms in addition to the 1-4 heteroatoms); or

a 4-12 membered saturated or partially unsaturated bivalent bicyclic ring system that is fused, bridged, or spirocyclic selected from carbocyclylene or heterocyclylene (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

wherein Ring A is substituted with 0-4 independently selected R^B substituents;

-L- is a linker selected from -C(O)-, -S(O)-, -S(O)₂-, and ;

R^{1a} is selected from:

a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with 1-3 groups independently selected from halogen, C₁-C₆aliphatic, C₃-C₆cycloalkyl, haloC₁-C₆alkyl, C₁-C₆alkoxy, and C₃-C₆cycloalkoxy, wherein said 5-6 membered heteroaryl is further substituted with 0-3 independently selected R^B ;

a 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted with 1 or 2 groups independently selected from C₁-C₆aliphatic, C₃-C₆cycloalkyl, C₁-C₆alkoxy, C₃-C₆cycloalkoxy, and -OR, wherein said 4-7 membered saturated or partially unsaturated heterocyclyl is further substituted with 0-3 independently selected R^B ;

a 4-12 membered saturated or partially unsaturated bicyclic ring system that is fused, bridged, or spirocyclic selected from carbocyclyl or heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein said carbocyclyl or heterocyclyl is substituted with 0-3 independently selected R^B ; and

H, halogen, C₁-C₆aliphatic, C₃-C₇cycloalkyl, C₁-C₆alkylene-O-C₁-C₆alkyl, CN, -OR, -OR¹⁰, -NR¹⁰R¹¹, -C(O)NR¹⁰R¹¹, -CH₂NR¹⁰R¹¹, or -SO₂R¹², wherein said C₁-C₆aliphatic, C₃-C₇cycloalkyl, or C₁-C₆alkylene-O-C₁-C₆alkyl is substituted with 0-5 independently selected R^B ;

or R^{1a} and one R^{1b} on adjacent atoms of Ring B, taken together with the adjacent Ring B atoms to which they are attached, form a cyclic group fused to Ring B selected from phenyl, a 5-6 membered heteroaryl (having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur), a 4-

7 membered saturated or partially unsaturated carbocyclyl, or a 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur), wherein said cyclic group fused to Ring B is substituted with 0-3 independently selected R^B ;

R^2 is $C(R^C)_2C(O)N(R)R^{2A}$;

R^{2A} is phenyl or pyridyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1 - C_4 aliphatic, halo C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, halo C_3 - C_6 cycloalkyl, -OH, -CN, C_1 - C_4 alkoxy, halo C_1 - C_4 alkoxy, and $-SF_5$, and wherein two substituents on adjacent atoms of the phenyl or pyridyl, together with said adjacent atoms, form a 4-7 membered carbocyclyl fused to the phenyl or pyridyl, and wherein two substituents on adjacent atoms of the phenyl or pyridyl together with said adjacent atoms form a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) fused to the phenyl or pyridyl, wherein said fused 4-7 membered carbocyclyl or fused 4-7 membered heterocyclyl is substituted with 0-5 independently selected halogen; or

R^{2A} is 2-benzimidazolyl, 2-naphthyl, or 3-quinolinyl, each of which is optionally substituted with 1, 2 or 3 substituents independently selected from halogen, C_1 -4alkyl, and -OH;

R^3 is hydrogen, C_1 - C_4 aliphatic, C_3 - C_5 cycloalkyl, C_1 - C_4 alkoxy, $-NHR^{3A}$, $-N(R^{3A})_2$, or C_1 - C_4 alkylthio, each of which, besides hydrogen, is optionally substituted with -OH, 1-5 independently selected halogen, OR, $-C(O)NR^{10}R^{11}$, or $N(R)C(O)R$;

each R^{3A} is independently selected from C_1 - C_4 alkyl;

R^4 is phenyl or a first 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) wherein said phenyl or first 5-6 membered heteroaryl is substituted with 0-5 R^B ; and optionally two adjacent atoms of said phenyl or first 5-6 membered heteroaryl have two substituents that together with said adjacent atoms form a cyclic group fused to the phenyl or first 5-6 membered heteroaryl selected from a 4-7 membered carbocyclyl, a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or a second 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said fused cyclic group is substituted with 0-3 independently selected R^B ; or

R⁴ is a C₁-C₄aliphatic, C₁-C₄alkoxy, or C₃-C₆cycloalkyl, each of which is substituted with 0-3 groups independently selected from halogen, -CN, -OH, C₁-C₄alkyl, C₁-C₄alkoxy, optionally substituted 5-6 membered heterocyclyl, and optionally substituted 5-6 membered heterocycloxy;

R¹⁰ is H, C₁-C₆aliphatic, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, -C(O)C₁-C₆alkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R¹⁰ except H being optionally substituted with 1 or 2 independently selected R^B;

R¹¹ is H, C₁-C₆aliphatic, or C₃-C₆cycloalkyl, or R¹⁰ and R¹¹ are taken together with the nitrogen atom to which they are attached to form a 5-6 membered ring optionally substituted with 1, 2, or 3 substituents independently selected from halogen, -OH, -CN, C₁-C₄alkoxy, and haloC₁-C₄alkoxy;

R¹² is C₁-C₆aliphatic, C₃-C₆cycloalkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R¹² optionally substituted with 1 or 2 groups independently selected from halogen, C₁-C₆aliphatic, haloC₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, and C₃-C₆cycloalkoxy;

R^B is independently selected at each occurrence from the group consisting of optionally substituted phenyl, optionally substituted 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), halogen, optionally substituted C₁-C₆aliphatic, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, C₁-C₆alkoxy, haloC₁-C₆alkoxy, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy, C₁-C₆alkylene-O-C₁-C₆alkyl, -CN, -NO₂, oxo, -OR, -SR, NR₂, S(O)₂R, S(O)₂NR₂, S(O)R, S(O)NR₂, C(O)R, C(O)OR, -C(O)NR₂, C(O)N(R)OR, OC(O)R, OC(O)NR₂, -N(R)C(O)OR, N(R)C(O)R, N(R)C(O)NR₂, N(R)C(NR)NR₂, N(R)S(O)₂NR₂, and -N(R)S(O)₂R;

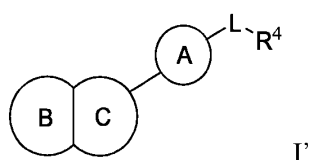
R^C is independently selected at each occurrence from hydrogen, -CH₃, or -CH₂CH₃, or two R^C taken together with the carbon to which they are attached form a cyclopropyl ring;

each R is independently hydrogen, or an optionally substituted C₁-aliphatic group, an optionally substituted phenyl, an optionally substituted 3-7 membered saturated or partially unsaturated

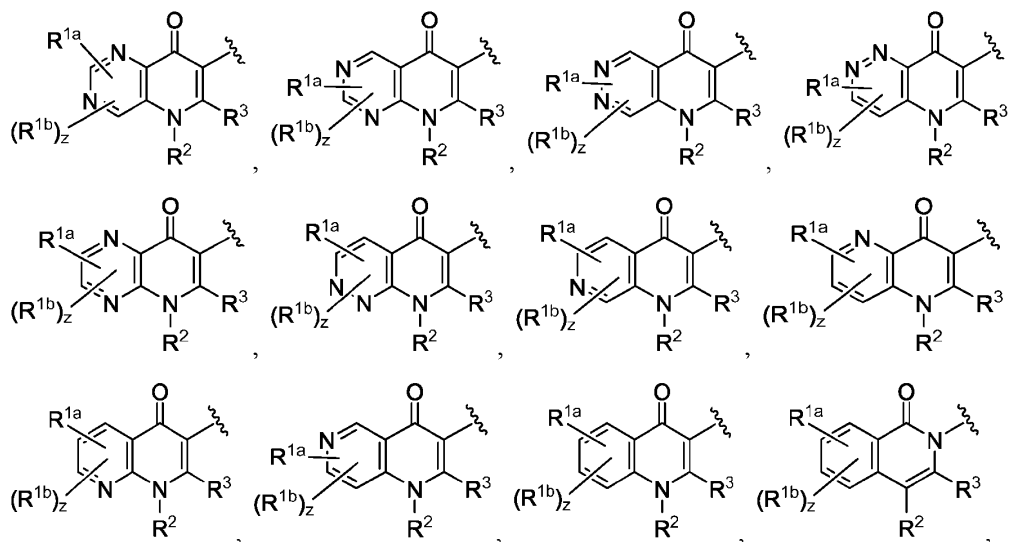
carbocyclic ring, an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or an optionally substituted 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); or

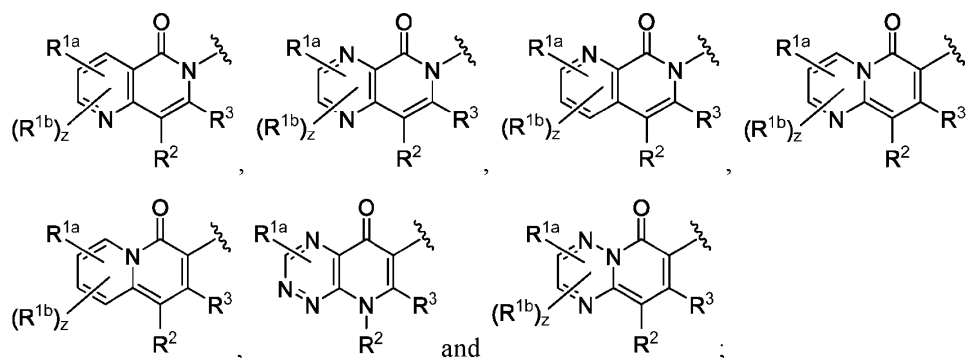
two R groups on the same atom are taken together with the same atom to form a cyclic group selected from an optionally substituted 4-7 membered saturated ring, a 4-7 membered partially unsaturated ring, or a 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said cyclic group has 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

[0068] In one aspect, the disclosure provides a compound of Formula I', or a pharmaceutically acceptable salt thereof:



wherein bicyclic Ring BC is selected from one of the following:





wherein denotes the point of attachment to Ring A;

and wherein each R^{1b} group is independently selected from H, halogen, CN, OH, C_1 - C_6 aliphatic, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, C_1 - C_6 alkylene-O- C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, halo C_1 - C_6 alkoxy, and C_3 - C_6 cycloalkoxy, wherein said C_1 - C_6 aliphatic, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, C_1 - C_6 alkylene-O- C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, halo C_1 - C_6 alkoxy, and C_3 - C_6 cycloalkoxy are each independently and optionally substituted with 1-5 halogen, OH, CN, C_1 - C_6 alkyl, or C_3 - C_6 cycloalkyl groups; wherein z is 0, 1, or 2;

Ring A is:

a 4-7 membered saturated or partially unsaturated bivalent monocyclic carbocyclylene or 4-7 membered saturated or partially unsaturated bivalent heterocyclylene ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 0 or 1 nitrogen atoms in addition to the 1-4 heteroatoms); or

a 4-12 membered saturated or partially unsaturated bivalent bicyclic ring system that is fused, bridged, or spirocyclic selected from carbocyclylene or heterocyclylene (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

wherein Ring A is substituted with 0-4 independently selected R^B substituents;

-L- is a linker selected from -C(O)-, -S(O)-, -S(O)₂-, and ;

R^{1a} is selected from:

a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with 1-3 groups independently selected from halogen, C₁-C₆aliphatic, C₃-C₆cycloalkyl, haloC₁-C₆alkyl, C₁-C₆alkoxy, and C₃-C₆cycloalkoxy, wherein said 5-6 membered heteroaryl is further substituted with 0-3 independently selected R^B;

a 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted with 1 or 2 groups independently selected from C₁-C₆aliphatic, C₃-C₆cycloalkyl, C₁-C₆alkoxy, C₃-C₆cycloalkoxy, and -OR, wherein said 4-7 membered saturated or partially unsaturated heterocyclyl is further substituted with 0-3 independently selected R^B;

a 4-12 membered saturated or partially unsaturated bicyclic ring system that is fused, bridged, or spirocyclic selected from carbocyclyl or heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein said carbocyclyl or heterocyclyl is substituted with 0-3 independently selected R^B; and

H, halogen, C₁-C₆aliphatic, C₃-C₇cycloalkyl, C₁-C₆alkylene-O-C₁-C₆alkyl, CN, -OR, -OR¹⁰, -NR¹⁰R¹¹, -C(O)NR¹⁰R¹¹, -CH₂NR¹⁰R¹¹, -SO₂R¹², wherein said C₁-C₆aliphatic, C₃-C₇cycloalkyl, or C₁-C₆alkylene-O-C₁-C₆alkyl is substituted with 0-5 independently selected R^B;

or R^{1a} and one R^{1b} on adjacent atoms of Ring B, taken together with the adjacent Ring B atoms to which they are attached, form a cyclic group fused to Ring B selected from phenyl, a 5-6 membered heteroaryl (having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur), a 4-7 membered saturated or partially unsaturated carbocyclyl, or a 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur), wherein said cyclic group fused to Ring B is substituted with 0-3 independently selected R^B;

R² is selected from C(R^C)₂C(O)N(R)R^{2A}, C(R^C)₂C(R^C)₂C(O)N(R)R^{2A}, C(R^C)₂C(R^C)₂N(R)C(O)N(R)R^{2A}, and C(R^C)₂C(R^C)₂N(R)C(O)R^{2A};

R^{2A} is phenyl, pyridyl, cubanyl, a saturated or partially unsaturated 4-8 membered monocyclic ring, a saturated or partially unsaturated bridged, fused, or spirocyclic 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered ring, wherein said saturated or partially unsaturated monocyclic ring, or saturated or partially unsaturated bridged, fused, or spirocyclic ring contains 0, 1, 2, 3, or 4 heteroatoms

independently selected from nitrogen, oxygen, and sulfur; and wherein said phenyl, pyridyl, cubanyl, saturated or partially unsaturated monocyclic ring, or saturated or partially unsaturated bridged, fused, or spirocyclic ring are each optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C₁-C₄aliphatic, haloC₁-C₄alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, -OH, -CN, C₁-C₄alkoxy, haloC₁-C₄alkoxy, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy and -SF₅, and wherein two substituents on adjacent atoms of the phenyl or pyridyl, together with said adjacent atoms, optionally form a 4-7 membered carbocyclyl fused to the phenyl or pyridyl, and wherein two substituents on adjacent atoms of the phenyl or pyridyl together with said adjacent atoms optionally form a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) fused to the phenyl or pyridyl, wherein said fused 4-7 membered carbocyclyl or fused 4-7 membered heterocyclyl is substituted with 0-5 independently selected halogen, and wherein two substituents on the same atom of said saturated or partially unsaturated monocyclic ring, or saturated or partially unsaturated bridged, fused, or spirocyclic ring optionally form a cyclic group selected from:

- an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclyl, and
- an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

R^{2A} is 2-benzimidazolyl, 2-naphthyl, or 3-quinolinyl, each of which is optionally substituted with 1, 2 or 3 substituents independently selected from halogen, C₁-4alkyl, and -OH;

R³ is hydrogen, C₁-C₄aliphatic, C₃-C₅cycloalkyl, C₁-C₄alkoxy, -NHR^{3A}, -N(R^{3A})₂, or C₁-C₄alkylthio, each of which, besides hydrogen, is optionally substituted with -OH, 1-5 independently selected halogen, OR, -C(O)NR¹⁰R¹¹, or N(R)C(O)R;

each R^{3A} is independently selected from C₁-C₄alkyl;

R⁴ is phenyl or a first 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) wherein said phenyl or first 5-6 membered heteroaryl is substituted with 0-5 R^B; and optionally two adjacent atoms of said phenyl or first 5-6 membered heteroaryl have two substituents that together with said adjacent atoms form a cyclic group fused to the phenyl or first 5-6 membered heteroaryl selected from a 4-7 membered carbocyclyl, a 4-7

membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or a second 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said fused cyclic group is substituted with 0-3 independently selected R^B; or

R⁴ is a C₁-C₄aliphatic, C₁-C₄alkoxy, or C₃-C₆cycloalkyl, each of which is substituted with 0-3 groups independently selected from halogen, -CN, -OH, C₁-C₄alkyl, C₁-C₄alkoxy, optionally substituted 5-6 membered heterocyclyl, and optionally substituted 5-6 membered heterocycloxy;

R¹⁰ is H, C₁-C₆aliphatic, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, -C(O)C₁-C₆alkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R¹⁰ except H being optionally substituted with 1 or 2 independently selected R^B;

R¹¹ is H, C₁-C₆aliphatic, or C₃-C₆cycloalkyl, or R¹⁰ and R¹¹ are taken together with the nitrogen atom to which they are attached to form a 5-6 membered ring optionally substituted with 1, 2, or 3 substituents independently selected from halogen, -OH, -CN, C₁-C₄alkoxy, and haloC₁-C₄alkoxy;

R¹² is C₁-C₆aliphatic, C₃-C₆cycloalkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R¹² optionally substituted with 1 or 2 groups independently selected from halogen, C₁-C₆aliphatic, haloC₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, and C₃-C₆cycloalkoxy;

R^B is independently selected at each occurrence from the group consisting of optionally substituted phenyl, optionally substituted 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), halogen, optionally substituted C₁-C₆aliphatic, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, C₁-C₆alkoxy, haloC₁-C₆alkoxy, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy, C₁-C₆alkylene-O-C₁-C₆alkyl, -CN, -NO₂, oxo, -OR, -SR, NR₂, S(O)₂R, S(O)₂NR₂, S(O)R, S(O)NR₂, C(O)R, C(O)OR, -C(O)NR₂, C(O)N(R)OR, OC(O)R, OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, N(R)C(O)NR₂, N(R)C(NR)NR₂, N(R)S(O)₂NR₂, and -N(R)S(O)₂R;

R^C is independently selected at each occurrence from hydrogen, -CH₃, or -CH₂CH₃, or two R^C taken together with the carbon to which they are attached form a cyclopropyl ring;

each R is independently hydrogen, or an optionally substituted C₁₋₆aliphatic group, an optionally substituted phenyl, an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or an optionally substituted 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); or

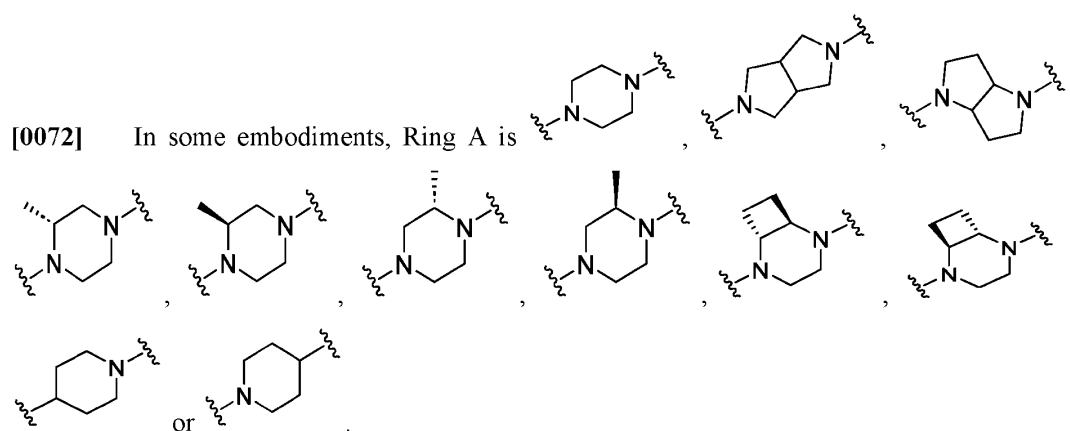
two R groups on the same atom are taken together with the same atom to form a cyclic group selected from an optionally substituted 4-7 membered saturated ring, a 4-7 membered partially unsaturated ring, or a 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said cyclic group has 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

[0069] In some embodiments, Ring A is a 4-7 membered saturated or partially unsaturated bivalent monocyclic carbocyclylene or 4-7 membered saturated or partially unsaturated bivalent heterocyclylene ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 0 or 1 nitrogen atoms in addition to the 1-4 heteroatoms). In some embodiments, Ring A is a 4-7 membered saturated or partially unsaturated bivalent monocyclic carbocyclylene, wherein Ring A is substituted with 0-4 independently selected R^B substituents. In some embodiments, Ring A is a 4-7 membered saturated or partially unsaturated bivalent monocyclic heterocyclylene (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 0 or 1 nitrogen atoms in addition to the 1-4 heteroatoms), wherein Ring A is substituted with 0-4 independently selected R^B substituents.

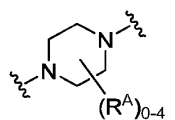
[0070] In some embodiments, Ring A is a 4-12 membered saturated or partially unsaturated bivalent bicyclic ring system that is fused, bridged, or spirocyclic selected from carbocyclylene or heterocyclylene (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur). In some embodiments, Ring A is a 4-12 membered saturated or partially unsaturated bivalent bicyclic ring system that is fused, bridged, or spirocyclic and is a carbocyclylene, wherein Ring A is substituted with 0-4 independently selected R^B substituents. In some embodiments, Ring A is a 4-12 membered saturated or partially unsaturated bivalent bicyclic ring system that is fused,

bridged, or spirocyclic and is a heterocyclylene (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein Ring A is substituted with 0-4 independently selected R^B substituents.

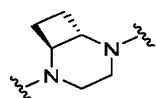
[0071] In some embodiments, Ring A is a 4-12 membered saturated or partially unsaturated bivalent bicyclic ring system comprising 2 fused rings. In some embodiments, Ring A is a 4-12 membered saturated or partially unsaturated bivalent bicyclic ring system comprising a spirocyclic ring system. In some embodiments, Ring A is a 4-12 membered saturated or partially unsaturated bivalent bicyclic ring system comprising a bridged ring system.



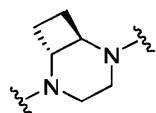
[0073] In some embodiments, Ring A is



[0074] In some embodiments, Ring A is

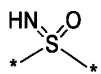


[0075] In some embodiments, Ring A is



[0076] In some embodiments, Ring A is as selected from one of the substituents of **Table 1** or **Table 1a**.

[0077] As described generally above, L is a linker selected from -C(O)-, -S(O)-, -S(O)₂-, and



[0078] In some embodiments, linker L is -C(O)-.

[0079] In some embodiments, linker L is -S(O)-.

[0080] In some embodiments, linker L is -S(O)₂-.



[0081] In some embodiments, linker L is

[0082] In some embodiments, linker L is as selected from one of the substituents of **Table 1** or **Table 1a**.

[0083] As described generally above, R^{1a} is selected from:

- a) a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with 1-3 groups independently selected from halogen, C₁-C₆aliphatic, C₃-C₆cycloalkyl, haloC₁-C₆alkyl, C₁-C₆alkoxy, and C₃-C₆cycloalkoxy, wherein said 5-6 membered heteroaryl is further substituted with 0-3 independently selected R^B;

a 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted with 1 or 2 groups independently selected from C₁-C₆aliphatic, C₃-C₆cycloalkyl, C₁-C₆alkoxy, C₃-C₆cycloalkoxy, and -OR, wherein said 4-7 membered saturated or partially unsaturated heterocyclyl is further substituted with 0-3 independently selected R^B;

a 4-12 membered saturated or partially unsaturated bicyclic ring system that is fused, bridged, or spirocyclic selected from carbocyclyl or heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein said carbocyclyl or heterocyclyl is substituted with 0-3 independently selected R^B; and

H, halogen, C₁-C₆aliphatic, C₃-C₇cycloalkyl, C₁-C₆alkylene-O-C₁-C₆alkyl, CN, -OR, -OR¹⁰, -NR¹⁰R¹¹, -C(O)NR¹⁰R¹¹, -CH₂NR¹⁰R¹¹, -SO₂R¹², wherein said C₁-C₆aliphatic, C₃-C₇cycloalkyl, or C₁-C₆alkylene-O-C₁-C₆alkyl is substituted with 0-5 independently selected R^B;

or R^{1a} and one R^{1b} on adjacent atoms of Ring B, taken together with the adjacent Ring B atoms to which they are attached, form a cyclic group fused to Ring B selected from phenyl, a 5-6 membered heteroaryl (having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur), a 4-7 membered saturated or partially unsaturated carbocyclyl, or a 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur), wherein said cyclic group fused to Ring B is substituted with 0-3 independently selected R^B.

[0084] In some embodiments, R^{1a} is a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with 1 or 2 groups independently selected from C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, and C₃-C₆cycloalkoxy, wherein said 5-6 membered heteroaryl is further substituted with 0-3 independently selected R^B. In some embodiments, R^{1a} is a 4-6 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), said heterocyclyl substituted with 0-2 R^B groups independently selected from halogen, oxo, -NR₂, optionally substituted C₁-4aliphatic, -OR, azetidiny optionally substituted with 1 or 2 independently selected halogen, and pyrrolidinyl optionally substituted with 1 or 2 independently selected halogen. In some embodiments, R^{1a} is a 6-8 membered saturated or partially unsaturated bridged bicyclic heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), said heterocyclyl substituted with 0-2 R^B groups independently selected from halogen, oxo, -NR₂, optionally substituted C₁-4aliphatic, -OR, azetidiny optionally substituted with 1 or 2 independently selected halogen, and pyrrolidinyl optionally substituted with 1 or 2 independently selected halogen. In some embodiments, R^{1a} is a 3-7 membered optionally substituted carbocyclyl. In some embodiments, R^{1a} is an optionally substituted C₂-C₄alkenyl. In some embodiments, R^{1a} is cyclopropyl substituted C₂-C₄alkenyl. In some embodiments, R^{1a} is methyl substituted C₂-C₄alkenyl.

[0085] In some embodiments, R^{1a} is a 6-membered partially unsaturated heterocyclyl (having 1 oxygen atom). In some embodiments, R^{1a} is a 4-membered saturated heterocyclyl (having 1

oxygen atom). In some embodiments, R^{1a} is a 6-membered heteroaryl (having 1 nitrogen atom), said heteroaryl may be optionally substituted with 1 or 2 groups independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, and C_3 - C_6 cycloalkoxy, wherein said heteroaryl is further substituted with 0-1 R^B , wherein R^B is an optionally substituted C_{1-6} aliphatic group. In some embodiments, R^{1a} is a 6-membered heteroaryl (having 2 nitrogen atoms), said heteroaryl may be optionally substituted with 1 or 2 groups independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, and C_3 - C_6 cycloalkoxy, wherein said heteroaryl is further substituted with 0-1 R^B , wherein R^B is an optionally substituted C_{1-6} aliphatic group. In some embodiments, R^{1a} is $-NR^{10}R^{11}$ wherein R^{10} is a 5-6 membered heteroaryl (having 1 or 2 nitrogen atoms) optionally substituted with 1 or 2 groups independently selected from halogen, CH_3 , OCH_3 , C_3 - C_6 cycloalkyl, and C_3 - C_6 cycloalkoxy and wherein R^{11} is H or CH_3 . In some embodiments, R^{1a} is $-CH_2NR^{10}R^{11}$ wherein R^{10} is a 5-6 membered heteroaryl (having 1 or 2 nitrogen atoms) optionally substituted with 1 or 2 groups independently selected from halogen, CH_3 , OCH_3 , C_3 - C_6 cycloalkyl, and C_3 - C_6 cycloalkoxy and wherein R^{11} is H or CH_3 . In some embodiments, R^{1a} is C_2 - C_4 alkene wherein said alkene is optionally substituted with OCH_3 or 1, 2, or 3 fluorine. In some embodiments, R^{1a} is C_2 - C_4 alkyne wherein said alkyne is optionally substituted with OCH_3 or 1, 2, or 3 fluorine. In some embodiments, R^{1a} is $-SO_2R^{12}$ wherein R^{12} is selected from CH_3 or a 5-6 membered heteroaryl having 1-2 nitrogen heteroatoms optionally substituted with 1 or 2 groups independently selected from halogen and CH_3 . In some embodiments, R^{1a} is cyclopropyl optionally substituted with 1-2 fluorine. In some embodiments, R^{1a} is C_1 - C_6 alkyl optionally substituted with OH or 1-2 fluorine. In some embodiments, R^{1a} is $-C(O)NR^{10}R^{11}$ wherein R^{10} is H or CH_3 and wherein R^{11} is H or CH_3 .

[0086] In some embodiments, R^{1a} is a 5-membered heteroaryl (having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with 1 or 2 groups independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, and C_3 - C_6 cycloalkoxy, wherein said 5-membered heteroaryl is optionally further substituted with 0-3 independently selected R^B . In some embodiments, R^{1a} is a 5-membered heteroaryl (having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with 1 or 2 groups independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, and C_3 - C_6 cycloalkoxy. In some embodiments, R^{1a} is a 5-membered heteroaryl (having 2 nitrogen atoms) optionally substituted with 1 or 2 groups independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 -

C₆cycloalkyl, and C₃-C₆cycloalkoxy, wherein said 5-membered heteroaryl is optionally further substituted with 0-1 R^B, wherein R^B is hydroxyl substituted C₁-C₄alkyl.

[0087] In some embodiments, R^{1a} is a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with one group of C₁-C₆alkoxy or C₃-C₆cycloalkyl, wherein said 5-6 membered heteroaryl is optionally further substituted with 0-3 independently selected R^B.

[0088] In some embodiments, R^{1a} is pyridyl substituted with C₁-C₄alkoxy and further substituted with 0-2 R^B.

[0089] In some embodiments, R^{1a} is 5-membered heteroaryl (having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur, and 0 or 1 additional ring nitrogen atoms), wherein said 5-membered heteroaryl is optionally substituted with C₁-C₆alkyl, or C₃-C₅cycloalkyl and further substituted with 0-2 R^B.

[0090] In some embodiments, R^{1a} is selected from groups a-d:

- a) a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with 1 or 2 groups independently selected from C₁-C₆alkyl, C₃-C₆cycloalkyl, C₁-C₆alkoxy, and C₃-C₆cycloalkoxy, wherein said 5-6 membered heteroaryl is further substituted with 0-3 independently selected R^B;

a 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted with 1 or 2 groups independently selected from C₁-C₆alkyl, C₃-C₆cycloalkyl, C₁-C₆alkoxy, C₃-C₆cycloalkoxy, and -OR, wherein said 4-7 membered saturated or partially unsaturated heterocyclyl is further substituted with 0-3 independently selected R^B;

a 4-12 membered saturated or partially unsaturated bivalent bicyclic ring system that is fused, bridged, or spirocyclic selected from carbocyclene or heterocyclene (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), said carbocyclene or heterocyclene is substituted with 0-3 independently selected R^B, and

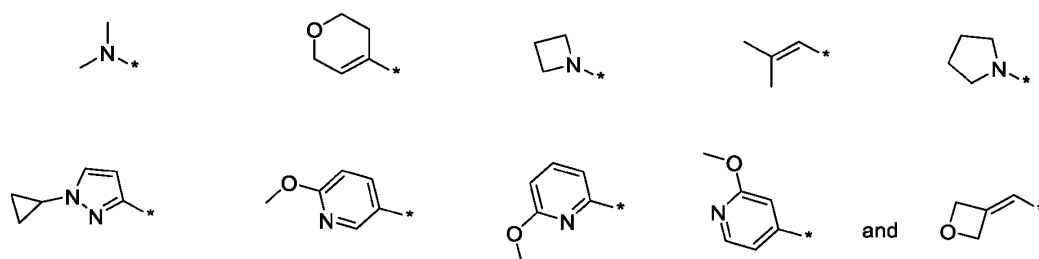
H, halogen, C₁-C₆alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₇cycloalkyl, C₁-C₆alkyl-O-C₁-C₆alkyl, CN, -OR, -NR¹⁰R¹¹, -C(O)NR¹⁰R¹¹, -CH₂NR¹⁰R¹¹, -SO₂R¹², wherein C₁-C₆alkyl, C₂-C₄ alkenyl,

C₂-C₄alkynyl, C₃-C₇cycloalkyl, or C₁-C₆alkylene-O-C₁-C₆alkyl may be substituted with 0-5 independently selected R^B.

[0091] In some embodiments, R^{1a} is a 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted with 1 or 2 groups independently selected from C₁-C₆alkyl, C₃-C₆cycloalkyl, C₁-C₆alkoxy, and C₃-C₆cycloalkoxy, and -OR, wherein said 4-7 membered saturated or partially unsaturated heterocyclyl is further substituted with 0-3 independently selected R^B.

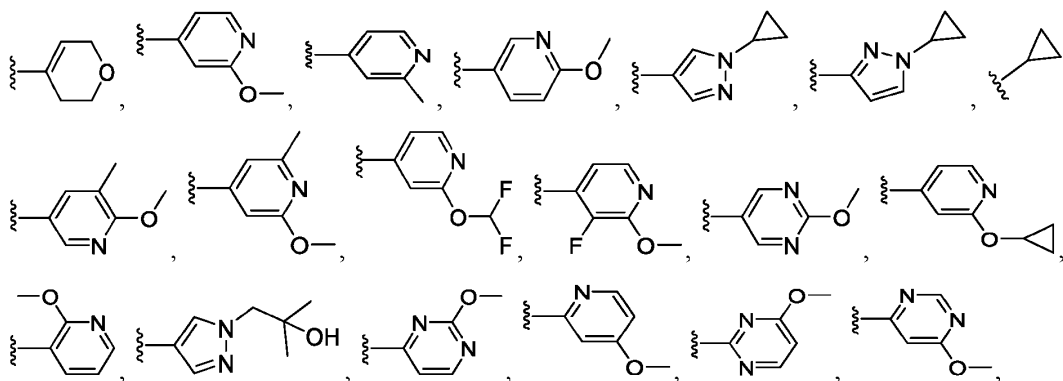
[0092] In some embodiments, R^{1a} is a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with 1 or 2 groups independently selected from C₁-C₆alkyl, C₃-C₆cycloalkyl, C₁-C₆alkoxy, and C₃-C₆cycloalkoxy, wherein said 5-6 membered heteroaryl is further substituted with 0-3 independently selected R^B.

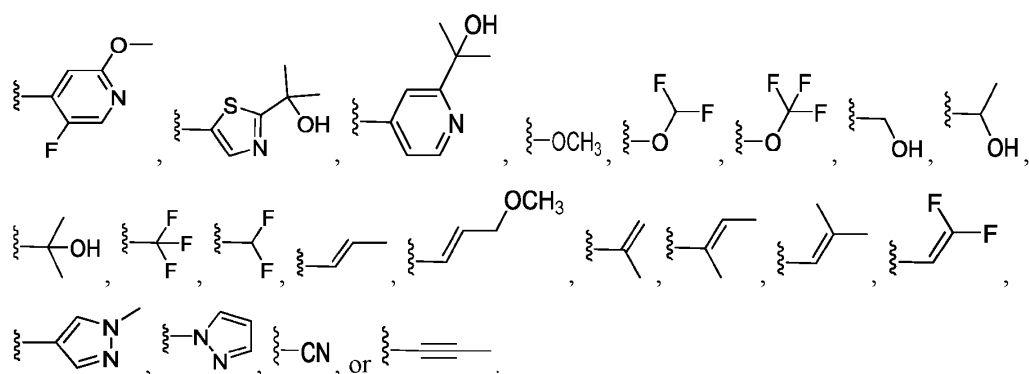
[0093] In some embodiments, R^{1a} is selected from the group consisting of:



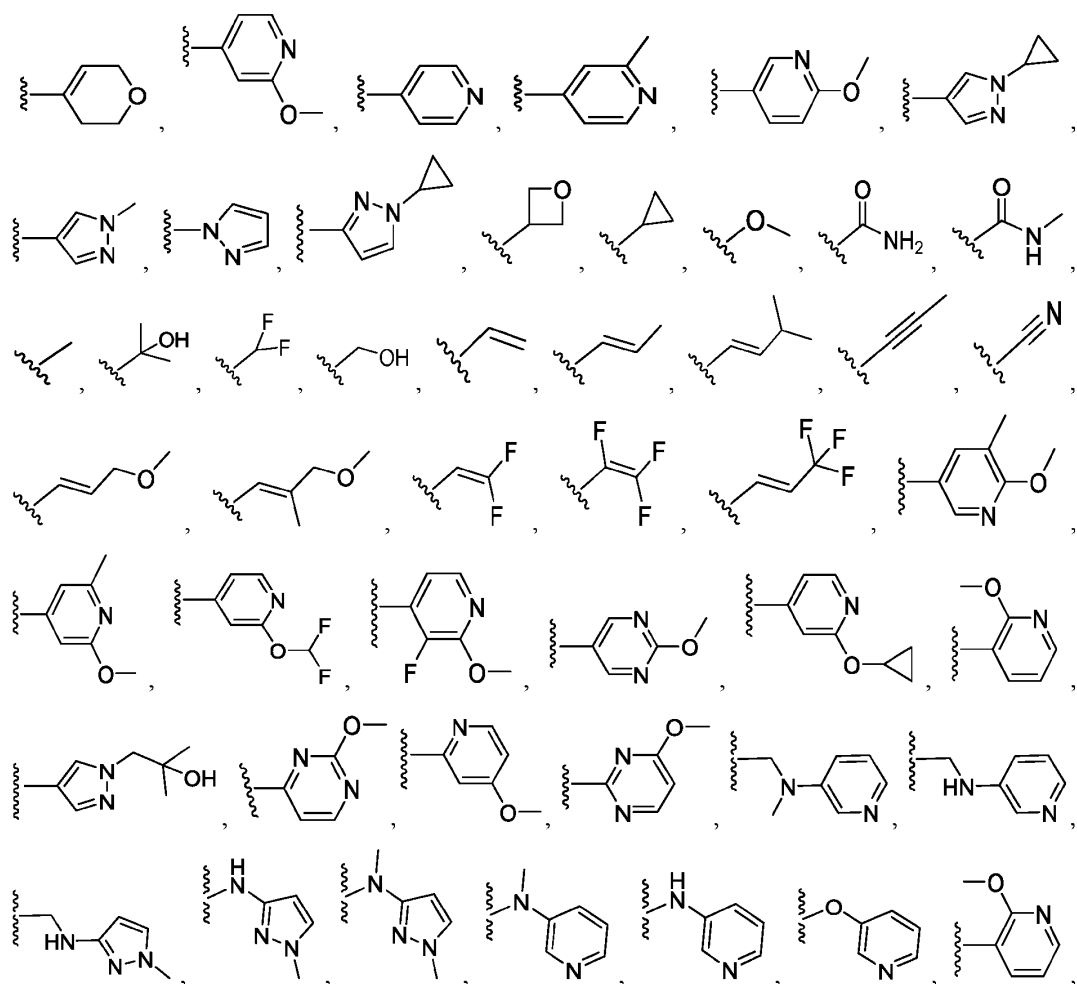
wherein * is the point of attachment to Ring B.

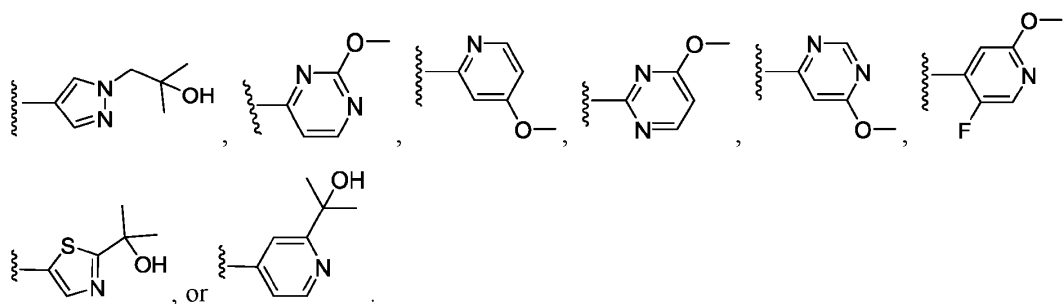
[0094] In some embodiments, R^{1a} is



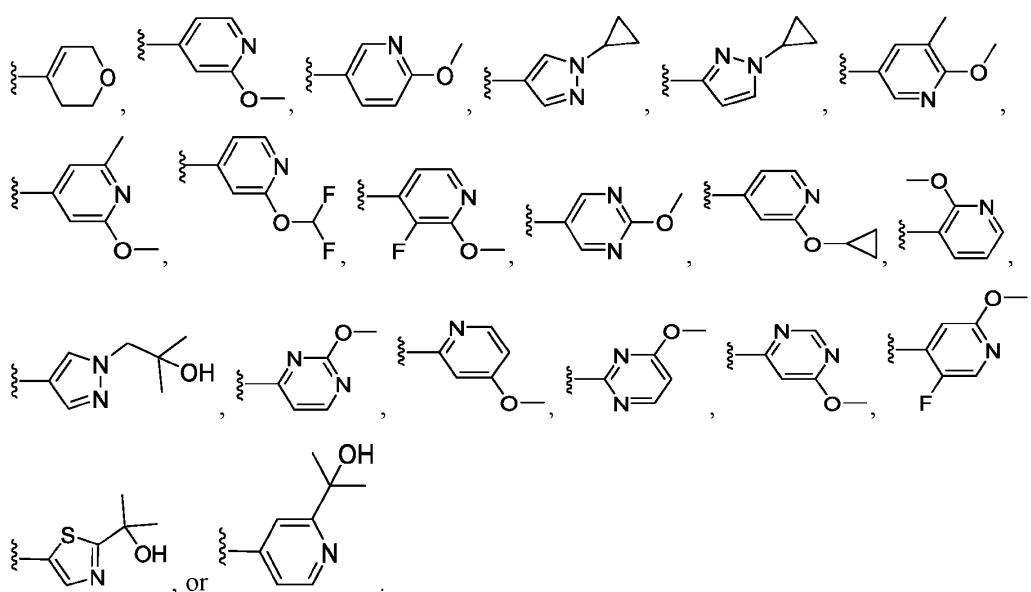


[0095] In some embodiments, R^{1a} is

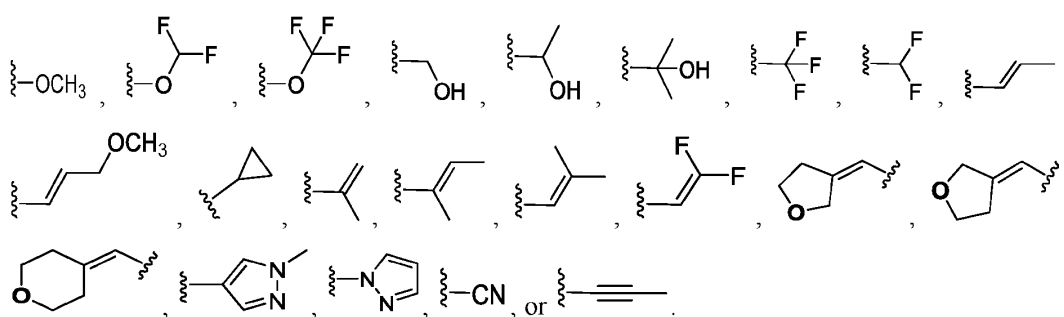




[0096] In some embodiments, R^{1a} is

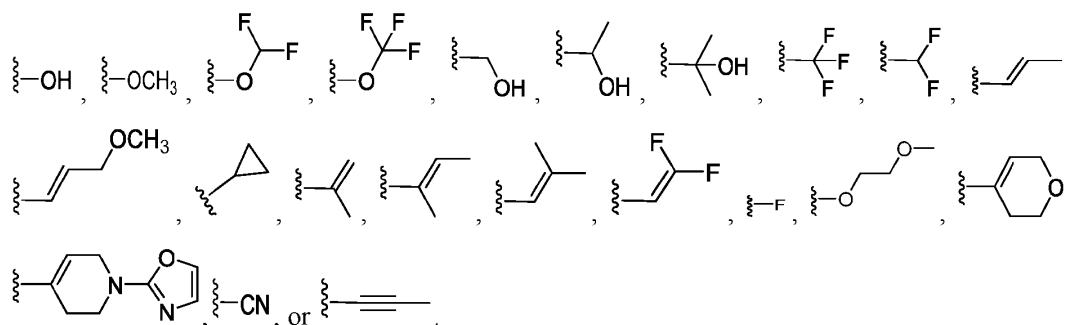


[0097] In some embodiments, R^{1a} is



[0098] In some embodiments, R^{1a} is as selected from one of the substituents of **Table 1** or **Table 1a**.

[0099] In some embodiments, R^{1a} is



[0100] As described generally above, each R^{1b} is independently selected from H, halogen, CN, OH, C₁-C₆aliphatic, C₁-C₆alkoxy, C₃-C₆cycloalkyl, C₁-C₆alkylene-O-C₁-C₆alkyl, haloC₁-C₆alkyl, haloC₁-C₆alkoxy, and C₃-C₆cycloalkoxy, wherein said C₁-C₆aliphatic, C₁-C₆alkoxy, C₃-C₆cycloalkyl, C₁-C₆alkylene-O-C₁-C₆alkyl, haloC₁-C₆alkyl, haloC₁-C₆alkoxy, and C₃-C₆cycloalkoxy are each independently and optionally substituted with 1-5 halogen, OH, CN, C₁-C₆alkyl, or C₃-C₆cycloalkyl groups.

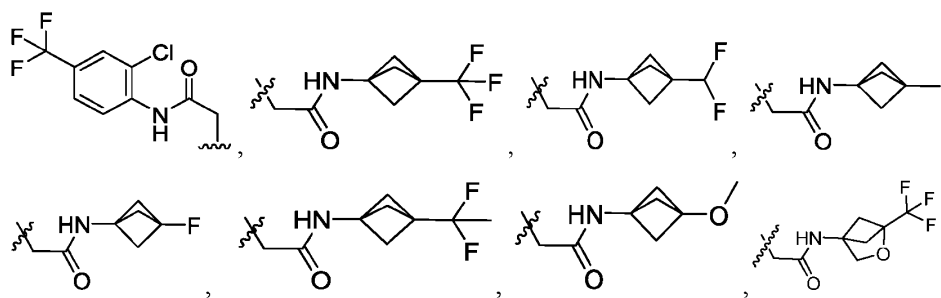
[0101] In some embodiments, R^{1a} and one R^{1b} on adjacent atoms of Ring B, taken together with the adjacent Ring B atoms to which they are attached, form a cyclic group fused to Ring B selected from phenyl, a 5-6 membered heteroaryl (having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur), a 4-7 membered saturated or partially unsaturated carbocyclyl, or a 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur), wherein said cyclic group fused to Ring B is substituted with 0-3 independently selected R^B.

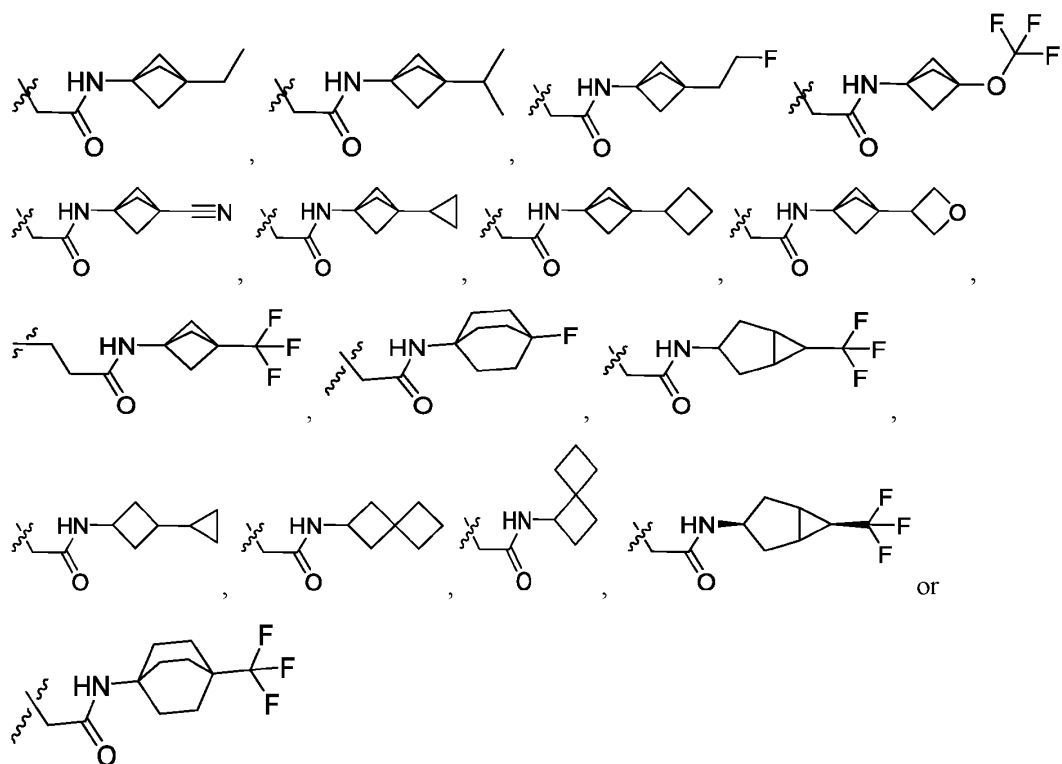
[0102] In some embodiments, R^{1a} and one R^{1b} on adjacent atoms of Ring B, taken together with the adjacent Ring B atoms to which they are attached, form a cyclic group fused to Ring B of phenyl, wherein said cyclic group fused to Ring B is substituted with 0-3 independently selected R^B. In some embodiments, R^{1a} and one R^{1b} on adjacent atoms of Ring B, taken together with the adjacent Ring B atoms to which they are attached, form a cyclic group fused to Ring B of a 5-6 membered heteroaryl (having 1-3 heteroatoms independently selected from nitrogen, oxygen and

sulfur), wherein said cyclic group fused to Ring B is substituted with 0-3 independently selected R^B . In some embodiments, R^{1a} and one R^{1b} on adjacent atoms of Ring B, taken together with the adjacent Ring B atoms to which they are attached, form a cyclic group fused to Ring B of a 4-7 membered saturated or partially unsaturated carbocyclyl, wherein said cyclic group fused to Ring B is substituted with 0-3 independently selected R^B . In some embodiments, R^{1a} and one R^{1b} on adjacent atoms of Ring B, taken together with the adjacent Ring B atoms to which they are attached, form a cyclic group fused to Ring B of a 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur), wherein said cyclic group fused to Ring B is substituted with 0-3 independently selected R^B .

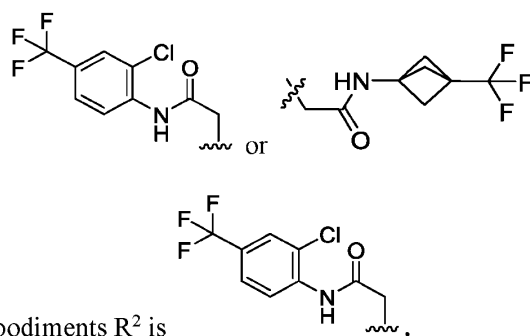
[00103] As described generally above, R^2 is $C(R^C)_2C(O)N(R)R^{2A}$. In some embodiments, R^2 is $C(R^C)_2C(R^C)_2C(O)N(R)R^{2A}$. In some embodiments, R^2 is $C(R^C)_2C(R^C)_2N(R)C(O)N(R)R^{2A}$. In some embodiments, R^2 is $C(R^C)_2C(R^C)_2N(R)C(O)R^{2A}$. In some embodiments, R^2 is $CH_2C(O)N(H)R^{2A}$. In some embodiments, R^2 is $CH_2CH_2C(O)N(H)R^{2A}$. In some embodiments, R^2 is $CH_2CH_2N(R)C(O)N(R)R^{2A}$. In some embodiments, R^2 is $CH_2CH_2N(H)C(O)R^{2A}$. In some embodiments, R^2 is $C(R^C)_2C(O)N(H)R^{2A}$, wherein R^{2A} is phenyl or bicyclo[1.1.1]pentyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1 - C_4 alkyl, or halo C_1 - C_4 alkyl. In some embodiments, R^2 is $C(R^C)_2C(O)N(H)R^{2A}$, wherein R^{2A} is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1 - C_4 alkyl, or halo C_1 - C_4 alkyl. In some embodiments, R^2 is $C(R^C)_2C(O)N(H)R^{2A}$, wherein R^{2A} is bicyclo[1.1.1]pentyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1 - C_4 alkyl, or halo C_1 - C_4 alkyl.

[00104] In some embodiments, R^2 is

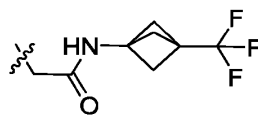




[00105] In some embodiments R^2 is



[00106] In some embodiments R^2 is



[00107] In some embodiments R^2 is

[00108] In some embodiments, R^2 is as selected from one of the substituents of **Table 1** or **Table 1a**.

[00109] As described generally above, R^{2A} is phenyl, pyridyl, cubanyl, a saturated or partially unsaturated 4-8 membered monocyclic ring, a saturated or partially unsaturated bridged, fused, or spirocyclic 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered ring, wherein said saturated or partially unsaturated monocyclic ring, or saturated or partially unsaturated bridged, fused, or spirocyclic ring contains 0, 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and wherein said phenyl, pyridyl, cubanyl, saturated or partially unsaturated monocyclic ring, or saturated or partially unsaturated bridged, fused, or spirocyclic ring are each optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C₁-C₄aliphatic, haloC₁-C₄alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, -OH, -CN, C₁-C₄alkoxy, haloC₁-C₄alkoxy, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy and -SF₅, and wherein two substituents on adjacent atoms of the phenyl or pyridyl, together with said adjacent atoms, optionally form a 4-7 membered carbocyclyl fused to the phenyl or pyridyl, and wherein two substituents on adjacent atoms of the phenyl or pyridyl together with said adjacent atoms optionally form a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) fused to the phenyl or pyridyl, wherein said fused 4-7 membered carbocyclyl or fused 4-7 membered heterocyclyl is substituted with 0-5 independently selected halogen, and wherein two substituents on the same atom of said saturated or partially unsaturated monocyclic ring, or saturated or partially unsaturated bridged, fused, or spirocyclic ring optionally form a cyclic group selected from:

- an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclyl, and
- an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

R^{2A} is 2-benzimidazolyl, 2-naphthyl, or 3-quinoliny, each of which is optionally substituted with 1, 2 or 3 substituents independently selected from halogen, C₁₋₄alkyl, and -OH.

[00110] In some embodiments, there are 1-6 respective instances of wherein 2 substituents on the same 1st, 2nd, 3rd, 4th, 5th, or 6th atom of said saturated or partially unsaturated monocyclic ring, or said saturated or partially unsaturated bridged, fused, or spirocyclic ring form 1-6 of said cyclic groups. In some embodiments, there is one instance wherein 2 substituents on the same atom of

said saturated or partially unsaturated monocyclic ring, or said saturated or partially unsaturated bridged, fused, or spirocyclic ring form one of said cyclic groups. In some embodiments, there 2 respective instances of wherein 2 substituents on the same 1st and 2nd atoms of said saturated or partially unsaturated monocyclic ring, or said saturated or partially unsaturated bridged, fused, or spirocyclic ring form both of said cyclic groups. In some embodiments, there are 3 respective instances of wherein 2 substituents on the same 1st, 2nd, and 3rd, atoms of said saturated or partially unsaturated monocyclic ring, or said saturated or partially unsaturated bridged, fused, or spirocyclic ring form the three of said cyclic groups. In some embodiments, there are 4 respective instances of wherein 2 substituents on the same 1st, 2nd, 3rd, and 4th atoms of said saturated or partially unsaturated monocyclic ring, or said saturated or partially unsaturated bridged, fused, or spirocyclic ring form the four of said cyclic groups. In some embodiments, there are 5 respective instances of wherein 2 substituents on the same 1st, 2nd, 3rd, 4th and 5th atoms of said saturated or partially unsaturated monocyclic ring, or said saturated or partially unsaturated bridged, fused, or spirocyclic ring form the five of said cyclic groups. In some embodiments, there 6 respective instances of wherein 2 substituents on the same 1st, 2nd, 3rd, 4th 5th, and 6th atoms of said saturated or partially unsaturated monocyclic ring, or said saturated or partially unsaturated bridged, fused, or spirocyclic ring form the six of said cyclic groups.

[00111] In some embodiments, R^{2A} is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C₁-C₄alkyl, haloC₁-C₄alkyl, C₃-C₆cycloalkyl, haloC₃-C₆-cycloalkyl, -OH, -CN, C₁-C₄alkoxy, haloC₁-C₄alkoxy, -SF₅, two optional substituents on adjacent atoms of the phenyl together with their intervening atoms form a 4-7 membered carbocyclyl fused to the phenyl, and two optional substituents on adjacent atoms of the phenyl together with their intervening atoms form a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) fused to the phenyl.

[00112] In some embodiments, R^{2A} is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C₁-C₄alkyl, haloC₁-C₄alkyl, C₃-C₆cycloalkyl, haloC₃-C₆-cycloalkyl, -OH, -CN, C₁-C₄alkoxy, haloC₁-C₄alkoxy, and -SF₅. In some embodiments, R^{2A} is phenyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C₁-C₄alkyl, and haloC₁-C₄alkyl. In some embodiments, R^{2A} is phenyl optionally substituted with a halogen, C₁-C₄alkyl, and haloC₁-C₄alkyl. In some embodiments, R^{2A} is phenyl optionally substituted with two substituents independently selected from halogen, C₁-C₄alkyl, and haloC₁-

C₄alkyl. In some embodiments, R^{2A} is phenyl optionally substituted with three substituents independently selected from halogen, C₁-C₄alkyl, and haloC₁-C₄alkyl.

[00113] In some embodiments, R^{2A} is pyridyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C₁-C₄alkyl, haloC₁-C₄alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, -OH, -CN, C₁-C₄alkoxy, haloC₁-C₄alkoxy, and -SF₅, two optional substituents on adjacent atoms of the pyridyl together with their intervening atoms form a 4-7 membered carbocyclyl fused to the pyridyl, and two optional substituents on adjacent atoms of the pyridyl together with their intervening atoms form a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) fused to the pyridyl.

[00114] In some embodiments, R^{2A} is pyridyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C₁-C₄alkyl, haloC₁-C₄alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, -OH, -CN, C₁-C₄alkoxy, haloC₁-C₄alkoxy, and -SF₅. In some embodiments, R^{2A} is pyridyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C₁-C₄alkyl, and haloC₁-C₄alkyl. In some embodiments, R^{2A} is pyridyl optionally substituted with a halogen, C₁-C₄alkyl, or haloC₁-C₄alkyl. In some embodiments, R^{2A} is pyridyl optionally substituted with 2 substituents independently selected from halogen, C₁-C₄alkyl, and haloC₁-C₄alkyl. In some embodiments, R^{2A} is pyridyl optionally substituted with 3 substituents independently selected from halogen, C₁-C₄alkyl, and haloC₁-C₄alkyl.

[00115] In some embodiments, R^{2A} is cubanyl, a saturated or partially unsaturated 4-8 membered monocyclic ring, a saturated or partially unsaturated bridged, fused, or spirocyclic 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered ring, wherein said saturated or partially unsaturated monocyclic ring, or saturated or partially unsaturated bridged, fused, or spirocyclic ring contains 0, 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and wherein said cubanyl, partially unsaturated monocyclic ring, or saturated or partially unsaturated bridged, fused, or spirocyclic ring are each optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C₁-C₄alkyl, haloC₁-C₄alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, -OH, -CN, C₁-C₄alkoxy, haloC₁-C₄alkoxy, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy and -SF₅. In some embodiments, R^{2A} is bicyclo[1.1.1]pentyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C₁-C₄alkyl, and haloC₁-C₄alkyl.

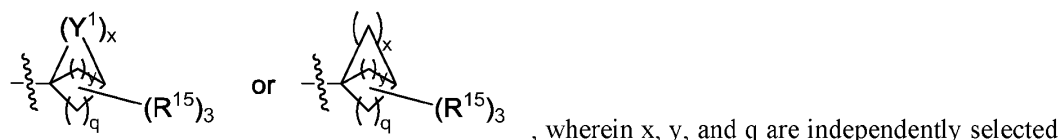
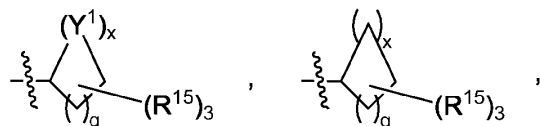
[00116] In some embodiments, R^{2A} is a saturated or partially unsaturated bridged ring, 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered ring, which contains 0, 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and wherein said bridged ring is optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1 - C_4 alkyl, halo C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, halo C_3 - C_6 cycloalkyl, -OH, -CN, C_1 - C_4 alkoxy, halo C_1 - C_4 alkoxy, C_3 - C_6 cycloalkoxy, halo C_3 - C_6 cycloalkoxy and $-SF_5$.

[00117] In some embodiments, R^{2A} is a saturated or partially unsaturated fused ring, 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered ring, which contains 0, 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and wherein said fused ring is optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1 - C_4 alkyl, halo C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, halo C_3 - C_6 cycloalkyl, -OH, -CN, C_1 - C_4 alkoxy, halo C_1 - C_4 alkoxy, C_3 - C_6 cycloalkoxy, halo C_3 - C_6 cycloalkoxy and $-SF_5$.

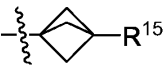
[00118] In some embodiments, R^{2A} is a saturated or partially unsaturated spirocyclic 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered ring, which contains 0, 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and wherein said spirocyclic ring is optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1 - C_4 alkyl, halo C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, halo C_3 - C_6 cycloalkyl, -OH, -CN, C_1 - C_4 alkoxy, halo C_1 - C_4 alkoxy, C_3 - C_6 cycloalkoxy, halo C_3 - C_6 cycloalkoxy and $-SF_5$.

[00119] In some embodiments, R^{2A} is bicyclo[1.1.1]pentyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1 - C_4 alkyl, halo C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, halo C_3 - C_6 cycloalkyl, -OH, -CN, C_1 - C_4 alkoxy, halo C_1 - C_4 alkoxy, C_3 - C_6 cycloalkoxy, halo C_3 - C_6 cycloalkoxy and $-SF_5$. In some embodiments, R^{2A} is bicyclo[1.1.1]pentyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1 - C_4 alkyl, and halo C_1 - C_4 alkyl. In some embodiments, R^{2A} is bicyclo[1.1.1]pentyl optionally substituted with a halogen, C_1 - C_4 alkyl, or halo C_1 - C_4 alkyl. In some embodiments, R^{2A} is bicyclo[1.1.1]pentyl optionally substituted with 2 substituents independently selected from halogen, C_1 - C_4 alkyl, and halo C_1 - C_4 alkyl. In some embodiments, R^{2A} is bicyclo[1.1.1]pentyl optionally substituted with 3 substituents independently selected from halogen, C_1 - C_4 alkyl, and halo C_1 - C_4 alkyl.

[00120] In some embodiments, R^{2A} is Ring F selected from the group consisting of:



, wherein x, y, and q are independently selected from 1, 2 or 3, Y^1 is independently selected from O, NR^{15} , CHR^{15} or $CR^{15}R^{15}$, wherein R^{15} is independently selected from H, halogen, C_1 - C_4 aliphatic, halo C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, halo C_3 - C_6 cycloalkyl, -OH, -CN, C_1 - C_4 alkoxy, halo C_1 - C_4 alkoxy, C_3 - C_6 cycloalkoxy, halo C_3 - C_6 cycloalkoxy and $-SF_5$.

[00121] In some embodiments, R^{2A} is Ring F of the following structure , wherein R^{15} is selected from halogen, C_1 - C_4 aliphatic, halo C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, halo C_3 - C_6 cycloalkyl, -OH, -CN, C_1 - C_4 alkoxy, halo C_1 - C_4 alkoxy, C_3 - C_6 cycloalkoxy, halo C_3 - C_6 cycloalkoxy and $-SF_5$.

[00122] In some embodiments, R^{2A} is 2-benzimidazolyl, 2-naphthyl, or 3-quinolinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1 -4alkyl and, -OH. In some embodiments, R^{2A} is 2-benzimidazolyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1 -4alkyl and, -OH. In some embodiments, R^{2A} is 2-naphthyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1 -4alkyl and, -OH. In some embodiments, R^{2A} is 3-quinolinyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1 -4alkyl and, -OH.

[00123] In some embodiments, R^{2A} is phenyl comprising a $-CF_3$ substituent or pyridyl comprising a $-CF_3$ substituent.

[00124] In some embodiments, R^{2A} is bicyclo[1.1.1]pentyl comprising a $-CF_3$ substituent or bicyclo[1.1.1]pentyl comprising a $-CHF_2$ substituent.

[00125] In some embodiments, R^{2A} is as selected from one of the substituents of **Table 1** or **Table 1a**.

[00126] As described generally above, R^3 is hydrogen, C_1 - C_4 alkyl, C_3 - C_5 cycloalkyl, C_1 - C_4 alkoxy, $-NHR^{3A}$, $-N(R^{3A})_2$ or C_1 - C_4 alkylthio each of which, besides hydrogen, is optionally substituted with $-OH$, 1-5 independently selected halogen, $-OR$, $-C(O)NR^{10}R^{11}$, or $N(R)C(O)R$.

[00127] In some embodiments, R^3 is hydrogen. In some embodiments, R^3 is C_1 - C_4 alkyl optionally substituted with $-OH$, 1-5 independently selected halogen, or C_1 - C_4 alkoxy. In some embodiments, R^3 is C_1 - C_4 alkyl. In some embodiments, R^3 is $-CH_2CH_3$. In some embodiments, R^3 is $-CH_3$. In some embodiments, R^3 is C_3 - C_5 cycloalkyl, C_1 - C_4 alkoxy, $-NHR^{3A}$, $-N(R^{3A})_2$ or C_1 - C_4 alkylthio optionally substituted with $-OH$, 1-5 independently selected halogen, or C_1 - C_4 alkoxy. In some embodiments, R^3 is C_3 - C_5 cycloalkyl optionally substituted with $-OH$, 1-5 independently selected halogen, or C_1 - C_4 alkoxy. In some embodiments, R^3 is C_1 - C_4 alkoxy optionally substituted with $-OH$, 1-5 independently selected halogen, or C_1 - C_4 alkoxy. In some embodiments, R^3 is $-NHR^{3A}$ optionally substituted with $-OH$, 1-5 independently selected halogen, or C_1 - C_4 alkoxy. In some embodiments, R^3 is $-N(R^{3A})_2$ optionally substituted with $-OH$, 1-5 independently selected halogen, or C_1 - C_4 alkoxy. In some embodiments, R^3 is C_1 - C_4 alkylthio optionally substituted with $-OH$, 1-5 independently selected halogen, or C_1 - C_4 alkoxy. In some embodiments, R^3 is selected from the group consisting of C_1 - C_4 alkyl and C_3 - C_5 cycloalkyl.

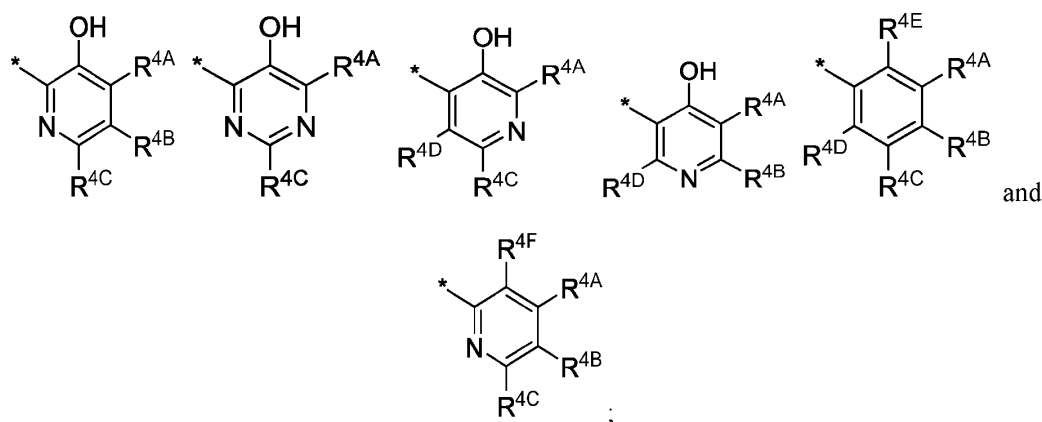
[00128] In some embodiments, R^3 is as selected from one of the substituents of **Table 1** or **Table 1a**.

[00129] As described generally above, each R^{3A} is independently selected at each occurrence from C_1 - C_4 alkyl. In some embodiments, R^{3A} is $-CH_3$. In some embodiments, R^{3A} is $-CH_2CH_3$. In some embodiments, R^{3A} is propyl. In some embodiments, R^{3A} is butyl.

[00130] In some embodiments, R^{3A} is as selected from one of the substituents of **Table 1** or **Table 1a**.

[00131] In some embodiments, R^4 is selected from one of a), b), and c):

a) R^4 is a Ring E that is selected from the group consisting of:



wherein * is a point of attachment to L; and

any substituents that are present on Ring E selected from R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{4E}, and R^{4F} are each independently selected from hydrogen; halogen; -CN; C₁-C₄alkyl; C₂-C₄alkenyl; C₂-C₄alkynyl; C₁-C₄alkoxy; haloC₁-C₄alkyl; C₁-C₃alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; haloC₁-C₄alkoxy; C₃-C₆cycloalkyl; C₃-C₆cycloalkoxy; and NR¹³R¹⁴; or

R^{4A} and R^{4B}, along with their intervening atoms, join to form a 4-7 membered carbocyclyl substituted with 0-3 independently selected R^B, a 4-7 membered heterocyclyl substituted with 0-3 independently selected R^B, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) substituted with 0-3 independently selected R^B; that is fused to Ring E; and any substituents that are present on Ring E selected from R^{4C}, R^{4D}, R^{4E}, and R^{4F} are each independently selected from hydrogen; halogen; -CN; C₁-C₄alkyl; C₂-C₄alkenyl; C₂-C₄alkynyl; haloC₁-C₄alkyl; C₁-C₃alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; haloC₁-C₄alkoxy; C₃-C₆cycloalkyl; C₃-C₆cycloalkoxy; and NR¹³R¹⁴; or

R^{4B} and R^{4C}, along with their intervening atoms, join to form a 4-7 membered carbocyclyl substituted with 0-3 independently selected R^B, a 4-7 membered heterocyclyl substituted with 0-3 independently selected R^B, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) substituted with 0-3 independently selected R^B; that is fused to Ring E;

and any substituents that are present on Ring E selected from R^{4A} , R^{4D} , R^{4E} , and R^{4F} are each independently selected from hydrogen; halogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and $NR^{13}R^{14}$; or

R^{4C} and R^{4D} , along with their intervening atoms, join to form a 4-7 membered carbocyclyl substituted with 0-3 independently selected R^B , a 4-7 membered heterocyclyl substituted with 0-3 independently selected R^B , or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) substituted with 0-3 independently selected R^B ; that is fused to Ring E; and any substituents that are present on Ring E selected from R^{4A} , R^{4B} , R^{4E} and R^{4F} are each independently selected from hydrogen; halogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and $NR^{13}R^{14}$; or

R^{4E} is halogen or -OH, and R^{4A} , R^{4B} , R^{4C} , and R^{4D} are each independently selected from hydrogen; halogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and $NR^{13}R^{14}$; or

R^{4E} and R^{4A} , along with their intervening atoms, join to form a 5-6 membered optionally substituted heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) substituted with 0-3 independently selected R^B ; that is fused to Ring E; and R^{4B} , R^{4C} , and R^{4D} are each independently selected from hydrogen; halogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and $NR^{13}R^{14}$; or

R^{4F} and R^{4A} , along with their intervening atoms, join to form a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) substituted with 0-3 independently selected R^B ; that is fused to Ring E; and R^{4B} and R^{4C} are each independently selected from hydrogen; halogen; -CN; C_1 -

C₄alkyl; C₂-C₄alkenyl; C₂-C₄alkynyl; haloC₁-C₄alkyl; C₁-C₃alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; haloC₁-C₄alkoxy; C₃-C₆cycloalkyl; C₃-C₆cycloalkoxy; and NR¹³R¹⁴;

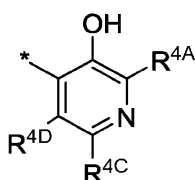
R¹³ is independently selected at each occurrence from hydrogen and C₁-C₄alkyl optionally substituted with -OH, -OCH₃, or -OCH₂CH₃; and

R¹⁴ is hydrogen, or R¹³ and R¹⁴ combine with the nitrogen atom to which they are attached to form a heterocyclic ring selected from azetidiny, pyrrolidinyl, or piperidinyl, said heterocyclic ring optionally substituted with -CH₃; or

R⁴ is a 5-membered heteroaryl (having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur and 0, 1, 2, or 3 additional ring nitrogen atoms), wherein said heteroaryl is substituted with 0-4 groups independently selected from halogen, -OH, -CN, C₁-C₄alkyl, haloC₁-C₄alkyl, C₃-C₆cycloalkyl, and C₁-C₄alkoxy; and

R⁴ is a C₁-C₄alkyl, C₁-C₄alkoxy, or C₃-C₆cycloalkyl, each of which is substituted with 0-3 groups independently selected from halogen, -CN, -OH, C₁-C₄alkyl, C₁-C₄alkoxy, optionally substituted 5-6 membered heterocyclyl, and optionally substituted 5-6 membered heterocycloxy.

[00132] In some embodiments, R⁴ is Ring E of the following structure:



wherein * is a point of attachment to linker L that is bonded to Ring A in Formula I, I', or I'';

and wherein:

R^{4A}, R^{4C}, and R^{4D} are each independently selected from hydrogen; halogen; -CN; C₁-C₄alkyl; C₂-C₄alkenyl; C₂-C₄alkynyl; haloC₁-C₄alkyl; C₁-C₃alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; haloC₁-C₄alkoxy; C₃-C₆cycloalkyl; C₃-C₆cycloalkoxy; and NR¹³R¹⁴; or

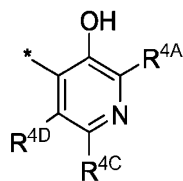
R^{4C} and R^{4D}, along with their intervening atoms, join to form 4-7 membered carbocyclyl) substituted with 0-3 independently selected R^B, a 4-7 membered

heterocyclyl substituted with 0-3 independently selected R^B , or 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) substituted with 0-3 independently selected R^B , that is fused to Ring E; and R^{4A} is hydrogen; halogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and $NR^{13}R^{14}$, and

R^{13} is independently selected at each occurrence from hydrogen and C_1 - C_4 alkyl optionally substituted with -OH, -OCH₃, or -OCH₂CH₃; and $NR^{13}R^{14}$, taken in combination form a heterocyclic ring selected from azetidiny, pyrrolidiny, or piperidiny, said heterocyclic ring optionally substituted with -CH₃.

R^{14} is hydrogen, or R^{13} and R^{14} combine with the nitrogen atom to which they are attached to form a heterocyclic ring selected from azetidiny, pyrrolidiny, or piperidiny, said heterocyclic ring optionally substituted with -CH₃.

[00133] In some embodiments, R^4 is Ring E of the following structure:



wherein * is a point of attachment to linker L that is bonded to Ring A in Formula I, I', or I'';

and wherein:

R^{4A} is -OCH₃, -OCH₂CH₃, or -OCHF₂;

R^{4C} and R^{4D} are each independently selected from hydrogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and $NR^{13}R^{14}$, and

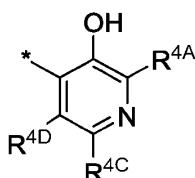
R^{13} is independently selected at each occurrence from hydrogen or C_1 - C_4 alkyl optionally substituted with -OH, -OCH₃, or -OCH₂CH₃; or $NR^{13}R^{14}$, taken in combination form a heterocyclic ring selected from azetidiny, pyrrolidiny, or piperidiny, said heterocyclic ring optionally substituted with -CH₃;

R^{14} is hydrogen, or R^{13} and R^{14} combine with the nitrogen atom to which they are attached to form a heterocyclic ring selected from azetidiny, pyrrolidiny, or piperidiny, said heterocyclic ring optionally substituted with $-CH_3$.

or

R^4 is a 5-membered heteroaryl (having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur and 0, 1, 2, or 3 additional ring nitrogen atoms), wherein said heteroaryl is substituted with 0-4 substituents independently selected from halogen, $-OH$, $-CN$, C_1 - C_4 alkyl, halo C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, and C_1 - C_4 alkoxy.

[00134] In some embodiments, R^4 is Ring E of the following structure:



wherein * is a point of attachment to linker L that is bonded to Ring A in Formula I, I', or I'';

and wherein:

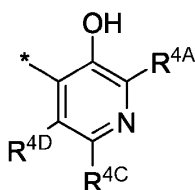
R^{4A} is $-OCH_3$, $-OCH_2CH_3$, or $-OCHF_2$;

R^{4C} and R^{4D} are each independently selected from hydrogen; $-CN$; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with $-OH$, $-OCH_3$, or $-OCH_2CH_3$; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and $NR^{13}R^{14}$; and

R^{13} is independently selected at each occurrence from hydrogen or C_1 - C_4 alkyl optionally substituted with $-OH$, $-OCH_3$, or $-OCH_2CH_3$; or $NR^{13}R^{14}$, taken in combination form a heterocyclic ring selected from azetidiny, pyrrolidiny, or piperidiny, said heterocyclic ring optionally substituted with $-CH_3$; and

R^{14} is hydrogen.

[00135] In some embodiments, R^4 is Ring E of the following structure:

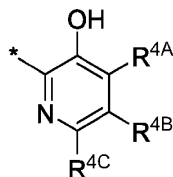


wherein * is a point of attachment to linker L that is bonded to Ring A in Formula I, I', or I'';

and wherein:

R^{4A} , R^{4C} , and R^{4D} are each independently selected from hydrogen; halogen; and C_1 - C_4 alkyl.

[00136] In some embodiments, R^4 is Ring E of the following structure:



wherein * is a point of attachment to linker L that is bonded to Ring A in Formula I, I', or I'';

and wherein:

R^{4A} , R^{4B} , and R^{4C} are each independently selected from hydrogen; halogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; C_1 - C_4 alkoxy; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and NR¹³R¹⁴; or

R^{4A} and R^{4B} , along with their intervening atoms, join to form 4-7 membered carbocyclyl or heterocyclyl or 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) that is fused to Ring E; and R^{4C} is hydrogen; halogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; or NR¹³R¹⁴; or

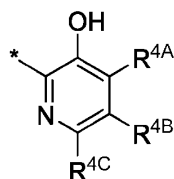
R^{4B} and R^{4C} , along with their intervening atoms, join to form a 4-7 membered carbocyclyl substituted with 0-3 independently selected R^B, a 4-7 membered heterocyclyl substituted with 0-3 independently selected R^B, or a 5-6 membered

heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) substituted with 0-3 independently selected R^B ; that is fused to Ring E; and R^{4A} is selected from hydrogen; halogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and $NR^{13}R^{14}$; and

R^{13} is independently selected at each occurrence from hydrogen or C_1 - C_4 alkyl optionally substituted with -OH, -OCH₃, or -OCH₂CH₃; or $NR^{13}R^{14}$, taken in combination form a heterocyclic ring selected from azetidiny, pyrrolidinyl, or piperidinyl, said heterocyclic ring optionally substituted with -CH₃; and

R^{14} is hydrogen.

[00137] In some embodiments, R^4 is Ring E of the following structure:



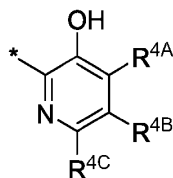
wherein * is a point of attachment to linker L that is bonded to Ring A in Formula I, I', or I'';

and wherein:

R^{4A} and R^{4B} , along with their intervening atoms, join to form 4-7 membered carbocyclyl, 4-7 membered heterocyclyl, or 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) that is fused to Ring E; and

R^{4C} is hydrogen.

[00138] In some embodiments, R^4 is Ring E of the following structure:



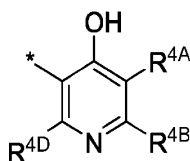
wherein * is a point of attachment to linker L that is bonded to Ring A in Formula I, I', or I'';

and wherein:

R^{4A} and R^{4B} , along with their intervening atoms, join to form 5-membered heterocyclyl (having 1 oxygen atom) that is fused to Ring E; and

R^{4C} is hydrogen.

[00139] In some embodiments, R^4 is Ring E of the following structure:



wherein * is a point of attachment linker L that is bonded to Ring A in Formula I, I', or I'';

and wherein:

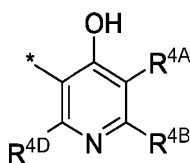
R^{4A} , R^{4B} , and R^{4D} are each independently selected from hydrogen; halogen; -CN; C₁-C₄alkyl; C₂-C₄alkenyl; C₂-C₄alkynyl; C₁-C₄alkoxy; haloC₁-C₄alkyl; C₁-C₃alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; haloC₁-C₄alkoxy; C₃-C₆cycloalkyl; C₃-C₆cycloalkoxy; and NR¹³R¹⁴; or

R^{4A} and R^{4B} , along with their intervening atoms, join to form a 4-7 membered carbocyclyl, a 4-7 membered heterocyclyl, a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) that is fused to Ring E; and R^{4D} is hydrogen; halogen; -CN; C₁-C₄alkyl; C₂-C₄alkenyl; C₂-C₄alkynyl; haloC₁-C₄alkyl; C₁-C₃alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; haloC₁-C₄alkoxy; C₃-C₆cycloalkyl; C₃-C₆cycloalkoxy; or NR¹³R¹⁴; and

R^{13} is independently selected at each occurrence from hydrogen or C₁-C₄alkyl optionally substituted with -OH, -OCH₃, or -OCH₂CH₃; or NR¹³R¹⁴, taken in combination form a heterocyclic ring selected from azetidiny, pyrrolidiny, or piperidiny, said heterocyclic ring optionally substituted with -CH₃; and

R^{14} is H.

[00140] In some embodiments, R^4 is Ring E of the following structure:



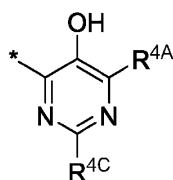
wherein * is a point of attachment to linker L that is bonded to Ring A in Formula I, I', or I'';

and wherein:

R^{4A} and R^{4D} are each hydrogen; and

R^{4B} is C_1 - C_4 alkyl.

[00141] In some embodiments, R^4 is Ring E of the following structure:



wherein * is a point of attachment linker L that is bonded to Ring A in Formula I, I', or I'';

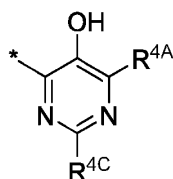
and wherein:

R^{4A} and R^{4C} are each independently selected from hydrogen; halogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; C_1 - C_4 alkoxy; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and $NR^{13}R^{14}$; and

R^{13} is independently selected at each occurrence from hydrogen or C_1 - C_4 alkyl optionally substituted with -OH, -OCH₃, or -OCH₂CH₃; or $NR^{13}R^{14}$, taken in combination form a heterocyclic ring selected from azetidyl, pyrrolidinyl, or piperidinyl, said heterocyclic ring optionally substituted with -CH₃; and

R^{14} is H.

[00142] In some embodiments, R^4 is Ring E of the following structure:

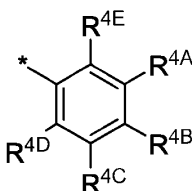


wherein * is a point of attachment to linker L that is bonded to Ring A in Formula I, I', or I'';

and wherein:

R^{4A} and R^{4C} are each independently selected from hydrogen and C_1 - C_4 alkyl.

[00143] In some embodiments, R^4 is Ring E of the following structure:



wherein * is a point of attachment to linker L that is bonded to Ring A in Formula I, I', or I'';

and wherein:

R^{4A} , R^{4B} , R^{4C} , R^{4D} , and R^{4E} are each independently selected from hydrogen; halogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; C_1 - C_4 alkoxy; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and $NR^{13}R^{14}$; or

R^{4A} and R^{4B} , along with their intervening atoms, join to form 4-7 membered carbocyclyl, 4-7 membered heterocyclyl, or 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) that is fused to Ring E; and R^{4C} , R^{4D} , and R^{4E} are each independently selected from hydrogen; halogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and $NR^{13}R^{14}$; or

R^{4C} and R^{4D} , along with their intervening atoms, join to form 4-7 membered carbocyclyl, 4-7 membered heterocyclyl, 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) that is fused

to Ring E; and R^{4A} , R^{4B} , and R^{4E} are each independently selected from hydrogen; halogen; -CN; C₁-C₄alkyl; C₂-C₄alkenyl; C₂-C₄alkynyl; haloC₁-C₄alkyl; C₁-C₃alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; haloC₁-C₄alkoxy; C₃-C₆cycloalkyl; C₃-C₆cycloalkoxy; and NR¹³R¹⁴; or

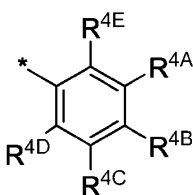
R^{4E} is halogen or -OH, and R^{4A} , R^{4B} , R^{4C} , and R^{4D} are each independently selected from hydrogen; halogen; -CN; C₁-C₄alkyl; C₂-C₄alkenyl; C₂-C₄alkynyl; haloC₁-C₄alkyl; C₁-C₃alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; haloC₁-C₄alkoxy; C₃-C₆cycloalkyl; C₃-C₆cycloalkoxy; and NR¹³R¹⁴; or

R^{4E} and R^{4A} , along with their intervening atoms, join to form 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) fused to Ring E; and R^{4B} , R^{4C} , and R^{4D} are each independently selected from hydrogen; halogen; -CN; C₁-C₄alkyl; C₂-C₄alkenyl; C₂-C₄alkynyl; haloC₁-C₄alkyl; C₁-C₃alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; haloC₁-C₄alkoxy; C₃-C₆cycloalkyl; C₃-C₆cycloalkoxy; and NR¹³R¹⁴; and

R^{13} is independently selected at each occurrence from hydrogen or C₁-C₄alkyl optionally substituted with -OH, -OCH₃, or -OCH₂CH₃; or NR¹³R¹⁴, taken in combination form a heterocyclic ring selected from azetidiny, pyrrolidiny, or piperidiny, said heterocyclic ring optionally substituted with -CH₃; and

R^{14} is H.

[00144] In some embodiments, R^4 is Ring E of the following structure:



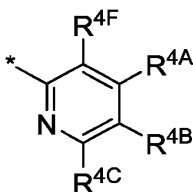
wherein * is a point of attachment to linker L that is bonded to Ring A in Formula I, I', or I'';

and wherein:

R^{4A} , R^{4B} , R^{4C} , R^{4D} , and R^{4E} are each independently selected from hydrogen; halogen; C₁-C₄alkyl; and C₁-C₄alkoxy; or

R^{4C} and R^{4D} , along with their intervening atoms, join to form a 4-7 membered heterocyclyl (having 1-3 nitrogen atoms) fused to Ring E; and R^{4A} , R^{4B} , and R^{4E} are each hydrogen.

[00145] In some embodiments, R^4 is Ring E of the following structure:



wherein * is a point of attachment to linker L that is bonded to Ring A in Formula I, I', or I'';

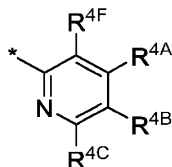
and wherein:

R^{4F} and R^{4A} , along with their intervening atoms, join to form 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) fused to Ring E; and R^{4B} and R^{4C} are each independently selected from hydrogen; halogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and $NR^{13}R^{14}$;

R^{13} is independently selected at each occurrence from hydrogen or C_1 - C_4 alkyl optionally substituted with -OH, -OCH₃, or -OCH₂CH₃; or $NR^{13}R^{14}$, taken in combination form a heterocyclic ring selected from azetidiny, pyrrolidinyl, or piperidinyl, said heterocyclic ring optionally substituted with -CH₃; and

R^{14} is H.

[00146] In some embodiments, R^4 is Ring E of the following structure:



wherein * is a point of attachment to linker L that is bonded to Ring A in Formula I, I', or I'';

and wherein:

R^{4F} and R^{4A} , along with their intervening atoms, join to form 5-6 membered heteroaryl (having 1-2 nitrogen atoms) fused to Ring E; and R^{4B} and R^{4C} are each hydrogen.

[00147] In some embodiments, R^4 is a 5-membered heteroaryl (having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur and 0, 1, 2, or 3 additional ring nitrogen atoms), wherein said heteroaryl is substituted with 0-4 groups independently selected from halogen, -OH, -CN, C_1 - C_4 alkyl, halo C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, and C_1 - C_4 alkoxy.

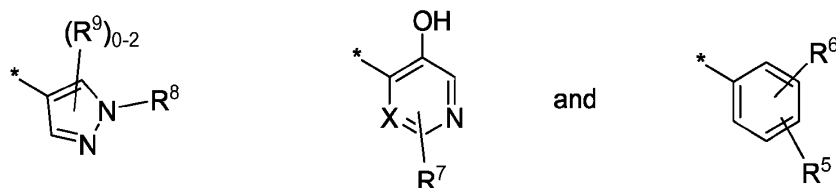
[00148] In some embodiments, R^4 is a 5-membered heteroaryl (having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur and 0, 1, 2, or 3 additional ring nitrogen atoms), wherein said heteroaryl is substituted with 0-4 groups independently selected from OH, -CH₃, -CHF₂, cyclopropyl, and -OCH₃.

[00149] In some embodiments, R^4 is a C_1 - C_4 alkyl, C_1 - C_4 alkoxy, or C_3 - C_6 cycloalkyl, each of which is substituted with 0-3 groups independently selected from halogen, -CN, -OH, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, optionally substituted 5-6 membered heterocyclyl, and optionally substituted 5-6 membered heterocyclyloxy. In some embodiments, R^4 is a C_1 - C_4 alkyl, substituted with 0-3 independently selected halogen, -CN, -OH, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy. In some embodiments, R^4 is a C_1 - C_4 alkoxy, substituted with 0-3 independently selected halogen, -CN, -OH, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy. In some embodiments, R^4 is a C_3 - C_6 cycloalkyl, substituted with 0-3 independently selected halogen, -CN, -OH, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy.

[00150] In some embodiments, R^4 is an isoxazolyl substituted with -OH or C_1 - C_4 alkoxy.

[00151] In some embodiments, R^4 is a 5-membered heteroaryl (having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur and 0, 1, 2, or 3 additional ring nitrogen atoms) selected from the group consisting of thiophenyl, imidazolyl, pyrazolyl, tetrazolyl, thiazolyl, isothiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, oxazolyl, isoxazolyl, 1,2,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, wherein said heteroaryl is substituted with 0-4 groups independently selected from halogen, -OH, -CN, C_1 - C_4 alkyl, halo C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, and C_1 - C_4 alkoxy.

[00152] In some embodiments, R^4 is selected from the group consisting of:



wherein * indicated the point of attachment to L, and R^{1a} , R^{1b} , R^2 , and R^3 , are as defined herein, both singly and in combination, and wherein:

X is CH, CR^7 , or N;

R^5 is -OH or halogen;

R^6 is halogen, C_{1-4} alkyl, or C_{1-4} alkoxy;

each R^7 is independently hydrogen, halogen, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^8 is C_{1-4} alkyl;

each of the 0-2 instances of R^9 is independently a hydrogen or C_{1-4} alkyl.

In some embodiments:

X is CH or N;

R^5 is -OH or fluoro;

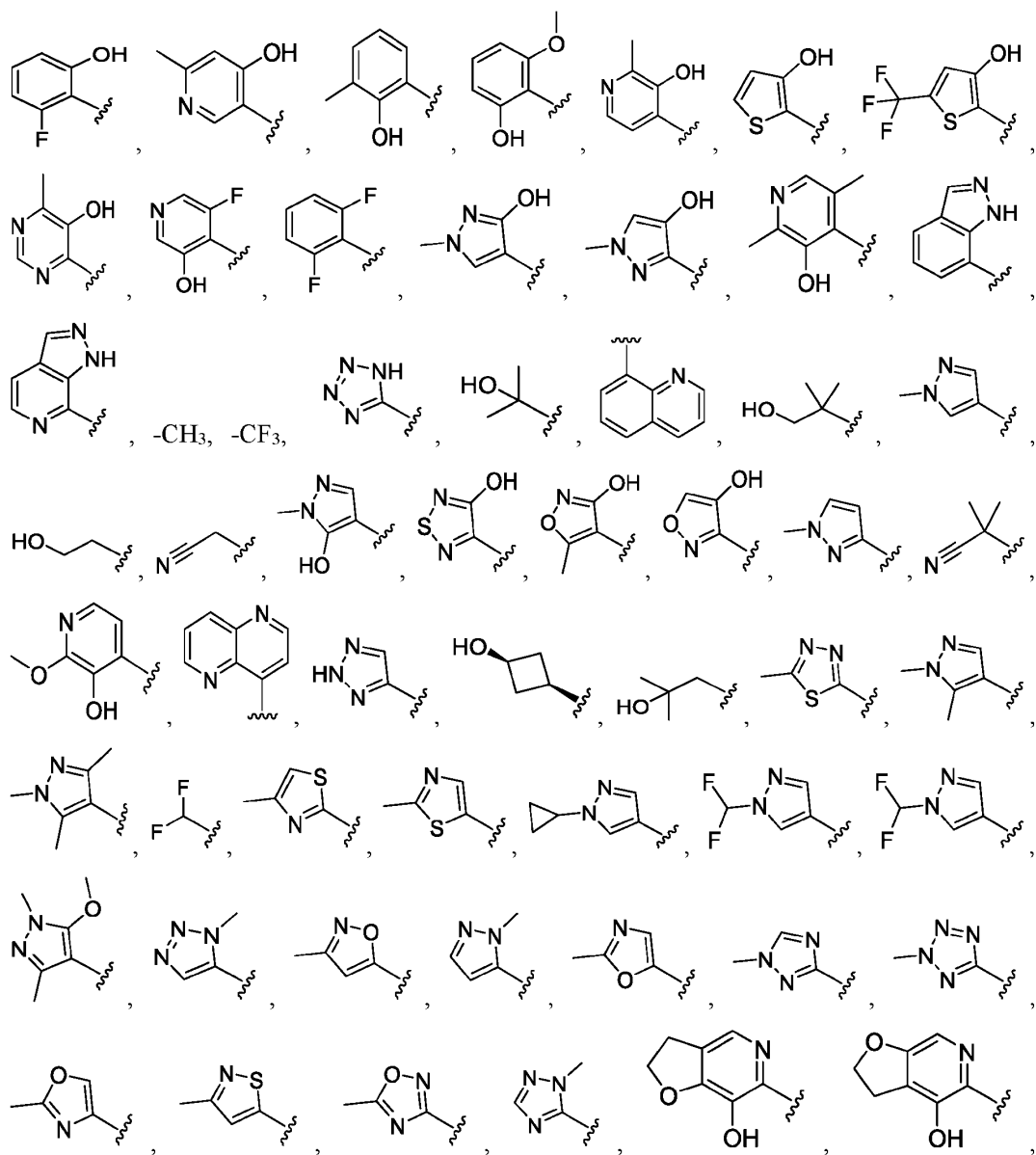
R^6 is fluoro, -CH₃, or -OCH₃;

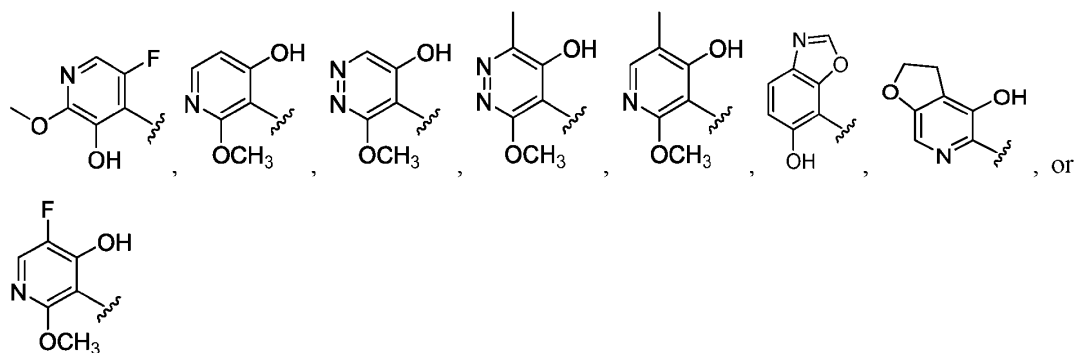
each R^7 is independently hydrogen, fluoro, -CH₃, or -OCH₃;

R^8 is -CH₃;

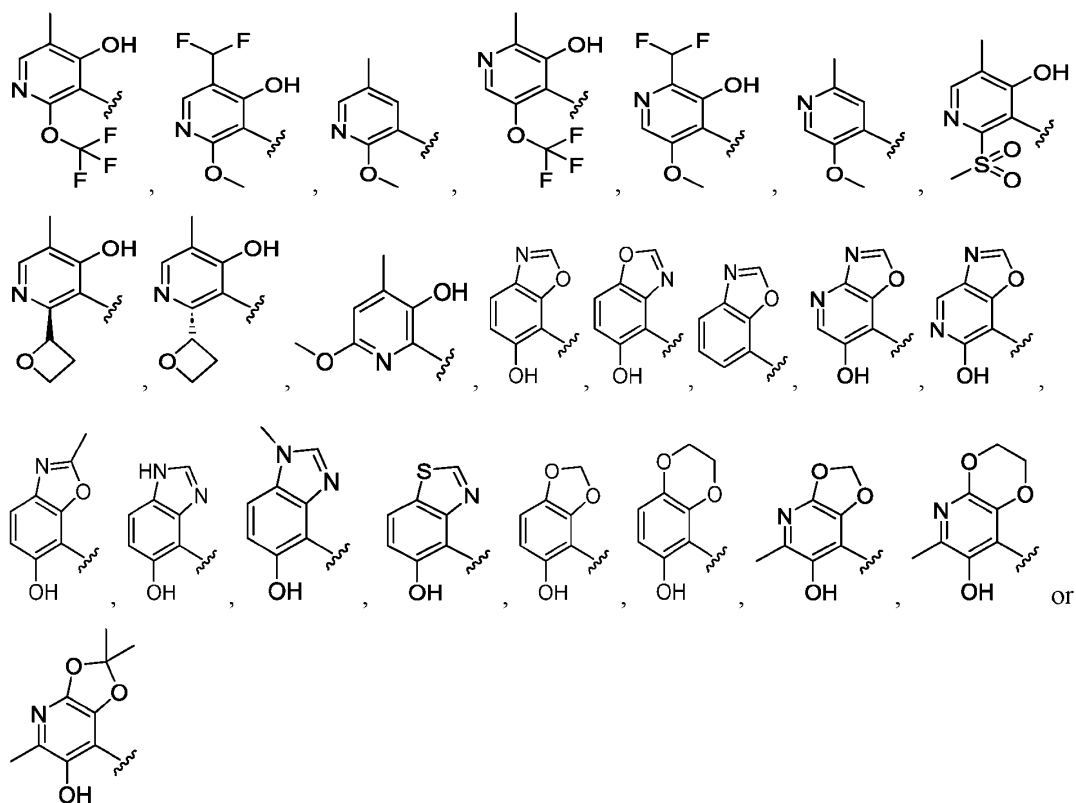
each instance of R^9 is independently a hydrogen or -CH₃.

[00153] In some embodiments, R^4 is





[00154] In some embodiments, R^4 is



[00155] In some embodiments, R^4 is as shown in a substituent of **Table 1** or **Table 1a**.

[00156] As described generally above, R^{10} is H, C_1 - C_6 aliphatic, halo C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo C_3 - C_6 cycloalkyl, $-C(O)C_1$ - C_6 alkyl, or a 5-6 membered heteroaryl (having 1-4

heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R¹⁰ except H being optionally substituted with 1 or 2 independently selected R^B.

[00157] In some embodiments, R¹⁰ is H. In some embodiments, R¹⁰ is C₁-C₆aliphatic, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, -C(O)C₁-C₆alkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R¹⁰ being optionally substituted with 1 or 2 independently selected R^B. In some embodiments, R¹⁰ is C₁-C₆aliphatic, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, or -C(O)C₁-C₆alkyl; each R¹⁰ being optionally substituted with 1 or 2 independently selected R^B. In some embodiments, R¹⁰ is a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); R¹⁰ being optionally substituted with 1 or 2 independently selected R^B.

[00158] In some embodiments, R¹⁰ is as shown in a substituent of **Table 1** or **Table 1a**.

[00159] As described generally above, R¹¹ is H, C₁-C₆aliphatic, or C₃-C₆cycloalkyl, or R¹⁰ and R¹¹ are taken together with the nitrogen atom to which they are attached to form a 5-6 membered ring optionally substituted with 1, 2, or 3 substituents independently selected from halogen, -OH, -CN, C₁-C₄alkoxy, and haloC₁-C₄alkoxy.

[00160] In some embodiments, R¹¹ is H, C₁-C₆aliphatic, or C₃-C₆cycloalkyl. In some embodiments, R¹¹ is H. In some embodiments, R¹¹ is C₁-C₆aliphatic. In some embodiments, R¹¹ is C₃-C₆cycloalkyl. In some embodiments, R¹⁰ and R¹¹ are taken together with the nitrogen atom to which they are attached to form a 5-6 membered ring optionally substituted with 1, 2, or 3 substituents independently selected from halogen, -OH, -CN, C₁-C₄alkoxy, and haloC₁-C₄alkoxy.

[00161] In some embodiments, R¹¹ is as shown in a substituent of **Table 1** or **Table 1a**.

[00162] As described generally above, R¹² is C₁-C₆aliphatic, C₃-C₆cycloalkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R¹² optionally substituted with 1 or 2 groups independently selected from halogen, C₁-C₆aliphatic, haloC₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, and C₃-C₆cycloalkoxy.

[00163] In some embodiments, R¹² is C₁-C₆aliphatic optionally substituted with 1 or 2 groups independently selected from halogen, C₁-C₆aliphatic, haloC₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, and C₃-C₆cycloalkoxy. In some embodiments, R¹² is C₁-C₆aliphatic optionally substituted with 1 or 2 groups independently selected from halogen, C₁-C₆aliphatic, haloC₁-

C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, and C₃-C₆cycloalkoxy. In some embodiments, R¹² is C₃-C₆cycloalkyl optionally substituted with 1 or 2 groups independently selected from halogen, C₁-C₆aliphatic, haloC₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, and C₃-C₆cycloalkoxy. In some embodiments, R¹² is a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with 1 or 2 groups independently selected from halogen, C₁-C₆aliphatic, haloC₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, and C₃-C₆cycloalkoxy.

[00164] As described generally above, R^B is independently selected at each occurrence from the group consisting of optionally substituted phenyl, optionally substituted 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), halogen, optionally substituted C₁-C₆aliphatic, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, halo-C₃-C₆cycloalkyl, C₁-C₆alkoxy, halo-C₁-C₆alkoxy, C₃-C₆cycloalkoxy, halo-C₃-C₆cycloalkoxy, C₁-C₆alkylene-O-C₁-C₆alkyl, -CN, -NO₂, oxo, -OR, -SR, NR₂, S(O)₂R, S(O)₂NR₂, S(O)R, S(O)NR₂, C(O)R, C(O)OR, -C(O)NR₂, C(O)N(R)OR, OC(O)R, OC(O)NR₂, -N(R)C(O)OR, N(R)C(O)R, N(R)C(O)NR₂, N(R)C(NR)NR₂, N(R)S(O)₂NR₂, and -N(R)S(O)₂R.

[00165] In some embodiments, R^B is independently selected at each occurrence from the group consisting of halogen, -OR, or an optionally substituted C₁-6aliphatic group. In some embodiments, R^B is independently selected at each occurrence from a halogen. In some embodiments, R^B is independently selected at each occurrence from -OR. In some embodiments, R^B is independently selected at each occurrence from an optionally substituted C₁-6aliphatic group.

[00166] In some embodiments, R^B is as selected from one of the substituents of **Table 1** or **Table 1a**.

[00167] As described generally above, R^C is independently selected at each occurrence from hydrogen, -CH₃, and -CH₂CH₃, or two R^C taken together with the carbon to which they are attached form a cyclopropyl ring. In some embodiments, R^C is independently selected at each occurrence from hydrogen, -CH₃, and -CH₂CH₃. In some embodiments, R^C is hydrogen. In some embodiments, one R^C is -CH₃, and the other R^C is hydrogen. In some embodiments, two R^C taken together with the carbon to which they are attached form a cyclopropyl ring.

[00168] In some embodiments, R^C is as selected from one of the substituents of **Table 1** or **Table 1a**.

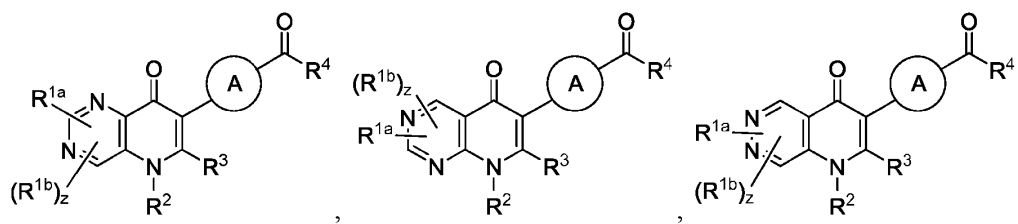
[00169] As described generally above, each R is independently hydrogen, or an optionally substituted C₁₋₆aliphatic group, an optionally substituted phenyl, an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or an optionally substituted 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); or two R groups on the same atom are taken together with the same atom to form a cyclic group selected from an optionally substituted 4-7 membered saturated ring, a 4-7 membered partially unsaturated ring, or a 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said cyclic group has 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

[00170] In some embodiments, each R is hydrogen. In some embodiments, each R is independently an optionally substituted C₁₋₆aliphatic group, an optionally substituted phenyl, an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or an optionally substituted 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

[00171] In some embodiments, two R groups on the same atom are taken together with the same atom to form a cyclic group selected from an optionally substituted 4-7 membered saturated ring, a 4-7 membered partially unsaturated ring, or a 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said cyclic group has 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur). In some embodiments, each R is independently hydrogen or a C₁₋₆ alkyl.

[00172] In some embodiments, each R is as selected from one or more of the substituents of **Table 1** or **Table 1a**.

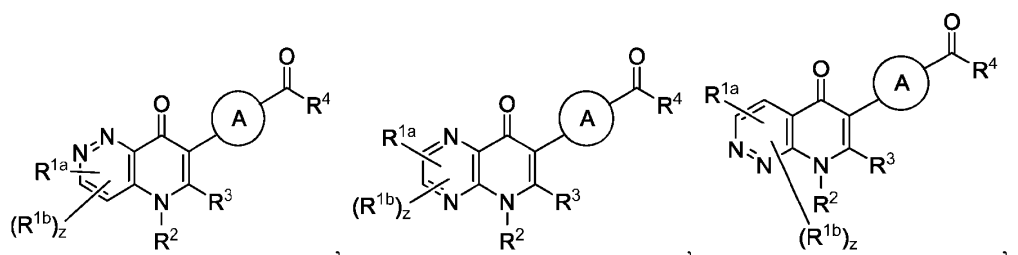
[00173] In some embodiments, the compound of Formula I is a compound of Formula IIa - Formula IIs:



II-a

II-b

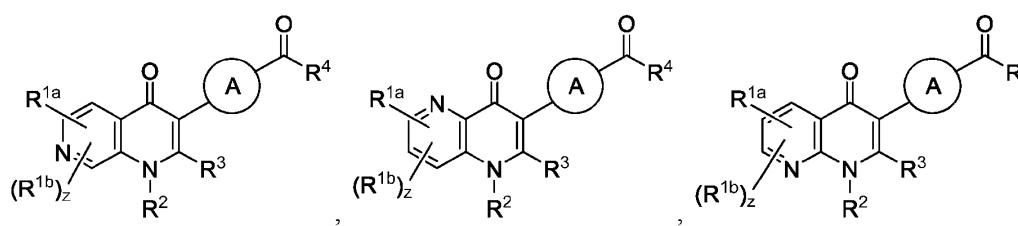
II-c



II-d

II-e

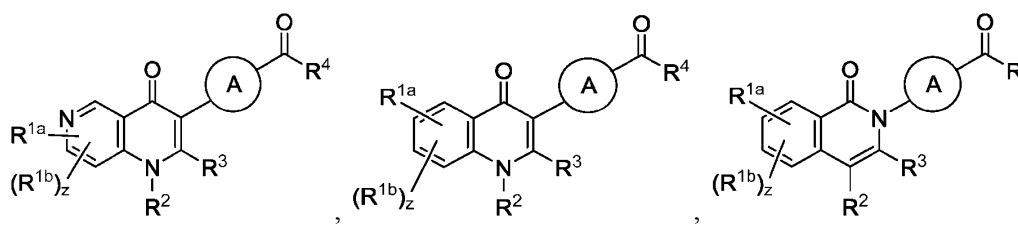
II-f



II-g

II-h

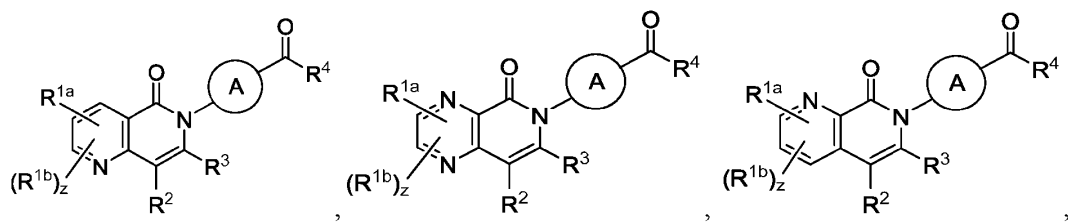
II-i



II-j

II-k

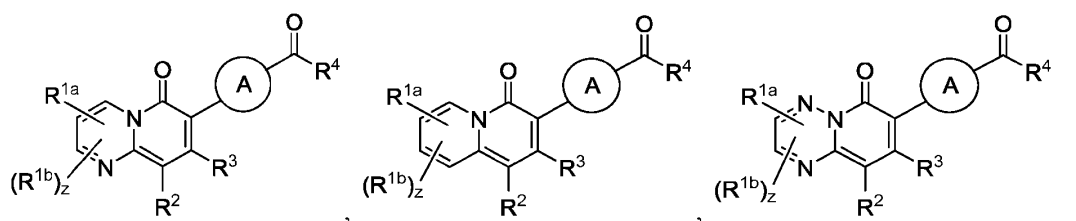
II-l



II-m

II-n

II-o

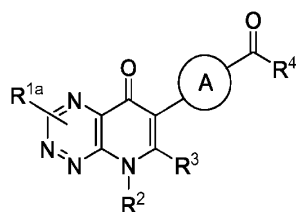


II-p

II-q

II-r,

and

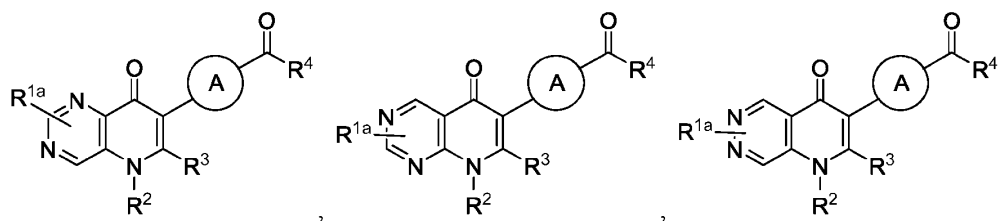


II-s

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , z , Ring A, R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

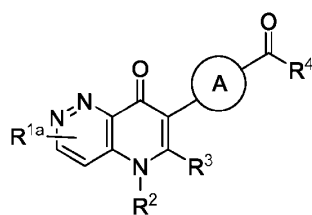
[00174] In some embodiments, the compound of Formula I is a compound of Formula IIa' - Formula II-s':



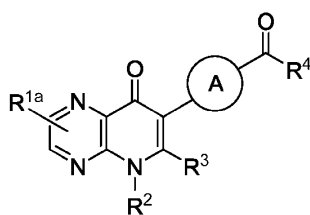
II-a'

II-b'

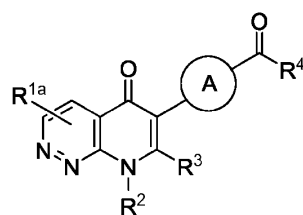
II-c'



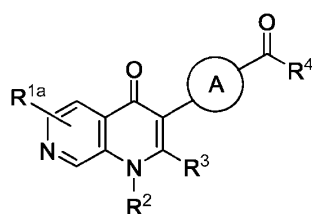
II-d'



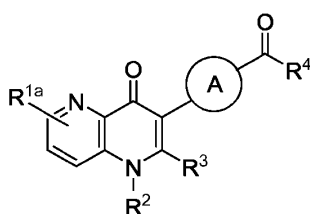
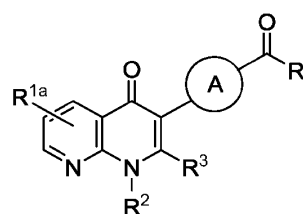
II-e'



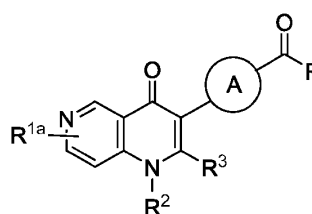
II-f



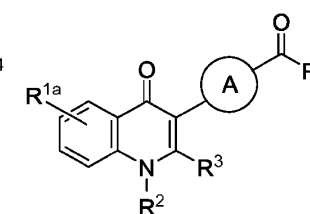
II-g'

II-h⁹

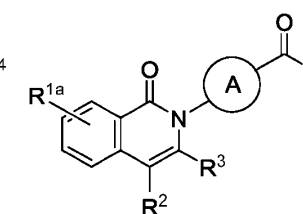
II-i'



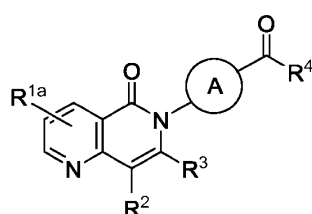
II-j'



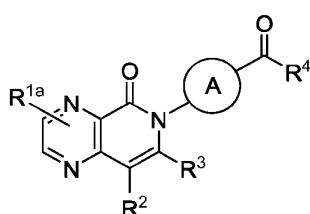
II-k'



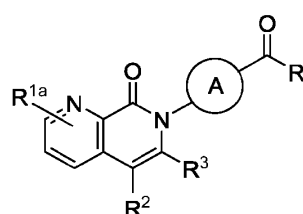
II-1'



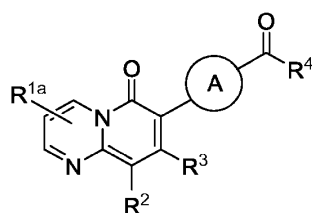
II-m'



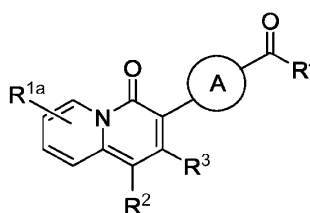
II-n'



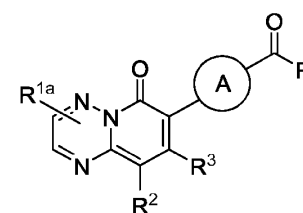
II-o'



II-m'

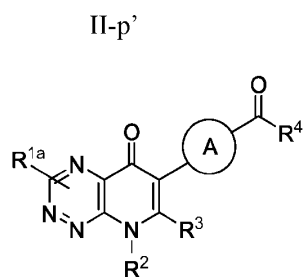


II-n'



II-o'

, and



II-p'

II-q'

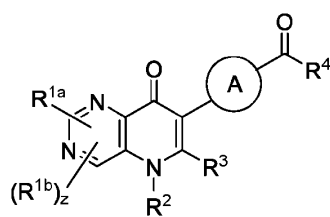
II-r'

II-s'

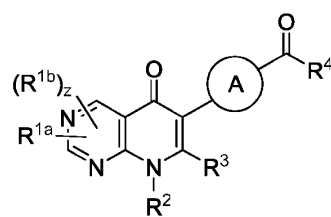
or a pharmaceutically acceptable salt thereof;

wherein R^{1a}, Ring A, R², R³, and R⁴, are as defined herein, both singly and in combination.

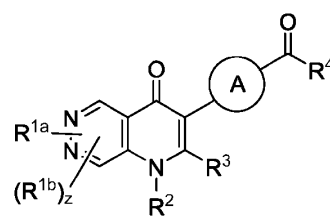
[00175] In some embodiments, the compound of Formula I is a compound of Formula IIa - Formula IIs:



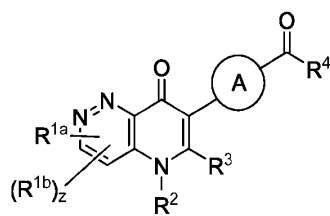
II-a



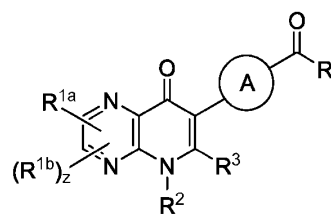
II-b



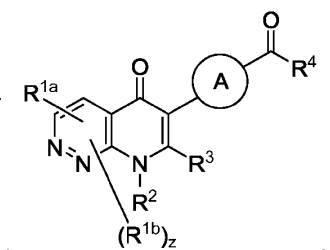
II-c



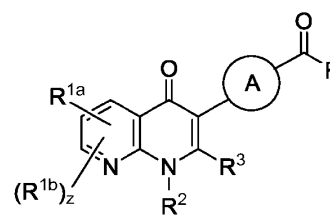
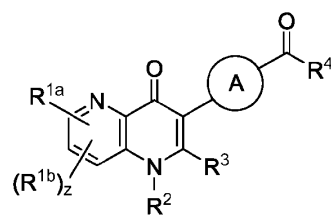
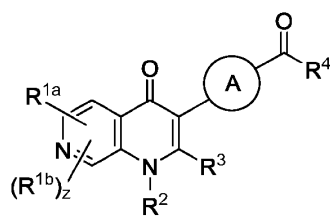
II-d



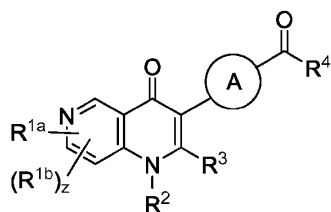
II-e



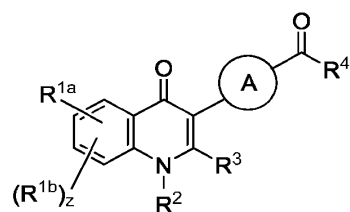
II-f



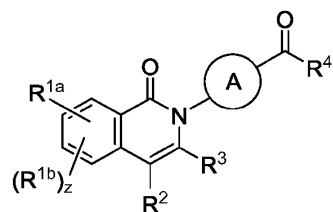
II-g



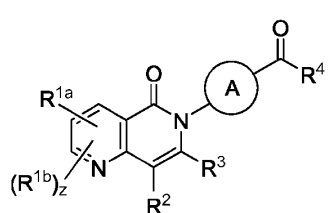
II-h



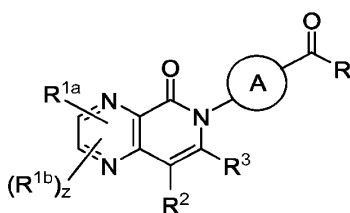
II-i



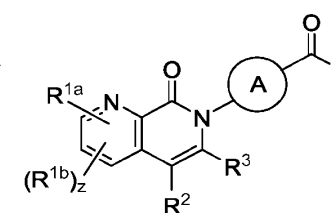
II-j



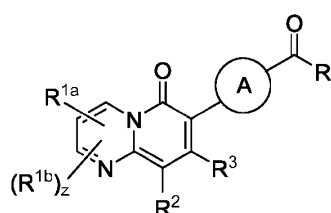
II-k



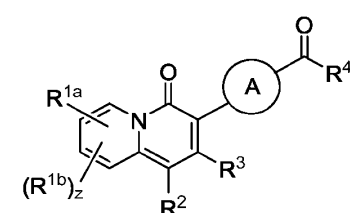
II-l



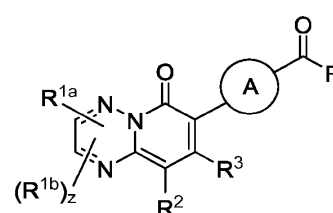
II-m



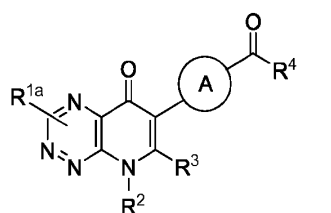
II-n



II-o



II-p



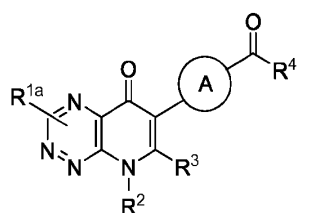
II-q



II-r, and

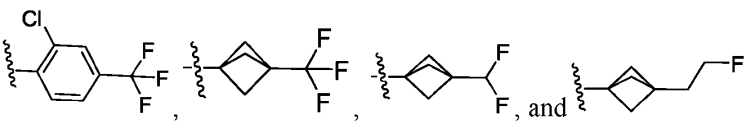


II-s

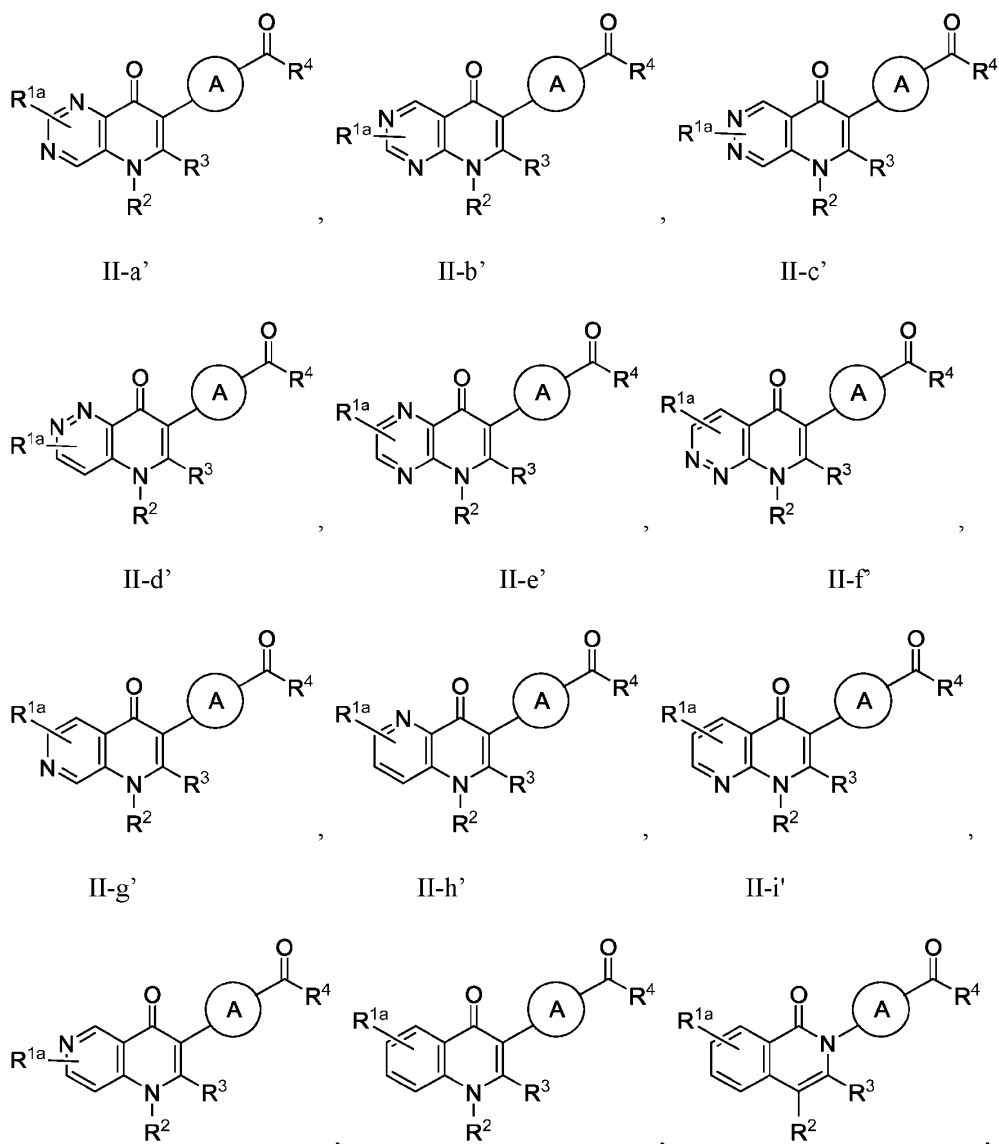


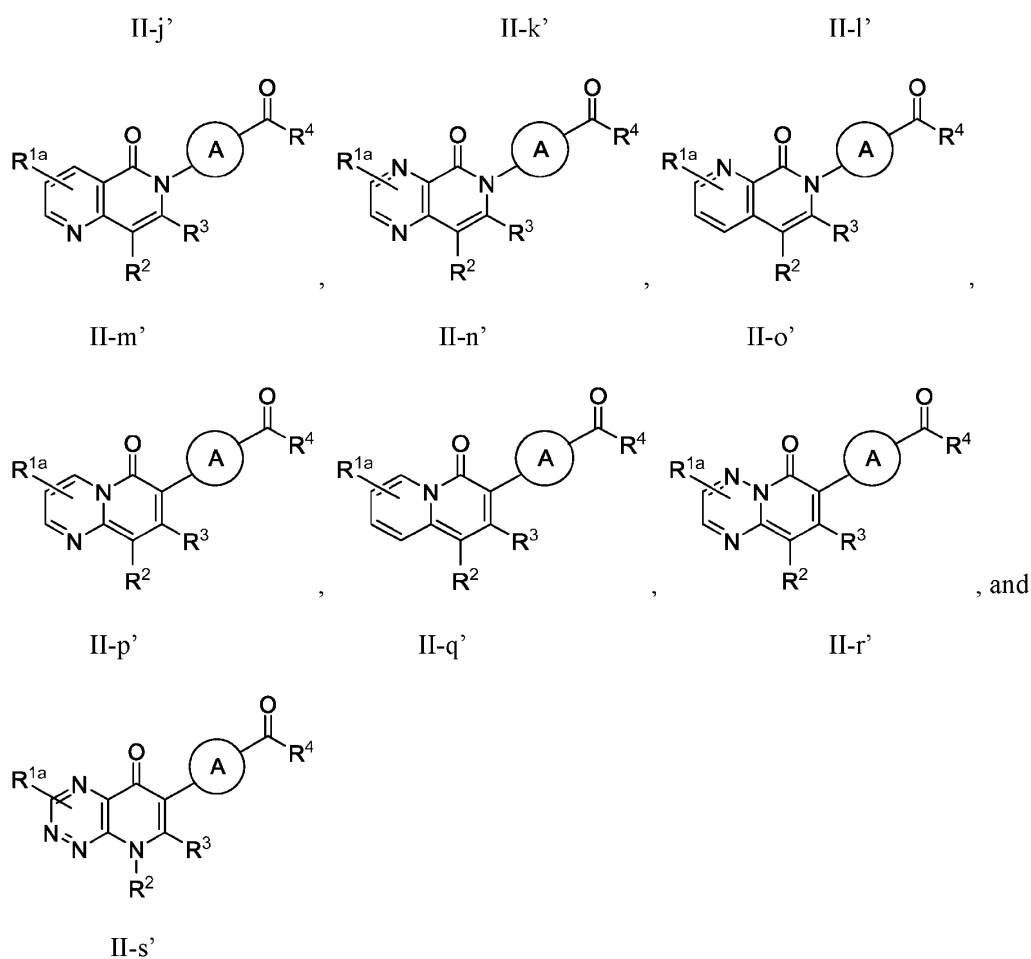
or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , z , Ring A, R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination

and R^{2a} is selected from .

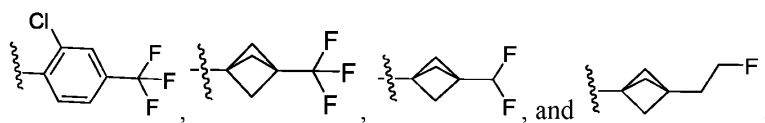
[00176] In some embodiments, the compound of Formula I is a compound of Formula IIa' - Formula IIi':



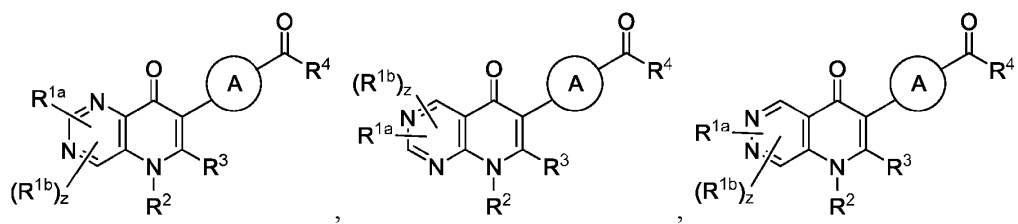


or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , Ring A, R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination

and R^{2a} is selected from .

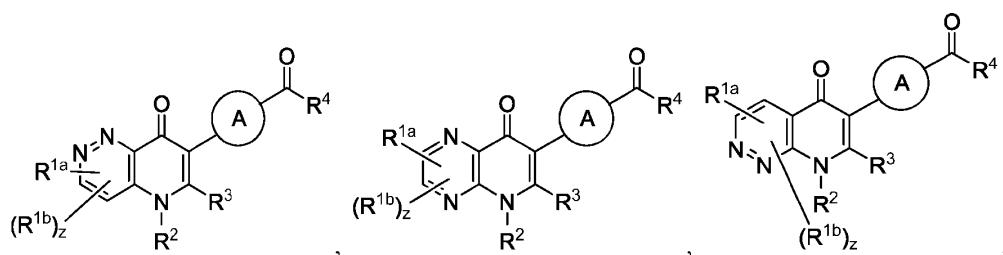
[00177] In some embodiments, the compound of Formula I is a compound of Formula IIa - Formula IIs:



II-a

II-b

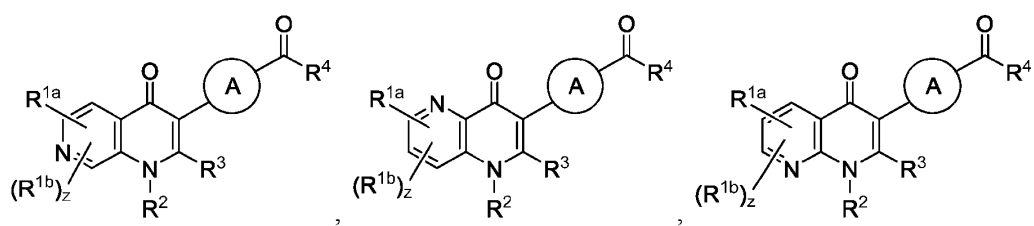
II-c



II-d

II-e

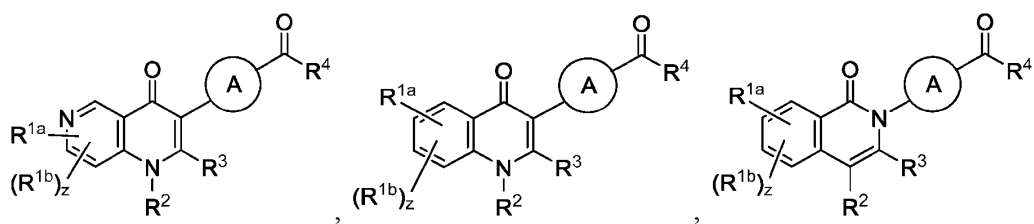
II-f



II-g

II-h

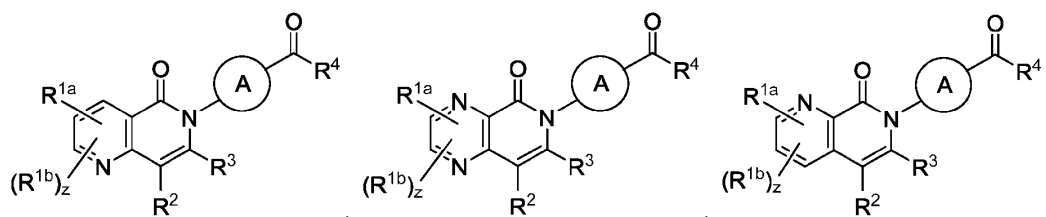
II-i



II-j

II-k

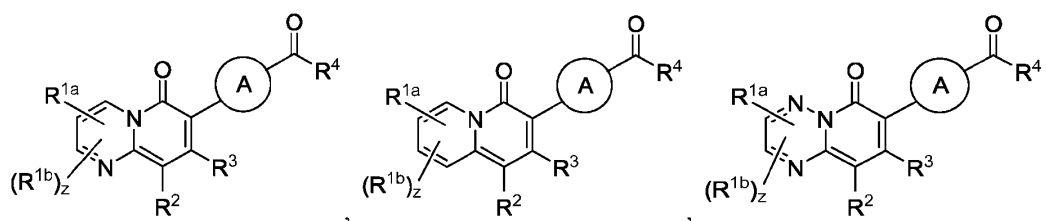
II-l



II-m

II-n

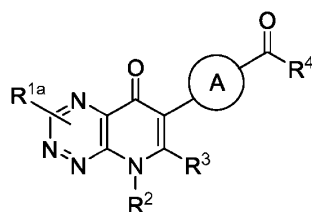
II-o



II-p

II-q

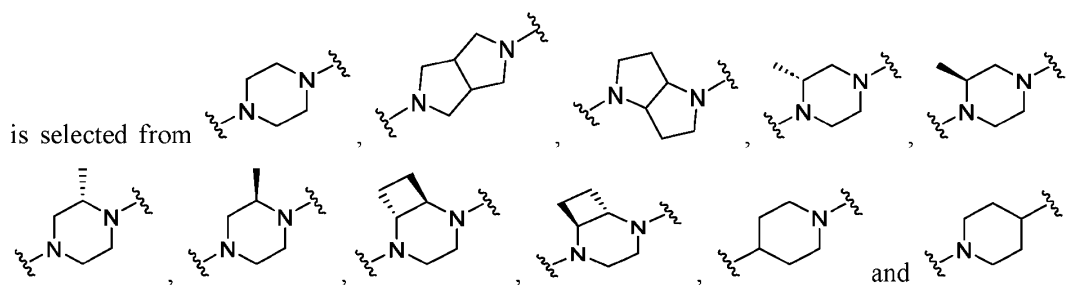
II-r, and



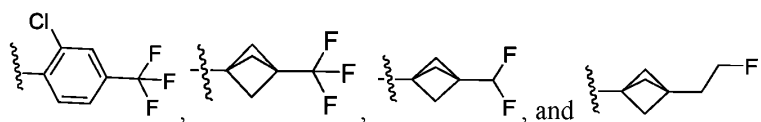
II-s

or a pharmaceutically acceptable salt thereof;

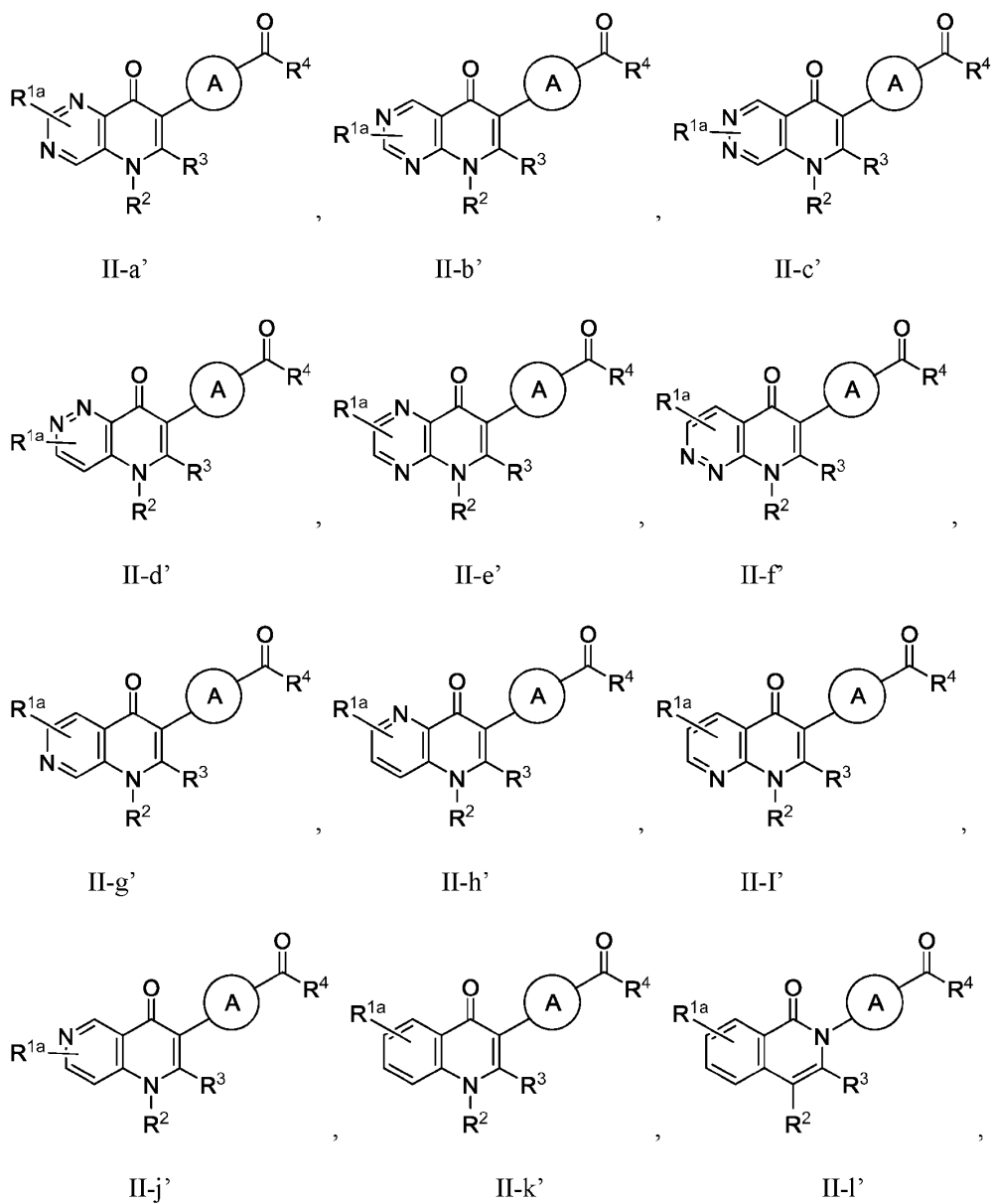
wherein R^{1a} , R^{1b} , z , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination, Ring A

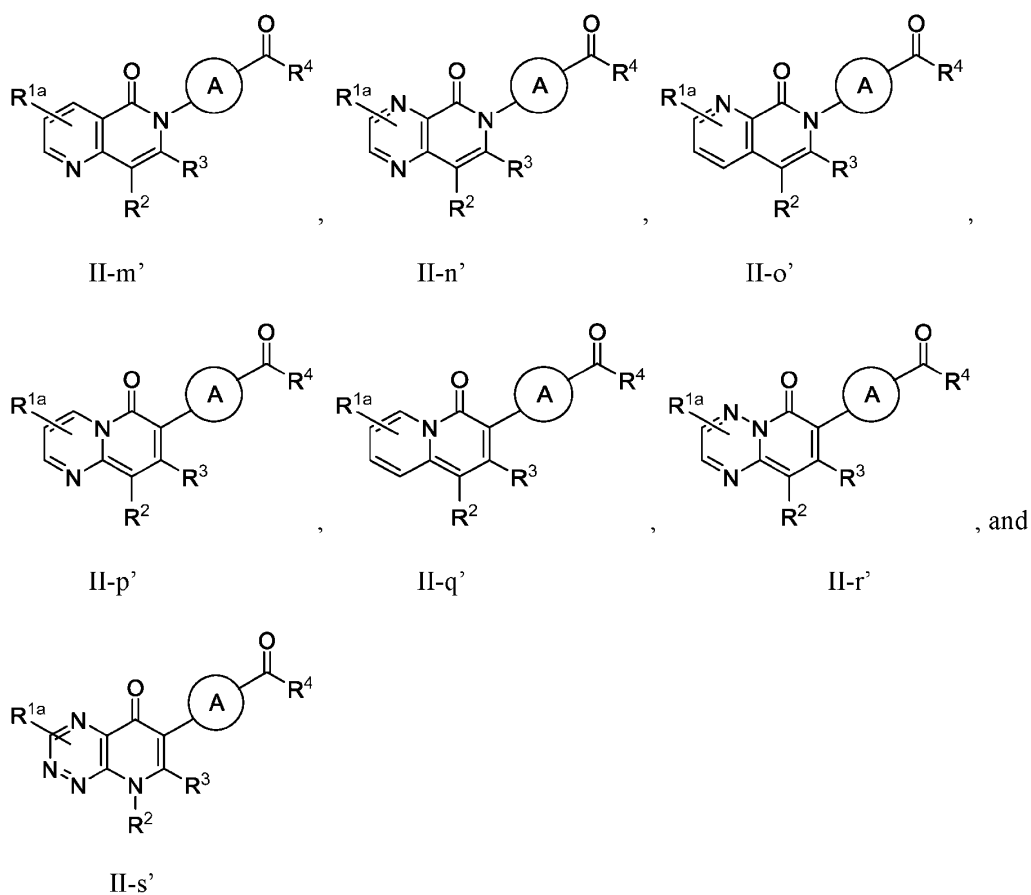


and R^{2a} is selected from



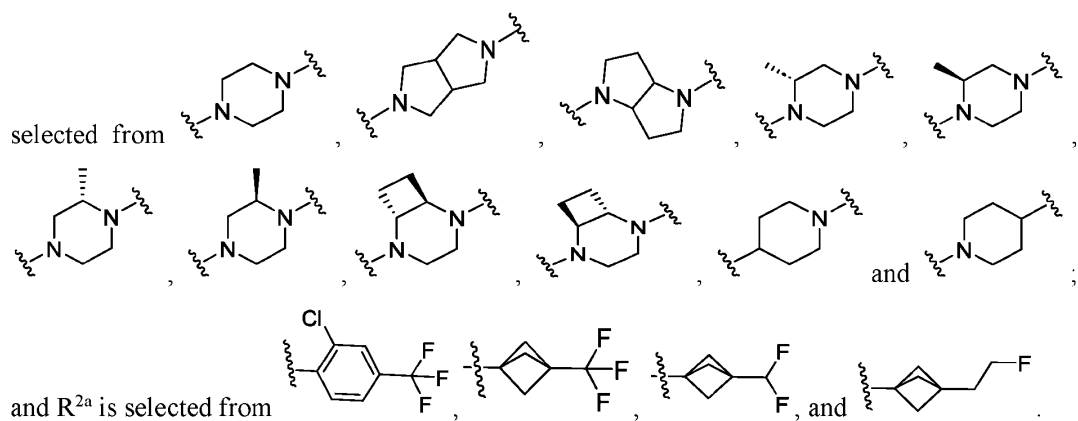
[00178] In some embodiments, the compound of Formula I is a compound of Formula IIa' - Formula IIk':



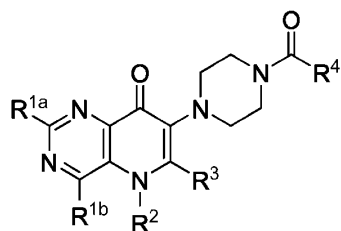


or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination, Ring A is



[00179] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-a:

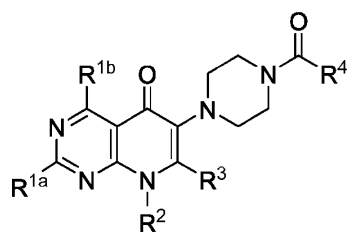


III-a

or a pharmaceutically acceptable salt thereof;

wherein R^{1a}, R^{1b}, R², R³, and R⁴, are as defined herein, both singly and in combination.

[00180] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-b:

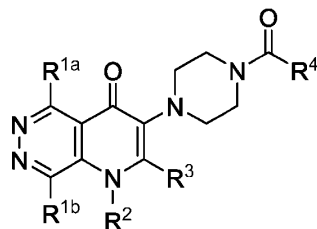


III-b

or a pharmaceutically acceptable salt thereof;

wherein R^{1a}, R^{1b}, R², R³, and R⁴, are as defined herein, both singly and in combination.

[00181] In some embodiments, the compound of Formula I, I', or I'' is a compound of III-c:

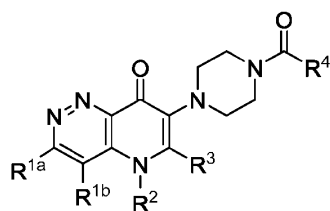


III-c

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00182] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-d:

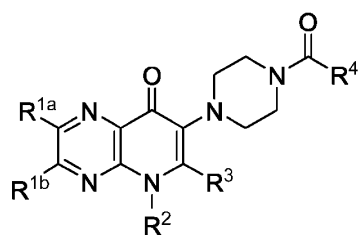


III-d

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00183] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-e:

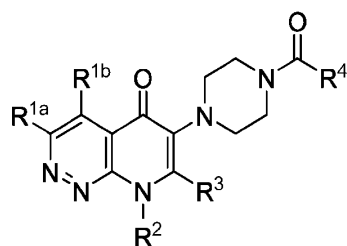


III-e

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00184] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-f:

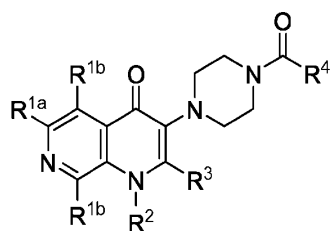


III-f

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00185] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-g:

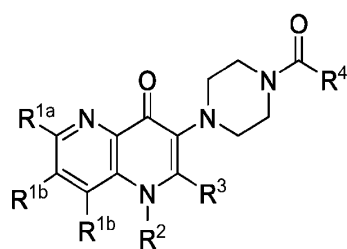


III-g

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00186] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-h:

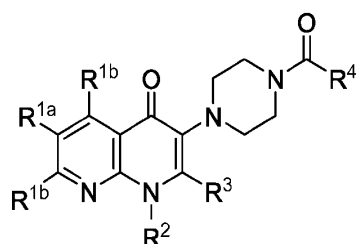


III-h

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00187] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-i:

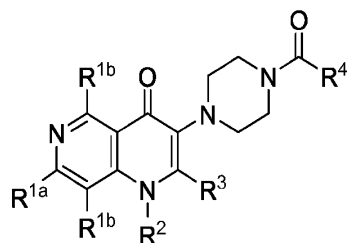


III-i

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00188] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-j:

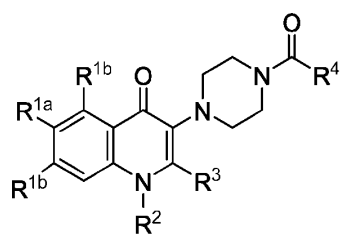


III-j

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00189] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-k:

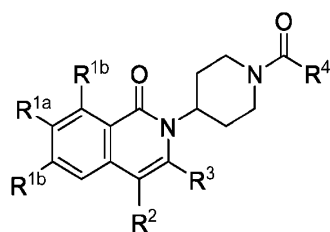


III-k

or a pharmaceutically acceptable salt thereof;

wherein R^{1a}, R^{1b}, R², R³, and R⁴, are as defined herein, both singly and in combination.

[00190] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-l:

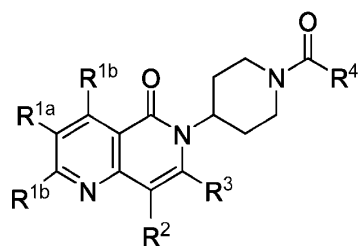


III-l

or a pharmaceutically acceptable salt thereof;

wherein R^{1a}, R^{1b}, R², R³, and R⁴, are as defined herein, both singly and in combination.

[00191] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-m:

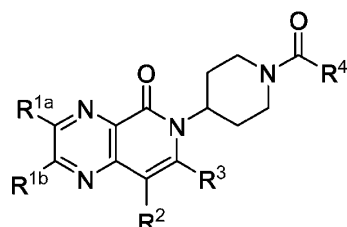


III-m

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00192] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-n:

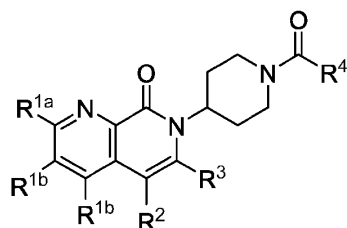


III-n

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00193] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-o:

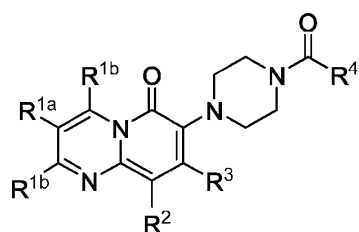


III-o

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00194] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-p:

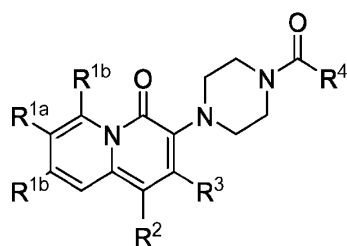


III-p

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00195] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-q:

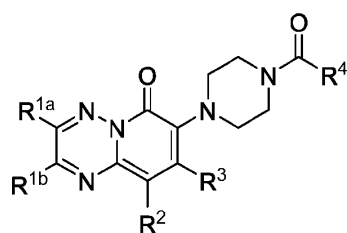


III-q

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00196] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-r:

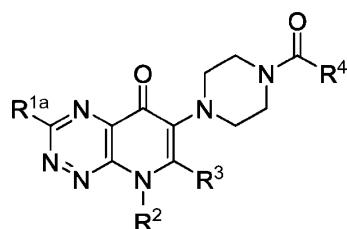


III-r

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00197] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-s:

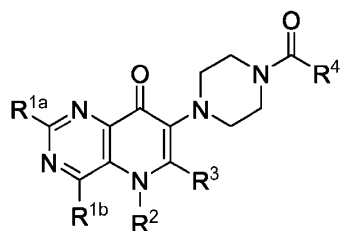


III-s

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

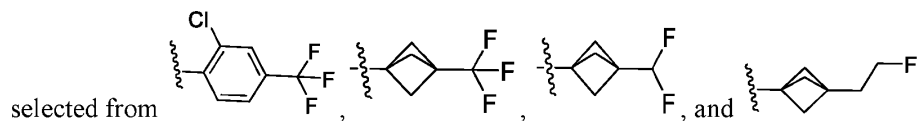
[00198] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-a:



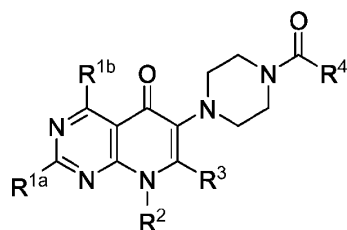
III-a

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination and R^{2a} is



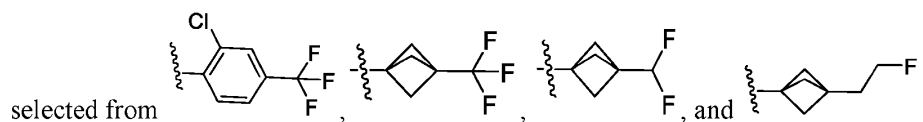
[00199] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-b:



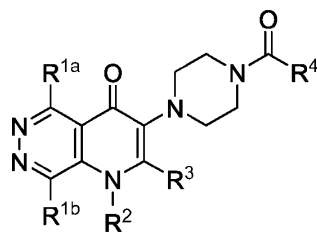
III-b

or a pharmaceutically acceptable salt thereof;

wherein R^{1a}, R^{1b}, R², R³, and R⁴, are as defined herein, both singly and in combination and R^{2a} is



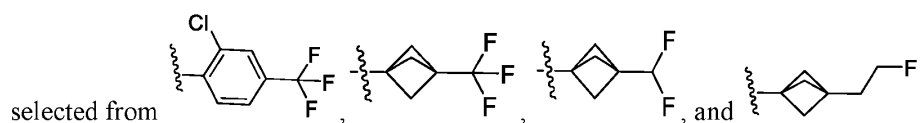
[00200] In some embodiments, the compound of Formula I, I', or I'' is a compound of III-c:



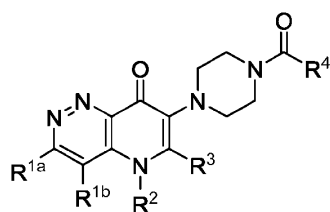
III-c

or a pharmaceutically acceptable salt thereof;

wherein R^{1a}, R^{1b}, R², R³, and R⁴, are as defined herein, both singly and in combination and R^{2a} is



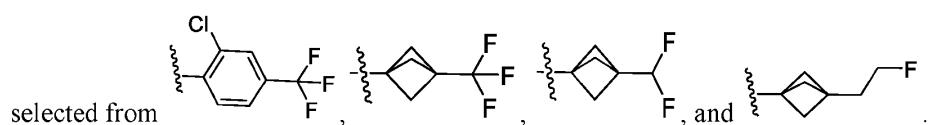
[00201] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-d:



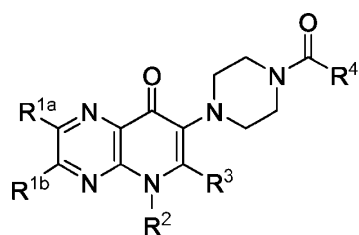
III-d

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination and R^{2a} is



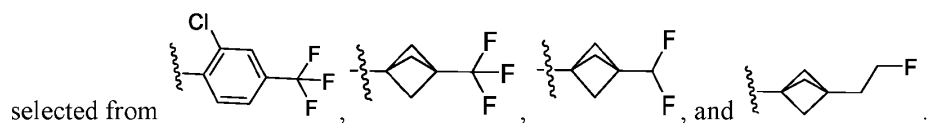
[00202] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-e:



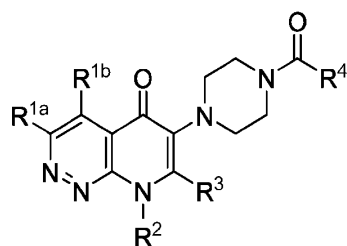
III-e

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination and R^{2a} is



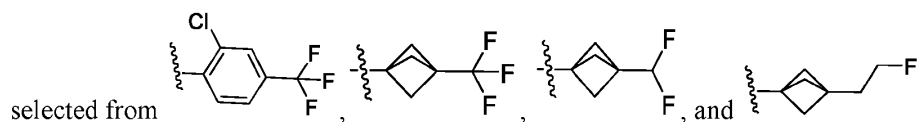
[00203] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-f:



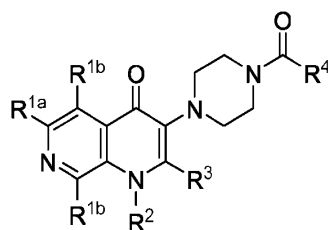
III-f

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination and R^{2a} is



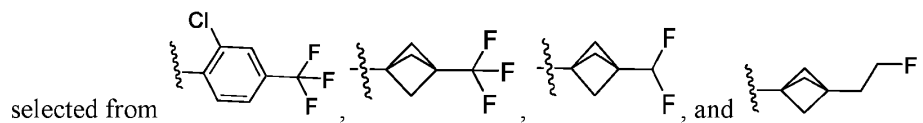
[00204] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-g:



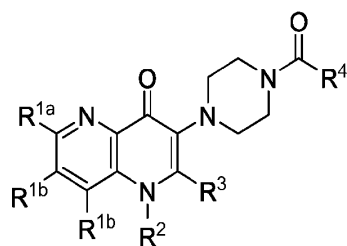
III-g

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination and R^{2a} is



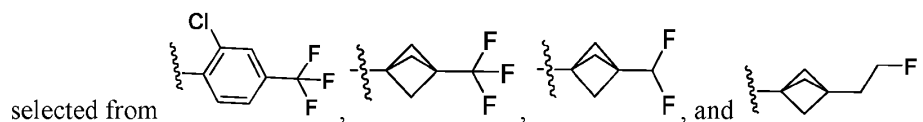
[00205] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-h:



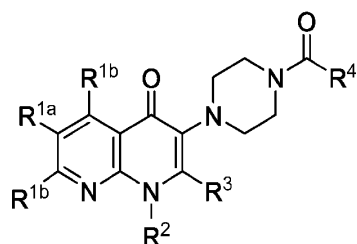
III-h

or a pharmaceutically acceptable salt thereof;

wherein R^{1a}, R^{1b}, R², R³, and R⁴, are as defined herein, both singly and in combination and R^{2a} is



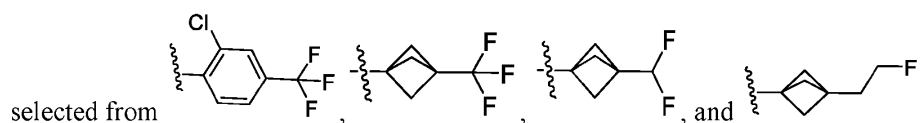
[00206] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-i:



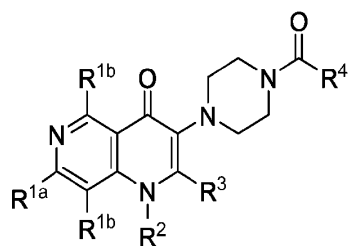
III-i

or a pharmaceutically acceptable salt thereof;

wherein R^{1a}, R^{1b}, R², R³, and R⁴, are as defined herein, both singly and in combination and R^{2a} is



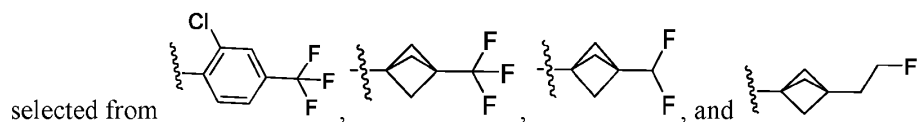
[00207] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-j:



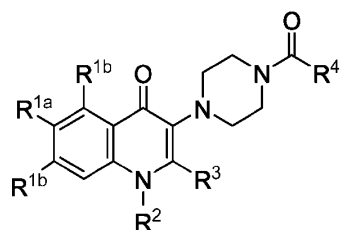
III-j

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination and R^{2a} is



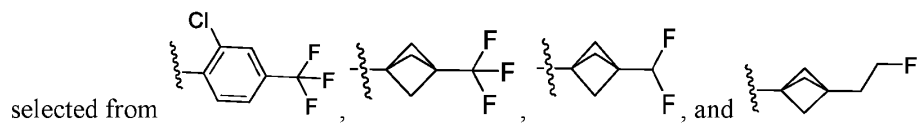
[00208] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-k:



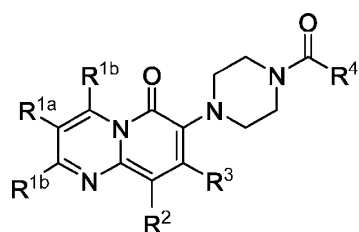
III-k

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination and R^{2a} is



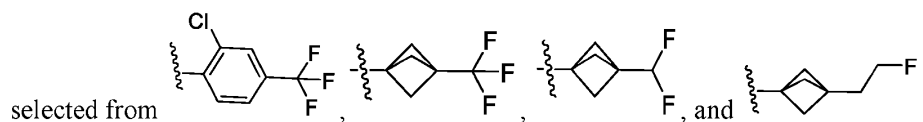
[00209] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-p:



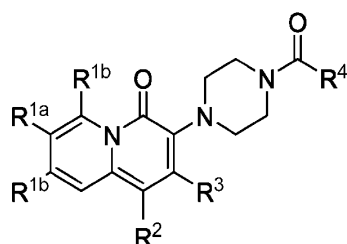
III-p

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination and R^{2a} is



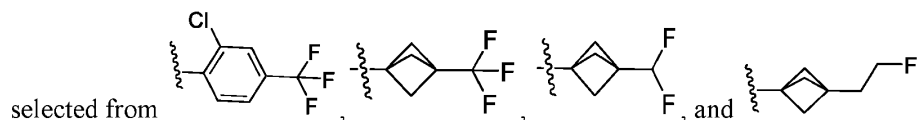
[00210] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-q:



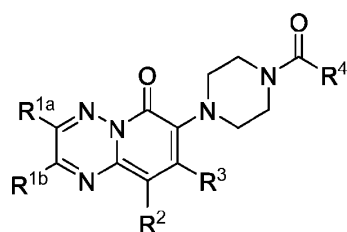
III-q

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination and R^{2a} is



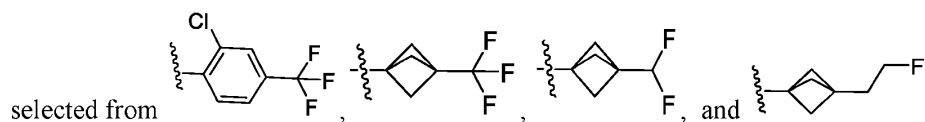
[00211] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-r:



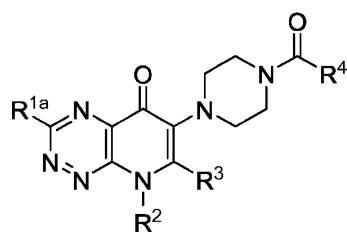
III-r

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination and R^{2a} is



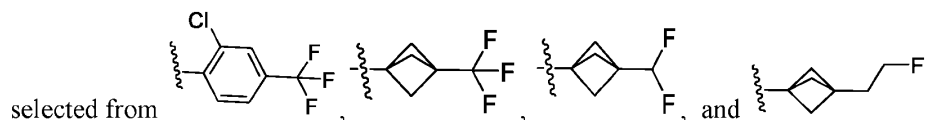
[00212] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula III-s:



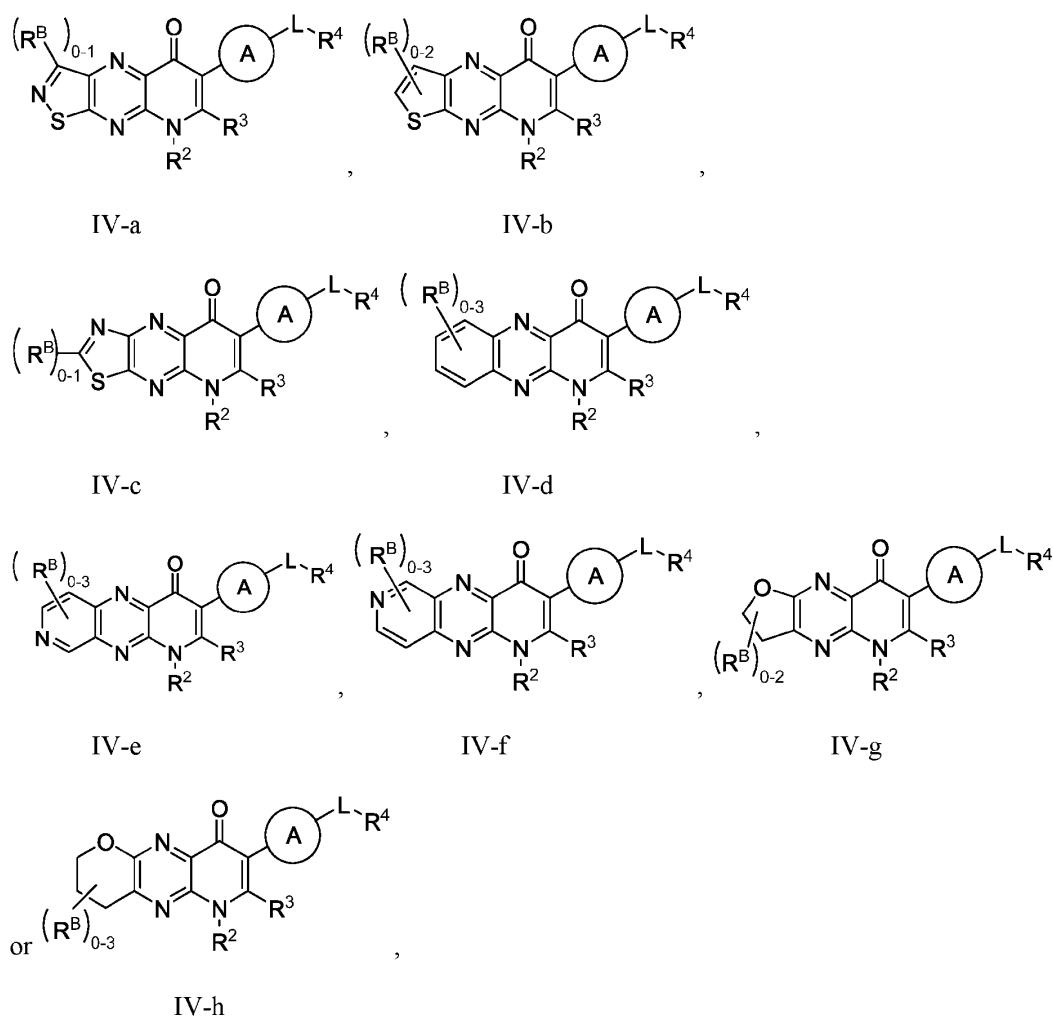
III-s

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} , R^{1b} , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination and R^{2a} is



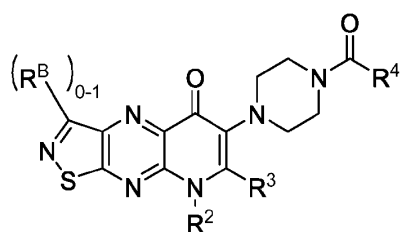
[00213] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula IV-a – IV-h:



or a pharmaceutically acceptable salt thereof;

wherein R^B , R^2 , R^3 , Ring A, linker L and R^4 , are as defined herein, both singly and in combination.

[00214] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula V-a:

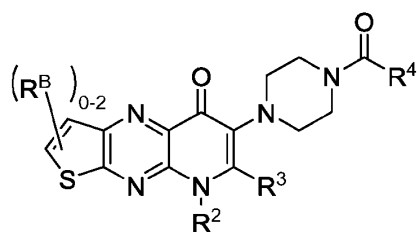


V-a

or a pharmaceutically acceptable salt thereof;

wherein R^B , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00215] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula V-b:

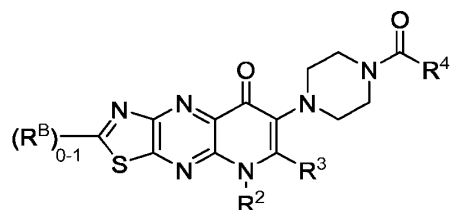


V-b

or a pharmaceutically acceptable salt thereof;

wherein R^B , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00216] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula V-c:

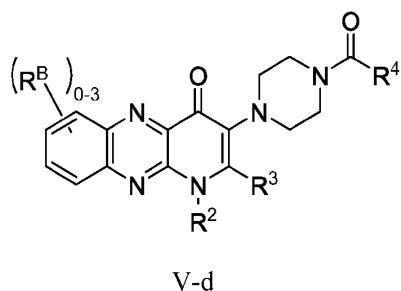


V-c

or a pharmaceutically acceptable salt thereof;

wherein R^B , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

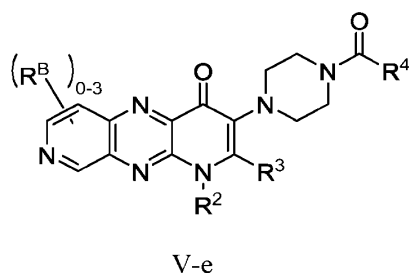
[00217] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula V-d:



or a pharmaceutically acceptable salt thereof;

wherein R^B , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

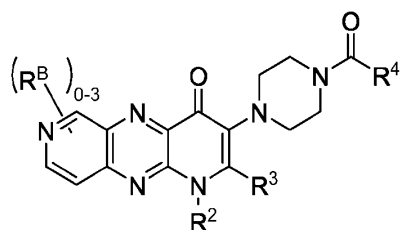
[00218] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula V-e:



or a pharmaceutically acceptable salt thereof;

wherein R^B , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00219] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula V-f:

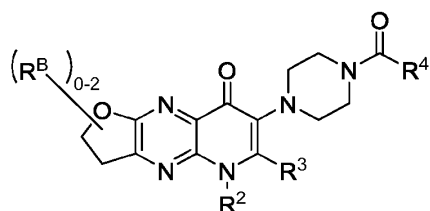


V-f

or a pharmaceutically acceptable salt thereof;

wherein R^B , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00220] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula V-g:

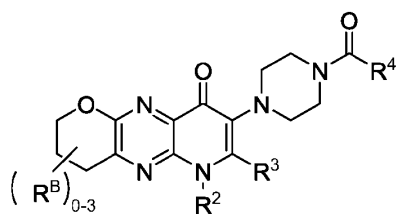


V-g

or a pharmaceutically acceptable salt thereof;

wherein R^B , R^2 , R^3 , and R^4 , are as defined herein, both singly and in combination.

[00221] In some embodiments, the compound of Formula I, I', or I'' is a compound of Formula V-h:



V-h

or a pharmaceutically acceptable salt thereof;

wherein R^B, R², R³, and R⁴, are as defined herein, both singly and in combination.

[00222] In some embodiments, the compound of Formula I, I', or I'' is selected from one of those depicted in Table 1 or Table 1a, or a pharmaceutically acceptable salt thereof. Table 1 or Table 1a, identifies compounds by their IUPAC name and Table 2 or Table 2a lists the same compounds and shows their chemical structure. In the event of any discrepancy between Table 1's or Table 1a's name for a compound and Table 2's or Table 2a's structure for that same compound, Table 2's or Table 2a's compound structures will dominate and identify the compound corresponding to each respective compound number (I-#) in Table 1 or 1a.

Table 1

Compound No.	IUPAC Name
I-1	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-2	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-3-methyl-7-(4-(1-methyl-1H-pyrazole-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-3	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(3-hydroxypicolinoyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-4	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(3-hydroxy-2-methoxyisonicotinoyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-5	2-(7-(4-acetylpiperazin-1-yl)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide
I-6	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(4-hydroxy-2-methoxynicotinoyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-7	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-methoxypyridin-4-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

I-8	(E)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(prop-1-en-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-9	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(prop-1-en-2-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-10	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-cyclopropyl-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-11	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(prop-1-yn-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-12	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methoxy-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-13	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-14	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-15	(E)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(2-ethoxyvinyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-16	<i>rac</i> -N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-methoxy-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (racemic mixture, trans)

I-17	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-cyclopropyl-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-18	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxo-2-vinylpyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-19	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-chloro-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-20	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(methylamino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-21	(E)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxo-2-(prop-1-en-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-22	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-hydroxypropan-2-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-23	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxo-2-(prop-1-en-2-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-24	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-hydroxy-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-25	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(hydroxymethyl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-26	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethoxy)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

I-27	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(2-oxopyrrolidin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-28	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-29	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-30	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(N-methylacetamido)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-31	2-(2-acetamido-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide
I-32	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(4-hydroxy-3-methyl-1H-pyrazole-5-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-33	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(7-hydroxy-1H-indazole-6-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-34	<i>rac</i> -N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (racemic mixture, trans)
I-35	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-((dihydrofuran-3(2H)-ylidene)methyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

I-36	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-((tetrahydro-4H-pyran-4-ylidene)methyl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-37	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-methylprop-1-en-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-38	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(cyclobutylidenemethyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-39	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1, trans)
I-40	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2, trans)
I-41	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-hydroxyethyl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-42	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(piperidin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-43	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3-chloro-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

I-44	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-(3-hydroxy-3-methylazetidin-1-yl)-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-45	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(3-hydroxyazetidin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-46	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-47	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-(3-hydroxy-3-methylpyrrolidin-1-yl)-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-48	5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-N,N-dimethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazine-2-carboxamide
I-49	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(morpholinomethyl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-50	5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-5,8-dihydropyrido[2,3-b]pyrazine-2-carboxamide
I-51	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(4-hydroxy-2-methoxynicotinoyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-52	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-morpholino-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

I-53	2-(2-(azetidin-1-yl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide
I-54	5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-N-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazine-2-carboxamide
I-55	(E)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(3-methoxyprop-1-en-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-56	(R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(3-hydroxypyrrolidin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-57	(R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-3-methylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-58	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(cyclopropyl(methyl)amino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-59	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-((3-hydroxy-3-methylcyclobutyl)(methyl)amino)-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-60	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-((3-methoxycyclobutyl)(methyl)amino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-61	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methyl-5-oxopyrido[2,3-b]thieno[3,2-e]pyrazin-8(5H)-yl)acetamide

I-62	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-fluoro-3-hydroxy-2-methoxyisonicotinoyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-63	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-2-(1-methyl-1H-pyrazol-4-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-64	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2,3-dimethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-65	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-methoxypyridin-4-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-66	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(3-methoxyazetidin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-67	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-(4-(2,6-dihydroxybenzoyl)piperazin-1-yl)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-68	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(7-hydroxy-2,3-dihydrofuro[3,2-c]pyridine-6-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-69	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(4-hydroxy-2,3-dihydrofuro[2,3-c]pyridine-5-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-70	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-3-methyl-8-oxo-7-(4-(2-oxo-2,3-dihydrobenzo[d]oxazole-4-carbonyl)piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-71	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(6-hydroxy-1H-benzo[d]imidazole-7-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

I-72	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-((2-methoxyethyl)(methyl)amino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-73	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-((2-hydroxyethyl)(methyl)amino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-74	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-(ethyl(methyl)amino)-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-75	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(pyrrolidin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-76	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-1H-indazole-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-77	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(4-hydroxyisoxazole-3-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-79	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(1-methyl-1H-pyrazol-4-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-80	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-81	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methoxy-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

I-82	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(3,6-dihydro-2H-pyran-4-yl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-83	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-cyano-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-84	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-hydroxypropan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-86	2-(2-bromo-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide
I-87	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-3,3-dimethylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-88	(S)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(3-hydroxypyrrolidin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-89	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-90	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(2,5-dihydrofuran-3-yl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-91	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(2,3-dihydro-1H-imidazo[1,2-b]pyrazol-1-yl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

I-92	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(((1 <i>r</i> ,3 <i>r</i>)-3-methoxycyclobutyl)(methyl)amino)-8-oxopyrido[2,3- <i>b</i>]pyrazin-5(8H)-yl)acetamide
I-93	2-(2-(2-azabicyclo[3.1.0]hexan-2-yl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3- <i>b</i>]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide
I-94	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(1H-pyrazol-4-yl)pyrido[2,3- <i>b</i>]pyrazin-5(8H)-yl)acetamide
I-95	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methyl-8-oxopyrido[2,3- <i>b</i>]thiazolo[4,5- <i>e</i>]pyrazin-5(8H)-yl)acetamide
I-96	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-3-(methoxymethyl)piperazin-1-yl)-8-oxopyrido[2,3- <i>b</i>]pyrazin-5(8H)-yl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2)
I-97	<i>rac</i> -N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(methylamino)-8-oxopyrido[2,3- <i>b</i>]pyrazin-5(8H)-yl)acetamide (racemic mixture, trans)
I-98	(<i>S</i>)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl)-8-oxopyrido[2,3- <i>b</i>]pyrazin-5(8H)-yl)acetamide
I-99	(<i>R</i>)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl)-8-oxopyrido[2,3- <i>b</i>]pyrazin-5(8H)-yl)acetamide

I-100	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-cyclopropyl-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-101	2-(2-(bis(methyl-d3)amino)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide
I-102	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-cyclopropoxy-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-103	2-(2-(dimethylamino)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-methyl-4-(trifluoromethyl)phenyl)acetamide
I-104	2-(2-(dimethylamino)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(4-(trifluoromethyl)phenyl)acetamide
I-105	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxo-2-(pyrrolidin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-106	<i>rac</i> -N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (racemic mixture, <i>cis</i>)

I-107	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-108	2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide
I-109	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-(dimethylamino)-2-ethyl-7-fluoro-3-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-4-oxo-1,5-naphthyridin-1(4H)-yl)acetamide
I-110	2-(2-(dimethylamino)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide
I-111	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-ethyl-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-3-(2-methylprop-1-en-1-yl)-5-oxopyrido[3,2-e][1,2,4]triazin-8(5H)-yl)acetamide
I-112	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methyl-5-oxofuro[2,3-b]pyrido[3,2-e]pyrazin-8(5H)-yl)acetamide
I-113	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methyl-8-oxopyrido[2,3-b]thieno[2,3-e]pyrazin-5(8H)-yl)acetamide
I-114	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-methyl-8-oxopyrido[2,3-b]thiazolo[4,5-e]pyrazin-5(8H)-yl)acetamide

I-115	2-(7-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methyl-5-oxopyrido[2,3-b]thieno[3,2-e]pyrazin-8(5H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide
I-116	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-1-methyl-8-oxo-1,2,3,8-tetrahydro-5H-pyrido[2,3-b]pyrrolo[2,3-e]pyrazin-5-yl)acetamide
I-117	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-((3-methoxycyclobutylidene)methyl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-118	(S)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3-(dimethylamino)-7-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl)-5-oxopyrido[3,2-e][1,2,4]triazin-8(5H)-yl)acetamide
I-119	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(cyclopropyl(methyl)amino)-6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, trans)
I-120	2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]-N-[4-(trifluoromethoxy)phenyl]acetamide
I-121	2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]-N-[2-fluoro-4-(trifluoromethyl)phenyl]acetamide

I-122	2-(2-((1R*,5S*)-2-azabicyclo[3.1.0]hexan-2-yl)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide
I-123	2-{11-[(4aS,7aS)-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-octahydro-1H-cyclopenta[b]pyrazin-1-yl]-12-ethyl-5-methyl-10-oxo-4-oxa-2,8,13-triazatricyclo[7.4.0.0 [^] {3,7}]trideca-1,3(7),5,8,11-pentaen-13-yl}-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide
I-124	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[6-(dimethylamino)-2-ethyl-3-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-4-oxo-1,4-dihydro-1,8-naphthyridin-1-yl]acetamide
I-125	2-{2-cyclopropyl-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}-N-[2-fluoro-4-(trifluoromethyl)phenyl]acetamide
I-126	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2,3-dimethyl-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-127	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(4-hydroxy-2-methoxy-5-methylpyridine-3-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2,3-dimethyl-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-128	2-(6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2,3-dimethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide
I-129	2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-3-methyl-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]-N-[2-fluoro-4-(trifluoromethyl)phenyl]acetamide

I-130	2-{7-[(4aS,7aS)-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-octahydro-1H-cyclopenta[b]pyrazin-1-yl]-2-(dimethylamino)-6-ethyl-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide
I-131	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-[cyclobutyl(methyl)amino]-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-132	N-[2-chloro-4-(pentafluoro-lambda6-sulfanyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-133	N-[2-chloro-6-fluoro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-134	(2E)-3-[5-({2-chloro-4-(trifluoromethyl)phenyl}carbonyl)methyl]-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-2-yl]-N,N-dimethylprop-2-enamide
I-135	<i>rac</i> -N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(2-ethoxyvinyl)-6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (racemic mixture, trans)
I-136	<i>rac</i> -N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-[(1E)-2-ethoxyethenyl]-6-ethyl-7-[5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide (racemic mixture, trans)
I-137	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-2-(1-methyl-1H-pyrazol-5-yl)-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide

I-138	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-2-[(1E)-3-hydroxy-3-methylbut-1-en-1-yl]-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-139	<i>rac</i> -N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[-5-(4-hydroxy-2-methoxypyridine-3-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide (racemic mixture, trans)
I-140	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-2-(oxetan-3-yloxy)-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-141	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-cyclobutoxy-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-142	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-2-[(2-methylcyclobutylidene)methyl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-143	<i>rac</i> -N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-((2-methoxycyclobutyl)(methyl)amino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (racemic mixture, trans)
I-144	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-[(1E)-2-cyclobutylethenyl]-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-145	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{7-[4-(5-cyano-3-hydroxy-2-methylpyridine-4-carbonyl)piperazin-1-yl]-6-ethyl-3-methyl-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide

I-146	<i>rac</i> -N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-((2-methoxycyclobutyl)(methyl)amino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (racemic mixture, <i>cis</i>)
I-147	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-1,4-diazepan-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-148	N-[2,6-difluoro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-149	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-2-[(2S)-2-methylpyrrolidin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-150	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-2-[(2R)-2-methylpyrrolidin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-151	2-(2-{6-azaspiro[3.4]octan-6-yl}-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl)-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide
I-152	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-2-[2-(2-hydroxypropan-2-yl)pyrrolidin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-153	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-2-[(2S)-2-(2-hydroxypropan-2-yl)pyrrolidin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide

I-154	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-(2-{[2-(dimethylamino)ethyl](methyl)amino}-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-155	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-[(1R,5S,6S)-6-(dimethylamino)-3-azabicyclo[3.1.0]hexan-3-yl]-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-156	2-(2-{3-azabicyclo[3.1.0]hexan-3-yl}-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl)-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide
I-157	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[6-ethyl-2-(1-fluoroethenyl)-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-158	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{7-[4-(5-cyano-3-hydroxy-2-methylpyridine-4-carbonyl)piperazin-1-yl]-6-ethyl-2-methyl-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-159	methyl 3-[5-({[2-chloro-4-(trifluoromethyl)phenyl]carbamoyl}methyl)-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-2-yl]-2,5-dihydro-1H-pyrrole-1-carboxylate
I-160	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(3,3-difluoroazetidin-1-yl)-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-161	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(cyclobutylamino)-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-162	2-(2-{5-azaspiro[2.3]hexan-5-yl}-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl)-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide

I-163	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-2-{2-oxa-6-azaspiro[3.4]octan-6-yl}-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-164	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[6-ethyl-2-(3-fluoroazetidin-1-yl)-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-165	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(cyclopropylamino)-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-166	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(cyclopentylidenemethyl)-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-167	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-[(2,2-difluoroethyl)(methyl)amino]-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-168	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[9-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-169	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-[cyclopropyl(methyl)amino]-6-ethyl-7-[5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide (single stereoisomer, first eluting compound as stereoisomer 1, trans)
I-170	2-(2-{1-azaspiro[3.3]heptan-1-yl}-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl)-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide

I-171	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(methylamino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1, trans)
I-172	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(methylamino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2, trans)
I-173	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(3S)-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-3-methylpiperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-174	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[6-ethyl-2-(2-fluoropropan-2-yl)-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-175	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-2-[methyl(propan-2-yl)amino]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-176	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-4,7-diazaspiro[2.5]octan-7-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-177	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(3,3-difluoropyrrolidin-1-yl)-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-178	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-3-(hydroxymethyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide

I-179	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dicyclopropylamino)-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-180	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-2-[(3-hydroxy-3-methylcyclobutylidene)methyl]-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-181	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-cyclobutoxy-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-182	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-methoxy-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-183	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-3-methoxypyridazine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-184	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-(1-methyl-1H-pyrazole-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-185	N-[2-chloro-4-(pentafluoro-lambda6-sulfanyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(2S)-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-186	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-[(cyclopropylmethyl)amino]-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide

I-187	2-[2-(azetidin-1-yl)-6-ethyl-7-[(2S)-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide
I-188	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(2S)-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl]-2-[(2S)-2-(methoxymethyl)azetidin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-189	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(2S)-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl]-2-[(2R)-2-(methoxymethyl)azetidin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-190	2-[2-(azetidin-1-yl)-6-ethyl-7-[(2S)-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]-N-[2-chloro-4-(pentafluoro-lambda6-sulfanyl)phenyl]acetamide
I-191	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(2S)-2-ethyl-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-192	2-(2-(2-azabicyclo[3.1.0]hexan-2-yl)-6-ethyl-7-((S)-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1, cis)
I-193	2-(2-(2-azabicyclo[3.1.0]hexan-2-yl)-6-ethyl-7-((S)-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2, cis)

I-194	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-[cyclopropyl(methyl)amino]-6-ethyl-7-(4-{4-hydroxy-2H,3H-furo[2,3-c]pyridine-5-carbonyl}piperazin-1-yl)-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-195	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-cyclopropoxy-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-196	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,3-dimethylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1, cis)
I-197	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{7-[(3R)-3-(difluoromethyl)-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-2-(dimethylamino)-6-ethyl-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-198	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,3-dimethylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2, cis)
I-199	N-[2-chloro-4-(trifluoromethoxy)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-200	N-[2-chloro-4-(pentafluoro-lambda6-sulfanyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-201	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-2-(1H-pyrazol-1-yl)-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide

I-203	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-[cyclopropyl(methyl)amino]-6-ethyl-7-(4-{7-hydroxy-2H,3H-furo[3,2-c]pyridine-6-carbonyl}piperazin-1-yl)-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-204	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[4-(4-hydroxy-2-methoxy-5-methylpyridine-3-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-205	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-2-[methyl(1-methylcyclopropyl)amino]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-206	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(1R,5S)-8-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-207	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-2-{6-oxa-1-azaspiro[3.3]heptan-1-yl}-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-208	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)octahydro-1H-cyclopenta[b]pyrazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1, cis)
I-209	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)octahydro-1H-cyclopenta[b]pyrazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2, cis)

I-210	2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]-N-[2-fluoro-4-(trifluoromethoxy)phenyl]acetamide
I-211	2-{2-[bis(methyl- <i>d</i> 3)amino]-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}-N-[2-fluoro-4-(trifluoromethyl)phenyl]acetamide
I-212	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[4-(4-fluoro-3-hydroxypyridine-2-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-213	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[1-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-1,2,3,6-tetrahydropyridin-4-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-214	2-{2-[di(2H3)methylamino]-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}-N-[2-fluoro-4-(trifluoromethyl)phenyl]acetamide
I-215	2-{7-[(4aR,7aR)-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-octahydro-1H-cyclopenta[b]pyrazin-1-yl]-2-(dimethylamino)-6-ethyl-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide
I-216	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-5,8-diazaspiro[3.5]nonan-8-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide

I-217	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-2-(N-methylmethanesulfonamido)-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-218	2-{7-[4-(4-chloro-3-hydroxypyridine-2-carbonyl)piperazin-1-yl]-2-(dimethylamino)-6-ethyl-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide
I-219	2-(2-(2-azabicyclo[3.1.0]hexan-2-yl)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1, cis)
I-220	2-(2-(2-azabicyclo[3.1.0]hexan-2-yl)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2, cis)
I-221	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[1-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperidin-4-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-222	N-[2-chloro-6-(trifluoromethyl)pyridin-3-yl]-2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-223	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-cyclobutyl-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-224	2-(2-{4-azaspiro[2.4]heptan-4-yl}-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl)-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide

I-225	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-cyclopropyl-6-ethyl-7-[(2S)-4-(4-hydroxy-2-methoxy-5-methylpyridine-3-carbonyl)-2-methylpiperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-226	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-[(methyl-d3)amino]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-227	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-(methylamino)-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-228	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(2S)-4-(4-hydroxy-2-methoxy-5-methylpyridine-3-carbonyl)-2-methylpiperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-229	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[3-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-3-azabicyclo[4.1.0]heptan-6-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-230	<i>rac</i> -2-(2-(2-azabicyclo[3.2.0]heptan-2-yl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (racemic mixture, <i>cis</i>)
I-231	2-(2-(2-azabicyclo[3.1.0]hexan-2-yl)-6-ethyl-7-((S)-4-(4-hydroxy-2-methoxy-5-methylnicotinoyl)-2-methylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1, <i>trans</i>)

I-232	2-(2-(2-azabicyclo[3.1.0]hexan-2-yl)-6-ethyl-7-((S)-4-(4-hydroxy-2-methoxy-5-methylnicotinoyl)-2-methylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2, trans)
I-233	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,3-dimethylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1, trans)
I-234	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,3-dimethylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2, trans)
I-236	2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]-N-[5-fluoro-2-methyl-4-(trifluoromethyl)phenyl]acetamide
I-237	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-[(1R)-2,2-difluorocyclopropyl]-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide (single stereoisomer, first eluting compound as stereoisomer 1)
I-238	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-[(1R)-2,2-difluorocyclopropyl]-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide (single stereoisomer, second eluting compound as stereoisomer 2)
I-239	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{2-cyclopropyl-6-ethyl-7-[4-(4-hydroxy-2-methoxy-5-methylpyridine-3-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide

I-240	N-[2-chloro-4-(difluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-241	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-(1-methyl-1H-pyrazol-5-yl)-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-242	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-(3-methoxyazetidin-1-yl)-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-243	2-{7-[(4aS,7aS)-4-(4-hydroxy-2-methoxy-5-methylpyridine-3-carbonyl)-octahydro-1H-cyclopenta[b]pyrazin-1-yl]-2-(dimethylamino)-6-ethyl-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide
I-244	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(2R)-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-(hydroxymethyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-245	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(3,3-difluoroazetidin-1-yl)-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-246	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[6-ethyl-2-(3-hydroxy-3-methylazetidin-1-yl)-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide

I-247	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[2.2.2]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1)
I-248	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[2.2.2]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2)
I-249	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,2-dimethylpiperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-250	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-(morpholin-4-yl)-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-251	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(4-hydroxy-2-methoxy-5-methylnicotinoyl)octahydro-1H-cyclopenta[b]pyrazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1, cis)
I-252	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(4-hydroxy-2-methoxy-5-methylnicotinoyl)octahydro-1H-cyclopenta[b]pyrazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2, cis)

I-253	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-2-(2-oxopyrrolidin-1-yl)-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-254	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(1-cyanocyclopropyl)-6-ethyl-7-[4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-255	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-[(2-methoxyethyl)(methyl)amino]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-256	<i>rel</i> -N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-[(1R,4R)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2)
I-257	<i>rel</i> -N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-[(1R,4R)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1)
I-258	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-259	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-(2-methoxy-5-methylpyridine-3-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide

I-260	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(2S)-2-ethynyl-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-261	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-(4-hydroxy-2-methoxy-5-methylpyridine-3-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-262	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-methyl-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-263	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-2-(piperazin-1-yl)-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-264	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-[(2-hydroxyethyl)(methyl)amino]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-265	2-{7-[(1S,6S)-5-(1,3-benzoxazole-7-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-(dimethylamino)-6-ethyl-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide
I-266	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-[(2R,3S)-3-hydroxybutan-2-yl]amino}-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide

I-267	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-{methyl[(1r,3r)-3-methoxycyclobutyl]amino}-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-268	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-2-(1H-pyrazol-4-yl)-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-269	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-{[(2S)-2-methoxypropyl](methyl)amino}-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-270	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-[(3R)-3-hydroxypyrrolidin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-271	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-[(3S)-3-hydroxypyrrolidin-1-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-272	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-2-(1,3-thiazol-5-yl)-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-273	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-{4-hydroxy-5-methyl-2-[(1-methyl-1H-pyrazol-4-yl)oxy]pyridine-3-carbonyl}-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide

I-274	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-(4-hydroxy-2,5-dimethoxypyridine-3-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-275	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-7-[(1S,6S)-5-(2-ethoxy-4-hydroxy-5-methylpyridine-3-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-6-ethyl-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-276	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(3-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-3-azabicyclo[4.1.0]heptan-6-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1, trans)
I-277	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(3-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-3-azabicyclo[4.1.0]heptan-6-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2, trans)
I-278	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)hexahydrofuro[3,4-b]pyrazin-1(2H)-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1, trans)
I-279	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)hexahydrofuro[3,4-b]pyrazin-1(2H)-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2, trans)
I-280	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{7-[(1S,6S)-5-[5-(difluoromethyl)-4-hydroxy-2-methoxypyridine-3-carbonyl]-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-(dimethylamino)-6-ethyl-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide

I-281	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{7-[(1S,6S)-5-[2-(difluoromethoxy)-4-hydroxy-5-methylpyridine-3-carbonyl]-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-(dimethylamino)-6-ethyl-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-282	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-[4-hydroxy-2-(2-methoxyethoxy)-5-methylpyridine-3-carbonyl]-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-283	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-(2-methoxypyridin-4-yl)-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-284	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(3,6-dihydro-2H-pyran-4-yl)-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-285	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-[(morpholin-4-yl)methyl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-286	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{7-[(1S,6S)-5-(5-cyclopropyl-4-hydroxy-2-methoxypyridine-3-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-(dimethylamino)-6-ethyl-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-287	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-[4-hydroxy-2-methoxy-5-(oxolan-3-yl)pyridine-3-carbonyl]-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide

I-288	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-[(3-hydroxycyclopentyl)(methyl)amino]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-289	N-(2-chloro-4-methoxyphenyl)-2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-290	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-{2-oxa-6-azaspiro[3.4]octan-6-yl}-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-291	<i>rac</i> -N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-(6,6-difluoro-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)octahydro-1H-cyclopenta[b]pyrazin-1-yl)-2-(dimethylamino)-6-ethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (racemic mixture, trans)
I-292	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[2-(dimethylamino)-6-ethyl-7-[(1S,6S)-5-[4-hydroxy-2-methoxy-5-(methoxymethyl)pyridine-3-carbonyl]-2,5-diazabicyclo[4.2.0]octan-2-yl]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl]acetamide
I-293	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-[(2-hydroxycyclobutyl)(methyl)amino]-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-294	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)hexahydrofuro[3,4-b]pyrazin-1(2H)-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1, cis)

I-295	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)hexahydrofuro[3,4-b]pyrazin-1(2H)-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2, cis)
I-296	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-(6,6-difluoro-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)octahydro-1H-cyclopenta[b]pyrazin-1-yl)-2-(dimethylamino)-6-ethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1, trans)
I-297	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-(6,6-difluoro-4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)octahydro-1H-cyclopenta[b]pyrazin-1-yl)-2-(dimethylamino)-6-ethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2, trans)
I-299	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-[(1S,3S)-3-hydroxycyclopentyl](methyl)amino}-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-300	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-[(1R,3S)-3-hydroxycyclopentyl](methyl)amino}-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-301	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-[(1R,3R)-3-hydroxycyclopentyl](methyl)amino}-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide
I-302	N-[2-chloro-4-(trifluoromethyl)phenyl]-2-{6-ethyl-7-[(1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl]-2-[(1S,3R)-3-hydroxycyclopentyl](methyl)amino}-8-oxo-5H,8H-pyrido[2,3-b]pyrazin-5-yl}acetamide

I-303	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-3-(methoxymethyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1)
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Table 1a

No.	IUPAC Name
I-3a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-ethyl-8-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-9-oxo-2,3,4,9-tetrahydro-6H-pyrano[2,3-b]pyrido[2,3-e]pyrazin-6-yl)acetamide
I-4a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(pyridin-4-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-5a	2-(7-chloro-2-ethyl-3-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-4-oxo-1,5-naphthyridin-1(4H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide
I-14a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-ethyl-3-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-4-oxopyrido[2,3-b]quinoxalin-1(4H)-yl)acetamide
I-15a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxo-2-(1H-pyrazol-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-16a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3,6-diethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-17a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3,6-diethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

I-18a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(hydroxymethyl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-23a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-[1,3]dioxolo[4,5-b]pyrido[2,3-e]pyrazin-5(8H)-yl)acetamide
I-24a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-3,8-dihydrofuro[2,3-b]pyrido[2,3-e]pyrazin-5(2H)-yl)acetamide
I-25a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-5-oxo-2,3-dihydrofuro[2,3-b]pyrido[3,2-e]pyrazin-8(5H)-yl)acetamide
I-28a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-ethyl-3-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-4-oxodipyrido[2,3-b:4',3'-e]pyrazin-1(4H)-yl)acetamide
I-29a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-ethyl-3-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-4-oxodipyrido[2,3-b:3',4'-e]pyrazin-1(4H)-yl)acetamide
I-31a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(oxetan-3-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-32a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-2-(oxetan-3-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-33a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-ethyl-3-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-4-oxo-6,8-dihydrofuro[3,4-b]pyrido[2,3-e]pyrazin-1(4H)-yl)acetamide
I-34a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-((methyl(pyridin-3-yl)amino)methyl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

I-35a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-((pyridin-3-ylamino)methyl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-36a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(((1-methyl-1H-pyrazol-3-yl)amino)methyl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-37a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-((1-methyl-1H-pyrazol-3-yl)amino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-38a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(methyl(1-methyl-1H-pyrazol-3-yl)amino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-39a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(methyl(pyridin-3-yl)amino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-40a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(pyridin-3-ylamino)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-41a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(pyridin-3-yloxy)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-42a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-(methylsulfonyl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-43a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-((1-methyl-1H-pyrazol-3-yl)sulfonyl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-44a	2-(3-acetamido-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide

I-45a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-ethyl-3-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-4,8-dioxo-4,6,7,8-tetrahydro-1H-pyrido[2,3-b]pyrrolo[3,4-e]pyrazin-1-yl)acetamide
I-46a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-ethyl-3-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-(2-methoxypyridin-4-yl)-4,8-dioxo-4,6,7,8-tetrahydro-1H-pyrido[2,3-b]pyrrolo[3,4-e]pyrazin-1-yl)acetamide
I-47a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-ethyl-3-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-7-(2-methoxypyridin-4-yl)-4,6-dioxo-4,6,7,8-tetrahydro-1H-pyrido[2,3-b]pyrrolo[3,4-e]pyrazin-1-yl)acetamide
I-48a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-ethyl-3-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-4,6-dioxo-4,6,7,8-tetrahydro-1H-pyrido[2,3-b]pyrrolo[3,4-e]pyrazin-1-yl)acetamide
I-49a	5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-N-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazine-3-carboxamide
I-50a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-3-(pyrrolidine-1-carbonyl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-55a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxo-2-(prop-1-yn-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-56a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-2-(2-methylprop-1-en-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-58a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-cyano-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-59a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2,2-difluoro-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-[1,3]dioxolo[4,5-b]pyrido[2,3-e]pyrazin-5(8H)-yl)acetamide

I-60a	(Z)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(3-methoxyprop-1-en-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-61a	(E)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-(3-methoxyprop-1-en-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-62a	(Z)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-(3-methoxyprop-1-en-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-64a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(2,2-difluorovinyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-65a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(1,2,2-trifluorovinyl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-66a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3-(2,2-difluorovinyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-67a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-3-(1,2,2-trifluorovinyl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-68a	(E)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(3-methoxy-2-methylprop-1-en-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-69a	(E)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-(3-methoxy-2-methylprop-1-en-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-70a	(E)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-3-(3,3,3-trifluoroprop-1-en-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

I-71a	(E)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(3,3,3-trifluoroprop-1-en-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide
I-72a	<i>rac</i> -2-(2-(cyclopropyl(methyl)amino)-6-ethyl-7-(-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (racemic mixture, trans)
I-73a	<i>rac</i> -2-(2-(cyclopropylamino)-6-ethyl-7-(-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (racemic mixture, trans)
I-74a	<i>rac</i> -2-(2-(azetidin-1-yl)-6-ethyl-7-(-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (racemic mixture, trans)
I-75a	<i>rac</i> -2-(6-ethyl-7-(-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(methylamino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (racemic mixture, trans)
I-76a	<i>rac</i> -2-(2-(bis(methyl-d3)amino)-6-ethyl-7-(-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (racemic mixture, trans)
I-77a	<i>rac</i> -2-(2-(cyclobutylidenemethyl)-6-ethyl-7-(-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (racemic mixture, trans)
I-78a	<i>rac</i> -2-(6-ethyl-7-(-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-methoxy-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (racemic mixture, trans)
I-79a	<i>rac</i> -2-(2-(cyclopropyl-6-ethyl-7-(-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (racemic mixture, trans)

I-80a	<i>rac</i> -2-(6-ethyl-7-(-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(((1 <i>r</i> ,3 <i>R</i>)-3-methoxycyclobutyl)(methylamino)-3-methyl-8-oxopyrido[2,3- <i>b</i>]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (racemic mixture, trans)
I-81a	<i>rac</i> -2-(6-ethyl-7-(-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxo-2-(pyrrolidin-1-yl)pyrido[2,3- <i>b</i>]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (racemic mixture, trans)
I-82a	<i>rac</i> -2-(7-ethyl-6-(-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-methyl-5-oxopyrido[2,3- <i>b</i>]thieno[3,2- <i>e</i>]pyrazin-8(5H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (racemic mixture, trans)
I-83a	<i>rac</i> -2-(6-ethyl-7-(-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-methyl-8-oxopyrido[2,3- <i>b</i>]thiazolo[4,5- <i>e</i>]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (racemic mixture, trans)
I-84a	<i>rac</i> -2-(6-ethyl-7-(-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-1-methyl-8-oxo-1,2,3,8-tetrahydro-5H-pyrido[2,3- <i>b</i>]pyrrolo[2,3- <i>e</i>]pyrazin-5-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (racemic mixture, trans)
I-85a	<i>rac</i> -2-(2-(dimethylamino)-6-ethyl-7-(-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-3-methyl-8-oxopyrido[2,3- <i>b</i>]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (racemic mixture, trans)
I-86a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3-(dimethylamino)-7-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-5-oxopyrido[3,2- <i>e</i>][1,2,4]triazin-8(5H)-yl)acetamide
I-87a	<i>rac</i> -N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3-(dimethylamino)-7-ethyl-6-(-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-5-oxopyrido[3,2- <i>e</i>][1,2,4]triazin-8(5H)-yl)acetamide (racemic mixture, trans)

I-89a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3-(cyclobutylidenemethyl)-7-ethyl-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-5-oxopyrido[3,2-e][1,2,4]triazin-8(5H)-yl)acetamide
I-91a	2-(2-(dimethylamino)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide
I-95a	N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(methyl(methyl-d ₃)amino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

4. *Pharmaceutical compositions, methods of treatment and uses of compounds*

[00223] In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In a further embodiment, the composition comprises at least two pharmaceutically acceptable carriers, such as those described herein. The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, parenteral administration (e.g. by injection, infusion, transdermal or topical administration), and rectal administration, in particular oral administration. Topical administration may also pertain to inhalation or intranasal application. The pharmaceutical compositions of the present invention can be made up in a solid form (including, without limitation, capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including, without limitation, solutions, suspensions or emulsions). Tablets may be either film coated or enteric coated according to methods known in the art. Typically, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with one or more of:

- a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;
- b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethylene glycol; for tablets also
- c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

- d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and
- e) absorbents, colorants, flavors and sweeteners.

[00224] Typical approaches to solubilize compounds for parenteral administration are the optimization of the pH or the use of co-solvents (*e.g.* PEG300, PEG400, propylene glycol, or ethanol). If these approaches are, for any reason, not feasible, the use of surfactants may be considered (*e.g.* Tween® 80 or Cremophor EL®). Cyclodextrins are established as safe solubilizing agents. Compounds with a high solubility in natural oils may be solubilized in parenteral fat emulsions.

[00225] There is also provided a pharmaceutical composition comprising a compound of Formula I, I', or I'' as described herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

Uses

[00226] The compounds of Formula I, I', or I'' of the present invention in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, *e.g.* WRN inhibiting properties, *e.g.* as indicated in vitro tests as provided in the next sections, and are therefore indicated for therapy, or for use as research chemicals, *e.g.* as a chemical probe, and as tool compounds.

[00227] Also provided is a compound of Formula I, I', or I'', as described herein. Said compound can be used as a research chemical, a compound herein comprising an added biotin moiety, for example a tool compound or chemical probe, in particular for research on WRN. In another embodiment there is provided the use of a compound of Formula I, I', or I'', as described herein, as a research chemical, for example tool compound or chemical probe, in particular for research on WRN.

[00228] There is also provided a compound of Formula I, I', or I'' as described herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer. Cancers that may be treated by WRN inhibition include cancers that are characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). In particular, a compound of Formula I, I', or I'' as described herein, or a pharmaceutically acceptable salt thereof, may be useful in the treatment

of a cancer that is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

[00229] There is also provided a compound of Formula I, I', or I'' as described herein, or a pharmaceutically acceptable salt thereof, for use as a medicament. In particular, said use is:

- for the treatment of a disease that is treated by WRN inhibition,
- for the treatment of cancer,
- for the treatment of cancer that is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR),
- for the treatment of cancer that is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), such as colorectal, gastric, prostate, endometrial, adrenocortical, uterine, cervical, esophageal, breast, kidney and ovarian cancer,
- for the treatment of cancer that is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) is selected from colorectal, gastric, prostate and endometrial cancer, or
- for the treatment of cancer wherein the cancer characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) is selected from uterine corpus endometrial carcinoma, colon adenocarcinoma, stomach adenocarcinoma, rectal adenocarcinoma, adrenocortical carcinoma, uterine carcinosarcoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, esophageal carcinoma, breast carcinoma, kidney renal clear cell carcinoma, prostate cancer and ovarian serous cystadenocarcinoma.

[00230] There is also provided a method of:

- modulating WRN activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of Formula I, I', or I'' as described herein, or a pharmaceutically acceptable salt thereof,

- inhibiting WRN in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of Formula I, I', or I'' as described herein, or a pharmaceutically acceptable salt thereof,
- treating a disorder or disease which can be treated by WRN inhibition in a subject, comprising administering to the subject a therapeutically effective amount of the compound of Formula I, I', or I'' as described herein, or a pharmaceutically acceptable salt thereof,
- treating cancer in a subject, comprising administering to the subject a therapeutically effective amount of the compound of Formula I, I', or I'' as described herein, or a pharmaceutically acceptable salt thereof,
- treating cancer in a subject, comprising administering a compound of Formula I, I', or I'' as described herein, wherein the cancer is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). In particular, the cancer characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) is selected from colorectal, gastric, prostate, endometrial, adrenocortical, uterine, cervical, esophageal, breast, kidney and ovarian cancer. More particularly, the cancer characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) is selected from colorectal, gastric, prostate and endometrial cancer. Examples include uterine corpus endometrial carcinoma, colon adenocarcinoma, stomach adenocarcinoma, rectal adenocarcinoma, adrenocortical carcinoma, uterine carcinosarcoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, esophageal carcinoma, breast carcinoma, kidney renal clear cell carcinoma, prostate cancer and ovarian serous cystadenocarcinoma.

[00231] There is also provided the use of a compound of Formula I, I', or I'' as described herein, or a pharmaceutically acceptable salt thereof:

- in therapy,
- in the manufacture of a medicament,

- in the manufacture of a medicament for the treatment of cancer. In particular, said cancer is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR),
- in the manufacture of a medicament for treatment of a disease which may be treated by WRN inhibition,

wherein in particular, the cancer is characterized by microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), for example colorectal, gastric, prostate, endometrial, adrenocortical, uterine, cervical, esophageal, breast, kidney and ovarian cancer, in particular, colorectal, gastric, prostate or endometrial cancer, or uterine corpus endometrial carcinoma, colon adenocarcinoma, stomach adenocarcinoma, rectal adenocarcinoma, adrenocortical carcinoma, uterine carcinosarcoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, esophageal carcinoma, breast carcinoma, kidney renal clear cell carcinoma and ovarian serous cystadenocarcinoma.

[00232] In some embodiments, the subject has or is identified as having a microsatellite instable (MSI-H) cancer, e.g., in reference to a control, e.g., a normal, subject. In one embodiment, the subject has MSI-H advanced solid tumors, a colorectal cancer (CRC), endometrial, uterine, stomach or other MSI-H cancer. In some embodiments, the subject has a colorectal (CRC), endometrial or stomach cancer, which cancer has or is identified as having a microsatellite instability (MSI-H), e.g., in reference to a control, e.g., a normal, subject. Such identification techniques are known in the art.

Forms

[00233] Depending on the choice of the starting materials and procedures, the compounds can be present in the form of one of the possible stereoisomers or as mixtures thereof, for example as pure optical isomers, or as stereoisomer mixtures, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. The present invention is meant to include all such possible stereoisomers, including racemic mixtures, diastereomeric mixtures and optically pure forms. Optically active (R)- and (S)-stereoisomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted

cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

[00234] Any formula given herein is intended to represent unlabeled forms as well as isotopically labeled forms of the compounds, in addition to the deuteration specifically claimed in Formula I, I', or I''. Isotopically labeled compounds have structures depicted by the formulae given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Isotopes that can be incorporated into compounds of the invention include, for example, isotopes of hydrogen.

[00235] Further, incorporation of certain isotopes, particularly deuterium (i.e., 2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index or tolerability. It is understood that deuterium in this context is regarded as a substituent of a compound of the present invention. The concentration of deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted as being deuterium, such compound has 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 incorporation), 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). It should be understood that the term "isotopic enrichment factor" can be applied to any isotope in the same manner as described for deuterium.

[00236] Other examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as 3H , 11C , 13C , 14C , 15N , 18F , 31P , 32P , 35S , 36Cl , 123I , 124I , and 125I , respectively. Accordingly it should be understood that the invention includes compounds that incorporate one or more of any of the aforementioned isotopes, including for example, radioactive isotopes, such as 3H and 14C , or those into which non-radioactive isotopes, such as 2H and 13C are present. Such

isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds of the present invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

[00237] A “compound of the present invention” or a “compound of Formula I, I’, or I’” includes a zwitterion thereof, a non-zwitterion thereof (non-charged form), or a pharmaceutically acceptable salt of said zwitterionic or non-zwitterionic form thereof. “Zwitterion” or “zwitterionic form” means a compound containing both positive and negatively charged functional groups.

[00238] The term “cancer” refers to a disease characterized by the rapid and uncontrolled growth of aberrant cells. Cancer cells can spread locally or through the bloodstream and lymphatic system to other parts of the body. Examples of various cancers are described herein and include but are not limited to colorectal, gastric, endometrial, prostate, adrenocortical, uterine, cervical, esophageal, breast, kidney, ovarian cancer and the like.

[00239] The terms “tumor” and “cancer” are used interchangeably herein, e.g., both terms encompass solid and liquid, e.g., diffuse or circulating, tumors. As used herein, the term “cancer” or “tumor” includes premalignant, as well as malignant cancers and tumors.

[00240] “WRN inhibitor” or “WRN helicase inhibitor” as used herein means a compound that inhibits Werner Syndrome RecQ DNA helicase (WRN). The term “WRN” as used herein refers to the protein of Werner Syndrome RecQ DNA helicase. The term “WRN” includes mutants, fragments, variants, isoforms, and homologs of full-length wild-type WRN. In one embodiment, the protein is encoded by the WRN gene (Entrez gene ID 7486; Ensembl ID ENSG00000165392). Exemplary WRN sequences are available at the Uniprot database under accession number Q14191.

[00241] “Disease or condition mediated by WRN” includes a disease or condition, such as cancer, which is treated by WRN inhibition. In particular this can include cancers characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

[00242] “Microsatellite unstable cancer,” “microsatellite instability-high cancer,” “microsatellite high cancer” and “MSI-high cancer,” “MSIhi” and “MSI-H” when used herein, are used interchangeably, and describe cancers that have a high number of alterations in the length of simple repetitive genomic sequences within microsatellites.

[00243] The determination of MSI-H or dMMR tumor status for patients can be performed using, e.g., polymerase chain reaction (PCR) tests for MSI-H status or immunohistochemistry (IHC) tests for dMMR. Methods for identification of MSI-H or dMMR tumor status are described, e.g., in Ryan et al. *Crit Rev Oncol Hematol.* 2017; 116:38-57; Dietmaier and Hofstadter. *Lab Invest* 2001, 81:1453-1456; and Kawakami et al. *Curr Treat Options Oncol.* 2015; 16(7): 30).

[00244] Microsatellite instability can be found in colorectal cancer, gastric cancer and endometrial cancer in particular, but also in adrenocortical, uterine, cervical, esophageal, breast, kidney, prostate and ovarian cancers. Examples of microsatellite high cancers include uterine corpus endometrial carcinoma, colon adenocarcinoma, stomach adenocarcinoma, rectal adenocarcinoma, adrenocortical carcinoma, uterine carcinosarcoma, cervical squamous cell carcinoma, endocervical adenocarcinoma, esophageal carcinoma, breast carcinoma, kidney renal clear cell carcinoma and ovarian serous cystadenocarcinoma.

[00245] A cancer that has “defective mismatch repair” (dMMR) or “dMMR character” includes cancer types associated with documented MLH1, PMS2, MSH2, MSH3, MSH6, MLH3, and PMS1 mutations or epigenetic silencing, microsatellite fragile sites, or other gene inactivation mechanisms, including but not limited to cancers of the lung, breast, kidney, large intestine, ovary, prostate, upper aerodigestive tract, stomach, endometrium, liver, pancreas, haematopoietic and lymphoid tissue, skin, thyroid, pleura, autonomic ganglia, central nervous system, soft tissue, pediatric rhabdoid sarcomas, melanomas and other cancers. A cell or cancer with “defective” mismatch repair has a significantly reduced (e.g., at least about 25%, 30%, 40%, 50%, 60%, 70%, 80% or 90% decrease) amount of mismatch repair. In some cases, a cell or cancer which is defective in mismatch repair will perform no mismatch repair.

[00246] As used herein, the term “pharmaceutical composition” refers to a compound of the invention, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, in a form suitable for oral or parenteral administration.

[00247] As used herein, the term “pharmaceutically acceptable carrier” refers to a substance useful in the preparation or use of a pharmaceutical composition and includes, for example, suitable diluents, solvents, dispersion media, surfactants, antioxidants, preservatives, isotonic agents, buffering agents, emulsifiers, absorption delaying agents, salts, drug stabilizers, binders, excipients, disintegration agents, lubricants, wetting agents, sweetening agents, flavoring agents, dyes, and combinations thereof, as would be known to those skilled in the art (see, for example, Remington The Science and Practice of Pharmacy, 22nd Ed. Pharmaceutical Press, 2013, pp. 1049-1070).

[00248] The terms “synthetic lethality,” and “synthetically lethal” are used to refer to reduced cell viability and/or a reduced rate of cell proliferation caused by a combination of mutations or approaches to cause loss of function (e.g., RNA interference or protein function inhibition) in two or more genes but not by the loss of function of only one of these genes.

[00249] The term “a therapeutically effective amount” of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In some embodiments, the methods of the invention comprise administration of a therapeutically effective amount of a compound herein.

[00250] In one embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviate, prevent and/or ameliorate a condition, or a disorder or a disease (i) mediated by WRN, or (ii) associated with WRN activity, or (iii) characterized by activity (normal or abnormal) of WRN; or (2) reduce or inhibit the activity of WRN.

[00251] In another embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity of WRN, or reducing WRN protein levels.

[00252] As used herein, the term “subject” refers to primates (e.g., humans, male or female), dogs, rabbits, guinea pigs, pigs, rats and mice. In certain embodiments, the subject is a primate, a rat or a mouse. In yet other embodiments, the subject is a human.

[00253] As used herein, the term “inhibit,” “inhibition” or “inhibiting” refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

[00254] As used herein, the term “treat,” “treating” or “treatment” of any disease or disorder refers to alleviating or ameliorating the disease or disorder (i.e., slowing or arresting the development of the disease or at least one of the clinical symptoms thereof); or alleviating or ameliorating at least one physical parameter or biomarker associated with the disease or disorder, including those which may not be discernible to the patient.

[00255] As used herein, the term “prevent,” “preventing” or “prevention” of any disease or disorder refers to the prophylactic treatment of the disease or disorder; or delaying the onset or progression of the disease or disorder.

[00256] As used herein, a subject is “in need of” a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

[00257] As used herein, the term “a,” “an,” “the” and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

[00258] “May join” means joins or does not join.

[00259] “May be replaced by deuterium” means is replaced by deuterium, or is not replaced by deuterium.

[00260] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. “such as”) provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

Isomeric forms

[00261] Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (R)-, (S)- or (R, S)-configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (R)- or (S)- configuration. Substituents at atoms with unsaturated double bonds may, if possible, be present in cis-(Z)- or trans-(E)- form.

[00262] Accordingly, as used herein a compound of the present invention can be in the form of one of the possible stereoisomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (cis or trans) stereoisomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

[00263] Any resulting mixtures of stereoisomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

[00264] Any resulting racemates of compounds of the present invention or of intermediates can be resolved into the optical antipodes by known methods, e.g., by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, e.g., by fractional crystallization of a salt formed with an optically active acid, e.g., tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-O,O'-p-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic compounds of the present invention or racemic intermediates can also be resolved by chiral chromatography, e.g., high pressure liquid chromatography (HPLC) using a chiral adsorbent.

[00265] Compounds of the invention, i.e. compounds of Formula I, I', or I'' that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of Formula I, I', or I'' by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of Formula I, I', or I''

with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of Formula I, I', or I''.

[00266] Furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

[00267] The compounds of the present invention may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the invention embrace both solvated and unsolvated forms. The term “solvate” refers to a molecular complex of a compound of the present invention (including pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term “hydrate” refers to the complex where the solvent molecule is water.

Dosage Forms

[00268] The pharmaceutical composition or combination of the present invention may, for example, be in unit dosage of about 1-1000 mg of active ingredient(s) for a subject of about 50-70 kg.

Combinations

[00269] “Combination” refers to either a fixed combination in one dosage unit form, or a combined administration where a compound of Formula I, I', or I'', or a pharmaceutically acceptable salt thereof, and a combination partner (e.g. another drug as explained below, also referred to as “therapeutic agent” or “co-agent”) may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a cooperative, e.g. synergistic effect. The single components may be packaged in a kit or separately. One or both of the components (e.g., powders or liquids) may be reconstituted or diluted to a desired dose prior to administration. The terms “co-administration” or “combined administration” or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (e.g. a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. The term “pharmaceutical combination” as used herein

means a product that results from the mixing or combining of more than one therapeutic agent and includes both fixed and non-fixed combinations of the therapeutic agents. The term “fixed combination” means that the therapeutic agents, e.g. a compound of the present invention and a combination partner, are both administered to a patient simultaneously in the form of a single entity or dosage.

[00270] The term “non-fixed combination” means that the therapeutic agents, e.g. a compound of the present invention and a combination partner, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more therapeutic agents.

[00271] The combinations described herein can include a compound of Formula I, I', or I'' and one or more additional therapeutic agents, e.g., one or more anti-cancer agents, cytotoxic or cytostatic agents, hormone treatment, vaccines, and/or other immunotherapies. In other embodiments, the combination is further administered or used in combination with other therapeutic treatment modalities, including surgery, radiation, cryosurgery, and/or thermotherapy. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with the treatment.

[00272] There is also provided a combination comprising a compound of Formula I, I', or I'' as described herein, or a pharmaceutically acceptable salt thereof, as described herein, and one or more additional therapeutically active agents. The additional therapeutic agent is, for example, a chemical compound, peptide, antibody, antibody fragment or nucleic acid, which is therapeutically active or enhances the therapeutic activity when administered to a patient in combination with a compound of the present disclosure. In particular, an additional therapeutically active agent is:

- an anti-cancer agent,
- a chemotherapy,
- chemotherapy selected from anastrozole (Arimidex®), bicalutamide (Casodex®), bleomycin sulfate (Blenoxane®), busulfan (Myleran®), busulfan injection (Busulfex®), capecitabine (Xeloda®), N4-pentoxycarbonyl-5-deoxy-5-

fluorocytidine, carboplatin (Paraplatin®), carmustine (BiCNU®), chlorambucil (Leukeran®), cisplatin (Platinol®), cladribine (Leustatin®), cyclophosphamide (Cytosan® or Neosar®), cytarabine, cytosine arabinoside (Cytosar-U®), cytarabine liposome injection (DepoCyt®), dacarbazine (DTIC-Dome®), dactinomycin (Actinomycin D, Cosmegan), daunorubicin hydrochloride (Cerubidine®), daunorubicin citrate,

- liposome injection (DaunoXome®), dexamethasone, docetaxel (Taxotere®), doxorubicin hydrochloride (Adriamycin®, Rubex®), etoposide (Vepesid®), fludarabine phosphate (Fludara®), 5-fluorouracil (Adrucil®, Efudex®), flutamide (Eulexin®), tezacitibine, Gemcitabine (difluorodeoxycytidine), hydroxyurea (Hydrea®), Idarubicin (Idamycin®), ifosfamide (IFEX®), irinotecan (Camptosar®), L-asparaginase (ELSPAR®), leucovorin calcium, melphalan (Alkeran®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), mitoxantrone (Novantrone®), mylotarg, paclitaxel (Taxol®), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (Gliadel®), tamoxifen citrate (Nolvadex®), teniposide (Vumon®), 6-thioguanine, thiotepa, tirapazamine (Tirazone®), topotecan hydrochloride for injection (Hycamptin®), vinblastine (Velban®), vincristine (Oncovin®), and vinorelbine (Navelbine®), in particular fluorouracil (5-FU) and irinotecan (Camptosar®).
- a PD-1 inhibitor,
- an anti-PD-1 antibody molecule,
- a PD-1 inhibitor selected from spartalizumab (Novartis), nivolumab (Bristol-Myers Squibb), pembrolizumab (Merck & Co), pidilizumab (CureTech), MED10680 (Medimmune), cemiplimab (REGN2810, Regeneron), dostarlimab (TSR-042, Tesaro), PF-06801591 (Pfizer), tislelizumab (BGB-A317, Beigene), BGB-108 (Beigene), INCSHR1210 (Incyte), balstilimab (AGEN2035, Agenus), sintilimab (InnoVent), toripalimab (Shanghai Junshi Bioscience), camrelizumab (Jiangsu Hengrui Medicine Co.), AMP-224 (Amplimmune), penpulimab (Akeso Biopharma Inc), zimberelimab (Arcus Biosciences Inc), and prolgolimab (Biocad Ltd),

- spartalizumab, or
- tislelizumab (BGB-A317, Beigene).

[00273] In a further embodiment, the additional therapeutically active agent is the chemotherapy irinotecan (Camptosar®).

[00274] In another embodiment, the additional therapeutically active agent is an inhibitor of PD-1, e.g., human PD-1. In another embodiment, the immunomodulator is an inhibitor of PD-L1, e.g., human PD-L1. In one embodiment, the inhibitor of PD-1 or PD-L1 is an antibody molecule to PD-1 or PD-L1. In another embodiment, the additional therapeutically active agent is an anti-PD-1 antibody molecule.

[00275] In a further embodiment, the PD-1 inhibitor is an anti-PD-1 antibody molecule as described in US 2015/0210769, published on July 30, 2015, entitled “Antibody Molecules to PD-1 and Uses Thereof.”

[00276] In another embodiment, there is provided a combination of a compound of Formula I, I', or I'' or a pharmaceutically acceptable salt thereof, and a chemotherapy, and a PD-1 inhibitor. In particular, the chemotherapy and PD-1 inhibitor are selected from those described above. In some embodiments, the PD-1 inhibitor is pembrolizumab, nivolumab, cemiplimab, dostarlimab, or retifanlimab.

[00277] The above-mentioned compounds, which can be used in combination with a compound of the present invention, can be prepared and administered as described in the art, such as in the documents cited above.

[00278] In one embodiment, the invention provides a product comprising a compound of the present invention and at least one other therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy. In one embodiment, the therapy is the treatment of a disease or condition mediated by WRN. Products provided as a combined preparation include a composition comprising the compound of Formula I, I', or I'' and the other therapeutic agent(s) together in the same pharmaceutical composition, or the compound of the present invention and the other therapeutic agent(s) in separate form, e.g. in the form of a kit.

[00279] In one embodiment, the invention provides a kit comprising two or more separate pharmaceutical compositions, at least one of which contains a compound of the present invention.

In one embodiment, the kit comprises means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is a blister pack, as typically used for the packaging of tablets, capsules and the like.

[00280] The kit of the invention may be used for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit of the invention typically comprises directions for administration.

[00281] In the combination therapies of the invention, the compound of the present invention and the other therapeutic agent may be manufactured and/or formulated by the same or different manufacturers. Moreover, the compound of the present invention and the other therapeutic may be brought together into a combination therapy: (i) prior to release of the combination product to physicians (e.g. in the case of a kit comprising the compound of the present invention and the other therapeutic agent); (ii) by the physician themselves (or under the guidance of the physician) shortly before administration; (iii) in the patient themselves, e.g. during sequential administration of the compound of the present invention and the other therapeutic agent.

[00282] Accordingly, the invention provides the use of a compound of the present invention for treating a disease or condition mediated by WRN, wherein the medicament is prepared for administration with another therapeutic agent. The invention also provides the use of another therapeutic agent for treating a disease or condition mediated by WRN, wherein the medicament is administered with a compound of the present invention.

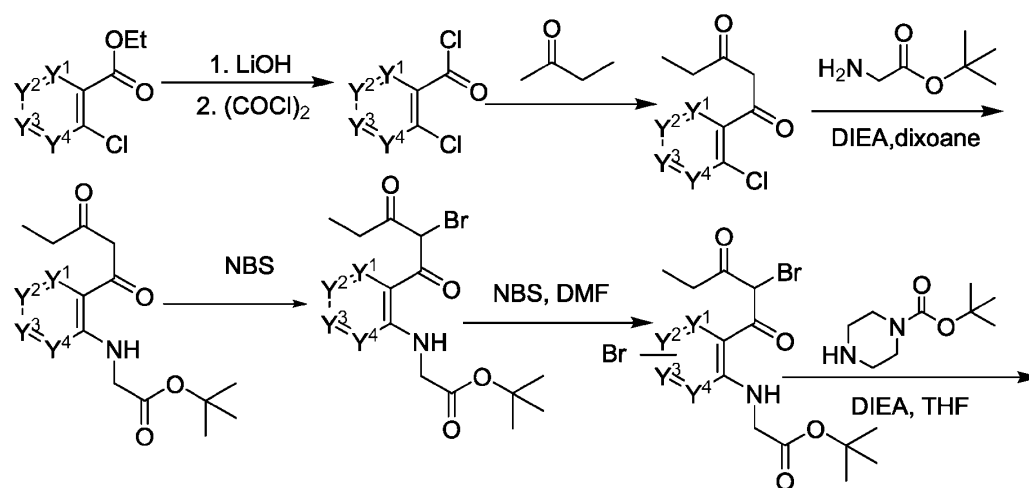
[00283] The invention also provides a compound of the present invention for use in treating a disease or condition mediated by WRN, wherein the compound of the present invention is prepared for administration with another therapeutic agent. The invention also provides another therapeutic agent for use in treating a disease or condition mediated by WRN, wherein the other therapeutic agent is prepared for administration with a compound of the present invention. The invention also provides a compound of the present invention for use in treating a disease or condition mediated by WRN, wherein the compound of the present invention is administered with another therapeutic agent. The invention also provides another therapeutic agent for use in a method of treating a disease or condition mediated by WRN, wherein the other therapeutic agent is administered with a compound of the present invention.

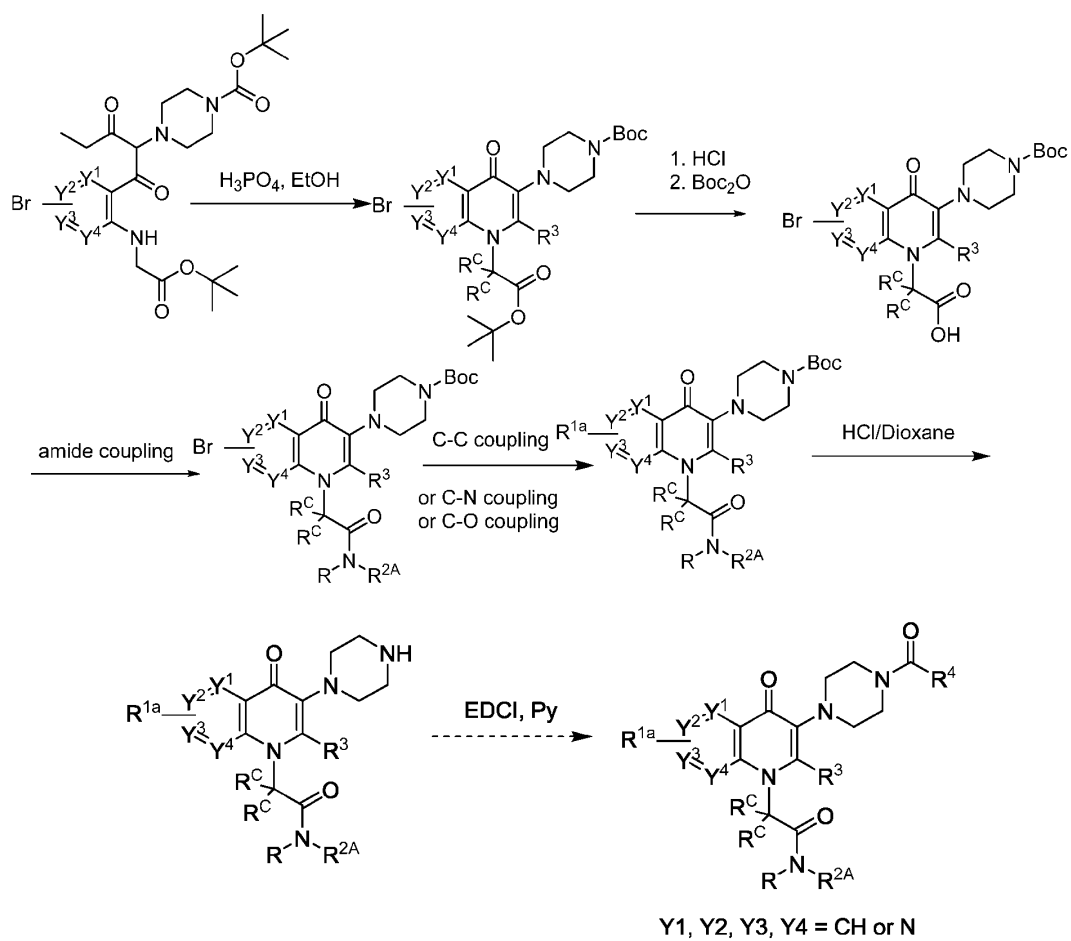
[00284] The invention also provides the use of a compound of the present invention for treating a disease or condition mediated by WRN, wherein the patient has previously (e.g. within 24 hours) been treated with another therapeutic agent. The invention also provides the use of another therapeutic agent for treating a disease or condition mediated by WRN, wherein the patient has previously (e.g. within 24 hours) been treated with compound of the present invention.

5. General synthetic methods of producing compounds of the disclosure

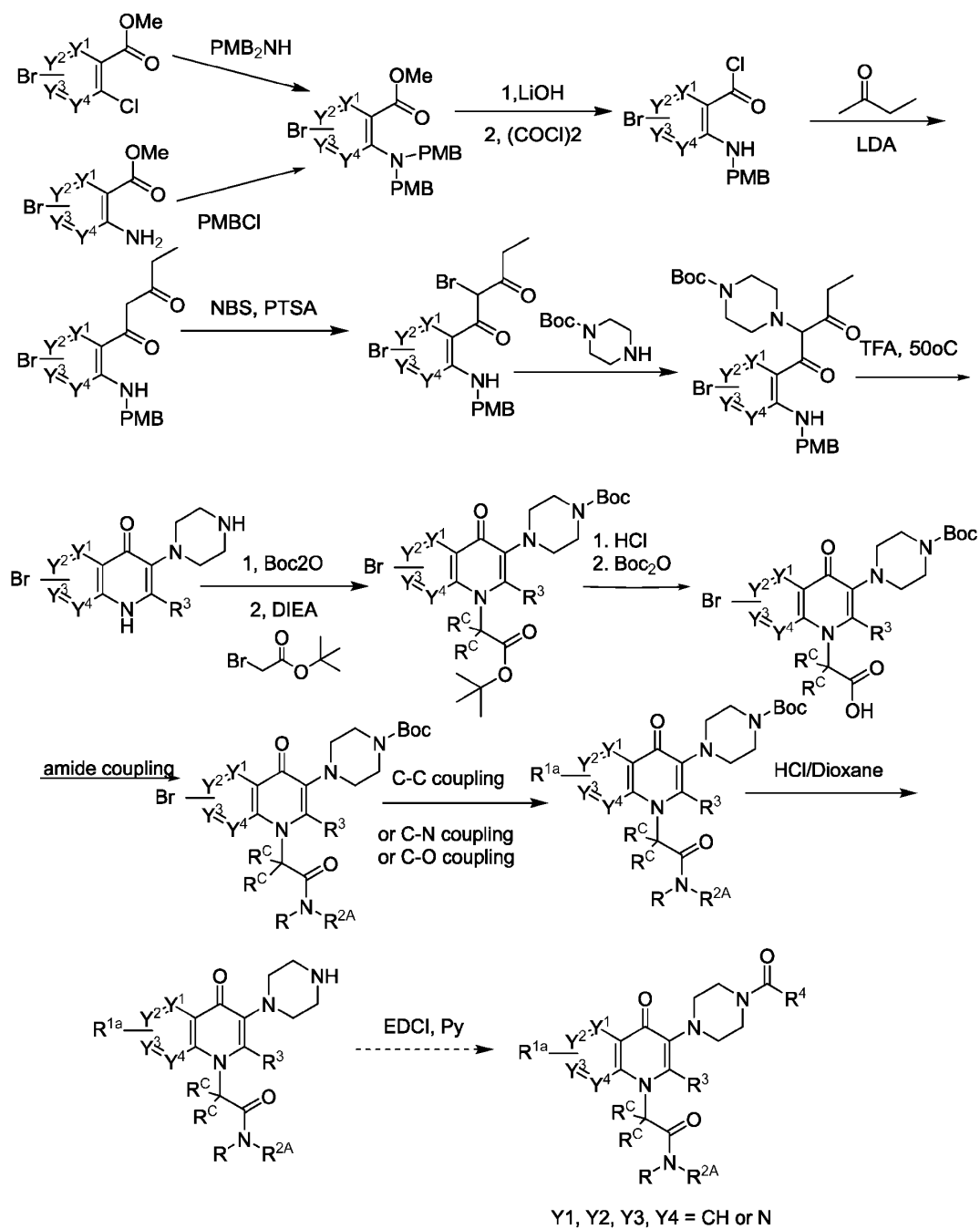
[00285] Compounds of the present invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying synthetic schemes.

Scheme 1

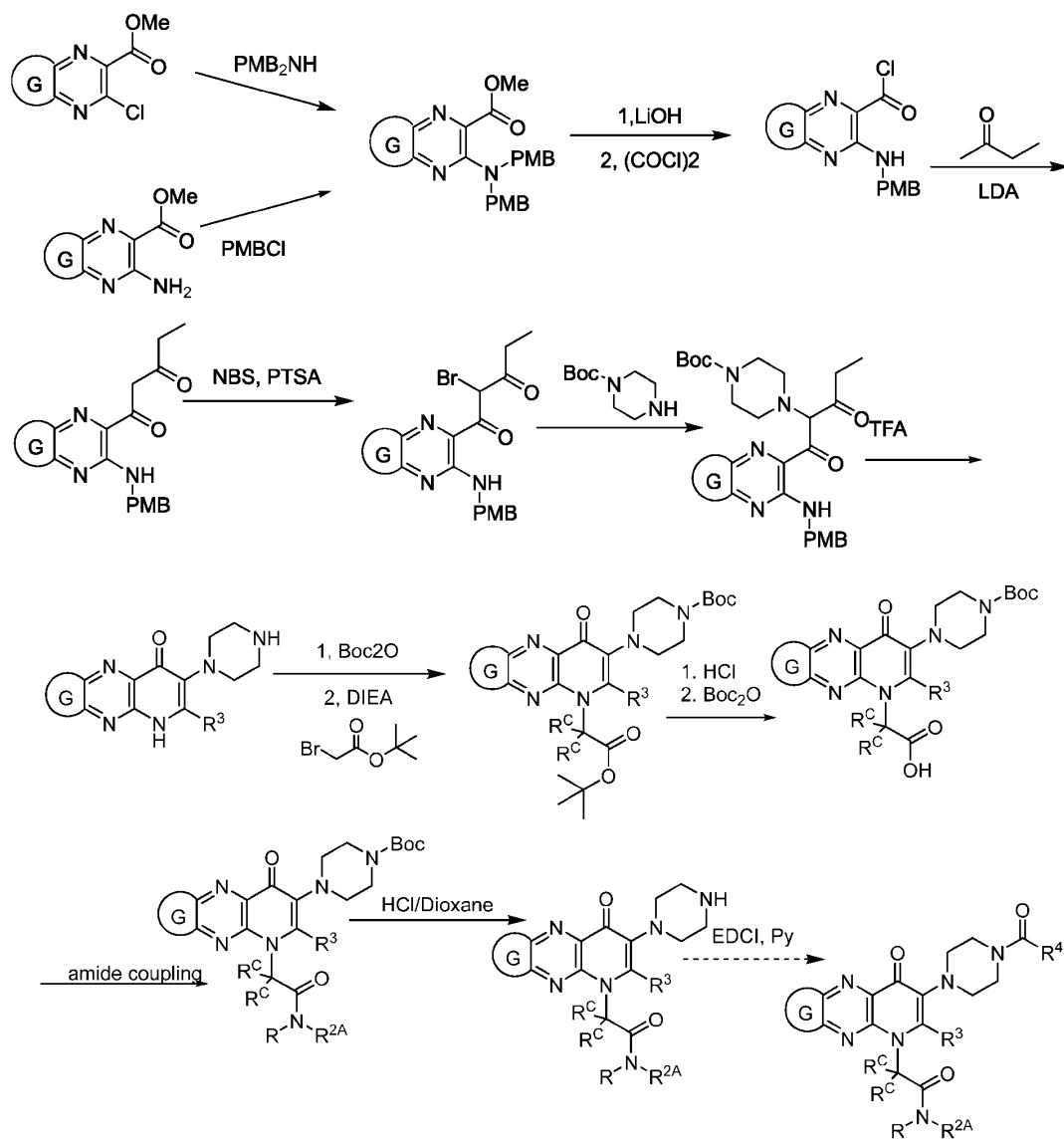




Scheme 2

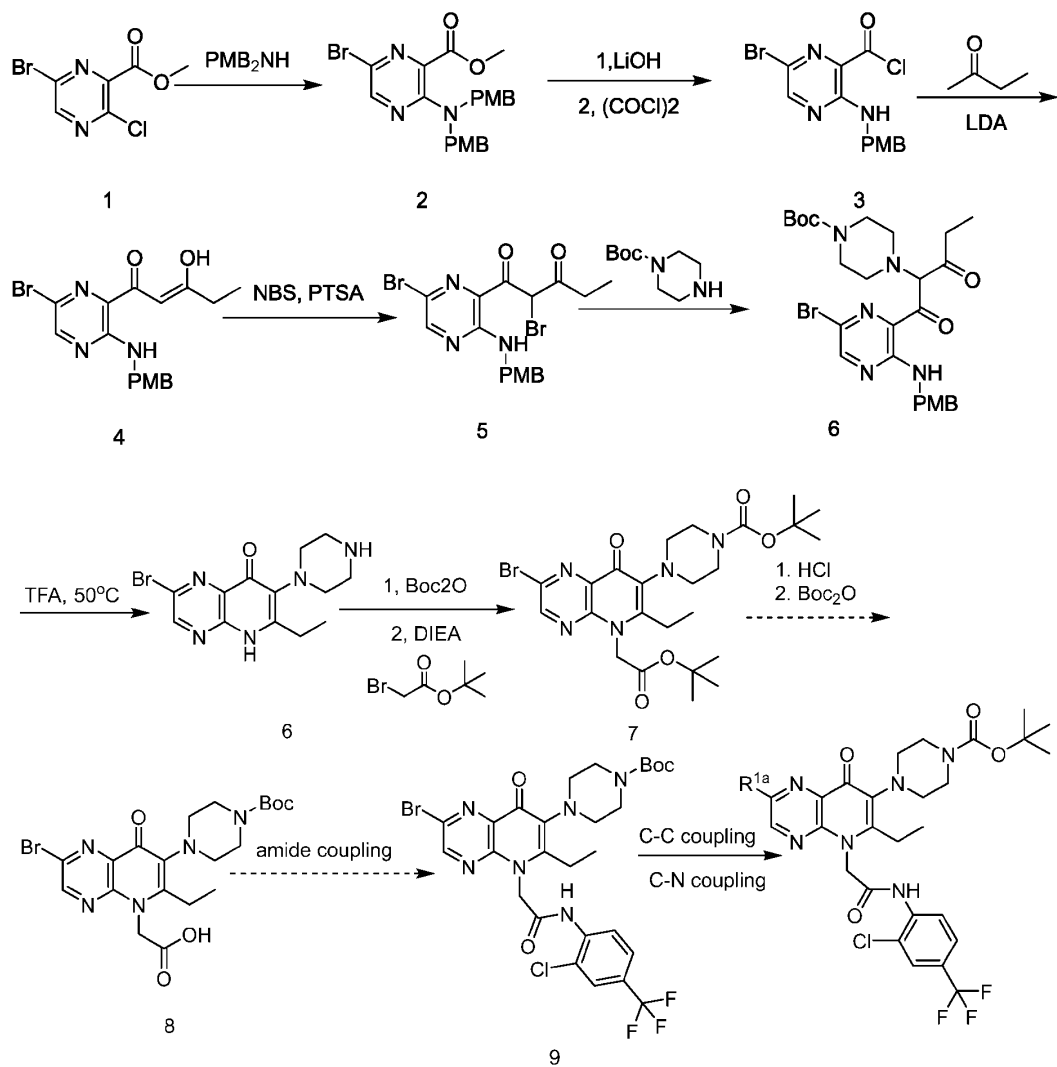


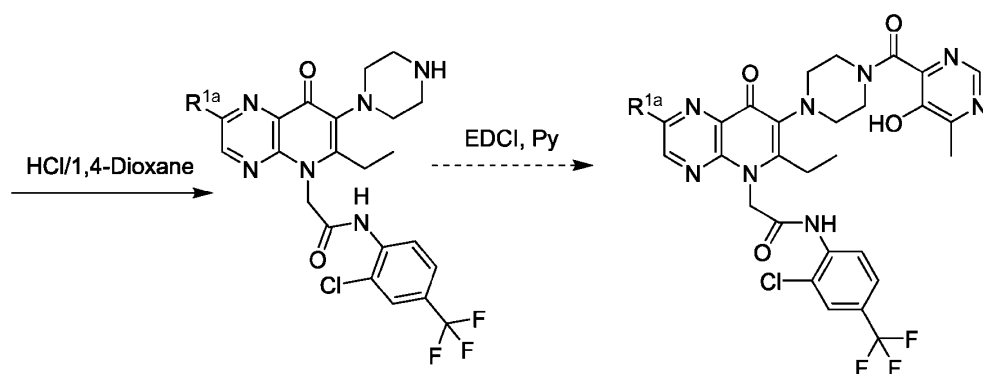
Scheme 3



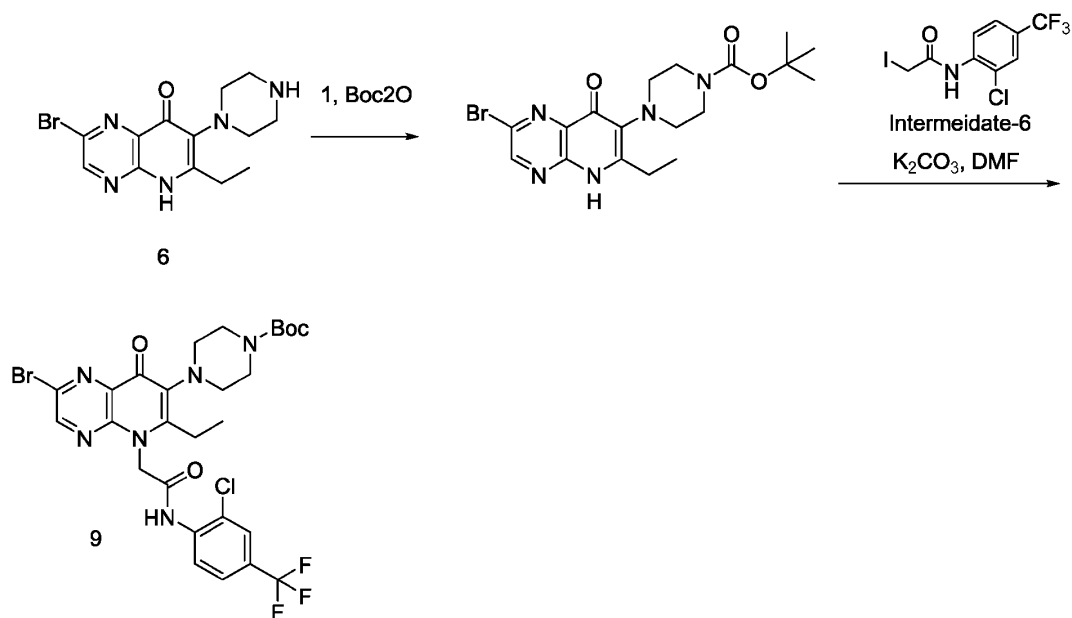
Ring **G**: optionally substituted phenyl, pyridyl or a 5-6 membered aromatic ring, 4-7 membered saturated or partially unsaturated carbocycle or a 4-7 membered saturated or partially unsaturated heterocycle

Scheme 4

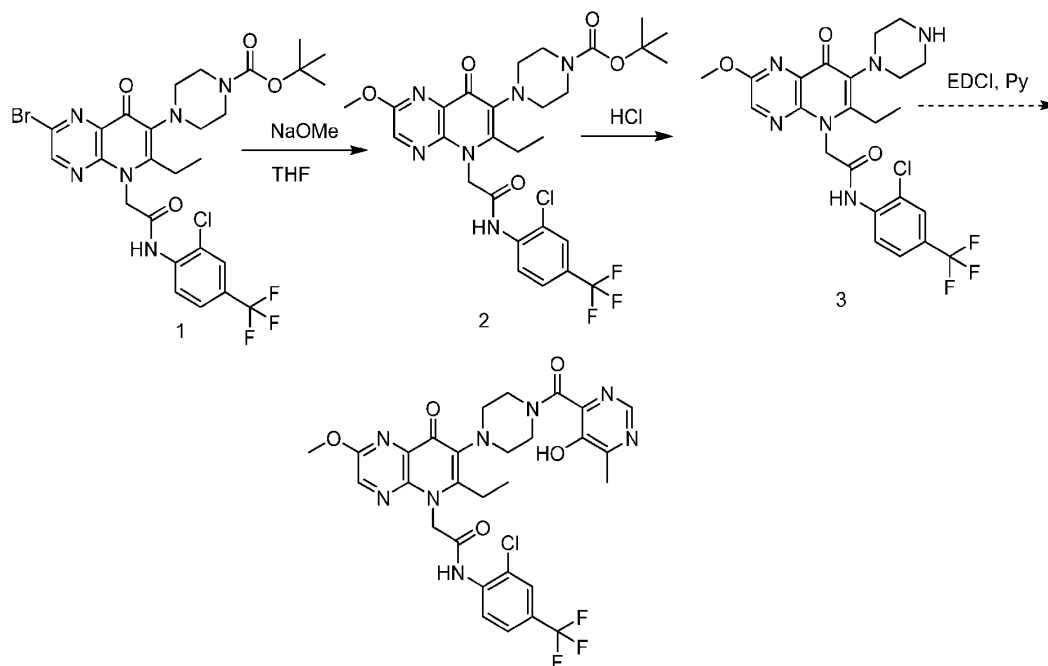




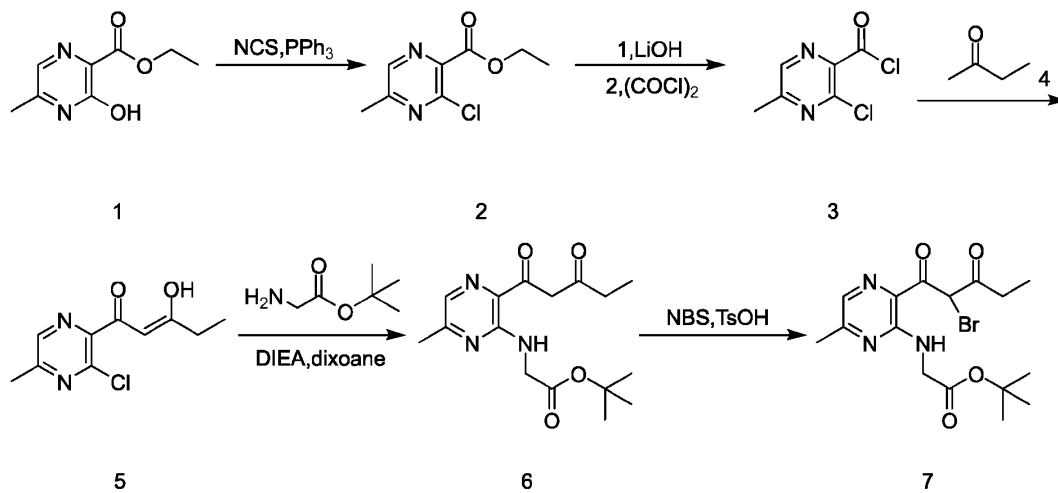
Scheme 5

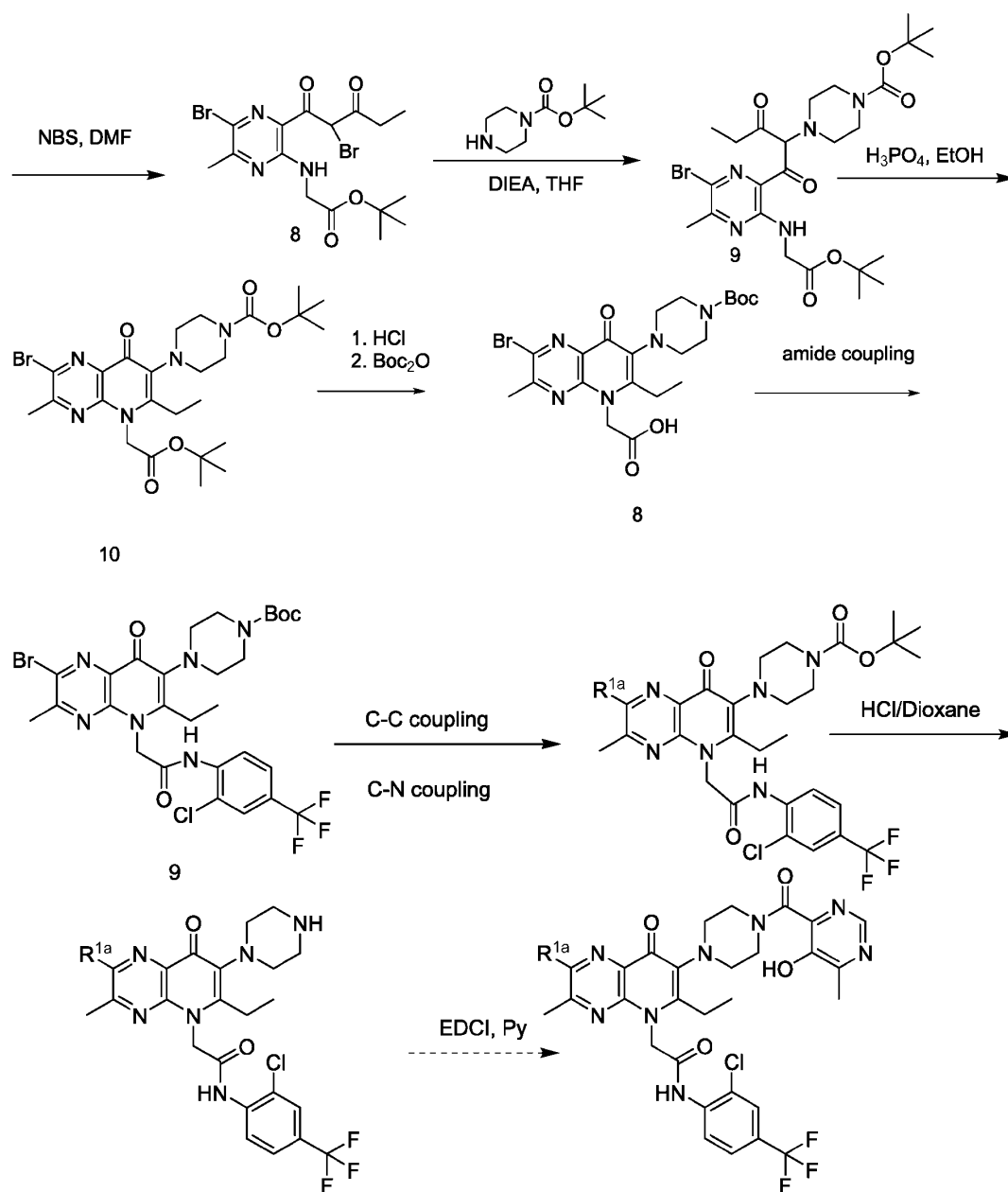


Scheme 6



Scheme 7

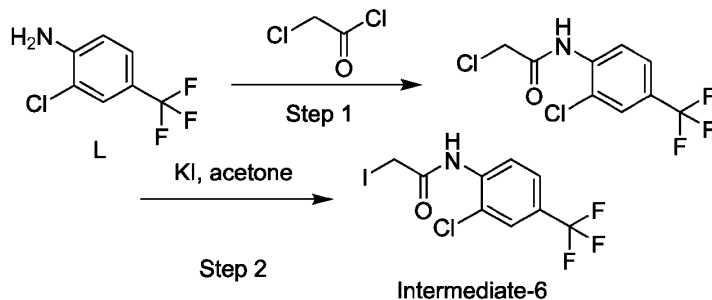




[00286] Synthesis of Intermediate-6 which is representative of R² moieties within the present genus may be prepared as shown below in Scheme 8. Substituted anilines such as **L** may be used in the amide coupling of the above schemes. Alternatively, **L** may be used to furnish Intermediate-

6 as shown below to produce a substrate amenable to nucleophilic substitution to produce compounds of the disclosure.

Scheme 8



[00287] Those having ordinary skill in the art will be able to adapt such synthetic procedures to afford variably substituted compounds of Formula I, I', or I'' for synthesis of the compounds of the disclosure.

EXAMPLES

[00288] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the procedures provided herein. It will be appreciated that, although the methods depict the synthesis of certain compounds of the present disclosure, the methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

[00289] List of abbreviations:

NCS: *N*-chlorosuccinimide

THF: tetrahydrofuran

LiOH·H₂O: Lithium hydroxide monohydrate

(COCl)₂: Oxalyl chloride

DIEA: *N,N*-diisopropylethylamine

NBS: *N*-bromosuccinimide

TsOH·H₂O: 4-methylbenzenesulfonic acid monohydrate

TsOH: 4-Methylbenzenesulfonic acid

H₃PO₄: phosphoric acid

EtOH: ethanol

TFA: trifluoroacetic acid

Boc₂O: Di-tert-butyl dicarbonate

POCl₃: Phosphoryl chloride

HCl: hydrochloric acid

EDCI: *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride

ppm: parts per million

LCMS: liquid chromatography–mass spectrometry

HPLC: high-performance liquid chromatography

NMR: nuclear magnetic resonance

CDCl₃: deuterated chloroform

H₂O: water

DCM: dichloromethane

MeOH: methanol

DMF: *N,N*-dimethyl formamide

EtOAc: ethyl acetate

PE: petroleum ether

Na₂SO₄: sodium sulfate

br: broad

s: singlet

d: doublet

t: triplet

m: multiplet

q: quartet

dq: doublet of quartets

PPh₃: triphenyl phosphine

LDA: Lithium diisopropylamide

ACN: acetonitrile

NH₄HCO₃: ammonium bicarbonate

eq: equivalent

N: normality

aq.: aqueous

M: molar concentration

Boc: tert-butyloxycarbonyl

FA: formic acid

Et₃N: triethylamine

NaOH: sodium hydroxide

N₂: nitrogen

Pd(dppf)Cl₂: bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex

K₃PO₄: tripotassium phosphate

NH₄Cl: ammonium chloride

pH: potential of hydrogen

TLC: thin layer chromatography

CuCN: Copper(I) cyanide

DMA: Dimethylacetamide

NaIO₄: sodium periodate

NaHCO₃: Sodium hydrogen carbonate

NaBH₄: sodium borohydride

K₃PO₄: Tripotassium phosphate anhydrous

Cs₂CO₃: cesium carbonate

CuI: Copper(I) iodide

Pd(PPh₃)₂Cl₂: dichloropalladium triphenylphosphane

Rose Bengal: dipotassium 4,5,6,7-tetrachloro-2',4',5',7'-tetraiodo-3-oxospiro[2-benzofuran-1,9'-xanthene]-3',6'-diolate

Pd(PPh₃)₄: Tetrakis(triphenylphosphine)palladium(0)

NaH: Sodium Hydride

K₂OsO₄·2H₂O: potassium osmate (VI) dihydrate

DAST: Diethylaminosulfur trifluoride

LiOH: Lithium Hydroxide

K₂CO₃: Potassium carbonate, anhydrous

Pd(dppf)Cl₂-CH₂Cl₂: [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane

O₂: Oxygen

DMSO: Dimethyl sulfoxide

LED: light emitting diode

br: broad

s: singlet

d: doublet

t: triplet

m: multiplet

q: quartet

h: hour

PPh₃: triphenyl phosphine

LDA: Lithium diisopropylamide

ACN: acetonitrile

NH₄HCO₃: ammonium bicarbonate

eq: equivalent

N: normality

aq: aqueous

M: molar concentration

Boc: tert-butyloxycarbonyl

FA: formic acid

Et₃N: triethylamine

NaOH: sodium hydroxide

N₂: nitrogen

Pd(dppf)Cl₂: bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex

pH: potential of hydrogen

Co(acac)₂: Cobalt(II) acetylacetonate

Na₂S: sodium sulfide

NH₃: ammonia

CO: carbon monoxide

t-BuOK: potassium t-butoxide

NaBH(OAc)₃: Sodium triacetoxyborohydride

SFC: Supercritical fluid chromatography

PMB: 4-methoxybenzyl

CD₃OD: deuterated methanol

MeMgBr: methylmagnesium bromide

HBr: hydrobromic acid

HI: Hydriodic acid

N₂: nitrogen

DMSO-*d*₆: deuterated dimethyl sulfoxide

P₂S₅: phosphorus pentasulfide

DMAP: 4-dimethylaminopyridine

NMP:

N-methylpyrrolidone

DEA: Diethylamine

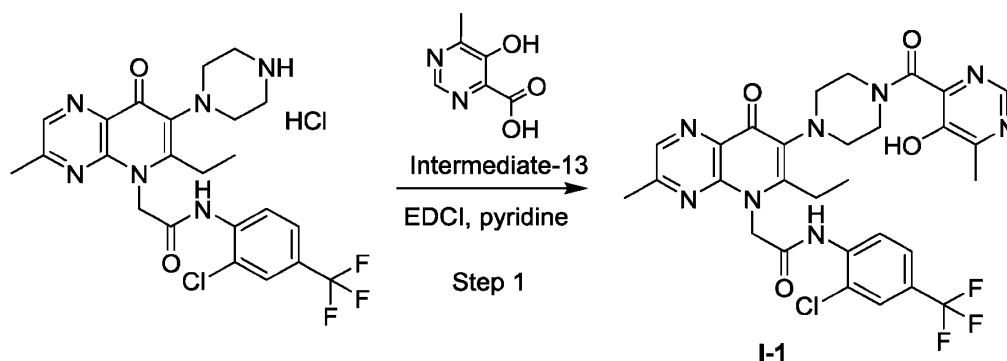
BOP: (Benzotriazolyl)oxytris(dimethylamino)phosphonium hexafluorophosphate

KI: potassium iodide

MTBE: methyl tertiary butyl ether

Example 1: Synthesis of Compounds of the disclosure

[00290] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-1)*



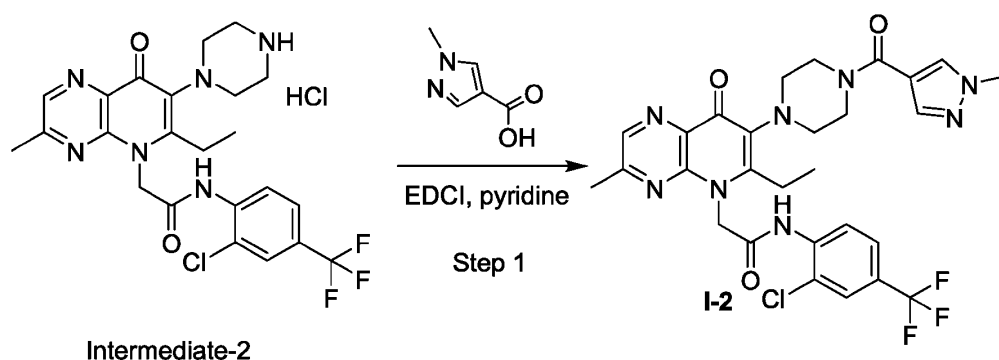
[00291] Step 1: Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00292] To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (27 mg, 0.17 mmol, 1.1 eq) in pyridine (2 mL) was added EDCI (33 mg, 0.17 mmol, 1.1 eq) and the mixture was stirred at room temperature for 0.5 h. Then N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-3-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride (Intermediate-2, prepared according to general methods of the Schemes above) (80 mg, 0.16 mmol, 1.0 eq) was added to the mixture and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and then diluted with H₂O (10 mL). The resulting mixture was adjusted to pH 5 with aq. 1 N HCl solution, extracted with DCM (10 mL*2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, H₂O (10 mmol/L NH₄HCO₃)-ACN) to afford the title compound.

[00293] ¹H NMR (400MHz, CDCl₃) δ ppm 11.82 (br s, 1H), 8.65 (s, 1H), 8.59 (s, 1H), 8.49 (d, 1H), 8.42 (s, 1H), 7.64 (s, 1H), 7.55 (br d, 1H), 5.75 – 5.51 (m, 1H), 5.38 (br s, 2H), 4.79 (br d, 1H), 4.16 – 3.93 (m, 2H), 3.63 – 3.47 (m, 1H), 3.29 (br d, 2H), 3.10 (br d, 1H), 2.92 – 2.74 (m, 2H), 2.71 (s, 3H), 2.57 (s, 3H), 1.36 (t, 3H).

[00294] LCMS: 645.4 [M+H]⁺.

[00295] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-3-methyl-7-(4-(1-methyl-1H-pyrazole-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-2)*

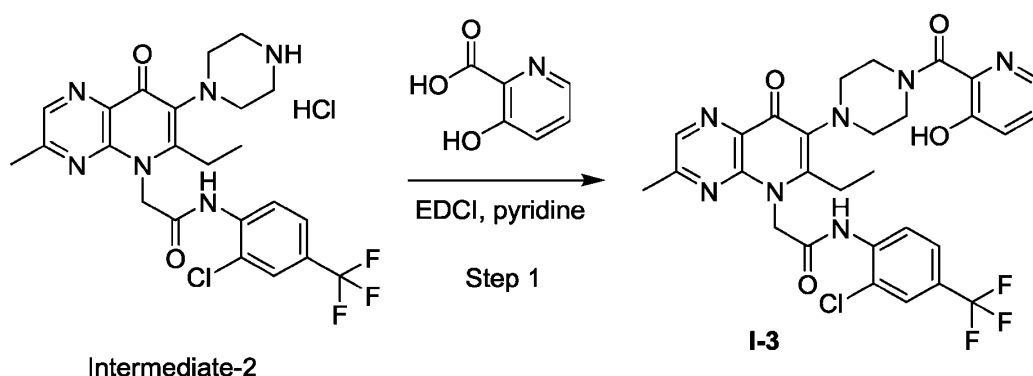


[00296] Step 1. N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-3-methyl-7-(4-(1-methyl-1H-pyrazole-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00297] A solution of 1-methyl-1H-pyrazole-4-carboxylic acid was reacted and worked up according the procedure described for **I-1**.

[00298] LCMS: 617.2 [M+H]⁺.

[00299] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(3-hydroxypicolinoyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-3)*

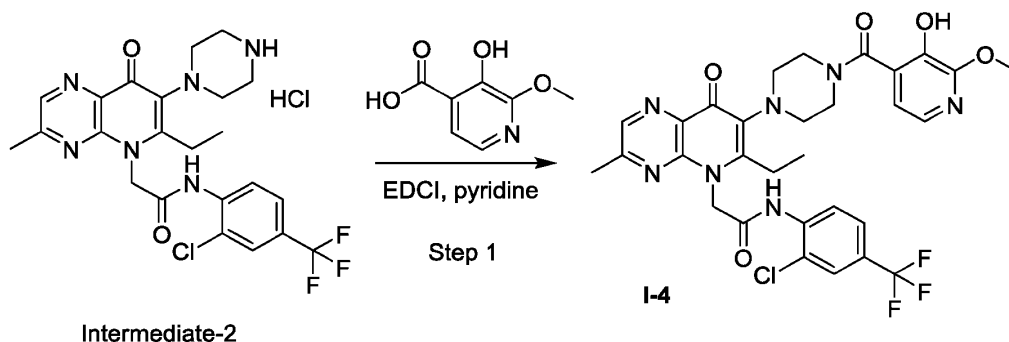


[00300] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(3-hydroxypicolinoyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00301] A solution of 3-hydroxypicolinic acid was reacted and worked up according the procedure described for **I-1**.

[00302] LCMS: 630.2 [M+H]⁺.

[00303] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(3-hydroxy-2-methoxyisonicotinoyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-4)*

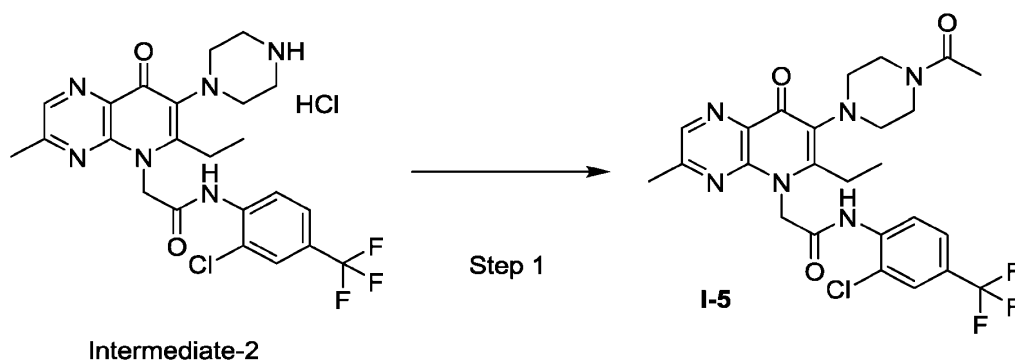


[00304] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(3-hydroxy-2-methoxyisonicotinoyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00305] A solution of 3-hydroxy-2-methoxyisonicotinic acid was reacted and worked up according the procedure described for **I-1**.

[00306] LCMS: 660.4 [M+H]⁺.

[00307] *Synthesis of 2-(7-(4-acetylpiperazin-1-yl)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (I-5)*

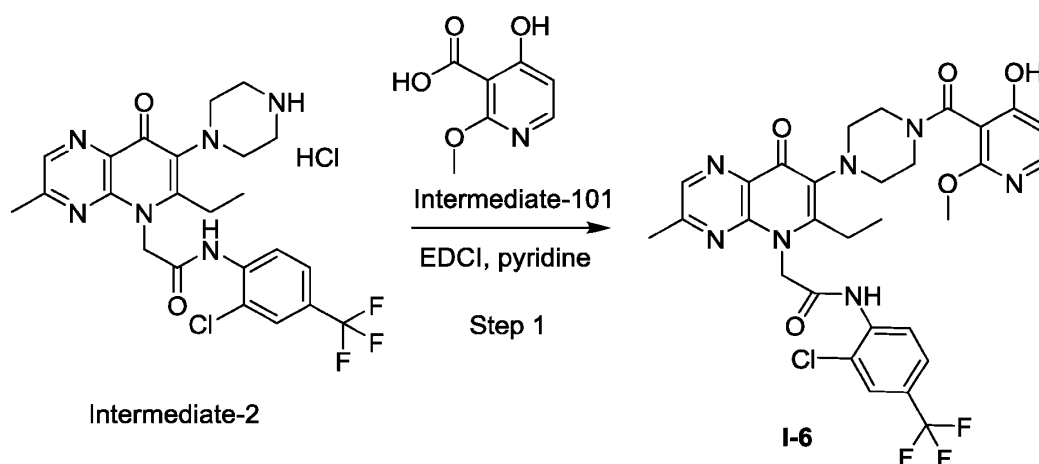


[00308] Step 1. Synthesis of 2-(7-(4-acetylpiperazin-1-yl)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide

[00309] Acetic acid was reacted and worked up according the procedure described for **I-1**.

[00310] LCMS: 551.2 [M+H]⁺.

[00311] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(4-hydroxy-2-methoxynicotinoyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-6)*

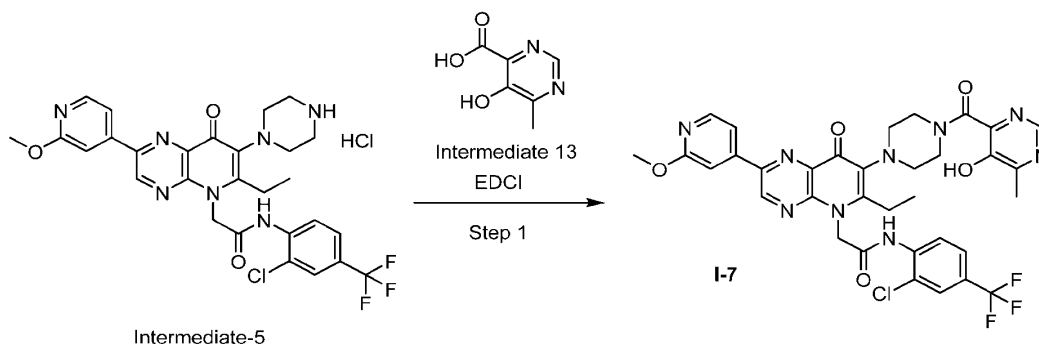


[00312] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(3-hydroxy-2-methoxyisonicotinoyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00313] A solution of 4-hydroxy-2-methoxy-pyridine-3-carboxylic acid (Intermediate-101) was reacted and worked up according to the procedure described for I-1.

[00314] LCMS: 660.2 [M+H]⁺.

[00315] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-methoxypyridin-4-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-7)*



[00316] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-methoxypyridin-4-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00317] To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (44 mg, 0.29 mmol, 8.0 eq) in pyridine (0.5 mL) was added EDCI (55 mg, 0.29 mmol, 8.0 eq) and the resulting mixture was stirred at room temperature for 0.5 h. N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-(2-methoxypyridin-4-yl)-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride (Intermediate-5) (23 mg, 36 μ mol, 1.0 eq) was added to the mixture and the reaction was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00318] **LCMS: 738.2 [M+H]⁺.**

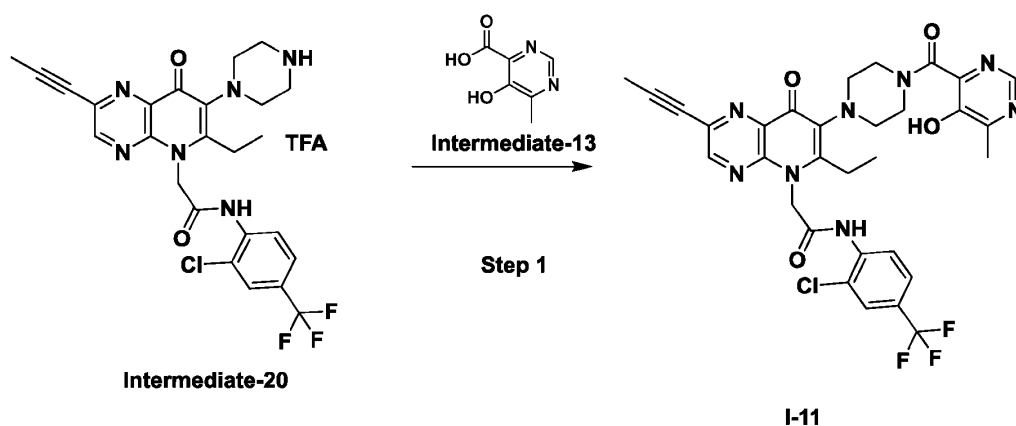
[00319] **¹H NMR (400 MHz, CDCl₃)** δ ppm 11.79 (br s, 1H), 9.08 (s, 1H), 8.65 (s, 1H), 8.59 (s, 1H), 8.50 (d, 1H), 8.32 (d, 1H), 7.69 - 7.63 (m, 2H), 7.54 (br d, 1H), 7.45 (s, 1H), 5.59 (br s, 1H), 5.42 (br s, 2H), 4.79 (br s, 1H), 4.08 - 3.96 (m, 5H), 3.54 (br s, 1H), 3.31 (br s, 2H), 3.11 (br s, 1H), 2.84 (br d, 2H), 2.58 (s, 3H), 1.39 (br t, 3H).

[00320] **Synthesis of (E)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(prop-1-en-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-8):** I-8 was synthesized from Intermediate-3 according to chemistry outlined in scheme 4.

[00321] **Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(prop-1-en-2-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-9):** I-9 was synthesized from Intermediate-3 according to chemistry outlined in scheme 4.

[00322] **Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-cyclopropyl-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-10):** I-10 was synthesized from Intermediate-3 according to chemistry outlined in scheme 4.

[00323] **Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(prop-1-yn-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-11)**



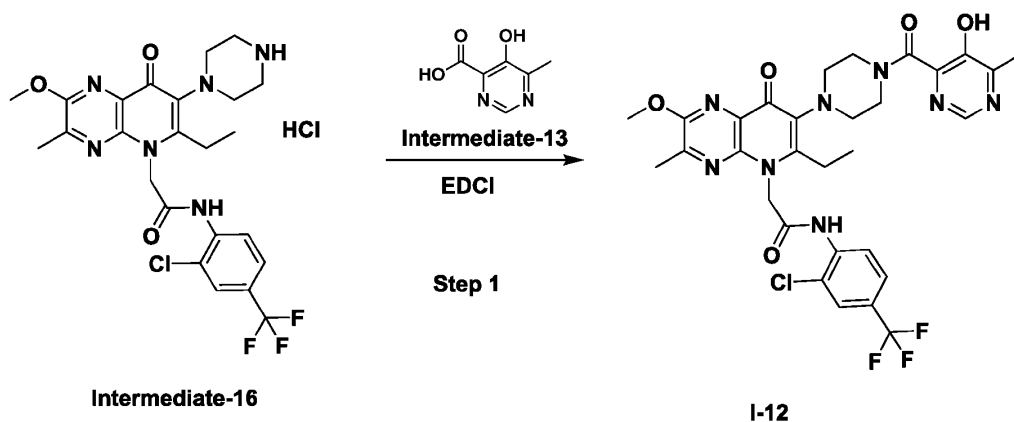
[00324] Step 1: Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(prop-1-yn-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00325] To a solution of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-8-oxo-7-(piperazin-1-yl)-2-(prop-1-yn-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide trifluoroacetate (Intermediate-20) (33 mg, 62 μ mol, 1.0 eq) and 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (19 mg, 0.12 mmol, 2.0 eq) in pyridine (1 mL) was added EDCI (24 mg, 0.12 mmol, 2.0 eq) and then the resulting mixture was stirred at 40 °C for 15 h. The mixture was quenched with H₂O (10 mL) and extracted with EtOAc (20 mL*3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00326] LCMS: 669.4 [M+H]⁺.

[00327] ¹H NMR (400 MHz, CDCl₃) δ ppm 12.05 (s, 1H), 8.67 - 8.59 (m, 3H), 8.51 (br d, 1H), 7.67 (s, 1H), 7.56 (br d, 1H), 5.73 - 5.51 (m, 1H), 5.37 (br d, 2H), 4.88 - 4.67 (m, 1H), 4.07 - 3.95 (m, 2H), 3.62 - 3.44 (m, 1H), 3.37 - 3.22 (m, 2H), 3.17 - 3.04 (m, 1H), 2.90 - 2.73 (m, 2H), 2.60 (s, 3H), 2.15 (s, 3H), 1.39 (br t, 3H).

[00328] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methoxy-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-12)*



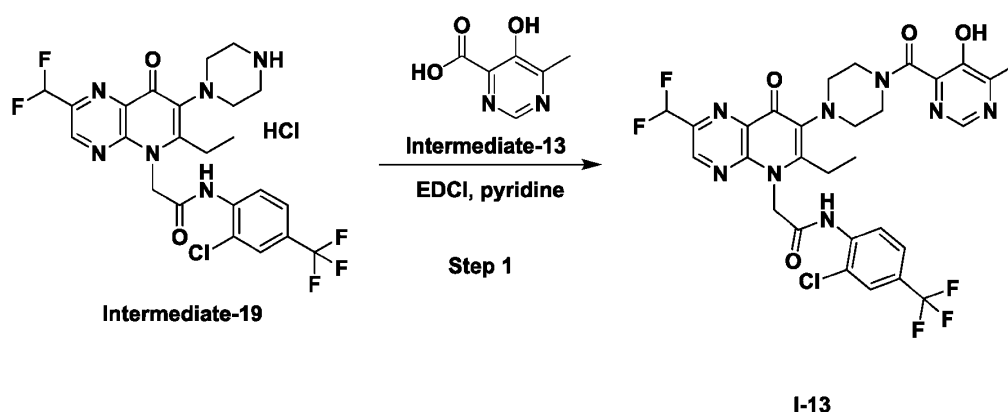
[00329] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methoxy-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00330] To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (22 mg, 0.15 mmol, 3.0 eq) in pyridine (1 mL) was added EDCI (28 mg, 0.15 mmol, 3.0 eq) and it was stirred at room temperature for 0.5 h. Then a solution of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-methoxy-3-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride (Intermediate-16) (26 mg, 48 μ mol, 1.0 eq) in pyridine (1 mL) was added, and the resulting mixture was stirred at room temperature for 3 h. The mixture was concentrated and then purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00331] LCMS: 675.0 [M+H]⁺.

[00332] ¹H NMR (400 MHz, CDCl₃) δ ppm 11.88 (s, 1H), 8.58 (s, 1H), 8.51 (d, 1H), 8.36 (s, 1H), 7.63 (s, 1H), 7.55 (br d, 1H), 5.63 - 5.48 (m, 1H), 5.37 (br s, 2H), 4.86 - 4.69 (m, 1H), 4.17 (s, 3H), 4.09 - 3.98 (m, 2H), 3.60 - 3.46 (m, 1H), 3.33 - 3.20 (m, 2H), 3.16 - 3.03 (m, 1H), 2.91 - 2.70 (m, 2H), 2.61 (s, 3H), 2.57 (s, 3H), 1.34 (br t, 3H).

[00333] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-13)*



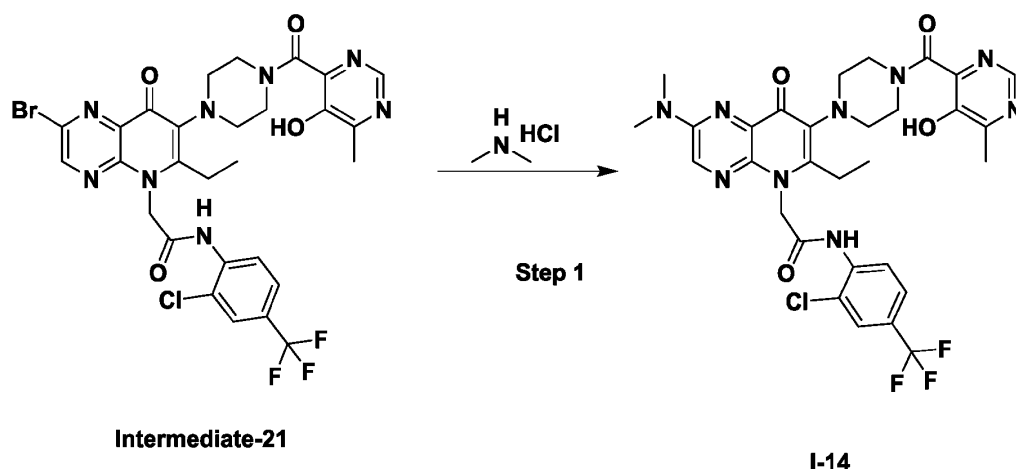
[00334] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00335] To a solution of 5-hydroxy-6-methyl-pyrimidine-4-carboxylic acid (Intermediate-13) (21 mg, 134 μ mol, 6.0 eq) in pyridine (0.5 mL) was added EDCI (26 mg, 134 μ mol, 6.0 eq) and it was stirred at room temperature for 0.5 h. N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethyl)-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride (Intermediate-19) (13 mg, 22 μ mol, 1.0 eq) was added to the mixture and the reaction was stirred at 30 °C for 1 h. The mixture was concentrated under reduced pressure, the residue was purified by reverse phase HPLC (water (0.1% FA)-ACN) to afford the title compound.

[00336] LCMS: 681.2 [M+H]⁺.

[00337] ¹H NMR (400MHz, CDCl₃) δ ppm 11.81 (br s, 1H), 9.00 (s, 1H), 8.60 (s, 1H), 8.52 – 8.44 (m, 2H), 7.68 (s, 1H), 7.55 (br d, 1H), 7.08 – 6.77 (m, 1H), 5.62 (br d, 1H), 5.40 (br s, 2H), 4.80 (br d, 1H), 3.98 (br t, 2H), 3.53 (br s, 1H), 3.31 (br s, 2H), 3.18 – 2.98 (m, 1H), 2.83 (m, 2H), 2.58 (s, 3H), 1.39 (t, 3H).

[00338] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-14)*



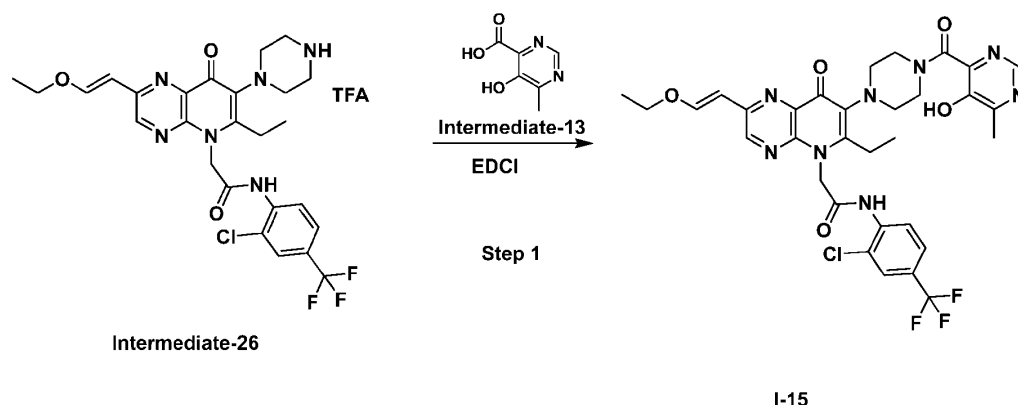
[00339] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00340] To a solution of 2-(2-bromo-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (Intermediate-21) (20 mg, 28 μ mol, 1.0 eq) in 1,4-dioxane (0.5 mL) was added dimethylamine hydrochloride (11 mg, 0.14 mmol, 5.0 eq) and DIEA (22 mg, 0.17 mmol, 6.0 eq). The resulting mixture was stirred at 100 °C for 1 h and then concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00341] LCMS: 674.4 [M+H]⁺.

[00342] ¹H NMR (400 MHz, CDCl₃) δ ppm 11.91 (s, 1H), 8.58 (s, 2H), 8.54 (d, 1H), 8.20 (s, 1H), 7.61 (d, 1H), 7.53 (dd, 1H), 5.53 (br dd, 1H), 5.31 (br s, 2H), 4.84 - 4.68 (m, 1H), 4.05 (dt, 2H), 3.60 - 3.44 (m, 1H), 3.27 (s, 6H), 3.24 (br s, 2H), 3.15 - 3.00 (m, 1H), 2.88 - 2.67 (m, 2H), 2.56 (s, 3H), 1.34 (t, 3H).

[00343] *Synthesis of (E)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(2-ethoxyvinyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-15)*



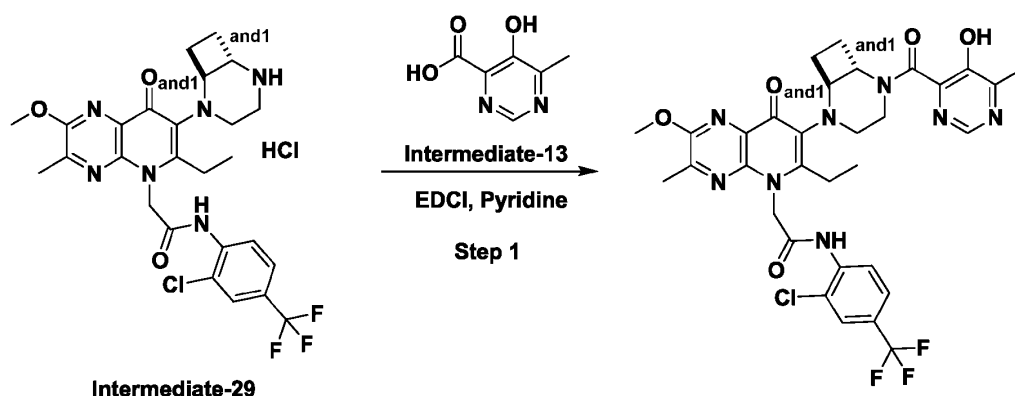
[00344] Step 1. Synthesis of (E)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(2-ethoxyvinyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00345] To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (22 mg, 0.14 mmol, 4.0 eq) in pyridine (0.5 mL) was added EDCI (27 mg, 0.14 mmol, 4.0 eq) and (E)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(2-ethoxyvinyl)-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide trifluoroacetate (Intermediate-26) (20 mg, 35 μ mol, 1.0 eq). The resulting mixture was stirred at 40 °C for 1h and then concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00346] LCMS: 701.4 [M+H]⁺.

[00347] ¹H NMR (400 MHz, CDCl₃) δ ppm 11.88 (s, 1H), 8.68 (s, 1H), 8.59 (s, 1H), 8.52 (d, 1H), 8.41 (s, 1H), 7.87 (d, 1H), 7.63 (s, 1H), 7.54 (br d, 1H), 6.02 (d, 1H), 5.64 - 5.50 (m, 1H), 5.42 - 5.23 (m, 2H), 4.84 - 4.72 (m, 1H), 4.08 - 3.94 (m, 4H), 3.59 - 3.45 (m, 1H), 3.33 - 3.23 (m, 2H), 3.16 - 3.03 (m, 1H), 2.89 - 2.72 (m, 2H), 2.57 (s, 3H), 1.36 (dt, 6H).

[00348] *Synthesis of rac-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-methoxy-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (racemic mixture, trans (I-16))*



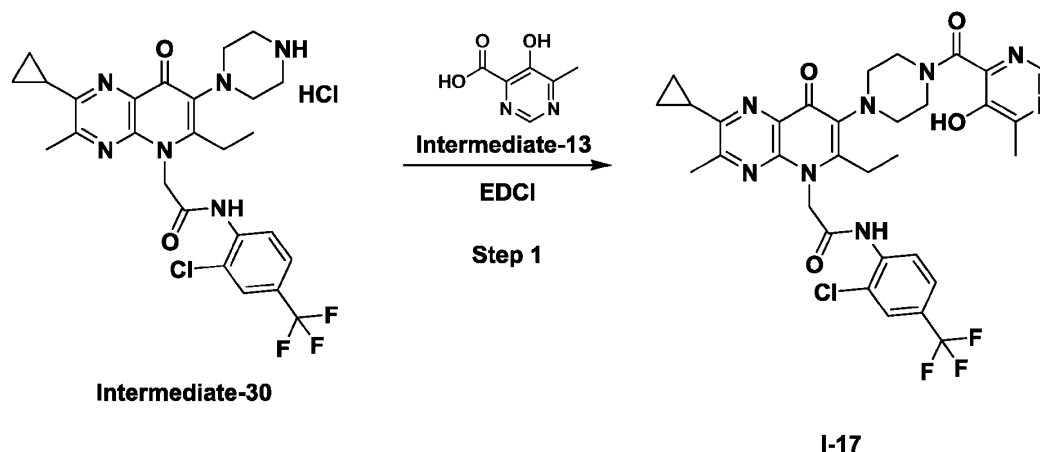
[00349] Step 1. Synthesis of *rac*-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-methoxy-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (racemic mixture, trans)

[00350] To a solution of *rac*-2-(7-(2,5-diazabicyclo[4.2.0]octan-2-yl)-6-ethyl-2-methoxy-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide hydrochloride (racemic mixture, trans) (Intermediate-29) (45 mg, 80 μ mol, 1.0 eq) and 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (15 mg, 95 μ mol, 1.2 eq) in pyridine (1 mL) was added EDCI (46 mg, 0.24 mmol, 3.0 eq) and the resulting mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved into MeOH (0.25 mL), THF (0.25 mL) and H₂O (0.5 mL). Aqueous LiOH solution (0.5 mL, 1 M) was added, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and then purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00351] LCMS: 701.4 [M+H]⁺.

[00352] ¹H NMR (400 MHz, CDCl₃) δ 8.61 (br s, 1H), 8.51 (d, 1H), 8.26 (br s, 1H), 7.62 (s, 1H), 7.54 (br d, 1H), 5.42 - 5.28 (m, 3H), 5.03 - 4.24 (m, 2H), 4.20 (s, 3H), 4.05 - 3.57 (m, 2H), 3.37 (br d, 2H), 3.25 - 3.13 (m, 1H), 2.62 (s, 3H), 2.55 (s, 3H), 2.38 - 1.94 (m, 2H), 1.52 - 1.39 (m, 2H), 1.34 (br t, 3H).

[00353] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-cyclopropyl-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-17)*



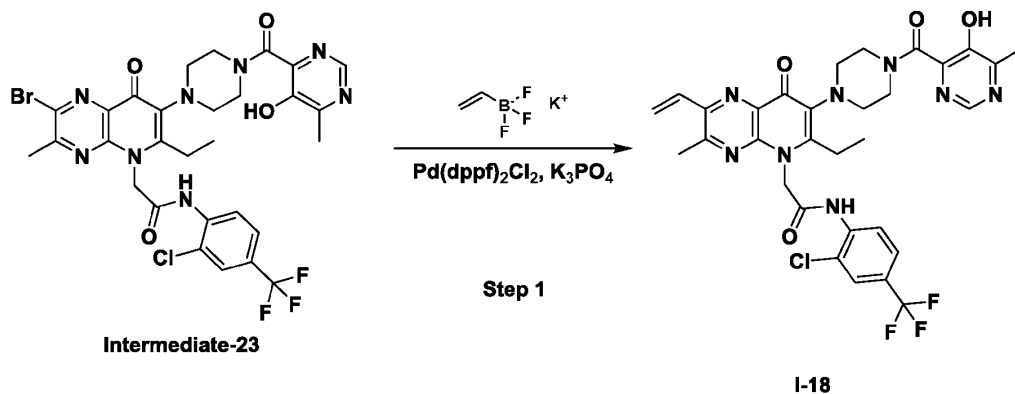
[00354] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-cyclopropyl-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00355] To a mixture of N-[2-chloro-4-(trifluoromethyl)phenyl]-2-(2-cyclopropyl-6-ethyl-3-methyl-8-oxo-7-piperazin-1-yl-pyrido[2,3-b]pyrazin-5-yl)acetamide hydrochloride (Intermediate-30) (37 mg, 67 μ mol, 1.0 eq) and 5-hydroxy-6-methyl-pyrimidine-4-carboxylic acid (Intermediate-13) (21 mg, 0.14 mmol, 2.0 eq) in pyridine (1 mL) was added EDCI (26 mg, 0.14 mmol, 2.0 eq), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched by H₂O (10 mL) and extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, H₂O (10 mmol/L NH₄HCO₃)-ACN) to afford the title compound.

[00356] LCMS: 685.2 [M+H]⁺.

[00357] ¹H NMR (400 MHz, CDCl₃) δ ppm 11.67 (br s, 1H), 8.58 (s, 1H), 8.51 (d, 1H), 8.43 (s, 1H), 7.63 (d, 1H), 7.55 (br d, 1H), 5.65 – 5.43 (m, 1H), 5.36 (br s, 2H), 4.76 (br dd, 1H), 4.02 (dt, 2H), 3.62 – 3.39 (m, 1H), 3.34 – 3.19 (m, 2H), 3.18 – 2.96 (m, 1H), 2.89 – 2.71 (m, 5H), 2.57 (s, 3H), 2.24 – 2.16 (m, 1H), 1.37 – 1.30 (m, 5H), 1.10 (br dd, 2H).

[00358] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxo-2-vinylpyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-18)*



[00359] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxo-2-vinylpyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

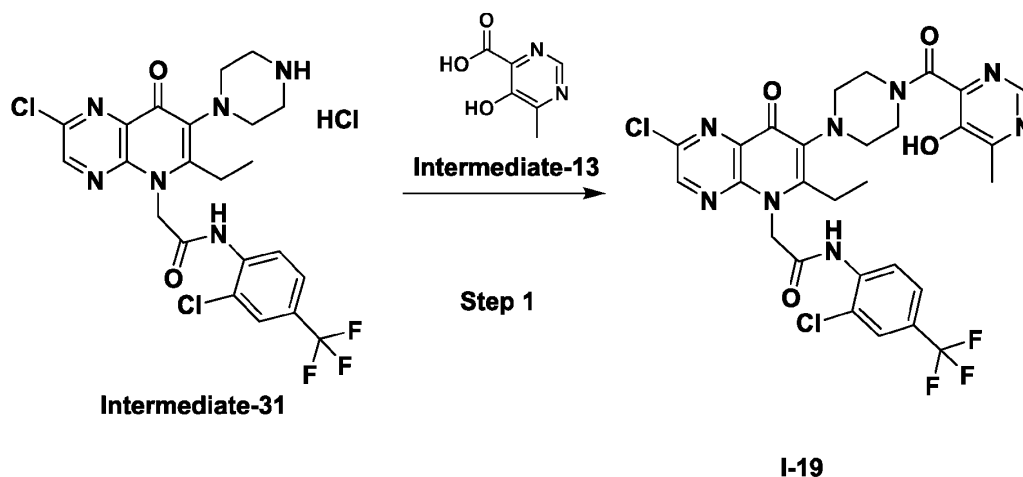
[00360] To a solution of 2-(2-bromo-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (Intermediate-23) (40 mg, 55 μ mol, 1.0 eq) and potassium trifluoro(vinyl)borate (7 mg, 55 μ mol, 1.0 eq) in dioxane (4 mL) and H₂O (0.8 mL) was added Pd(dppf)Cl₂ (4 mg, 6 μ mol, 0.1 eq) and K₃PO₄ (23 mg, 0.11 mmol, 2.0 eq). The reaction was degassed and purged with N₂ for 3 times, and then stirred at 80 °C for 1 h under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was diluted with H₂O (10 mL) and extracted with EtOAc (10 mL * 2). The combined organic layers were washed with brine (7.5 mL * 2), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00361] LCMS: 671.2 [M+H]⁺.

[00362] ¹H NMR (400 MHz, CDCl₃) δ ppm 11.81 (s, 1H), 8.59 (s, 1H), 8.51 (d, 1H), 8.39 (br s, 1H), 7.63 (s, 1H), 7.55 (br d, 1H), 7.09 - 6.99 (m, 1H), 6.74 (d, 1H), 5.73 (d, 1H), 5.64 - 5.53 (m, 1H), 5.36 (br d, 2H), 4.87 - 4.70 (m, 1H), 4.08 - 3.96 (m, 2H), 3.60 - 3.46 (m, 1H), 3.34 -

3.22 (m, 2H), 3.16 - 3.04 (m, 1H), 2.95 - 2.77 (m, 2H), 2.75 (s, 3H), 2.58 (s, 3H), 1.39 - 1.34 (m, 3H).

[00363] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-chloro-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-19)*



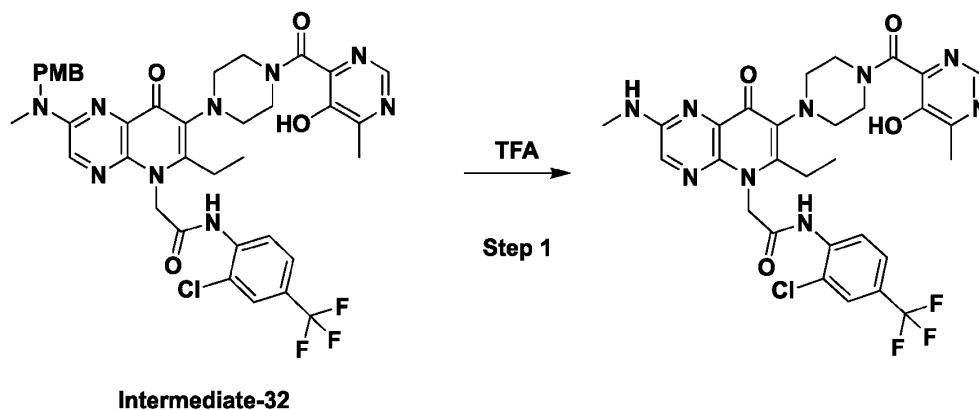
[00364] Step 1: Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-chloro-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00365] To a solution of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-chloro-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride (Intermediate-31) (390 mg, 737 μ mol, 1.0 eq) and 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (227 mg, 1.47 mmol, 2.0 eq) in pyridine (5 mL) was added EDCI (282 mg, 1.47 mmol, 2.0 eq), the resulting mixture was stirred at 40 °C for 15 h. The mixture was concentrated under reduced pressure and the residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00366] **LCMS:** 665.4[M+H]⁺.

[00367] **¹H NMR** (400 MHz, CDCl₃) δ 11.83 (s, 1H), 8.62 (d, 2H), 8.52 - 8.42 (m, 2H), 7.69 (d, 1H), 7.56 (d, 1H), 5.69 - 5.57 (m, 1H), 5.39 (br s, 2H), 4.88 - 4.73 (m, 1H), 4.08 - 3.93 (m, 2H), 3.62 - 3.48 (m, 1H), 3.30 (br d, 2H), 3.17 - 3.04 (m, 1H), 2.91 - 2.72 (m, 2H), 2.59 (s, 3H), 1.39 (t, 3H).

[00368] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(methylamino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-20)*



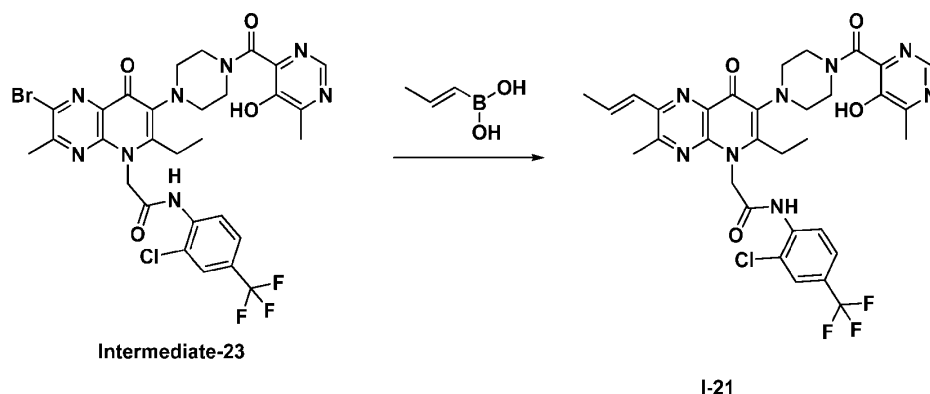
[00369] Step 1: Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(methylamino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00370] N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-((4-methoxybenzyl)(methyl)amino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (Intermediate-32) (15 mg, 19 μ mol, 1.0 eq) was dissolved in TFA (0.5 mL) and then stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure and the residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00371] **LCMS: 660.4 [M+H]⁺.**

[00372] **¹H NMR** (400 MHz, CDCl₃) δ ppm 8.99 (s, 1H), 8.60 (s, 1H), 8.40 (br d, 1H), 8.22 (s, 1H), 7.64 (s, 1H), 7.50 (br d, 1H), 5.70 - 5.32 (m, 3H), 4.85 - 4.65 (m, 1H), 4.02 - 3.75 (m, 2H), 3.61 - 3.41 (m, 1H), 3.27 (br s, 2H), 3.13 - 2.97 (m, 4H), 2.87 - 2.72 (m, 2H), 2.58 (s, 3H), 1.35 (br t, 3H).

[00373] *Synthesis of (E) N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxo-2-(prop-1-en-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-21)*



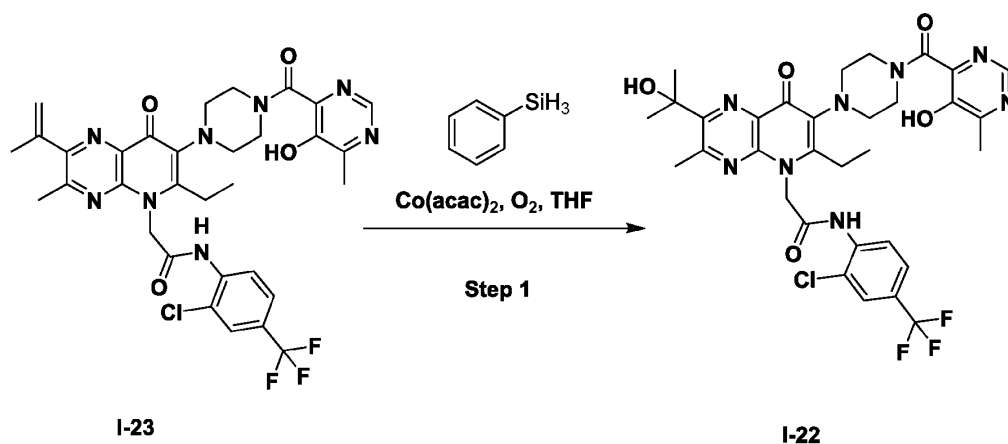
[00374] Step 1. Synthesis (E)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxo-2-(prop-1-en-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00375] To a solution of 2-(2-bromo-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (Intermediate-23) (50 mg, 69 μ mol, 1.0 eq and (E)-prop-1-en-1-ylboronic acid (6 mg, 69 μ mol, 1.0 eq) in 1,4-dioxane (1 mL) and H₂O (0.2 mL) was added Pd(dppf)Cl₂-CH₂Cl₂ (6 mg, 7 μ mol, 0.1 eq) and K₃PO₄ (29 mg, 0.14 mmol, 2.0 eq), and the resulting mixture was stirred at 80 °C for 1 h under N₂ atmosphere. The reaction mixture was quenched by saturated NH₄Cl aqueous solution (100 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, H₂O (10 mmol/L NH₄HCO₃)-ACN) to afford the title compound.

[00376] LCMS: 685.2 [M+H]⁺.

[00377] ¹H NMR (400 MHz, CDCl₃) δ ppm 11.68 (br s, 1H), 8.60 (s, 1H), 8.52 (br d, 1H), 8.47 (br s, 1H), 7.63 (s, 1H), 7.56 (br d, 1H), 7.37 - 7.30 (m, 1H), 6.69 (br d, 1H), 5.73 - 5.51 (m, 1H), 5.37 (br s, 2H), 4.91 - 4.67 (m, 1H), 4.11 - 3.92 (m, 2H), 3.65 - 3.45 (m, 1H), 3.36 - 3.23 (m, 2H), 3.19 - 3.02 (m, 1H), 2.91 - 2.76 (m, 2H), 2.73 (s, 3H), 2.59 (s, 3H), 2.01 (br d, 3H), 1.37 (br t, 3H).

[00378] Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-hydroxypropan-2-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-22)



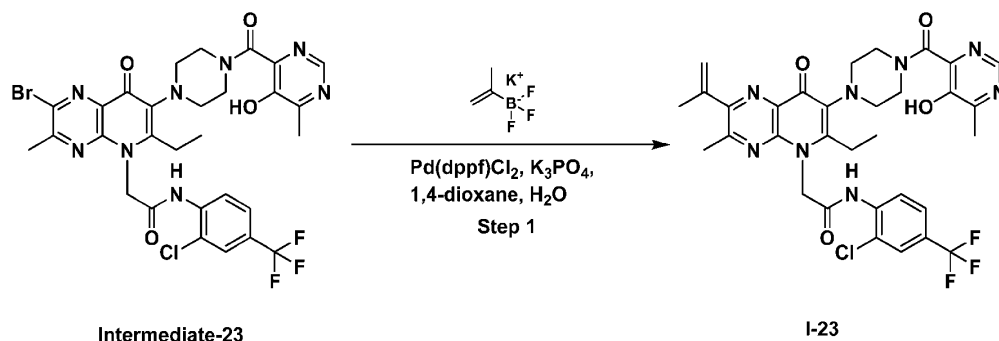
[00379] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2-hydroxypropan-2-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00380] To a solution of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxo-2-(prop-1-en-2-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (**I-23**) (30 mg, 44 μ mol, 1 eq) in THF (1 mL) was added phenylsilane (9 mg, 88 μ mol, 2.0 eq) and bis[(Z)-1-methyl-3-oxo-but-1-en-1-yl]cobalt (1 mg, 2 μ mol, 0.05 eq). The resulting mixture was stirred at room temperature for 16 h under O₂ atmosphere. The reaction mixture was concentrated under reduced pressure and then purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound

[00381] LCMS: 703.4 [M+H]⁺.

[00382] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.58 (s, 1H), 8.48 (br d, 1H), 8.42 – 8.24 (m, 1H), 7.65 (s, 1H), 7.55 (br d, 1H), 7.49 – 7.28 (m, 1H), 5.75 – 5.50 (m, 1H), 5.48 – 5.13 (m, 2H), 5.12 – 4.84 (m, 1H), 4.83 – 4.59 (m, 1H), 4.32 – 3.76 (m, 2H), 3.62 – 3.39 (m, 1H), 3.38 – 3.18 (m, 2H), 3.18 – 2.98 (m, 1H), 2.97 – 2.82 (m, 3H), 2.81 – 2.70 (m, 1H), 2.57 (s, 3H), 1.70 (br s, 6H), 1.36 (br t, 3H).

[00383] Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxo-2-(prop-1-en-2-yl)pyrido[2,3-

b]pyrazin-5(8*H*)-yl)acetamide (1-23)

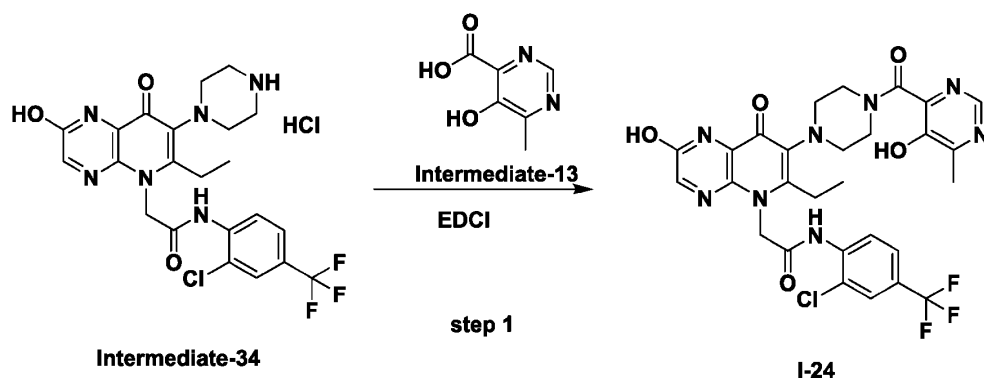
[00384] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxo-2-(prop-1-en-2-yl)pyrido[2,3-*b*]pyrazin-5(8*H*)-yl)acetamide

[00385] To a solution of 2-(2-bromo-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-*b*]pyrazin-5(8*H*)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (Intermediate-23) (50 mg, 69 μmol , 1.0 eq) and potassium trifluoro(prop-1-en-2-yl)borate (11 mg, 76 μmol , 1.1 eq) in 1,4-dioxane (1 mL) and H₂O (0.2 mL) was added Pd(dppf)Cl₂ (5 mg, 7 μmol , 0.1 eq) and K₃PO₄ (29 mg, 0.14 mmol, 2.0 eq). The resulting mixture was stirred at 80 °C for 2 h under N₂ atmosphere. After being cooled to room temperature, the reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (5 mL * 3), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00386] LCMS: 685.4 [M+H]⁺.

[00387] ¹H NMR (400 MHz, CDCl₃) δ ppm 11.79 (br s, 1H), 8.58 (s, 1H), 8.49 (br d, 2H), 7.63 (s, 1H), 7.55 (br d 1H), 5.69 - 5.50 (m, 2H), 5.49 - 5.28 (m, 2H), 5.22 (s, 1H), 4.89 - 4.65 (m, 1H), 4.12 - 3.87 (m, 2H), 3.63 - 3.41 (m, 1H), 3.40 - 3.18 (m, 2H), 3.17 - 2.99 (m, 1H), 2.98 - 2.76 (m, 2H), 2.74 (s, 3H), 2.57 (s, 3H), 2.24 (s, 3H), 1.42 - 1.28 (m, 3H).

[00388] Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-hydroxy-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-*b*]pyrazin-5(8*H*)-yl)acetamide (1-24)



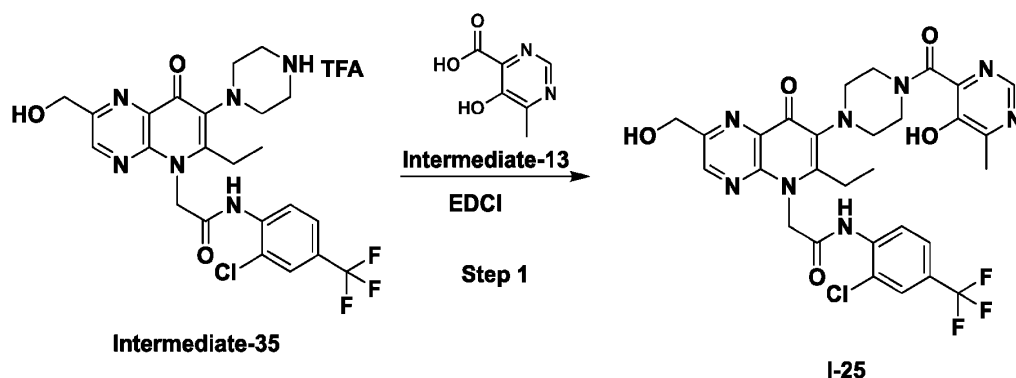
[00389] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-hydroxy-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00390] To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (29 mg, 0.16 mmol, 4.0 eq) in pyridine (0.5 mL) was added EDCI (32 mg, 0.16 mmol, 4.0 eq), and the mixture was stirred at room temperature for 0.5 h. Then N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-hydroxy-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride (Intermediate-34) (21 mg, 41 μ mol, 1.0 eq) was added at room temperature and the reaction mixture was stirred at 40 °C for 16 h. The reaction mixture was concentrated under reduced pressure and then purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00391] LCMS: 647.1 [M+H]⁺.

[00392] ¹H NMR (400 MHz, CHCl₃) δ 11.65 (br s, 1H), 8.60 (s, 1H), 8.50 (d, 1H), 8.37 (s, 1H), 8.32 (s, 1H), 7.70 (s, 1H), 7.57 (br d, 1H), 5.59 - 5.44 (m, 1H), 5.36 (br s, 2H), 4.90 - 4.73 (m, 1H), 4.01 (br t, 2H), 3.59 - 3.41 (m, 1H), 3.32 - 3.19 (m, 2H), 3.14 - 3.02 (m, 1H), 2.90 - 2.71 (m, 2H), 2.58 (s, 3H), 1.35 (br t, 3H).

[00393] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(hydroxymethyl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-25)*



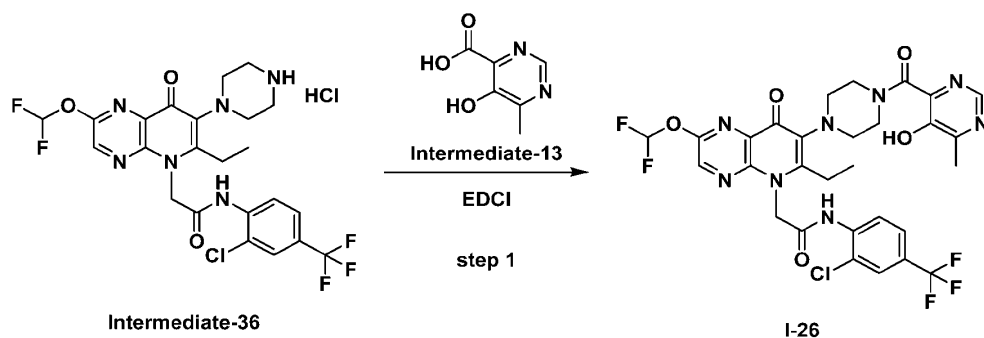
[00394] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(hydroxymethyl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00395] To a solution of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-(hydroxymethyl)-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide trifluoroacetate (Intermediate-35) (40 mg, 76 μ mol, 1.0 eq) in pyridine (0.8 mL) was added EDCI (44 mg, 0.23 mmol, 3.0 eq) and 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (40 mg, 0.23 mmol, 3.0 eq). The mixture was stirred at 40 °C for 16 h and then concentrated under reduced pressure. The residue was purified by reverse phase HPLC (water (0.1% FA)-ACN) to afford the title compound.

[00396] LCMS: 661.1 [M+H]⁺.

[00397] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.86 (br d, 1H), 8.80 (s, 1H), 8.58 (s, 1H), 8.43 (br d, 1H), 7.63 (s, 1H), 7.51 (br d, 1H), 5.55 - 5.39 (m, 3H), 5.00 (s, 2H), 4.77 - 4.70 (m, 1H), 4.04 - 3.92 (m, 2H), 3.55 - 3.46 (m, 1H), 3.29 (br s, 2H), 3.10 - 3.04 (m, 1H), 2.85 - 2.75 (m, 2H), 2.56 (s, 3H), 1.36 (br t, 3H).

[00398] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethoxy)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-26)*



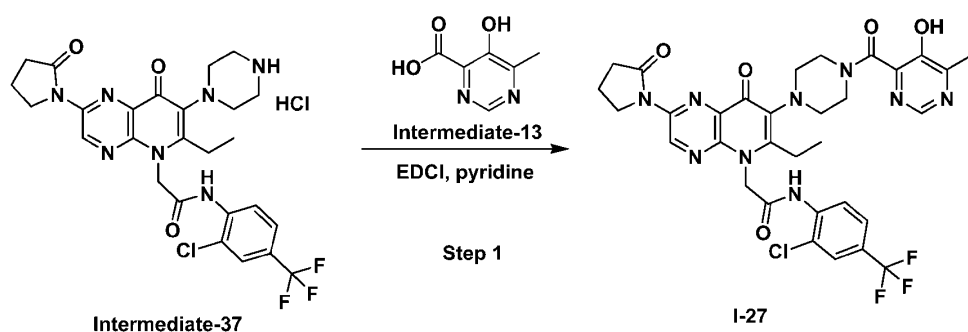
[00399] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethoxy)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00400] To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (18 mg, 0.10 mmol, 4.0 eq) in pyridine (0.5mL) was added EDCI (19 mg, 0.10 mmol, 4.0 eq), and the mixture was stirred at room temperature for 0.5 h. Then, N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethoxy)-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride (Intermediate-36) (14 mg, 25 μ mol, 1.0 eq) was added and the mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure, the residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00401] LCMS: 697.1 [M+H]⁺.

[00402] ¹H NMR (400 MHz, CDCl₃) δ ppm 11.75 (br s, 1H), 8.59 (s, 1H), 8.48 (d, 1H), 8.45 (s, 1H), 8.41 (s, 1H), 7.75 (t, 1H), 7.67 (d, 1H), 7.55 (d, 1H), 5.59 (d, 1H), 5.38 (s, 2H), 4.77 (s, 1H), 4.06 - 3.89 (m, 2H), 3.52 (s, 1H), 3.28 (s, 2H), 3.10 (s, 1H), 2.92 - 2.68 (m, 2H), 2.57 (s, 3H), 1.37 (t, 3H).

[00403] Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(2-oxopyrrolidin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-27)



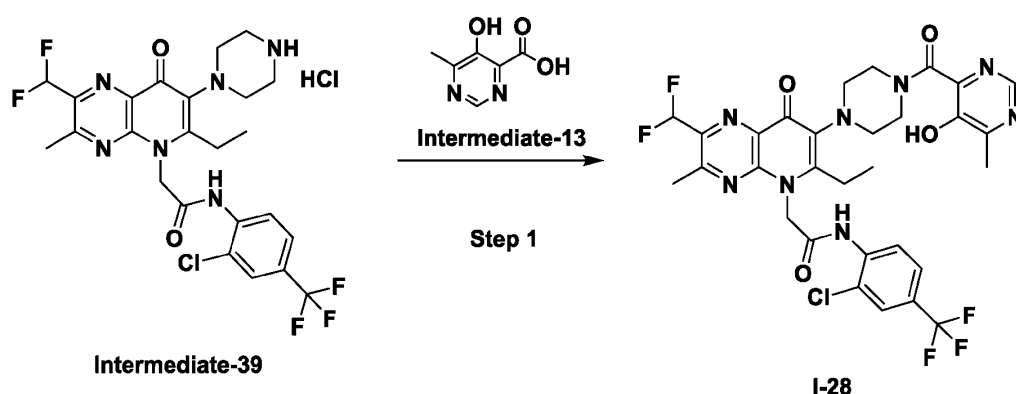
[00404] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxo-2-(2-oxopyrrolidin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00405] To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (34 mg, 0.22 mmol, 5.0 eq) in pyridine (0.5 mL) was added EDCI (42 mg, 0.22 mmol, 5.0 eq) and the mixture was stirred at room temperature for 0.5 h. N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-8-oxo-2-(2-oxopyrrolidin-1-yl)-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride (Intermediate-37) (27 mg, 44 μ mol, 1.0 eq) was added to the mixture and the reaction mixture was stirred at 30 °C for 1 h. The mixture was concentrated under reduced pressure, the residue was purified by reverse phase HPLC (water (0.1% FA)-ACN) to afford the title compound.

[00406] LCMS: 714.2 [M+H]⁺.

[00407] ¹H NMR (400MHz, CDCl₃) δ ppm 11.79 (br s, 1H), 9.88 (s, 1H), 8.64 (s, 1H), 8.59 (s, 1H), 8.51 (d, 1H), 7.64 (s, 1H), 7.53 (d, 1H), 5.57 (br s, 1H), 5.37 (br s, 2H), 4.77 (br s, 1H), 4.28 (t, 2H), 4.08 - 3.96 (m, 2H), 3.61 - 3.45 (m, 1H), 3.32 (br d, 2H), 3.11 (br s, 1H), 2.82 (br d, 2H), 2.73 (t, 2H), 2.57 (s, 3H), 2.23 (m, 2H), 1.38 (t, 3H).

[00408] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (1-28)*



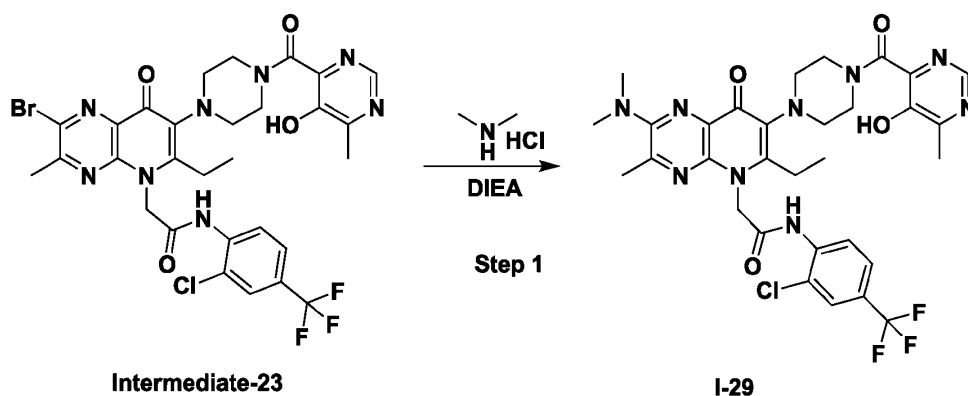
[00409] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00410] To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (69 mg, 0.45 mmol, 5.0 eq) in pyridine (1 mL) was added EDCI (77 mg, 0.40 mmol, 4.5 eq) and the resulting mixture was stirred at room temperature for 0.5 h. Then N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethyl)-6-ethyl-3-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride (Intermediate-39) (50 mg, 89 μ mol, 1.0 eq) was added and the resulting mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated under reduced pressure and then purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00411] LCMS: 695.1 [M+H]⁺.

[00412] ¹H NMR (400 MHz, CDCl₃) δ 11.84 (s, 1H), 8.60 (s, 1H), 8.47 (d, 1H), 8.30 (s, 1H), 7.68 (d, 1H), 7.59 - 7.52 (m, 1H), 7.12 - 6.79 (m, 1H), 5.68 - 5.53 (m, 1H), 5.44 - 5.31 (m, 2H), 4.90 - 4.72 (m, 1H), 4.05 - 3.93 (m, 2H), 3.59 - 3.46 (m, 1H), 3.33 - 3.21 (m, 2H), 3.17 - 3.05 (m, 1H), 2.87 (s, 3H), 2.85 - 2.73 (m, 2H), 2.57 (s, 3H), 1.39 - 1.35 (m, 3H).

[00413] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-29)*



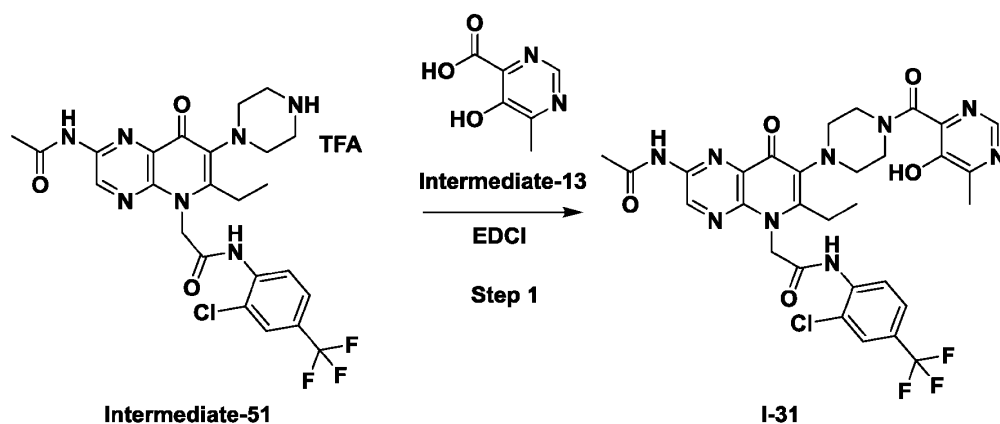
[00414] Step 1. N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00415] To a solution of 2-(2-bromo-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (50 mg, 69 μ mol, 1.0 eq) and dimethylamine hydrochloride (41 mg, 0.35 mmol, 5.0 eq) in 1,4-dioxane (1 mL) was added DIEA (54 mg, 0.41 mmol, 6.0 eq) and the resulting mixture was stirred at 100 °C for 1 h. The reaction mixture was concentrated under reduced pressure and then purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00416] LCMS: 688.2 [M+H]⁺.

[00417] ¹H NMR (400 MHz, CDCl₃) δ 8.78 - 8.66 (m, 1H), 8.61 (s, 1H), 8.40 (br d, 1H), 7.65 (s, 1H), 7.53 (br d, 1H), 5.57 (br s, 3H), 4.86 - 4.73 (m, 1H), 3.97 (br t, 2H), 3.60 - 3.46 (m, 1H), 3.32 (br d, 2H), 3.09 (s, 7H), 2.94 - 2.78 (m, 2H), 2.72 (s, 3H), 2.58 (s, 3H), 1.36 (t, 3H).

[00418] *Synthesis of 2-(2-acetamido-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (I-31)*



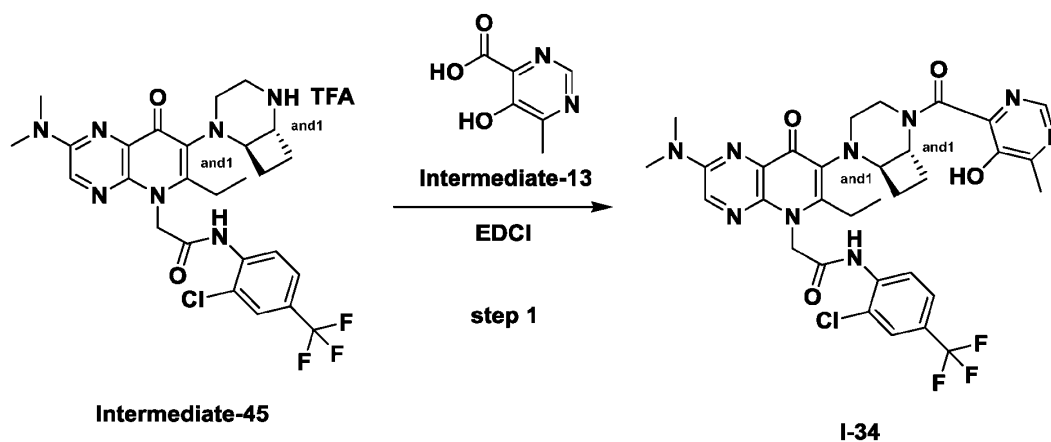
[00419] Step 1. Synthesis of 2-(2-acetamido-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide

[00420] To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (45 mg, 0.29 mmol, 4.0 eq) in pyridine (1 mL) was added EDCI (56 mg, 0.29 mmol, 4.0 eq) and 2-(2-acetamido-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate (Intermediate-51) (40 mg, 72 μ mol, 1.0 eq), and the resulting mixture was stirred at 40 °C overnight. The reaction mixture was concentrated under reduced pressure and then purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00421] LCMS: 688.3 [M+H]⁺.

[00422] ¹H NMR (400 MHz, CDCl₃) δ ppm 9.66 (s, 1H), 9.29 - 9.04 (m, 1H), 8.74 - 8.61 (m, 1H), 8.59 (s, 1H), 8.48 (d, 1H), 7.65 (d, 1H), 7.58 - 7.48 (m, 1H), 5.64 - 5.47 (m, 1H), 5.46 - 5.19 (m, 2H), 4.88 - 4.66 (m, 1H), 4.06 - 3.88 (m, 2H), 3.51 (br t, 1H), 3.38 - 3.24 (m, 2H), 3.10 (br d, 1H), 2.87 - 2.73 (m, 2H), 2.56 (s, 3H), 2.26 (s, 3H), 1.37 (br t, 3H).

[00423] Synthesis of *rac-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (racemic mixture, trans, I-34)*



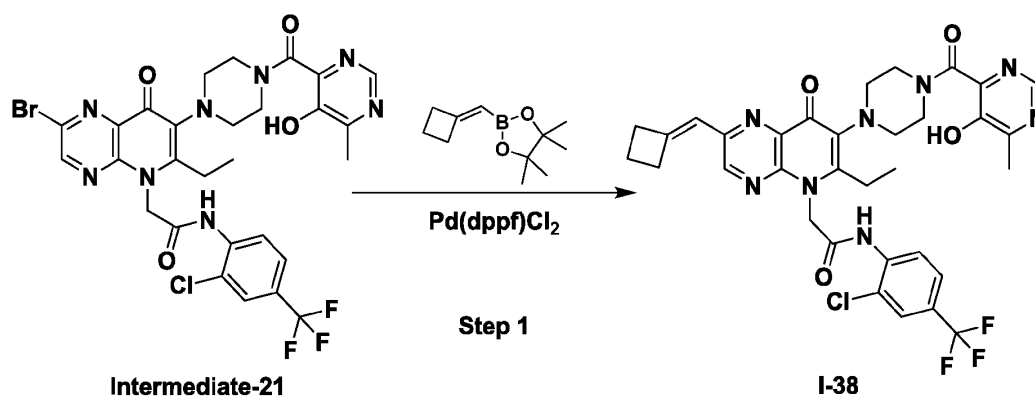
[00424] Step 1: Synthesis of *rac*-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (racemic mixture, trans)

[00425] To a mixture of *rac*-2-(7-(2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(dimethylamino)-6-ethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate (racemic mixture, trans) (Intermediate-45) (80 mg, 0.14 mmol, 1.0 eq) and 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (44 mg, 0.28 mmol, 2.0 eq) in pyridine (2 mL) was added EDCI (54 mg, 0.28 mmol, 2.0 eq). The mixture was stirred at room temperature for 1 h and then quenched with H₂O (100 mL). The resulting mixture was extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00426] LCMS: 700.4 [M+H]⁺.

[00427] ¹HNMR: (400 MHz, CDCl₃) δ ppm 12.71 (s, 1H), 8.61 (br s, 1H), 8.54 (d, 1H), 8.45 (s, 1H), 8.22 (s, 1H), 7.60 (s, 1H), 7.53 (br d, 1H), 5.78 - 4.87 (m, 3H), 4.57 - 4.10 (m, 2H), 4.02 - 3.53 (m, 2H), 3.37 (br d, 2H), 3.29 (s, 6H), 3.21 - 3.11 (m, 1H), 2.61 - 1.95 (m, 5H), 1.57 - 1.38 (m, 2H), 1.34 (br t, 3H).

[00428] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(cyclobutylidenemethyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-38)*



[00429] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(cyclobutylidenemethyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00430] To a solution of 2-(2-bromo-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (Intermediate-21) (30 mg, 42 μ mol, 1.0 eq) and 2-(cyclobutylidenemethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8 mg, 42 μ mol, 1.0 eq) in 1,4-dioxane (0.5 mL) and H₂O (0.1 mL) was added Pd(dppf)Cl₂ (3 mg, 4 μ mol, 0.1 eq) and K₃PO₄ (18 mg, 85 μ mol, 2.0 eq). The resulting mixture was stirred at 80 °C for 1 h and then concentrated in vacuo. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

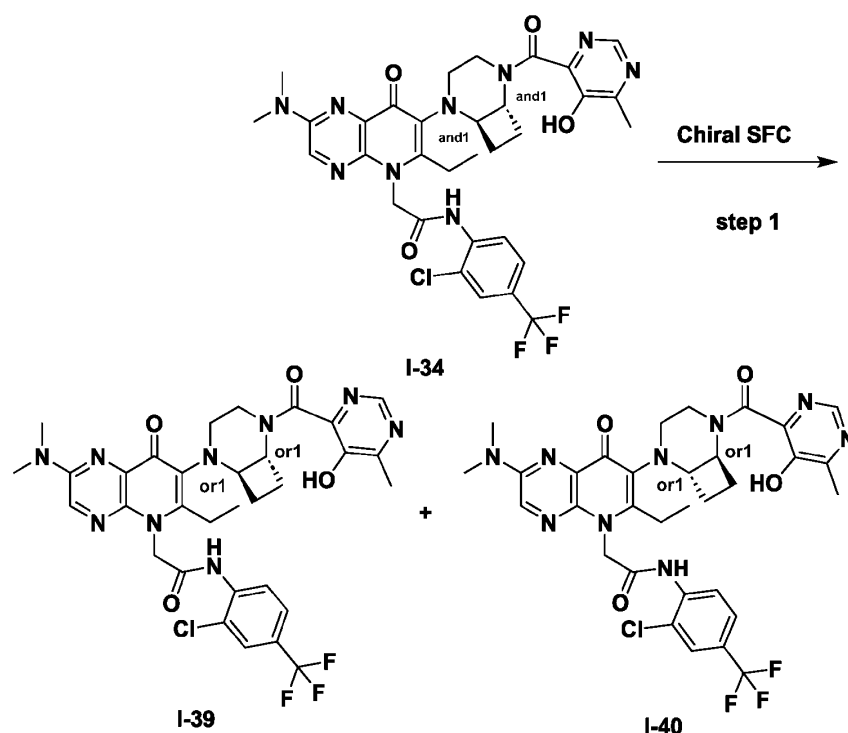
[00431] LCMS: 697.2 [M+H]⁺.

[00432] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.70 (br s, 1H), 8.58 (s, 1H), 8.55 - 8.49 (m, 2H), 7.63 (d, 1H), 7.54 (br d, 1H), 6.47 (br s, 1H), 5.64 - 5.51 (m, 1H), 5.34 (br s, 2H), 4.86 - 4.72 (m, 1H), 4.11 - 3.96 (m, 2H), 3.60 - 3.44 (m, 1H), 3.38 - 3.20 (m, 4H), 3.17 - 3.05 (m, 1H), 2.98 (br t, 2H), 2.89 - 2.71 (m, 2H), 2.57 (s, 3H), 2.18 (q, 2H), 1.36 (br t, 3H).

[00433] Chiral separation of *rac*-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (racemic mixture, *trans*, I-34) to yield first and second eluting; stereoisomer 1 and stereoisomer 2; (I-39 and I-40)

[00434] N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, first eluting compound as stereoisomer 1, trans) (**I-39**); and

N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, second eluting compound as stereoisomer 2, trans) (**I-40**)



[00435] *rac*-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (racemic mixture, trans) was separated by chiral SFC (SFC Preparative Method: Instrument: Waters 80Q Preparative SFC system; Column: Daicel Chiralpak OD column, 250×25 mm I.D., 10 μm particle size; Mobile phase A: CO₂, Mobile Phase B: EtOH (0.1% saturated aqueous NH₃); Isocratic elution: 35 % Phase B in Supercritical CO₂; Flow rate:

70 g/min; Retention time: Peak1: 5.40min, Peak2: 7.86min; Back Pressure: 100 bar to keep the CO₂ in Supercritical flow; Wave Length: 220 nm) to afford the title compounds.

[00436] SFC Analytical method:

Instrument	SHIMADZU LC-30ADsf		
column	Chiralcel OD-3 50×4.6mm I.D., particle size 3μm		
Mobile Phase	Phase A for CO ₂	Phase B for EtOH (0.05% diethylamine)	
Gradient	Time (min)	A(%)	B(%)
	0.01	95	5
	1.80	60	40
	2.70	60	40
	2.71	95	5
	3.00	95	5
Flow rate	3.0mL/min		
Column Temp	35°C		
Back pressure	100bar		
UV	220nm		

[00437] N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide, single isomer, first eluting stereoisomer as stereoisomer 1, retention time (SFC analytical method): 2.09 minutes.

[00438] LCMS: 700.4 [M+H]⁺.

[00439] ¹HNMR: (400 MHz, CDCl₃) δ ppm 8.61 (br s, 1H), 8.55 (d, 1H), 8.43 (s, 1H), 8.22 (s, 1H), 7.60 (d, 1H), 7.54 (br d, 1H), 5.64 - 4.97 (m, 3H), 4.52 - 4.18 (m, 2H), 4.02 - 3.73 (m, 2H), 3.37 (br d, 2H), 3.29 (s, 6H), 3.23 - 3.11 (m, 1H), 2.68 - 1.87 (m, 5H), 1.43 (br d, 2H), 1.34 (t, 3H).

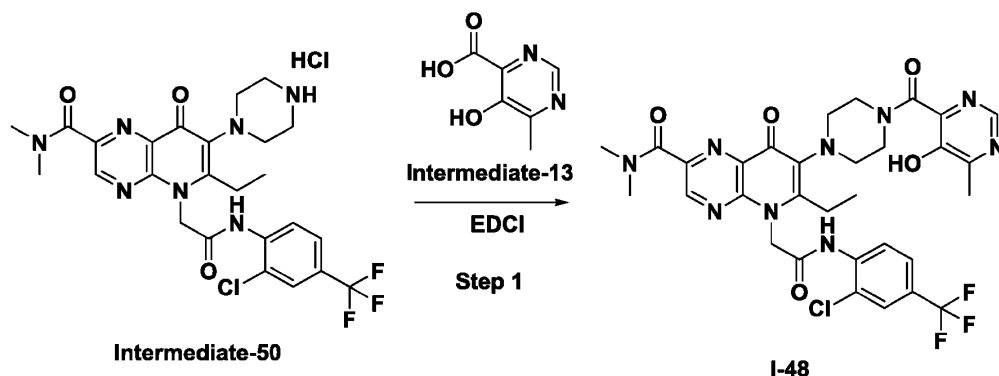
[00440] N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide, single stereoisomer, second eluting stereoisomer as stereoisomer 2, retention time (SFC analytical method): 2.30 minutes.

[00441] LCMS: 700.4 [M+H]⁺.

[00442] ¹HNMR: (400 MHz, CDCl₃) δ ppm 8.60 (br s, 1H), 8.54 (d, 1H), 8.45 (br s, 1H), 8.22 (s, 1H), 7.60 (s, 1H), 7.53 (br d, 1H), 5.58 - 4.91 (m, 3H), 4.51 - 4.19 (m, 2H), 4.03 - 3.64 (m, 2H),

3.37 (br d, 2H), 3.29 (s, 6H), 3.19-3.17 (m, 1H), 2.64 - 2.58 (m, 1H), 2.55 (s, 3H), 2.33 - 2.23 (m, 1H), 1.71 - 1.62 (m, 1H), 1.43 - 1.37 (m, 1H), 1.34 (t, 3H).

[00443] *Synthesis of 5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-N,N-dimethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazine-2-carboxamide (I-48)*



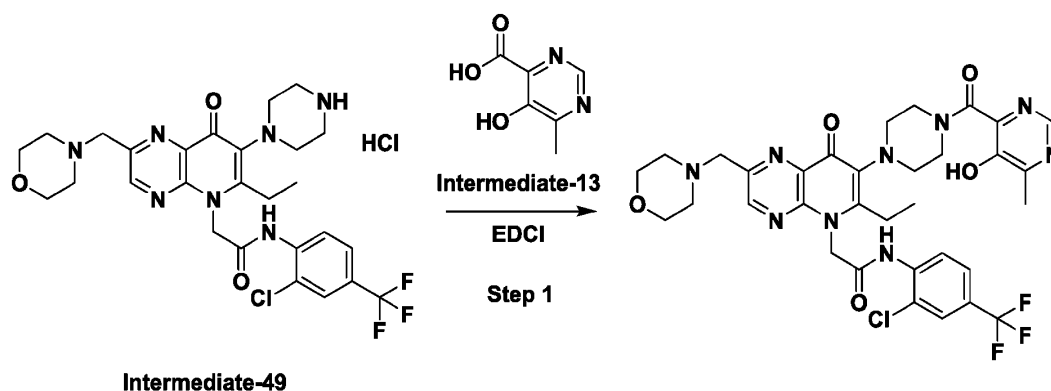
[00444] Step 1. 5-[2-[2-chloro-4-(trifluoromethyl)anilino]-2-oxo-ethyl]-6-ethyl-7-[4-(5-hydroxy-6-methyl-pyrimidine-4-carbonyl)piperazin-1-yl]-N,N-dimethyl-8-oxo-pyrido[2,3-b]pyrazine-2-carboxamide

[00445] To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (22 mg, 0.14 μ mol, 2.0 eq) in pyridine (1 mL) was added EDCI (27 mg, 0.14 mmol, 2.0 eq) and 5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-N,N-dimethyl-8-oxo-7-(piperazin-1-yl)-5,8-dihydropyrido[2,3-b]pyrazine-2-carboxamide hydrochloride (Intermediate-50) (40 mg, 71 μ mol, 1.0 eq). The mixture was stirred at 40 °C for 1 h and then concentrated in vacuo. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00446] LCMS: 702.2 [M+H]⁺.

[00447] ¹H NMR (400 MHz, CDCl₃) δ ppm 9.18 (s, 1H), 8.93 - 8.65 (m, 1H), 8.58 (s, 1H), 8.45 (br d, 1H), 7.67 (s, 1H), 7.53 (br d, 1H), 5.69 - 5.51 (m, 1H), 5.50 - 5.30 (m, 2H), 4.90 - 4.66 (m, 1H), 3.99 (br t, 2H), 3.59 - 3.46 (m, 1H), 3.39 (s, 3H), 3.35 - 3.24 (m, 2H), 3.18 (s, 3H), 3.12 - 3.03 (m, 1H), 2.95 - 2.74 (m, 2H), 2.57 (s, 3H), 1.38 (br t, 3H).

[00448] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(morpholinomethyl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-49)*



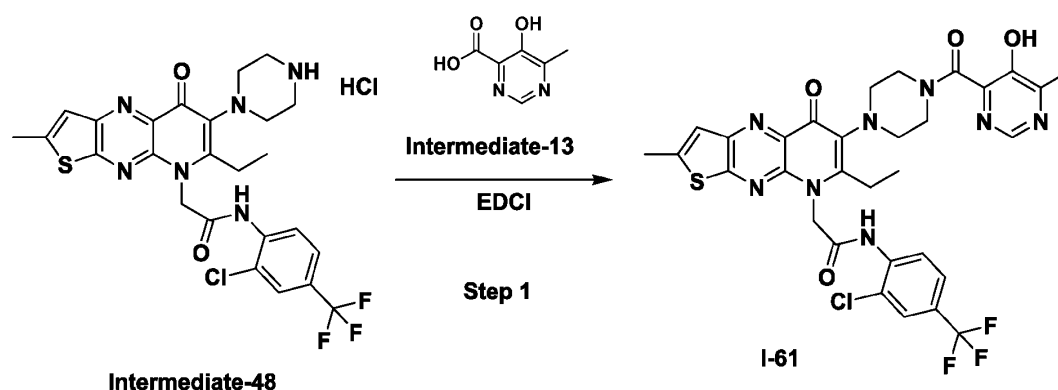
[00449] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(morpholinomethyl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00450] To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (31 mg, 0.20 μ mol, 2.0 eq) in pyridine (1 mL) was added EDCI (39 mg, 0.20 mmol, 2.0 eq) and N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-(morpholinomethyl)-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride (Intermediate-49) (60 mg, 0.10 μ mol, 1.0 eq). The mixture was stirred at 40 °C for 1 h and then concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00451] LCMS: 730.2 [M+H]⁺.

[00452] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.87 (s, 1H), 8.84 (br s, 1H), 8.58 (s, 1H), 8.48 (d, 1H), 7.64 (d, 1H), 7.53 (br d, 1H), 5.56 (br d, 1H), 5.42 (br s, 2H), 4.82 - 4.69 (m, 1H), 4.10 - 3.94 (m, 2H), 3.90 (s, 2H), 3.77 - 3.65 (m, 4H), 3.50 (br d, 1H), 3.30 (br d, 2H), 3.09 (br s, 1H), 2.91 - 2.72 (m, 2H), 2.68 - 2.44 (m, 7H), 1.36 (t, 3H).

[00453] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methyl-5-oxopyrido[2,3-b]thieno[3,2-e]pyrazin-8(5H)-yl)acetamide (I-61)*



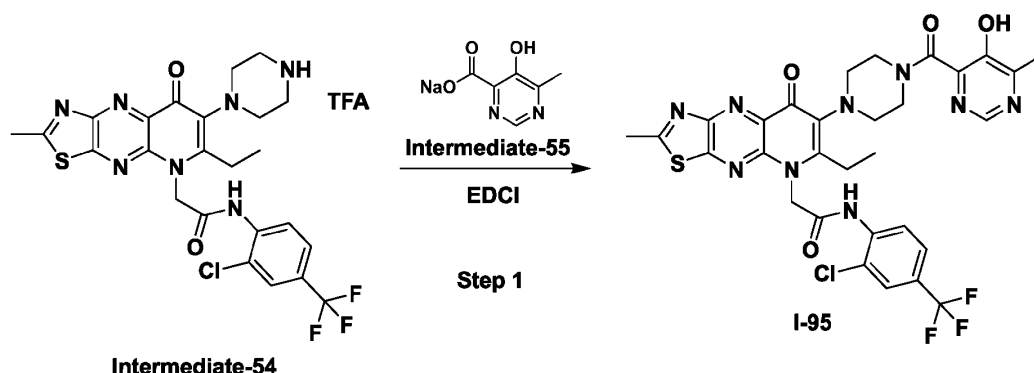
[00454] Step 1. Synthesis of tert-butyl 4-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-7-ethyl-2-methyl-5-oxo-5,8-dihydropyrido[2,3-b]thieno[3,2-e]pyrazin-6-yl)piperazine-1-carboxylate

[00455] To a solution of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-ethyl-2-methyl-5-oxo-6-(piperazin-1-yl)pyrido[2,3-b]thieno[3,2-e]pyrazin-8(5H)-yl)acetamide hydrochloride (Intermediate-48) (27 mg, 45 μ mol, 1 eq) and 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (27 mg, 0.14 mmol, 3 eq) in pyridine (0.5 mL) was added EDCI (26 mg, 0.14 mmol, 3 eq). The mixture was stirred at 60 °C for 1h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-TLC (SiO₂, Eluent of MeOH / DCM) and reversed-phase HPLC (C18 column, water (FA)-ACN) to afford the title compound.

[00456] ¹H NMR (400 MHz, CD₃OD) δ ppm 8.57 (s, 1H), 8.09 (d, 1H), 7.83 (s, 1H), 7.61 (d, 1H), 7.39 - 7.31 (m, 1H), 5.68 (s, 2H), 4.82 - 4.68 (m, 2H), 4.64 - 4.57 (m, 1H), 4.19 - 4.07 (m, 1H), 3.97 (q, 2H), 3.54 - 3.42 (m, 1H), 3.23 - 3.12 (m, 1H), 3.01 - 2.89 (m, 1H), 2.86 - 2.77 (m, 1H), 2.74 (s, 3H), 2.55 (s, 3H), 1.40 (t, 3H).

[00457] LCMS: 701.2 [M+H]⁺.

[00458] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methyl-8-oxopyrido[2,3-b]thiazolo[4,5-e]pyrazin-5(8H)-yl)acetamide (I-95)*



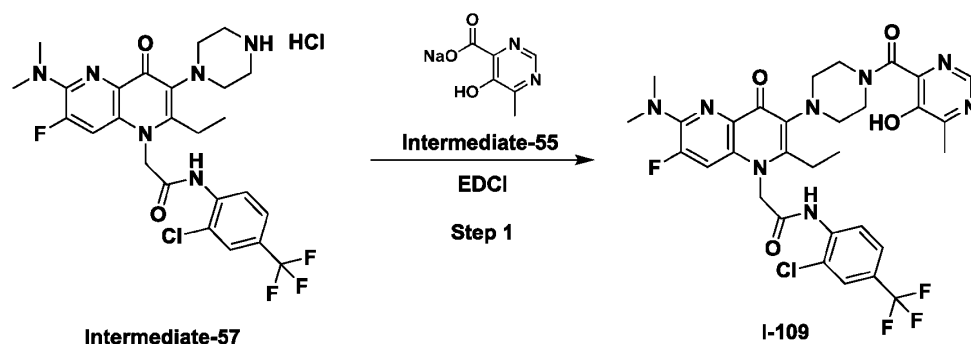
[00459] Step 15. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methyl-8-oxopyrido[2,3-b]thiazolo[4,5-e]pyrazin-5(8H)-yl)acetamide

[00460] To a solution of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]thiazolo[4,5-e]pyrazin-5(8H)-yl)acetamide trifluoroacetate (Intermediate-54) (21 mg, 31 μ mol, 1 eq) and sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate (Intermediate-55) (25 mg, 0.13 mmol, 4 eq) in pyridine (1 mL) EDCI (24 mg, 0.13 mmol, 4 eq) was added and the mixture was stirred at 25 °C for 14 h. Then sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate (6 mg, 31 μ mol, 1 eq) and EDCI (6 mg, 31 μ mol, 1 eq) were added at 60 °C and the reaction mixture was stirred for 1 h at 60 °C. The addition of sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate (6 mg, 31 μ mol, 1 eq) and EDCI (6 mg, 31 μ mol, 1 eq) followed by stirring for 1 h at 60 °C was repeated five times. The reaction mixture was concentrated to give a residue. The residue was purified by Prep-TLC (SiO₂, Eluent of MeOH / DCM) to afford the title compound.

[00461] ¹H NMR (400 MHz, CD₃OD) δ ppm 8.54 (s, 1H), 8.07 (d, 1H), 7.80 (d, 1H), 7.58 (m, 1H), 5.69 (s, 2H), 4.12 - 4.09 (m, 1H), 3.96 - 3.90 (m, 2H), 3.54 - 3.40 (m, 1H), 3.36 - 3.32 (m, 2H), 3.21 - 3.11 (m, 1H), 3.01 - 2.85 (m, 5H), 2.82 - 2.73 (m, 1H), 2.52 (s, 3H), 1.38 (t, 3H).

[00462] LCMS: 702.3 [M+H]⁺.

[00463] Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-(dimethylamino)-2-ethyl-7-fluoro-3-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-4-oxo-1,5-naphthyridin-1(4H)-yl)acetamide (I-109)



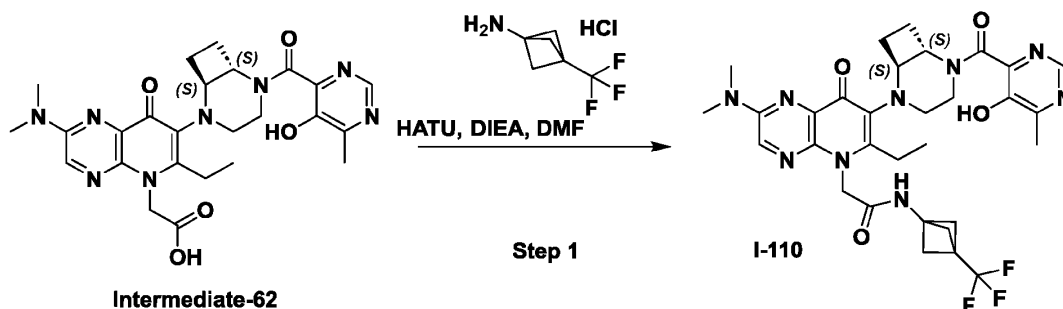
[00464] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl) phenyl)-2-(6-(dimethylamino)-2-ethyl-7-fluoro-3-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl) piperazin-1-yl)-4-oxo-1,5-naphthyridin-1(4H)-yl) acetamide

[00465] To a solution of N-[2-chloro-4-(trifluoromethyl) phenyl]-2-[6-(dimethylamino)-2-ethyl-7-fluoro-4-oxo-3-piperazin-1-yl-1,5-naphthyridin-1-yl] acetamide hydrochloride (Intermediate-57) (14 mg, 23 μ mol, 1 eq) and sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate (Intermediate-55) (23 mg, 118 μ mol, 5 eq) in pyridine (0.4 mL) was added EDCI (18 mg, 95 μ mol, 4 eq). The mixture was stirred at 20°C for 2 h. To the reaction mixture was added brine (15 mL) and the mixture was extracted with EtOAc (10 mL * 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Prep-TLC (SiO₂, DCM:MeOH) to afford the title compound.

[00466] ¹H NMR (400 MHz, CDCl₃) δ ppm 12.30 - 11.04 (m, 1H), 9.02 (br s, 1H), 8.56 (s, 1H), 8.44 (d, 1H), 7.60 (s, 1H), 7.53 (d, 1H), 7.34 (d, 1H), 5.63 - 5.40 (m, 1H), 5.09 (s, 2H), 4.90 - 4.63 (m, 1H), 4.60 - 4.29 (m, 1H), 4.07 (q, 2H), 3.49 (s, 1H), 3.26 - 3.00 (m, 7H), 2.90 - 2.67 (m, 2H), 2.55 (s, 3H), 2.10 - 1.97 (m, 1H), 1.27 (t, 3H).

[00467] LCMS: 691.3 [M+H]⁺.

[00468] Synthesis of 2-(2-(dimethylamino)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (I-110)



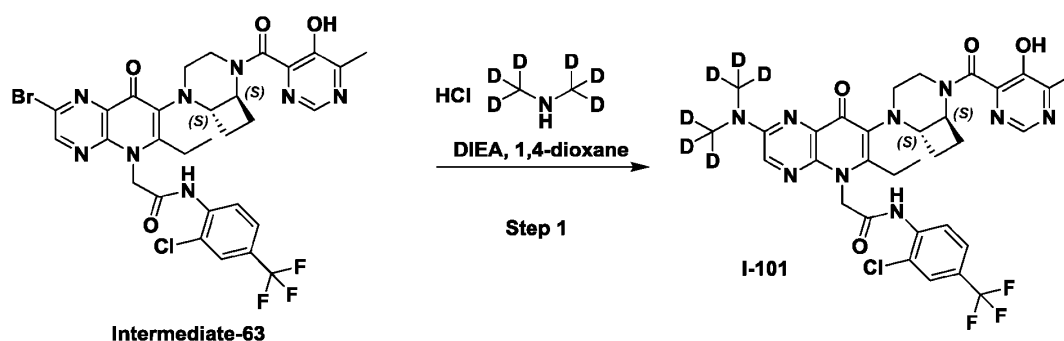
[00469] Step 1. Synthesis of 2-(2-(dimethylamino)-6-ethyl-7-((1*S*,6*S*)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-*b*]pyrazin-5(8*H*)-yl)-*N*-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide

[00470] To a solution of 2-(2-(dimethylamino)-6-ethyl-7-((1*S*,6*S*)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-*b*]pyrazin-5(8*H*)-yl)acetic acid (Intermediate-62) (17 mg, 33 μ mol, 1.0 eq) and 3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-amine hydrochloride (12 mg, 65 μ mol, 2.0 eq) in DMF (1 mL) was added HATU (25 mg, 65 μ mol, 2.0 eq) and DIEA (13 mg, 98 μ mol, 3.0 eq), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00471] LCMS: 656.5 [M+H]⁺.

[00472] ¹H NMR (400 MHz, CDCl₃) δ ppm 12.60 (s, 1H), 8.74 – 8.49 (m, 1H), 8.32 (br s, 1H), 6.90 – 6.43 (m, 1H), 5.75 – 4.79 (m, 3H), 4.39 – 4.08 (m, 2H), 4.00 – 3.51 (m, 2H), 3.40 (br s, 1H), 3.31 (s, 6H), 3.28 – 3.22 (m, 1H), 3.13 (br s, 1H), 2.55 (s, 3H), 2.29 (s, 8H), 1.56 – 1.36 (m, 2H), 1.30 (br t, 3H).

[00473] Synthesis of 2-(2-(bis(methyl-*d*3)amino)-6-ethyl-7-((1*S*,6*S*)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-*b*]pyrazin-5(8*H*)-yl)-*N*-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (I-101)



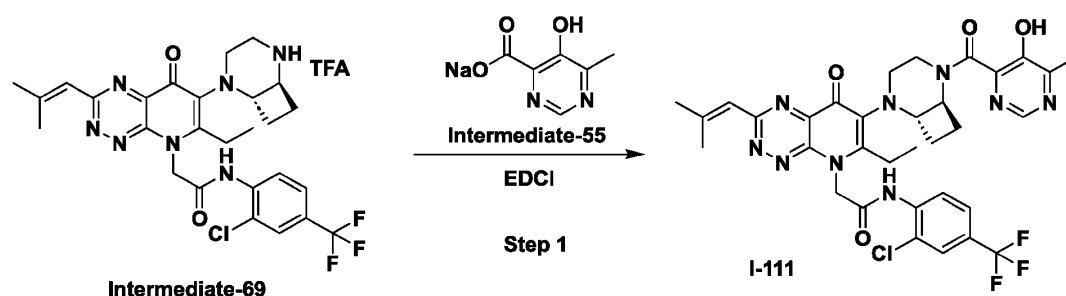
[00474] Step 1. Synthesis of 2-(2-(bis(methyl-d₃)amino)-6-ethyl-7-((1*S*,6*S*)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-*b*]pyrazin-5(8*H*)-yl)-*N*-(2-chloro-4-(trifluoromethyl)phenyl)acetamide

[00475] To a solution of 2-(2-bromo-6-ethyl-7-((1*S*,6*S*)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-*b*]pyrazin-5(8*H*)-yl)-*N*-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (Intermediate-63) (40 mg, 54 μmol, 1.0 eq) in 1,4-dioxane (1 mL) was added DIEA (42 mg, 326 μmol, 6.0 eq) and bis(methyl-d₃)amine hydrochloride (24 mg, 272 μmol, 5.0 eq). The resulting mixture was stirred at 100 °C for 1 h and then concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00476] LCMS: 706.3 [M+H]⁺.

[00477] ¹H NMR (400 MHz, CDCl₃) δ 12.68 (s, 1H), 8.61 (br s, 1H), 8.55 (d, 1H), 8.41 (s, 1H), 8.21 (s, 1H), 7.60 (s, 1H), 7.54 (d, 1H), 5.80 - 4.89 (m, 3H), 4.54 - 4.14 (m, 2H), 4.06 - 3.56 (m, 2H), 3.47 - 3.27 (m, 2H), 3.25 - 3.00 (m, 1H), 2.61 - 1.94 (m, 5H), 1.50 - 1.39 (m, 2H), 1.34 (t, 3H).

[00478] Synthesis of *N*-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-ethyl-6-((1*S*,6*S*)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-3-(2-methylprop-1-en-1-yl)-5-oxopyrido[3,2-*e*][1,2,4]triazin-8(5*H*)-yl)acetamide (I-111)



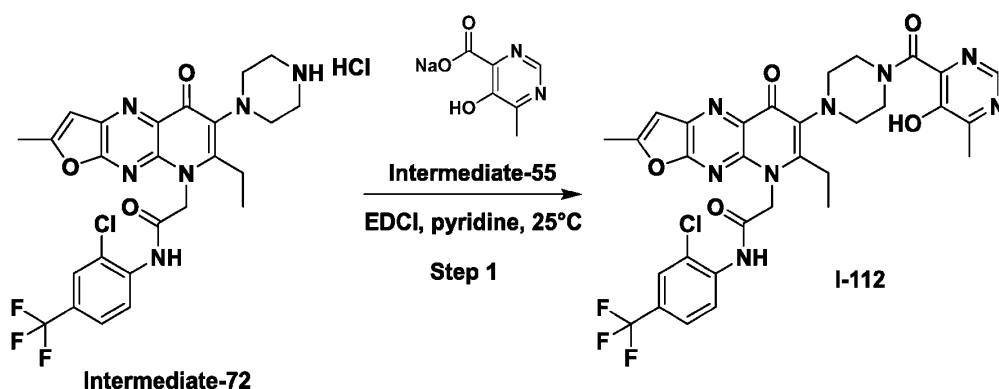
[00479] Step 1: Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-ethyl-6-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-3-(2-methylprop-1-en-1-yl)-5-oxopyrido[3,2-e][1,2,4]triazin-8(5H)-yl)acetamide

[00480] To a solution of 2-(6-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-ethyl-3-(2-methylprop-1-en-1-yl)-5-oxopyrido[3,2-e][1,2,4]triazin-8(5H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate (Intermediate-69) (170 mg, 295 μ mol, 1.0 eq) and sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate (Intermediate-55) (91 mg, 590 μ mol, 2.0 eq) in pyridine (2 mL) was added EDCI (141 mg, 738 μ mol, 2.5 eq), and it was stirred at room temperature overnight. The reaction mixture was diluted with saturated NH_4Cl aqueous solution (10 mL), and then extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00481] LCMS: 712.2 $[\text{M}+\text{H}]^+$.

[00482] ^1H NMR (400 MHz, CDCl_3) δ ppm 12.48 (m, 1H), 8.74 (s, 1H), 8.53 (s, 1H), 8.34 (d, 1H), 7.56 (s, 1H), 7.42 (d, 1H), 6.73 (s, 1H), 5.58 (s, 2H), 4.80 (d, 1H), 4.15 (s, 2H), 3.96 - 3.45 (m, 2H), 3.41 - 3.01 (m, 3H), 2.47 (s, 3H), 2.37 - 2.16 (m, 4H), 2.03 (s, 3H), 1.97 - 1.72 (m, 2H), 1.39 (s, 1H), 1.31 (t, 3H).

[00483] Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methyl-5-oxofuro[2,3-b]pyrido[3,2-e]pyrazin-8(5H)-yl)acetamide (I-112)



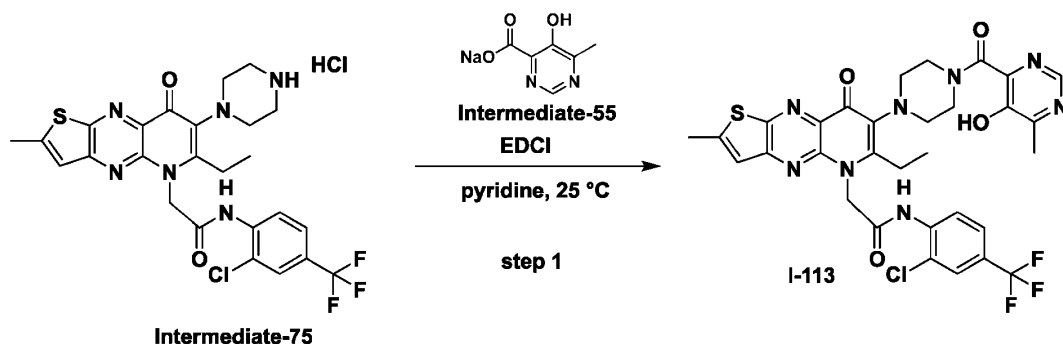
[00484] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methyl-5-oxofuro[2,3-b]pyrido[3,2-e]pyrazin-8(5H)-yl)acetamide

[00485] To a solution of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-ethyl-2-methyl-5-oxo-6-(piperazin-1-yl)furo[2,3-b]pyrido[3,2-e]pyrazin-8(5H)-yl)acetamide hydrochloride (Intermediate-72) (80 mg, 137 μ mol, 1 eq) in pyridine (2 mL) was added EDCI (131 mg, 685 μ mol, 5 eq) and sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate (Intermediate-55) (120 mg, 685 μ mol, 5 eq). The mixture was stirred at 25 °C for 12 h. The mixture was poured into H₂O (20 mL) and extracted with DCM (10 mL*3). The combined organic layer was concentrated in vacuum to give a residue. The residue was purified by reverse Phase HPLC (C18 column, water (10 mmol/L FA)-ACN) to afford the title compound.

[00486] ¹H NMR (400 MHz, CD₃OD) δ ppm 8.55 (s, 1H), 8.11 (d, 1H), 7.81 (d, 1H), 7.58 (d, 1H), 6.87 (s, 1H), 5.64 (s, 2H), 4.71- 4.68 (m, 1H), 4.18 - 4.05 (m, 1H), 3.95 - 3.93 (m, 2H), 3.53 - 3.40 (m, 1H), 3.30 - 3.29 (m, 2H), 3.21 - 3.09 (m, 1H), 3.00 - 2.87 (m, 1H), 2.82 - 2.73 (m, 1H), 2.61 (s, 3H), 2.52 (s, 3H), 1.37 (t, 3H).

[00487] LCMS: 685.3 [M+H]⁺.

[00488] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methyl-8-oxopyrido[2,3-b]thieno[2,3-e]pyrazin-5(8H)-yl)acetamide (I-113)*



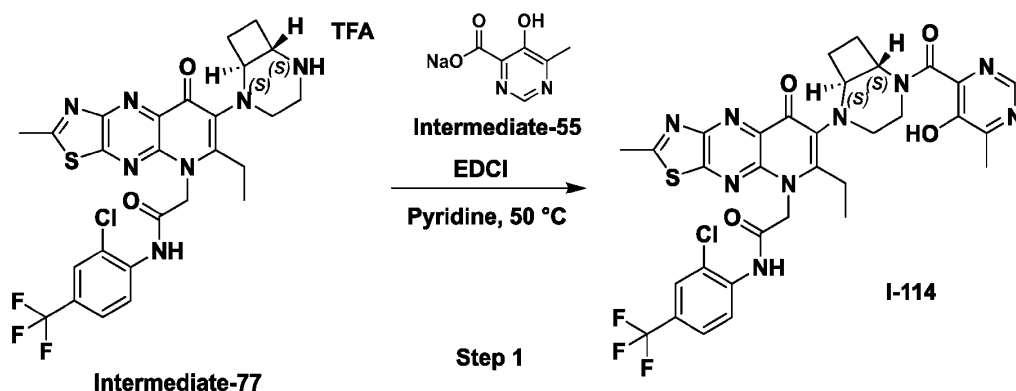
[00489] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidin-4-carbonyl)piperazin-1-yl)-2-methyl-8-oxopyrido[2,3-b]thieno[2,3-e]pyrazin-5(8H)-yl)acetamide

[00490] To a solution of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]thieno[2,3-e]pyrazin-5(8H)-yl)acetamide hydrochloride (Intermediate-75) (22 mg, 37 μ mol, 1 eq) and sodium 5-hydroxy-6-methylpyrimidin-4-carboxylate (Intermediate-55) (26 mg, 148 μ mol, 4 eq) in pyridine (0.5 mL) was added EDCI (25 mg, 129 μ mol, 3.5 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with H₂O (5 mL) and was extracted with DCM (5 mL * 2). The combined organic phase was washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by prep-TLC (SiO₂, Eluent: EtOAc) to afford the title compound.

[00491] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.73 (s, 1H), 8.60 (s, 1H), 8.52 (d, 1H), 7.61 (s, 1H), 7.54 (d, 1H), 7.18 (s, 1H), 5.60 (s, 1H), 5.42 (s, 2H), 4.82 - 4.79 (m, 1H), 4.06 - 4.01 (m, 2H), 3.58 - 3.50 (m, 1H), 3.36 - 3.35 (m, 2H), 3.19 - 3.06 (m, 1H), 2.89 - 2.80 (m, 3H), 2.77 (s, 3H), 2.58 (s, 3H), 1.39 (t, 3H).

[00492] LCMS: 701.3 [M+H]⁺.

[00493] Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidin-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-methyl-8-oxopyrido[2,3-b]thiazolo[4,5-e]pyrazin-5(8H)-yl)acetamide (I-114)



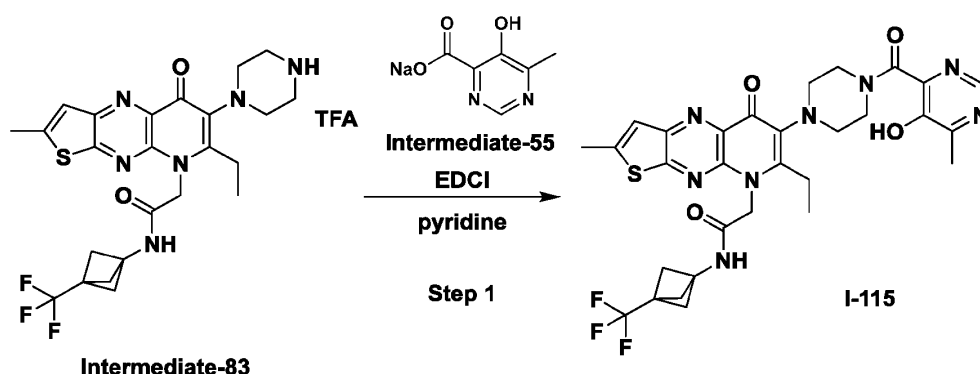
[00494] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl) phenyl)-2-(6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo [4.2.0] octan-2-yl)-2-methyl-8-oxopyrido[2,3-b] thiazolo[4,5-e] pyrazin-5(8H)-yl) acetamide

[00495] To a solution of 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-6-ethyl-2-methyl-8-oxopyrido[2,3-b]thiazolo[4,5-e]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate (Intermediate-77) (80 mg, 113 μ mol, 1 eq) in pyridine (2 mL) was added and sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate (Intermediate-55) (112 mg, 662 μ mol, 5.5 eq) and EDCI (109 mg, 565 μ mol, 5 eq). The mixture was stirred at 50 °C for 12 hr. The mixture was concentrated in vacuum to give a residue. The residue was purified by reverse Phase HPLC (C18 column, water (10 mmol/L FA)-ACN) to afford the title compound.

[00496] ¹H NMR (400 MHz, CD₃OD) δ ppm 8.57 (s, 1H), 8.08 (d, 1H), 7.82 (s, 1H), 7.60 (d, 1H), 5.67 (s, 2H), 4.82 - 4.69 (m, 1H), 4.22 - 4.02 (m, 1H), 3.84 - 3.59 (m, 3H), 3.57 - 3.34 (m, 3H), 2.98 (s, 3H), 2.52 (s, 3H), 1.83 - 1.62 (m, 2H), 1.58 - 1.44 (m, 2H), 1.39 (t, 3H).

[00497] LCMS: 728.1 [M+H]⁺.

[00498] *Synthesis of 2-(7-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methyl-5-oxopyrido[2,3-b]thieno[3,2-e]pyrazin-8(5H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (I-115)*



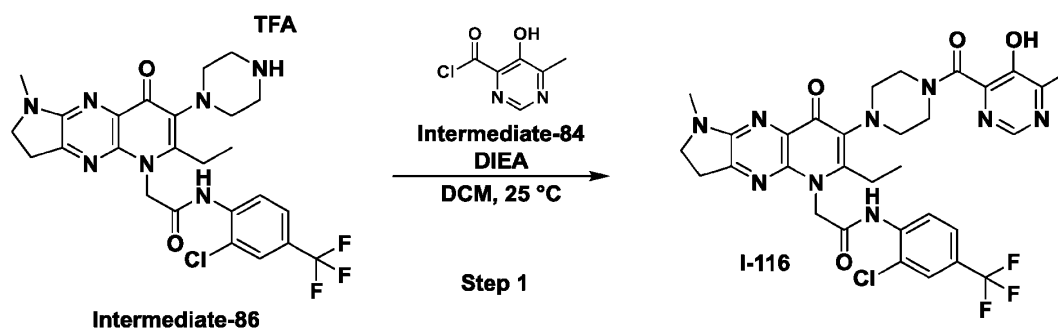
[00499] Step 1. Synthesis of 2-(7-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-methyl-5-oxopyrido[2,3-b]thieno[3,2-e]pyrazin-8(5H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide

[00500] To a solution of 2-(7-ethyl-2-methyl-5-oxo-6-(piperazin-1-yl)pyrido[2,3-b]thieno[3,2-e]pyrazin-8(5H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide trifluoroacetate (Intermediate-83) (120 mg, 189 μ mol, 1 eq) and sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate (Intermediate-55) (155 mg, 880 μ mol, 4.6 eq) in pyridine (3 mL) was added EDCI (181 mg, 946 μ mol, 5 eq). The mixture was stirred at 60 °C for 6 h. The mixture was concentrated in vacuum directly to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) and reverse Phase HPLC (C18 column, water (10 mmol/L FA)-ACN) to afford the title compound.

[00501] ¹H NMR (400 MHz, CD₃OD) δ ppm 8.57 (s, 1H), 7.36 (s, 1H), 5.32 (s, 2H), 4.76 - 4.65 (m, 1H), 4.19 - 3.88 (m, 3H), 3.53 - 3.39 (m, 1H), 3.23 (q, 2H), 3.19 - 3.11 (m, 1H), 2.96 - 2.85 (m, 1H), 2.78 - 2.74 (m, 4H), 2.53 (s, 3H), 2.29 (s, 6H), 1.33 (t, 3H).

[00502] LCMS: 657.3 [M+H]⁺.

[00503] Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-1-methyl-8-oxo-1,2,3,8-tetrahydro-5H-pyrido[2,3-b]pyrrolo[2,3-e]pyrazin-5-yl)acetamide (I-116)



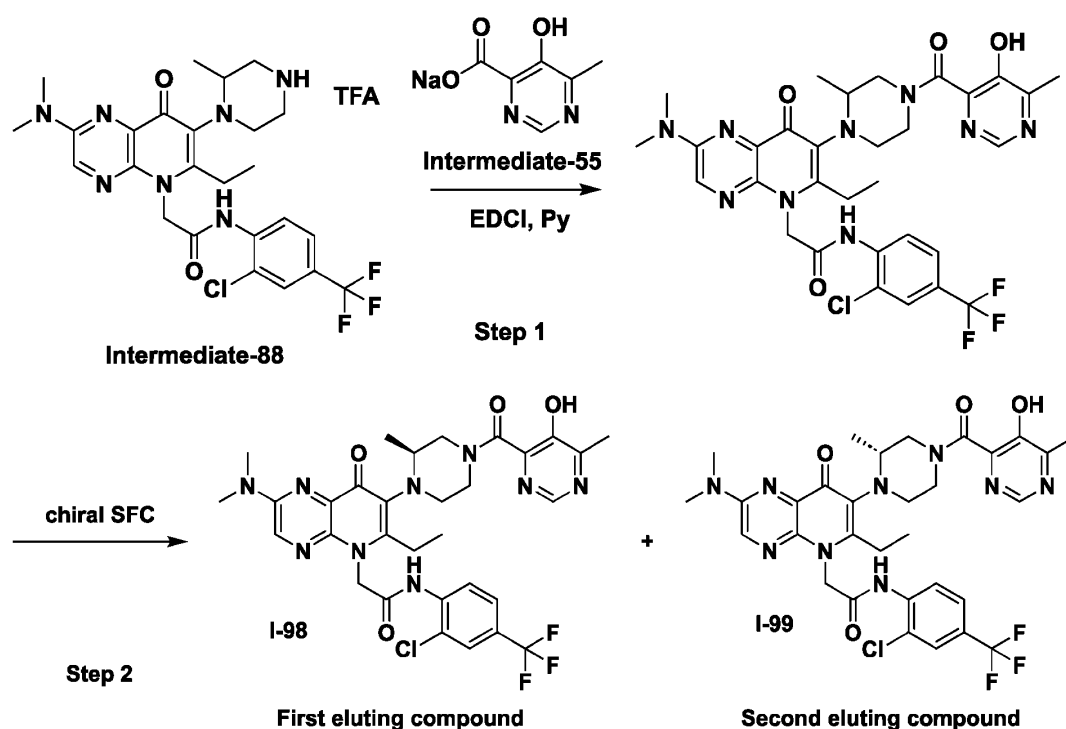
[00504] Step 1: Synthesis of N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[11-ethyl-12-[4-(5-hydroxy-6-methyl-pyrimidine-4-carbonyl)piperazin-1-yl]-4-methyl-13-oxo-2,4,8,10-tetrazatricyclo[7.4.0.0^{3,7}]trideca-1(9),2,7,11-tetraen-10-yl]acetamide

[00505] To a solution of N-[2-chloro-4-(trifluoromethyl)phenyl]-2-(11-ethyl-4-methyl-13-oxo-12-piperazin-1-yl-2,4,8,10-tetrazatricyclo[7.4.0.0^{3,7}]trideca-1(9),2,7,11-tetraen-10-yl)acetamide trifluoroacetate (Intermediate-86) (8 mg, 15 μ mol, 1.0 eq) in DCM (2 mL) was added DIEA (8 mg, 58 μ mol, 4.0 eq) and 5-hydroxy-6-methyl-pyrimidine-4-carbonyl chloride (Intermediate-84) (12 mg, 73 μ mol, 5.0 eq). And the resulting mixture was stirred at room temperature for 10 min. The reaction mixture was diluted with H₂O (10 mL), extracted with DCM (10 mL*2). The organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00506] ¹H NMR (400 MHz, CDCl₃) δ ppm 11.79 (s, 1H), 8.58 (s, 1H), 8.54 (d, 1H), 8.29 (s, 1H), 7.61 (s, 1H), 7.55 (d, 1H), 5.50 (s, 1H), 5.29 (s, 2H), 4.76 (d, 1H), 4.13 - 4.00 (m, 2H), 3.74 (t, 2H), 3.50 (s, 1H), 3.23 (t, 4H), 3.15 (s, 3H), 3.08 (s, 1H), 2.87 - 2.67 (m, 2H), 2.57 (s, 3H), 1.32 (t, 3H).

[00507] LCMS: 686.5[M+H]⁺.

[00508] Synthesis of (S)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-98) and (R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-99)



[00509] Step 1. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00510] To a solution of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(2-methylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (Intermediate-88) (175 mg, 317 μ mol, 1.0 eq) in pyridine (3 mL) was added EDCI (365 mg, 1.90 mmol, 6.0 eq) and sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate (Intermediate-55) (279 mg, 1.59 mmol, 5.0 eq), and the resulting mixture was stirred at 40 °C overnight. The reaction mixture was concentrated under reduced pressure and then purified by reverse phase HPLC (water (0.1% FA)-ACN) to afford the title compound.

[00511] Step 2. Synthesis of (S)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (single stereoisomer, first eluting compound) and (R)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-

6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl)-8-oxopyrido[2,3-b] pyrazin-5(8H)-yl) acetamide (single stereoisomer, second eluting compound)

[00512] N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide was separated by chiral SFC (SFC Preparative Method: Instrument: Waters 80Q Preparative SFC system; Column: DAICEL CHIRALCEL OX, 250×30mm I.D., 10μm particle size; Mobile phase A: CO₂, Mobile Phase B: MeOH/ACN=7/3=100% (0.1%NH₃-H₂O); Isocratic elution: 50% Phase B in Supercritical CO₂; Flow rate: 80 g/min; Retention Time: Peak1: 3.23min, Peak2: 4.59min; Back Pressure: 100 bar to keep the CO₂ in Supercritical flow; Wave Length: 220 nm) to afford the title compounds.

[00513] **I-98**

[00514] **LCMS: 688.2 [M+H]⁺.**

[00515] ¹H NMR (400 MHz, CDCl₃) δ 8.58 (br s, 1H), 8.54 (d, 1H), 8.45 (br s, 1H), 8.20 (s, 1H), 7.60 (s, 1H), 7.53 (br d, 1H), 5.61 - 5.29 (m, 2H), 5.29 - 5.05 (m, 1H), 4.83 - 4.63 (m, 1H), 4.25 - 4.10 (m, 1H), 3.94 (dt, 1H), 3.60 - 3.50 (m, 1H), 3.26 (s, 6H), 3.07 (br dd, 2H), 2.92 - 2.60 (m, 2H), 2.56 (s, 3H), 1.33 (br t, 3H), 1.01 - 0.79 (m, 3H).

[00516] Analytical Chiral SFC Retention time: 0.919 min.

[00517] **I-99**

[00518] **LCMS: 688.2 [M+H]⁺.**

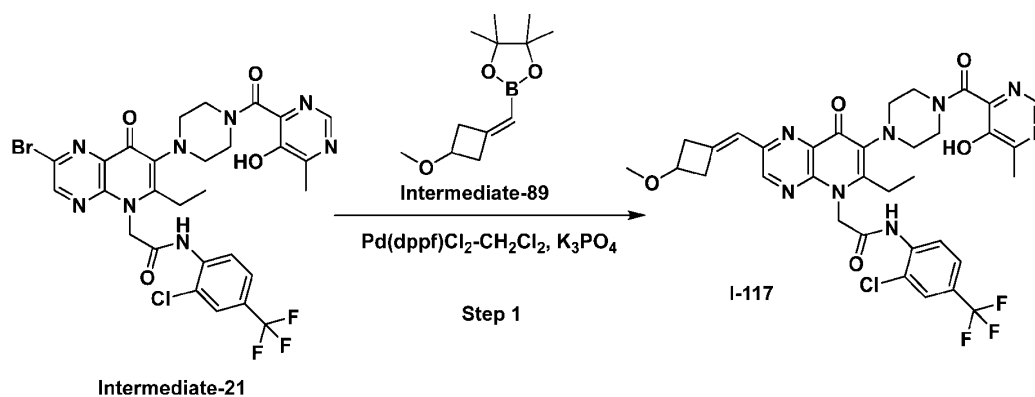
[00519] ¹H NMR (400 MHz, CDCl₃) δ 8.58 (br s, 1H), 8.54 (d, 1H), 8.42 (s, 1H), 8.20 (s, 1H), 7.60 (s, 1H), 7.53 (d, 1H), 5.62 - 5.33 (m, 2H), 5.30 - 5.11 (m, 1H), 4.82 - 4.68 (m, 1H), 4.24 - 4.11 (m, 1H), 3.94 (dt, 1H), 3.57 - 3.48 (m, 1H), 3.27 (s, 6H), 3.19 - 2.97 (m, 2H), 2.97 - 2.59 (m, 2H), 2.57 (s, 3H), 1.34 (br t, 3H), 0.98 - 0.83 (m, 3H).

[00520] Analytical Chiral SFC Retention time: 1.519 min.

[00521] Analytical SFC Method:

[00522] Instrument: SHIMADZU LC-30Aadsf, Column: Cellulose-4 50×4.6mm I.D., 3μm; Mobile phase: Phase A for CO₂, and Phase B for MeOH+ACN(0.05% DEA); Isocratic elution: 40% MeOH + ACN(0.05% DEA) in CO₂; Flow rate: 3mL/min; Detector: PDA; Column Temp: 35 °C; Back Pressure: 100Bar.

[00523] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-((3-methoxycyclobutylidene)methyl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-117)*



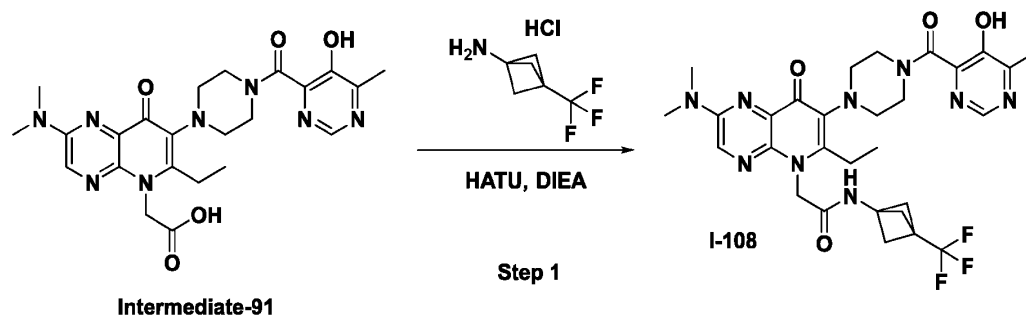
[00524] Step 1. Synthesis of N-[2-chloro-4-(trifluoromethyl)phenyl]-2-[6-ethyl-7-[4-(5-hydroxy-6-methyl-pyrimidine-4-carbonyl)piperazin-1-yl]-2-[(3-methoxycyclobutylidene)methyl]-8-oxo-pyrido[2,3-b]pyrazin-5-yl]acetamide

[00525] To a mixture of 2-(2-bromo-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (Intermediate-21) (50 mg, 70 μ mol, 1.0 eq) and 2-((3-methoxycyclobutylidene)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate-89) (16 mg, 70 μ mol, 1.0 eq) in 1,4-dioxane (1 mL) and H₂O (0.2 mL) was added Pd(dppf)Cl₂·CH₂Cl₂ (17 mg, 21 μ mol, 0.3 eq) and K₃PO₄ (45 mg, 211 μ mol, 3.0 eq), and the resulting mixture was stirred at 80 °C for 2 h under N₂ atmosphere. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by reverse phase HPLC (water (0.1% FA)-ACN) to afford the title compound.

[00526] **LCMS: 727.4 [M+H]⁺.**

[00527] **¹H NMR** (400 MHz, CDCl₃) δ ppm 12.28 (s, 1H), 8.72 - 8.61 (m, 1H), 8.58 (s, 1H), 8.52 (br d, 2H), 7.64 (s, 1H), 7.54 (br d, 1H), 6.72 - 6.51 (m, 1H), 5.73 - 5.51 (m, 1H), 5.51 - 5.18 (m, 2H), 4.92 - 4.65 (m, 1H), 4.14 - 3.98 (m, 3H), 3.67 - 3.48 (m, 2H), 3.37 - 3.28 (m, 5H), 3.23 - 3.07 (m, 3H), 3.00 - 2.92 (m, 1H), 2.90 - 2.71 (m, 2H), 2.57 (s, 3H), 1.37 (br d, 3H).

[00528] *Synthesis of 2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide (I-108)*



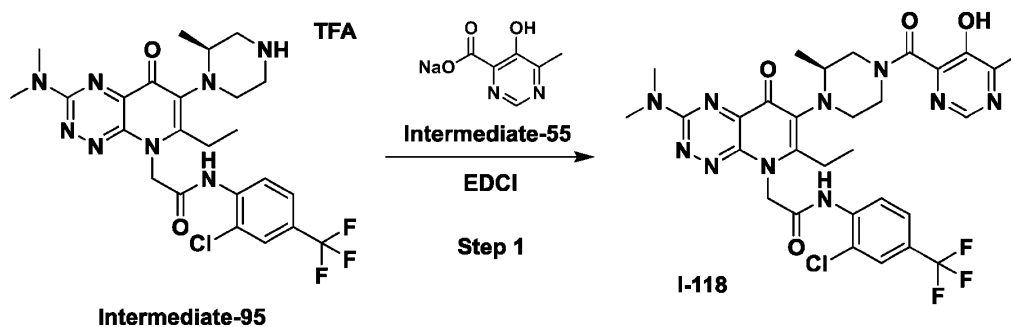
[00529] Step 1. Synthesis of 2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide

[00530] To a mixture of 2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid (Intermediate-91) (20 mg, 40 μ mol, 1.0 eq) and 3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-amine hydrochloride (15 mg, 81 μ mol, 2.0 eq) in DMF (1 mL) was added HATU (31 mg, 81 μ mol, 2.0 eq) and DIEA (16 mg, 121 μ mol, 3.0 eq), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA-ACN) to afford the title compound.

[00531] **LCMS: 630.3 [M+H]⁺.**

[00532] **¹H NMR** (400 MHz, CDCl₃) δ ppm 12.07 (s, 1H), 8.58 (s, 1H), 8.23 (s, 1H), 6.84 - 6.52 (m, 1H), 5.64 - 5.37 (m, 1H), 5.15 (br d, 2H), 4.86 - 4.60 (m, 1H), 4.06 - 3.87 (m, 2H), 3.62 - 3.42 (m, 1H), 3.24 (s, 6H), 3.18 - 3.04 (m, 3H), 2.87 - 2.75 (m, 2H), 2.57 (s, 3H), 2.29 (s, 6H), 1.28 (br t, 3H).

[00533] *Synthesis of (S)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3-(dimethylamino)-7-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl)-5-oxopyrido[3,2-e][1,2,4]triazin-8(5H)-yl)acetamide (I-118)*



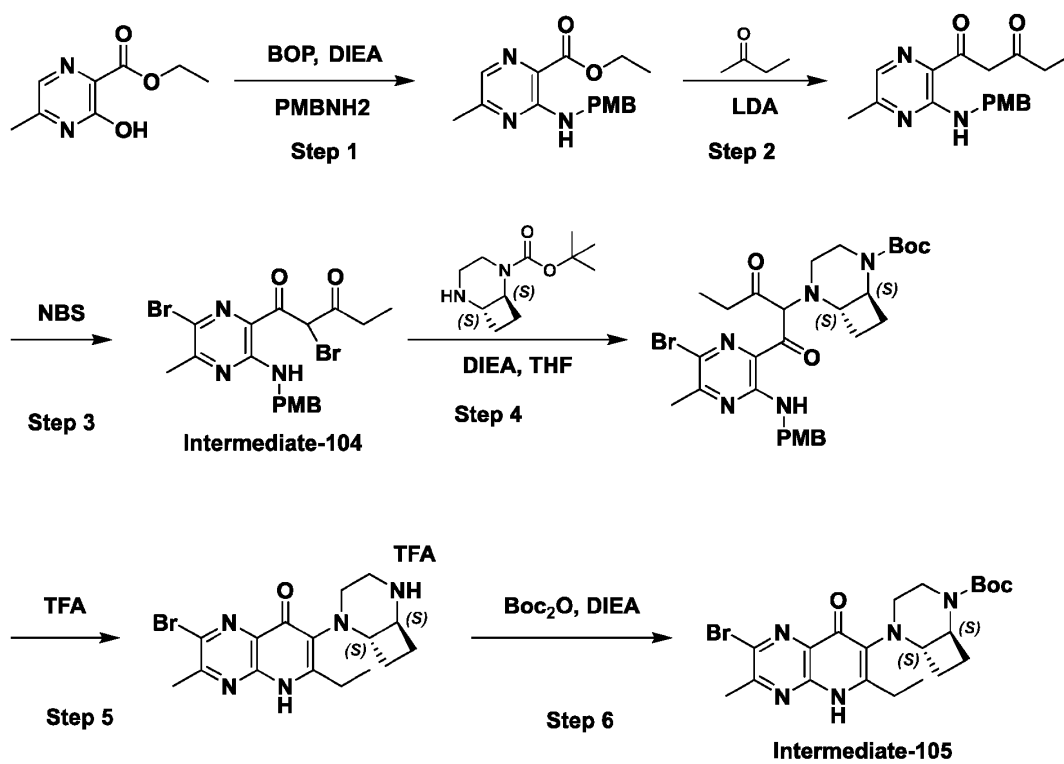
[00534] Step 1: Synthesis of (S)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3-(dimethylamino)-7-ethyl-6-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2-methylpiperazin-1-yl)-5-oxopyrido[3,2-e][1,2,4]triazin-8(5H)-yl)acetamide

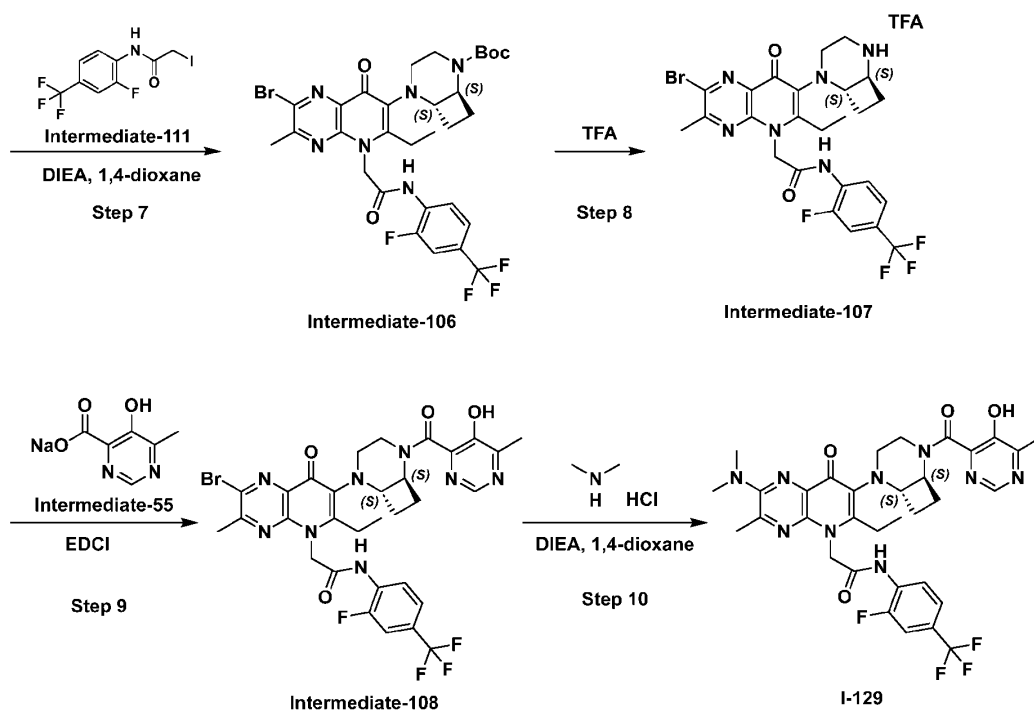
[00535] To a solution of (S)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3-(dimethylamino)-7-ethyl-6-(2-methylpiperazin-1-yl)-5-oxopyrido[3,2-e][1,2,4]triazin-8(5H)-yl)acetamide trifluoroacetate (Intermediate-95) (33 mg, 60 μ mol, 1.0 eq) and sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate (Intermediate-55) (14 mg, 90 μ mol, 1.5 eq) in pyridine (1 mL) was added EDCI (23 mg, 119 μ mol, 2.0 eq), and the resulting mixture was stirred at room temperature overnight. The reaction mixture was poured into saturated NH_4Cl aqueous solution (10 mL), and then extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00536] LCMS: 689.4 $[\text{M}+\text{H}]^+$.

[00537] ^1H NMR (400 MHz, CDCl_3) δ 8.56 - 8.44 (m, 2H), 8.42 (d, 1H), 7.57 (d, 1H), 7.44 (br d, 1H), 5.71 - 5.16 (m, 3H), 4.76 - 4.55 (m, 1H), 4.08 - 3.92 (m, 1H), 3.84 - 3.71 (m, 1H), 3.50 - 3.41 (m, 1H), 3.31 (s, 6H), 3.06 - 2.90 (m, 2H), 2.82 - 2.54 (m, 2H), 2.49 (s, 3H), 1.28 (br t, 3H), 0.93 - 0.75 (m, 3H).

[00538] Synthesis of 2-(2-(dimethylamino)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide (I-129)





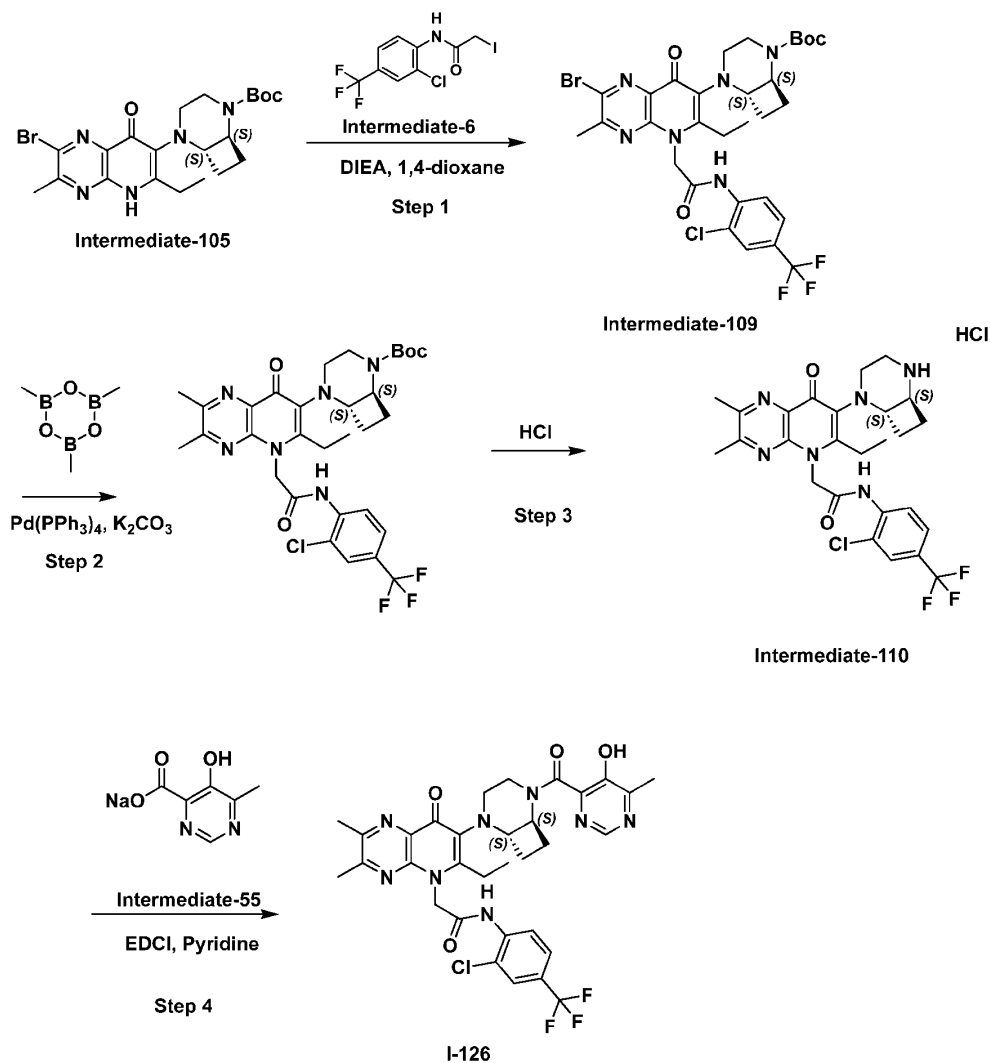
[00539] Step 10: Synthesis of 2-(2-(dimethylamino)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide

[00540] To a solution of 2-(2-bromo-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide (Intermediate-108) (80 mg, 109 μ mol, 1.0 eq) and dimethylamine hydrochloride (89 mg, 1.09 mmol, 10.0 eq) in 1,4-dioxane (1 mL) was added DIEA (211 mg, 1.64 mmol, 15.0 eq), and the resulting mixture was stirred at 100 °C for 3 h. The reaction mixture was concentrated under reduced pressure and then purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00541] LCMS: 698.3 [M+H]⁺.

[00542] ¹H NMR (400 MHz, CDCl₃) δ 11.79 (br s, 1H), 8.99 (s, 1H), 8.60 (s, 1H), 8.48 - 8.44 (t, 1H), 7.42 - 7.40 (d, 1H), 7.35 - 7.32 (d, 1H), 5.64 - 5.23 (m, 3H), 4.34 - 4.29 (m, 2H), 3.92 - 3.76 (m, 2H), 3.38 - 3.35 (m, 2H), 3.23 - 3.20 (m, 1H), 3.06 (s, 6H), 2.71 (s, 3H), 2.54 (s, 3H), 2.43 - 2.26 (m, 1H), 1.71 - 1.69 (m, 1H), 1.43 - 1.42 (m, 1H), 1.42 - 1.34 (m, 2H), 1.32 (t, 3H).

[00543] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2,3-dimethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (I-126)*



[00544] **Step 4:** Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2,3-dimethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

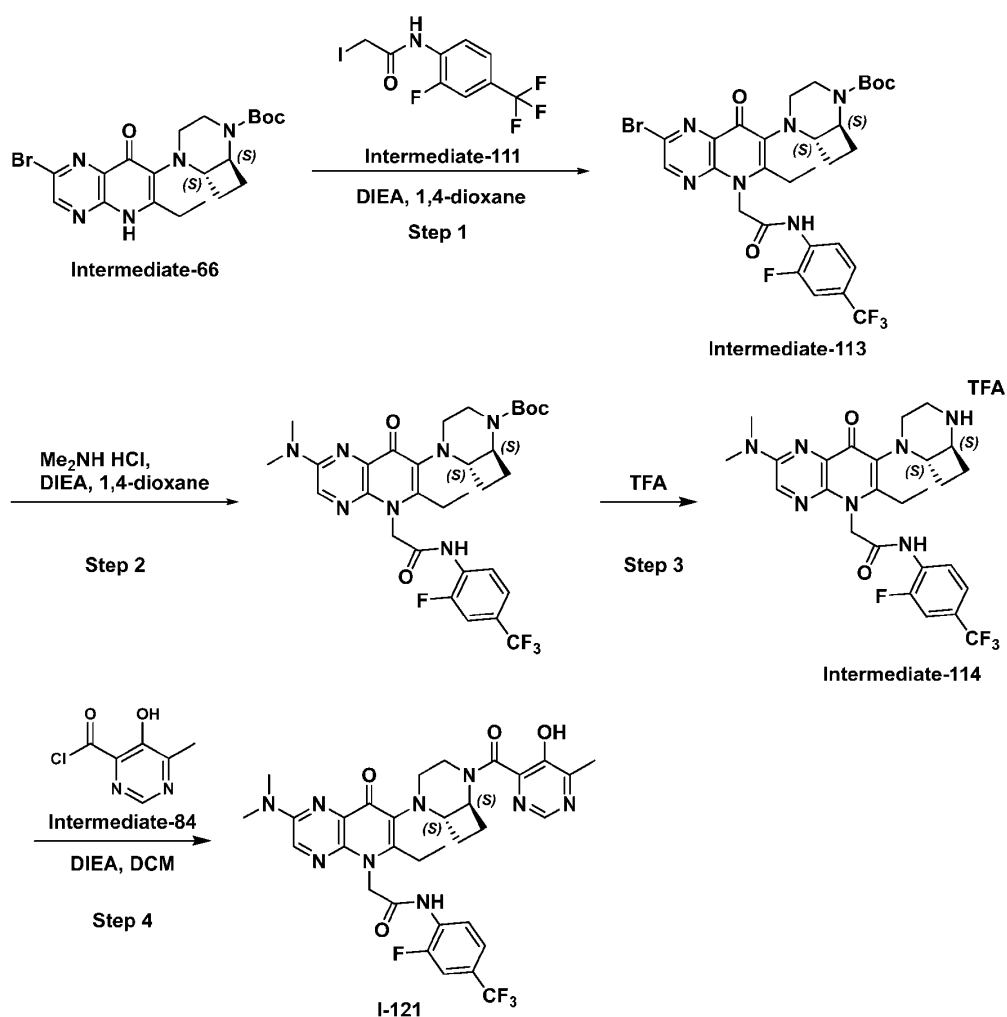
[00545] To a solution of 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-6-ethyl-2,3-dimethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide

hydrochloride (Intermediate-110) (80 mg, 145.72 μ mol, 1.0 eq) and sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate (Intermediate-55) (67 mg, 437 μ mol, 3.0 eq) in pyridine (1.0 mL) was added EDCI (140 mg, 728 μ mol, 5 eq), and the resulting mixture was stirred at 30 °C for 3 h. A solution of aqueous NaOH (1 M, 1 mL) was added to the reaction mixture and stirred for 15 min. The resulting mixture was adjust to pH = 6 with aqueous HCl solution (1 M) and extracted with EtOAc (10 mL * 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00546] LCMS: 685.3 [M+H]⁺.

[00547] ¹H NMR (400 MHz, CDCl₃) δ 11.72 (br s, 1H), 8.61 (s, 1H), 8.50 - 8.48 (d, 1H), 8.34 (s, 1H), 7.62 (s, 1H), 7.55 - 7.43 (d, 1H), 5.66 - 4.92 (m, 3H), 4.26 (s, 2H), 3.90 - 3.70 (m, 2H), 3.39 - 3.22 (m, 3H), 2.74 (s, 3H), 2.69 (s, 3H), 2.55 (s, 3H), 2.30 - 2.28 (m, 1H), 1.46 (br s, 2H), 1.37 - 1.33 (t, 3H), 1.32 - 1.26 (m, 1H).

[00548] *Synthesis of 2-(2-(dimethylamino)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide (I-121)*



[00549] Step 4: Synthesis of 2-(2-(dimethylamino)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide

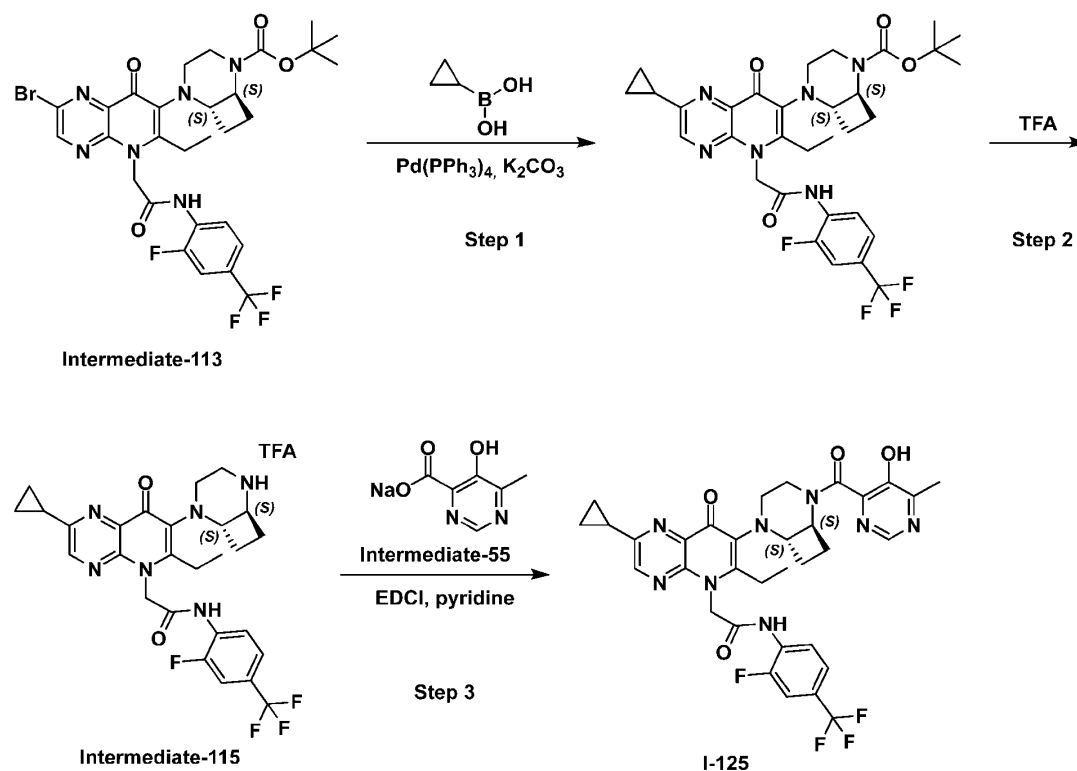
[00550] To a solution of 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(dimethylamino)-6-ethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate (Intermediate-114) (50 mg, 91 μmol , 1.0 eq) in DCM (1 mL) was added DIEA (94 mg, 731 μmol , 8.0 eq) and a solution of 5-hydroxy-6-methylpyrimidine-4-carbonyl chloride (Intermediate-84) (79 mg, 457 μmol , 5.0 eq) in DCM (0.5 mL), and the resulting mixture was stirred at room temperature for 15 min. The reaction mixture was quenched with H_2O (10 mL),

and then extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00551] LCMS: 684.3 [M+H]⁺.

[00552] ¹H NMR (400 MHz, CDCl₃) δ 12.01 (s, 1H), 8.71 (br s, 1H), 8.61 (br s, 1H), 8.47 (t, 1H), 8.23 (s, 1H), 7.41 (br d, 1H), 7.34 (br d, 1H), 5.80 - 4.88 (m, 3H), 4.56 - 4.10 (m, 2H), 4.08 - 3.82 (m, 1H), 3.81 - 3.58 (m, 1H), 3.37 (br d, 2H), 3.29 (s, 6H), 3.25 - 3.14 (m, 1H), 2.55 (s, 3H), 1.45 (dt, 2H), 1.33 (br t, 4H), 1.26 (br s, 1H).

[00553] *Synthesis of 2-(2-cyclopropyl-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide (I-125)*



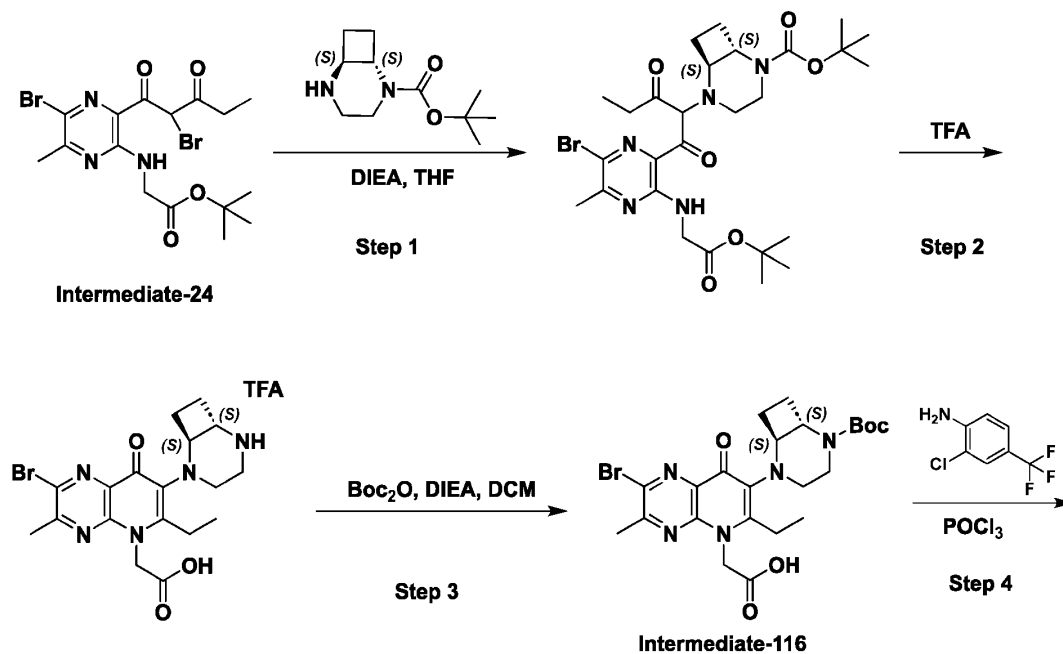
[00554] Step 3: Synthesis of 2-(2-cyclopropyl-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide

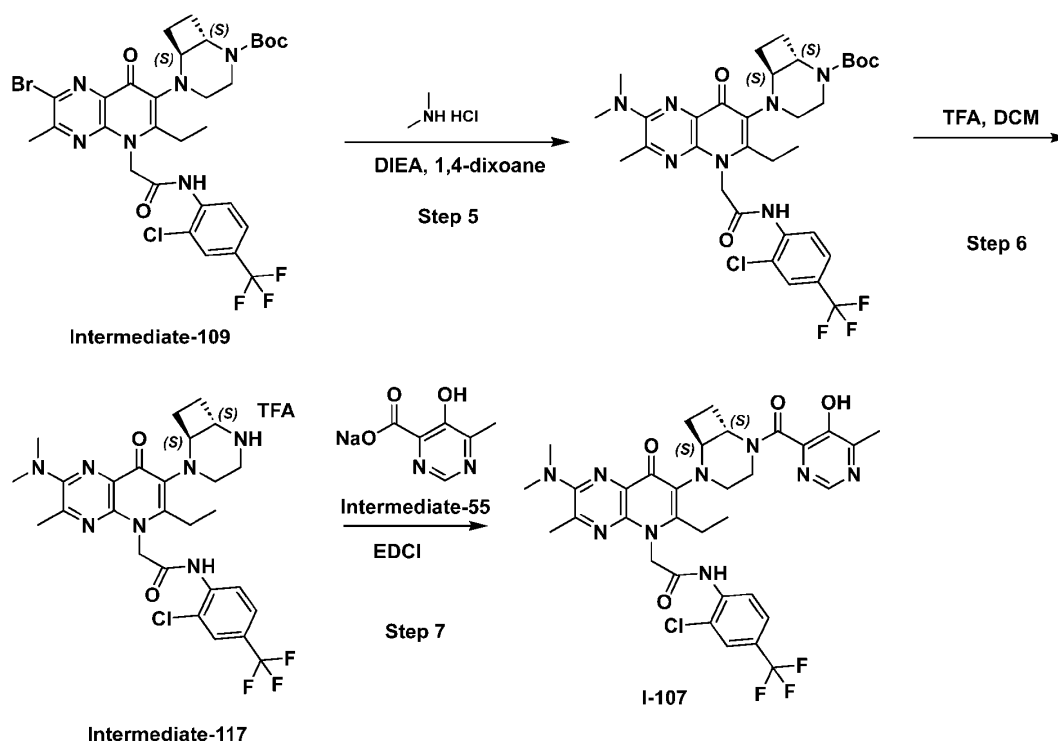
[00555] To a solution of 2-(7-((1*S*,6*S*)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-cyclopropyl-6-ethyl-8-oxopyrido[2,3-*b*]pyrazin-5(8*H*)-yl)-*N*-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate (Intermediate-115) (160 mg, 294 μ mol, 1.0 *eq*) and sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate (Intermediate-55) (136 mg, 881 μ mol, 3.0 *eq*) in pyridine (4 mL) was added EDCI (225 mg, 1.18 mmol, 4.0 *eq*), and the resulting mixture was stirred at 45 °C for 1.5 h. The mixture was diluted with H₂O (20 mL) and extracted with DCM (25 mL * 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00556] LCMS: 681.2 [M+H]⁺.

[00557] ¹H NMR (400 MHz, CDCl₃) δ 11.62 (s, 1H), 8.78 (br s, 1H), 8.61 (br s, 1H), 8.57 (s, 1H), 8.45 (t, 1H), 7.41 (br d, 1H), 7.36 (br d, 1H), 5.92 - 4.80 (m, 3H), 4.47 - 4.11 (m, 2H), 4.02 - 3.55 (m, 2H), 3.47 - 3.32 (m, 2H), 3.26 - 3.11 (m, 1H), 2.55 (s, 3H), 2.47 - 2.19 (m, 2H), 1.71 (br dd, 1H), 1.52 - 1.38 (m, 2H), 1.37 - 1.28 (m, 5H), 1.16 (dd, 2H).

[00558] *Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-((1*S*,6*S*)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-3-methyl-8-oxopyrido[2,3-*b*]pyrazin-5(8*H*)-yl)acetamide (I-107)*





[00559] Step 7: Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00560] To a solution of 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(dimethylamino)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate (Intermediate-117) (110 mg, 190 μmol , 1.0 eq) in pyridine (2 mL) was added EDCI (292 mg, 1.52 mmol, 8.0 eq) and sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate (Intermediate-55) (88 mg, 571 μmol , 3.0 eq), and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated and then purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

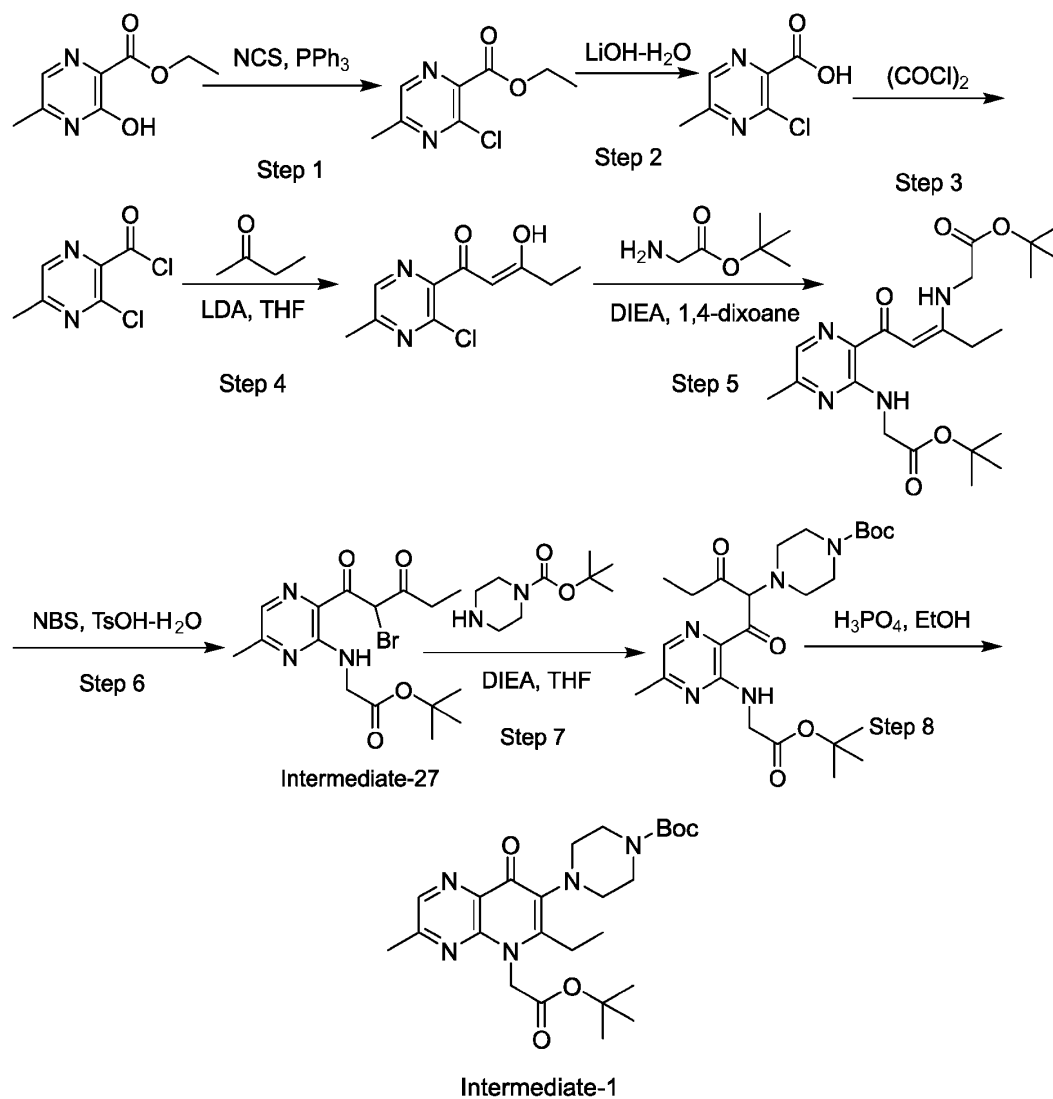
[00561] LCMS: 714.2 $[\text{M}+\text{H}]^+$.

[00562] ^1H NMR (400 MHz, CDCl_3) δ 12.75 (s, 1H), 8.64 - 8.55 (m, 1H), 8.52 (d, 1H), 8.27 (s, 1H), 7.60 (s, 1H), 7.54 (d, 1H), 5.81 - 4.85 (m, 3H), 4.59 - 4.13 (m, 2H), 4.07 - 3.50 (m, 2H),

3.45 - 3.27 (m, 2H), 3.23 - 2.90 (m, 7H), 2.68 (s, 3H), 2.54 (s, 3H), 2.38 - 2.17 (m, 1H), 1.73 - 1.38 (m, 3H), 1.32 (t, 3H).

[00563] Synthesis of Intermediates of the disclosure

[00564] Intermediate-1: tert-butyl 4-(5-(2-(tert-butoxy)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate



[00565] Step 1: Synthesis of ethyl 3-chloro-5-methylpyrazine-2-carboxylate

[00566] To a solution of PPh₃ (64.79 g, 247.0 mmol, 3.0 eq) in 1,4-dioxane (200 mL) was added NCS (33.53 g, 251.1 mmol, 3.05 eq) and the mixture was stirred at 10 °C for 1 h. Then ethyl 3-

hydroxy-5-methylpyrazine-2-carboxylate (15.00 g, 82.34 mmol, 1.0 eq) was added and the resulting mixture was stirred at 100 °C overnight. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound. **LCMS: 201.1 [M+H]⁺**.

[00567] Step 2: Synthesis of 3-chloro-5-methylpyrazine-2-carboxylic acid

[00568] To a solution of ethyl 3-chloro-5-methylpyrazine-2-carboxylate (11.70 g, 58.32 mmol, 1.0 eq) in MeOH (40 mL) and H₂O (40 mL) was added LiOH-H₂O (3.92 g, 93.3 mmol, 1.6 eq) and the reaction was stirred at 5 °C for 20 mins. The reaction mixture was diluted with H₂O (40 mL), and then adjusted to pH 3 with aq. 1 N HCl solution. The resulting mixture was extracted with DCM (50 mL*2). The combined organic phase was washed with brine (40 mL), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[00569] Step 3: Synthesis of 3-chloro-5-methylpyrazine-2-carbonyl chloride

[00570] To a solution of 3-chloro-5-methylpyrazine-2-carboxylic acid (10.00 g, 57.95 mmol, 1 eq) in DCM (80 mL) was added (COCl)₂ (11.03 g, 86.92 mmol, 1.5 eq) and DMF (85 mg, 1.2 mmol, 0.02 eq). The reaction was stirred at room temperature for 2 h under N₂ atmosphere. The resulting mixture was concentrated under reduced pressure to afford the title compound, it was used into next step without further purification.

[00571] Step 4: Synthesis of 1-(3-chloro-5-methylpyrazin-2-yl)-3-hydroxypent-2-en-1-one

[00572] To a solution of butan-2-one (6.23 g, 86.4 mmol, 1.5 eq) in THF (40 mL) was added LDA (2 M in THF, 43.2 mL, 86.4 mmol, 1.5 eq) at -65 °C. The reaction mixture was stirred for 5 mins, 3-chloro-5-methylpyrazine-2-carbonyl chloride (11.0 g, 57.6 mmol, 1.0 eq) in THF (40 mL) was added dropwise to the mixture at -65 °C. The resulting mixture was warmed to room temperature and stirred at room temperature for 1 h. The reaction was quenched with water (10 mL), adjusted to pH 4 with aq. 1 N HCl solution, and then extracted with EtOAc (50 mL*2). The organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄, concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[00573] ¹H NMR (400MHz, CDCl₃) δ ppm 15.45 (br s, 1H), 8.42 (s, 1H), 6.39 (s, 1H), 2.63 (s, 3H), 2.49 (q, 2H), 1.23 (t, 3H).

[00574] Step 5: Synthesis of tert-butyl (1-(3-((2-(tert-butoxy)-2-oxoethyl)amino)-5-methylpyrazin-2-yl)-1-oxopent-2-en-3-yl)glycinate

[00575] To a solution of 1-(3-chloro-5-methylpyrazin-2-yl)-3-hydroxypent-2-en-1-one (3.00 g, 13.2 mmol, 1.0 eq) in 1,4-dioxane (30 mL) was added DIEA (2.57 g, 19.9 mmol, 1.5 eq) and tert-butyl 2-aminoacetate (1.74 g, 13.2 mmol, 1.0 eq). The reaction was stirred at 100 °C for 2 h. The mixture was diluted with H₂O (40 mL), extracted with EtOAc (20 mL*2). The organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[00576] ¹H NMR (400MHz, CDCl₃) δ ppm 11.23 (br s, 1H), 9.57 (br s, 1H), 7.68 (s, 1H), 6.47 (s, 1H), 4.17 (br d, 2H), 4.02 (d, 2H), 2.39 (s, 3H), 2.33 (q, 2H), 1.51 (s, 9H), 1.48 (s, 9H), 1.23 (t, 3H).

[00577] Step 6: Synthesis of tert-butyl (3-(2-bromo-3-oxopentanoyl)-6-methylpyrazin-2-yl)glycinate

[00578] To a solution of tert-butyl (1-(3-((2-(tert-butoxy)-2-oxoethyl)amino)-5-methylpyrazin-2-yl)-1-oxopent-2-en-3-yl)glycinate (1.70 g, 3.91 mmol, 1.0 eq) in DCM (15 mL) was added TsOH-H₂O (135 mg, 710 μmol, 0.18 eq) and NBS (627 mg, 3.52 mmol, 0.9 eq). The mixture was stirred at room temperature for 0.5 h. The reaction mixture was diluted with H₂O (10 mL) and then extracted with DCM (30 mL*2). The organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to afford the title compound, which was used in the next step without further purification. LCMS: 400.2 [M+H]⁺.

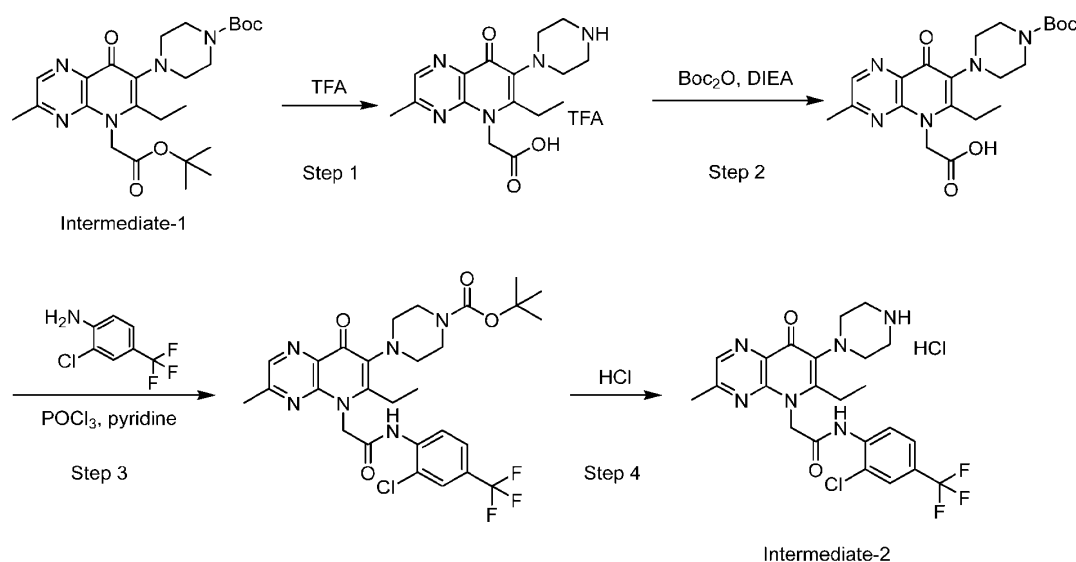
[00579] Step 7: Synthesis of tert-butyl 4-(1-(3-((2-(tert-butoxy)-2-oxoethyl)amino)-5-methylpyrazin-2-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate

[00580] To a solution of tert-butyl (3-(2-bromo-3-oxopentanoyl)-6-methylpyrazin-2-yl)glycinate (Intermediate-27) (1.50 g, 3.75 mmol, 1.0 eq) in THF (9 mL) was added tert-butyl piperazine-1-carboxylate (698 mg, 3.75 mmol, 1.0 eq) and DIEA (969 mg, 7.50 mmol, 2.0 eq) and the mixture was stirred at room temperature for 0.5 h. The reaction mixture was diluted with H₂O (10 mL) and then extracted with EtOAc (10 mL*2). The organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄, concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound, which was used in the next step without further purification. LCMS: 506.3 [M+H]⁺.

[00581] Step 8: Synthesis of tert-butyl 4-(5-(2-(tert-butoxy)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00582] To a solution of tert-butyl 4-(1-(3-((2-(tert-butoxy)-2-oxoethyl)amino)-5-methylpyrazin-2-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate (1.20 g, 2.37 mmol, 1.0 eq) in EtOH (10 mL) was added H₃PO₄ (465 mg, 4.75 mmol, 2.0 eq) and the resulting mixture was stirred at 60 °C overnight. The reaction mixture was concentrated under reduced pressure. The residue was diluted with H₂O (10 mL) and then extracted with EtOAc (10 mL*2). The organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄, concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound. **LCMS: 488.3 [M+H]⁺.**

[00583] Intermediate-2: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-3-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride



[00584] Step 1: Synthesis of 2-(6-ethyl-3-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid trifluoroacetate

[00585] To a solution of tert-butyl 4-(5-(2-(tert-butoxy)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-1) (550 mg, 1.13 mmol, 1.0 eq) in DCM (1 mL) was added TFA (5 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used in the next step without further purification.

[00586] LCMS: 332.2 [M+H]⁺.

[00587] Step 2: Synthesis of 2-(7-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid

[00588] To a solution of 2-(6-ethyl-3-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid trifluoroacetate (500 mg, 1.12 mmol, 1.0 eq) in DCM (8 mL) was added DIEA (725 mg, 5.61 mmol, 5.0 eq) and Boc₂O (245 mg, 1.12 mmol, 1.0 eq). The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into H₂O (10 mL) and extracted with DCM (10 mL*2). The organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to afford the title compound, which was used in the next step without further purification.

[00589] LCMS: 432.2 [M+H]⁺.

[00590] Step 3: Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00591] To a solution of 2-(7-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid (100 mg, 231 μmol, 1.0 eq) and 2-chloro-4-(trifluoromethyl) aniline (68 mg, 0.35 mmol, 1.5 eq) in pyridine (1 mL) and DCM (1 mL) was added POCl₃ (53 mg, 0.35 μmol, 1.5 eq) dropwise at -10 °C. The reaction mixture was stirred at -10 °C for 1 h and then poured into H₂O (10 mL). The resulting solution was extracted with EtOAc (10 mL*2), the organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to afford the title compound, which was used in the next step without further purification.

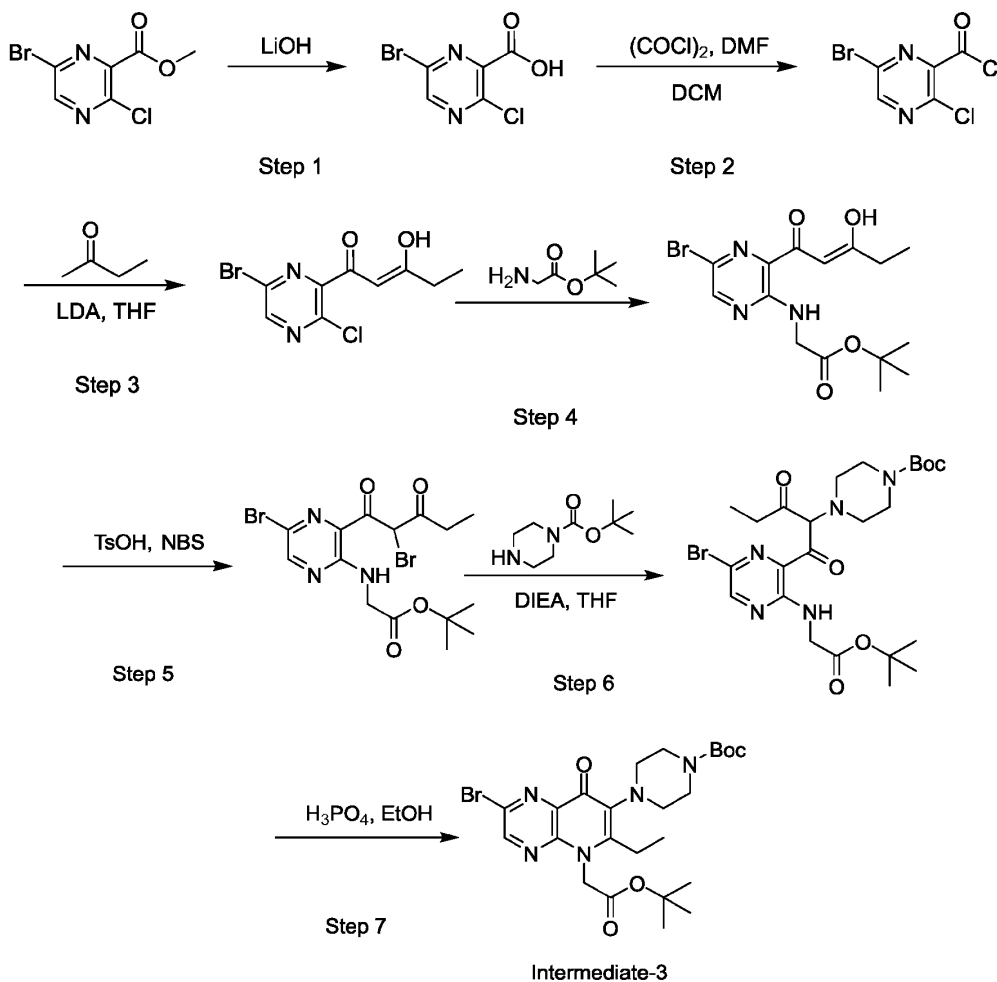
[00592] LCMS: 609.2 [M+H]⁺.

[00593] Step 4: Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-3-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride

[00594] tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (130 mg, 213 μmol, 1.0 eq) was added to a 4 M solution of HCl in 1,4-dioxane (2 mL) and then stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used in the next step without further purification.

[00595] LCMS: 509.2 [M+H]⁺.

[00596] Intermediate-3: tert-butyl 4-(2-bromo-5-(2-(tert-butoxy)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate



[00597] Step 1. Synthesis of 6-bromo-3-chloropyrazine-2-carboxylic acid

[00598] To a solution of methyl 6-bromo-3-chloropyrazine-2-carboxylate (21.45 g, 85.30 mmol, 1.0 eq) in THF (30 mL) was added MeOH (60 mL), H_2O (60 mL) and LiOH- H_2O (7.16 g, 171 mmol, 2.0 eq) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with H_2O (100 mL) and then adjusted pH 2~3 with aq. 6 N HCl solution. The resulting mixture was extracted with DCM (100 mL * 3). The combined organic layers were washed with brine (50 mL * 3), dried over anhydrous Na_2SO_4 , filtered and the filtrate was

concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[00599] Step 2. Synthesis of 6-bromo-3-chloropyrazine-2-carbonyl chloride

[00600] To a solution of 6-bromo-3-chloropyrazine-2-carboxylic acid (9.50 g, 40.0 mmol, 1.0 eq) in DCM (95 mL) was added (COCl)₂ (7.62 g, 60.0 mmol, 5.25 mL, 1.5 eq) and DMF (58 mg, 0.80 mmol, 0.02 eq) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used in the next step without further purification.

[00601] Step 3. Synthesis of (Z)-1-(6-bromo-3-chloropyrazin-2-yl)-3-hydroxypent-2-en-1-one

[00602] To a solution of butan-2-one (3.95 g, 54.7 mmol, 2.0 eq) in THF (70 mL) was added a 2 M solution of LDA (27.4 mL, 54.7 μ mol, 2.0 eq) in THF at -65 °C and the reaction mixture was stirred at -65 °C for 0.5 h. 6-bromo-3-chloropyrazine-2-carbonyl chloride (7.00 g, 27.4 mmol, 1.0 eq) was added at -65 °C and the mixture was stirred at -65 °C for 1 h. The reaction mixture was quenched by addition of saturated aq. NH₄Cl solution (20 mL) at -65 °C and allowed to warm to room temperature slowly. The resulting mixture was diluted with H₂O (100 mL) and extracted with EtOAc (100 mL * 2). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00603] ¹H NMR (400 MHz, CDCl₃) δ ppm 15.32 (s, 1H), 8.56 (s, 1H), 6.36 (s, 1H), 2.51 (q, 2H), 1.23 (br t, 3H).

[00604] Step 4. Synthesis of tert-butyl (Z)-(5-bromo-3-(3-hydroxypent-2-enoyl)pyrazin-2-yl)glycinate

[00605] To a solution of tert-butyl glycinate (450 mg, 3.43 mmol, 2.0 eq) in 1,4-dioxane (10 mL) was added (Z)-1-(6-bromo-3-chloropyrazin-2-yl)-3-hydroxypent-2-en-1-one (1.00 g, 1.72 mmol, 1.0 eq) in 1,4-dioxane (10 mL) dropwise over 10 min at 100 °C. The mixture was stirred at 100 °C for 10 min after addition. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00606] LCMS: 330.2 [M-55]⁺.

[00607] Step 5. Synthesis of tert-butyl (5-bromo-3-(2-bromo-3-oxopentanoyl)pyrazin-2-yl)glycinate

[00608] To a solution of tert-butyl (Z)-(5-bromo-3-(3-hydroxypent-2-enoyl)pyrazin-2-yl)glycinate (330 mg, 854 μ mol, 1.0 eq) in DCM (5 mL) was added TsOH-H₂O (15 mg, 85 μ mol, 0.1 eq), NBS (152 mg, 854 μ mol, 1.0 eq) at 0 °C and it was stirred at 0 °C for 0.5 h. The reaction mixture was quenched with H₂O (10 mL) and extracted with DCM (10 mL*2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[00609] LCMS: 410.0 [M-55]⁺.

[00610] Step 6. Synthesis of tert-butyl 4-(1-(6-bromo-3-((2-(tert-butoxy)-2-oxoethyl)amino)pyrazin-2-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate

[00611] To a solution of tert-butyl (5-bromo-3-(2-bromo-3-oxopentanoyl)pyrazin-2-yl)glycinate (397 mg, 853 μ mol, 1.0 eq) in THF (5 mL) was added tert-butyl piperazine-1-carboxylate (238 mg, 1.28 mmol, 1.5 eq), DIEA (110 mg, 853 μ mol, 1.0 eq) and the mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with DCM (10 mL*2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

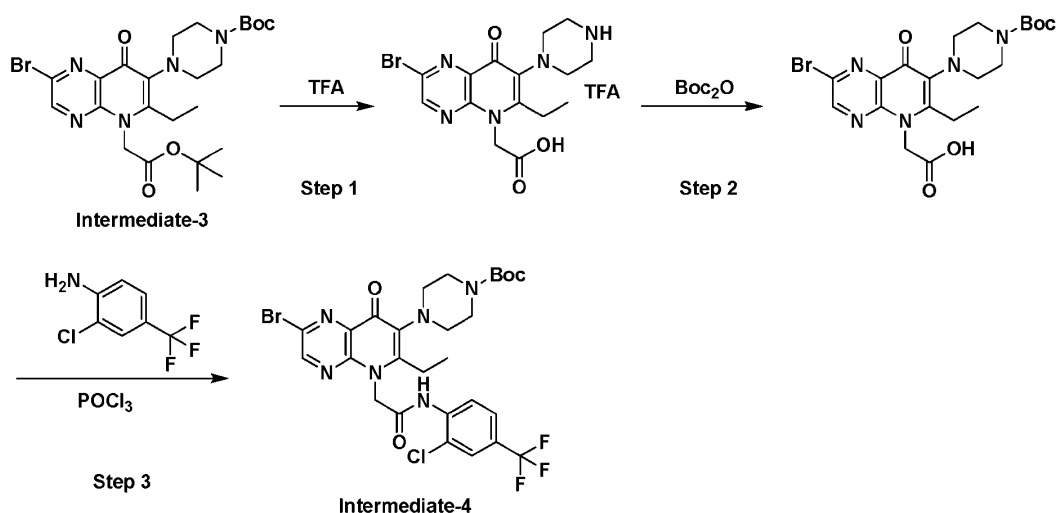
[00612] LCMS: 572.2 [M+H]⁺.

[00613] Step 7. Synthesis of tert-butyl 4-(2-bromo-5-(2-(tert-butoxy)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00614] To a solution of tert-butyl 4-(1-(6-bromo-3-((2-(tert-butoxy)-2-oxoethyl)amino)pyrazin-2-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate (350 mg, 613 μ mol, 1.0 eq) in EtOH (4 mL) was added H₃PO₄ (120 mg, 1.23 mmol, 2.0 eq) and the resulting mixture was stirred at 60 °C for 12 h. The reaction mixture was diluted with H₂O (10 mL) and then basified with 1 N aq. NaOH solution to pH 8. The resulting mixture was extracted with EtOAc (10 mL*2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00615] LCMS: 554.1 [M+H]⁺.

[00616] Intermediate-4: tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate



[00617] Step 1. Synthesis of 2-(2-bromo-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid trifluoroacetate

[00618] The solution of tert-butyl 4-(2-bromo-5-(2-(tert-butoxy)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-3) (100 mg, 181 μ mol, 1.0 eq) in DCM (1 mL) was added TFA (3 mL), and it was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[00619] LCMS: 396.0 $[M+H]^+$.

[00620] Step 2. Synthesis of 2-(2-bromo-7-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-ethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid

[00621] To a solution of 2-(2-bromo-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid trifluoroacetate (92 mg, 0.18 mmol, 1.0 eq) in DCM (2 mL) was added Et_3N (182 mg, 1.80 mmol, 10.0 eq) and Boc_2O (39 mg, 0.18 mmol, 1.0 eq). The reaction was stirred at room temperature for 0.5 h. The reaction mixture was diluted with H_2O (10 mL) and basified with 1 N aq. NaOH solution to pH 9. The resulting mixture was extracted with DCM (10 mL*2). The DCM phase was discarded. The aq. phase was adjusted to pH 6 with 1 N aq. HCl solution and then extracted with DCM (10 mL*2), the organic phase was washed with brine (20 mL),

dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated under vacuum to afford the title compound, which was used into the next step without further purification.

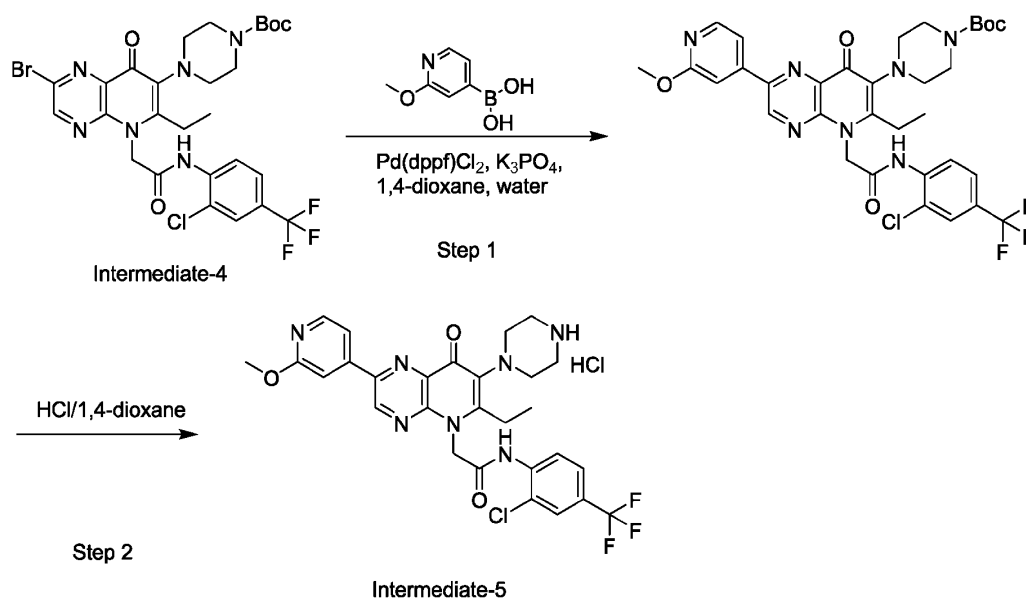
[00622] LCMS: 496.1 $[\text{M}+\text{H}]^+$.

[00623] Step 3. Synthesis of tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00624] To a solution of 2-(2-bromo-7-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-ethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid (96 mg, 0.19 mmol, 1.0 eq) and 2-chloro-4-(trifluoromethyl)aniline (57 mg, 0.29 mmol, 1.5 eq) in pyridine (1 mL) and DCM (1 mL) was added POCl_3 (44 mg, 0.29 mmol, 1.5 eq) at -10°C , and the resulting mixture was stirred at -10°C for 1 h under N_2 atmosphere. The reaction mixture was quenched with H_2O (10 mL) and extracted with DCM (10 mL*2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00625] LCMS: 673.1 $[\text{M}+\text{H}]^+$.

[00626] Intermediate-5: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-(2-methoxypyridin-4-yl)-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride



[00627] Step 1. Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-(2-methoxypyridin-4-yl)-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00628] To a solution of tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-4) (40 mg, 59 μ mol, 1.0 eq) and (2-methoxypyridin-4-yl)boronic acid (9 mg, 0.06 mmol, 1.0 eq) in 1,4-dioxane (1 mL) and H₂O (0.2 mL) was added Pd(dppf)Cl₂ (4 mg, 6 μ mol, 0.1 eq) and K₃PO₄ (25 mg, 0.12 mmol, 2.0 eq), the resulting mixture was stirred at 80 °C for 1 h under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure and then purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

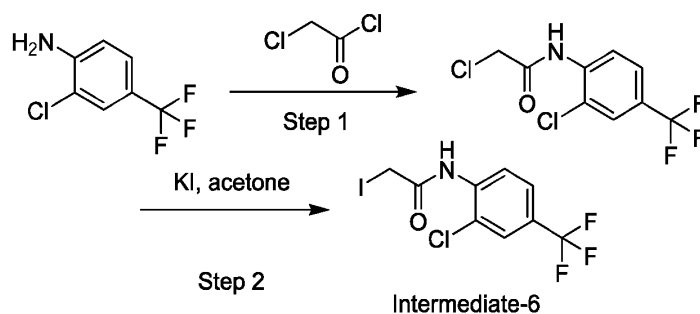
[00629] LCMS: 702.2 [M+H]⁺.

[00630] Step 2. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-(2-methoxypyridin-4-yl)-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride

[00631] To a solution of 4 M HCl in 1,4-dioxane (2 mL) was added tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-(2-methoxypyridin-4-yl)-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (31 mg, 44 μ mol, 1.0 eq), and it was stirred at room temperature for 0.5 h. The resulting mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[00632] LCMS: 602.2 [M+H]⁺.

[00633] Intermediate-6: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-iodoacetamide



[00634] Step 1. Synthesis of 2-chloro-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide

[00635] To a solution of 2-chloro-4-(trifluoromethyl)aniline (19.1 g, 97.7 mmol, 1.0 eq) and TEA (19.76 g, 195.3 mmol, 2.0 eq) in DCM (200 mL) was added dropwise a solution of 2-chloroacetyl chloride (11.03 g, 97.7 mmol, 1.0 eq) in DCM (50 mL) at 0 °C. After addition, the resulting mixture was warmed to room temperature and stirred at room temperature overnight. The reaction mixture was purified by column chromatography on silica gel (eluent of EtOAc/PE) to afford the title compound.

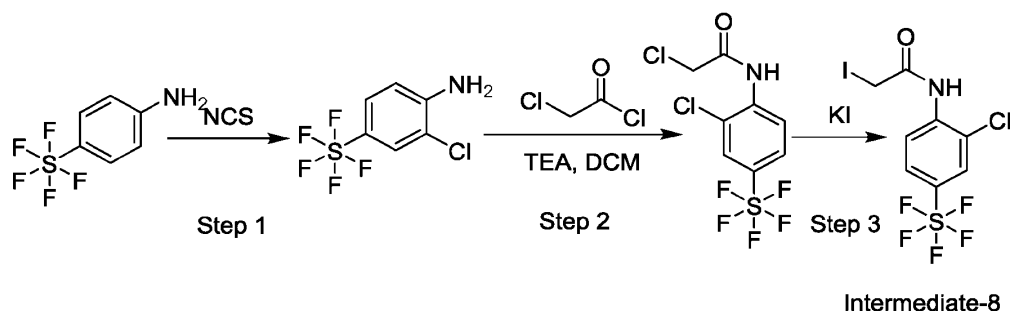
[00636] LCMS: 273.9 [M+H]⁺.

[00637] Step 2. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-iodoacetamide

[00638] To a solution of 2-chloro-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide (7.70 g, 28.3 mmol, 1.0 eq) in acetone (60 mL) was added KI (5.17 g, 31.1 mmol, 1.1 eq), the resulting mixture was stirred at 60 °C for 2 h. The mixture was cooled to room temperature, filtered and the filtrate was concentrated in vacuum to afford the title compound, which was used in the next step without further purification.

[00639] LCMS: 363.9 [M+H]⁺.

[00640] Intermediate-8: N-(2-chloro-4-(pentafluoro-λ⁶-sulfanyl)phenyl)-2-iodoacetamide



[00641] Step 1. Synthesis of 2-chloro-4-(pentafluoro-λ⁶-sulfanyl)aniline

[00642] To a solution of 4-(pentafluoro-λ⁶-sulfanyl)aniline (5.00 g, 22.8 mmol, 1.0 eq) in ACN (50 mL) was added NCS (3.35 g, 25.1 mmol, 1.1 eq). The resulting mixture was stirred at 60 °C for 0.5 h and then purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00643] LCMS: 254.2 [M+H]⁺.

[00644] Step 2. Synthesis of 2-chloro-N-(2-chloro-4-(pentafluoro-λ⁶-sulfanyl)phenyl)acetamide

[00645] To a solution of 2-chloro-4-(pentafluoro- λ^6 -sulfaneyl)aniline (1.00 g, 3.94 mmol, 1.0 eq) in DCM (10 mL) was added 2-chloroacetyl chloride (534 mg, 4.73 mmol, 1.2 eq) and TEA (798 mg, 7.89 mmol, 2.0 eq). The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with DCM (20 mL * 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

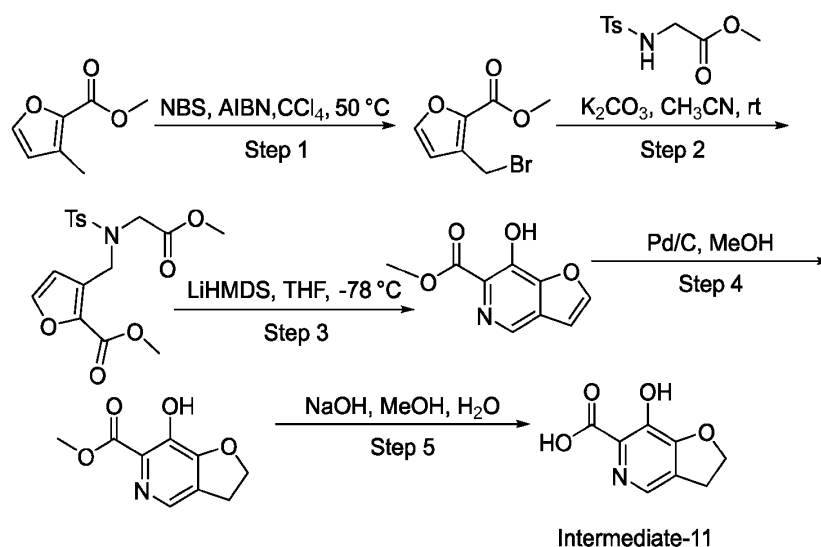
[00646] LCMS: 330.0 [M+H]⁺.

[00647] Step 3. Synthesis of N-(2-chloro-4-(pentafluoro- λ^6 -sulfaneyl)phenyl)-2-iodoacetamide

[00648] To a solution of 2-chloro-N-(2-chloro-4-(pentafluoro- λ^6 -sulfaneyl)phenyl)acetamide (1.00 g, 3.03 mmol, 1.0 eq) in acetone (10 mL) was added KI (835 mg, 5.03 mmol, 1.66 eq). The resulting mixture was stirred at 80 °C for 2 h. The reaction was diluted with H₂O (30 mL) and extracted with EtOAc (20 mL*3). The combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to afford the title compound, which was used in the next step without further purification.

[00649] LCMS: 421.9 [M+H]⁺.

[00650] Intermediate-11: 7-hydroxy-2,3-dihydrofuro[3,2-c]pyridine-6-carboxylic acid



[00651] Step 1. Synthesis of methyl 3-(bromomethyl)furan-2-carboxylate

[00652] To a solution of methyl 3-methylfuran-2-carboxylate (5.00 g, 35.7 mmol, 1.00 eq) in CCl_4 (50.0 mL) were added NBS (6.68 g, 37.5 mmol, 1.05 eq) and AIBN (2.35 g, 14.3 mmol, 0.40 eq) at room temperature. The mixture was degassed three times with N_2 and stirred at 50 °C for 16 h. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (eluent of EtOAc/PE) to afford the title compound.

[00653] LCMS: 219/221 [M+H]⁺.

[00654] Step 2. Synthesis of methyl 3-(((N-(2-methoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)methyl)furan-2-carboxylate

[00655] To a solution of methyl 3-(bromomethyl)furan-2-carboxylate (4.70 g, 21.5 mmol, 1.00 eq) and K_2CO_3 (5.93 g, 43.0 mmol, 2.00 eq) in ACN (47.0 mL) was added methyl 2-(4-methylbenzenesulfonamido)acetate (5.23 g, 21.5 mmol, 1.00 eq) and the mixture was stirred at room temperature for 16 h. The reaction was filtered, and the filtrate was concentrated in vacuum. The residue was purified by column chromatography on silica (Eluent of EtOAc/PE) to afford the title compound.

[00656] LCMS: 382 [M+H]⁺.

[00657] Step 3. Synthesis of methyl 7-hydroxyfuro[3,2-c]pyridine-6-carboxylate

[00658] To a solution of methyl 3-(((N-(2-methoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)methyl)furan-2-carboxylate (1.80 g, 4.72 mmol, 1.00 eq) in THF (18.0 mL) was added a 1 M solution of LiHMDS (14.2 mL, 14.2 mmol, 3.00 eq) in THF dropwise at -78 °C under N_2 atmosphere. After addition, the reaction mixture was allowed to warm to 0 °C and stirred for 5 h under N_2 atmosphere. A saturated NH_4Cl (aq.) solution was added to the reaction mixture and the aq. phase was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[00659] LCMS: 194 [M+H]⁺.

[00660] Step 4. Synthesis of methyl 7-hydroxy-2,3-dihydrofuro[3,2-c]pyridine-6-carboxylate

[00661] To a mixture of methyl 7-hydroxyfuro[3,2-c]pyridine-6-carboxylate (760 mg, 3.93 mmol, 1.00 eq) in MeOH (10.0 mL) was added Pd/C (152 mg, 20%). The mixture was degassed and purged with H_2 gas (40 psi). Then it was stirred at 50 °C for 16 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of DCM/MeOH) to afford the title compound.

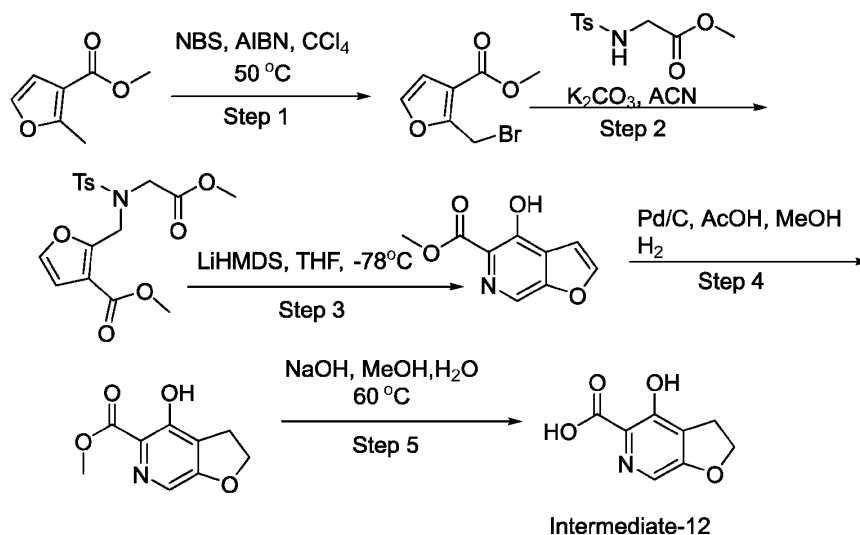
[00662] LCMS: 196 [M+H]⁺.

[00663] Step 5. Synthesis of 7-hydroxy-2,3-dihydrofuro[3,2-c]pyridine-6-carboxylic acid

[00664] To a mixture of methyl 7-hydroxy-2,3-dihydrofuro[3,2-c]pyridine-6-carboxylate (680 mg, 3.48 mmol, 1.00 eq) in H₂O (3.00 mL) and MeOH (3.00 mL) was added NaOH (557 mg, 13.9 mmol, 4.00 eq) at room temperature and the resulting mixture was stirred at 60 °C for 16 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was diluted with H₂O and acidified by 3 N HCl. The precipitated solids were collected by filtration and dried to afford the title compound, which was used in the next step directly without further purification.

[00665] LCMS: 182 [M+H]⁺.

[00666] Intermediate-12: 4-hydroxy-2,3-dihydrofuro[2,3-c]pyridine-5-carboxylic acid



[00667] Step 1. Synthesis of methyl 2-(bromomethyl)furan-3-carboxylate

[00668] To a stirred solution of methyl 2-methylfuran-3-carboxylate (10.0 g, 71.4 mmol, 1.00 eq) in CCl₄ (55.0 mL) were added NBS (15.2 g, 85.6 mmol, 1.20 eq) and AIBN (586 mg, 3.57 mmol, 0.05 eq) at room temperature. The resulting mixture was degassed three times with N₂ and stirred overnight at 50 °C under N₂. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (eluent of EtOAc/PE) to afford the title compound.

[00669] ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.86 (d, 1H), 6.80 (d, 1H), 4.95 (s, 2H), 3.82 (s, 3H).

[00670] Step 2. Synthesis of methyl 2-(((N-(2-methoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)methyl)furan-3-carboxylate

[00671] To a stirred solution of methyl 2-(bromomethyl)furan-3-carboxylate (12.0 g, 54.8 mmol, 1.00 eq) and methyl 2-(4-methylbenzenesulfonamido)acetate (13.3 g, 54.8 mmol, 1.00 eq) in ACN (100 mL) was added K₂CO₃ (15.1 g, 110 mmol, 2.00 eq) at room temperature. The resulting mixture was degassed three times with N₂ and then stirred overnight at room temperature. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (eluent of EtOAc/PE) to afford the title compound.

[00672] LCMS: 382.1 [M+H]⁺.

[00673] Step 3. Synthesis of methyl 4-hydroxyfuro[2,3-c]pyridine-5-carboxylate

[00674] To a stirred solution of methyl 2-([N-(2-methoxy-2-oxoethyl)-4-methylbenzenesulfonamido]methyl)furan-3-carboxylate (9.00 g, 23.6 mmol, 1.00 eq) in THF (50.0 mL) was added a 1 M solution of LiHMDS (70.0 mL, 70.0 mmol, 3.00 eq) in THF at -78 °C under N₂. The resulting mixture was stirred for 1h at room temperature under N₂. The reaction mixture was quenched with saturated NH₄Cl solution at 0 °C and diluted with H₂O (200 mL). The resulting mixture was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (eluent of EtOAc/PE) to afford a crude product, which was purified by trituration with PE (250 mL) to afford the title compound.

[00675] LCMS: 194.0 [M+H]⁺.

[00676] Step 4. Synthesis of methyl 4-hydroxy-2,3-dihydrofuro[2,3-c]pyridine-5-carboxylate

[00677] To a solution of methyl 4-hydroxyfuro[2,3-c]pyridine-5-carboxylate (1.00 g, 5.18 mmol, 1.00 eq) in AcOH (1.00 mL) and MeOH (10.0 mL) was added Pd/C (1.65 g, 10%). The mixture was degassed three times with H₂, and then stirred at room temperature for 1 h under H₂. The reaction mixture was filtered, and the filter cake was washed with MeOH. The filtrate was concentrated under reduced pressure and the residue was purified by reverse phase HPLC (C18 column, H₂O (10mmol/L NH₄HCO₃)-ACN) to afford the title compound.

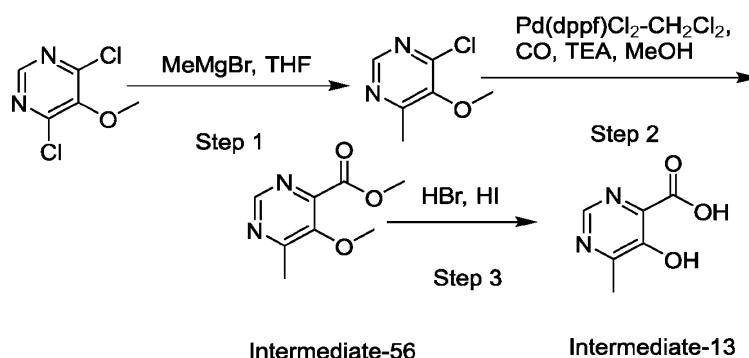
[00678] LCMS: 195.9 [M+H]⁺.

[00679] Step 5. Synthesis of 4-hydroxy-2,3-dihydrofuro[2,3-c]pyridine-5-carboxylic acid

[00680] To a stirred solution of methyl 4-hydroxy-2H,3H-furo[2,3-c]pyridine-5-carboxylate (300 mg, 1.54 mmol, 1.00 eq) in MeOH (3.00 mL) were added NaOH (246 mg, 6.15 mmol, 4.00 eq) and H₂O (3.00 mL) at room temperature. The reaction mixture was stirred overnight at 60 °C. The mixture was acidified to pH = 3 with 1 N HCl. The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound, which was used in the next step directly without further purification.

[00681] LCMS: 181.9 [M+H]⁺.

[00682] Intermediate-13: 5-hydroxy-6-methylpyrimidine-4-carboxylic acid; and
Intermediate-56: methyl 5-methoxy-6-methylpyrimidine-4-carboxylate



[00683] Step 1: Synthesis of 4-chloro-5-methoxy-6-methylpyrimidine

[00684] To a mixture of 4,6-dichloro-5-methoxypyrimidine (30.00 g, 167.6 mmol, 1.0 eq) in THF (300 mL) was added a 3 M solution of MeMgBr (61.45 mL, 184.4 mmol, 1.1 eq) in diethyl ether dropwise at 0 °C and then the mixture was stirred at 5 °C for 1 h. The resulting mixture was poured into H₂O (200 mL) and extracted with EtOAc (100 mL*3). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated in vacuum. The residue was purified by flash silica gel chromatography (eluent of EtOAc/PE) to afford the title compound.

[00685] LCMS: 159.1 [M+H]⁺.

[00686] Step 2: Synthesis of methyl 5-methoxy-6-methylpyrimidine-4-carboxylate

[00687] To a mixture of 4-chloro-5-methoxy-6-methylpyrimidine (22.00 g, 138.7 mmol, 1.0 eq) in MeOH (250 mL) was added Pd(dppf)Cl₂-CH₂Cl₂ (6.80 g, 8.32 mmol, 0.06 eq) and TEA (28.1 g, 278 mmol, 2.0 eq). The reaction was purged with CO (50 psi) and stirred at 50 °C overnight. The resulting mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (eluent of EtOAc/PE) to afford the title compound.

[00688] LCMS: 183.1 [M+H]⁺.

[00689] Step 3: Synthesis of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid

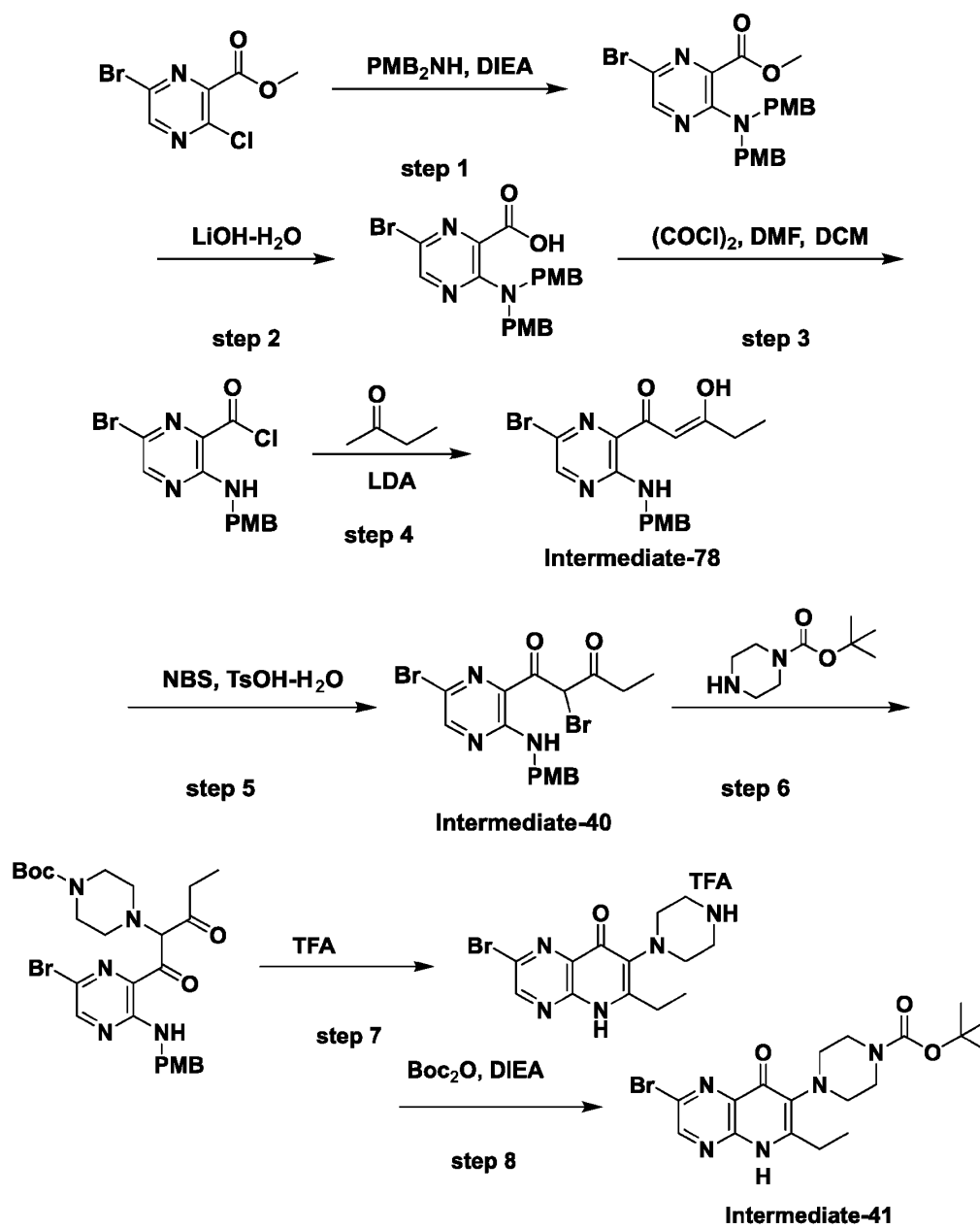
[00690] A mixture of methyl 5-methoxy-6-methylpyrimidine-4-carboxylate (Intermediate-56) (16.00 g, 87.83 mmol, 1.0 eq) in HBr solution (aq.) (68.5 mL, 68%) was stirred at 50 °C overnight. Then HI solution (aq.) (67.2 mL, 56%) was added and stirred at 50 °C for 6 h. The reaction mixture was cooled to room temperature and basified with 50% NaOH solution (aq.) to pH 9 at 0 °C, then adjusted to pH 7 with 2 M HCl solution (aq.) at 0 °C. The mixture was filtered, the filter cake was dried in vacuum to afford the title compound, which was used in the next step without further purification. LCMS: 155.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 15.46 (br s, 1H), 8.37 (s, 1H), 2.34 (s, 3H).

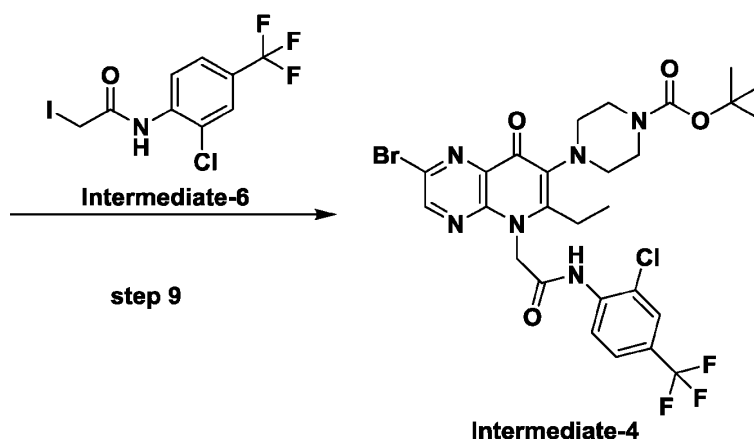
[00691] Alternative Synthesis of Intermediate-4

[00692] Intermediate-4: tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00693] Intermediate-40: 2-bromo-1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)pentane-1,3-dione

[00694] Intermediate-41: tert-butyl 4-(2-bromo-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate





[00695] Step 1: Synthesis of methyl 3-(bis(4-methoxybenzyl)amino)-6-bromopyrazine-2-carboxylate

[00696] To a solution of methyl 6-bromo-3-chloropyrazine-2-carboxylate (100.00 g, 397.67 mmol, 1.0 eq) in 1,4-dioxane (1000 mL) was added DIEA (77.09 g, 596.5 mmol, 1.5 eq) and bis(4-methoxybenzyl)amine (112.56 g, 437.44 mmol, 1.1 eq), the resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was diluted with H₂O (800 mL) and extracted with EtOAc (400 mL * 3). The combined organic layers were washed with brine (200 mL * 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00697] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.26 (s, 1H), 7.05 (d, 4H), 6.83 (d, 4H), 4.55 (s, 4H), 3.84 (s, 3H), 3.82 - 3.74 (m, 6H).

[00698] Step 2: Synthesis of 3-(bis(4-methoxybenzyl)amino)-6-bromopyrazine-2-carboxylic acid

[00699] To a solution of methyl 3-(bis(4-methoxybenzyl)amino)-6-bromopyrazine-2-carboxylate (161 g, 340 mmol, 1.0 eq) in MeOH (1500 mL), THF (1500 mL) and H₂O (1500 mL) was added LiOH-H₂O (57.2 g, 1.36 mol, 4.0 eq), the resulting mixture was stirred at room temperature overnight. To the mixture was added H₂O (1600 mL) and the pH adjusted to 2-3 with 1 N HCl. The reaction mixture was concentrated under reduced pressure to remove organic solvent, the aqueous solution was extracted with DCM (600 mL * 3). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na₂SO₄, filtered and

concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[00700] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.26 (s, 1H), 7.05 (d, 4H), 6.83 (d, 4H), 4.55 (s, 4H), 3.84 (s, 3H), 3.82 - 3.74 (m, 6H).

[00701] Step 3: Synthesis of 6-bromo-3-((4-methoxybenzyl)amino)pyrazine-2-carbonyl chloride

[00702] To a solution of 3-(bis(4-methoxybenzyl)amino)-6-bromopyrazine-2-carboxylic acid (140.00 g, 305.47 mmol, 1.0 eq) and DMF (233 mg, 3.05 mmol, 0.01 eq) in DCM (1400 mL) was added oxalyl dichloride (46.50 g, 366.6 mmol, 1.2 eq) dropwise at room temperature and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used directly in the next step without further purification.

[00703] Step 4: Synthesis of 1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)-3-hydroxypent-2-en-1-one

[00704] To a solution of butan-2-one (44.49 g, 616.9 mmol, 2.2 eq) in THF (160 mL) was added LDA (2 M in THF, 308.5 mL, 616.9 mmol, 2.2 eq) at -65 °C and it was stirred at -65 °C for 0.5 h. Then 6-bromo-3-((4-methoxybenzyl)amino)pyrazine-2-carbonyl chloride (100.00 g, 280.42 mmol, 1.0 eq) in THF (1000 mL) was added dropwise to the mixture at -65 °C and the resulting mixture was stirred at -65 °C for 1 h. The reaction mixture was slowly poured into aqueous HCl solution (1 M, 1L), and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (50 mL * 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00705] ¹H NMR (400 MHz, CDCl₃) δ ppm 15.01 (s, 1H), 8.96 (br s, 1H), 8.27 (s, 1H), 7.33 - 7.28 (m, 1H), 6.93 - 6.85 (m, 3H), 6.78 (s, 1H), 4.65 (d, 2H), 3.81 (s, 3H), 2.40 (q, 2H), 1.23 (t, 3H).

[00706] Step 5: Synthesis of 2-bromo-1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)pentane-1,3-dione

[00707] To a solution of 1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)-3-hydroxypent-2-en-1-one (Intermediate-78) (19.00 g, 48.44 mmol, 1.0 eq) in DCM (200 mL) was added TsOH·H₂O (1.70 g, 39.7 mmol, 0.2 eq) and NBS (8.61 g, 48.4 mmol, 1.0 eq) at 0 °C and

the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with H₂O (300 mL) and extracted with EtOAc (100 mL * 3). The combined organic layers were washed with brine (50 mL * 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound, which was used in the next step without further purification.

[00708] LCMS: 472.0 [M+H]⁺.

[00709] Step 6: Synthesis of tert-butyl 4-(1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate

[00710] To a solution of 2-bromo-1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)pentane-1,3-dione (Intermediate-40) (23.00 g, 48.82 mmol, 1.0 eq) in THF (250 mL) was added DIEA (12.61 g, 50.93 mmol, 2.0 eq) and tert-butyl piperazine-1-carboxylate (9.09 g, 48.8 mmol, 1.0 eq) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with H₂O (200 mL) and extracted with EtOAc (100 mL * 3). The combined organic layers were washed with brine (50 mL * 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00711] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.80 (br t, 1H), 8.30 (s, 1H), 7.25 (s, 1H), 6.88 (d, 2H), 5.32 (s, 1H), 4.63 (dq, 2H), 3.81 (s, 3H), 3.53 - 3.35 (m, 4H), 3.02 - 2.83 (m, 3H), 2.72 - 2.59 (m, 2H), 1.59 (s, 2H), 1.46 (s, 9H), 1.14 (t, 3H).

[00712] Step 7: Synthesis of 2-bromo-6-ethyl-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-8(5H)-one trifluoroacetate tert-butyl 4-(1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate (21.00 g, 36.43 mmol, 1.0 eq) was dissolved into TFA (40 mL) and then it was stirred at 50 °C for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used in the next step without further purification.

[00713] LCMS: 338.1 [M+H]⁺.

[00714] Step 8: Synthesis of tert-butyl 4-(2-bromo-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00715] To a solution of 2-bromo-6-ethyl-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-8(5H)-one trifluoroacetate (12.00 g, 35.48 mmol, 1.0 eq) in DCM (150 mL) was added DIEA (22.92 g, 177.4 mmol, 5.0 eq) and Boc₂O (7.68 g, 35.5 mmol, 1.0 eq), and then the resulting mixture was

stirred at room temperature for 1 h. The reaction mixture was diluted with H₂O (200 mL) and extracted with DCM (50 mL * 3). The combined organic layers were washed with brine (50 mL * 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was triturated in a mixed solvent of DCM/PE (DCM:PE = 2:1, 30 mL) at room temperature for 10 mins and then filtered. The filter cake was dried under reduced pressure to afford the title compound, which was used in the next step without further purification.

[00716] LCMS: 440.1 [M+H]⁺.

[00717] Step 9: Synthesis of tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00718] To a solution of tert-butyl 4-(2-bromo-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-41) (13.00 g, 29.66 mmol, 1.0 eq) in DMF (600 mL) was added K₂CO₃ (4.10 g, 29.66 mmol, 1.0 eq) and N-(2-chloro-4-(trifluoromethyl)phenyl)-2-iodoacetamide (Intermediate-6) (10.78 g, 29.66 mmol, 1.0 eq) and the mixture was stirred at room temperature for 1.5 h. Then the second batch of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-iodoacetamide (Intermediate-6) (2.16 g, 5.93 mmol, 0.2 eq) and K₂CO₃ (819 mg, 5.93 mmol, 0.2 eq) was added, and the reaction was stirred at room temperature for another 2 h. The reaction mixture was poured into H₂O (300 mL), the resulting suspension was filtered and the filter cake was dried under reduced pressure. The resulting crude product was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00719] LCMS: 675.2 [M+H]⁺.

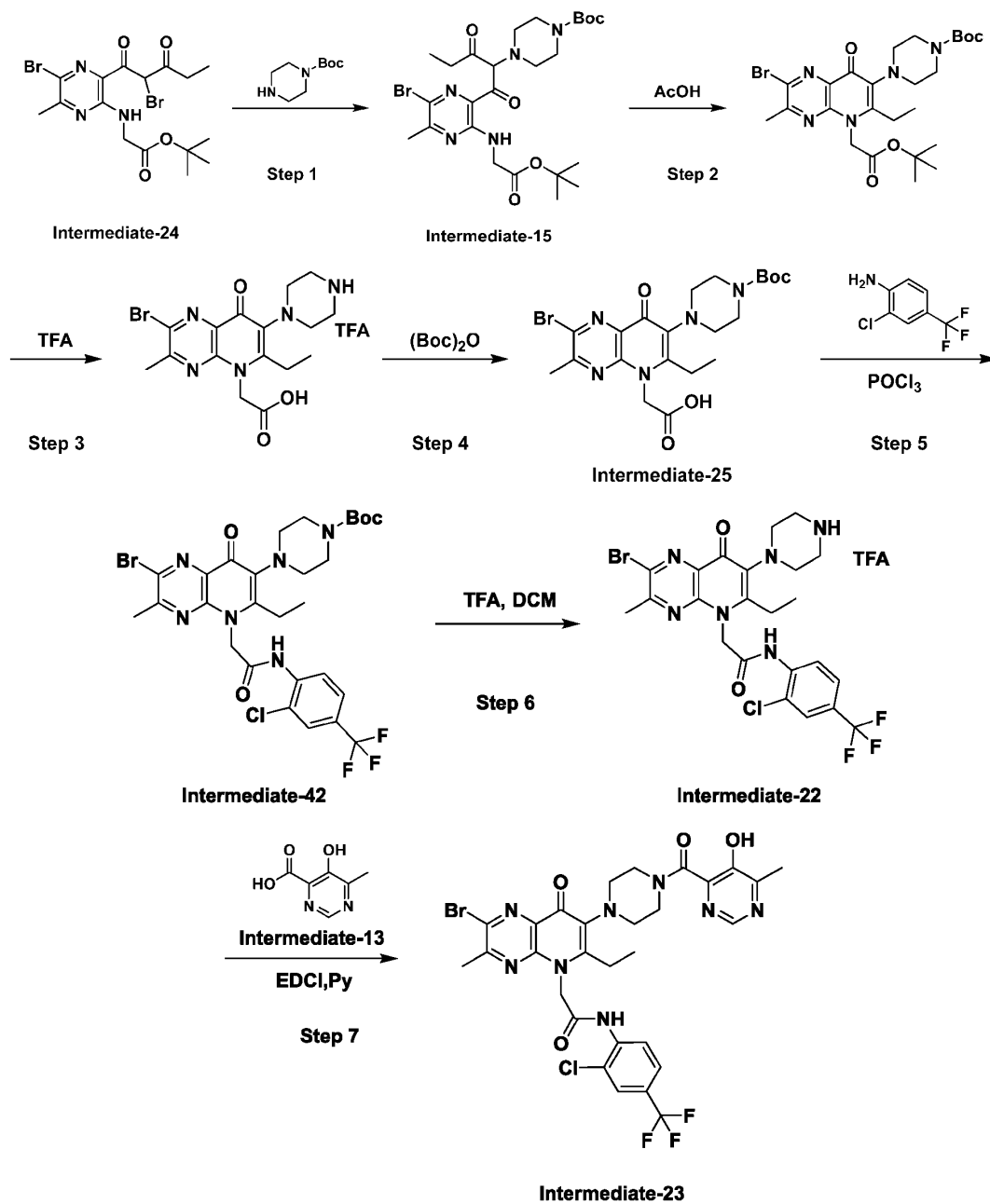
[00720] Intermediate-15: tert-butyl 4-(1-(6-bromo-3-((2-(tert-butoxy)-2-oxoethyl)amino)-5-methylpyrazin-2-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate

[00721] Intermediate-22: 2-(2-bromo-6-ethyl-3-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate

[00722] Intermediate-23: 2-(2-bromo-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide

[00723] Intermediate-42: tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00724] Intermediate-25: 2-(2-bromo-7-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid



[00725] Step 1. Synthesis of tert-butyl 4-(1-(6-bromo-3-((2-(tert-butoxy)-2-oxoethyl)amino)-5-methylpyrazin-2-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate

[00726] To a solution of tert-butyl (5-bromo-3-(2-bromo-3-oxopentanoyl)-6-methylpyrazin-2-yl)glycinate (Intermediate-24) (19.00 g, 27.76 mmol, 1.0 eq) in THF (200 mL) was added DIEA (7.17 g, 55.5 mmol, 2.0 eq) and tert-butyl piperazine-1-carboxylate (7.75 g, 41.6 mmol, 1.5 eq), the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched by H₂O (100 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00727] LCMS: 586.3 [M+H]⁺.

[00728] Step 2. Synthesis of tert-butyl 4-(2-bromo-5-(2-(tert-butoxy)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00729] A solution of tert-butyl 4-(1-(6-bromo-3-((2-(tert-butoxy)-2-oxoethyl)amino)-5-methylpyrazin-2-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate (Intermediate-15) (9.60 g, 16.4 mmol, 1.0 eq) in AcOH (100 mL) was stirred at 60 °C for 12 h. The reaction mixture was quenched by saturated NaHCO₃ aqueous solution (100 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00730] LCMS: 566.2 [M+H]⁺.

[00731] Step 3. Synthesis of 2-(2-bromo-6-ethyl-3-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid trifluoroacetate

[00732] To a solution of tert-butyl 4-(2-bromo-5-(2-(tert-butoxy)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (3.50 g, 6.18 mmol, 1.0 eq) in DCM (10 mL) was added TFA (50 mL) and the resulting mixture was stirred at 30 °C for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[00733] LCMS: 466.2 [M+H]⁺.

[00734] Step 4. Synthesis of 2-(2-bromo-7-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid

[00735] To a solution of 2-(2-bromo-6-ethyl-3-methyl-8-oxo-7-piperazin-1-yl-pyrido[2,3-b]pyrazin-5-yl)acetic acid trifluoroacetate (2.50 g, 6.09 mmol, 1.0 eq) in DCM (20 mL) was

added (Boc)₂O (1.33 g, 6.09 mmol, 1.0 eq) and DIEA (3.94 g, 30.5 mmol, 5.0 eq), and the resulting mixture was stirred at 30 °C for 1 h. The reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00736] LCMS: 510.1 [M+H]⁺.

[00737] Step 5. Synthesis of tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00738] To a solution of 2-(2-bromo-7-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid (Intermediate-25) (2.00 g, 3.92 mmol, 1.0 eq) and 2-chloro-4-(trifluoromethyl)aniline (766 mg, 3.92 mmol, 1.0 eq) in pyridine (5 mL) and DCM (5 mL) was added POCl₃ (901 mg, 5.88 mmol, 1.5 eq) at -10 °C, and it was stirred at -10 °C for 1 h. The reaction mixture was quenched by H₂O (100 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[00739] LCMS: 689.3 [M+H]⁺.

[00740] Step 6. Synthesis of 2-(2-bromo-6-ethyl-3-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate

[00741] To a solution of tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (1.00 g, 1.45 mmol, 1.0 eq) in DCM (40 mL) was added TFA (10 mL), and it was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[00742] LCMS: 589.0 [M+H]⁺.

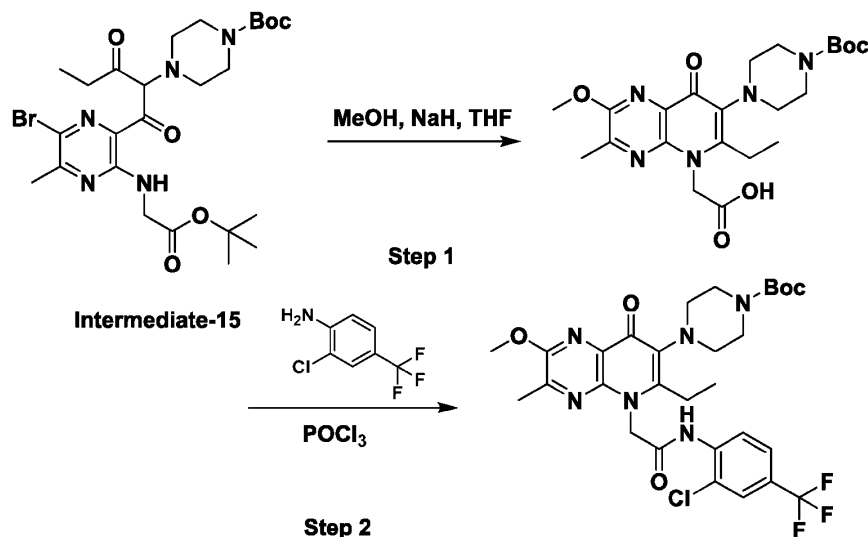
[00743] Step 7. Synthesis of 2-(2-bromo-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide

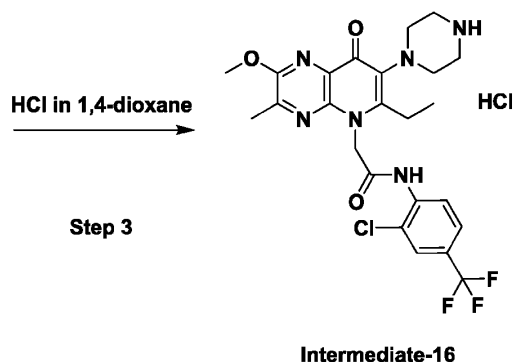
[00744] To a mixture of 2-(2-bromo-6-ethyl-3-methyl-8-oxo-7-piperazin-1-yl-pyrido[2,3-b]pyrazin-5-yl)-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide trifluoroacetate (Intermediate-22) (1.00 g, 1.70 mmol, 1.0 eq) and 5-hydroxy-6-methyl-pyrimidine-4-carboxylic acid (524 mg, 3.40 mmol, 2.0 eq) in pyridine (10 mL) were added EDCI (652 mg, 3.40 mmol, 2.0 eq), and then the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched by saturated NH_4Cl aqueous solution (100 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00745] LCMS: 725.1 $[\text{M}+\text{H}]^+$.

[00746] ^1H NMR (400 MHz, CDCl_3) δ ppm 12.05 (br s, 1H), 8.77 (s, 1H), 8.58 (s, 1H), 8.42 (d, 1H), 7.64 (d, 1H), 7.53 (br d, 1H), 5.58 (br d, 1H), 5.47 (br s, 2H), 4.86 - 4.70 (m, 1H), 3.99 (br t, 2H), 3.58 - 3.42 (m, 1H), 3.26 (br d, 2H), 3.16 - 3.02 (m, 1H), 2.93 - 2.77 (m, 2H), 2.77 (s, 3H), 2.57 (s, 3H), 1.34 (t, 3H).

[00747] Intermediate-16: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-methoxy-3-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride





[00748] Step 1. Synthesis of 2-(7-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-ethyl-2-methoxy-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid

[00749] To a mixture of MeOH (38 mg, 1.2 mmol, 3.5 eq) in THF (6 mL) was added NaH (48 mg, 1.2 mmol, 60% in mineral oil, 3.5 eq) at 0 °C and then it was stirred at 0 °C for 0.5 h. A solution of tert-butyl 4-(1-(6-bromo-3-((2-(tert-butoxy)-2-oxoethyl)amino)-5-methylpyrazin-2-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate (Intermediate-15) (200 mg, 342 μmol, 1.0 eq) in THF (4 mL) was added to the reaction at 0 °C and the resulting mixture was stirred at room temperature for 0.5 h. The mixture was quenched by H₂O (30mL), the pH was adjusted to 4 by aqueous HCl solution (1 N), and extracted with EtOAc (30mL*2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to afford title compound, which was used directly in the next step without further purification.

[00750] LCMS: 462.1 [M+H]⁺.

[00751] Step 2. Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-methoxy-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00752] To a solution of 2-(7-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-ethyl-2-methoxy-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid (100 mg, 217 μmol, 1.0 eq) and 2-chloro-4-(trifluoromethyl)aniline (47 mg, 0.24 mmol, 1.1 eq) in pyridine (1 mL) and DCM (1 mL) was added POCl₃ (50 mg, 0.33 mmol, 1.5 eq) dropwise at -10°C, and the resulting mixture was stirred at -10 °C for 10 mins. The reaction mixture was quenched by H₂O (30 mL) and extracted with EtOAc (30 mL * 2). The combined organic layers were washed with saturated citric acid aqueous solution (30 mL), then dried over anhydrous Na₂SO₄, filtered and the filtrate

was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[00753] LCMS: 639.3 [M+H]⁺.

[00754] Step 3. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-methoxy-3-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride

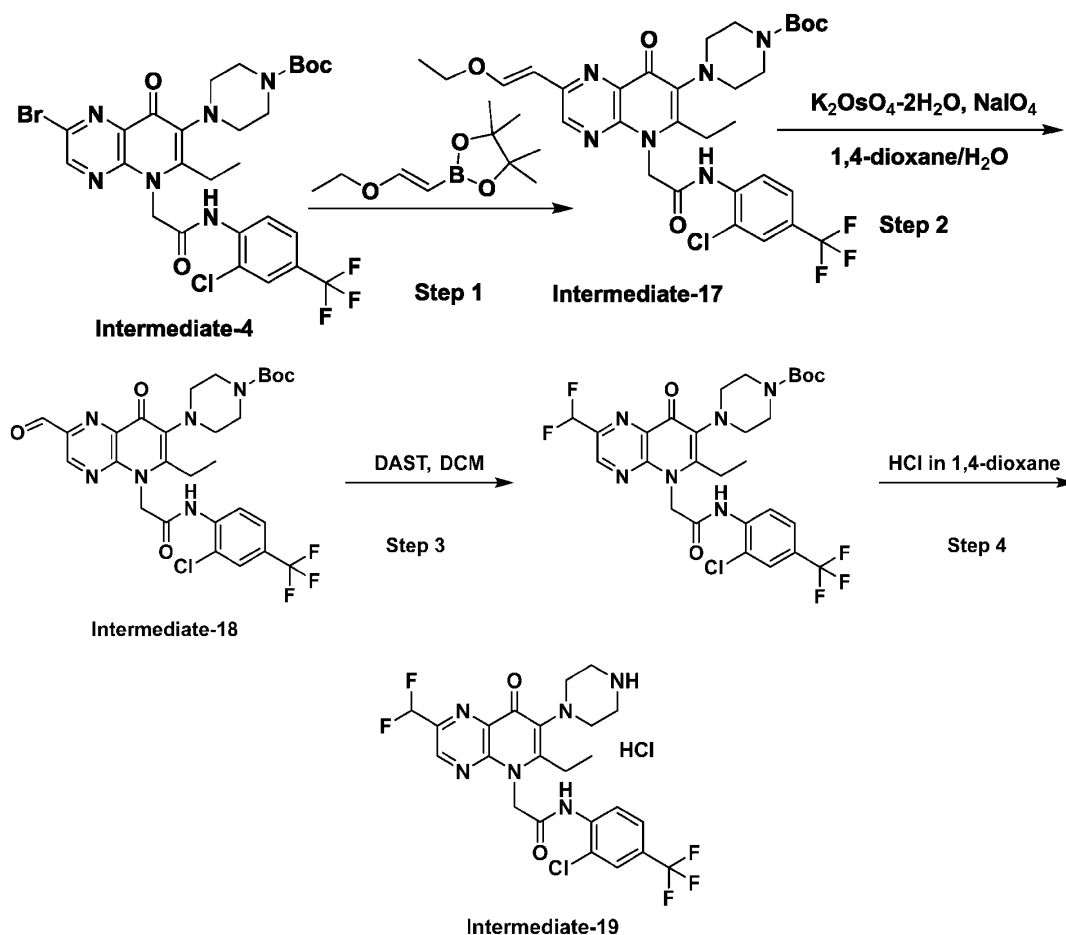
[00755] To tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-methoxy-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (32 mg, 50 μ mol, 1.0 eq) was added a solution of HCl in 1,4-dioxane (2 mL, 4 M) and it was stirred at room temperature for 0.2 h. The mixture was concentrated to afford the title compound, which was used directly in the next step without further purification.

[00756] LCMS: 539.1 [M+H]⁺.

[00757] Intermediate-17: tert-butyl (E)-4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(2-ethoxyvinyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00758] Intermediate-18: tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-formyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00759] Intermediate-19: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethyl)-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride



[00760] Step 1. Synthesis of tert-butyl (E)-4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(2-ethoxyvinyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate to a solution of tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-4) (200 mg, 296 μ mol, 1.0 eq) and (E)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (59 mg, 296 μ mol, 1.0 eq) in 1,4-dioxane (5 mL) and H_2O (1 mL) was added $Pd(dppf)Cl_2$ (22 mg, 29 μ mol, 0.1 eq) and K_3PO_4 (126 mg, 593 μ mol, 2.0 eq). The mixture was stirred at 80 $^{\circ}C$ for 1 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure and then purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00761] LCMS: 665.2 $[M+H]^+$.

[00762] Step 2. Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-formyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00763] To a solution of tert-butyl (E)-4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(2-ethoxyvinyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-17) (100 mg, 150 μ mol, 1.0 eq) in 1,4-dioxane (2 mL) and H₂O (0.4 mL) was added K₂OsO₄·2H₂O (11 mg, 30 μ mol, 0.2 eq) and NaIO₄ (64 mg, 0.30 mmol, 2.0 eq), and then the mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with H₂O (10 mL), extracted with EtOAc (10 mL*2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00764] LCMS: 623.2 [M+H]⁺.

[00765] Step 3. Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(difluoromethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00766] To a solution of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-formyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-18) (20 mg, 32 μ mol, 1.0 eq) in DCM (2 mL) was added DAST (16 mg, 96 μ mol, 3.0 eq) at 0 °C and it was stirred at 0 °C for 3 h under N₂ atmosphere. The reaction mixture was poured into saturated NaHCO₃ aqueous solution (10 mL), extracted with DCM (10 mL*2). The organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to afford the title compound, which was used directly in the next step without further purification.

[00767] LCMS: 645.2 [M+H]⁺.

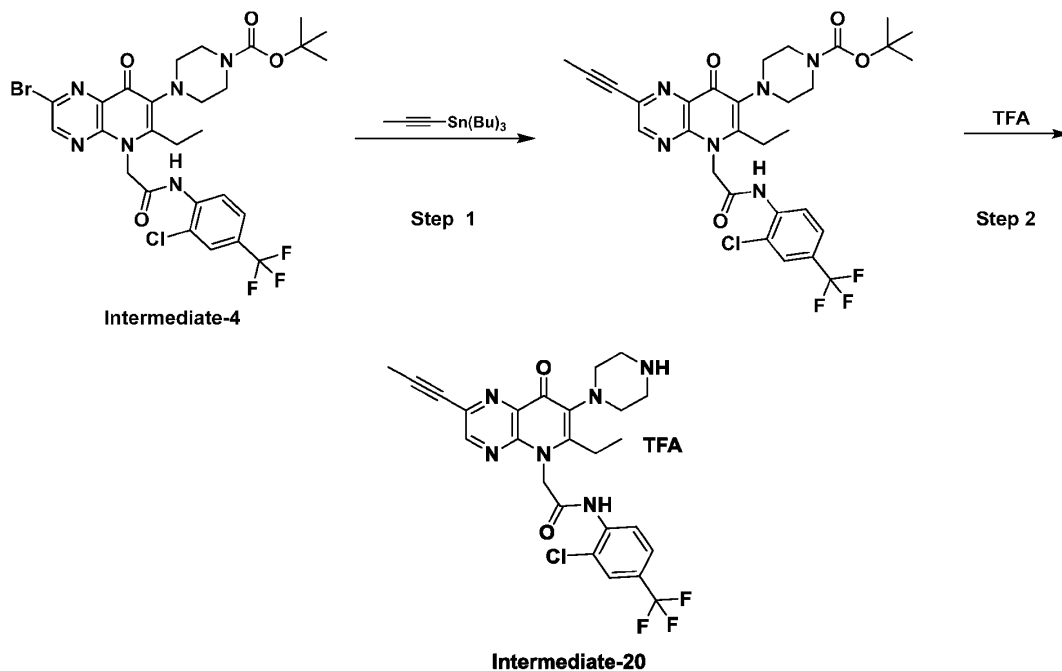
[00768] Step 4. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethyl)-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride

[00769] To tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(difluoromethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (15 mg, 23 μ mol, 1.0 eq) was added a solution of HCl in 1,4-dioxane (0.5 mL, 4 M) and it was

stirred at room temperature for 0.5 h. The mixture was concentrated under reduced pressure to afford the title compound, which was used directly in the next step without further purification.

[00770] LCMS: 545.2 [M+H]⁺.

[00771] Intermediate-20: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-8-oxo-7-(piperazin-1-yl)-2-(prop-1-yn-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide trifluoroacetate



[00772] Step1: Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-2-(prop-1-yn-1-yl)-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00773] To a solution of tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-4) (80 mg, 0.12 mmol, 1.0 eq) and tributyl(prop-1-yn-1-yl)stannane (59 mg, 0.18 mmol, 1.5 eq) in toluene (1 mL) was added CuI (5 mg, 23 μmol, 0.2 eq) and Pd(PPh₃)₂Cl₂ (8 mg, 12 μmol, 0.1 eq). Then the mixture was stirred at 60 °C for 15 h under N₂ atmosphere. The reaction mixture was poured into ice-water (10 mL) and extracted with EtOAc (10 mL*3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

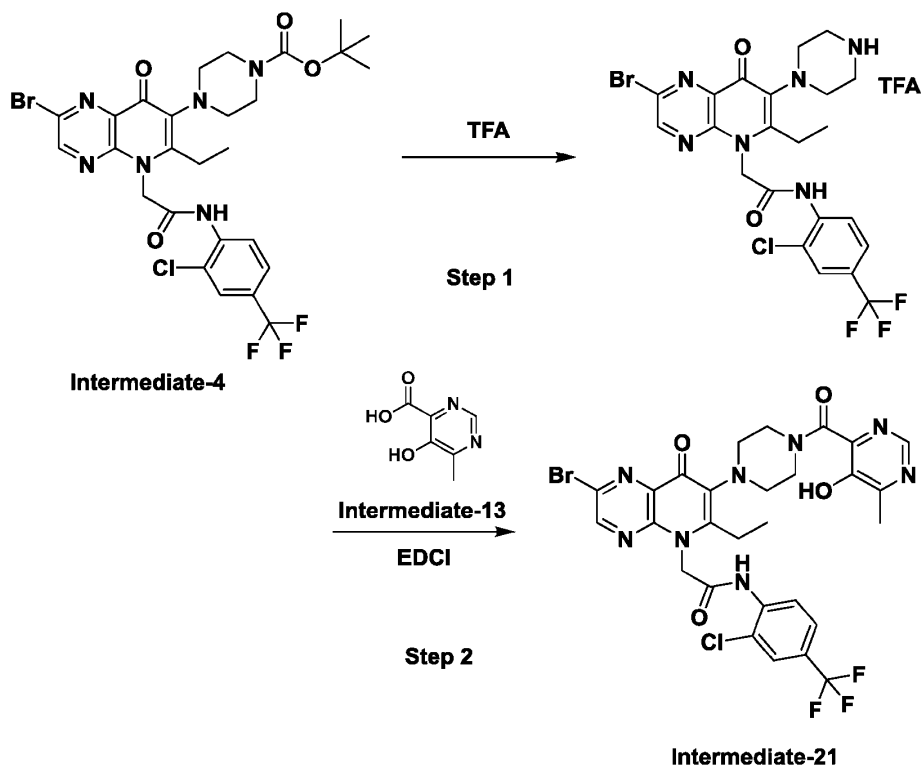
[00774] LCMS: 633.4[M+H]⁺.

[00775] Step 2: Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-8-oxo-7-(piperazin-1-yl)-2-(prop-1-yn-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide trifluoroacetate

[00776] To a solution of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-2-(prop-1-yn-1-yl)-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (40 mg, 63 μmol, 1.0 eq) in DCM (1 mL) was added TFA (0.4 mL) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used directly in the next step without further purification.

[00777] LCMS: 533.4[M+H]⁺.

[00778] Intermediate-21: 2-(2-bromo-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide



[00779] Step 1. Synthesis of 2-(2-bromo-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate

[00780] To a solution of tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-4) (70 mg, 0.10 mmol, 1.0 eq) in DCM (1.2 mL) was added TFA (0.3 mL), and the resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used directly in the next step without further purification.

[00781] LCMS: 575.2 [M+H]⁺.

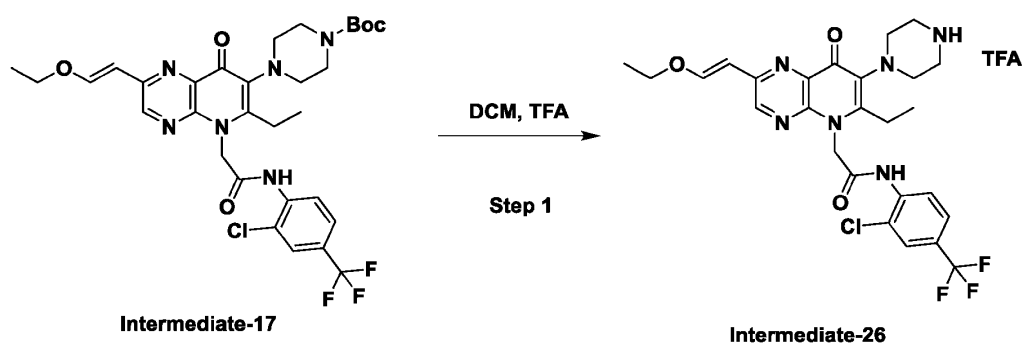
[00782] Step 2. Synthesis of 2-[2-bromo-6-ethyl-7-[4-(5-hydroxy-6-methyl-pyrimidine-4-carbonyl)piperazin-1-yl]-8-oxo-pyrido[2,3-b]pyrazin-5-yl]-N-[2-chloro-4-(trifluoromethyl)phenyl]acetamide

[00783] To a solution of 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate-13) (64 mg, 0.42 mmol, 4.0 eq) in pyridine (1 mL) was added EDCI (80 mg, 0.42 mmol, 4.0 eq) and 2-(2-bromo-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate (60 mg, 0.10 mmol, 1.0 eq), the resulting mixture was stirred at 40 °C for 1h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by reverse phase HPLC (C18 column, H₂O (10 mmol/L NH₄HCO₃-ACN) to afford the title compound.

[00784] LCMS: 711.2 [M+H]⁺.

[00785] ¹H NMR (400 MHz, CDCl₃) δ 11.80 (br s, 1H), 8.68 (s, 1H), 8.59 (s, 2H), 8.46 (br d, 1H), 7.66 (s, 1H), 7.56 - 7.49 (m, 1H), 5.69 - 5.54 (m, 1H), 5.53 - 5.30 (m, 2H), 4.87 - 4.69 (m, 1H), 4.05 - 3.90 (m, 2H), 3.60 - 3.40 (m, 1H), 3.35 - 3.20 (m, 2H), 3.17 - 3.00 (m, 1H), 2.90 - 2.69 (m, 2H), 2.57 (s, 3H), 1.36 (br t, 3H).

[00786] Intermediate-26: (E)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(2-ethoxyvinyl)-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide trifluoroacetate



[00787] Step 1. Synthesis of (E)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(2-ethoxyvinyl)-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide trifluoroacetate

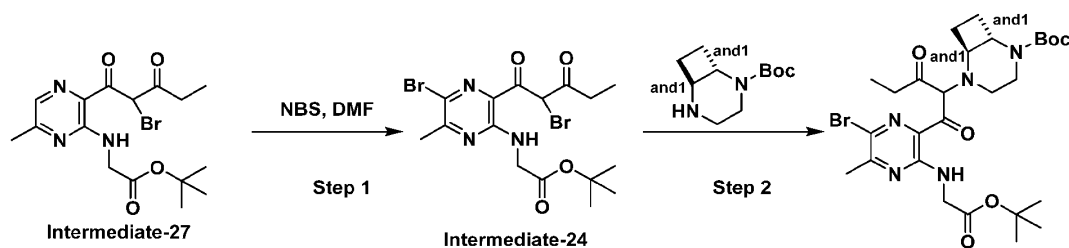
[00788] To a solution of tert-butyl (E)-4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(2-ethoxyvinyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-17) (30 mg, 45 μ mol, 1 eq) in DCM (0.8 mL) was added TFA (0.2 mL) and the resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used in the next step without further purification.

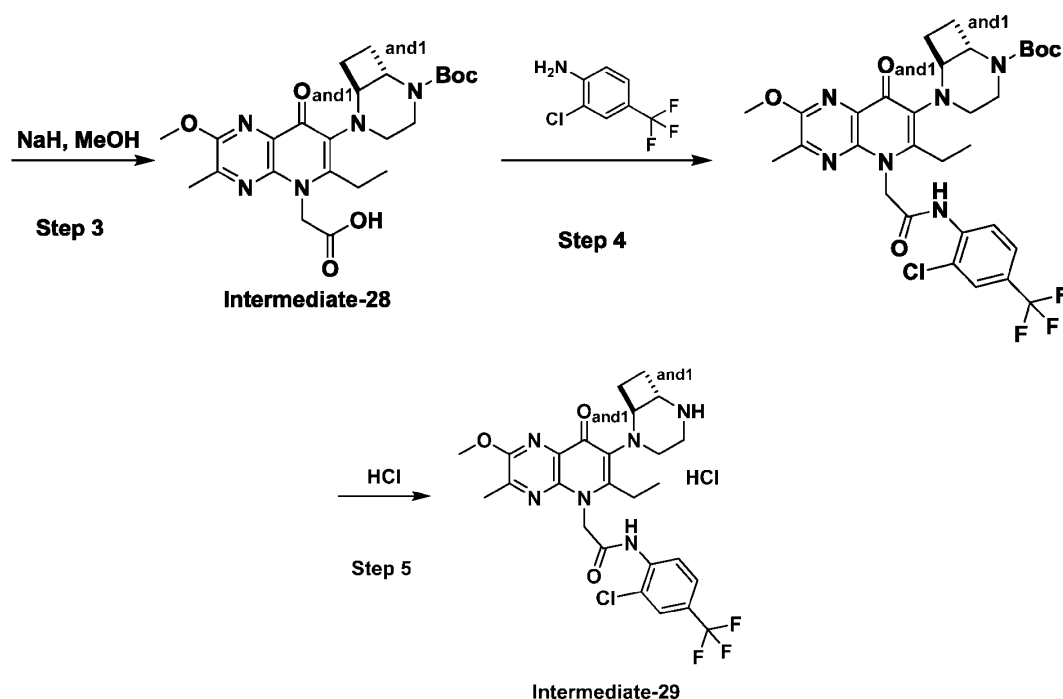
[00789] LCMS: 565.2 [M+H]⁺.

[00790] Intermediate-24: tert-butyl (5-bromo-3-(2-bromo-3-oxopentanoyl)-6-methylpyrazin-2-yl)glycinate

[00791] Intermediate-28: *rac*-2-(7-(-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-6-ethyl-2-methoxy-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid (racemic mixture, trans)

[00792] Intermediate-29: *rac*-2-(7-(2,5-diazabicyclo[4.2.0]octan-2-yl)-6-ethyl-2-methoxy-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide hydrochloride (racemic mixture, trans)





[00793] Step 1. Synthesis of tert-butyl (5-bromo-3-(2-bromo-3-oxopentanoyl)-6-methylpyrazin-2-yl)glycinate

[00794] To a solution of tert-butyl (3-(2-bromo-3-oxopentanoyl)-6-methylpyrazin-2-yl)glycinate (Intermediate-27) (11.00 g, 27.48 mmol, 1.0 eq) in DMF (110 mL) was added NBS (2.45 g, 13.74 mmol, 0.5 eq) and the resulting mixture was stirred at room temperature for 1 h. Second batch of NBS (978 mg, 5.50 mmol, 0.2 eq) was added and the reaction was stirred for another 0.3 h at room temperature. The reaction mixture was diluted with H₂O (50 mL), extracted with EtOAc (50 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford title compound, which was used directly in the next step without further purification.

[00795] Step 2. Synthesis of *rac*-tert-butyl -5-(1-(6-bromo-3-((2-(tert-butoxy)-2-oxoethyl)amino)-5-methylpyrazin-2-yl)-1,3-dioxopentan-2-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (racemic mixture, *trans*)

[00796] To a solution of tert-butyl (5-bromo-3-(2-bromo-3-oxopentanoyl)-6-methylpyrazin-2-yl)glycinate (Intermediate-24) (1.70 g, 3.55 mmol, 1.0 eq) and *rel*-tert-butyl (1*R*,6*R*)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (CAS: 2648861-36-1, racemic mixture, *trans*, 753 mg,

3.55 mmol, 1.0 eq) in DMF (20 mL) was added DIEA (917 mg, 7.10 mmol, 2.0 eq) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched by H₂O (100 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated to afford the title compound, which was used into the next step without further purification.

[00797] LCMS: 609.4 [M+H]⁺.

[00798] Step 3. Synthesis of *rac*-2-(7-(5-(tert-butoxycarbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-6-ethyl-2-methoxy-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid (racemic mixture, trans)

[00799] To a mixture of MeOH (312 mg, 9.75 mmol, 3.5 eq) in THF (45 mL) was added NaH (390 mg, 9.75 mmol, 60% in mineral oil, 3.5 eq) at 0 °C and the mixture was stirred at 0 °C for 0.5 h. To the resulting mixture was added a solution of *rac*-tert-butyl -5-(1-(6-bromo-3-((2-(tert-butoxy)-2-oxoethyl)amino)-5-methylpyrazin-2-yl)-1,3-dioxopentan-2-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (racemic mixture, trans) (1.70 g, 2.78 mmol, 1.0 eq) in THF (30 mL) at room temperature and the mixture was stirred at room temperature for 0.5 h. The reaction mixture was quenched by saturated NH₄Cl aqueous solution (100 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00800] LCMS: 488.3 [M+H]⁺.

[00801] Step 4. Synthesis of *rac*-tert-butyl -5-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-methoxy-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (racemic mixture, trans)

[00802] To a solution of *rac*-2-(7-(5-(tert-butoxycarbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-6-ethyl-2-methoxy-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid (racemic mixture, trans) (intermediate-28) (70 mg, 0.14 mmol, 1.0 eq) and 2-chloro-4-(trifluoromethyl)aniline (31 mg, 0.16 mmol, 1.1 eq) in DCM (1 mL) was added POCl₃ (33 mg, 0.22 mmol, 1.5 eq) at -10 °C and the mixture was stirred at -10 °C for 5 mins. The reaction mixture was poured into water (10

mL), adjusted to pH 8 by saturated NaHCO_3 aqueous solution. The resulting aqueous solution was extracted with EtOAc (10 mL*3). The combined organic layers were dried with anhydrous Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

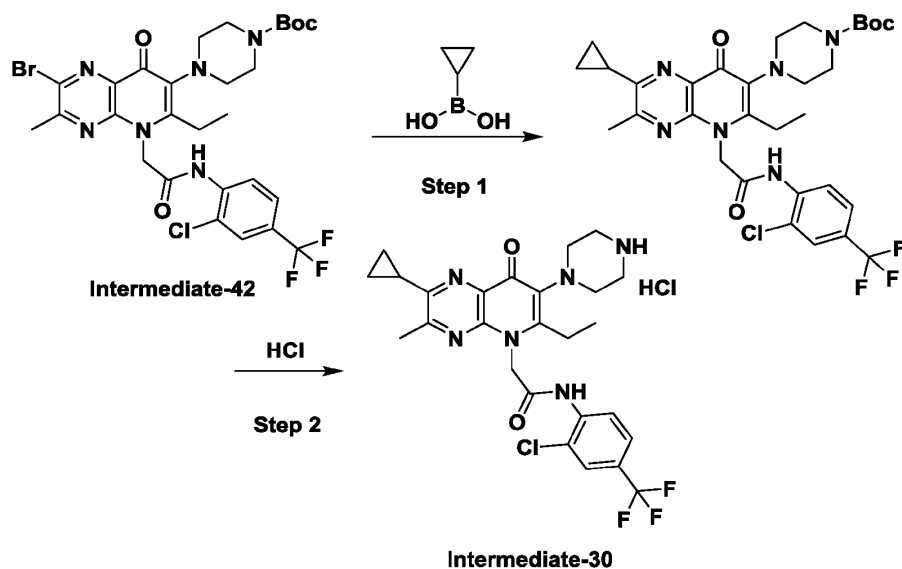
[00803] LCMS: 665.2 $[\text{M}+\text{H}]^+$.

[00804] Step 5. Synthesis of *rac*-2-(7-(2,5-diazabicyclo[4.2.0]octan-2-yl)-6-ethyl-2-methoxy-3-methyl-8-oxopyrido[2,3-*b*]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide hydrochloride (racemic mixture, trans)

[00805] To *rac*-tert-butyl -5-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-methoxy-3-methyl-8-oxo-5,8-dihydropyrido[2,3-*b*]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (racemic mixture, trans) (30 mg, 45 μmol , 1.0 eq) was added a 4 M of solution of HCl in 1,4-dioxane (1 mL) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used directly in the next step without further purification.

[00806] LCMS: 565.2 $[\text{M}+\text{H}]^+$.

[00807] Intermediate-30: N-[2-chloro-4-(trifluoromethyl)phenyl]-2-(2-cyclopropyl-6-ethyl-3-methyl-8-oxo-7-piperazin-1-yl-pyrido[2,3-*b*]pyrazin-5-yl)acetamide hydrochloride



[00808] Step 1. Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-cyclopropyl-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00809] To a solution of tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-42) (110 mg, 160 μ mol, 1.0 eq) and cyclopropylboronic acid (27 mg, 0.32 mmol, 2.0 eq) in 1,4-dioxane (2 mL) was added K_2CO_3 (44 mg, 0.32 mmol, 2.0 eq) and $Pd(PPh_3)_4$ (18 mg, 16 μ mol, 0.1 eq), the resulting mixture was stirred at 110 °C under N_2 atmosphere for 12 h. The reaction mixture was quenched by H_2O (100 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

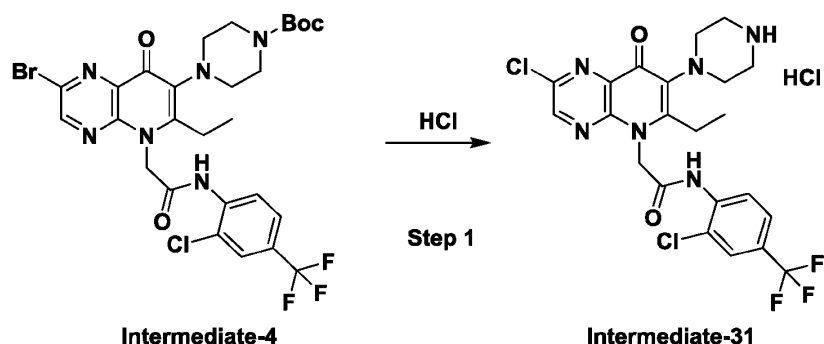
[00810] LCMS: 649.2 $[M+H]^+$.

[00811] Step 2. Synthesis of N-[2-chloro-4-(trifluoromethyl)phenyl]-2-(2-cyclopropyl-6-ethyl-3-methyl-8-oxo-7-piperazin-1-yl-pyrido[2,3-b]pyrazin-5-yl)acetamide hydrochloride

[00812] To a solution of HCl in 1,4-dioxane (1 mL, 4M) was added tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-cyclopropyl-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (100 mg, 154 μ mol, 1.0 eq), and it was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[00813] LCMS: 549.2 $[M+H]^+$.

[00814] Intermediate-31: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-chloro-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride

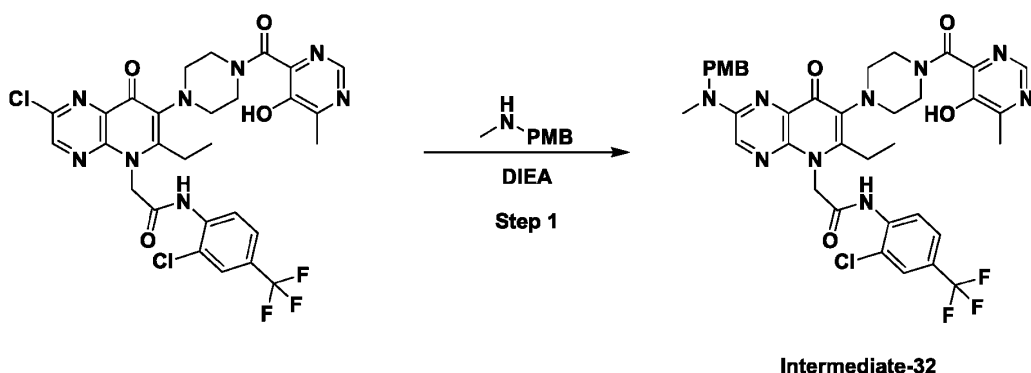


[00815] Step 1: Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-chloro-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride

[00816] To tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-4) (500 mg, 742 μ mol, 1.0 eq) was added a solution of HCl in 1,4-dioxane (6 mL, 4 M), and it was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used in the next step without further purification.

[00817] LCMS: 529.4 [M+H]⁺.

[00818] Intermediate-32: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-((4-methoxybenzyl)(methyl)amino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide



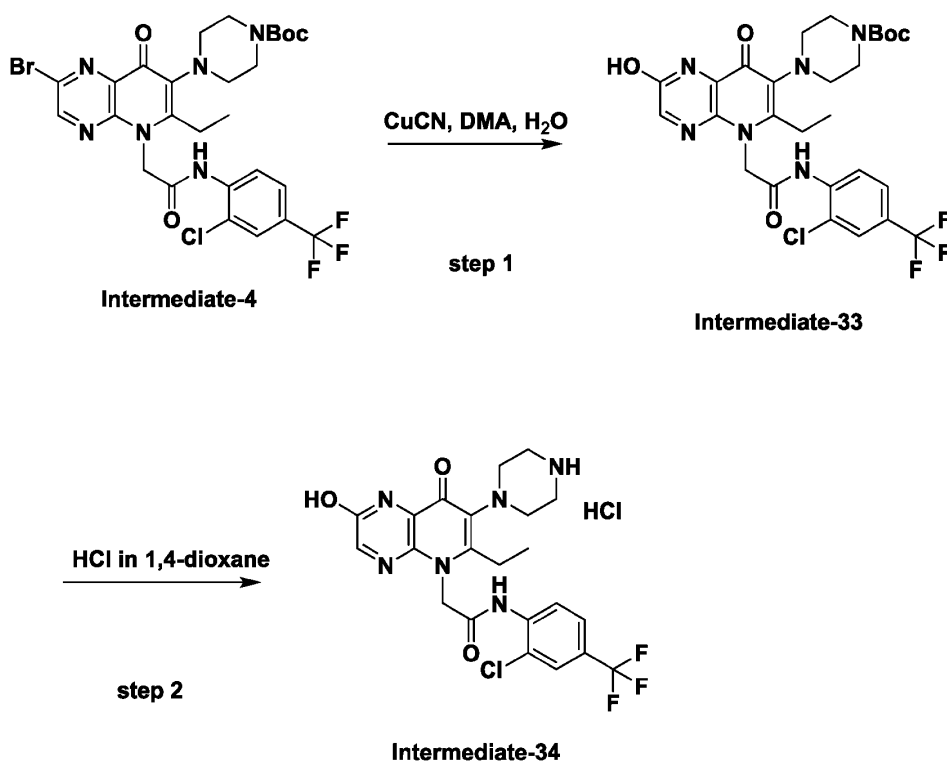
[00819] Step 1: Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-((4-methoxybenzyl)(methyl)amino)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide

[00820] To a solution of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-chloro-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (100 mg, 150 μ mol, 1.0 eq) and 1-(4-methoxyphenyl)-N-methylmethanamine (45 mg, 0.31 mmol, 2.0 eq) in 1,4-dioxane (2 mL) was added DIEA (58 mg, 0.45 mmol, 3.0 eq). The mixture was stirred at 100 °C for 15 h and then concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[00821] LCMS: 780.4 [M+H]⁺.

[00822] Intermediate-33: tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-hydroxy-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00823] Intermediate-34: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-hydroxy-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride



[00824] Step 1. Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-hydroxy-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00825] To a solution of tert-butyl 4-[2-bromo-5-[2-[2-chloro-4-(trifluoromethyl)anilino]-2-oxo-ethyl]-6-ethyl-8-oxo-pyrido[2,3-b]pyrazin-7-yl]piperazine-1-carboxylate (Intermediate-4) (400 mg, 593 μ mol, 1.0 eq) in DMA (4 mL) and H₂O (0.8 mL) was added CuCN (53 mg, 0.60 mmol, 1.0 eq), and then the mixture was stirred at 100 °C for 4 h. After being cooled to room temperature, the reaction mixture was poured into H₂O (50 mL) and extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)- ACN) to afford the title compound.

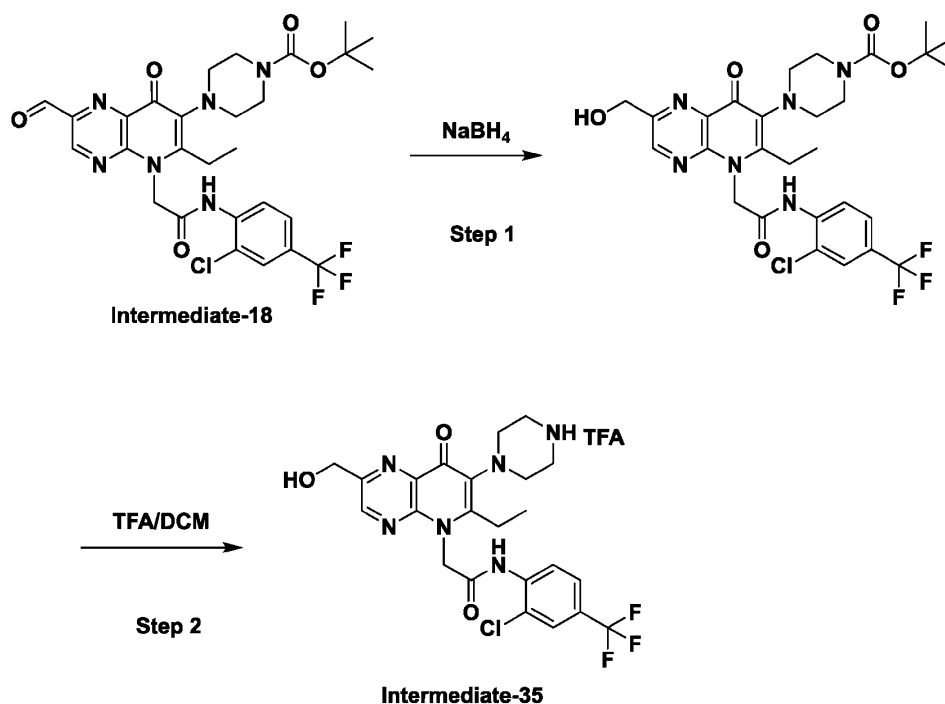
[00826] LCMS: 611.4 [M+H]⁺.

[00827] Step 2. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-hydroxy-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride

[00828] Tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-hydroxy-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-33) (25 mg, 41 μ mol, 1.0 eq) was dissolved into a solution of HCl in 1,4-dioxane (0.4 mL, 4 M), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used in the next step without further purification.

[00829] LCMS: 511.2 [M+H]⁺.

[00830] Intermediate-35: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-(hydroxymethyl)-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide trifluoroacetate



[00831] Step 1. Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-(hydroxymethyl)-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00832] To a solution of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-formyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-18) (60 mg, 96 μ mol, 1.0 eq) in THF (3 mL) and H₂O (0.6 mL) was added NaBH₄ (5 mg, 0.14 mmol, 1.5 eq), the mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by saturated NH₄Cl aqueous solution (5 mL) at 0°C, then diluted with H₂O (10 mL) and extracted with EtOAc (10 mL * 2). The combined organic layers were washed with brine (7.5 mL * 2), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

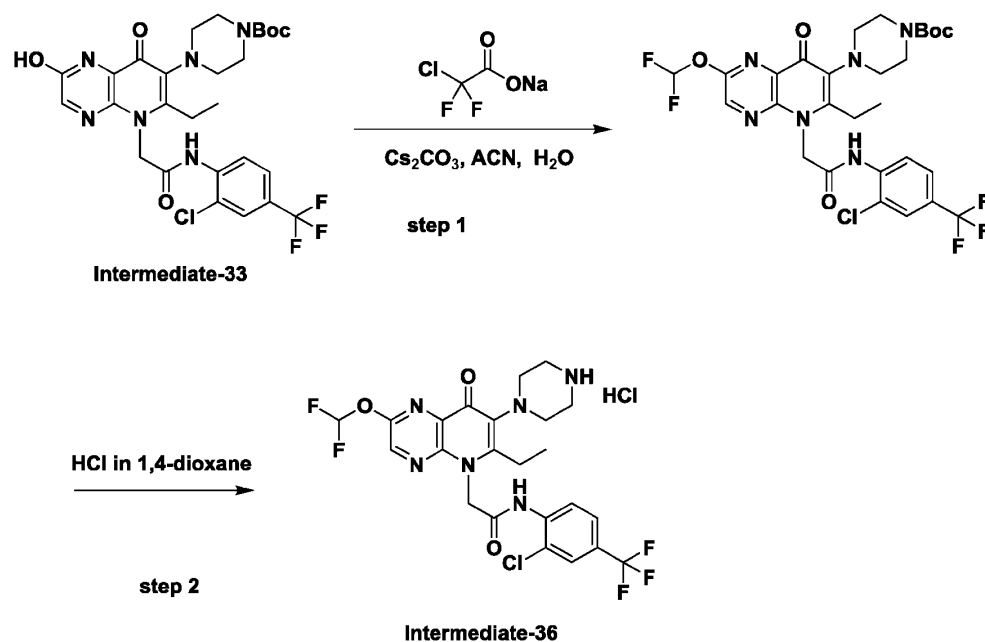
[00833] LCMS: 625.4 [M+H]⁺.

[00834] Step 2. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-(hydroxymethyl)-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide trifluoroacetate

[00835] To a solution of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-(hydroxymethyl)-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (50 mg, 80 μ mol, 1.0 eq) in DCM (4 mL) was added TFA (1 mL) and the resulting mixture was stirred at room temperature for 0.5 h. The mixture was concentrated under reduced pressure to afford the title compound, which was used in the next step without further purification.

[00836] LCMS: 525.1 [M+H]⁺.

[00837] Intermediate-36: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethoxy)-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride



[00838] Step 1. Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(difluoromethoxy)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00839] To a solution of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-hydroxy-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-33) (37 mg, 60 μ mol, 1.0 eq) and sodium 2-chloro-2,2-difluoroacetate (21 mg, 0.14 mmol, 2.3 eq) in ACN (2 mL) and H₂O (0.2 mL) was added Cs₂CO₃ (26 mg, 78 μ mol, 1.3 eq), and the mixture was stirred at 80 °C for 48 h under N₂ atmosphere. After being

cooled to room temperature, the reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (10 mL*3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (PE/EtOAc) to afford the title compound.

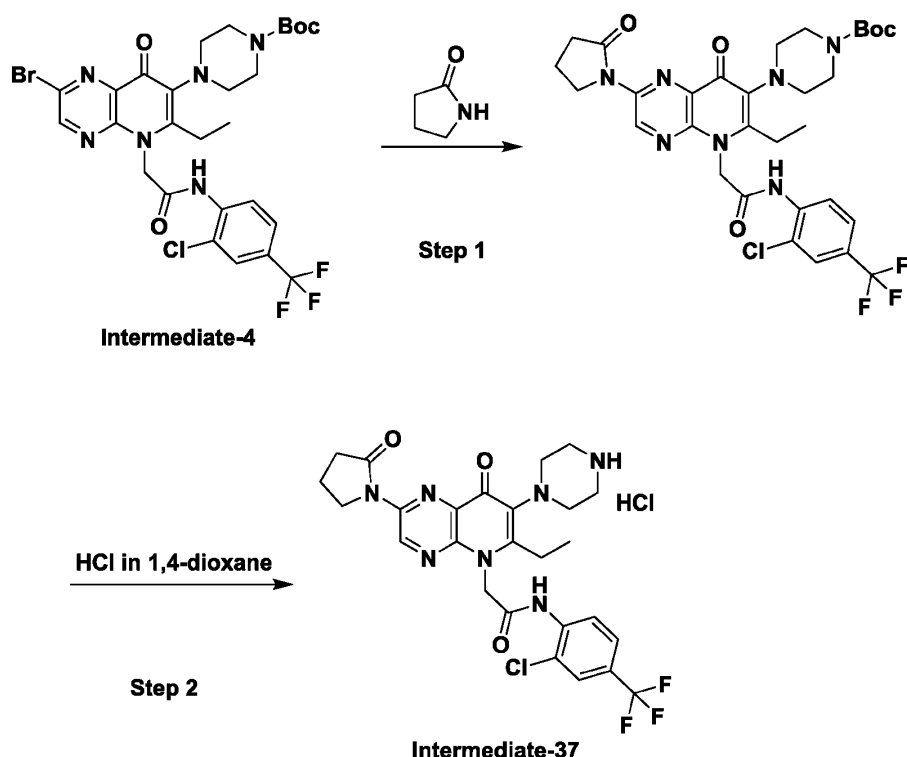
[00840] LCMS: 661.2 [M+H]⁺.

[00841] Step 2. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethoxy)-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride

[00842] To tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(difluoromethoxy)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (17 mg, 25 μ mol, 1.0 eq) was added a solution of HCl in 1,4-dioxane (0.5 mL, 4 M), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used directly in the next step without further purification.

[00843] LCMS: 561.2 [M+H]⁺.

[00844] Intermediate-37: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-8-oxo-2-(2-oxopyrrolidin-1-yl)-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride



[00845] Step 1. Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-2-(2-oxopyrrolidin-1-yl)-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00846] To a solution of tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-4) (50 mg, 74 μ mol, 1.0 eq) in 1,4-dioxane (2 mL) was added CuI (1 mg, 7 μ mol, 0.1 eq), pyrrolidin-2-one (13 mg, 0.15 mmol, 2.0 eq), K_3PO_4 (32 mg, 0.15 mmol, 2.0 eq) and N,N'-dimethylethane-1,2-diamine (1 mg, 15 μ mol, 0.2 eq) at room temperature. The mixture was stirred at 80 °C for 12 h under N_2 atmosphere and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00847] LCMS: 678.2 $[M+H]^+$.

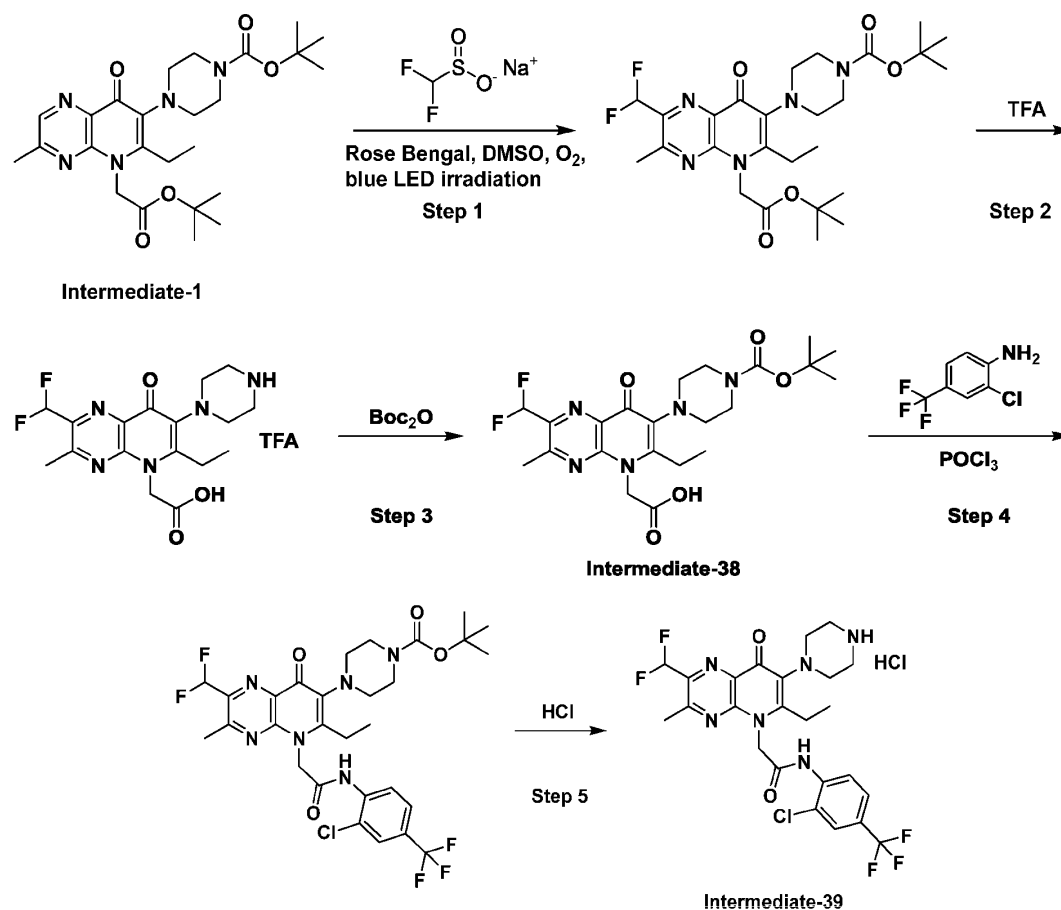
[00848] Step 2. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-8-oxo-2-(2-oxopyrrolidin-1-yl)-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride

[00849] To tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-2-(2-oxopyrrolidin-1-yl)-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (30 mg, 44 μ mol, 1.0 eq) was added a solution of HCl in 1,4-dioxane (1 mL, 4 M) and it was stirred at room temperature for 0.5 h. The mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[00850] LCMS: 578.2 [M+H]⁺.

[00851] Intermediate-38: 2-(7-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-(difluoromethyl)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid

[00852] Intermediate-39: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethyl)-6-ethyl-3-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride



[00853] Step 1. Synthesis of tert-butyl 4-(5-(2-(tert-butoxy)-2-oxoethyl)-2-(difluoromethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00854] To a solution of tert-butyl 4-(5-(2-(tert-butoxy)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-1) (500 mg, 1.03 mmol, 1.0 eq) and sodium difluoromethanesulfinate (283 mg, 2.05 mmol, 2 eq) in DMSO (10 mL) was added rose bengal (21 mg, 21 μ mol, 0.02 eq). The resulting mixture was irradiated with a 525 nm green LED and stirred at room temperature for 48 h under O₂ atmosphere. The reaction mixture was poured into H₂O (50 mL) and extracted with EtOAc (50 mL*2). The combined organic layers were washed with H₂O (50 mL*3), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[00855] LCMS: 538.2 [M+H]⁺.

[00856] Step 2. Synthesis of 2-(7-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-(difluoromethyl)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid trifluoroacetate

[00857] To a solution of tert-butyl 4-(5-(2-(tert-butoxy)-2-oxoethyl)-2-(difluoromethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (140 mg, 260 μ mol, 1.0 eq) in DCM (0.5 mL) was added TFA (2 mL), and it was stirred at 30°C for 10 mins. The resulting mixture was concentrated to dryness to afford the title compound, which was used into the next step without further purification.

[00858] LCMS: 382.2 [M+H]⁺.

[00859] Step 3. Synthesis of 2-(7-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-(difluoromethyl)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid

[00860] To a mixture of 2-(7-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-(difluoromethyl)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid trifluoroacetate (99 mg, 0.26 mmol, 1.0 eq) in DCM (2 mL) was added DIEA (134 mg, 1.04 mmol, 181 μ L, 4.0 eq) and (Boc)₂O (62 mg, 0.29 mmol, 1.1 eq) at 0°C. The mixture was stirred at room temperature for 0.5 h. The reaction mixture was diluted with H₂O (50 mL), extracted with EtOAc (30 mL*2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, the filtrate was concentrated to dryness. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA-ACN) to afford the title compound.

[00861] LCMS: 482.2 [M+H]⁺.

[00862] Step 4. Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(difluoromethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00863] To a solution of 2-(7-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-(difluoromethyl)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid (Intermediate-38) (84 mg, 0.17 mmol, 1.0 eq) and 2-chloro-4-(trifluoromethyl)aniline (38 mg, 0.19 mmol, 1.1 eq) in DCM (1 mL) and pyridine (1 mL) was added POCl₃ (40 mg, 0.26 mmol, 1.5 eq) at -10 °C, and the resulting mixture was stirred at -10 °C for 5 mins. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (5 mL*3). The organic layer was discarded, the aqueous phase was adjusted to pH 8 by saturated NaHCO₃ aqueous solution. The resulting aqueous solution was extracted with EtOAc (10 mL*3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[00864] LCMS: 659.2 [M+H]⁺.

[00865] Step 5. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(difluoromethyl)-6-ethyl-3-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride

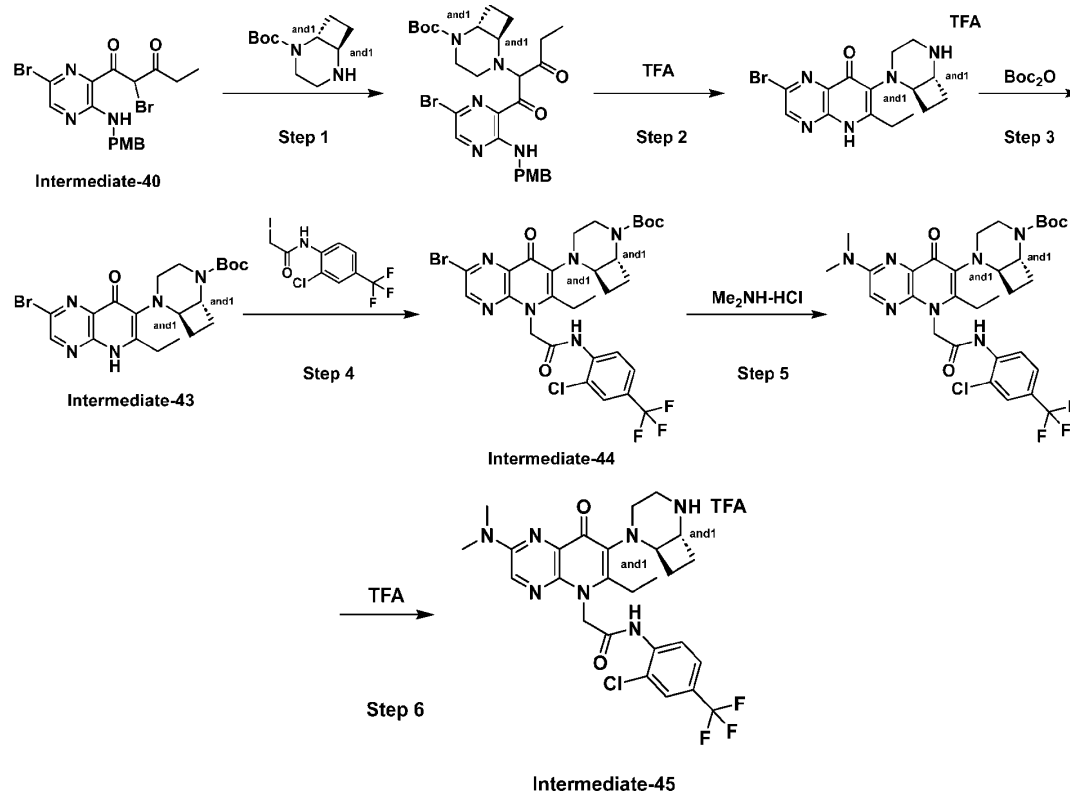
[00866] To tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(difluoromethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (74 mg, 0.11 mmol, 1.0 eq) was added a 4 M solution of HCl in 1,4-dioxane (1 mL). The mixture was stirred at room temperature for 1 h and then concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[00867] LCMS: 559.3 [M+H]⁺.

[00868] Intermediate-43: rac-tert-butyl -5-(2-bromo-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (racemic mixture, trans)

[00869] Intermediate-44: rac-tert-butyl -5-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (racemic mixture, trans)

[00870] Intermediate-45: *rac*-2-(7-(2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(dimethylamino)-6-ethyl-8-oxopyrido[2,3-*b*]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate (racemic mixture, *trans*)



[00871] Step1: Synthesis of *rac*-tert-butyl 5-(1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)-1,3-dioxopentan-2-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (racemic mixture, *trans*)

[00872] To a solution of 2-bromo-1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)pentane-1,3-dione (Intermediate-40) (5.00 g, 5.31 mmol, 1.0 eq) in THF (10 mL) was added DIEA (1.37 g, 10.6 mmol, 2.0 eq) and *rel*-tert-butyl (1*R*,6*R*)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (CAS: 2648861-36-1, racemic mixture, *trans*, 1.69 g, 7.96 mmol, 1.5 eq). The mixture was stirred at room temperature for 0.5 h and then quenched with H₂O (100 mL). The resulting mixture was extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00873] LCMS: 602.1 [M+H]⁺.

[00874] Step 2: Synthesis of *rac*-7-(2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-6-ethylpyrido[2,3-b]pyrazin-8(5H)-one trifluoroacetate (racemic mixture, trans)

[00875] A solution of *rac*-tert-butyl -5-(1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)-1,3-dioxopentan-2-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (racemic mixture, trans) (700 mg, 1.16 mmol, 1.0 eq) in TFA (3.5 mL) was stirred at 50 °C for 3 h and then concentrated under reduced pressure to afford the title compound, which was used in the next step without further purification.

[00876] LCMS: 364.1 [M+H]⁺.

[00877] Step 3: Synthesis of *rac*-tert-butyl -5-(2-bromo-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (racemic mixture, trans)

[00878] To a solution of *rac*-7-(2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-6-ethylpyrido[2,3-b]pyrazin-8(5H)-one trifluoroacetate (racemic mixture, trans) (400 mg, 1.10 mmol, 1.0 eq) in DCM (8 mL) was added DIEA (710 mg, 5.49 mmol, 5.0 eq) and Boc₂O (264 mg, 1.21 mmol, 1.1 eq). The mixture was stirred at room temperature for 0.5 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with DCM (10 mL * 2). The combined organic layers were washed with brine (10 mL * 2), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00879] LCMS: 466.1 [M+H]⁺.

[00880] Step 4: Synthesis of *rac*-tert-butyl-5-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (racemic mixture, trans)

[00881] To a solution of *rac*-tert-butyl-5-(2-bromo-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (racemic mixture, trans) (Intermediate-43) (250 mg, 431 μmol, 1.0 eq) in DMF (3 mL) was added K₂CO₃ (60 mg, 0.43 mmol, 1.0 eq) and N-(2-chloro-4-(trifluoromethyl)phenyl)-2-iodoacetamide (157 mg, 431 μmol, 1.0 eq). The reaction mixture was stirred at room temperature for 2 h and then quenched with saturated NH₄Cl aqueous solution (100 mL). The resulting solution was extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄,

filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00882] LCMS: 701.1 [M+H]⁺.

[00883] Step 5: Synthesis of *rac*-tert-butyl-5-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(dimethylamino)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (racemic mixture, trans)

[00884] To a solution of *rac*-tert-butyl-5-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (racemic mixture, trans) (Intermediate-44) (90 mg, 0.13 mmol, 1.0 eq) in 1,4-dioxane (2 mL) was added dimethylamine hydrochloride (52 mg, 0.64 mmol, 5.0 eq) and DIEA (100 mg, 771 μ mol, 6.0 eq). The mixture was stirred at 100 °C for 1 h and then quenched by H₂O (100 mL). The resulting solution was extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuo to afford the title compound, which was used in the next step without further purification.

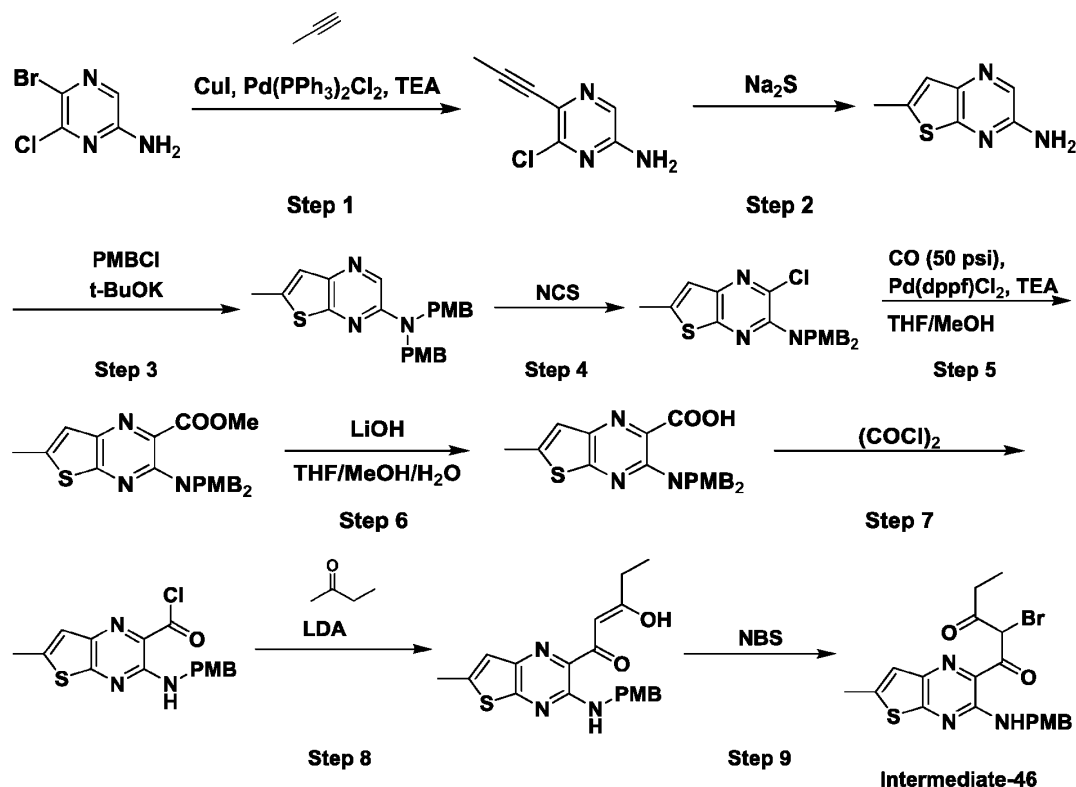
[00885] LCMS: 664.2 [M+H]⁺.

[00886] Step 6: Synthesis of *rac*-2-(7-(2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(dimethylamino)-6-ethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate (racemic mixture, trans)

[00887] To a solution of *rac*-tert-butyl-5-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(dimethylamino)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (racemic mixture, trans) (85 mg, 0.13 mmol, 1.0 eq) in DCM (1 mL) was added TFA (5 mL) and the resulting mixture was stirred at 30 °C for 1 h. The reaction mixture was concentrated in vacuo to afford the title compound, which was used into the next step without further purification.

[00888] LCMS: 564.3 [M+H]⁺.

[00889] Intermediate-46: 2-bromo-1-(3-((4-methoxybenzyl)amino)-6-methylthieno[2,3-b]pyrazin-2-yl)pentane-1,3-dione



[00890] Step 1. Synthesis of 6-chloro-5-(prop-1-yn-1-yl)pyrazin-2-amine

[00891] To a solution of methyl 5-bromo-6-chloro-pyrazin-2-amine (20.00 g, 95.95 mmol, 1 eq) in THF (20 mL) was added Et₃N (33.98 g, 335.8 mmol, 46.74 mL, 3.5 eq), Pd(PPh₃)₂Cl₂ (6.73 g, 9.59 mmol, 0.1 eq), CuI (914 mg, 4.80 mmol, 0.05 eq) and prop-1-yne (1 M in THF, 191.90 mL, 2 eq). The mixture was stirred at 50 °C for 2 h. The reaction solution was filtered and the filtrate was concentrated under reduced pressure to give the residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[00892] ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.76 (s, 1H), 7.18 (s, 2H), 2.07 (s, 3H).

[00893] LCMS: 168.0 [M+H]⁺.

[00894] Step 2. Synthesis of 6-methylthieno[2,3-b]pyrazin-3-amine

[00895] To a solution of 6-chloro-5-prop-1-ynyl-pyrazin-2-amine (10.00 g, 59.67 mmol, 1 eq) in DMF (100 mL) and H₂O (15 mL) was added Na₂S (13.97 g, 179.0 mmol, 3 eq). The mixture was stirred at 90 °C for 3 h. The reaction mixture was diluted with H₂O (150 mL) and extracted with EtOAc (80 mL * 3). The combined organic layers were washed with brine (100 mL * 2),

dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[00896] ¹H NMR (400 MHz, CDCl₃) δ ppm 7.98 (s, 1H), 6.97 (s, 1H), 4.58 (br s, 2H), 2.57 (s, 3H).

[00897] LCMS: 166.0 [M+H]⁺.

[00898] Step 3. Synthesis of N,N-bis(4-methoxybenzyl)-6-methylthieno[2,3-b]pyrazin-3-amine

[00899] To a solution of 6-methylthieno[2,3-b]pyrazin-3-amine (3.60 g, 21.79 mmol, 1 eq) in THF (80 mL) was added t-BuOK (7.34 g, 65.4 mmol, 3 eq) and 1-(chloromethyl)-4-methoxybenzene (8.19 g, 52.3 mmol, 7.10 mL, 2.4 eq). The mixture was stirred at 60 °C for 1 h. The reaction mixture was diluted by water (80 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (60 mL * 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[00900] ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.06 (s, 1H), 7.21 - 7.19 (m, 4H), 7.00 (s, 1H), 6.90 - 6.83 (m, 4H), 4.77 (s, 4H), 3.72 - 3.69 (s, 6H), 2.49 (s, 3H).

[00901] LCMS: 406.2 [M+H]⁺.

[00902] Step 4. Synthesis of 2-chloro-N,N-bis(4-methoxybenzyl)-6-methylthieno[2,3-b]pyrazin-3-amine

[00903] To a solution of N,N-bis[(4-methoxyphenyl)methyl]-6-methyl-thieno[2,3-b]pyrazin-3-amine (6.50 g, 12.0 mmol, 1eq) in DMF (65 mL) was added NCS (1.77 g, 13.2 mmol, 1.1 eq). The mixture was stirred at 80 °C for 0.5 h. The reaction mixture was diluted by H₂O (80 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (60 mL * 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[00904] ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.23 - 7.21 (m, 4H), 7.17 (s, 1H), 6.89 - 6.82 (m, 4H), 4.43 (s, 4H), 3.69 (s, 6H), 2.57 (s, 3H).

[00905] LCMS: 440.1 [M+H]⁺.

[00906] Step 5. Synthesis of methyl 3-(bis(4-methoxybenzyl)amino)-6-methylthieno[2,3-b]pyrazine-2-carboxylate

[00907] To a solution of 2-chloro-N,N-bis[(4-methoxyphenyl)methyl]-6-methyl-thieno[2,3-b]pyrazin-3-amine (2.30 g, 5.23 mmol, 1 eq) and Pd(dppf)Cl₂ (382 mg, 523 μmol, 0.1 eq) in MeOH (50 mL) was added Et₃N (1.59 g, 15.7 mmol, 2.18 mL, 3 eq) under N₂ atmosphere. The suspension was degassed under vacuum and purged with CO three times. The mixture was stirred at 50 °C for 12 h under CO (50 Psi). The reaction solution was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[00908] ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.14 (s, 1H), 7.14 - 7.12 (m, 4H), 6.87 - 6.85 (m, 4H), 4.51 (s, 4H), 3.82 (s, 3H), 3.70 (s, 6H), 2.57 (s, 3H).

[00909] LCMS: 464.3 [M+H]⁺.

[00910] Step 6. Synthesis of 3-(bis(4-methoxybenzyl)amino)-6-methylthieno[2,3-b]pyrazine-2-carboxylic acid

[00911] To a solution of methyl 3-[bis[(4-methoxyphenyl)methyl]amino]-6-methyl-thieno[2,3-b]pyrazine-2-carboxylate (1.80 g, 3.88 mmol, 1 eq) in THF (12 mL), MeOH (4 mL) and H₂O (4 mL) was added LiOH-H₂O (1.63 g, 38.83 mmol, 10 eq). The mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated in vacuum, the resulting residue was diluted with H₂O (150 mL), saturated citric acid aqueous solution was added until the pH of mixture was acidified to 4~5. Then the mixture was extracted with EtOAc (100 mL * 3). The combined organic layer was washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound.

[00912] ¹H NMR (400 MHz, CDCl₃) δ ppm 7.18 (s, 1H), 7.12 - 7.10 (m, 4H), 6.78 - 6.76 (m, 4H), 4.41 (s, 4H), 3.75 (s, 6H), 2.69 (s, 3H).

[00913] Step 7. Synthesis of 3-((4-methoxybenzyl)amino)-6-methylthieno[2,3-b]pyrazine-2-carbonyl chloride

[00914] To a solution of 3-[bis[(4-methoxyphenyl)methyl]amino]-6-methyl-thieno[2,3-b]pyrazine-2-carboxylic acid (1.60 g, 3.56 mmol, 1 eq) in DCM (20 mL) was added (COCl)₂ (678 mg, 5.34 mmol, 467 μL, 1.5 eq) and DMF (5 mg, 71 μmol, 5 μL, 0.02 eq) at 0 °C. The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated in vacuum, the resulting residue was diluted with THF (8 mL) and concentrated under reduced pressure, this

process was repeated three times to obtain the title compound, which was used in the next step directly without further purification.

[00915] Step 8. Synthesis of 3-hydroxy-1-(3-((4-methoxybenzyl)amino)-6-methylthieno[2,3-b]pyrazin-2-yl)pent-2-en-1-one.

[00916] To a solution of butan-2-one (407 mg, 5.65 mmol, 505 μ L, 1.5 eq) in THF (8 mL) was added LDA (2 M, 2.82 mL, 1.5 eq) at -78 °C under N₂ atmosphere, then the mixture was stirred at -78 °C for 0.5 h. A solution of 3-[(4-methoxyphenyl)methylamino]-6-methylthieno[2,3-b]pyrazine-2-carbonyl chloride (1.31 g, 3.77 mmol, 1 eq) in THF (8 mL) was added dropwise into the butan-3-one solution. The mixture was stirred at 25 °C for another 1 h. The reaction mixture was poured into saturated NH₄Cl aqueous solution (100 mL) and extracted with EtOAc (50 mL * 3). The combined organic layer was washed with brine (150 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[00917] LCMS: 384.1 [M+H]⁺.

[00918] Step 9. Synthesis of 2-bromo-1-(3-((4-methoxybenzyl)amino)-6-methylthieno[2,3-b]pyrazin-2-yl)pentane-1,3-dione

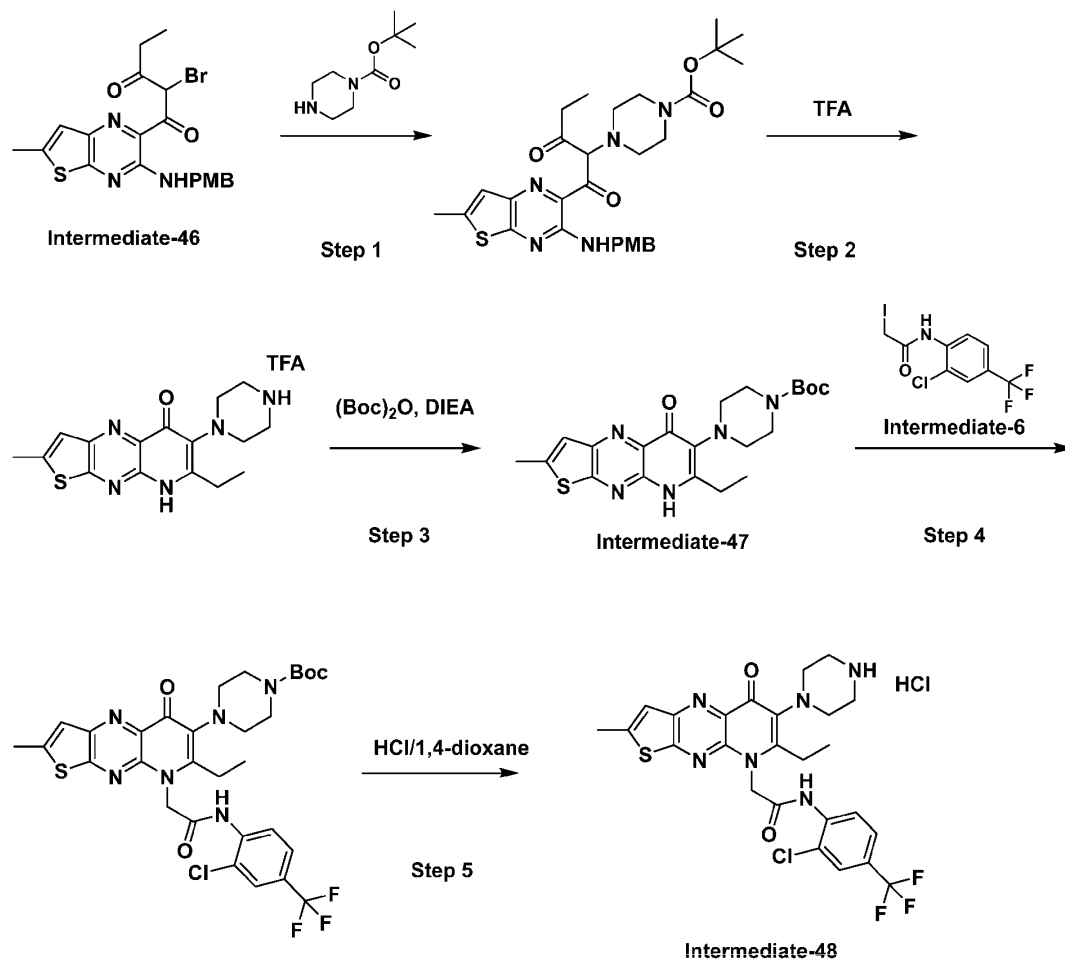
[00919] To a solution of (Z)-3-hydroxy-1-[3-[(4-methoxyphenyl)methylamino]-6-methylthieno[2,3-b]pyrazin-2-yl]pent-2-en-1-one (230 mg, 600 μ mol, 1 eq) in DCM (4 mL) was added NBS (107 mg, 600 μ mol, 1 eq). The mixture was stirred at -10 °C for 1 h. The reaction mixture was quenched with saturated Na₂SO₃ aqueous solution (10 mL) and extracted with DCM (5 mL * 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[00920] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.71- 8.69 (m, 1H), 7.32 - 7.30 (m, 2H), 6.91 - 6.87 (m, 2H), 6.82 (s, 1H), 6.31 (s, 1H), 4.77 - 4.64 (m, 2H), 3.81 (s, 3H), 2.95 (q, 2H), 2.57 (s, 3H), 1.18 (t, 3H).

[00921] LCMS: 464.0 [M+H]⁺.

[00922] Intermediate-47: tert-butyl 4-(7-ethyl-2-methyl-5-oxo-5,8-dihydropyrido[2,3-b]thieno[3,2-e]pyrazin-6-yl)piperazine-1-carboxylate

[00923] Intermediate-48: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-ethyl-2-methyl-5-oxo-6-(piperazin-1-yl)pyrido[2,3-b]thieno[3,2-e]pyrazin-8(5H)-yl)acetamide hydrochloride



[00924] Step 1. Synthesis of tert-butyl 4-(1-(3-((4-methoxybenzyl)amino)-6-methylthieno[2,3-b]pyrazin-2-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate

[00925] To a solution of 2-bromo-1-[3-[(4-methoxyphenyl)methylamino]-6-methylthieno[2,3-b]pyrazin-2-yl]pentane-1,3-dione (Intermediate-46) (180 mg, 389 μmol , 1 eq) and tert-butyl piperazine-1-carboxylate (80 mg, 0.43 mmol, 1.1 eq) in THF (2 mL) was added DIEA (101 mg, 779 μmol , 136 μL , 2 eq). The mixture was stirred at 25 $^{\circ}\text{C}$ for 2 h. The reaction mixture was concentrated in vacuum to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[00926] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.87 - 8.85 (m, 1H), 7.32 - 7.30 (m, 2H), 6.89 - 6.87 (m, 2H), 6.81 (s, 1H), 5.56 (s, 1H), 4.76 - 4.62 (m, 2H), 3.81 (s, 3H), 3.52 - 3.39 (m, 4H), 2.93 - 2.81 (m, 3H), 2.74 - 2.59 (m, 3H), 2.56 (s, 3H), 1.45 (s, 9H), 1.12 (t, 3H).

[00927] LCMS: 568.3 [M+H]⁺.

[00928] Step 2. Synthesis of 7-ethyl-2-methyl-6-(piperazin-1-yl)pyrido[2,3-b]thieno[3,2-e]pyrazin-5(8H)-one trifluoroacetate

[00929] A mixture of tert-butyl 4-[1-[3-[(4-methoxyphenyl)methylamino]-6-methylthieno[2,3-b]pyrazine-2-carbonyl]-2-oxobutyl]piperazine-1-carboxylate (200 mg, 352 μmol, 1 eq) in TFA (4 mL) was stirred at 50 °C for 1 h. The reaction mixture was concentrated in vacuum to obtain the title compound, which was used into the next step directly without further purification.

[00930] LCMS: 330.1 [M+H]⁺.

[00931] Step 3. Synthesis of tert-butyl 4-(7-ethyl-2-methyl-5-oxo-5,8-dihydropyrido[2,3-b]thieno[3,2-e]pyrazin-6-yl)piperazine-1-carboxylate

[00932] To a solution of 7-ethyl-2-methyl-6-(piperazin-1-yl)pyrido[2,3-b]thieno[3,2-e]pyrazin-5(8H)-one trifluoroacetate (160 mg, 361 μmol, 1 eq) in DCM (4 mL) was added DIEA (140 mg, 1.08 mmol, 189 μL, 3.0 eq) and Boc₂O (94 mg, 0.43 mmol, 99 μL, 1.2 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated in vacuum to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[00933] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.52 - 8.50 (brs, 1H), 7.30 (s, 1H), 4.14 - 3.98 (m, 2H), 3.97 - 3.79 (m, 2H), 3.10 - 2.84 (m, 4H), 2.70 (s, 3H), 2.68 - 2.53 (m, 2H), 1.50 (s, 9H), 1.37 (t, 3H).

[00934] LCMS: 430.2 [M+H]⁺.

[00935] Step 4. Synthesis of tert-butyl 4-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-7-ethyl-2-methyl-5-oxo-5,8-dihydropyrido[2,3-b]thieno[3,2-e]pyrazin-6-yl)piperazine-1-carboxylate

[00936] To a solution of tert-butyl 4-(7-ethyl-2-methyl-5-oxo-5,8-dihydropyrido[2,3-b]thieno[3,2-e]pyrazin-6-yl)piperazine-1-carboxylate (Intermediate-47) (80 mg, 0.19 mmol, 1 eq) and N-[2-chloro-4-(trifluoromethyl)phenyl]-2-iodo-acetamide (Intermediate-6) (102 mg, 279 μmol, 1.5) in 1,4-dioxane (4 mL) was added DIEA (72 mg, 0.56 mmol, 97 μL, 3 eq). The

mixture was stirred at 80 °C for 2 h. The reaction mixture was cooled at room temperature and concentrated in vacuum to give a residue. The residue was triturated with EtOAc (5 mL) and purified by Prep-TLC (SiO₂, Eluent of MeOH / DCM) to afford the title compound.

[00937] ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.43 (s, 1H), 8.14 - 7.83 (m, 2H), 7.78 - 7.60 (m, 1H), 7.46 (s, 1H), 5.53 (s, 2H), 3.96 - 3.93 (m, 2H), 3.66 (q, 2H), 3.17 - 3.15 (m, 2H), 3.03 - 2.83 (m, 2H), 2.71 (s, 3H), 2.64 - 2.62 (m, 2H), 1.45 (s, 9H), 1.25 (t, 3H).

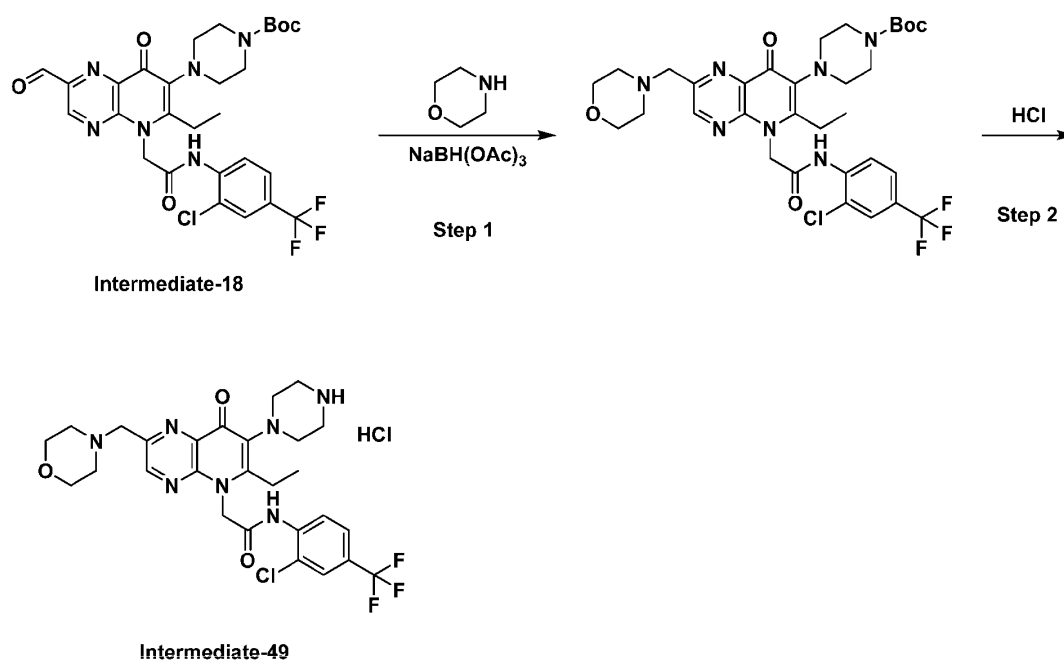
[00938] LCMS: 665.2 [M+H]⁺.

[00939] Step 5. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-ethyl-2-methyl-5-oxo-6-(piperazin-1-yl)pyrido[2,3-b]thieno[3,2-e]pyrazin-8(5H)-yl)acetamide hydrochloride

[00940] A mixture of tert-butyl 4-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-7-ethyl-2-methyl-5-oxo-5,8-dihydropyrido[2,3-b]thieno[3,2-e]pyrazin-6-yl)piperazine-1-carboxylate (30 mg, 45 μmol, 1 eq) in HCl/1,4-dioxane (2 M, 2.57 mL, 114 eq) was stirred at 25 °C for 1 h. The reaction mixture was concentrated in vacuum to obtain the title compound, which was used into the next step directly without further purification.

[00941] LCMS: 565.2 [M+H]⁺.

[00942] Intermediate-49: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-(morpholinomethyl)-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride



[00943] Step 1. Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-(morpholinomethyl)-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00944] To a solution of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-(morpholinomethyl)-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-18) (80 mg, 0.13 mmol, 1.0 eq) and morpholine (56 mg, 0.64 mmol, 5.0 eq) in DCM (2 mL) was added $\text{NaBH}(\text{OAc})_3$ (136 mg, 0.64 mmol, 5.0 eq). The mixture was stirred at room temperature for 1 h and then concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[00945] LCMS: 694.4 $[\text{M}+\text{H}]^+$.

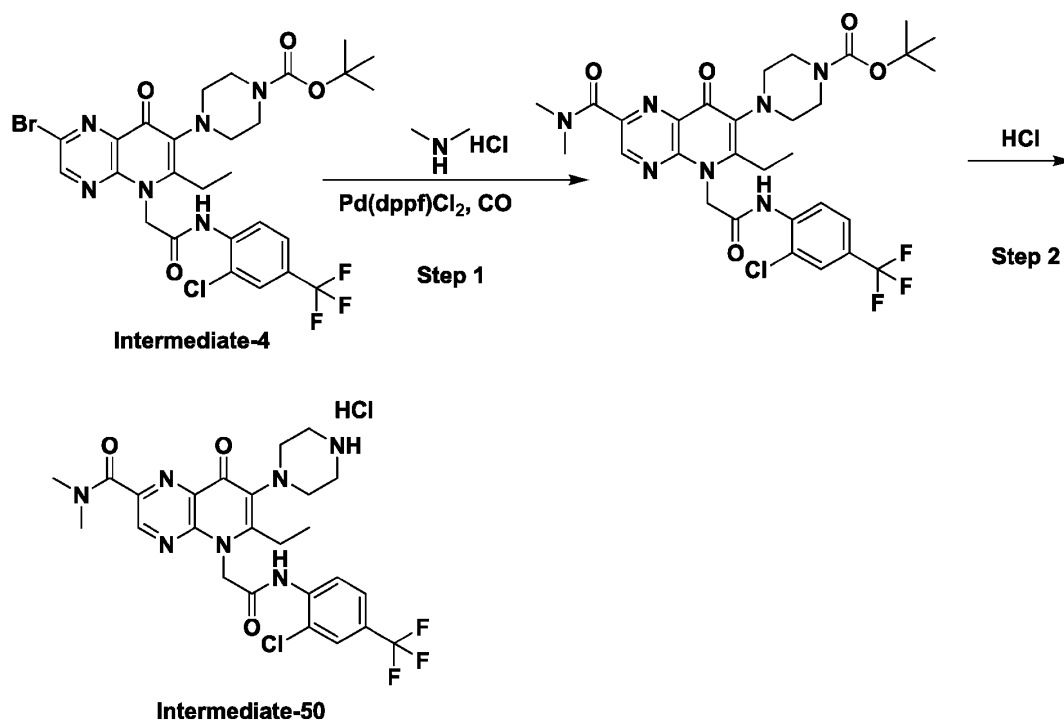
[00946] Step 2. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-(morpholinomethyl)-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)acetamide hydrochloride

[00947] To a solution of HCl in 1,4-dioxane (2 M, 2 mL) was added tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-(morpholinomethyl)-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (60 mg, 86 μmol , 1.0 eq), and then the

resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[00948] LCMS: 594.4 [M+H]⁺.

[00949] Intermediate-50: 5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-N,N-dimethyl-8-oxo-7-(piperazin-1-yl)-5,8-dihydropyrido[2,3-b]pyrazine-2-carboxamide hydrochloride



[00950] Step 1. Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(dimethylcarbamoyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00951] To a solution of tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-4) (100 mg, 148 μ mol, 1.0 eq) in DMF (3 mL) was added Pd(dppf)Cl₂ (11 mg, 15 μ mol, 0.1 eq), DIEA (96 mg, 0.74 μ mol, 5.0 eq) and dimethylamine hydrochloride (36 mg, 0.45 mmol, 3.0 eq). The resulting mixture was purged with CO gas and then stirred at 80 °C overnight. The reaction was diluted with H₂O (10 mL) and extracted with

EtOAc (5 mL * 3). The combined organic layers were washed with brine (5 mL * 3), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

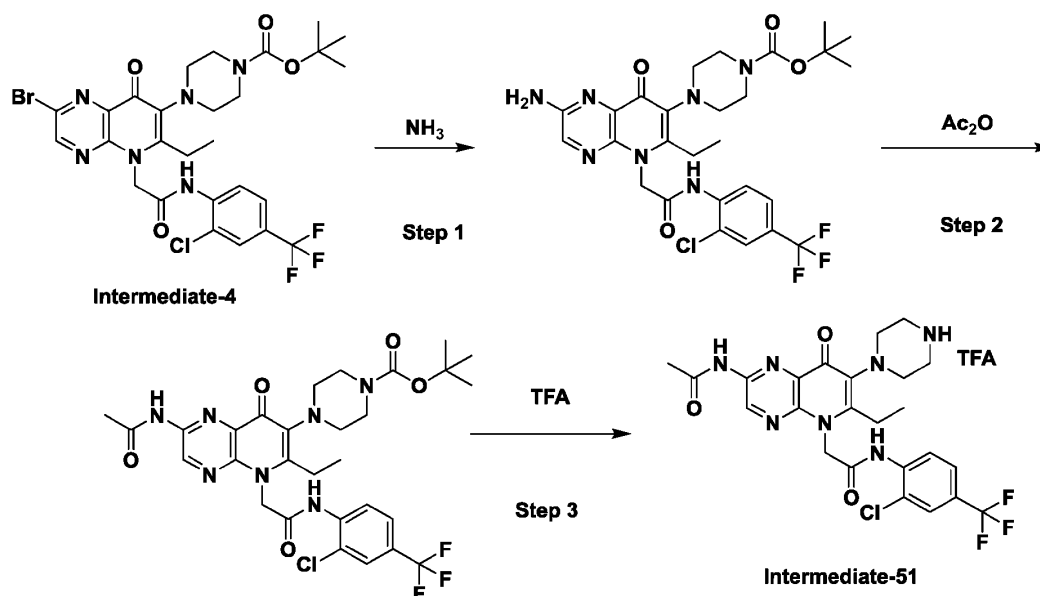
[00952] LCMS: 666.4 [M+H]⁺.

[00953] Step 2. 5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-N,N-dimethyl-8-oxo-7-(piperazin-1-yl)-5,8-dihydropyrido[2,3-b]pyrazine-2-carboxamide hydrochloride

[00954] To a solution of HCl in 1,4-dioxane (2 M, 2 mL) was added tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(dimethylcarbamoyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (44 mg, 66 μmol, 1.0 eq), and the resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[00955] LCMS: 566.3 [M+H]⁺.

[00956] Intermediate-51: 2-(2-acetamido-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate



[00957] Step 1. Synthesis of tert-butyl 4-(2-amino-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00958] To a solution of NH₃ in 1,4-dioxane (4 M, 6 mL) was added tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-4) (300 mg, 445 μmol, 1.0 eq). The mixture was stirred at 140 °C overnight in sealed tube. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[00959] LCMS: 610.4 [M+H]⁺.

[00960] Step 2. Synthesis of tert-butyl 4-(2-acetamido-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate

[00961] To a solution of tert-butyl 4-(2-amino-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (60 mg, 98 μmol, 1.0 eq) in DCM (1 mL) was added Ac₂O (0.5 mL), and then the resulting mixture was stirred at 40 °C overnight. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (5 mL * 3), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

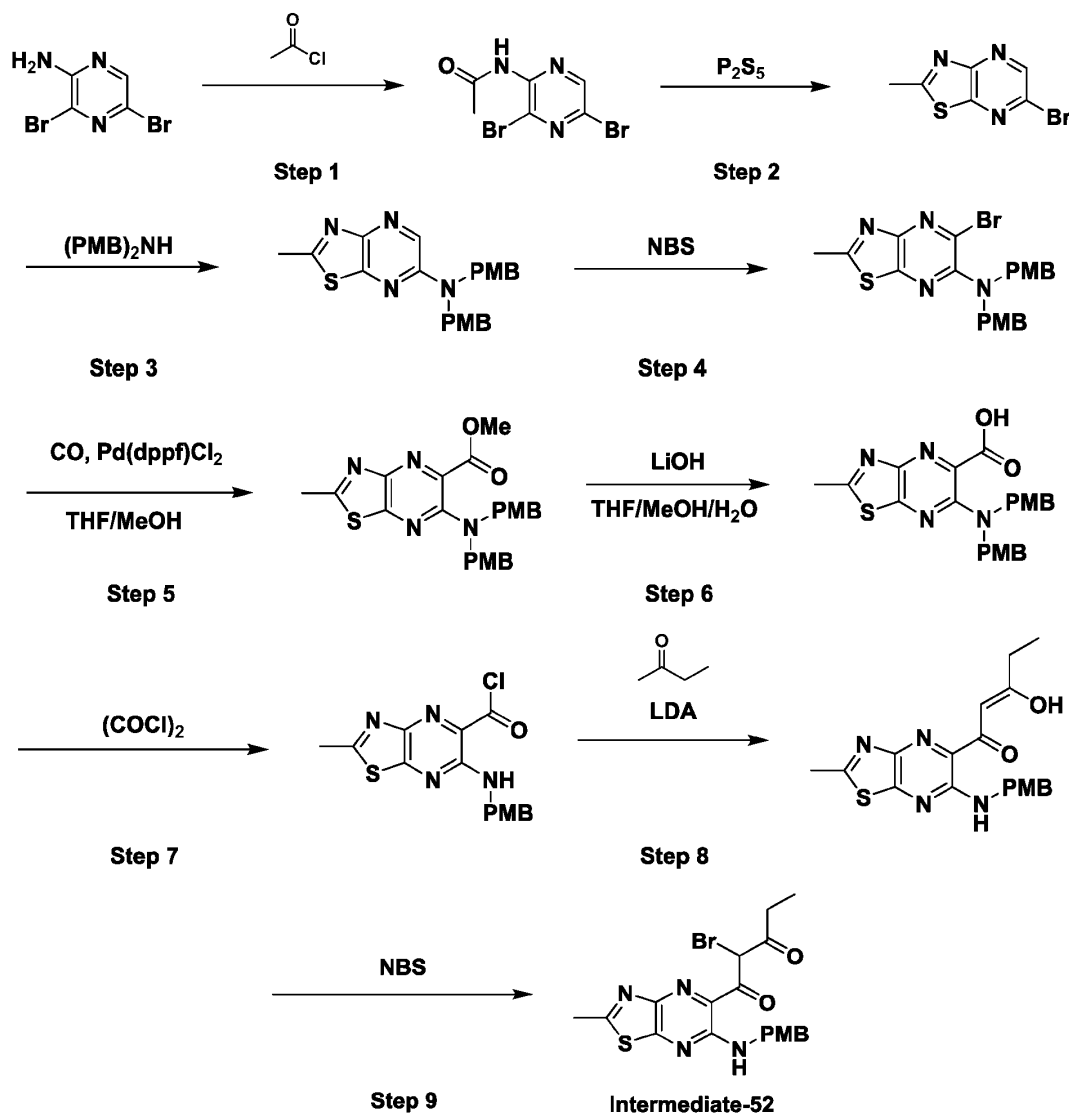
[00962] LCMS: 652.4 [M+H]⁺.

[00963] Step 3. Synthesis of 2-(2-acetamido-6-ethyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate

[00964] To a solution of tert-butyl 4-(2-acetamido-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)piperazine-1-carboxylate (40 mg, 61 μmol, 1.0 eq) in DCM (0.8 mL) was added TFA (0.2 mL) and the resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[00965] LCMS: 552.3 [M+H]⁺.

[00966] Intermediate-52: 2-bromo-1-(6-((4-methoxybenzyl)amino)-2-methylthiazolo[4,5-b]pyrazin-5-yl)pentane-1,3-dione



[00967] Step 1. Synthesis of N-(3,5-dibromopyrazin-2-yl)acetamide

[00968] To a solution of 3,5-dibromopyrazin-2-amine (10.00 g, 39.54 mmol, 1 eq) and DMAP (4.83 g, 39.5 mmol, 1 eq) in ACN (100 mL) was added acetyl chloride (9.31 g, 118 mmol, 8.43 mL, 3 eq), then the mixture was stirred at 80 °C for 1.5 h. The mixture was concentrated to give

a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[00969] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.38 (s, 1H), 7.91 (s, 1H), 2.45 (s, 3H).

[00970] LCMS: 296.0 [M+H]⁺.

[00971] Step 2. Synthesis of 6-bromo-2-methylthiazolo[4,5-b]pyrazine

[00972] To a solution of N-(3,5-dibromopyrazin-2-yl)acetamide (6.80 g, 23.1 mmol, 1 eq) in toluene (136 mL) was added P₂S₅ (3.07 g, 13.8 mmol, 1.47 mL, 0.6 eq), then the mixture was stirred at 110 °C for 1 h. The mixture was concentrated under reduced pressure and neutralized with saturated NaHCO₃ to pH = ~7. Then the mixture was extracted with EtOAc (150 mL * 3). Then the organic phase was washed with brine (300 mL), dried over anhydrous Na₂SO₄ and concentrated under reduce pressure to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[00973] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.71 (s, 1H), 2.94 (s, 3H).

[00974] LCMS: 232.1 [M+H]⁺.

[00975] Step 3. Synthesis of N,N-bis(4-methoxybenzyl)-2-methylthiazolo[4,5-b]pyrazin-6-amine

[00976] To a solution of 6-bromo-2-methylthiazolo[4,5-b]pyrazine (10.00 g, 43.46 mmol, 1 eq) and 1-(4-methoxyphenyl)-N-[(4-methoxyphenyl)methyl]methanamine (13.42 g, 52.15 mmol, 1.2 eq) in NMP (100 mL) was added DIEA (8.43 g, 65.2 mmol, 11.4 mL, 1.5 eq), the mixture was stirred at 140 °C for 16 h. The mixture was poured to water (500 mL). Then the mixture was extracted with EtOAc (150 mL * 3). The organic phase was washed with brine (500 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) and reversed-phase HPLC (C18 column, water (0.1% FA-ACN) to afford the title compound.

[00977] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.01 (s, 1H), 7.17 (d, 4H), 6.86 (d, 4H), 4.77 (s, 4H), 3.80 (s, 6H), 2.81 (s, 3H).

[00978] LCMS: 407.3 [M+H]⁺.

[00979] Step 4. Synthesis of 5-bromo-N,N-bis(4-methoxybenzyl)-2-methylthiazolo[4,5-b]pyrazin-6-amine

[00980] To a solution of N,N-bis(4-methoxybenzyl)-2-methylthiazolo[4,5-b]pyrazin-6-amine (10.00 g, 24.60 mmol, 1 eq) in DMF (100 mL) was added NBS (4.38 g, 24.6 mmol, 1 eq), then

the mixture was stirred at 25 °C for 1 h. The mixture was poured into water (500 mL). Then the mixture was extracted with EtOAc (200 mL * 3). Then the organic phase was washed with brine (500 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a residue. The residue was triturated with (EtOH/EtOAc=3/1, 100 mL) to afford the title compound.

[00981] ¹H NMR (400 MHz, CDCl₃) δ ppm 7.22 (d, 4H), 6.83 (d, 4H), 4.48 (s, 4H), 3.79 (s, 6H), 2.84 (s, 3H).

[00982] LCMS: 487.2 [M+H]⁺.

[00983] Step 5. Synthesis of methyl 6-(bis(4-methoxybenzyl)amino)-2-methylthiazolo[4,5-b]pyrazine-5-carboxylate

[00984] To a solution of 5-bromo-N,N-bis(4-methoxybenzyl)-2-methylthiazolo[4,5-b]pyrazin-6-amine (1.10 g, 2.27 mmol, 1 eq) and Et₃N (688 mg, 6.80 mmol, 946 μL, 3 eq) in MeOH (20 mL) and THF (20 mL) was added Pd(dppf)Cl₂ (166 mg, 227 μmol, 0.1 eq) under N₂. The mixture was degassed and purged with CO several times. The mixture was stirred under CO (50 psi) at 50 °C for 16 h. Then it was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[00985] ¹H NMR (400 MHz, CDCl₃) δ ppm 7.09 (d, 4H), 6.83 (d, 4H), 4.54 (s, 4H), 3.91 (s, 3H), 3.79 (s, 6H), 2.84 (s, 3H).

[00986] LCMS: 465.3 [M+H]⁺.

[00987] Step 6. Synthesis of 6-(bis(4-methoxybenzyl)amino)-2-methylthiazolo[4,5-b]pyrazine-5-carboxylic acid

[00988] To a solution of methyl 6-(bis(4-methoxybenzyl)amino)-2-methylthiazolo[4,5-b]pyrazine-5-carboxylate (920 mg, 1.98 mmol, 1 eq) in THF (9 mL), H₂O (3 mL) and MeOH (3 mL) was added LiOH-H₂O (415 mg, 9.90 mmol, 5 eq), then the mixture was stirred at 25 °C for 3 h. Acidified the mixture to pH = ~3 with saturated citric acid aqueous solution. And the mixture was extracted with EtOAc (100 mL * 3). Then the organic phase was washed with brine (200 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[00989] LCMS: 451.3 [M+H]⁺.

[00990] Step 7. Synthesis of 6-((4-methoxybenzyl)amino)-2-methylthiazolo[4,5-b]pyrazine-5-carbonyl chloride

[00991] To a solution of 6-(bis(4-methoxybenzyl)amino)-2-methylthiazolo[4,5-b]pyrazine-5-carboxylic acid (700 mg, 1.55 mmol, 1 eq) in DCM (7 mL) was added (COCl)₂ (237 mg, 1.86 mmol, 163 μ L, 1.2 eq) and DMF (2 mg, 31 μ mol, 2 μ L, 0.02 eq) at 0 °C, the mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to obtain the title compound, which was used into next step directly without further purification.

[00992] Step 8. Synthesis of 3-hydroxy-1-(6-((4-methoxybenzyl)amino)-2-methylthiazolo[4,5-b]pyrazin-5-yl)pent-2-en-1-one

[00993] To a solution of butan-2-one (167 mg, 2.32 mmol, 208 μ L, 1.5 eq) in THF (5 mL) was added LDA (2 M in THF, 1.16 mL, 1.5 eq) at -78 °C, then the mixture was stirred at -78 °C for 0.5 h. A solution of 6-((4-methoxybenzyl)amino)-2-methylthiazolo[4,5-b]pyrazine-5-carbonyl chloride (540 mg, 1.55 mmol, 1 eq) in THF (5 mL) was added, the mixture was stirred at 25 °C for 1 h. The mixture was poured to a saturated NH₄Cl (20 mL) aqueous solution. Then the mixture was extracted with EtOAc (20 mL * 3). Then the organic phase was washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

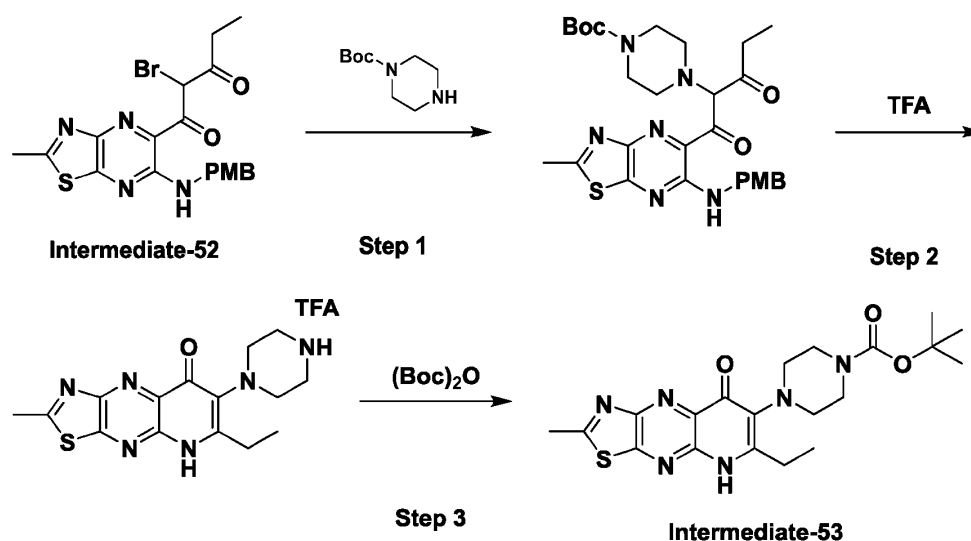
[00994] LCMS: 385.3 [M+H]⁺.

[00995] Step 9. Synthesis of 2-bromo-1-(6-((4-methoxybenzyl)amino)-2-methylthiazolo[4,5-b]pyrazin-5-yl)pentane-1,3-dione

[00996] To a solution of 3-hydroxy-1-(6-((4-methoxybenzyl)amino)-2-methylthiazolo[4,5-b]pyrazin-5-yl)pent-2-en-1-one (380 mg, 988 μ mol, 1 eq) in DCM (7 mL) was added NBS (176 mg, 988 μ mol, 1 eq), then the mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[00997] LCMS: 463.1 [M+H]⁺.

[00998] Intermediate-53: tert-butyl 4-(6-ethyl-2-methyl-8-oxo-5,8-dihydropyrido[2,3-b]thiazolo[4,5-e]pyrazin-7-yl)piperazine-1-carboxylate



[00999] Step 1. Synthesis of tert-butyl 4-(1-(6-((4-methoxybenzyl)amino)-2-methylthiazolo[4,5-b]pyrazin-5-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate

[001000] To a solution of 2-bromo-1-(6-((4-methoxybenzyl)amino)-2-methylthiazolo[4,5-b]pyrazin-5-yl)pentane-1,3-dione (Intermediate-52) (450 mg, 971 μ mol, 1 eq) and tert-butyl piperazine-1-carboxylate (181 mg, 971 μ mol, 1 eq) in THF (10 mL) was added DIEA (251 mg, 1.94 mmol, 338 μ L, 2 eq), the mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001001] **LCMS: 569.3 [M+H]⁺.**

[001002] Step 2. Synthesis of 6-ethyl-2-methyl-7-(piperazin-1-yl)pyrido[2,3-b]thiazolo[4,5-e]pyrazin-8(5H)-one trifluoroacetate

[001003] To a solution of tert-butyl 4-(1-(6-((4-methoxybenzyl)amino)-2-methylthiazolo[4,5-b]pyrazin-5-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate (130 mg, 229 μ mol, 1 eq) in TFA (3 mL) was stirred at 50 °C for 1 h. The reaction mixture was concentrated in vacuum to obtain the title compound, which was used into next step directly without further purification.

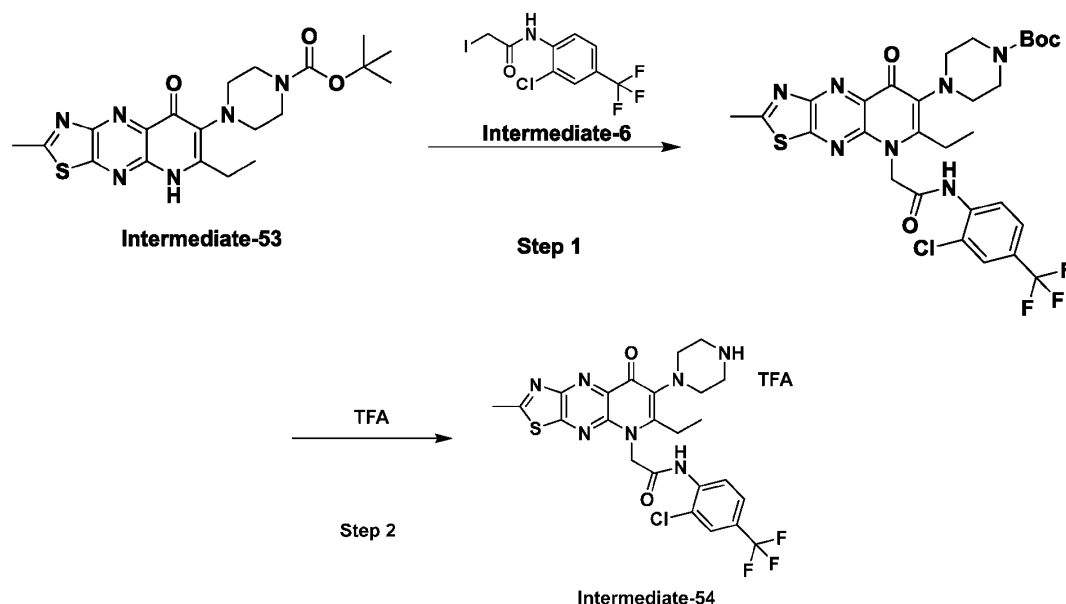
[001004] **LCMS: 331.2 [M+H]⁺.**

[001005] Step 3. Synthesis of tert-butyl 4-(6-ethyl-2-methyl-8-oxo-5,8-dihydropyrido[2,3-b]thiazolo[4,5-e]pyrazin-7-yl)piperazine-1-carboxylate

[001006] To a solution of 6-ethyl-2-methyl-7-(piperazin-1-yl)pyrido[2,3-b]thiazolo[4,5-e]pyrazin-8(5H)-one trifluoroacetate (101 mg, 227 μmol , 1 eq) and DIEA (88 mg, 681 μmol , 119 μL , 3 eq) in DCM (2 mL) was added (Boc)₂O (99 mg, 454 μmol , 104 μL , 2 eq), then the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated in vacuum to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001007] LCMS: 431.3 [M+H]⁺.

[001008] Intermediate-54: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]thiazolo[4,5-e]pyrazin-5(8H)-yl)acetamide trifluoroacetate



[001009] Step 1. Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-methyl-8-oxo-5,8-dihydropyrido[2,3-b]thiazolo[4,5-e]pyrazin-7-yl)piperazine-1-carboxylate

[001010] To a solution of tert-butyl 4-(6-ethyl-2-methyl-8-oxo-5,8-dihydropyrido[2,3-b]thiazolo[4,5-e]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-53) (50 mg, 0.12 mmol, 1 eq) and N-[2-chloro-4-(trifluoromethyl)phenyl]-2-iodoacetamide (Intermediate-6) (84 mg, 0.23 mmol, 2 eq) in dioxane (1 mL) was added DIEA (45 mg, 0.35 mmol, 61 μL , 3 eq), the mixture was stirred at 80 °C for 3 h. The mixture was concentrated under reduced pressure to give a

residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) and reversed-phase HPLC (C18 column, water (0.1% FA-ACN) to afford the title compound.

[001011] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.44 (s, 1H), 8.04 - 7.96 (m, 2H), 7.74 - 7.71 (m, 1H), 5.57 (s, 2H), 4.07 - 3.92 (m, 2H), 3.66 (q, 2H), 3.21 - 3.19 (m, 2H), 3.05 - 2.89 (m, 5H), 2.74 - 2.63 (m, 2H), 1.48 (s, 9H), 1.27 (t, 3H).

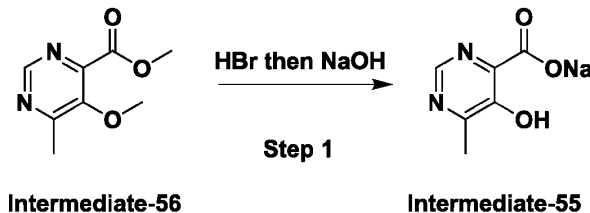
[001012] LCMS: 666.2 [M+H]⁺.

[001013] Step 2. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-*b*]thiazolo[4,5-*e*]pyrazin-5(8H)-yl)acetamide trifluoroacetate

[001014] To a solution of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-methyl-8-oxo-5,8-dihydropyrido[2,3-*b*]thiazolo[4,5-*e*]pyrazin-7-yl)piperazine-1-carboxylate (21 mg, 31 μmol, 1 eq) in DCM (2.4 mL) was added TFA (1.23 g, 10.8 mmol, 0.80 mL, 342 eq), the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated in vacuum to obtain the title compound, which was used into next step directly without further purification.

[001015] LCMS: 566.2 [M+H]⁺.

[001016] Intermediate-55: sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate

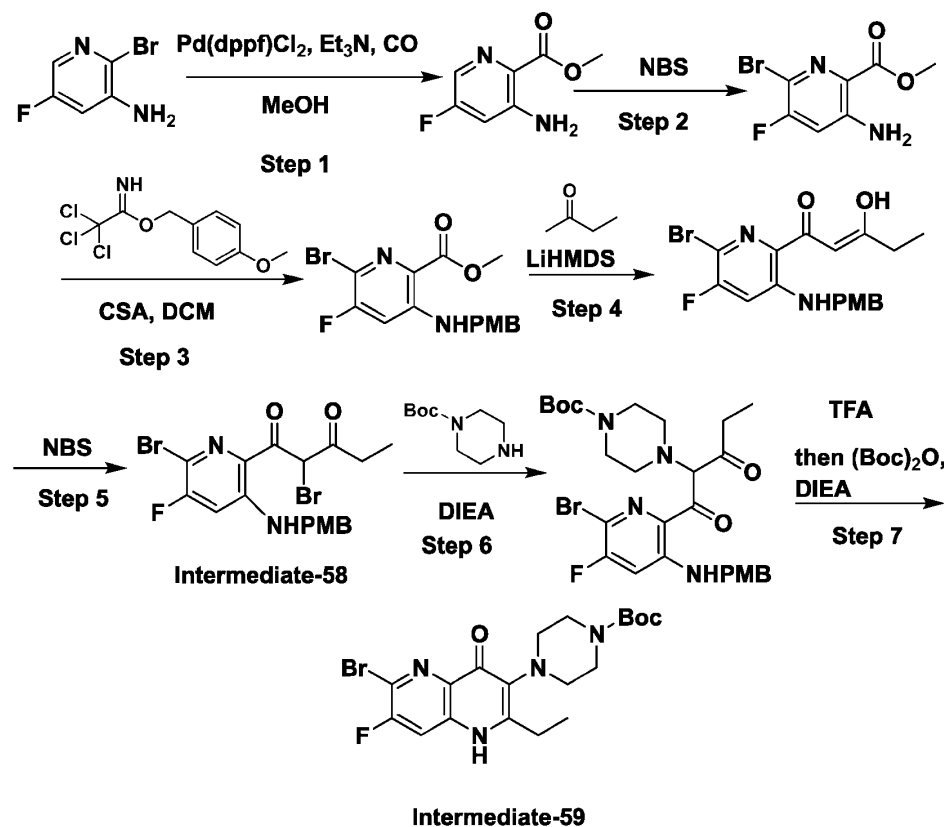


[001017] Step 1. Synthesis of sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate

[001018] To a solution of methyl 5-methoxy-6-methyl-pyrimidine-4-carboxylate (Intermediate-56) (210 g, 1.15 mol, 1 eq) was added 40% aqueous HBr (850 mL) at 20 °C. After addition, the mixture was stirred at 50 °C for 16 hr, and then was added 55% aqueous HI (600 mL) at 50 °C. The resulting mixture was stirred at 50 °C for 6 hr. The reaction mixture was filtered. The filtrate was adjusted to pH 8~9 with aqueous NaOH solution (30% in water) at 0~5 °C. The mixture was filtered, the filter cake was dried under reduced pressure to afford the title compound, which was used into next step directly without further purification.

[001019] ¹H NMR (400 MHz, CD₃OD) δ ppm 8.47 (s, 1H), 2.48 (s, 3H).

[001020] Intermediate-59: tert-butyl 4-(6-bromo-2-ethyl-7-fluoro-4-oxo-1,4-dihydro-1,5-naphthyridin-3-yl) piperazine-1-carboxylate



[001021] Step 1. Synthesis of methyl 3-amino-5-fluoropicolinate

[001022] To a solution of 2-bromo-5-fluoropyridin-3-amine (10.00 g, 52.36 mmol, 1 eq) in MeOH (350 mL) was added Et_3N (10.60 g, 104.71 mmol, 14.57 mL, 2 eq) and Pd(dppf)Cl_2 (1.92 g, 2.62 mmol, 0.05 eq). The mixture was stirred at 80°C for 16 h under CO (50 psi). 50 mL H_2O was added to the mixture and concentrated under reduced pressure to remove MeOH . Then the mixture was diluted with 100 mL H_2O and extracted with EtOAc (80 mL * 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001023] $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ ppm 7.81 (s, 1H), 7.03 (d, 1H), 6.94 (br s, 2H), 3.81 (s, 3H).

[001024] Step 2. Synthesis of methyl 3-amino-6-bromo-5-fluoropicolinate

[001025] To a solution of methyl 3-amino-5-fluoro-pyridine-2-carboxylate (27.00 g, 158.69 mmol, 1 eq) in ACN (500 mL) was added NBS (31.07 g, 174.56 mmol, 1.1 eq). The mixture was stirred at 20 °C for 2.5 h. 200 mL saturated NaHCO₃ aqueous solution was added to the reaction solution and the mixture was extracted with EtOAc (300 mL * 3). The combined organic layers were washed with brine (200 mL * 2), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was added dropwise into DCM (80 mL) and stirred for 10 min, filtered and the filter cake was dried under reduced pressure to give the title compound, which was used in next step directly without further purification.

[001026] ¹H NMR (400 MHz, CDCl₃) δ ppm 6.81 (d, 1H), 6.00 (br s, 2H), 3.95 (s, 3H).

[001027] LCMS: 250.8 [M+H]⁺.

[001028] Step 3. Synthesis of methyl 6-bromo-5-fluoro-3-((4-methoxybenzyl) amino) picolinate

[001029] To a solution of methyl 3-amino-6-bromo-5-fluoro-pyridine-2-carboxylate (35.00 g, 118.05 mmol, 1 eq) in DCM (350 mL) was added CSA (13.71 g, 59.03 mmol, 0.5 eq) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (50.03 g, 177.08 mmol, 1.5 eq). The mixture was stirred at 20 °C for 1 h. The reaction mixture was quenched by 200 mL saturated NaHCO₃ aqueous solution and extracted with DCM (100 mL * 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by trituration (MeOH, 30 mL) to afford the title compound.

[001030] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.21 (br s, 1H), 7.33 - 7.26 (m, 3H), 6.96 - 6.85 (m, 2H), 4.41 (d, 2H), 3.83 (s, 3H), 3.72 (s, 3H).

[001031] LCMS: 371.0 [M+H]⁺.

[001032] Step 4. Synthesis of 1-(6-bromo-5-fluoro-3-((4-methoxybenzyl) amino) pyridin-2-yl)-3-hydroxypent-2-en-1-one

[001033] To a solution of butan-2-one (10.01 g, 138.82 mmol, 12.42 mL, 2.5 eq) in THF (30 mL) was added LiHMDS (1 M, 138.82 mL, 138.82 mmol, 2.5 eq) at 0 °C under N₂ atmosphere. The reaction mixture was stirred at 25 °C for 0.5 h. Then a solution of methyl 6-bromo-5-fluoro-3-[(4-methoxyphenyl) methylamino] pyridine-2-carboxylate (20.50 g, 55.53 mmol, 1 eq) in THF (150 mL) was added to the mixture. Then the reaction mixture was stirred at 60 °C for 1.5 h under N₂ atmosphere. The reaction mixture was added into 250 mL saturated NH₄Cl aqueous solution

and extracted with EtOAc (150 mL * 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001034] ¹H NMR (400 MHz, CDCl₃) δ ppm 15.06 (s, 1H), 9.14 (br s, 1H), 7.31 - 7.28 (m, 1H), 6.98 - 6.88 (m, 2H), 6.82 - 6.71 (m, 2H), 4.38 (d, 2H), 3.85 (s, 3H), 2.43 (q, 2H), 1.27 (t, 3H).

[001035] LCMS: 409.0 [M+H]⁺.

[001036] Step 5. Synthesis of 2-bromo-1-(6-bromo-5-fluoro-3-((4-methoxybenzyl) amino) pyridin-2-yl) pentane-1,3-dione

[001037] To a solution of 1-[6-bromo-5-fluoro-3-[(4-methoxyphenyl) methylamino]-2-pyridyl]-3-hydroxy-pent-2-en-1-one (18.20 g, 44.47 mmol, 1 eq) in DCM (360 mL) was added NBS (6.73 g, 37.80 mmol, 0.85 eq). The mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with H₂O (300 mL) and extracted with DCM (100 mL * 3). The combined organic layer was washed with brine (100 mL * 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound, which was used in next step directly without further purification.

[001038] LCMS: 489.0 [M+H]⁺.

[001039] Step 6. Synthesis of tert-butyl 4-(1-(6-bromo-5-fluoro-3-((4-methoxybenzyl) amino) pyridin-2-yl)-1,3-dioxopentan-2-yl) piperazine-1-carboxylate

[001040] A mixture of 2-bromo-1-[6-bromo-5-fluoro-3-[(4-methoxyphenyl) methylamino]-2-pyridyl] pentane-1,3-dione (Intermediate-58) (23.90 g, 48.96 mmol, 1 eq), tert-butyl piperazine-1-carboxylate (9.12 g, 48.96 mmol, 1 eq) and DIEA (12.66 g, 97.92 mmol, 17.06 mL, 2 eq) in THF (250 mL) was stirred at 25 °C for 16 h. The reaction mixture was diluted with H₂O (300 mL) and extracted with EtOAc (100 mL* 3), the combined organic layer was washed with brine (100 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was triturated with EtOAc (40 mL) and purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001041] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.99 (br s, 1H), 7.22 (d, 2H), 6.89 (d, 2H), 6.74 (d, 1H), 5.32 (s, 1H), 4.33 (d, 2H), 3.81 (s, 3H), 3.56 - 3.37 (m, 4H), 3.08 - 2.96 (m, 1H), 2.95 - 2.86 (m, 2H), 2.76 - 2.57 (m, 3H), 1.46 (s, 9H), 1.14 (t, 3H).

[001042] LCMS: 595.2 [M+H]⁺.

[001043] Step 7. Synthesis of tert-butyl 4-(6-bromo-2-ethyl-7-fluoro-4-oxo-1,4-dihydro-1,5-naphthyridin-3-yl) piperazine-1-carboxylate

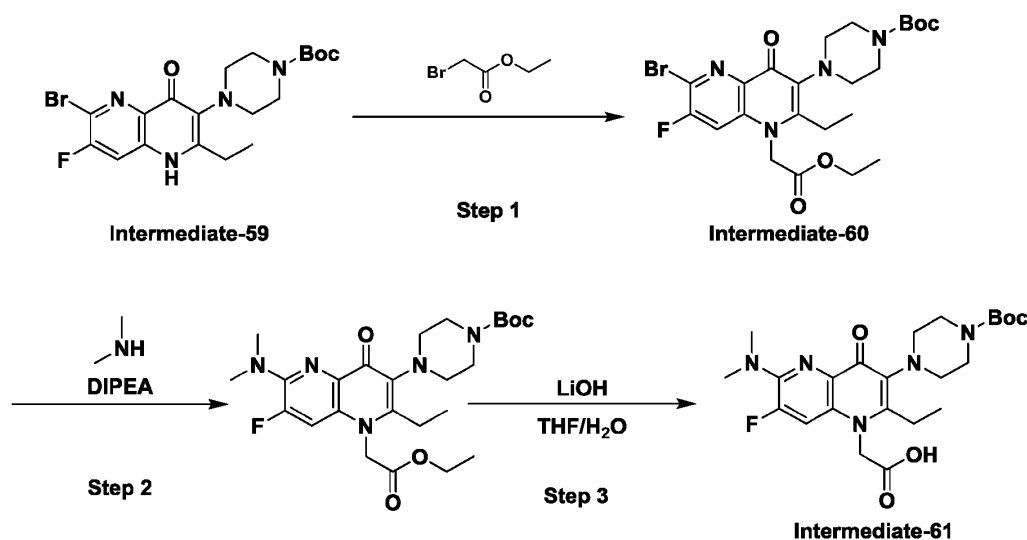
[001044] Tert-butyl 4-[1-[6-bromo-5-fluoro-3-[(4-methoxyphenyl) methylamino] pyridine-2-carbonyl]-2-oxobutyl] piperazine-1-carboxylate (10.00 g, 16.85 mmol, 1 eq) was added to TFA (80 mL) and stirred at 50 °C for 1 h. Then it was cooled to room temperature naturally and concentrated to dryness. Then it was dissolved in DCM (60 mL). DIEA (8.73 g, 67.57 mmol, 11.77 mL, 4 eq) and (Boc)₂O (11.06 g, 50.67 mmol, 11.64 mL, 3 eq) were added to the solution. The reaction mixture was stirred at 20 °C for 16 h and quenched by H₂O (100 mL) then extracted with DCM (30 mL * 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was and purified by silica gel chromatography (Eluent of DCM/MeOH) and triturated with EtOAc (10 mL) to afford the title compound.

[001045] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.80 (s, 1H), 7.83 (d, 1H), 4.08 - 3.75 (m, 2H), 3.69 - 3.39 (m, 2H), 3.07 - 2.75 (m, 4H), 2.60 - 2.50 (m, 2H), 1.43 (s, 9H), 1.23 (t, 3H).

[001046] LCMS: 455.0 [M+H]⁺.

[001047] Intermediate-60: tert-butyl 4-(6-bromo-1-(2-ethoxy-2-oxoethyl)-2-ethyl-7-fluoro-4-oxo-1,4-dihydro-1,5-naphthyridin-3-yl) piperazine -1-carboxylate

[001048] Intermediate-61: 2-(3-(4-(tert-butoxycarbonyl) piperazin-1-yl)-6-(dimethylamino)-2-ethyl-7-fluoro-4-oxo-1,5-naphthyridin-1(4H)-yl) acetic acid



[001049] Step 1. Synthesis of tert-butyl 4-(6-bromo-1-(2-ethoxy-2-oxoethyl)-2-ethyl-7-fluoro-4-oxo-1,4-dihydro-1,5-naphthyridin-3-yl) piperazine -1-carboxylate

[001050] To a solution of tert-butyl 4-(6-bromo-2-ethyl-7-fluoro-4-oxo-1H-1,5-naphthyridin-3-yl) piperazine -1-carboxylate (Intermediate-59) (4.00 g, 8.79 mmol, 1 eq) in 1,4-dioxane (120 mL) was added DIEA (6.82 g, 52.72 mmol, 9.18 mL, 6 eq), KI (1.46 g, 8.79 mmol, 1 eq) and ethyl 2-bromoacetate (8.80 g, 52.72 mmol, 5.84 mL, 6 eq). The reaction mixture was stirred at 110°C for 16 h. The reaction mixture was quenched by brine 100 mL and extracted with EtOAc (100 mL * 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001051] ¹H NMR (400 MHz, CDCl₃) δ ppm 7.36 (d, 1H), 4.86 (s, 2H), 4.74 - 4.41 (m, 2H), 4.31 (q, 2H), 4.16 - 4.00 (m, 2H), 3.83 (q, 2H), 3.36 - 2.80 (m, 2H), 2.61 - 2.59 (m, 2H), 1.49 (s, 9H), 1.32 (t, 3H), 1.26 (t, 3H).

[001052] LCMS: 543.1 [M+H]⁺.

[001053] Step 2. Synthesis of tert-butyl 4-(6-(dimethylamino)-1-(2-ethoxy-2-oxoethyl)-2-ethyl-7-fluoro-4-oxo-1,4-dihydro-1,5-naphthyridin-3-yl) piperazine-1-carboxylate

[001054] To a solution of tert-butyl 4-[6-bromo-1-(2-ethoxy-2-oxo-ethyl)-2-ethyl-7-fluoro-4-oxo-1,5-naphthyridin-3-yl] piperazine-1-carboxylate (Intermediate-60) (1.00 g, 1.85 mmol, 1 eq) and dimethylamine hydrochloride (602 mg, 7.39 mmol, 4 eq) in 1,4-dioxane (6 mL) was added DIEA (1.91 g, 14.78 mmol, 2.57 mL, 8 eq). The mixture was stirred at 100°C for 16 h. The reaction mixture was quenched by brine (50 mL) and extracted with EtOAc (40 mL * 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed-phase HPLC (C18 column, water (0.1% FA-ACN) to afford the title compound.

[001055] ¹H NMR (400 MHz, CDCl₃) δ ppm 7.16 (d, 1H), 4.81 (s, 2H), 4.29 (q, 2H), 4.18 - 3.96 (m, 2H), 3.94 - 3.80 (m, 2H), 3.21 (s, 6H), 3.13 - 2.81 (m, 4H), 2.68 - 2.50 (m, 2H), 1.49 (s, 9H), 1.30 (t, 3H), 1.24 (t, 3H).

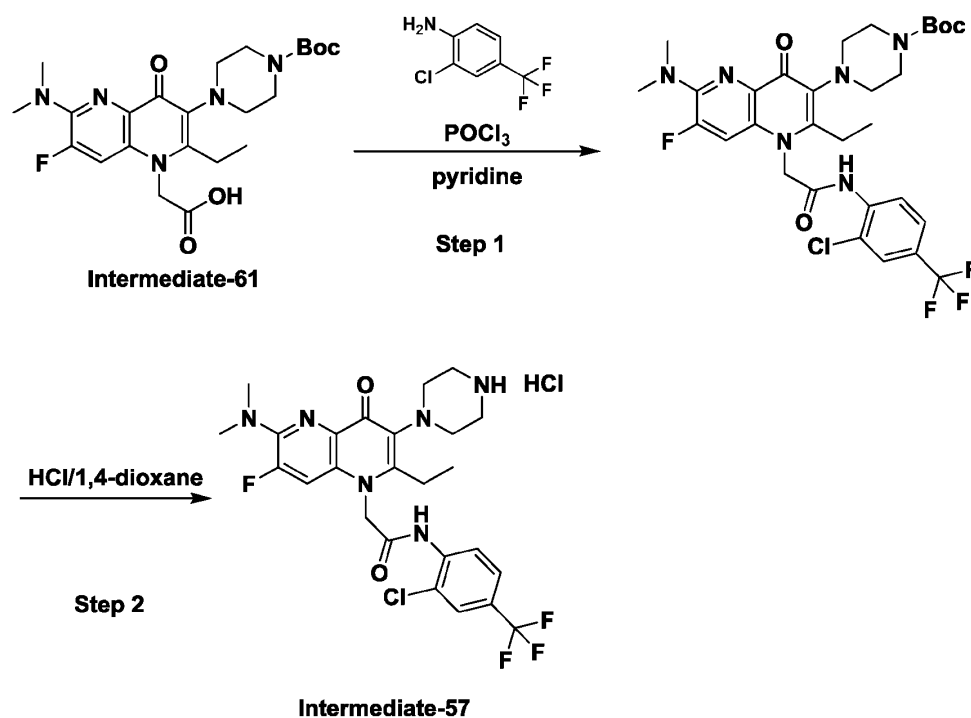
[001056] LCMS: 506.3 [M+H]⁺.

[001057] Step 3. Synthesis of 2-(3-(4-(tert-butoxycarbonyl) piperazin-1-yl)-6-(dimethylamino)-2-ethyl-7-fluoro-4-oxo-1,5-naphthyridin-1(4H)-yl) acetic acid

[001058] To a solution of tert-butyl 4-[6-(dimethylamino)-1-(2-ethoxy-2-oxo-ethyl)-2-ethyl-7-fluoro-4-oxo-1,5-naphthyridin-3-yl] piperazine-1-carboxylate (80 mg, 158 μmol , 1 eq) in H_2O (1 mL) and THF (2 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (13 mg, 316 μmol , 2 eq). The mixture was stirred at 20°C for 1 h. The reaction mixture was diluted by H_2O (5 mL) and pH was adjusted to about 4 by 0.5 M HCl aqueous solution. Then the mixture was extracted with EtOAc (30 mL * 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford the title compound, which was used in next step directly without further purification.

[001059] LCMS: 478.2 $[\text{M}+\text{H}]^+$.

[001060] Intermediate-57: N-(2-chloro-4-(trifluoromethyl) phenyl)-2-(6-(dimethylamino)-2-ethyl-7-fluoro-4-oxo-3-(piperazin-1-yl)-1,5-naphthyridin-1(4H)-yl) acetamide hydrochloride



[001061] Step 1. Synthesis of tert-butyl 4-(1-(2-((2-chloro-4-(trifluoromethyl) phenyl) amino)-2-oxoethyl)-6-(dimethylamino)-2-ethyl-7-fluoro-4-oxo-1,4-dihydro-1,5-naphthyridin-3-yl) piperazine-1-carboxylate

[001062] To a solution of 2-[3-(4-tert-butoxycarbonylpiperazin-1-yl)-6-(dimethylamino)-2-ethyl-7-fluoro-4-oxo-1,5-naphthyridin-1-yl] acetic acid (Intermediate-61) (70 mg, 147 μmol , 1

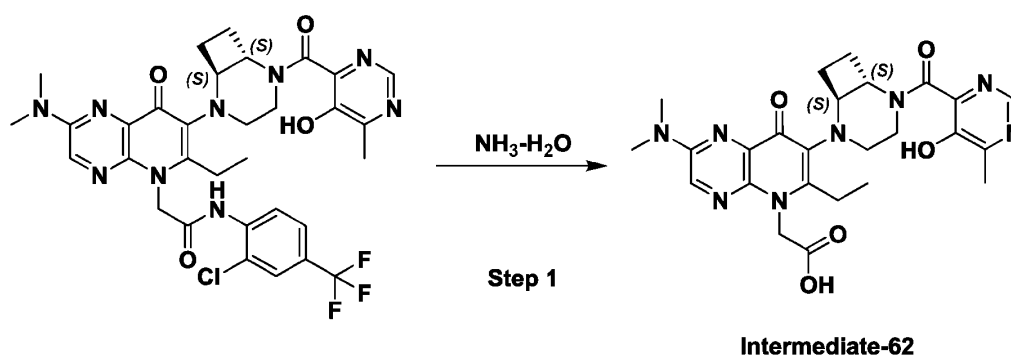
eq), 2-chloro-4-(trifluoromethyl) aniline (86 mg, 440 μ mol, 3 eq) in pyridine (1.2 mL) was added POCl₃ (45 mg, 293 μ mol, 27 μ L, 2 eq). The mixture was stirred at 60 °C for 1.5 h. The reaction mixture was diluted with H₂O (30 mL) and extracted with EtOAc (30 mL * 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE then DCM/MeOH) to afford the title compound.

[001063] LCMS: 655.3 [M+H]⁺.

[001064] Step 2. Synthesis of N-(2-chloro-4-(trifluoromethyl) phenyl)-2-(6-(dimethylamino)-2-ethyl-7-fluoro-4-oxo-3-(piperazin-1-yl)-1,5-naphthyridin-1(4H)-yl) acetamide hydrochloride

[001065] Tert-butyl 4-[1-[2-[2-chloro-4-(trifluoromethyl) anilino]-2-oxo-ethyl]-6-(dimethylamino)-2-ethyl-7-fluoro-4-oxo-1,5-naphthyridin-3-yl] piperazine-1-carboxylate (15 mg, 23 μ mol, 1 eq) was dissolved in HCl/1,4-dioxane (2 M, 572 μ L, 1.14 mmol, 50 eq). The mixture was stirred at 20 °C for 1h. Then the mixture was concentrated under reduced pressure to afford the title compound, which was used in next step directly without further purification.

[001066] Intermediate-62: 2-(2-(dimethylamino)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid



[001067] Step 1. Synthesis of 2-(2-(dimethylamino)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid

[001068] To a pressure tube was added N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-

diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide single enantiomer (50 mg, 71 μ mol, 1.0 eq) and $\text{NH}_3\text{-H}_2\text{O}$ (25% in water, 0.5 mL), the tube was sealed and then heated to 80 °C overnight. The reaction mixture was concentrated under reduced pressure and then purified by reverse phase HPLC (C18 column, water (0.1% FA-ACN) to afford the title compound.

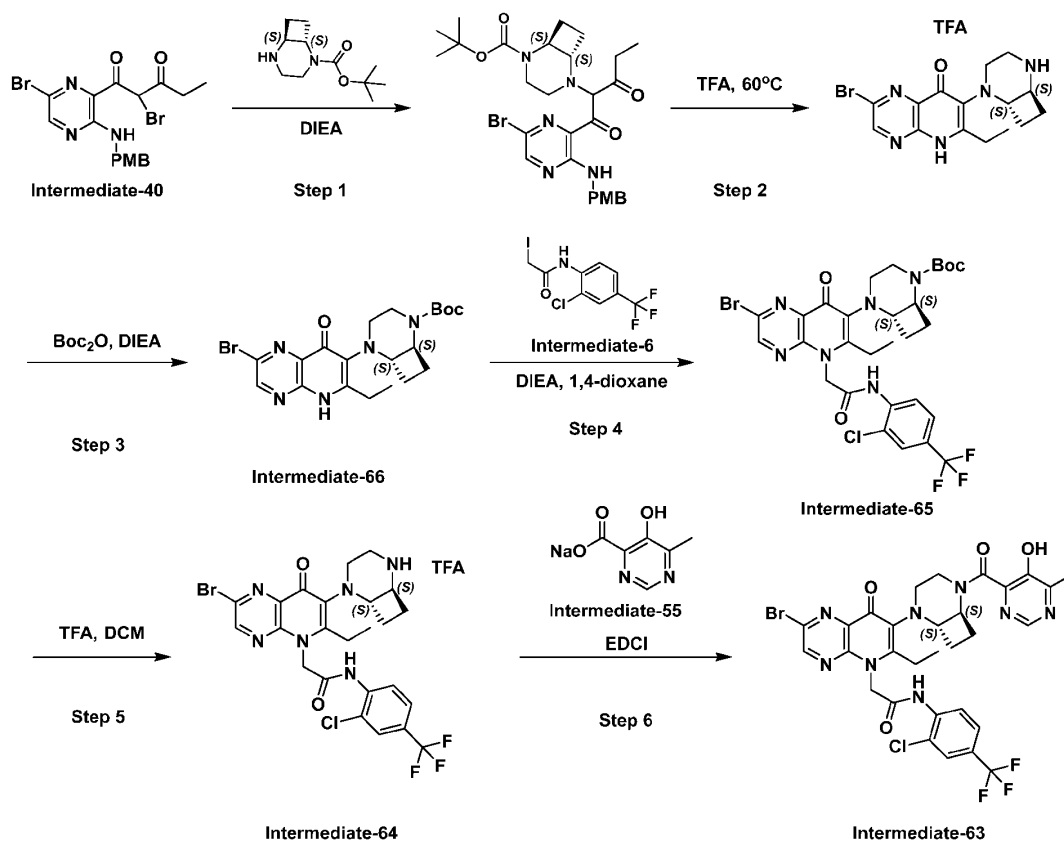
[001069] LCMS: 523.2 [M+H]⁺.

[001070] Intermediate-66: tert-butyl (1S,6S)-5-(2-bromo-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001071] Intermediate-65: tert-butyl (1S,6S)-5-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001072] Intermediate-64: 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-6-ethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate

[001073] Intermediate-63: 2-(2-bromo-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide



[001074] Step 1. Synthesis of tert-butyl (1S,6S)-5-(1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)-1,3-dioxopentane-2-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001075] To a solution of 2-bromo-1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)pentane-1,3-dione (Intermediate-40) (24.00 g, 50.94 mmol, 1.0 eq) in THF (250 mL) was added DIEA (13.17 g, 101.88 mmol, 2.0 eq) and tert-butyl (1S,6S)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (CAS: 2920219-11-8) (8.65 g, 40.75 mmol, 0.8 eq), and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with H₂O (200 mL) and extracted with EtOAc (60 mL * 3). The combined organic layers were washed with brine (50 mL * 3), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[001076] LCMS: 602.52 [M+H]⁺.

[001077] Step 2. Synthesis of 7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-6-ethylpyrido[2,3-b]pyrazin-8(5H)-one trifluoroacetate

[001078] tert-butyl (1S,6S)-5-(1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)-1,3-dioxopentan-2-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (24.30 g, 40.33 mmol, 1.0 eq) was dissolved into TFA (120 mL) and it was stirred at 60 °C for 2 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001079] LCMS: 364.24 [M+H]⁺.

[001080] Step 3. Synthesis of tert-butyl (1S,6S)-5-(2-bromo-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001081] To a solution of 7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-6-ethylpyrido[2,3-b]pyrazin-8(5H)-one trifluoroacetate (14.50 g, 39.81 mmol, 1.0 eq) in DCM (150 mL) was added DIEA (25.73 g, 199.04 mmol, 5.0 eq) and Boc₂O (9.56 g, 43.79 mmol, 1.1 eq), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with H₂O (100 mL) and extracted with DCM (60 mL * 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[001082] LCMS: 464.36 [M+H]⁺.

[001083] Step 4. Synthesis of tert-butyl (1S,6S)-5-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001084] To a solution of tert-butyl (1S,6S)-5-(2-bromo-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (Intermediae-66) (12.18 g, 26.23 mmol, 1.0 eq) in 1,4-dioxane (150 mL) was added DIEA (10.17 g, 78.69 mmol, 3.0 eq) and N-(2-chloro-4-(trifluoromethyl)phenyl)-2-iodoacetamide (Intermediate-6) (14.30 g, 39.34 mmol, 1.5 eq), and the resulting mixture was stirred at 80 °C for 2 h. The reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[001085] LCMS: 699.95 [M+H]⁺.

[001086] Step 5. Synthesis of 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-6-ethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate

[001087] To a solution of tert-butyl (1S,6S)-5-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (Intermediate-65) (100 mg, 143 μmol, 1.0 eq) in DCM (0.2 mL) was added TFA (1 mL), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001088] LCMS: 601.2 [M+H]⁺.

[001089] Step 6. Synthesis of 2-(2-bromo-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide

[001090] To a mixture of 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-6-ethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate (Intermediate-64) (100 mg, 167 μmol, 1.0 eq) and sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate (Intermediate-55) (77 mg, 500 μmol, 3.0 eq) in pyridine (40 mL) was added EDCI (192 mg, 1.00 mmol, 6.0 eq), and the resulting mixture was stirred at 40 °C for 1 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA-ACN) to afford the title compound.

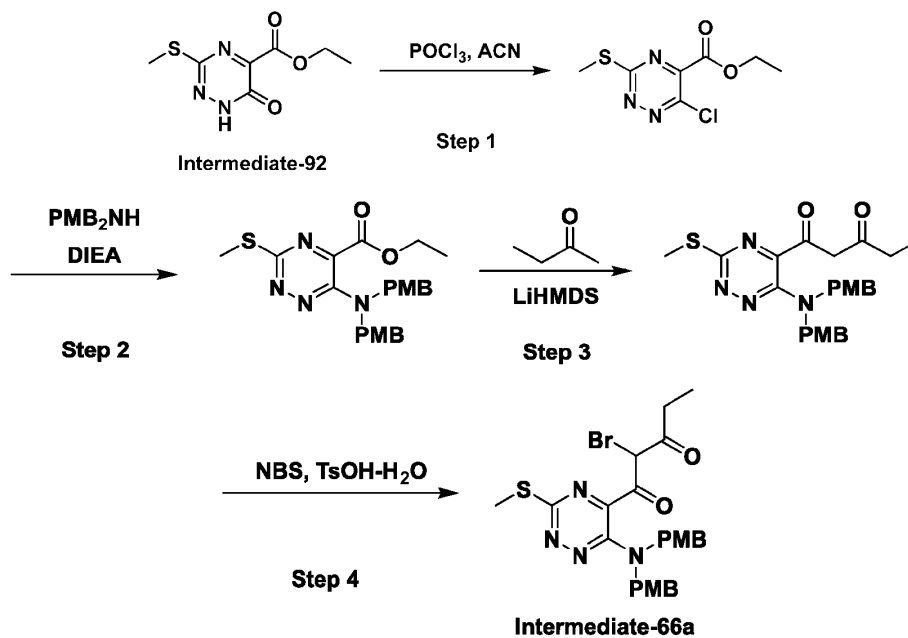
[001091] LCMS: 737.3 [M+H]⁺.

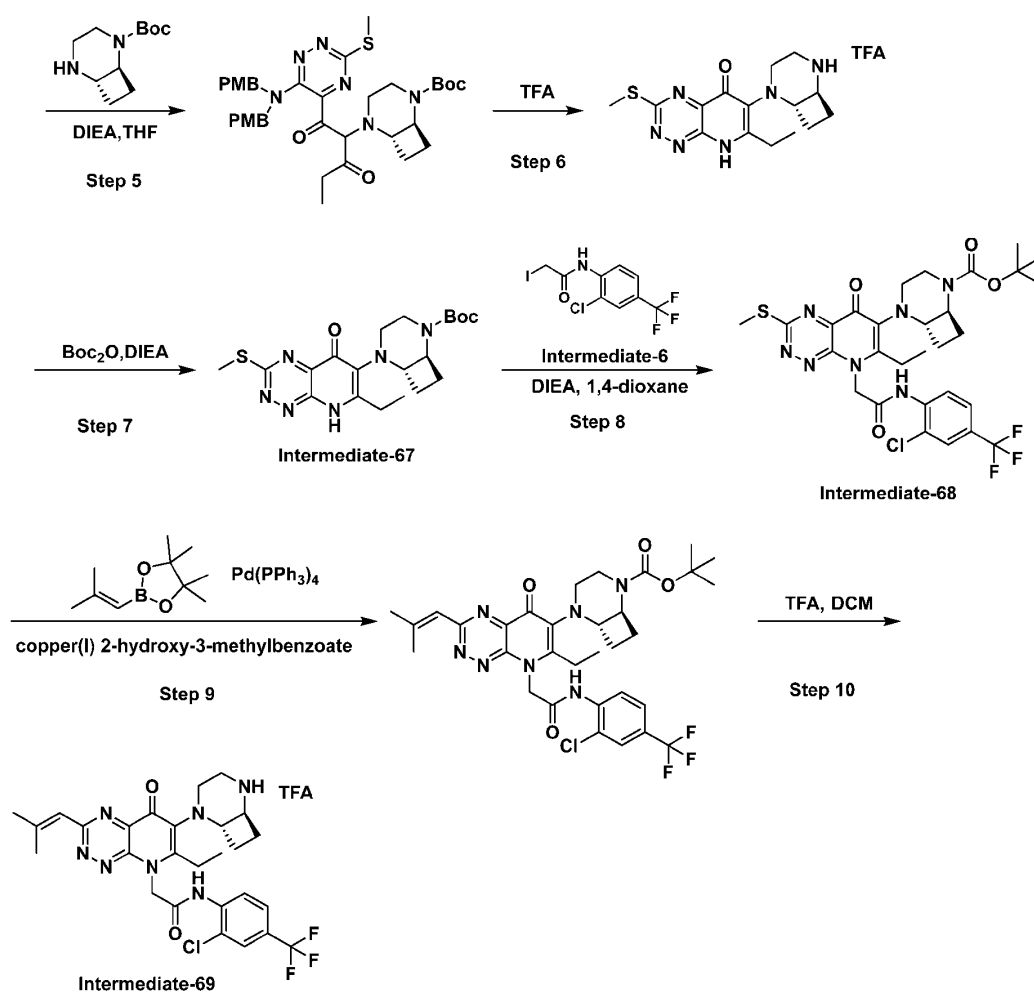
[001092] Intermediate-66a: 1-(6-(bis(4-methoxybenzyl)amino)-3-(methylthio)-1,2,4-triazin-5-yl)-2-bromopentane-1,3-dione

[001093] Intermediate-67: tert-butyl (1S,6S)-5-(7-ethyl-3-(methylthio)-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001094] Intermediate-68: tert-butyl(1S,6S) -5-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-7-ethyl-3-(methylthio)-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001095] Intermediate-69: 2-(6-((1*S*,6*S*)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-ethyl-3-(2-methylprop-1-en-1-yl)-5-oxopyrido[3,2-*e*][1,2,4]triazin-8(5*H*)-yl)-*N*-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate





[001096] Step 1: Synthesis of ethyl 6-chloro-3-(methylthio)-1,2,4-triazine-5-carboxylate

[001097] To a solution of POCl_3 (5.70 g, 37.17 mmol, 2.0 eq) in ACN (40 mL) was added ethyl 3-(methylthio)-6-oxo-1,6-dihydro-1,2,4-triazine-5-carboxylate (Intermediate-92) (4.0 g, 18.58 mmol, 1.0 eq), and the resulting mixture was stirred at 90 °C for 3 h. The reaction mixture was concentrated under reduced pressure, the residue was quenched with saturated NaHCO_3 aqueous solution (20 mL), and then extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001098] LCMS: 234.2[M+H]⁺.

[001099] Step 2: Synthesis of ethyl 6-(bis(4-methoxybenzyl)amino)-3-(methylthio)-1,2,4-triazine-5-carboxylate

[001100] To a solution of ethyl 6-chloro-3-(methylthio)-1,2,4-triazine-5-carboxylate (2.9 g, 12.41 mmol, 1.0 eq) and bis(4-methoxybenzyl)amine (3.83 g, 14.89 mmol, 1.2 eq) in 1,4-dioxane (15 mL) was added DIEA (4.81 g, 37.23 mmol, 3.0 eq), and the resulting mixture was stirred at 110 °C for 32 h. The reaction mixture was concentrated under reduced pressure and then purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001101] LCMS: 455.2[M+H]⁺.

[001102] ¹H NMR (400 MHz, CDCl₃) δ = 7.02 (d, 4H), 6.79 - 6.70 (m, 4H), 4.50 (s, 4H), 4.23 (q, 2H), 3.72 (s, 6H), 2.59 (s, 3H), 1.23 (t, 3H).

[001103] Step 3: Synthesis of 1-(6-(bis(4-methoxybenzyl)amino)-3-(methylthio)-1,2,4-triazin-5-yl)pentane-1,3-dione

[001104] To a solution of butan-2-one (1.43 g, 19.80 mmol, 3.0 eq) and ethyl 6-(bis(4-methoxybenzyl)amino)-3-(methylthio)-1,2,4-triazine-5-carboxylate (3.00 g, 6.60 mmol, 1.0 eq) in 2-methylfuran (30 mL) was added a solution of LiHMDS (1 M in THF, 19.80 mL, 3.0 eq), and the resulting mixture was stirred at 80 °C for 2 h. The reaction mixture was quenched with saturated NH₄Cl aqueous solution (100 mL), and then extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001105] LCMS: 481.2[M+H]⁺.

[001106] Step 4: Synthesis of 1-(6-(bis(4-methoxybenzyl)amino)-3-(methylthio)-1,2,4-triazin-5-yl)-2-bromopentane-1,3-dione

[001107] To a solution of 1-(6-(bis(4-methoxybenzyl)amino)-3-(methylthio)-1,2,4-triazin-5-yl)pentane-1,3-dione (2.3 g, 4.79 mmol, 1.0 eq) and TsOH-H₂O (165 mg, 957 μmol, 0.2 eq) in DCM (20 mL) was added NBS (767 mg, 4.31 mmol, 0.9 eq) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was poured into ice-water (20 mL) and extracted with DCM (20 mL*3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the title compound, which was used in the next step without further purification.

[001108] LCMS: 559.2[M+H]⁺.

[001109] Step 5: Synthesis of tert-butyl (1S,6S)-5-(1-(6-(bis(4-methoxybenzyl)amino)-3-(methylthio)-1,2,4-triazin-5-yl)-1,3-dioxopentan-2-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001110] To a solution of 1-(6-(bis(4-methoxybenzyl)amino)-3-(methylthio)-1,2,4-triazin-5-yl)-2-bromopentane-1,3-dione (Intermediate-66) (2.60 g, 4.65 mmol, 1.0 eq) and tert-butyl (1S,6S)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (CAS: 2920219-11-8) (987 mg, 4.65 mmol, 1.0 eq) in THF (26 mL) was added DIEA (1.20 g, 9.29 mmol, 2.0 eq), and the resulting mixture was stirred at 50 °C for 1.5 h. The reaction mixture was poured into water (20 mL) and extracted with EtOAc (20 mL*3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001111] LCMS: 691.2 [M+H]⁺.

[001112] Step 6: Synthesis of 6-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-ethyl-3-(methylthio)pyrido[3,2-e][1,2,4]triazin-5(8H)-one trifluoroacetate

[001113] A solution of tert-butyl (1S,6S)-5-(1-(6-(bis(4-methoxybenzyl)amino)-3-(methylthio)-1,2,4-triazin-5-yl)-1,3-dioxopentan-2-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (1.89 g, 2.74 mmol, 1.0 eq) in TFA (20 mL) was stirred at 50 °C for 1 h, and then it was concentrated in vacuo to afford the title compound, which was used into the next step without further purification.

[001114] LCMS: 333.2[M+H]⁺.

[001115] Step 7: Synthesis of tert-butyl (1S,6S)-5-(7-ethyl-3-(methylthio)-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001116] To a solution of 6-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-ethyl-3-(methylthio)pyrido[3,2-e][1,2,4]triazin-5(8H)-one trifluoroacetate (914 mg, 2.75 mmol, 1.0 eq) and DIEA (1.78 g, 13.75 mmol, 5.0 eq) in DCM (10 mL) was added Boc₂O (600 mg, 2.75 mmol, 1.0 eq), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into H₂O (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was triturated with a mixed solvent of PE and DCM (PE/DCM=4/1, 5 mL) to afford the title compound.

[001117] LCMS: 433.2 [M+H]⁺.

[001118] Step 8: Synthesis of tert-butyl (1S,6S)-5-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-7-ethyl-3-(methylthio)-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001119] To a solution of tert-butyl (1S,6S)-5-(7-ethyl-3-(methylthio)-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (Intermediate-67) (500 mg, 1.16 mmol, 1.0 eq) and N-(2-chloro-4-(trifluoromethyl)phenyl)-2-iodoacetamide (Intermediate-6) (462 mg, 1.27 mmol, 1.1 eq) in 1,4-dioxane (5 mL) was added DIEA (448 mg, 3.47 mmol, 3.0 eq), and the resulting mixture was stirred at 80 °C overnight. The mixture was concentrated in vacuo and then purified by reverse phase HPLC (C18 column, water (0.1% FA-ACN) to afford the title compound.

[001120] LCMS: 668.2 [M+H]⁺.

[001121] Step 9: Synthesis of tert-butyl (1S,6S)-5-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-7-ethyl-3-(2-methylprop-1-en-1-yl)-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001122] To a solution of tert-butyl (1S,6S)-5-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-7-ethyl-3-(methylthio)-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (Intermediate-68) (400 mg, 599 μmol, 1.0 eq) and 4,4,5,5-tetramethyl-2-(2-methylprop-1-en-1-yl)-1,3,2-dioxaborolane (150 mg, 1.50 mmol, 2.5 eq) in THF (4 mL) was added Pd(PPh₃)₄ (69 mg, 60 μmol, 0.1 eq) and copper(I) 2-hydroxy-3-methylbenzoate (321 mg, 1.50 mmol, 2.5 eq) under N₂ atmosphere, and then the resulting mixture was stirred at 60 °C overnight. The reaction mixture was concentrated in vacuo and then purified by reverse phase HPLC (C18 column, water (0.1% FA-ACN) to afford the title compound.

[001123] LCMS: 676.2 [M+H]⁺.

[001124] Step 10: Synthesis of 2-(6-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-7-ethyl-3-(2-methylprop-1-en-1-yl)-5-oxopyrido[3,2-e][1,2,4]triazin-8(5H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate

[001125] To a solution of tert-butyl (1S,6S)-5-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-7-ethyl-3-(2-methylprop-1-en-1-yl)-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (220 mg, 325 μmol, 1.0 eq) in DCM (0.3 mL) was added TFA (3.30 mL), and it was stirred at room

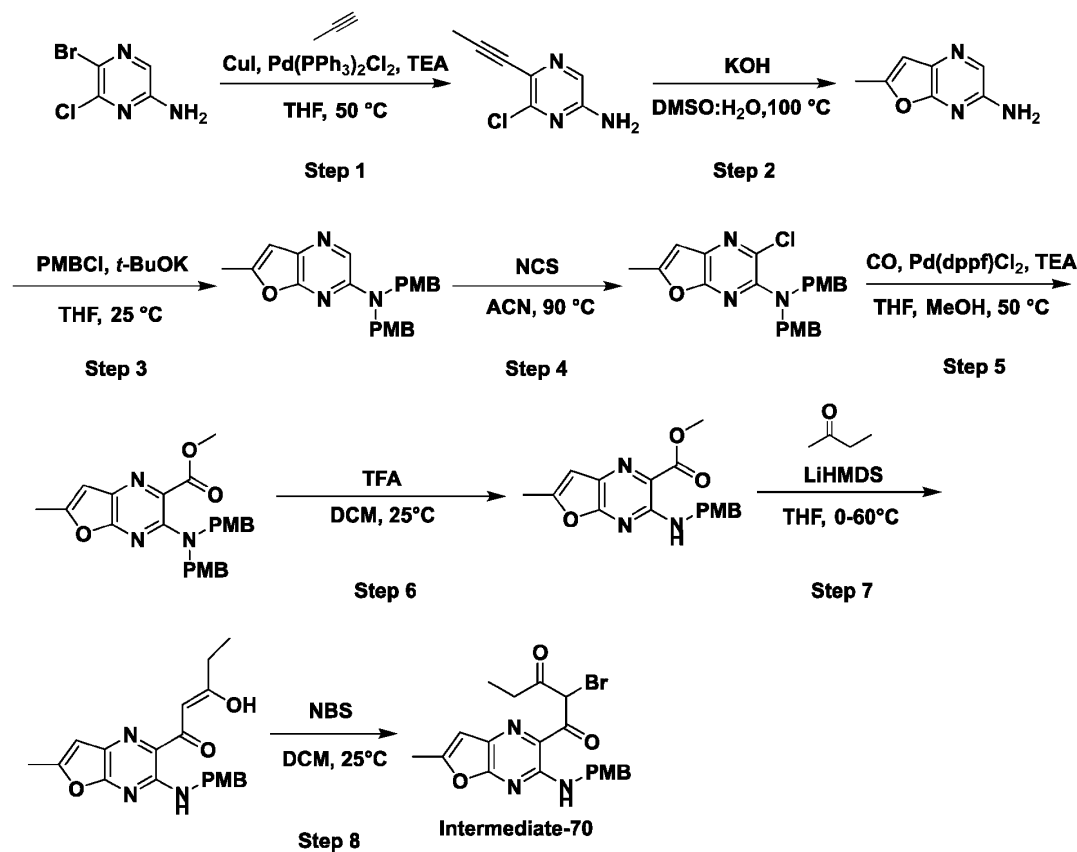
temperature for 1 h. The reaction mixture was concentrated in vacuo to afford the title compound, which was used into the next step without further purification.

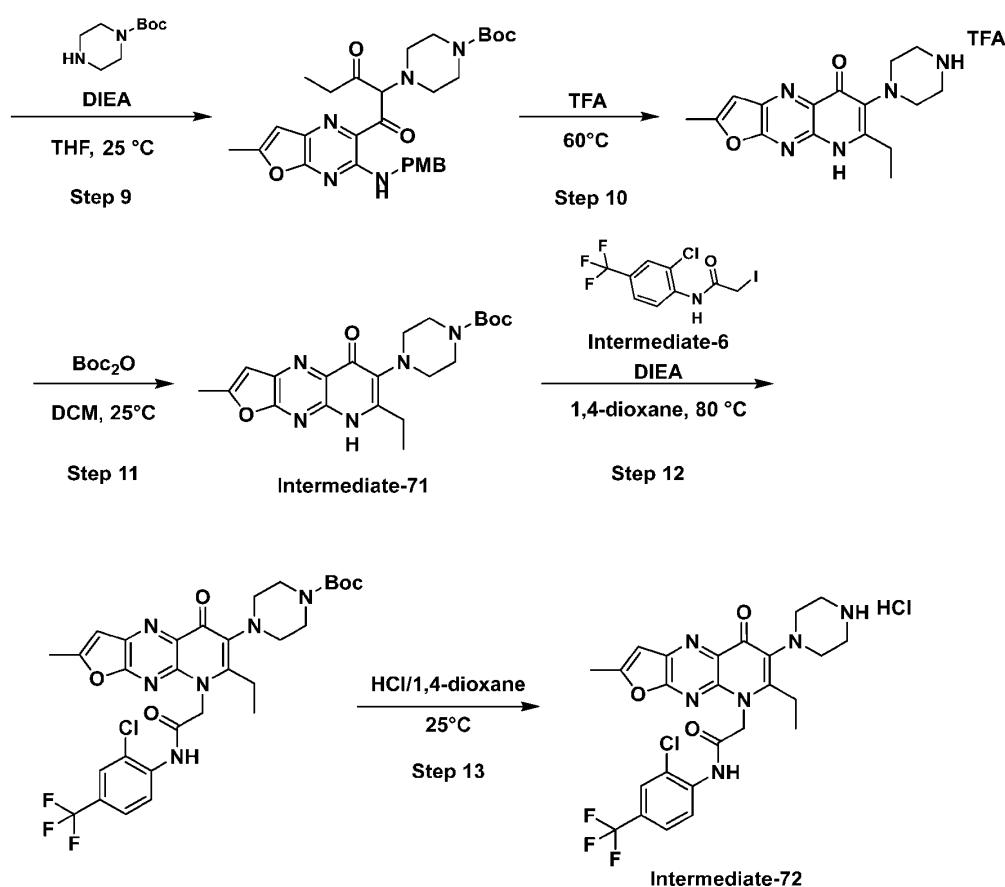
[001126] LCMS: 576.2 [M+H]⁺.

[001127] Intermediate-70: 2-bromo-1-(3-((4-methoxybenzyl)amino)-6-methylfuro[2,3-b]pyrazin-2-yl)pentane-1,3-dione

[001128] Intermediate-71: tert-butyl 4-(7-ethyl-2-methyl-5-oxo-5,8-dihydrofuro[2,3-b]pyrido[3,2-e]pyrazin-6-yl)piperazine-1-carboxylate

[001129] Intermediate-72: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-ethyl-2-methyl-5-oxo-6-(piperazin-1-yl)furo[2,3-b]pyrido[3,2-e]pyrazin-8(5H)-yl)acetamide hydrochloride





[001130] Step 1. Synthesis of 6-chloro-5-(prop-1-yn-1-yl)pyrazin-2-amine

[001131] To a solution of methyl 5-bromo-6-chloro-pyrazin-2-amine (10.00 g, 47.97 mmol, 1 eq) in THF (10 mL) was added Et_3N (16.99 g, 167.91 mmol, 23.37 mL, 3.5 eq), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (3.37 g, 4.80 mmol, 0.1 eq), CuI (457 mg, 2.40 mmol, 0.05 eq) and prop-1-yne (1 M, 95.95 mL, 2 eq). The mixture was stirred at 50 °C for 12 h. The resulting mixture was filtered to remove the insoluble and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001132] ^1H NMR (400 MHz, CDCl_3) δ ppm 7.83 (s, 1H), 4.89 (s, 2H), 2.13 (s, 3H).

[001133] LCMS: 168.0 $[\text{M}+\text{H}]^+$.

[001134] Step 2. Synthesis of 6-methylfuro[2,3-b]pyrazin-3-amine

[001135] To a solution of 6-chloro-5-prop-1-ynyl-pyrazin-2-amine (6.50 g, 38.78 mmol, 1 eq) in DMSO (65 mL) and H_2O (65 mL) was added KOH (4.35 g, 77.57 mmol, 2 eq). The mixture

was stirred at 100 °C for 16 h. The reaction mixture was poured into saturated NH₄Cl aqueous solution (400 mL) and extracted with EtOAc (200 mL * 3). The combined organic layer was washed with brine (100 mL * 2), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001136] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.76 (s, 1H), 6.54 (s, 1H), 6.42 (s, 2H), 2.38 (s, 3H).

[001137] LCMS: 150.2 [M+H]⁺.

[001138] Step 3. Synthesis of N,N-bis(4-methoxybenzyl)-6-methylfuro[2,3-*b*]pyrazin-3-amine

[001139] To a solution of 6-methylfuro[2,3-*b*]pyrazin-3-amine (1.50 g, 10.06 mmol, 1 eq) in THF (30 mL) was added *t*-BuOK (4.51 g, 40.24 mmol, 2.01 mL, 4 eq) and 1-(chloromethyl)-4-methoxy-benzene (5.36 g, 34.19 mmol, 4.64 mL, 3.4 eq). The mixture was stirred at 25 °C for 1 h. The mixture was poured into H₂O (80 mL). Then the mixture was extracted with EtOAc (30 mL * 3). Then the combined organic phase was washed with brine (40 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001140] ¹H NMR (400 MHz, CDCl₃) δ ppm 7.87 (s, 1H), 7.17 (d, 4H), 6.84 (d, 4H), 6.44 (s, 1H), 4.75 (s, 4H), 3.80 (s, 6H), 2.47 (s, 3H).

[001141] LCMS: 390.2 [M+H]⁺.

[001142] Step 4. Synthesis of 2-chloro-N,N-bis(4-methoxybenzyl)-6-methylfuro[2,3-*b*]pyrazin-3-amine

[001143] To a solution of N,N-bis[(4-methoxyphenyl)methyl]-6-methyl-furo[2,3-*b*]pyrazin-3-amine (2.10 g, 5.39 mmol, 1 eq) in ACN (25 mL) was added NCS (720 mg, 5.39 mmol, 1 eq). The mixture was stirred at 90 °C for 3 h. Then it was poured into H₂O (20 mL). The mixture was extracted with EtOAc (30 mL * 3) and the combined organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001144] LCMS: 424.2 [M+H]⁺.

[001145] Step 5. Synthesis of methyl 3-(bis(4-methoxybenzyl)amino)-6-methylfuro[2,3-b]pyrazine-2-carboxylate

[001146] To a solution of 2-chloro-N,N-bis[(4-methoxyphenyl)methyl]-6-methyl-furo[2,3-b]pyrazin-3-amine (1.00 g, 2.36 mmol, 1 eq) in THF (10 mL) and MeOH (10 mL) was added Et₃N (716 mg, 7.08 mmol, 985 μ L, 3 eq) and Pd(dppf)Cl₂ (173 mg, 236 μ mol, 0.1 eq). The mixture was degassed and purged with N₂ for 3 times then degassed and purged with CO for 3 times. The reaction was stirred under CO (50 psi) atmosphere at 50°C for 16 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001147] LCMS: 448.2 [M+H]⁺.

[001148] Step 6. Synthesis of methyl 3-((4-methoxybenzyl) amino)-6-methylfuro[2,3-b]pyrazine-2-carboxylate

[001149] To a solution of methyl 3-[bis[(4-methoxyphenyl)methyl]amino]-6-methyl-furo[2,3-b]pyrazine-2-carboxylate (950 mg, 2.12 mmol, 1 eq) in DCM (10 mL) was added TFA (726 mg, 6.37 mmol, 473 μ L, 3 eq). The mixture was stirred at 25 °C for 0.5 h. The mixture was adjusted pH to 7 by saturated NaHCO₃ aqueous solution (20 mL), then extracted with DCM (15 mL * 3). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give the title compound, which was used into next step without further purification.

[001150] LCMS: 328.0 [M+H]⁺.

[001151] Step 7. Synthesis of 3-hydroxy-1-(3-((4-methoxybenzyl)amino)-6-methylfuro[2,3-b]pyrazin-2-yl)pent-2-en-1-one

[001152] To a solution of butan-2-one (611 mg, 8.48 mmol, 758 μ L, 3 eq) in THF (5 mL) was added LiHMDS (1 M, 8.48 mL, 3 eq) at 0°C. The mixture was stirred at 0°C for 0.5 h. Then to the mixture was added a solution of methyl 3-((4-methoxybenzyl) amino)-6-methylfuro[2,3-b]pyrazine-2-carboxylate (925 mg, 2.83 mmol, 1 eq) in THF (5 mL) dropwise at 0°C. The reaction mixture was stirred at 60°C for 1 h. Then it was quenched by saturated NH₄Cl aqueous solution (20 mL) and extracted with EtOAc (20 mL * 3). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001153] LCMS: 368.2 [M+H]⁺.

[001154] Step 8. Synthesis of 2-bromo-1-(3-((4-methoxybenzyl)amino)-6-methylfuro[2,3-b]pyrazin-2-yl)pentane-1,3-dione

[001155] To a solution of 3-hydroxy-1-(3-((4-methoxybenzyl)amino)-6-methylfuro[2,3-b]pyrazin-2-yl)pent-2-en-1-one (330 mg, 898 μ mol, 1 eq) in DCM (5 mL) was added NBS (160 mg, 898 μ mol, 1 eq). The mixture was stirred at 25 °C for 1 h. The reaction was poured into H₂O (20 mL) and extracted with DCM (10 mL * 3). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001156] LCMS: 446.1 [M+H]⁺.

[001157] Step 9. Synthesis of tert-butyl 4-(1-(3-((4-methoxybenzyl)amino)-6-methylfuro[2,3-b]pyrazin-2-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate

[001158] To a solution of 2-bromo-1-(3-((4-methoxybenzyl)amino)-6-methylfuro[2,3-b]pyrazin-2-yl)pentane-1,3-dione (Intermediate-70) (350 mg, 784 μ mol, 1 eq) and tert-butyl piperazine-1-carboxylate (190 mg, 1.02 mmol, 1.3 eq) in THF (5 mL) was added DIEA (152 mg, 1.18 mmol, 205 μ L, 1.5 eq). The mixture was stirred at 25 °C for 2 h. The reaction was poured into H₂O (20 mL) and extracted with DCM (10 mL * 3). The combined organic layer was concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001159] LCMS: 552.3 [M+H]⁺.

[001160] Step 10. Synthesis of 7-ethyl-2-methyl-6-(piperazin-1-yl)furo[2,3-b]pyrido[3,2-e]pyrazin-5(8H)-one trifluoroacetate

[001161] A solution of tert-butyl 4-(1-(3-((4-methoxybenzyl)amino)-6-methylfuro[2,3-b]pyrazin-2-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate (360 mg, 653 μ mol, 1 eq) in TFA (5 mL) was stirred at 60 °C for 1 h. The mixture was concentrated in vacuum directly to afford the title compound, which was used into next step without further purification.

[001162] LCMS: 314.1 [M+H]⁺.

[001163] Step 11. Synthesis of tert-butyl 4-(7-ethyl-2-methyl-5-oxo-5,8-dihydrofuro[2,3-b]pyrido[3,2-e]pyrazin-6-yl)piperazine-1-carboxylate

[001164] To a solution of 7-ethyl-2-methyl-6-(piperazin-1-yl)furo[2,3-b]pyrido[3,2-e]pyrazin-5(8H)-one trifluoroacetate (350 mg, 1.12 mmol, 1 eq) in DCM (5 mL) was added Boc₂O (366 mg, 1.68 mmol, 385 μ L, 1.5 eq) and DIEA (433 mg, 3.35 mmol, 584 μ L, 3 eq). The mixture

was stirred at 25 °C for 1 h. The reaction was poured into H₂O (20 mL) and extracted with DCM (10 mL * 3), the combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001165] LCMS: 414.2 [M+H]⁺.

[001166] Step 12. Synthesis of tert-butyl 4-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-7-ethyl-2-methyl-5-oxo-5,8-dihydrofuro[2,3-b]pyrido[3,2-e]pyrazin-6-yl)piperazine-1-carboxylate

[001167] To a solution of tert-butyl 4-(7-ethyl-2-methyl-5-oxo-5,8-dihydrofuro[2,3-b]pyrido[3,2-e]pyrazin-6-yl)piperazine-1-carboxylate (Intermediate-71) (100 mg, 242 μmol, 1 eq) in 1,4-dioxane (3 mL) was added DIEA (94 mg, 726 μmol, 126 μL, 3 eq) and N-[2-chloro-4-(trifluoromethyl)phenyl]-2-iodo-acetamide (Intermediate-6) (132 mg, 363 μmol, 1.5 eq). The mixture was stirred at 80 °C for 1 h. The reaction mixture was poured into H₂O (10 mL) and extracted with DCM (10 mL * 3). The combined organic layer was concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001168] ¹H NMR (400 MHz, CD₃OD) δ ppm 8.12 (d, 1H), 7.81 (s, 1H), 7.59 (d, 1H), 6.89 (s, 1H), 5.64 (s, 2H), 4.05 - 4.03 (m, 2H), 3.86 - 3.65 (m, 3H), 3.15 - 3.09 (m, 3H), 2.73 - 2.70 (m, 2H), 2.62 (s, 3H), 1.49 (s, 9H), 1.34 (t, 3H).

[001169] LCMS: 649.2 [M+H]⁺.

[001170] Step 13. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(7-ethyl-2-methyl-5-oxo-6-(piperazin-1-yl)furo[2,3-b]pyrido[3,2-e]pyrazin-8(5H)-yl)acetamide hydrochloride

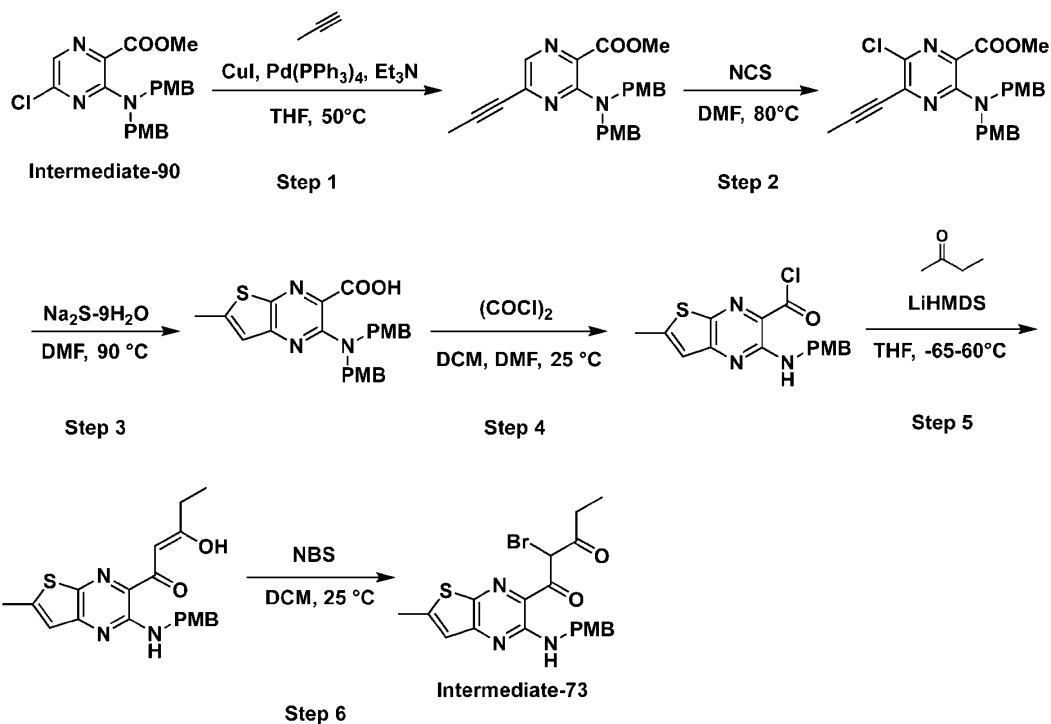
[001171] To a solution of tert-butyl 4-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-7-ethyl-2-methyl-5-oxo-5,8-dihydrofuro[2,3-b]pyrido[3,2-e]pyrazin-6-yl)piperazine-1-carboxylate (80 mg, 123 μmol, 1 eq) in DCM (0.5 mL) was added HCl/1,4-dioxane (2 M, 1.60 mL, 26 eq). The mixture was stirred at 25 °C for 20 min. The solution was concentrated in vacuum directly to give the title compound, which was used into next step without further purification.

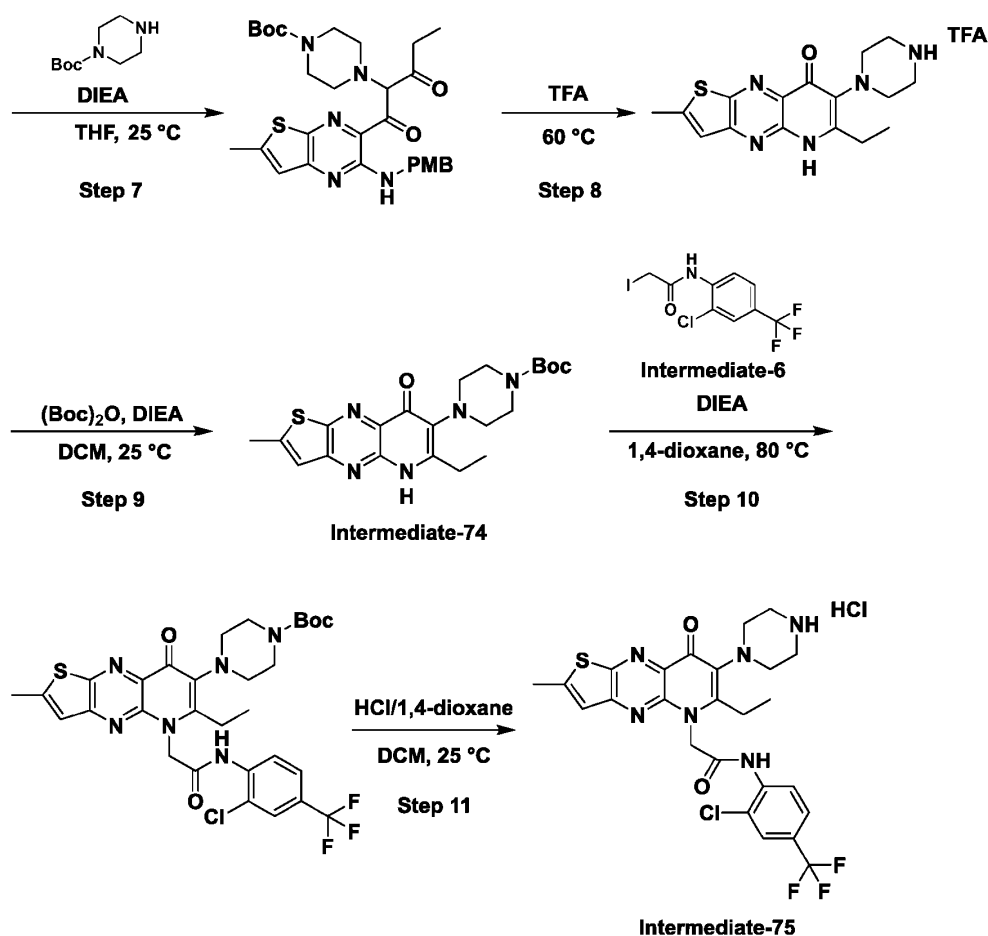
[001172] LCMS: 549.2 [M+H]⁺.

[001173] Intermediate-73: 2-bromo-1-(2-((4-methoxybenzyl) amino)-6-methylthieno[2,3-b]pyrazin-3-yl) pentane-1,3-dione

[001174] Intermediate-74: tert-butyl 4-(6-ethyl-2-methyl-8-oxo-5,8-dihydropyrido[2,3-b]thieno[2,3-e]pyrazin-7-yl)piperazine-1-carboxylate

[001175] Intermediate-75: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]thieno[2,3-e]pyrazin-5(8H)-yl)acetamide hydrochloride





[001176] Step 1. Synthesis of methyl 3-(bis(4-methoxybenzyl) amino)-5-(prop-1-yn-1-yl) pyrazine-2-carboxylate

[001177] To a solution of methyl 3-(bis(4-methoxybenzyl)amino)-5-chloropyrazine-2-carboxylate (Intermediate-90) (5.00 g, 11.69 mmol, 1 eq) in THF (50 mL) was added prop-1-yne (1 M THF solution, 35.06 mL, 3 eq), Pd(PPh₃)₄ (2.70 g, 2.34 mmol, 0.2 eq), CuI (445 mg, 2.34 mmol, 0.2 eq) and Et₃N (5.91 g, 58.43 mmol, 8.13 mL, 5 eq). The mixture was stirred at 50°C for 5 h. The resulting mixture was filtered to remove the insoluble and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001178] LCMS: 432.2 [M+H]⁺.

[001179] Step 2. Synthesis of methyl 3-(bis(4-methoxybenzyl) amino)-6-chloro-5-(prop-1-yn-1-yl) pyrazine-2-carboxylate

[001180] To a solution of methyl 3-(bis(4-methoxybenzyl) amino)-5-(prop-1-yn-1-yl) pyrazine-2-carboxylate (5.00 g, 11.59 mmol, 1 eq) in DMF (100 mL) was added NCS (1.55 g, 11.59 mmol, 1.0 eq). The mixture was stirred at 80°C for 1 h. Then it was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL * 2). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001181] ¹H NMR (400 MHz, CDCl₃) δ ppm 7.03 (d, 4H), 6.82 (d, 4H), 4.52 (s, 4H), 3.85 (s, 3H), 3.79 (s, 6H), 2.19 (s, 3H).

[001182] LCMS: 466.2 [M+H]⁺.

[001183] Step 3. Synthesis of 2-(bis(4-methoxybenzyl) amino)-6-methylthieno[2,3-b] pyrazine-3-carboxylic acid

[001184] To a solution of methyl 3-(bis(4-methoxybenzyl) amino)-6-chloro-5-(prop-1-yn-1-yl) pyrazine-2-carboxylate (4.50 g, 9.66 mmol, 1 eq) in DMF (45 mL) was added Na₂S₉H₂O (11.60 g, 48.29 mmol, 5 eq). The mixture was stirred at 90°C for 0.5 h. Then it was diluted with H₂O (100 mL) and filtered to remove the insoluble. The filtrate was extracted with DCM (100 mL * 2). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give the title compound, which was used into the next step directly without further purification.

[001185] LCMS: 450.2 [M+H]⁺.

[001186] Step 4. Synthesis of 2-((4-methoxybenzyl) amino)-6-methylthieno[2,3-b] pyrazine-3-carbonyl chloride

[001187] To a solution of 2-(bis(4-methoxybenzyl) amino)-6-methylthieno[2,3-b] pyrazine-3-carboxylic acid (2.40 g, 5.34 mmol, 1 eq) in DCM (48 mL) was added (COCl)₂ (814 mg, 6.41 mmol, 561 μL, 1.2 eq) and DMF (39 mg, 534 μmol, 41 μL, 0.1 eq). The mixture was stirred at 25°C for 20 min. Then the mixture was concentrated in vacuum to give the title compound, which was used into the next step directly without further purification.

[001188] Step 5. Synthesis of 3-hydroxy-1-(2-((4-methoxybenzyl) amino)-6-methylthieno[2,3-b] pyrazin-3-yl) pent-2-en-1-one

[001189] To a solution of butan-2-one (622 mg, 8.63 mmol, 772 μ L, 3 eq) in THF (16 mL) was added LiHMDS (1 M, 8.63 mL, 3 eq) at -65°C and stirred for 20 min. Then the solution of 2-((4-methoxybenzyl) amino)-6-methylthieno[2,3-b] pyrazine-3-carbonyl chloride (1.00 g, 2.88 mmol, 1 eq) in THF (8 mL) was added into the solution at -65°C dropwise and the mixture was stirred at 60°C for 1 h. The mixture was quenched by saturated NH_4Cl aqueous solution (50 mL) and extracted with EtOAc (50 mL * 2). The combined organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001190] LCMS: 384.1 $[\text{M}+\text{H}]^+$.

[001191] Step 6. Synthesis of 2-bromo-1-(2-((4-methoxybenzyl) amino)-6-methylthieno[2,3-b] pyrazin-3-yl) pentane-1,3-dione

[001192] To a solution of 3-hydroxy-1-(2-((4-methoxybenzyl) amino)-6-methylthieno[2,3-b] pyrazin-3-yl) pent-2-en-1-one (340 mg, 887 μ mol, 1 eq) in DCM (6 mL) was added the solution of NBS (142 mg, 798 μ mol, 0.9 eq) in DCM (1 mL) dropwise at 0°C. The mixture was stirred at 25°C for 0.5 h. The residue was diluted with H_2O (20 mL) and extracted with DCM (25 mL * 2). The combined organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001193] ^1H NMR (400 MHz, CDCl_3) δ ppm 7.32 (d, 2H), 6.93 (s, 1H), 6.88 (d, 2H), 6.32 (s, 1H), 4.71 - 4.67 (m, 2H), 3.81 (s, 3H), 2.94 (q, 2H), 2.66 (s, 3H), 1.18 (t, 3H).

[001194] LCMS: 464.0 $[\text{M}+\text{H}]^+$.

[001195] Step 7. Synthesis of tert-butyl 4-(1-(2-((4-methoxybenzyl) amino)-6-methylthieno[2,3-b] pyrazin-3-yl)-1,3-dioxopentan-2-yl) piperazine-1-carboxylate

[001196] To a solution of 2-bromo-1-(2-((4-methoxybenzyl) amino)-6-methylthieno[2,3-b] pyrazin-3-yl) pentane-1,3-dione (Intermediate-73) (270 mg, 584 μ mol, 1 eq) and tert-butyl piperazine-1-carboxylate (163 mg, 876 μ mol, 1.5 eq) in THF (4 mL) was added DIEA (226 mg, 1.75 mmol, 305 μ L, 3 eq). The mixture was stirred at 25°C for 1 h. The mixture was diluted with H_2O (20 mL) and was extracted with EtOAc (25 mL * 2). The combined organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuum to give a

residue. The residue was and purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001197] LCMS: 568.3 [M+H]⁺.

[001198] Step 8. Synthesis of 6-ethyl-2-methyl-7-(piperazin-1-yl)pyrido[2,3-b]thieno[2,3-e]pyrazin-8(5H)-one trifluoroacetate

[001199] A mixture of tert-butyl 4-(1-(2-((4-methoxybenzyl) amino)-6-methylthieno[2,3-b]pyrazin-3-yl)-1,3-dioxopentan-2-yl) piperazine-1-carboxylate (270 mg, 476 μmol, 1 eq) in TFA (2 mL) was stirred at 60 °C for 0.5 h. The mixture was concentrated in vacuum directly to afford the title compound, which was used into next step directly without further purification.

[001200] LCMS: 330.2 [M+H]⁺.

[001201] Step 9. Synthesis of tert-butyl 4-(6-ethyl-2-methyl-8-oxo-5,8-dihydropyrido[2,3-b]thieno[2,3-e]pyrazin-7-yl)piperazine-1-carboxylate

[001202] To a solution of 6-ethyl-2-methyl-7-(piperazin-1-yl) pyrido[2,3-b]thieno[2,3-e]pyrazin-8(5H)-one trifluoroacetate (145 mg, 440 μmol, 1 eq) in DCM (4 mL) was added DIEA (228 mg, 176 μmol, 307 μL, 4 eq) and Boc₂O (192 mg, 880 μmol, 202 μL, 2 eq). The mixture was stirred at 25 °C for 0.5 h. The mixture was diluted with H₂O (20 mL) and was extracted with DCM (25 mL * 2). The combined organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was and purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001203] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.45 (s, 1H), 7.01 (s, 1H), 4.08 - 4.02 (m, 2H), 3.79 - 3.78 (m, 2H), 2.93 (q, 2H), 2.91 - 2.75 (m, 2H), 2.67 (s, 3H), 2.59 - 2.55 (m, 2H), 1.42 (s, 9H), 1.29 (t, 3H).

[001204] LCMS: 430.3 [M+H]⁺.

[001205] Step 10. Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-methyl-8-oxo-5,8-dihydropyrido[2,3-b]thieno[2,3-e]pyrazin-7-yl)piperazine-1-carboxylate

[001206] To a solution of tert-butyl 4-(6-ethyl-2-methyl-8-oxo-5,8-dihydropyrido[2,3-b]thieno[2,3-e]pyrazin-7-yl)piperazine-1-carboxylate (Intermediate-74) (65 mg, 151 μmol, 1 eq) and N-[2-chloro-4-(trifluoromethyl)phenyl]-2-iodo-acetamide (Intermediate-6) (72 mg, 197 μmol, 1.3 eq) in 1,4-dioxane (1.3 mL) was added DIEA (59 mg, 454 μmol, 79 μL, 3 eq). The mixture was stirred at 80 °C for 0.5 h. The mixture was diluted with H₂O (20 mL) and was extracted with

EtOAc (25 mL * 2). The combined organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001207] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.70 (s, 1H), 8.52 (d, 1H), 7.59 (s, 1H), 7.53 (d, 1H), 7.17 (d, 1H), 5.40 (s, 2H), 4.20 - 4.02 (m, 2H), 3.92 - 3.86 (m, 2H), 3.32 - 3.30 (m, 2H), 2.99 (q, 2H), 2.77 (s, 3H), 2.67 - 2.64 (m, 2H), 1.50 (s, 9H), 1.35 (t, 3H).

[001208] LCMS: 665.2 [M+H]⁺.

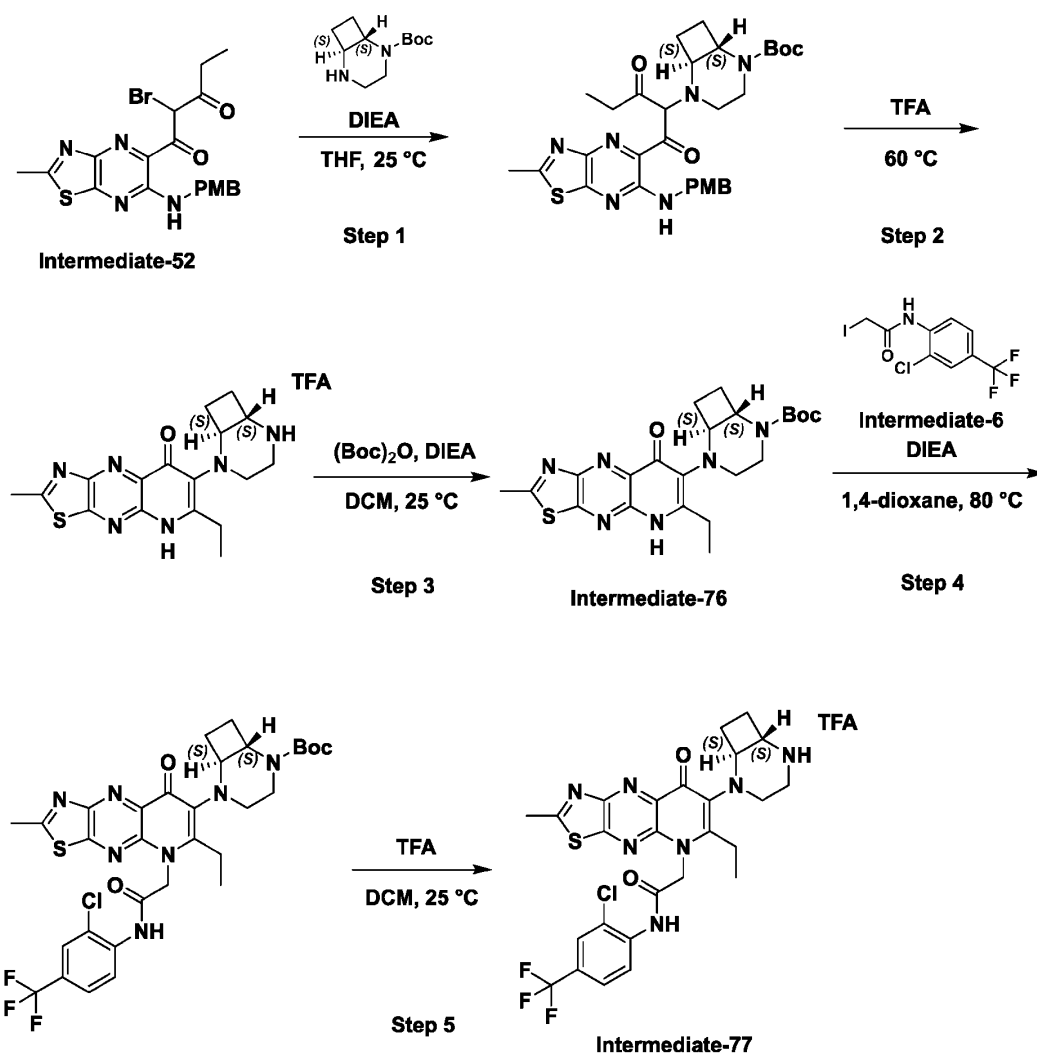
[001209] Step 11. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(6-ethyl-2-methyl-8-oxo-7-(piperazin-1-yl)pyrido[2,3-b]thieno[2,3-e]pyrazin-5(8H)-yl)acetamide hydrochloride

[001210] To a solution of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2-methyl-8-oxo-5,8-dihydropyrido[2,3-b]thieno[2,3-e]pyrazin-7-yl)piperazine-1-carboxylate (30 mg, 45 μmol, 1 eq) in DCM (0.5 mL) was added HCl/1,4-dioxane (2 M, 1 mL). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under vacuum to afford the title compound, which was used into the next step without further purification.

[001211] LCMS: 565.3 [M+H]⁺.

[001212] Intermediate-76: tert-butyl (1S,6S)-5-(6-ethyl-2-methyl-8-oxo-5,8-dihydropyrido[2,3-b]thiazolo[4,5-e]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001213] Intermediate-77: 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-6-ethyl-2-methyl-8-oxopyrido[2,3-b]thiazolo[4,5-e]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate



[001214] Step 1. Synthesis of tert-butyl (1S,6S)-5-(1-(6-((4-methoxybenzyl) amino)-2-methylthiazolo[4,5-b] pyrazin-5-yl)-1,3-dioxopentane-2-yl)-2,5-diazabicyclo [4.2.0] octane-2-carboxylate

[001215] To a solution of 2-bromo-1-(6-((4-methoxybenzyl) amino)-2-methylthiazolo[4,5-b] pyrazin-5-yl) pentane-1,3-dione (Intermediate-52) (830 mg, 1.79 mmol, 1 eq) and tert-butyl (1S,6S)-2,5-diazabicyclo [4.2.0] octane-2-carboxylate (399 mg, 1.88 mmol, 1.05 eq) in THF (16 mL) was added DIEA (463 mg, 3.58 mmol, 624 μ L, 2 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was poured into H₂O (20 mL) and extracted with DCM (30 mL * 3). The

combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[001216] LCMS: 595.3 [M+H]⁺.

[001217] Step 2. Synthesis of 7-((1S,6S)-2,5-diazabicyclo [4.2.0] octan-2-yl)-6-ethyl-2-methylpyrido[2,3-b] thiazolo[4,5-e] pyrazin-8(5H)-one trifluoroacetate

[001218] A solution of tert-butyl (1S,6S)-5-(1-(6-((4-methoxybenzyl) amino)-2-methylthiazolo[4,5-b] pyrazin-5-yl)-1,3-dioxopentan-2-yl)-2,5-diazabicyclo [4.2.0] octane-2-carboxylate (750 mg, 1.26 mmol, 1 eq) in TFA (8 mL) was stirred at 60°C for 4 h. The mixture was concentrated in vacuum directly to afford the title compound.

[001219] LCMS: 357.1 [M+H]⁺.

[001220] Step 3. Synthesis of tert-butyl (1S,6S)-5-(6-ethyl-2-methyl-8-oxo-5,8-dihydropyrido[2,3-b]thiazolo[4,5-e]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001221] To a solution of 7-((1S,6S)-2,5-diazabicyclo [4.2.0] octan-2-yl)-6-ethyl-2-methylpyrido[2,3-b] thiazolo[4,5-e] pyrazin-8(5H)-one trifluoroacetate (700 mg, 1.96 mmol, 1 eq) in DCM (7 mL) was added (Boc)₂O (471 mg, 2.16 mmol, 496 µL, 1.1 eq) and DIEA (1.27 g, 9.82 mmol, 1.71 mL, 5 eq). The mixture was stirred at 25°C for 1 h. Then it was poured into H₂O (20 mL) and extracted with DCM (30 mL * 3). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[001222] LCMS: 457.1 [M+H]⁺.

[001223] Step 4. Synthesis of tert-butyl (1S,6S)-5-(5-(2-((2-chloro-4-(trifluoromethyl) phenyl) amino)-2-oxoethyl)-6-ethyl-2-methyl-8-oxo-5,8-dihydropyrido[2,3-b] thiazolo[4,5-e] pyrazin-7-yl)-2,5-diazabicyclo [4.2.0] octane-2-carboxylate

[001224] To a solution of tert-butyl (1S,6S)-5-(6-ethyl-2-methyl-8-oxo-5,8-dihydropyrido[2,3-b]thiazolo[4,5-e]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (Intermediate-76) (150 mg, 328 µmol, 1 eq) and N-[2-chloro-4-(trifluoromethyl)phenyl]-2-iodoacetamide (Intermediate-6) (179 mg, 492 µmol, 1.5 eq) in 1,4-dioxane (3 mL) was added DIEA (64 mg, 492 µmol, 85 µL, 1.5 eq). The mixture was stirred at 80 °C for 1 h. The reaction was diluted with H₂O (20 mL) and extracted with DCM (30 mL * 3). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue

was purified by flash silica gel chromatography (Eluent of MeOH / DCM) to afford the title compound.

[001225] ¹H NMR (400 MHz, CD₃OD) δ ppm 8.08 (d, 1H), 7.81 (s, 1H), 7.59 (d, 1H), 5.66 (s, 2H), 4.17 - 4.06 (m, 1H), 3.98 - 3.97 (m, 1H), 3.71 - 3.61 (m, 1H), 3.47 - 3.37 (m, 1H), 3.32 - 3.28 (m, 2H), 3.15 (q, 2H), 2.96 (s, 3H), 2.33 - 2.20 (m, 1H), 2.06 - 1.93 (m, 1H), 1.86 - 1.71 (m, 1H), 1.57 - 1.52 (m, 1H), 1.48 (s, 9H), 1.38 (t, 3H).

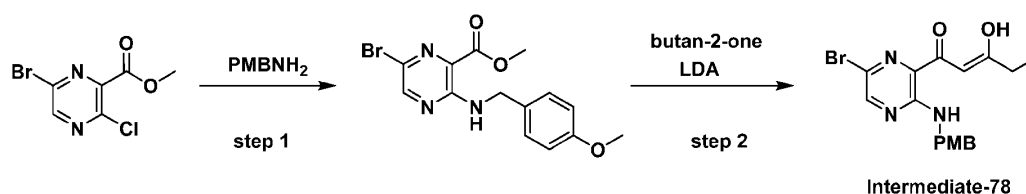
[001226] LCMS: 692.3 [M+H]⁺.

[001227] Step 5. Synthesis of 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-6-ethyl-2-methyl-8-oxopyrido[2,3-b]thiazolo[4,5-e]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate

[001228] To a solution of tert-butyl (1S,6S)-5-(5-(2-((2-chloro-4-(trifluoromethyl) phenyl) amino)-2-oxoethyl)-6-ethyl-2-methyl-8-oxo-5,8-dihydropyrido[2,3-b] thiazolo[4,5-e] pyrazin-7-yl)-2,5-diazabicyclo [4.2.0] octane-2-carboxylate (80 mg, 116 μmol, 1 eq) in DCM (1 mL) was added TFA (0.25 mL). The mixture was stirred at 25 °C for 0.5 h. Then it was concentrated in vacuum directly to afford the title compound.

[001229] LCMS: 592.3 [M+H]⁺.

[001230] Intermediate-78: 1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)-3-hydroxypent-2-en-1-one



[001231] Step 1: Synthesis of methyl 6-bromo-3-((4-methoxybenzyl)amino)pyrazine-2-carboxylate

[001232] To a solution of methyl 6-bromo-3-chloropyrazine-2-carboxylate (52.00 g, 206.79 mmol, 1.0 eq) in 1,4-dioxane (500 mL) was added DIEA (40.09 g, 310.18 mmol, 1.5 eq) and (4-methoxybenzyl)amine (31.20 g, 227.47 mmol, 1.1 eq), the resulting mixture was stirred at 100 °C overnight. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H₂O (1500 mL) and extracted with EtOAc (1000 mL * 2). The combined organic layers were washed with brine (1000 mL), dried over anhydrous Na₂SO₄, filtered and

concentrated under reduced pressure. The crude product was triturated with (PE:EtOAc = 10:1, 440 mL) to afford the title compound.

[001233] LCMS: 352.0 [M+H]⁺.

[001234] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.35 (s, 1H), 8.31 (br s, 1H), 7.29 (d, 2H), 6.90 (d, 2H), 4.65 (d, 2H), 3.97 (s, 3H), 3.82 (s, 3H).

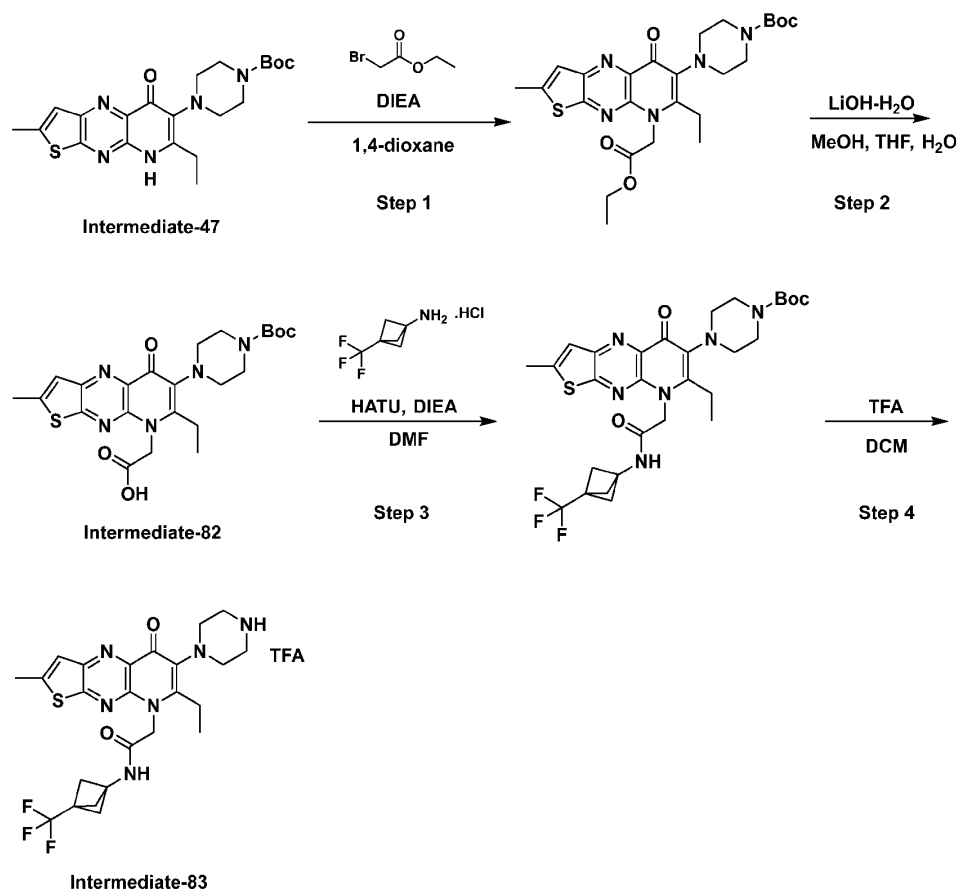
[001235] Step 2: Synthesis of 1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)-3-hydroxypent-2-en-1-one

[001236] To a solution of methyl 6-bromo-3-((4-methoxybenzyl)amino)pyrazine-2-carboxylate (61.50 g, 166.94 mmol, 1.0 eq) and butan-2-one (26.48 g, 367.27 mmol, 2.2 eq) in toluene (1500 mL) was added LDA (2 M in THF, 183.6 mL, 2.2 eq) dropwise at 0 °C. After addition, the mixture was stirred at 60 °C for 2 h. The reaction mixture was slowly poured into aqueous HCl solution (0.5 M, 1500 mL), and then extracted with EtOAc (1000 mL * 3). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[001237] LCMS: 392.0 [M+H]⁺.

[001238] Intermediate-82: 2-(6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-7-ethyl-2-methyl-5-oxopyrido[2,3-b]thieno[3,2-e]pyrazin-8(5H)-yl)acetic acid

[001239] Intermediate-83: 2-(7-ethyl-2-methyl-5-oxo-6-(piperazin-1-yl) pyrido[2,3-b]thieno[3,2-e]pyrazin-8(5H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide trifluoroacetate



[001240] Step 1. Synthesis of tert-butyl 4-(8-(2-ethoxy-2-oxoethyl)-7-ethyl-2-methyl-5-oxo-5,8-dihydropyrido[2,3-b]thieno[3,2-e]pyrazin-6-yl)piperazine-1-carboxylate

[001241] To a solution of tert-butyl 4-(7-ethyl-2-methyl-5-oxo-5,8-dihydropyrido[2,3-b]thieno[3,2-e]pyrazin-6-yl)piperazine-1-carboxylate (Intermediate-47) (350 mg, 815 μ mol, 1 eq) and ethyl 2-bromoacetate (272 mg, 1.63 mmol, 180 μ L, 2 eq) in 1,4-dioxane (7 mL) was added DIEA (316 mg, 2.44 mmol, 426 μ L, 3 eq). The mixture was stirred at 80 °C for 16 h. Then the second batch of ethyl 2-bromoacetate (272 mg, 1.63 mmol, 180 μ L, 2 eq) was added into the mixture and stirred at 80 °C for another 16 h. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001242] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.51 (s, 1H), 5.35 (s, 2H), 4.22 (q, 2H), 4.03 - 3.92 (m, 2H), 3.70 - 3.61 (m, 2H), 3.18 (q, 2H), 3.07 - 2.85 (m, 2H), 2.75 (s, 3H), 2.66 - 2.64 (m, 2H), 1.48 (s, 9H), 1.26 - 1.20 (m, 6H).

[001243] LCMS: 516.4 [M+H]⁺.

[001244] Step 2. Synthesis of 2-(6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-7-ethyl-2-methyl-5-oxopyrido[2,3-b]thieno[3,2-e]pyrazin-8(5H)-yl)acetic acid

[001245] To a solution of tert-butyl 4-(8-(2-ethoxy-2-oxoethyl)-7-ethyl-2-methyl-5-oxo-5,8-dihydropyrido[2,3-b]thieno[3,2-e]pyrazin-6-yl)piperazine-1-carboxylate (292 mg, 566 μmol, 1 eq) in THF (3 mL), MeOH (1 mL) and H₂O (1 mL) was added LiOH-H₂O (238 mg, 5.66 mmol, 10 eq). Then the mixture was stirred at 25 °C for 1 h. To the reaction mixture was added saturated citric acid until pH achieved was around 3. Then it was extracted with EtOAc (10 mL * 3) and the combined organic phase was washed with brine (40 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford the title compound, which was used into next step directly without further purification.

[001246] LCMS: 488.1 [M+H]⁺.

[001247] Step 3. Synthesis of tert-butyl 4-(7-ethyl-2-methyl-5-oxo-8-(2-oxo-2-((3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)amino)ethyl)-5,8-dihydropyrido[2,3-b]thieno[3,2-e]pyrazin-6-yl)piperazine-1-carboxylate

[001248] To a solution of 2-(6-(4-(tert-butoxycarbonyl)piperazin-1-yl)-7-ethyl-2-methyl-5-oxopyrido[2,3-b]thieno[3,2-e]pyrazin-8(5H)-yl)acetic acid (Intermediate-82) (276 mg, 566 μmol, 1 eq) and 3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-amine hydrochloride salt (212 mg, 1.13 mmol, 2 eq) in DMF (5 mL) was added HATU (430 mg, 1.13 mmol, 2 eq) and DIEA (219 mg, 1.70 mmol, 296 μL, 3 eq). The mixture was stirred at 25 °C for 1 h. 30 mL brine was added into the mixture and extracted with EtOAc (30 mL). Then the organic layer was washed with brine (20 mL * 3), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001249] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.95 (s, 1H), 7.46 (s, 1H), 3.93 (s, 2H), 3.68 - 3.54 (m, 2H), 3.05 - 3.03 (m, 2H), 2.89 (s, 3H), 2.73 (q, 2H), 2.72 - 2.71 (m, 2H), 2.62 - 2.59 (m, 2H), 2.22 (s, 6H), 1.44 (s, 9H), 1.16 (t, 3H).

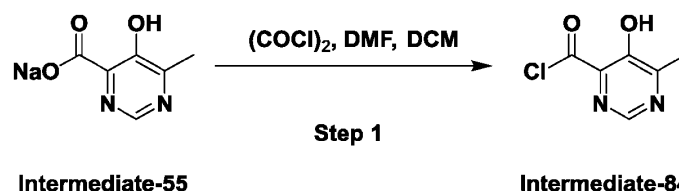
[001250] LCMS: 621.2 [M+H]⁺.

[001251] Step 4. Synthesis of 2-(7-ethyl-2-methyl-5-oxo-6-(piperazin-1-yl)pyrido[2,3-b]thieno[3,2-e]pyrazin-8(5H)-yl)-N-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)acetamide trifluoroacetate

[001252] To a solution of tert-butyl 4-(7-ethyl-2-methyl-5-oxo-8-(2-oxo-2-((3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)amino)ethyl)-5,8-dihydropyrido[2,3-b]thieno[3,2-e]pyrazin-6-yl)piperazine-1-carboxylate (100 mg, 161 μ mol, 1 eq) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 25 °C for 1 h. Then the mixture was concentrated in vacuum to afford the title compound, which was used into next step directly without further purification.

[001253] LCMS: 521.2 [M+H]⁺.

[001254] Intermediate-84: 5-hydroxy-6-methylpyrimidine-4-carbonyl chloride



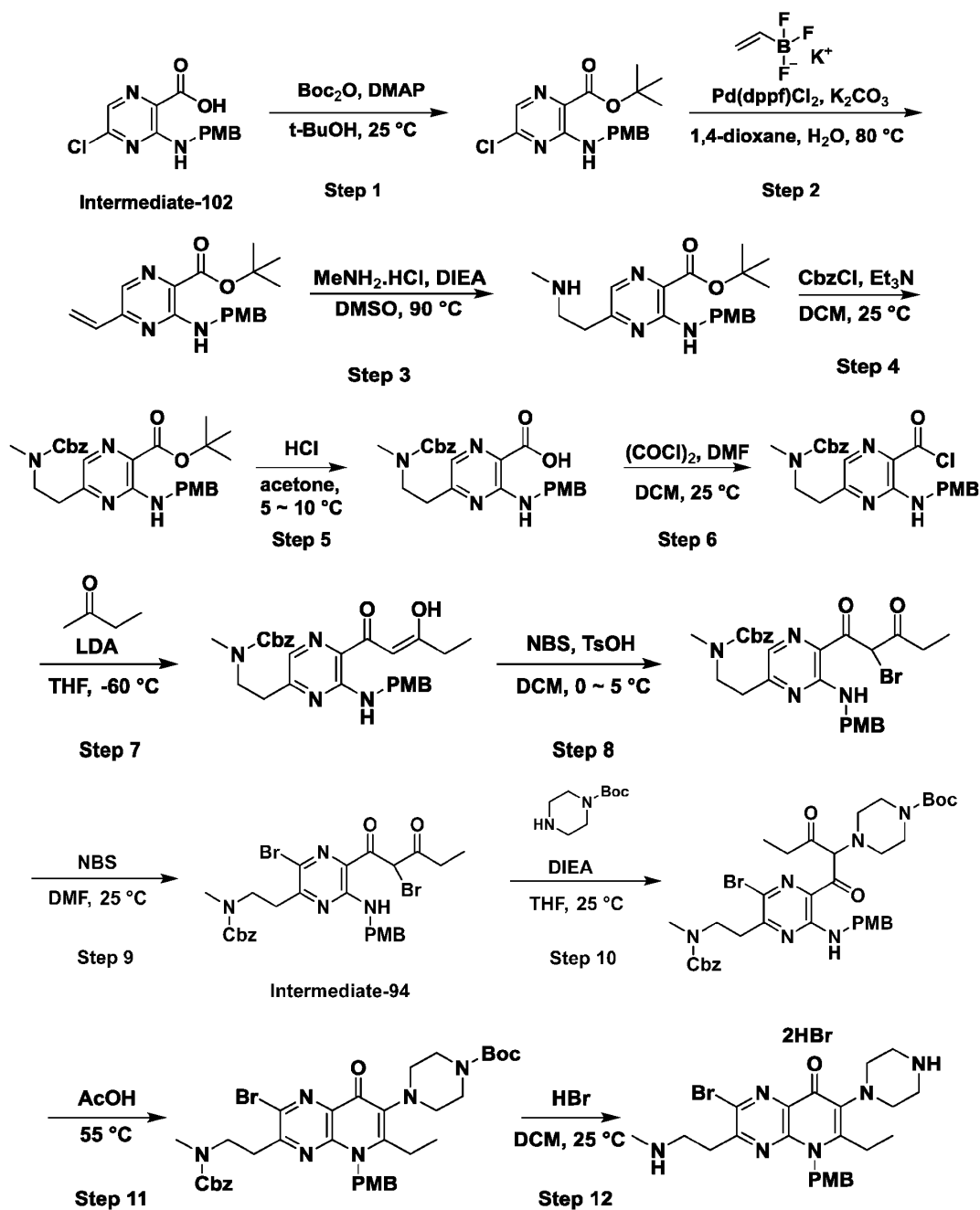
[001255] Step 1. Synthesis of 5-hydroxy-6-methylpyrimidine-4-carbonyl chloride

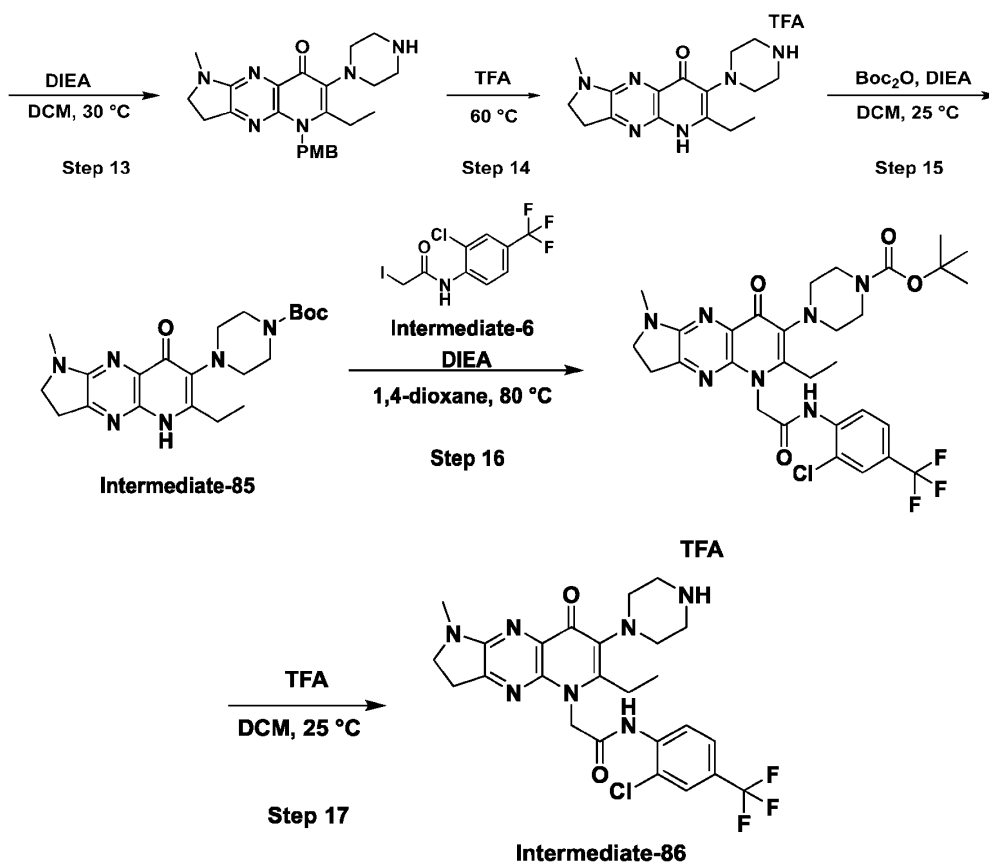
[001256] To a solution of sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate (Intermediate-55) (90 mg, 584 μ mol, 1.0 eq) in DCM (1 mL) was added oxalyl dichloride (148 mg, 1.17 mmol, 2.0 eq) and one drop of DMF. The resulting mixture was stirred at room temperature for 30 min and then concentrated in vacuo to afford the title compound, which was used into the next step without further purification.

[001257] Intermediate-94: benzyl (2-(3-bromo-5-(2-bromo-3-oxopentanoyl)-6-((4-methoxybenzyl)amino)pyrazin-2-yl)ethyl)(methyl)carbamate

[001258] Intermediate-85: tert-butyl 4-(11-ethyl-4-methyl-13-oxo-2,4,8,10-tetrazatricyclo[7.4.0.0.3,7]trideca-1(9),2,7,11-tetraen-12-yl)piperazine-1-carboxylate

[001259] Intermediate-86: N-[2-chloro-4-(trifluoromethyl)phenyl]-2-(11-ethyl-4-methyl-13-oxo-12-piperazin-1-yl-2,4,8,10-tetrazatricyclo[7.4.0.0.3,7]trideca-1(9),2,7,11-tetraen-10-yl)acetamide trifluoroacetate





[001260] Step 1: Synthesis of tert-butyl 5-chloro-3-((4-methoxybenzyl)amino)pyrazine-2-carboxylate

[001261] To a solution of 5-chloro-3-((4-methoxybenzyl)amino)pyrazine-2-carboxylic acid (Intermediate-102) (10.00 g, 34.05 mmol, 1 eq) in t-BuOH (100 mL) was added DMAP (5.41 g, 44.26 mmol, 1.3 eq), then Boc₂O (14.86 g, 68.10 mmol, 2.0 eq) was added to the mixture dropwise at room temperature, and the reaction was stirred at room temperature for 2 h. The reaction mixture was diluted with H₂O (100 mL), extracted with EtOAc (100 mL*2), the organic phase was washed with brine (100 mL), dried over anhydrous Na₂SO₄, concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE), then triturated with PE (40 mL) to afford the title compound.

[001262] LCMS: 350.1[M+H]⁺.

[001263] Step 2: Synthesis of tert-butyl 3-((4-methoxybenzyl)amino)-5-vinylpyrazine-2-carboxylate

[001264] To a solution of tert-butyl 5-chloro-3-((4-methoxybenzyl)amino)pyrazine-2-carboxylate (5.50 g, 15.72 mmol, 1.0 eq), potassium vinyltrifluoroborate (3.16 g, 23.58 mmol, 1.5 eq) in 1,4-dioxane (50 mL) and H₂O (10 mL) was added Pd(dppf)Cl₂ (575 mg, 786 μ mol, 0.05 eq), K₂CO₃ (4.35 g, 31.45 mmol, 2.0 eq), and the reaction was stirred at 80 °C overnight under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure and then purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001265] LCMS: 342.2 [M+H]⁺.

[001266] Step 3: Synthesis of tert-butyl 3-((4-methoxybenzyl)amino)-5-(2-(methylamino)ethyl)pyrazine-2-carboxylate

[001267] To a solution of tert-butyl 3-((4-methoxybenzyl)amino)-5-vinylpyrazine-2-carboxylate (1.00 g, 2.93 mmol, 1.0 eq) in DMSO (20 mL) was added methylamine hydrochloride (989 mg, 14.65 mmol, 5.0 eq) and DIEA (3.79 g, 29.29 mmol, 10.0 eq), the resulting mixture was stirred at 90 °C for 0.5 h. The reaction mixture was diluted with H₂O (200 mL), extracted with EtOAc (100 mL*2), the organic phase was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001268] LCMS: 373.2[M+H]⁺.

[001269] Step 4: Synthesis of tert-butyl 5-(2-(((benzyloxy)carbonyl)(methyl)amino)ethyl)-3-((4-methoxybenzyl)amino)pyrazine-2-carboxylate

[001270] To a solution of tert-butyl 3-((4-methoxybenzyl)amino)-5-(2-(methylamino)ethyl)pyrazine-2-carboxylate (5.00 g, 13.42 mmol, 1.0 eq) in DCM (50 mL) was added Et₃N (2.72 g, 26.85 mmol, 2.0 eq) and CbzCl (2.75 g, 16.11 mmol, 1.2 eq), and the resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was diluted with H₂O (30 mL), extracted with DCM (50 mL*2), the organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001271] LCMS: 507.4[M+H]⁺.

[001272] Step 5: Synthesis of 5-(2-(((benzyloxy)carbonyl)(methyl)amino)ethyl)-3-((4-methoxybenzyl)amino)pyrazine-2-carboxylic acid

[001273] To a solution of tert-butyl 5-(2-(((benzyloxy)carbonyl)(methyl)amino)ethyl)-3-((4-methoxybenzyl)amino)pyrazine-2-carboxylate (5.60 g, 11.05 mmol, 1.0 eq) in acetone (30 mL)

was added aqueous HCl solution (6 M, 36.85 mL, 20.0 eq) dropwise at 5-10 °C, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H₂O (50 mL), extracted with DCM (50 mL*2), and the organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001274] LCMS: 451.3[M+H]⁺.

[001275] Step 6: Synthesis of benzyl (2-(5-(chlorocarbonyl)-6-((4-methoxybenzyl)amino)pyrazin-2-yl)ethyl)(methyl)carbamate

[001276] To a solution of 5-(2-(((benzyloxy)carbonyl)(methyl)amino)ethyl)-3-((4-methoxybenzyl)amino)pyrazine-2-carboxylic acid (4.60 g, 10.21 mmol, 1.0 eq) in DCM (50 mL) was added two drops of DMF and (COCl)₂ (1.94 g, 15.32 mmol, 1.5 eq), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001277] Step 7: Synthesis of benzyl (2-(5-(3-hydroxypent-2-enoyl)-6-((4-methoxybenzyl)amino)pyrazin-2-yl)ethyl)(methyl)carbamate

[001278] To a solution of butan-2-one (1.41 g, 19.62 mmol, 2.0 eq) in THF (46 mL) was added LDA (2 M in THF, 9.81 mL, 2.0 eq) at -60 °C, and the mixture was stirred at -60 °C for 0.5 h under N₂ atmosphere. Then benzyl (2-(5-(chlorocarbonyl)-6-((4-methoxybenzyl)amino)pyrazin-2-yl)ethyl)(methyl)carbamate (4.60 g, 9.81 mmol, 1.0 eq) was added to the mixture, and the reaction was stirred at -60 °C for another 0.5 h under N₂ atmosphere. The reaction mixture was quenched with aqueous HCl solution (1N, 100 mL), extracted with EtOAc (50 mL*2), the organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001279] LCMS: 505.4[M+H]⁺.

[001280] Step 8: Synthesis of benzyl (2-(5-(2-bromo-3-oxopentanoyl)-6-((4-methoxybenzyl)amino)pyrazin-2-yl)ethyl)(methyl)carbamate

[001281] To a solution of benzyl (2-(5-(3-hydroxypent-2-enoyl)-6-((4-methoxybenzyl)amino)pyrazin-2-yl)ethyl)(methyl)carbamate (1.80 g, 3.57 mmol, 1.0 eq) in DCM (20 mL) was added TsOH.H₂O (123 mg, 713 μmol, 0.2 eq) and NBS (762 mg, 4.28 mmol, 1.2 eq)

at 0 °C, then the reaction was stirred at 0 °C for 0.5 h. The reaction mixture was quenched with H₂O (20 mL), extracted with DCM (20 mL*2), the organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001282] LCMS: 583.3[M+H]⁺.

[001283] Step 9: Synthesis of benzyl (2-(3-bromo-5-(2-bromo-3-oxopentanoyl)-6-((4-methoxybenzyl)amino)pyrazin-2-yl)ethyl)(methyl)carbamate (Intermediate-94)

[001284] To a solution of benzyl (2-(5-(2-bromo-3-oxopentanoyl)-6-((4-methoxybenzyl)amino)pyrazin-2-yl)ethyl)(methyl)carbamate (2.08 g, 3.56 mmol, 1 eq) in DMF (20 mL) was added NBS (634 mg, 3.56 mmol, 1.0 eq), and the reaction was stirred at room temperature for 2 h. The reaction mixture was quenched with H₂O (30 mL), extracted with EtOAc (20 mL*2), the organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001285] LCMS: 663.0[M+H]⁺.

[001286] Step 10: Synthesis of tert-butyl 4-(1-(5-(2-(((benzyloxy)carbonyl)(methyl)amino)ethyl)-6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate

[001287] To a solution of benzyl (2-(3-bromo-5-(2-bromo-3-oxopentanoyl)-6-((4-methoxybenzyl)amino)pyrazin-2-yl)ethyl)(methyl)carbamate (Intermediate-94) (1.50 g, 2.26 mmol, 1.0 eq) in THF (15 mL) was added DIEA (585 mg, 4.53 mmol, 2.0 eq) and tert-butyl piperazine-1-carboxylate (506 mg, 2.72 mmol, 1.2 eq), and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with H₂O (10 mL), extracted with EtOAc (10 mL*2), the organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001288] LCMS: 767.4[M+H]⁺.

[001289] Step 11: Synthesis of tert-butyl 4-[3-[2-[benzyloxycarbonyl(methyl)amino]ethyl]-2-bromo-6-ethyl-5-[(4-methoxyphenyl)methyl]-8-oxopyrido[2,3-b]pyrazin-7-yl]piperazine-1-carboxylate

[001290] A solution of tert-butyl 4-(1-(5-(2-(((benzyloxy)carbonyl)(methyl)amino)ethyl)-6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)-1,3-dioxopentan-2-yl)piperazine-1-carboxylate (1.00 g, 1.30 mmol, 1.0 eq) in AcOH (8 mL) was stirred at 55 °C for 6 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H₂O (20 mL), then the pH was adjusted to 7-8 with saturated NaHCO₃ aqueous solution. The resulting mixture was extracted with DCM (20 mL*2) and the organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001291] LCMS: 749.2[M+H]⁺.

[001292] Step 12: Synthesis of 2-bromo-6-ethyl-5-[(4-methoxyphenyl)methyl]-3-[2-(methylamino)ethyl]-7-piperazin-1-yl-pyrido[2,3-b]pyrazin-8-one dihydrobromide

[001293] To a solution of tert-butyl 4-[3-[2-[benzyloxycarbonyl(methyl)amino]ethyl]-2-bromo-6-ethyl-5-[(4-methoxyphenyl)methyl]-8-oxo-pyrido[2,3-b]pyrazin-7-yl]piperazine-1-carboxylate (700 mg, 934 μmol, 1.0 eq) in DCM (5 mL) was added HBr solution (768 μL, 33% in water), and the resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001294] LCMS: 515.2[M+H]⁺.

[001295] Step 13: Synthesis of 11-ethyl-10-[(4-methoxyphenyl)methyl]-4-methyl-12-piperazin-1-yl-2,4,8,10-tetrazatricyclo[7.4.0.0.3,7]trideca-1(9),2,7,11-tetraen-13-one

[001296] To a solution of 2-bromo-6-ethyl-5-[(4-methoxyphenyl)methyl]-3-[2-(methylamino)ethyl]-7-piperazin-1-ylpyrido[2,3-b]pyrazin-8-one dihydrobromide (500 mg, 970 μmol, 1.0 eq) in DCM (5 mL) was added DIEA (627 mg, 4.85 mmol, 5.0 eq), and the resulting mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and then purified by reverse phase HPLC (C18 column, water (0.1% FA-ACN) to afford the title compound.

[001297] LCMS: 435.3[M+H]⁺.

[001298] Step 14: Synthesis of 11-ethyl-4-methyl-12-piperazin-1-yl-2,4,8,10-tetrazatricyclo[7.4.0.0.3,7]trideca-1(9),2,7,11-tetraen-13-one trifluoroacetate

[001299] A solution of 11-ethyl-10-[(4-methoxyphenyl)methyl]-4-methyl-12-piperazin-1-yl-2,4,8,10-tetrazatricyclo[7.4.0.03,7]trideca-1(9),2,7,11-tetraen-13-one (60 mg, 138 μ mol, 1.0 eq) in TFA (0.5 mL) was stirred at 60 °C for 2.5 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001300] LCMS: 315.2[M+H]⁺.

[001301] Step 15: Synthesis of tert-butyl 4-(11-ethyl-4-methyl-13-oxo-2,4,8,10-tetrazatricyclo[7.4.0.03,7]trideca-1(9),2,7,11-tetraen-12-yl)piperazine-1-carboxylate

[001302] To a solution of 11-ethyl-4-methyl-12-piperazin-1-yl-2,4,8,10-tetrazatricyclo[7.4.0.03,7]trideca-1(9),2,7,11-tetraen-13-one trifluoroacetate (43 mg, 137 μ mol, 1.0 eq) in DCM (0.5 mL) was added DIEA (53 mg, 410 μ mol, 3.0 eq) and Boc₂O (45 mg, 205 μ mol, 1.5 eq), and the resulting mixture was stirred at room temperature for 20 min. The reaction mixture was diluted with H₂O (10 mL), extracted with DCM (10 mL*2), the organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by pre-TLC (SiO₂, DCM:MeOH = 10:1) to afford the title compound.

[001303] LCMS: 415.3[M+H]⁺.

[001304] Step 16: Synthesis of tert-butyl 4-[10-[2-[2-chloro-4-(trifluoromethyl)anilino]-2-oxo-ethyl]-11-ethyl-4-methyl-13-oxo-2,4,8,10-tetrazatricyclo[7.4.0.03,7]trideca-1(9),2,7,11-tetraen-12-yl]piperazine-1-carboxylate

[001305] To a solution of tert-butyl 4-(11-ethyl-4-methyl-13-oxo-2,4,8,10-tetrazatricyclo[7.4.0.03,7]trideca-1(9),2,7,11-tetraen-12-yl)piperazine-1-carboxylate (Intermediate-85) (20 mg, 48 μ mol, 1.0 eq) and N-[2-chloro-4-(trifluoromethyl)phenyl]-2-iodoacetamide (Intermediate-6) (21 mg, 58 μ mol, 1.2 eq) in 1,4-dioxane (0.5 mL) was added DIEA (12 mg, 96 μ mol, 2.0 eq), and the resulting mixture was stirred at 80 °C for 3 h under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure and then purified by reverse phase HPLC (C18 column, water (0.1% NH₃H₂O)-ACN) to afford the title compound.

[001306] LCMS: 650.3[M+H]⁺.

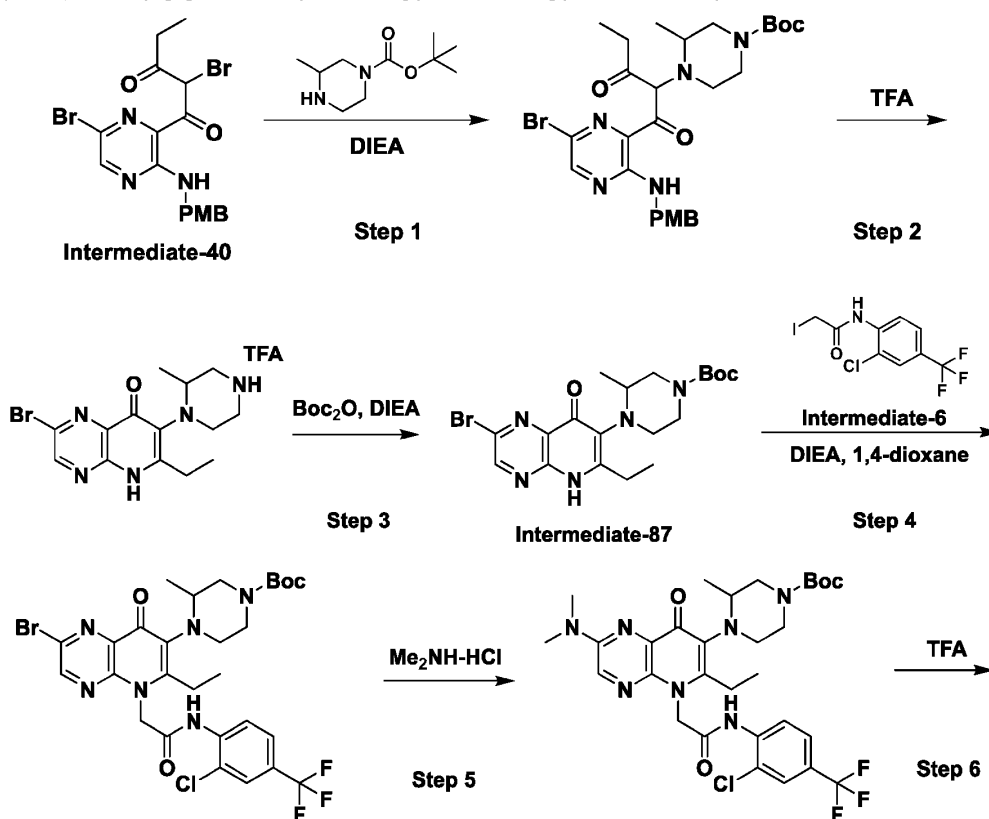
[001307] Step 17: Synthesis of N-[2-chloro-4-(trifluoromethyl)phenyl]-2-(11-ethyl-4-methyl-13-oxo-12-piperazin-1-yl-2,4,8,10-tetrazatricyclo[7.4.0.03,7]trideca-1(9),2,7,11-tetraen-10-yl)acetamide trifluoroacetate

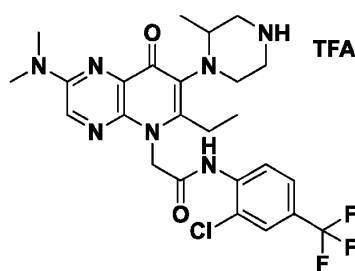
[001308] To a solution of tert-butyl 4-[10-[2-[2-chloro-4-(trifluoromethyl)anilino]-2-oxoethyl]-11-ethyl-4-methyl-13-oxo-2,4,8,10-tetrazatricyclo[7.4.0.0.3,7]trideca-1(9),2,7,11-tetraen-12-yl]piperazine-1-carboxylate (9 mg, 14 μ mol, 1.0 eq) in DCM (0.3 mL) was added TFA (0.6 mL), and the reaction was stirred at room temperature for 10 min. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001309] LCMS: 550.2[M+H]⁺.

[001310] Intermediate-87: tert-butyl 4-(2-bromo-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-3-methylpiperazine-1-carboxylate

[001311] Intermediate-88: N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(2-methylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide trifluoroacetate



**Intermediate-88**

[001312] Step 1. Synthesis of tert-butyl 4-(1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)-1,3-dioxopentane-2-yl)-3-methylpiperazine-1-carboxylate

[001313] To a solution of 2-bromo-1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)pentane-1,3-dione (Intermediate-40) (3.8 g, 8.07 mmol, 1.0 eq) in THF (40 mL) was added DIEA (2.08 g, 16.13 mmol, 2.0 eq) and tert-butyl 3-methylpiperazine-1-carboxylate (1.62 g, 8.07 mmol, 1.0 eq), and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with H₂O (100 mL) and then extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (40 mL * 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[001314] LCMS: 592.2 [M+H]⁺.

[001315] Step 2. Synthesis of 2-bromo-6-ethyl-7-(2-methylpiperazin-1-yl)pyrido[2,3-b]pyrazin-8(5H)-one trifluoroacetate

[001316] To a TFA (10 mL) solution was added tert-butyl 4-(1-(6-bromo-3-((4-methoxybenzyl)amino)pyrazin-2-yl)-1,3-dioxopentane-2-yl)-3-methylpiperazine-1-carboxylate (1.4 g, 2.37 mmol, 1.0 eq) and it was stirred at 55 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001317] LCMS: 354.1 [M+H]⁺.

[001318] Step 3. Synthesis of tert-butyl 4-(2-bromo-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-3-methylpiperazine-1-carboxylate

[001319] To a solution of 2-bromo-6-ethyl-7-(2-methylpiperazin-1-yl)pyrido[2,3-b]pyrazin-8(5H)-one trifluoroacetate (800 mg, 2.27 mmol, 1.0 eq) and DIEA (1.47 g, 11.36 mmol, 5.0 eq) in DCM (15 mL) was added (Boc)₂O (496 mg, 2.27 mmol, 1.0 eq), and the resulting mixture was

stirred at room temperature for 1 h. The reaction mixture was diluted with H₂O (20 mL) and then extracted with DCM (15 mL * 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[001320] LCMS: 454.1 [M+H]⁺.

[001321] Step 4. Synthesis of tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-3-methylpiperazine-1-carboxylate

[001322] To a solution of tert-butyl 4-(2-bromo-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-3-methylpiperazine-1-carboxylate (Intermediate-87) (300 mg, 663 μmol, 1.0 eq) in 1,4-dioxane (3 mL) was added DIEA (257 mg, 1.99 mmol, 3.0 eq) and N-(2-chloro-4-(trifluoromethyl)phenyl)-2-iodoacetamide (Intermediate-6) (241 mg, 663 μmol, 1.0 eq), and the resulting mixture was stirred at 80 °C overnight. The reaction mixture was concentrated under reduced pressure and then purified by reverse phase HPLC (water (0.1% FA-ACN) to afford the title compound.

[001323] LCMS: 689.1 [M+H]⁺.

[001324] Step 5. Synthesis of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(dimethylamino)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-3-methylpiperazine-1-carboxylate

[001325] To a solution of tert-butyl 4-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-3-methylpiperazine-1-carboxylate (230 mg, 334 μmol, 1.0 eq) in 1,4-dioxane (2.5 mL) was added dimethylamine hydrochloride (82 mg, 1.00 mmol, 3.0 eq) and DIEA (216 mg, 1.67 mmol, 5.0 eq), and the resulting mixture was stirred at 100 °C for 4 h. The reaction mixture was diluted with H₂O (50 mL) and extracted with EtOAc (30 mL * 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound, which was used into next step without further purification.

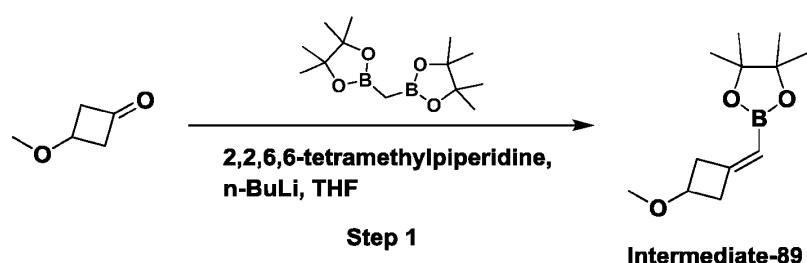
[001326] LCMS: 652.2 [M+H]⁺.

[001327] Step 6. Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(2-methylpiperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide trifluoroacetate

[001328] To a solution of tert-butyl 4-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(dimethylamino)-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-3-methylpiperazine-1-carboxylate (210 mg, 322 μ mol, 1.0 eq) in DCM (12 mL) was added TFA (3 mL), and it was stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into next step without further purification.

[001329] LCMS: 552.4 [M+H]⁺.

[001330] Intermediate-89: 2-((3-methoxycyclobutylidene)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

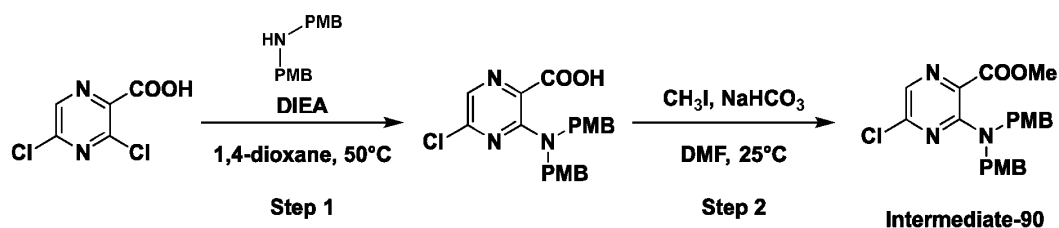


[001331] Step 1. Synthesis of 2-((3-methoxycyclobutylidene)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[001332] To a solution of 2,2,6,6-tetramethylpiperidine (508 mg, 3.60 mmol, 1.2 eq) in THF (2 mL) was added n-BuLi (2.5 M in THF, 1.32 mL, 1.1 eq) at -30 °C under N₂ atmosphere. After stirring at -30 °C for 0.5 h, the mixture was cooled to -78 °C, and then a solution of bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (803 mg, 3.00 mmol, 1.0 eq) in THF (2 mL) was added dropwise, and it was stirred at -78 °C for 0.5 h after addition. Then, a solution of 3-methoxycyclobutan-1-one (300 mg, 3.00 mmol, 1.0 eq) in THF (0.2 mL) was added dropwise at -78 °C, and the resulting mixture was slowly warmed to room temperature and stirred at room temperature overnight. The reaction mixture was poured into saturated NH₄Cl aqueous solution (80 mL) and extracted with EtOAc (70 mL*3). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[001333] LCMS: 225.2 [M+H]⁺.

[001334] Intermediate-90: methyl 3-(bis(4-methoxybenzyl)amino)-5-chloropyrazine-2-carboxylate



[001335] Step 1. Synthesis of 3-(bis(4-methoxybenzyl)amino)-5-chloropyrazine-2-carboxylic acid

[001336] To a solution of 3,5-dichloropyrazine-2-carboxylic acid (50.00 g, 259.08 mmol, 1 eq), 1-(4-methoxyphenyl)-N-[(4-methoxyphenyl) methyl] methanamine (66.67 g, 259.08 mmol, 1 eq) in 1,4-dioxane (1000 mL) was added DIEA (83.71 g, 647.71 mmol, 113 mL, 2.5 eq). The mixture was stirred at 50 °C for 16h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was suspended into DCM:EtOAc = 1:5 (500 mL) and stirred for 30 min. Then filtered, the filtrate was collected and concentrated under reduced pressure to give the title compound, which was used into the next step without further purification.

[001337] LCMS: 412.1 [M-H].

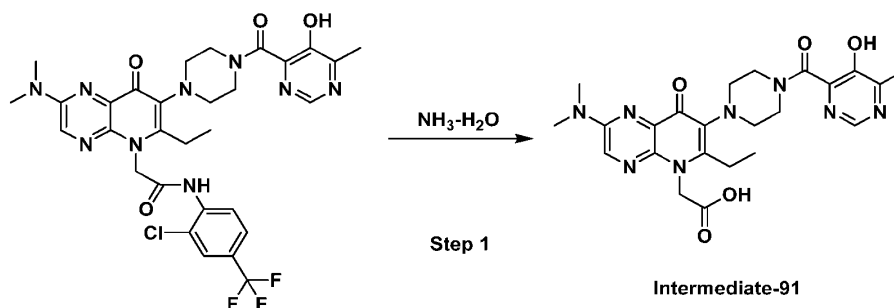
[001338] Step 2. Synthesis of methyl 3-(bis(4-methoxybenzyl) amino)-5-chloropyrazine-2-carboxylate

[001339] To a solution of 3-(bis(4-methoxybenzyl) amino)-5-chloropyrazine-2-carboxylic acid (90.00 g, 217.47 mmol, 1eq) in DMF (900 mL) was added CH₃I (92.60 g, 652.40 mmol, 40 mL, 3 eq) and NaHCO₃ (21.92 g, 260.96 mmol, 1.2 eq). Then the mixture was stirred at 25 °C for 5h. It was poured into saturated NH₄Cl aqueous solution (2.00 L) and extracted with EtOAc (800 mL * 3). The combined organic layer was washed with brine (100 mL *2), dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum to give a residue. The residue was purified by silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001340] ¹H NMR (400 MHz, CDCl₃) δ ppm 7.91 (s, 1H), 7.05 (d, 4H), 6.83 (d, 4H), 4.56 (s, 4H), 3.84 (s, 3H), 3.78 (s, 6H).

[001341] LCMS: 428.1 [M+H]⁺.

[001342] Intermediate-91: 2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid



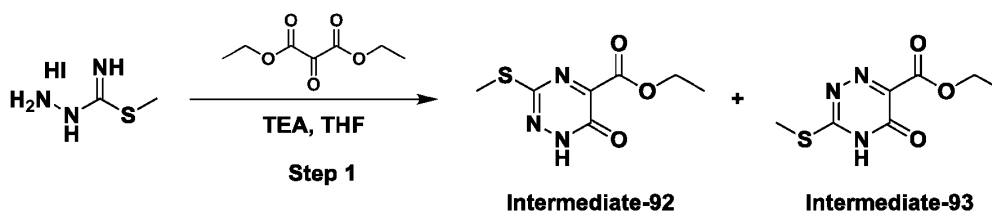
[001343] Step 1. Synthesis of 2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid

[001344] A solution of N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(2-(dimethylamino)-6-ethyl-7-(4-(5-hydroxy-6-methylpyrimidine-4-carbonyl)piperazin-1-yl)-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetamide (**I-14**) (100 mg, 148 μmol , 1.0 eq) in $\text{NH}_3\text{-H}_2\text{O}$ (2 mL) was stirred at 80 °C overnight. The reaction mixture was concentrated in vacuo and then purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[001345] LCMS: 497.3 $[\text{M}+\text{H}]^+$.

[001346] Intermediate-92: ethyl 3-(methylthio)-6-oxo-1,6-dihydro-1,2,4-triazine-5-carboxylate

[001347] Intermediate-93: ethyl 3-(methylthio)-5-oxo-4,5-dihydro-1,2,4-triazine-6-carboxylate



[001348] Step 1: Synthesis of ethyl 3-(methylthio)-6-oxo-1,6-dihydro-1,2,4-triazine-5-carboxylate and ethyl 3-(methylthio)-5-oxo-4,5-dihydro-1,2,4-triazine-6-carboxylate

[001349] To a solution of methyl hydrazinecarbamidomethylthioate hydroiodide hydroiodide (35.13 g, 150.73 mmol, 1.05 eq) and TEA (15.25 g, 150.73 mmol, 1.05 eq) in THF (400 mL) was added dropwise a solution of diethyl 2-oxomalonate (25 g, 143.55 mmol, 1.0 eq) at 0 °C under N_2 . The resulting mixture was stirred at 45 °C under N_2 atmosphere for 15 h. The reaction mixture was

filtered, the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compounds.

[001350] Analytical data of ethyl 3-(methylthio)-6-oxo-1,6-dihydro-1,2,4-triazine-5-carboxylate (Intermediate-92):

[001351] LCMS: 216.2 [M+H]⁺.

[001352] ¹H NMR (400 MHz, CDCl₃) δ 4.41 (q, 2H), 2.41 (s, 3H), 1.35 (t, 3H).

[001353] Analytical data of ethyl 3-(methylthio)-5-oxo-4,5-dihydro-1,2,4-triazine-6-carboxylate (Intermediate-93):

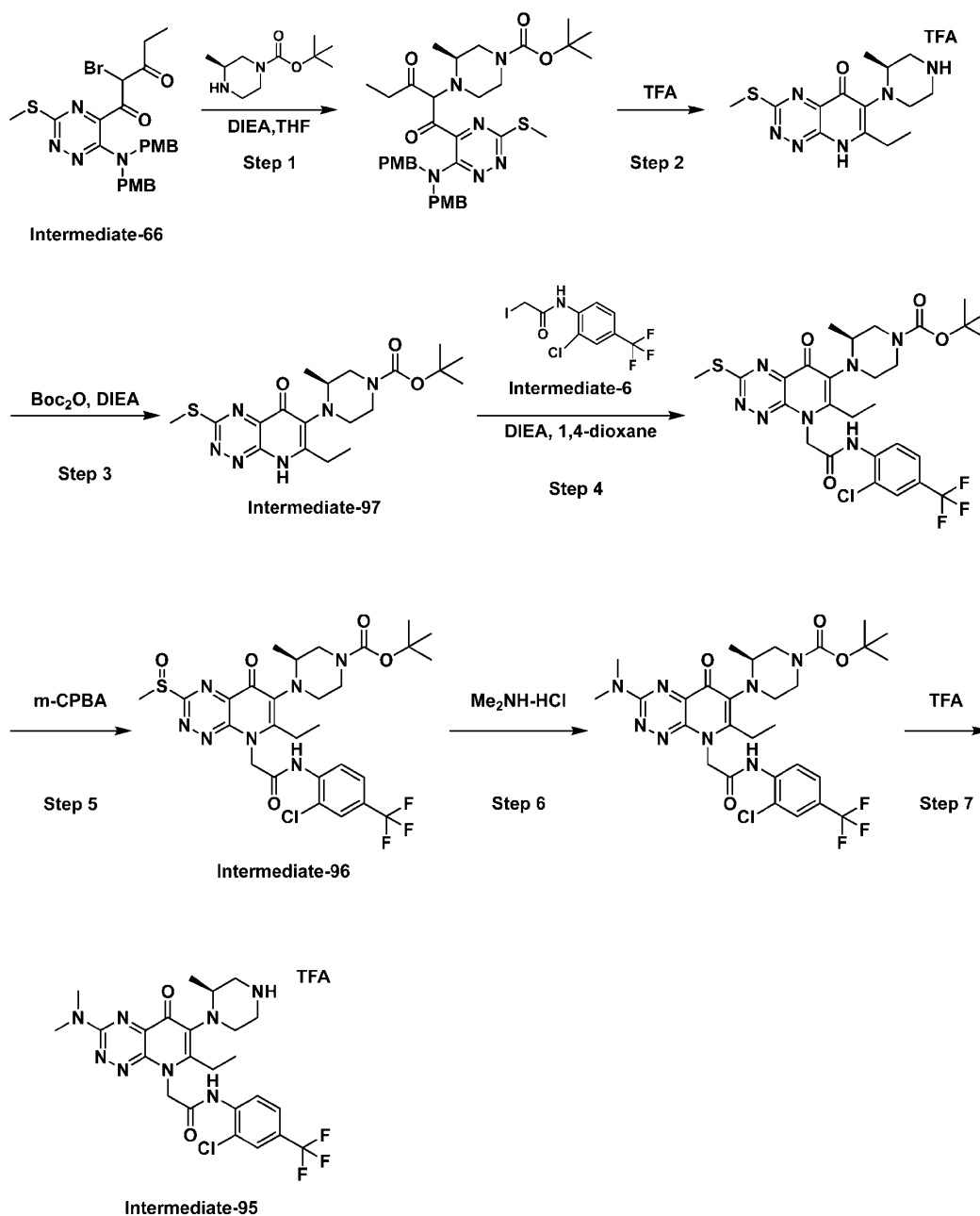
[001354] LCMS :216.1 [M+H]⁺.

[001355] ¹H NMR (400 MHz, CDCl₃) δ 4.48 (q, 2H), 2.63 (s, 3H), 1.45 - 1.40 (m, 3H).

[001356] Intermediate-96: tert-butyl (3S)-4-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-7-ethyl-3-(methylsulfinyl)-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-3-methylpiperazine-1-carboxylate

[001357] Intermediate-97: tert-butyl (S)-4-(7-ethyl-3-(methylthio)-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-3-methylpiperazine-1-carboxylate

[001358] Intermediate-95: (S)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3-(dimethylamino)-7-ethyl-6-(2-methylpiperazin-1-yl)-5-oxopyrido[3,2-e][1,2,4]triazin-8(5H)-yl)acetamide trifluoroacetate



[001359] Step 1: Synthesis of tert-butyl (3S)-4-(1-(6-(bis(4-methoxybenzyl)amino)-3-(methylthio)-1,2,4-triazin-5-yl)-1,3-dioxopentane-2-yl)-3-methylpiperazine-1-carboxylate

[001360] To a solution of 1-(6-(bis(4-methoxybenzyl)amino)-3-(methylthio)-1,2,4-triazin-5-yl)-2-bromopentane-1,3-dione (Intermediate-66) (1.8 g, 3.22 mmol, 1.0 eq) and tert-butyl (S)-3-

methylpiperazine-1-carboxylate (709 mg, 3.54 mmol, 1.1 eq) in THF (20 mL) was added DIEA (832 mg, 6.43 mmol, 2.0 eq), and the resulting mixture was stirred at 50 °C overnight. The reaction mixture was poured into ice-water (20 mL) and extracted with DCM (20 mL*3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001361] LCMS: 679.2 [M+H]⁺.

[001362] Step 2: Synthesis of (S)-7-ethyl-6-(2-methylpiperazin-1-yl)-3-(methylthio)pyrido[3,2-e][1,2,4]triazin-5(8H)-one trifluoroacetate

[001363] A solution of tert-butyl (3S)-4-(1-(6-(bis(4-methoxybenzyl)amino)-3-(methylthio)-1,2,4-triazin-5-yl)-1,3-dioxopentan-2-yl)-3-methylpiperazine-1-carboxylate (650 mg, 958 μmol, 1.0 eq) in TFA (7 mL) was stirred at 50 °C for 1 h and then concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001364] LCMS: 321.2[M+H]⁺.

[001365] Step 3: Synthesis of tert-butyl (S)-4-(7-ethyl-3-(methylthio)-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-3-methylpiperazine-1-carboxylate (Intermediate-97)

[001366] To a solution of (S)-7-ethyl-6-(2-methylpiperazin-1-yl)-3-(methylthio)pyrido[3,2-e][1,2,4]triazin-5(8H)-one trifluoroacetate (305 mg, 952 μmol, 1.0 eq) and DIEA (369 mg, 2.86 mmol, 3.0 eq) in DCM (4 mL) was added Boc₂O (208 mg, 952 μmol, 1.0 eq), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into H₂O (10 mL), and then extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The filtrate was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001367] LCMS: 421.2 [M+H]⁺.

[001368] Step 4: Synthesis of tert-butyl (S)-4-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-7-ethyl-3-(methylthio)-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-3-methylpiperazine-1-carboxylate

[001369] To a solution of tert-butyl (S)-4-(7-ethyl-3-(methylthio)-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-3-methylpiperazine-1-carboxylate (Intermediate-97) (100 mg, 238 μmol, 1.0 eq) and N-(2-chloro-4-(trifluoromethyl)phenyl)-2-iodoacetamide

(Intermediate-6) (95 mg, 262 μ mol, 1.1 eq) in 1,4-dioxane (2 mL) was added DIEA (77 mg, 594 μ mol, 2.5 eq), and the resulting mixture was stirred at 80 °C overnight. The reaction mixture was poured into H₂O (10 mL), and then extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA-ACN) to afford the title compound.

[001370] LCMS: 656.2 [M+H]⁺.

[001371] ¹H NMR (400 MHz, CDCl₃) δ 8.65 (s, 1H), 8.43 (d, 1H), 7.67 (d, 1H), 7.51 (br d, 1H), 5.85 - 5.42 (m, 2H), 4.23 - 3.96 (m, 2H), 3.96 - 3.85 (m, 1H), 3.70 (dt, 1H), 3.63 - 3.50 (m, 1H), 3.15 - 2.89 (m, 2H), 2.75 (s, 3H), 2.66 (br d, 1H), 2.60 - 2.49 (m, 1H), 1.50 (s, 9H), 1.36 (t, 3H), 0.86 (d, 3H).

[001372] Step 5: Synthesis of tert-butyl (3S)-4-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-7-ethyl-3-(methylsulfinyl)-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-3-methylpiperazine-1-carboxylate (Intermediate-96)

[001373] To a solution of tert-butyl (S)-4-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-7-ethyl-3-(methylthio)-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-3-methylpiperazine-1-carboxylate (62 mg, 95 μ mol, 1.0 eq) in DCM (1.5 mL) was added m-CPBA (38 mg, 189 μ mol, 85%, 2.0 eq) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was poured into saturated Na₂SO₃ aqueous solution (5 mL), and then extracted with DCM (5 mL * 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001374] LCMS: 672.2 [M+H]⁺.

[001375] Step 6: Synthesis of tert-butyl (S)-4-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-3-(dimethylamino)-7-ethyl-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-3-methylpiperazine-1-carboxylate

[001376] To a solution of tert-butyl (3S)-4-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-7-ethyl-3-(methylsulfinyl)-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-3-methylpiperazine-1-carboxylate (Intermediate-96) (64 mg, 95 μ mol, 1.0 eq) and dimethylamine hydrochloride (16 mg, 190 μ mol, 2.0 eq) in 1,4-dioxane

(2 mL) was added DIEA (37 mg, 286 μ mol, 3.0 eq), and the resulting mixture was stirred at 80 °C for 1 h. The reaction mixture was poured into ice-water (10 mL) and extracted with EtOAc (5 mL*3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001377] LCMS: 653.2 $[\text{M}+\text{H}]^+$.

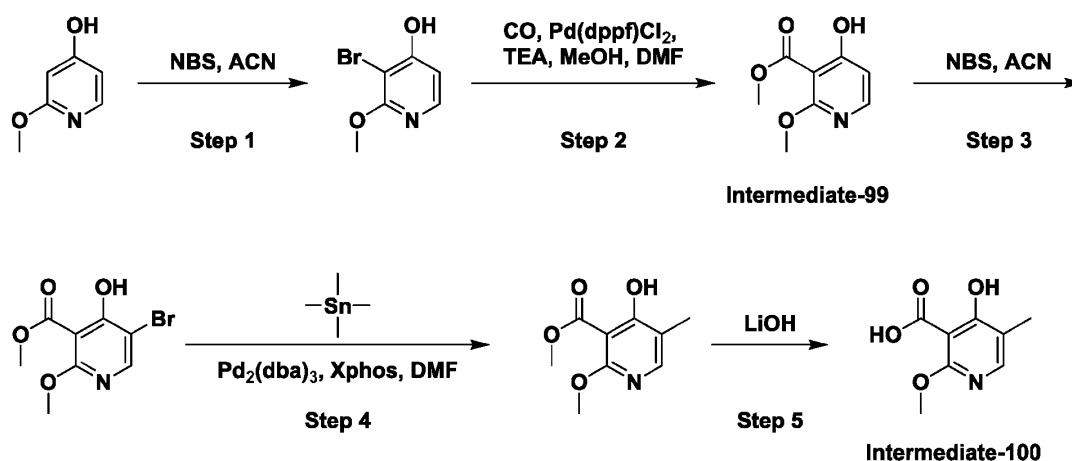
[001378] Step 7: Synthesis of (S)-N-(2-chloro-4-(trifluoromethyl)phenyl)-2-(3-(dimethylamino)-7-ethyl-6-(2-methylpiperazin-1-yl)-5-oxopyrido[3,2-e][1,2,4]triazin-8(5H)-yl)acetamide trifluoroacetate

[001379] To a solution of tert-butyl (S)-4-(8-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-3-(dimethylamino)-7-ethyl-5-oxo-5,8-dihydropyrido[3,2-e][1,2,4]triazin-6-yl)-3-methylpiperazine-1-carboxylate (39 mg, 60 μ mol, 1.0 eq) in DCM (0.5 mL) was added TFA (0.5 mL), and the resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001380] LCMS: 553.2 $[\text{M}+\text{H}]^+$.

[001381] Intermediate-99: methyl 4-hydroxy-2-methoxynicotinate

[001382] Intermediate-100: 4-hydroxy-2-methoxy-5-methylnicotinic acid



[001383] Step 1: Synthesis of 3-bromo-2-methoxypyridin-4-ol

[001384] To a solution of 2-methoxypyridin-4-ol (5.00 g, 39.96 mmol, 1.0 eq) in ACN (80 mL) was added NBS (7.11 g, 39.96 mmol, 1.0 eq) at 0 °C, and the resulting mixture was stirred

at room temperature overnight. The reaction mixture was diluted with H₂O (100 mL), and then extracted with EtOAc (100 mL * 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001385] LCMS: 203.9 [M+H]⁺.

[001386] ¹H NMR (400 MHz, CDCl₃) δ 7.92 (d, 1H), 6.63 (d, 1H), 4.03 (s, 3H).

[001387] Step 2: Synthesis of methyl 4-hydroxy-2-methoxynicotinate (Intermediate-99)

[001388] To a mixture of 3-bromo-2-methoxypyridin-4-ol (3.84 g, 18.82 mmol, 1.0 eq) in MeOH (20 mL) and DMF (20 mL) was added Pd(dppf)Cl₂.CH₂Cl₂ (1.54 g, 1.88 mmol, 0.1 eq) and TEA (5.71 g, 56.46 mmol, 3.0 eq), and the resulting mixture was stirred at 80 °C overnight under CO (50 psi) atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved into DCM (100 mL), washed with saturated NH₄Cl (70 mL * 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001389] ¹H NMR (400 MHz, CDCl₃) δ 12.26 (s, 1H), 8.05 (d, 1H), 6.57 (d, 1H), 4.01 (d, 6H).

[001390] Step 3: Synthesis of methyl 5-bromo-4-hydroxy-2-methoxynicotinate

[001391] To a solution of methyl 4-hydroxy-2-methoxynicotinate (Intermediate-99) (1.40 g, 7.64 mmol, 1.0 eq) in ACN (14 mL) was added NBS (1.36 g, 7.64 mmol, 1.0 eq), and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was filtered, the filter cake was washed with cold ACN (5 mL) and then dried in vacuo to afford the title compound, which was used into the next step without further purification.

[001392] LCMS: 262.1 [M+H]⁺.

[001393] ¹H NMR (400 MHz, CDCl₃) δ 12.90 (s, 1H), 8.15 (s, 1H), 3.92 (d, 6H).

[001394] Step 4: Synthesis of methyl 4-hydroxy-2-methoxy-5-methylnicotinate

[001395] To a mixture of methyl 5-bromo-4-hydroxy-2-methoxynicotinate (300 mg, 1.14 mmol, 1.0 eq) and tetramethylstannane (409 mg, 2.29 mmol, 2.0 eq) in DMF (2 mL) was added Pd₂(dba)₃ (105 mg, 114 μmol, 0.1 eq) and XPhos (109 mg, 229 μmol, 0.2 eq), and the resulting mixture was stirred at 120 °C overnight under N₂ atmosphere. The reaction mixture was diluted with H₂O (20 mL), extracted with EtOAc (10 mL * 3). The combined organic layers were

washed with brine (5 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[001396] LCMS: 198.3 $[\text{M}+\text{H}]^+$.

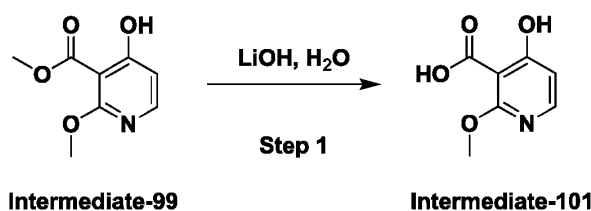
[001397] ^1H NMR (400 MHz, CDCl_3) δ 12.48 (s, 1H), 7.91 (s, 1H), 3.99 (d, 6H), 2.14 (s, 3H).

[001398] Step 5: Synthesis of 4-hydroxy-2-methoxy-5-methylnicotinic acid

[001399] To a solution of methyl 4-hydroxy-2-methoxy-5-methylnicotinate (30 mg, 152 μmol , 1.0 eq) in H_2O (0.2 mL), THF (0.2 mL) and MeOH (0.2 mL) was added aqueous LiOH solution (1 M, 608 μL , 4.0 eq) and it was stirred at 40 $^\circ\text{C}$ overnight. The reaction mixture was acidified by addition of aqueous HCl solution (1 M) to pH 5~6, and then extracted with EtOAc (5 mL * 10). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001400] LCMS: 184.1 $[\text{M}+\text{H}]^+$.

[001401] Intermediate-101: 4-hydroxy-2-methoxy-pyridine-3-carboxylic acid



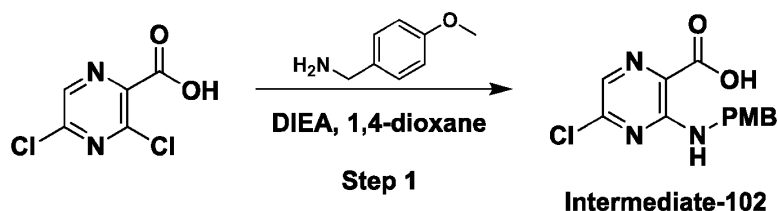
[001402] Step 1: Synthesis of 4-hydroxy-2-methoxy-pyridine-3-carboxylic acid

[001403] To a solution of methyl 4-hydroxy-2-methoxy-pyridine-3-carboxylate (Intermediate-99) (1.00 g, 5.46 mmol, 1.0 eq) in THF (5 mL), H_2O (5 mL) and MeOH (10 mL) was added LiOH- H_2O (1.37 g, 32.76 mmol, 6.0 eq) and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with H_2O (3 mL) and then separated. The aqueous phase was washed with EtOAc 6 mL (3 mL * 2) and then adjusted to pH = 6 with aqueous HCl solution (2 M). The resulting mixture was concentrated under reduced pressure and then purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[001404] LCMS: 170.1 $[\text{M}+\text{H}]^+$.

[001405] ¹H NMR (400 MHz, CDCl₃) δ ppm 12.60 (s, 1H), 11.28 - 10.86 (m, 1H), 8.08 (d, 1H), 6.68 (d, 1H), 4.19 (s, 3H).

[001406] Intermediate-102: Synthesis of 5-chloro-3-((4-methoxybenzyl)amino)pyrazine-2-carboxylic acid



[001407] Step 1. Synthesis of 5-chloro-3-((4-methoxybenzyl)amino)pyrazine-2-carboxylic acid

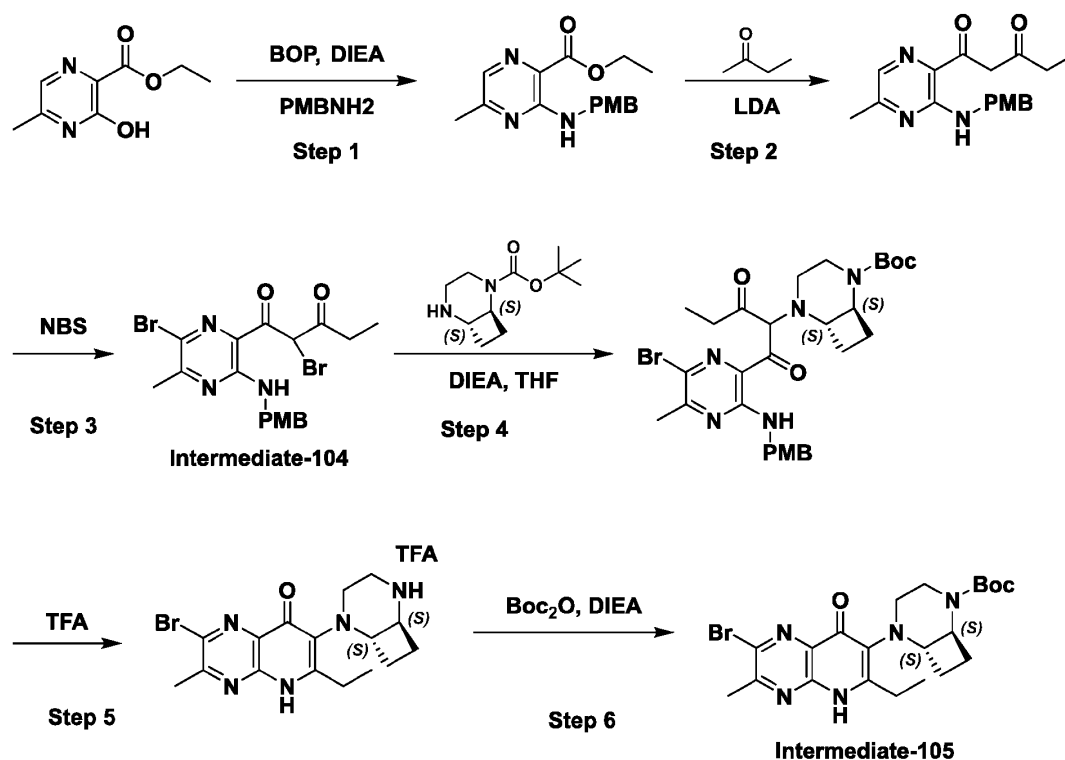
[001408] To a solution of 3,5-dichloropyrazine-2-carboxylic acid (200 mg, 1.04 mmol, 1.0 eq) and (4-methoxyphenyl)methanamine (142 mg, 1.04 mmol, 1.0 eq) in 1,4-dioxane (2 mL) was added DIEA (335 mg, 2.59 mmol, 2.5 eq), and the resulting mixture was stirred at 100°C for 2 h. The reaction mixture was acidized to pH 2 with aqueous HCl solution (1 M), and then extracted with EtOAc (30mL*2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001409] LCMS: 294.1[M+H]⁺.

[001410] ¹H NMR (400 MHz, CDCl₃) δ ppm 8.37 (br s, 1H), 7.72 (s, 1H), 7.32 - 7.27 (m, 2H), 6.91 - 6.86 (m, 2H), 4.66 (d, 2H), 3.81 (s, 3H).

[001411] Intermediate-104: 2-bromo-1-(6-bromo-3-((4-methoxybenzyl)amino)-5-methylpyrazin-2-yl)pentane-1,3-dione

[001412] Intermediate-105: tert-butyl (1S,6S)-5-(2-bromo-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate



[001413] Step 1: Synthesis of ethyl 3-((4-methoxybenzyl)amino)-5-methylpyrazine-2-carboxylate

[001414] To a solution of ethyl 3-hydroxy-5-methylpyrazine-2-carboxylate (10.00 g, 54.89 mmol, 1.0 eq) in DMF (100 mL) was added DIEA (10.64 g, 82.34 mmol, 1.5 eq) and BOP (26.71 g, 60.38 mmol, 1.1 eq), and the resulting mixture was stirred at 45 °C for 0.5 h. Then PMBNH₂ (9.04 g, 65.87 mmol, 1.2 eq) was added and the mixture was stirred at 45 °C overnight. The reaction mixture was diluted with H₂O (1000 mL) and extracted with EtOAc (300 mL * 3). The combined organic layers were washed with brine (300 mL * 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[001415] LCMS: 302.2 [M+H]⁺.

[001416] Step 2: Synthesis of 1-(3-((4-methoxybenzyl)amino)-5-methylpyrazin-2-yl)pentane-1,3-dione

[001417] To a solution of ethyl 3-((4-methoxybenzyl)amino)-5-methylpyrazine-2-carboxylate (10.50 g, 34.84 mmol, 1.0 eq) and butan-2-one (7.54 g, 104.53 mmol, 3.0 eq) in toluene (105 mL) was added LDA (2 M in hexane, 52.27 mL, 3.0 eq) at 0 °C under N₂ atmosphere, and the resulting mixture was stirred at 60 °C for 0.5 h. The reaction mixture was quenched by saturated NH₄Cl solution (300 mL), extracted with EtOAc (300 mL*3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[001418] LCMS: 328.2 [M+H]⁺.

[001419] Step 3: Synthesis of 2-bromo-1-(6-bromo-3-((4-methoxybenzyl)amino)-5-methylpyrazin-2-yl)pentane-1,3-dione (Intermediate-104)

[001420] To a solution of 1-(3-((4-methoxybenzyl)amino)-5-methylpyrazin-2-yl)pentane-1,3-dione (2.00 g, 6.11 mmol, 1.0 eq) in DCM (20 mL) was added NBS (1.09 g, 6.11 mmol, 1.0 eq) and TsOH-H₂O (316 mg, 1.83 mmol, 0.3 eq), and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with H₂O (30 mL) and extracted with DCM (20 mL * 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The obtained material was treated with DMF (20 mL) and NBS (1.16 g, 6.50 mmol, 1.1 eq) and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with H₂O (50 mL) and extracted with MTBE (50 mL * 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001421] LCMS: 486.0 [M+H]⁺.

[001422] Step 4: Synthesis of tert-butyl (1S,6S)-5-(1-(6-bromo-3-((4-methoxybenzyl)amino)-5-methylpyrazin-2-yl)-1,3-dioxopentan-2-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001423] To a solution of 2-bromo-1-(6-bromo-3-((4-methoxybenzyl)amino)-5-methylpyrazin-2-yl)pentane-1,3-dione (Intermediate-104) (2.87 g, 5.92 mmol, 1.0 eq) in THF (30 mL) was added tert-butyl (1S,6S)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (CAS: 2920219-11-8) (1.38 g, 6.51 mmol, 1.1 eq) and DIEA (1.53 g, 11.83 mmol, 2.0 eq), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were dried over anhydrous

Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[001424] LCMS: 618.3 [M+H]⁺.

[001425] Step 5: Synthesis of 7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-6-ethyl-3-methylpyrido[2,3-b]pyrazin-8(5H)-one trifluoroacetate

[001426] A solution of tert-butyl (1S,6S)-5-(1-(6-bromo-3-((4-methoxybenzyl)amino)-5-methylpyrazin-2-yl)-1,3-dioxopentan-2-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (2.80 g, 4.54 mmol, 1.0 eq) in TFA (30 mL) was stirred at room temperature for 2 h, and heated to 50 °C for another 2 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001427] LCMS: 378.1 [M+H]⁺.

[001428] Step 6: Synthesis of tert-butyl (1S,6S)-5-(2-bromo-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

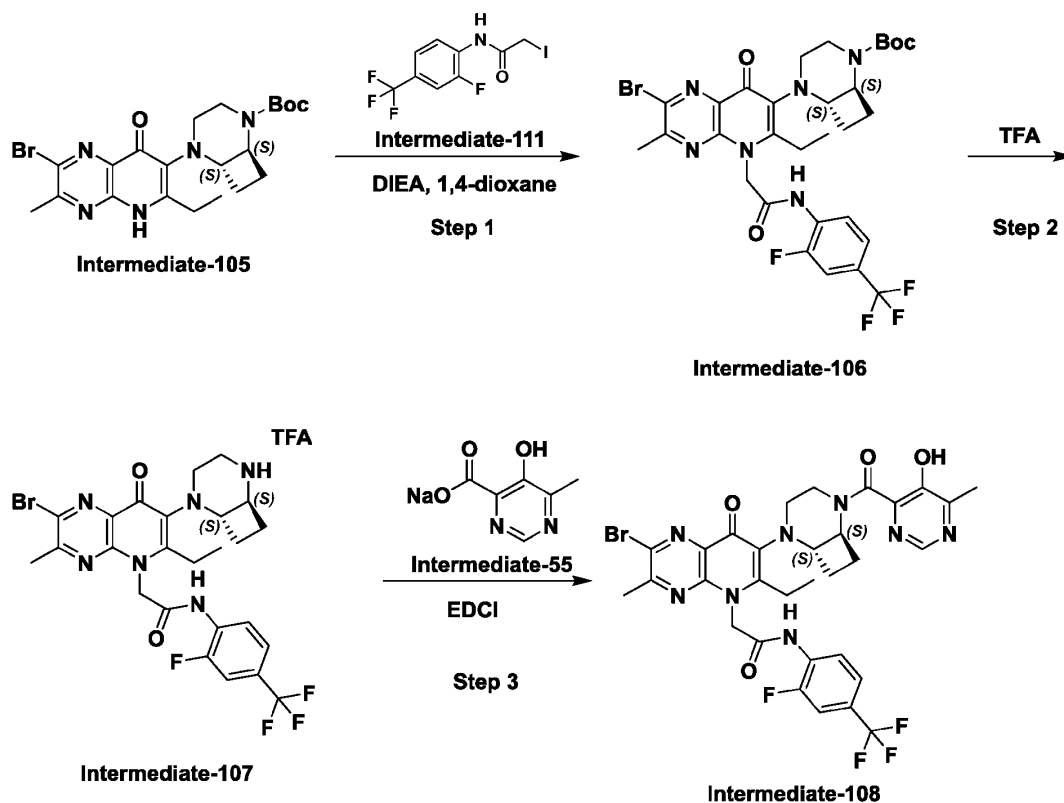
[001429] To a solution of 7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-6-ethyl-3-methylpyrido[2,3-b]pyrazin-8(5H)-one trifluoroacetate (1.70 g, 4.49 mmol, 1.0 eq) in DCM (20 mL) was added Boc₂O (1.08 g, 4.94 mmol, 1.1 eq) and DIEA (2.90 g, 22.47 mmol, 5.0 eq), and the resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was diluted with H₂O (50 mL) and extracted with MTBE (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[001430] LCMS: 480.2 [M+H]⁺.

[001431] Intermediate-106: tert-butyl (1S,6S)-5-(2-bromo-6-ethyl-5-(2-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001432] Intermediate-107: 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate

[001433] Intermediate-108: 2-(2-bromo-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide



[001434] Step 1: Synthesis of tert-butyl (1S,6S)-5-(2-bromo-6-ethyl-5-(2-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (Intermediate-106)

[001435] To a solution of tert-butyl (1S,6S)-5-(2-bromo-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (Intermediate-105) (500 mg, 1.05 mmol, 1.0 eq) and N-(2-fluoro-4-(trifluoromethyl)phenyl)-2-iodoacetamide (Intermediate-111) (544 mg, 1.57 mmol, 1.5 eq) in 1,4-dioxane (4.5 mL) was added DIEA (405 mg, 3.14 mmol, 3.0 eq), and the resulting mixture was stirred at 80 °C for 3 h. The reaction mixture was concentrated under reduced pressure and then purified by silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[001436] LCMS: 697.3 [M+H]⁺.

[001437] Step 2: Synthesis of 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate (Intermediate-107)

[001438] To a solution of tert-butyl (1S,6S)-5-(2-bromo-6-ethyl-5-(2-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (Intermediate-106) (700 mg, 1.00 mmol, 1.0 eq) in DCM (18 mL) was added TFA (6 mL), and it was stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001439] LCMS: 599.0 [M+H]⁺.

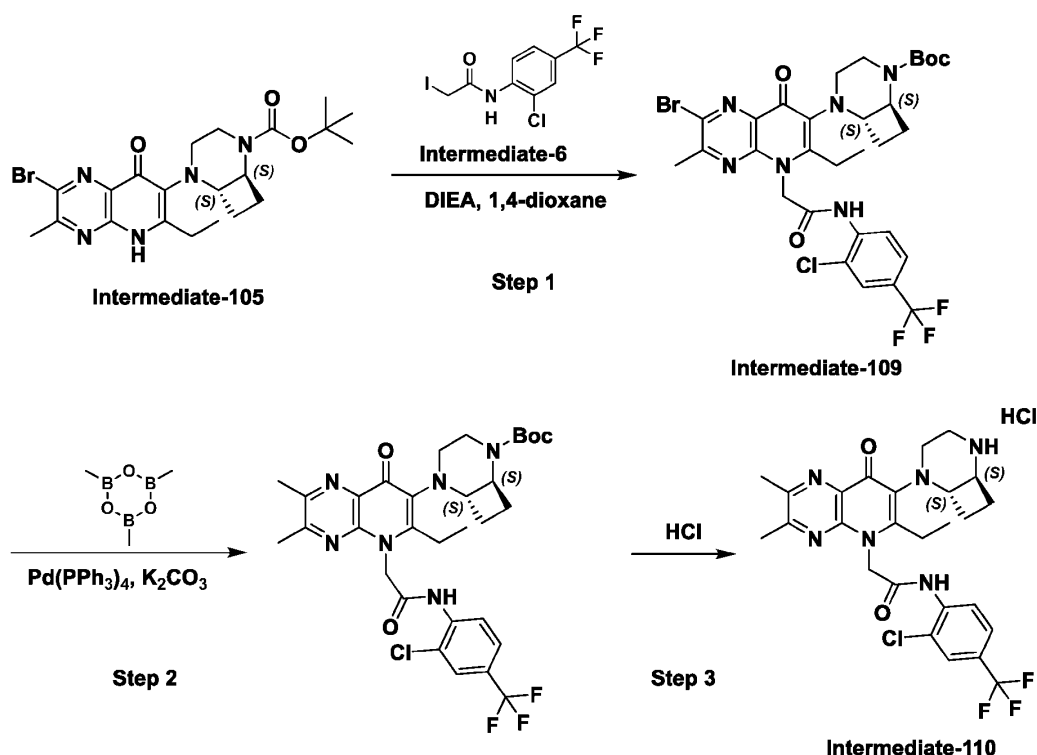
[001440] Step 3: Synthesis of 2-(2-bromo-6-ethyl-7-((1S,6S)-5-(5-hydroxy-6-methylpyrimidine-4-carbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide

[001441] To a solution of 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate (Intermediate-107) (549 mg, 919 μmol, 1.0 eq) and sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate (Intermediate-55) (425 mg, 2.76 mmol, 3.0 eq) in pyridine (5.5 mL) was added EDCI (3.52 g, 18.38 mmol, 20.0 eq), and the resulting mixture was stirred at 45 °C for 15 min. To the reaction mixture was added aqueous NaOH solution (1 M, 5.5 mL) and the mixture was stirred for 15 min at room temperature. Then the resulting mixture was adjusted to pH = 6 with aqueous HCl solution (1 M) and extracted with EtOAc (20 mL * 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[001442] LCMS: 735.3 [M+H]⁺.

[001443] Intermediate-109: tert-butyl (1S,6S)-5-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001444] Intermediate-110: 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-6-ethyl-2,3-dimethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide hydrochloride



[001445] Step 1: Synthesis of tert-butyl (1S,6S)-5-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (Intermediate-109)

[001446] To a solution of tert-butyl (1S,6S)-5-(2-bromo-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (Intermediate-105) (500 mg, 1.05 mmol, 1.0 eq) in 1,4-dioxane (5.0 mL) was added DIEA (405 mg, 3.14 mmol, 3.0 eq) and N-(2-chloro-4-(trifluoromethyl)phenyl)-2-iodoacetamide (Intermediate-6) (570 mg, 1.57 mmol, 1.5 eq), and the resulting mixture was stirred at 80 °C for 3 h. The mixture was concentrated under reduced pressure and then purified by silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[001447] LCMS: 715.3 $[\text{M}+\text{H}]^+$.

[001448] Step 2: Synthesis of tert-butyl (1S,6S)-5-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2,3-dimethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001449] To a solution of tert-butyl (1S,6S)-5-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (Intermediate-109) (200 mg, 280 μ mol, 1.0 eq) and 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (70 mg, 560 μ mol, 2.0 eq) in 1,4-dioxane (5 mL) was added K_2CO_3 (116 mg, 840 μ mol, 3.0 eq) and $Pd(PPh_3)_4$ (65 mg, 56 μ mol, 0.2 eq), the resulting mixture was degassed and purged with N_2 for 3 times, and then stirred at 110 $^{\circ}C$ overnight under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

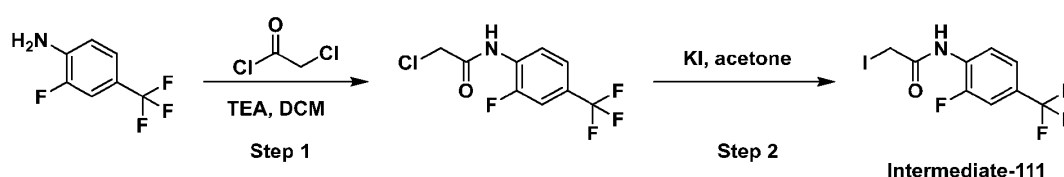
[001450] LCMS: 649.5 $[M+H]^+$.

[001451] Step 3: Synthesis of 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-6-ethyl-2,3-dimethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide hydrochloride

[001452] To a solution of HCl in 1,4-dioxane (2 M, 2 mL) was added tert-butyl (1S,6S)-5-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-2,3-dimethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (170 mg, 262 μ mol, 1.0 eq), and it was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001453] LCMS: 549.3 $[M+H]^+$.

[001454] Intermediate-111: N-(2-fluoro-4-(trifluoromethyl)phenyl)-2-iodoacetamide



Step 1. Synthesis of 2-chloro-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide

[001455] To a solution of 2-fluoro-4-(trifluoromethyl)aniline (1.00 g, 5.58 mmol, 1.0 eq) in DCM (10 mL) was added TEA (2.26 g, 22.33 mmol, 4.0 eq) and 2-chloroacetyl chloride (1.58 g, 13.96 mmol, 2.5 eq) in DCM (7.5 mL) at 0 $^{\circ}C$. After addition, the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with H_2O (20 mL) and extracted

with DCM (20 mL * 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[001456] LCMS: 255.9 [M+H]⁺.

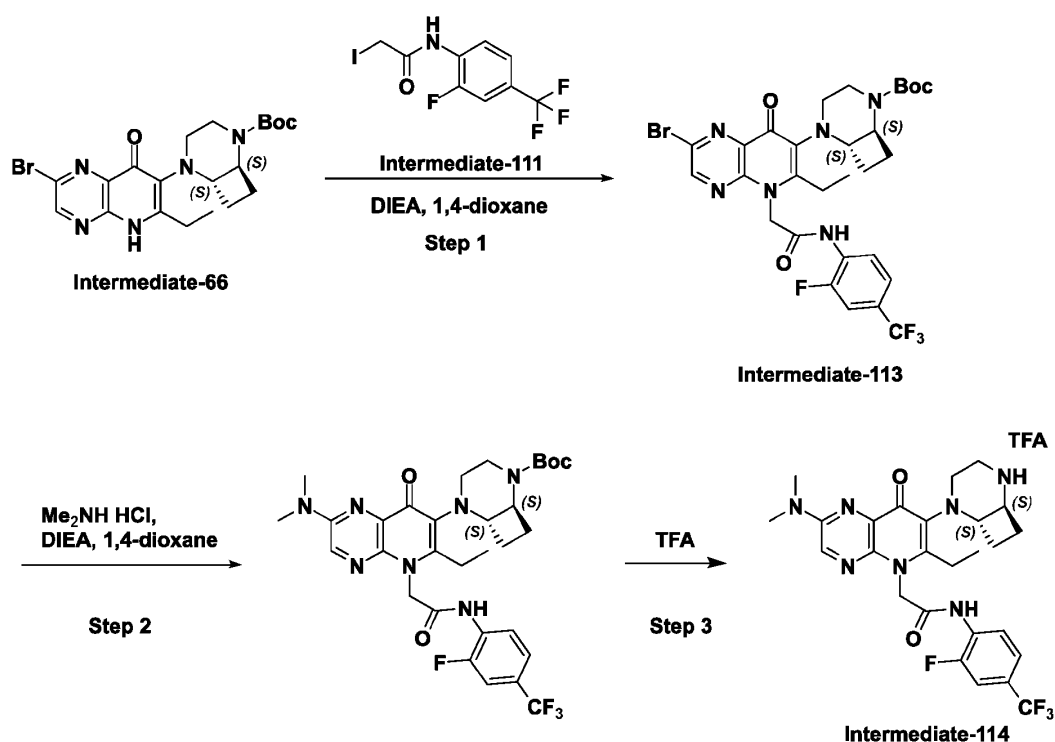
[001457] Step 2. Synthesis of N-(2-fluoro-4-(trifluoromethyl)phenyl)-2-iodoacetamide

[001458] To a solution of 2-chloro-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide (1.00 g, 3.91 mmol, 1.0 eq) in acetone (10 mL) was added KI (714 mg, 4.30 mmol, 1.1 eq), and the resulting mixture was stirred at 60 °C for 2 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001459] LCMS: 347.9 [M+H]⁺.

[001460] Intermediate-113: tert-butyl (1S,6S)-5-(2-bromo-6-ethyl-5-(2-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001461] Intermediate-114: 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(dimethylamino)-6-ethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate



[001462] Step 1. Synthesis of tert-butyl (1S,6S)-5-(2-bromo-6-ethyl-5-(2-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001463] To a solution of tert-butyl (1S,6S)-5-(2-bromo-6-ethyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (Intermediate-66) (100 mg, 215 μ mol, 1.0 eq) in 1,4-dioxane (1 mL) was added DIEA (84 mg, 646 μ mol, 3.0 eq) and N-(2-fluoro-4-(trifluoromethyl)phenyl)-2-iodoacetamide (Intermediate-111) (90 mg, 258 μ mol, 1.2 eq), and the resulting mixture was stirred at 80 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[001464] LCMS: 683.1 [M+H]⁺.

[001465] Step 2. Synthesis of tert-butyl (1S,6S)-5-(2-(dimethylamino)-6-ethyl-5-(2-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001466] To a solution of tert-butyl (1S,6S)-5-(2-bromo-6-ethyl-5-(2-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (Intermediate-113) (75 mg, 110 μ mol, 1.0 eq) in 1,4-dioxane (1 mL) was added dimethylamine hydrochloride (27 mg, 329 μ mol, 3.0 eq) and DIEA (71 mg, 549 μ mol, 5.0 eq), the resulting mixture was stirred at 100 °C for 2 h. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound, which was used into next step without further purification.

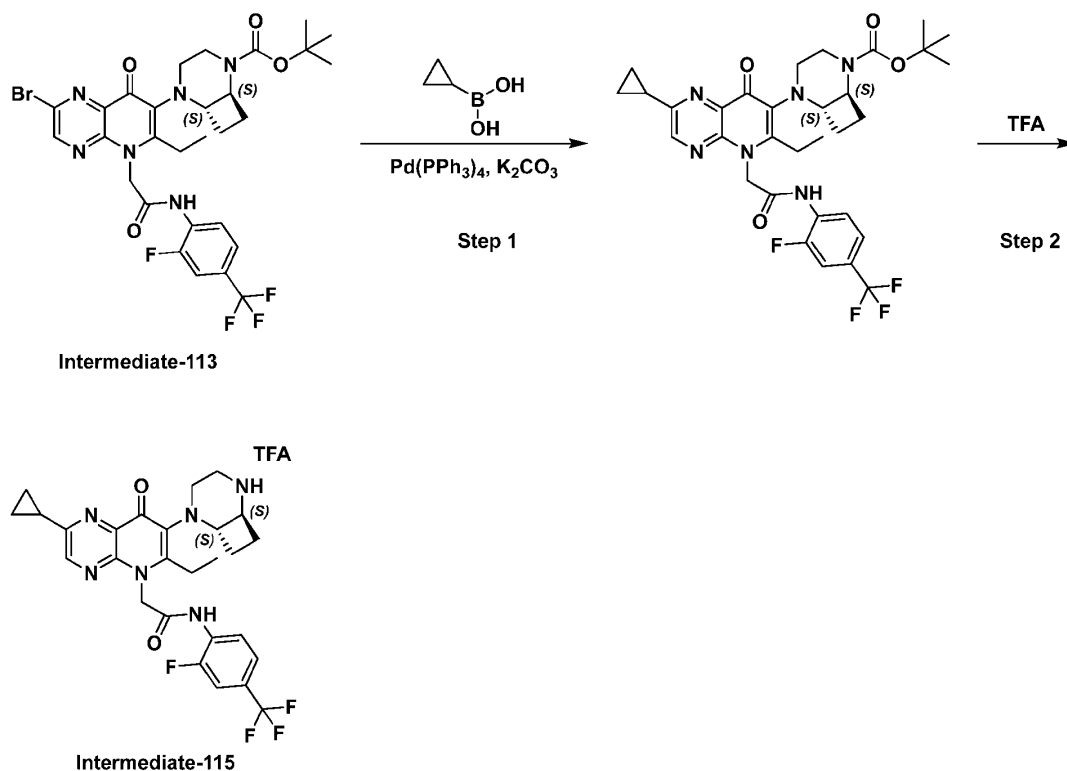
[001467] LCMS: 648.3 [M+H]⁺.

[001468] Step 3. Synthesis of 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(dimethylamino)-6-ethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate

[001469] To a solution of tert-butyl (1S,6S)-5-(2-(dimethylamino)-6-ethyl-5-(2-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (75 mg, 116 μ mol, 1.0 eq) in DCM (1.5 mL) was added TFA (0.7 mL), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001470] LCMS: 548.3 [M+H]⁺.

[001471] Intermediate-115: 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-cyclopropyl-6-ethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate



[001472] Step 1: Synthesis of tert-butyl (1S,6S)-5-(2-cyclopropyl-6-ethyl-5-(2-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001473] To a solution of tert-butyl (1S,6S)-5-(2-bromo-6-ethyl-5-(2-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (Intermediate-113) (300 mg, 439 μ mol, 1.0 *eq*) and cyclopropylboronic acid (75 mg, 878 μ mol, 2.0 *eq*) in 1,4-dioxane (5 mL) was added Pd(PPh₃)₄ (76 mg, 66 μ mol, 0.15 *eq*) and K₂CO₃ (182 mg, 1.32 mmol, 3.0 *eq*), the resulting mixture was degassed and then stirred at 110 °C for 4 h under N₂ atmosphere. The reaction mixture was poured into H₂O (50 mL) and extracted with EtOAc (50 mL * 2). The combined organic layers were washed with brine (50 mL * 2), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[001474] LCMS: 645.3 [M+H]⁺.

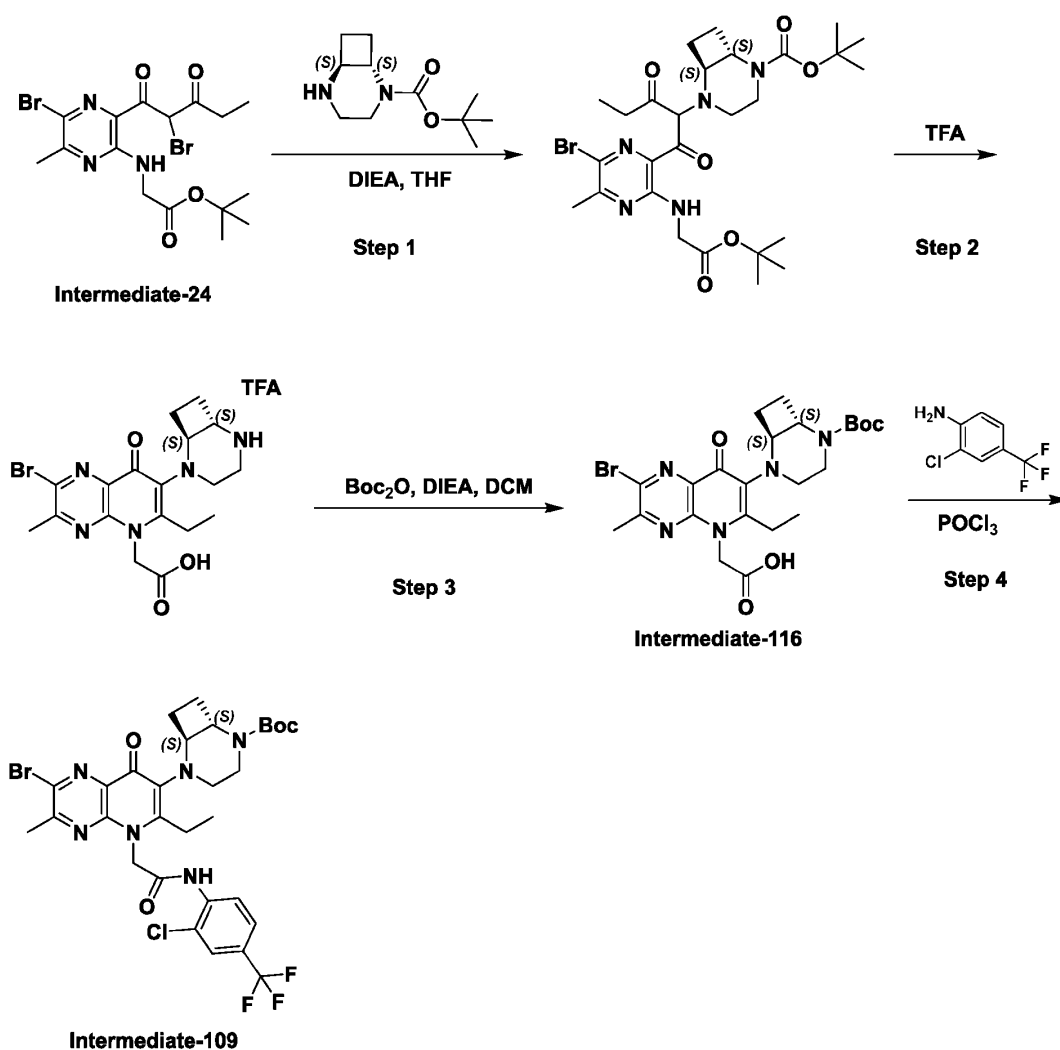
[001475] Step 2: Synthesis of 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-cyclopropyl-6-ethyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-fluoro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate

[001476] To a solution of tert-butyl (1S,6S)-5-(2-cyclopropyl-6-ethyl-5-(2-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (180 mg, 279 μ mol, 1.0 *eq*) in DCM (2 mL) was added TFA (2 mL), and it was stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to afford the title compound, which was used into the next step without further purification.

[001477] LCMS: 545.3 [M+H]⁺.

[001478] Alternative procedure for Intermediate-109: tert-butyl (1S,6S)-5-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001479] Intermediate-116: 2-(2-bromo-7-((1S,6S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid



[001480] Step 1: Synthesis of tert-butyl (1S,6S)-5-(1-(6-bromo-3-((2-(tert-butoxy)-2-oxoethyl)amino)-5-methylpyrazin-2-yl)-1,3-dioxopentan-2-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001481] To a solution of tert-butyl (5-bromo-3-(2-bromo-3-oxopentanoate)-6-methylpyrazin-2-yl)glycinate (Intermediate-24) (1.99 g, 4.15 mmol, 1.0 *eq*) in THF (10 mL) was added DIEA (1.61 g, 12.46 mmol, 3.0 *eq*) and tert-butyl (1S,6S)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (882 mg, 4.15 mmol, 1.0 *eq*), and the resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched by water (50 mL) and extracted with EtOAc (50 mL * 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous

Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (EtOAc/PE) to afford the title compound.

[001482] LCMS: 612.3 [M+H]⁺.

[001483] Step 2: Synthesis of 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid trifluoroacetate

[001484] A solution of tert-butyl (1S,6S)-5-(1-(6-bromo-3-((2-(tert-butoxy)-2-oxoethyl)amino)-5-methylpyrazin-2-yl)-1,3-dioxopentan-2-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (500 mg, 819 μmol, 1.0 eq) in TFA (10 mL) was stirred at 60 °C for 8 h. The reaction mixture concentrated in vacuo to afford the title compound, which was used into the next step without further purification.

[001485] LCMS: 436.1 [M+H]⁺.

[001486] Step 3: Synthesis of 2-(2-bromo-7-((1S,6S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[4.2.0]octan-2-yl)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid

[001487] To a solution of 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-bromo-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)acetic acid trifluoroacetate (400 mg, 917 μmol, 1.0 eq) in DCM (10 mL) was added DIEA (355 mg, 2.75 mmol, 3.0 eq) and Boc₂O (300 mg, 1.38 mmol, 1.5 eq), and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water (30 mL), and extracted with EtOAc (2 * 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by reverse phase HPLC (C18 column, water (0.1% FA)-ACN) to afford the title compound.

[001488] LCMS: 538.3 [M+H]⁺.

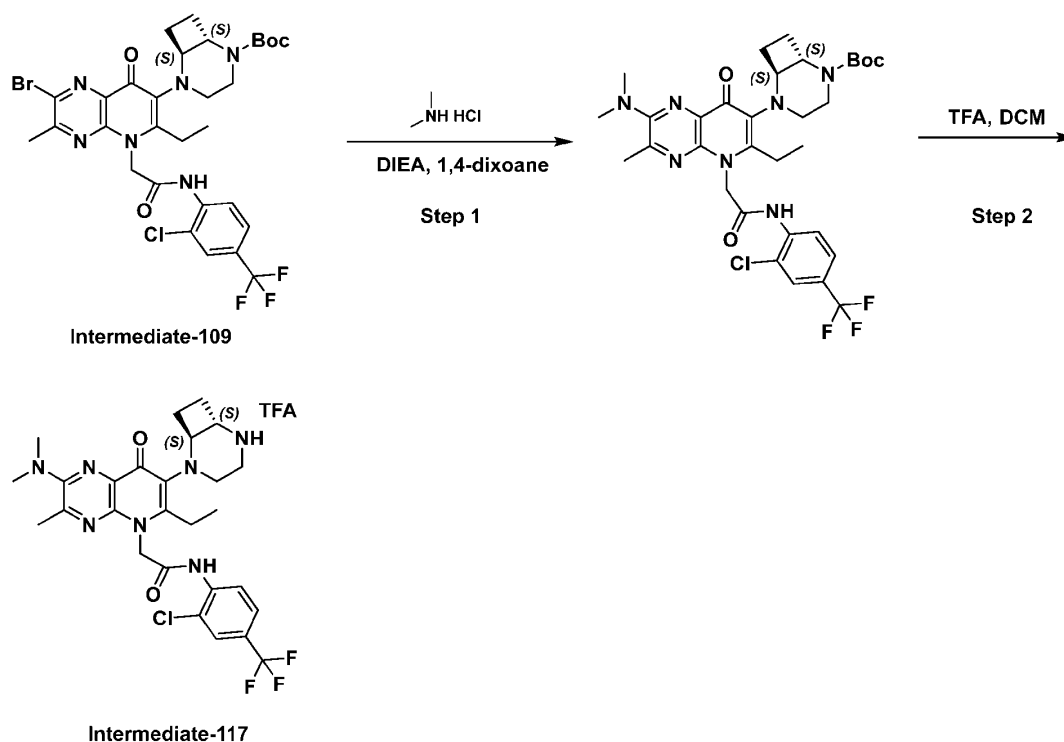
[001489] Step 4: Synthesis of tert-butyl (1S,6S)-5-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001490] To a solution of 2-[2-bromo-7-[(1S, 6S) -5-tert-butoxycarbonyl-2, 5-diazabicyclo[4.2.0]octan-2-yl]-6-ethyl-3-methyl-8-oxo-pyrido[2, 3-b]pyrazin-5-yl]acetic acid (Intermediate-116) (240 mg, 447 μmol, 1.0 eq) and 2-chloro-4-(trifluoromethyl)aniline (105 mg, 537 μmol, 1.2 eq) in DCM (3 mL) and pyridine (3 mL) was added POCl₃ (103 mg, 671 μmol, 1.5 eq) at -10 °C, and the resulting mixture was stirred at -10 °C for 10 min. The reaction mixture was quenched by H₂O (20 mL) and extracted with EtOAc (25 mL * 3). The combined organic layers

were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography (Eluent of EtOAc/PE) to afford the title compound.

[001491] LCMS: 715.2 $[\text{M}+\text{H}]^+$.

[001492] Intermediate-117: 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(dimethylamino)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate



[001493] Step 1: Synthesis of tert-butyl (1S,6S)-5-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(dimethylamino)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate

[001494] To a solution of tert-butyl (1S,6S)-5-(2-bromo-5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (Intermediate-109) (180 mg, 252 μmol , 1.0 eq) in 1,4-dioxane (2 mL) was added dimethylamine hydrochloride (103 mg, 1.26 mmol, 5.0 eq) and DIEA (163 mg, 1.26 mmol, 5.0 eq), the resulting mixture was stirred at 100

°C overnight. The reaction mixture was poured into water (20 mL), extracted with EtOAc (30 mL*3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the title compound, which was used into the next step without further purification.

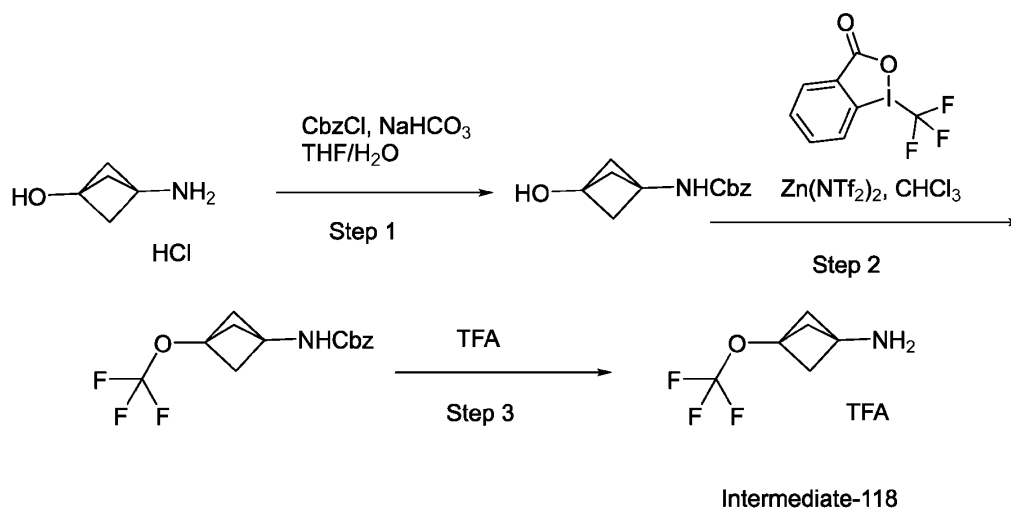
[001495] LCMS: 678.5 [M+H]⁺.

[001496] Step 2: Synthesis of 2-(7-((1S,6S)-2,5-diazabicyclo[4.2.0]octan-2-yl)-2-(dimethylamino)-6-ethyl-3-methyl-8-oxopyrido[2,3-b]pyrazin-5(8H)-yl)-N-(2-chloro-4-(trifluoromethyl)phenyl)acetamide trifluoroacetate

[001497] To a solution of tert-butyl (1S,6S)-5-(5-(2-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-(dimethylamino)-6-ethyl-3-methyl-8-oxo-5,8-dihydropyrido[2,3-b]pyrazin-7-yl)-2,5-diazabicyclo[4.2.0]octane-2-carboxylate (120 mg, 177 μmol, 1.0 eq) in DCM (2 mL) was added TFA (2 mL), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo to afford the title compound, which was used into the next step without further purification.

[001498] LCMS: 578.3 [M+H]⁺.

[001499] Intermediate-118: 3-(trifluoromethoxy)bicyclo[1.1.1]pentan-1-amine trifluoroacetate



[001500] Step 1. Synthesis of benzyl (3-hydroxybicyclo[1.1.1]pentan-1-yl)carbamate

[001501] To a suspension of 3-aminobicyclo[1.1.1]pentan-1-ol hydrochloride (530 mg, 3.91 mmol, 1 eq) in THF (5.4 mL) and H₂O (2.7 mL) was added NaHCO₃ (985 mg, 11.73 mmol, 3 eq)

at 20 °C. The mixture was cooled to 0 °C, then CbzCl (733 mg, 4.30 mmol, 613 µL, 1.1 eq) was added dropwise at 0 °C under N₂ atmosphere. The resulting mixture was stirred at 0 °C for 15 min, then warmed to 20 °C and stirred at 20 °C for 16 h under N₂ atmosphere. The mixture was diluted with brine (10 mL) and then extracted with EtOAc (3 x 10 ml). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

[001502] LCMS: 234.0 [M+H]⁺.

[001503] Step 2. Synthesis of benzyl (3-(trifluoromethoxy)bicyclo[1.1.1]pentan-1-yl)carbamate

[001504] To a solution of benzyl N-(3-hydroxy-1-bicyclo[1.1.1]pentanyl)carbamate (610 mg, 2.62 mmol, 1 eq) and Zn(NTf₂)₂ (1.96 g, 3.14 mmol, 1.2 eq) in CHCl₃ (5 mL) was added 1-(trifluoromethyl)-1,2-benziodoxol-3-one (992 mg, 3.14 mmol, 1.2 eq). The mixture was stirred at 25 °C for 16 h. The mixture was filtered and the filter cake was washed with DCM (2 x 5 mL). The combined filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of EtOAc / PE) to afford the title compound.

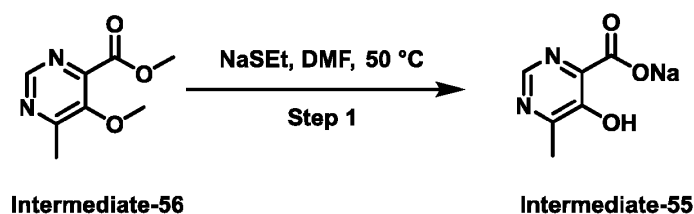
[001505] LCMS: 324.0 [M+Na]⁺.

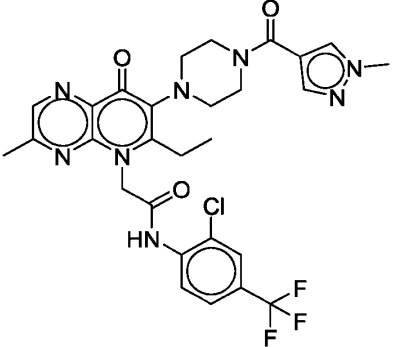
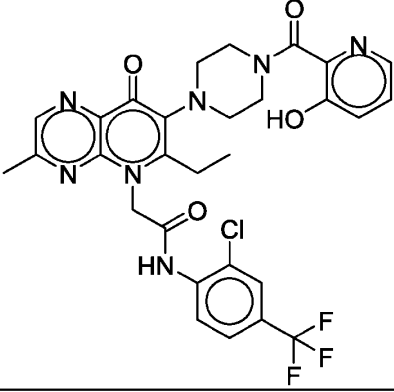
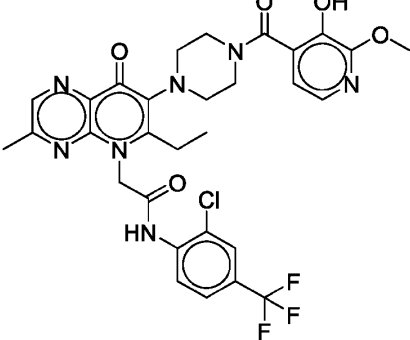
[001506] Step 3. Synthesis of 3-(trifluoromethoxy)bicyclo[1.1.1]pentan-1-amine trifluoroacetate

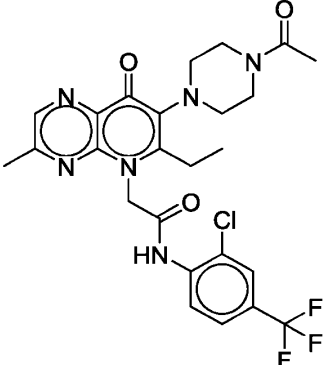
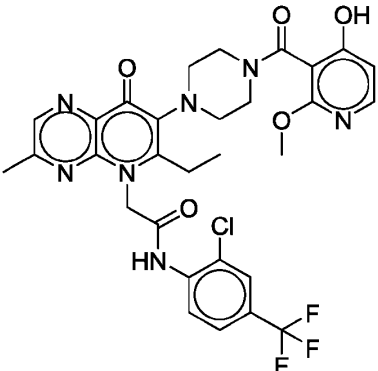
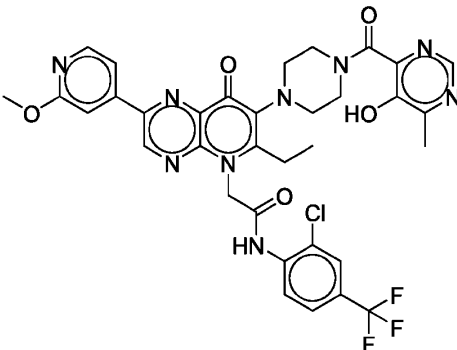
[001507] A solution of benzyl N-[3-(trifluoromethoxy)-1-bicyclo[1.1.1]pentanyl]carbamate (100 mg, 330 μ mol, 1eq) in TFA (3 mL) was stirred at 70 °C for 5 h. The mixture was concentrated under reduced pressure to afford the title compound, which was used directly in the next step without further purification.

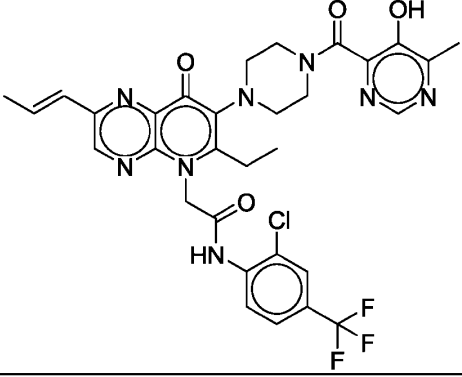
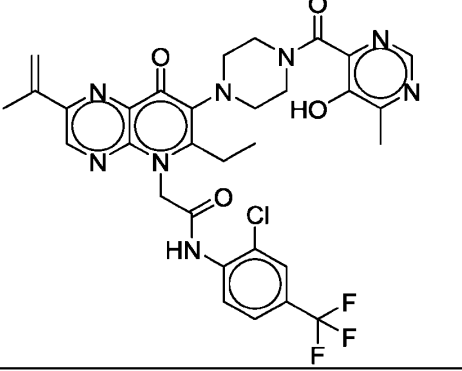
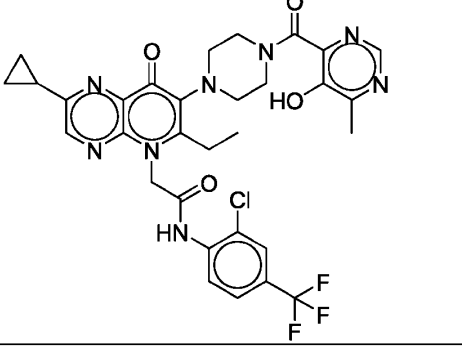
[001508] LCMS: 168.0 [M+H]⁺.

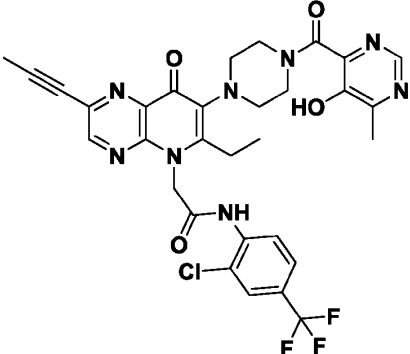
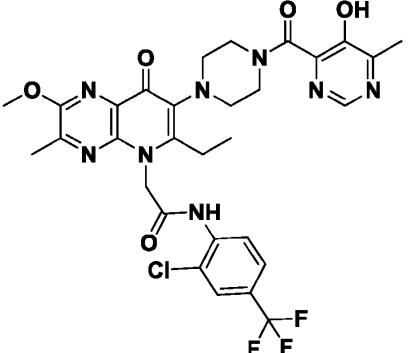
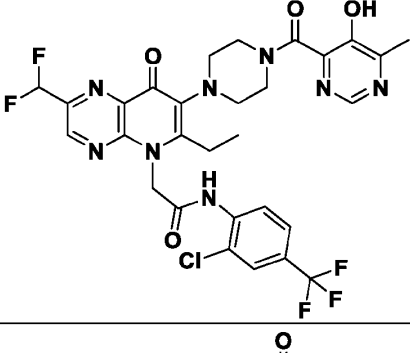
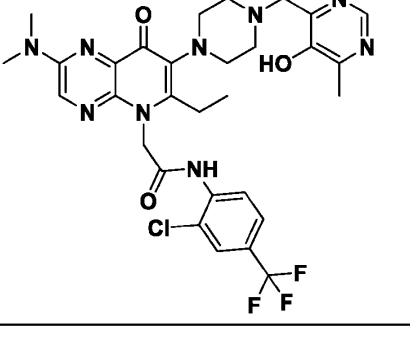
[001509] Alternative procedure for Intermediate-55: sodium 5-hydroxy-6-methylpyrimidine-4-carboxylate

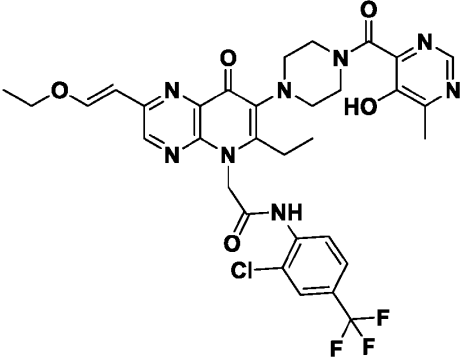
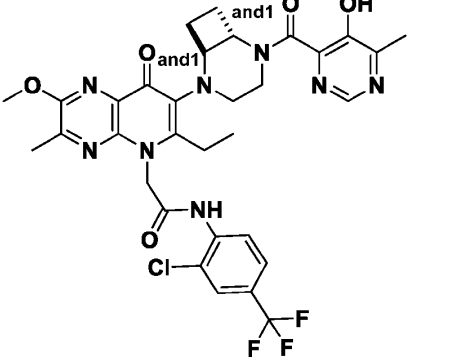
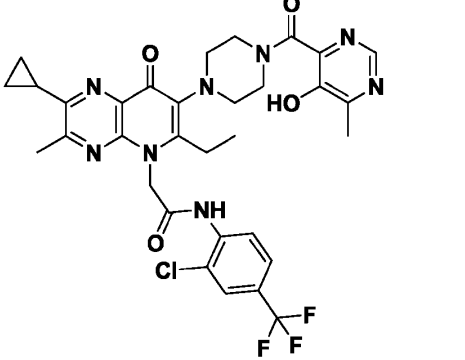


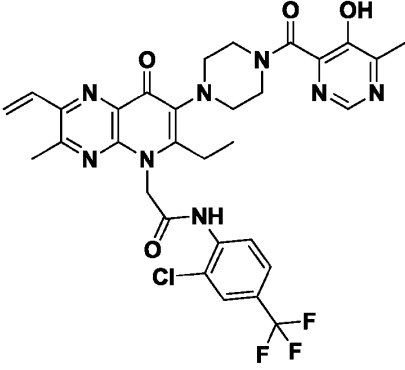
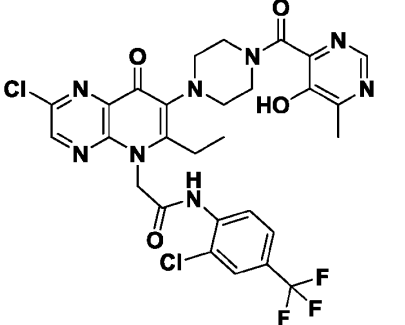
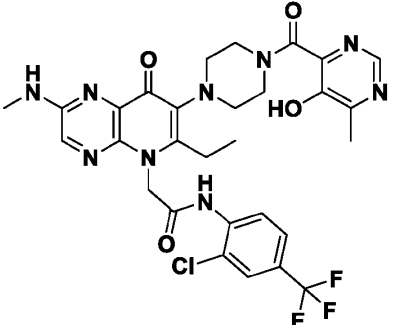
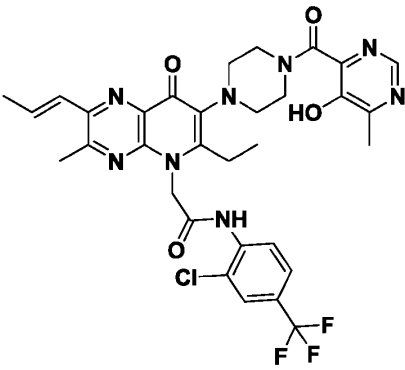
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I-3		LCMS 1	630.2	0.537
I-4		LCMS 1	660.4	0.585

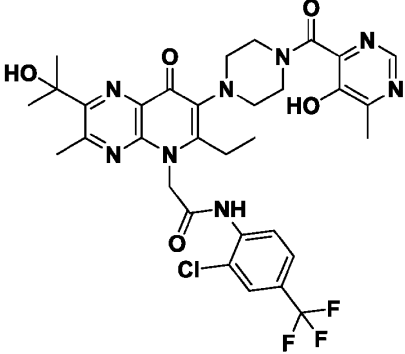
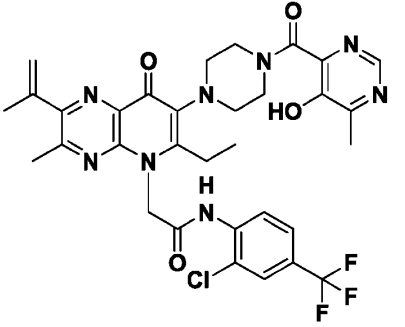
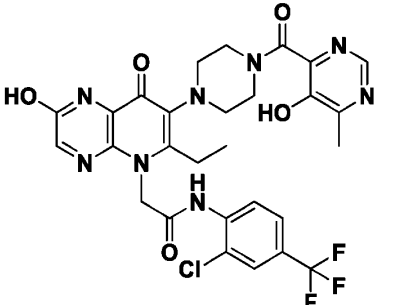
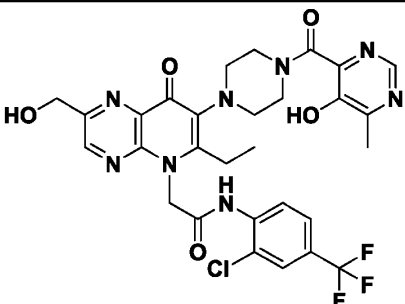
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I-6		LCMS 1	660.2	0.533
I-7		LCMS 1	738.2	0.576

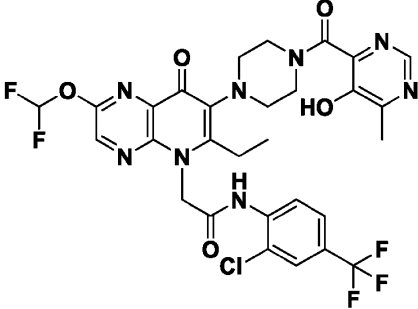
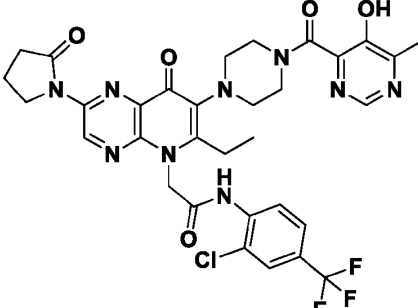
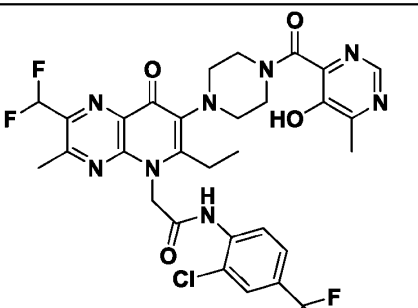
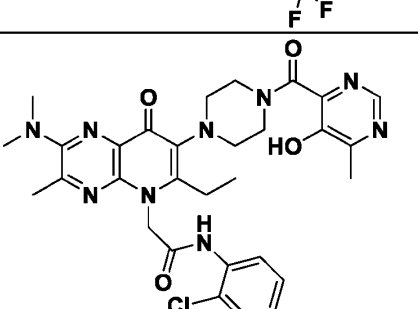
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I-9		LCMS 1	671.2	0.576
I-10		LCMS 1	671.4	0.594

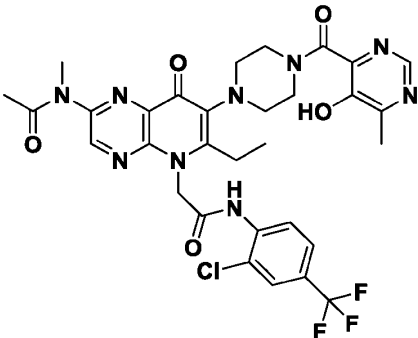
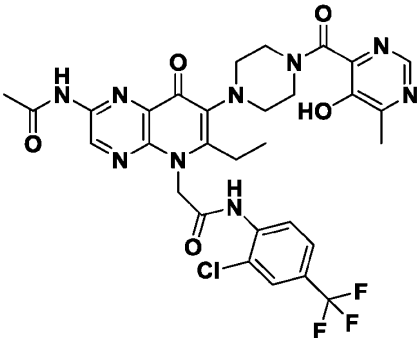
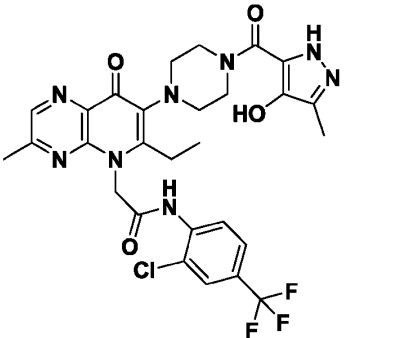
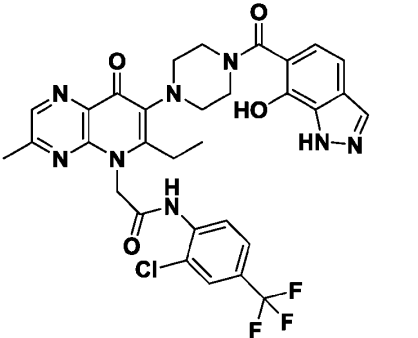
I-11		LCMS 1	669.4	0.598
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I-13		LCMS 1	681.2	0.566
I-14		LCMS 1	674.4	0.568

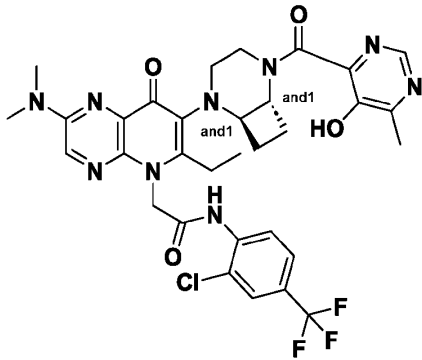
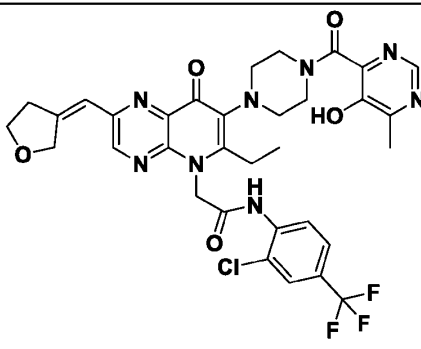
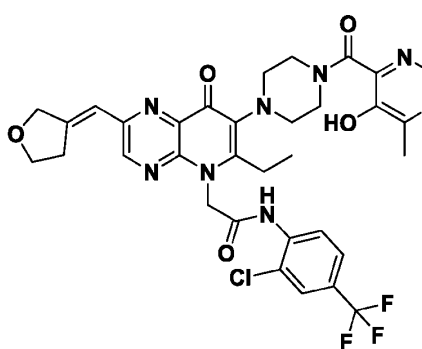
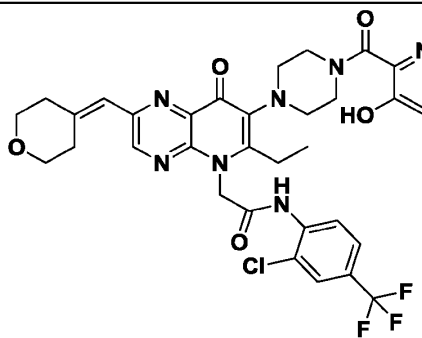
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I-17		LCMS 1	685.2	0.583

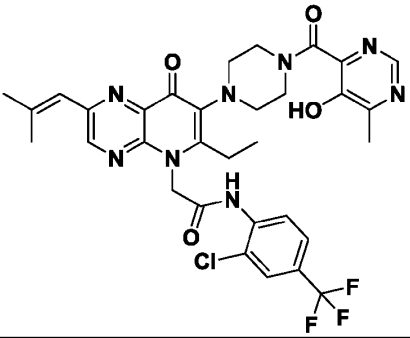
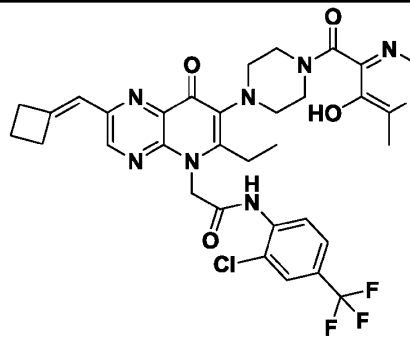
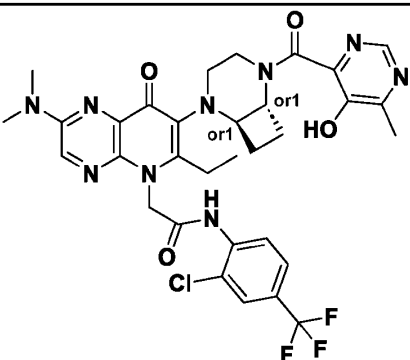
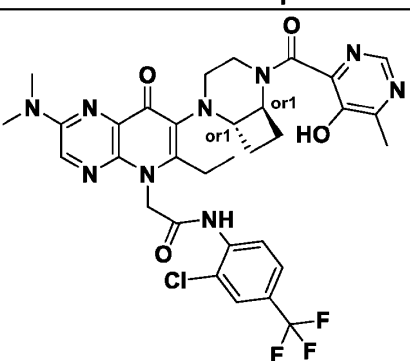
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I-20		LCMS 1	660.4	0.549
I-21		LCMS 1	685.2	0.594

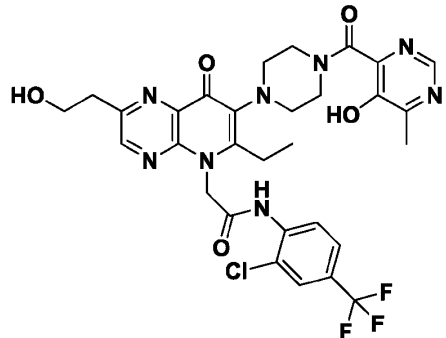
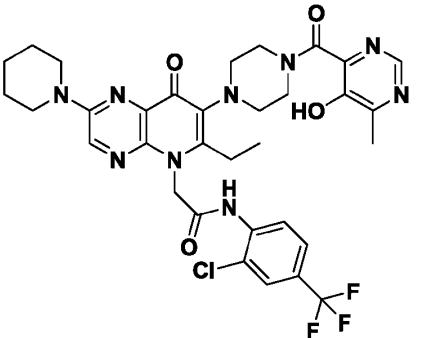
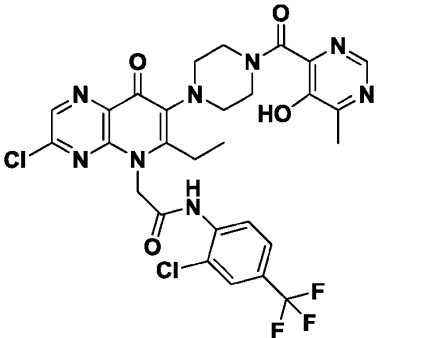
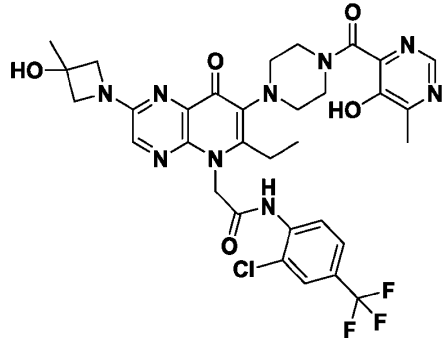
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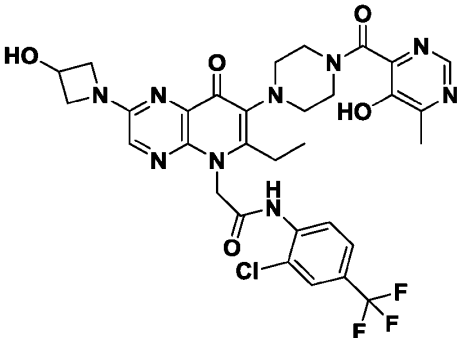
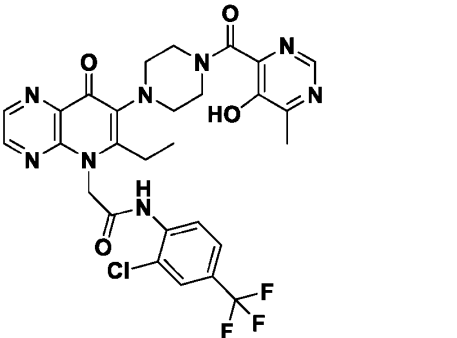
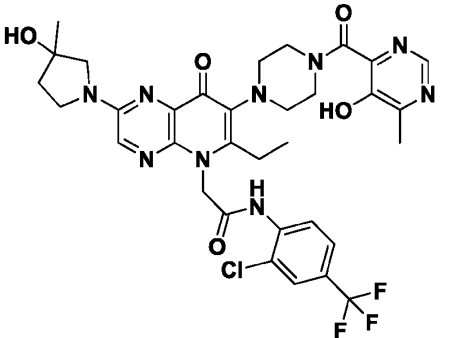
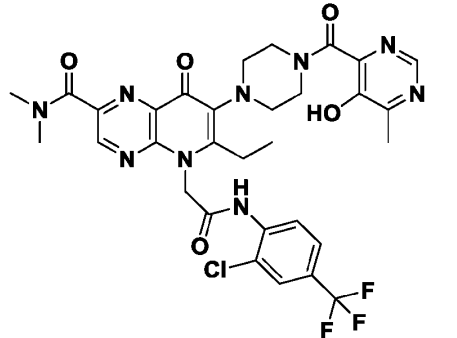
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I-29		LCMS 1	688.2	0.599

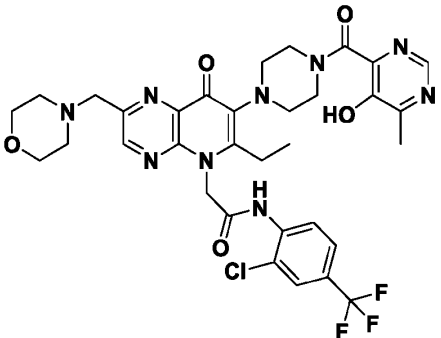
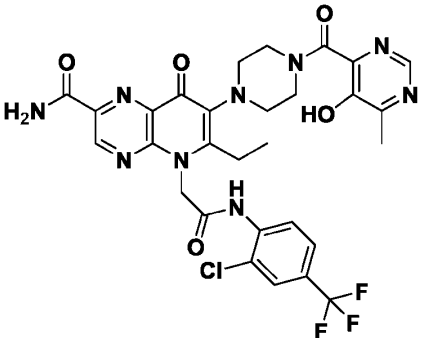
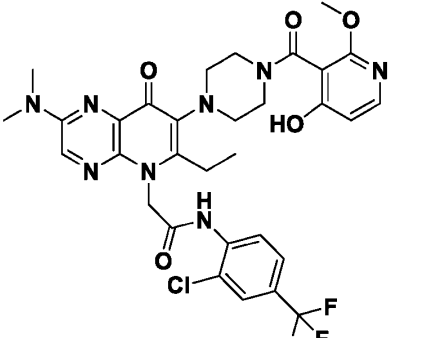
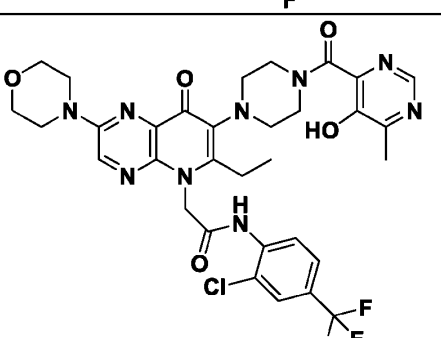
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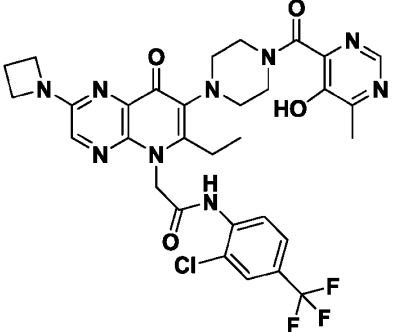
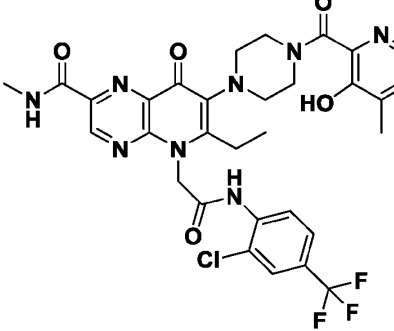
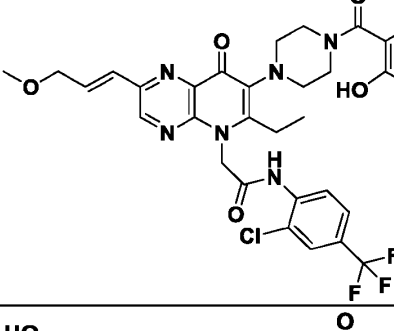
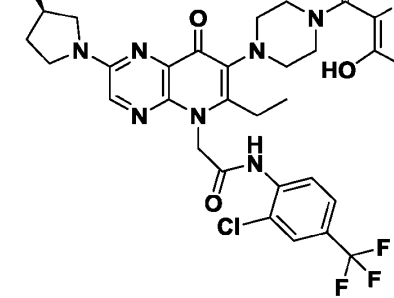
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I-35	 (A)			
	 (B)	LCMS 1	713.2	0.568
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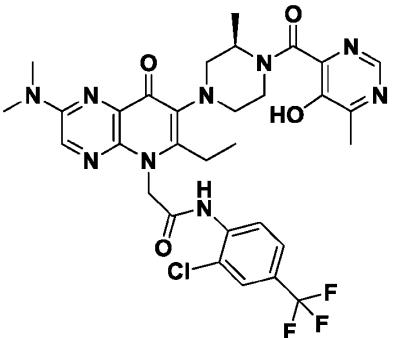
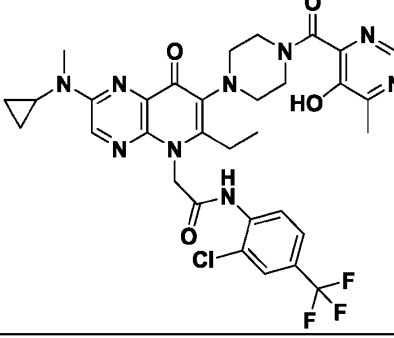
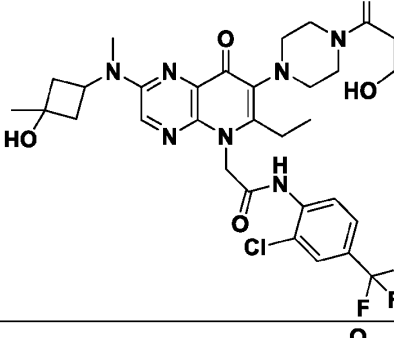
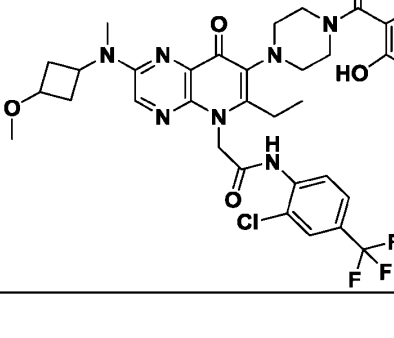
I-37		LCMS 1	685.2	0.597
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I-39		LCMS 1	700.4	0.593
I-40		LCMS 1	700.4	0.59

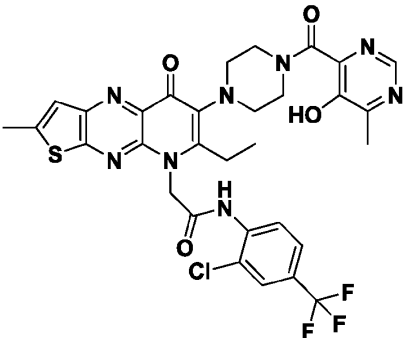
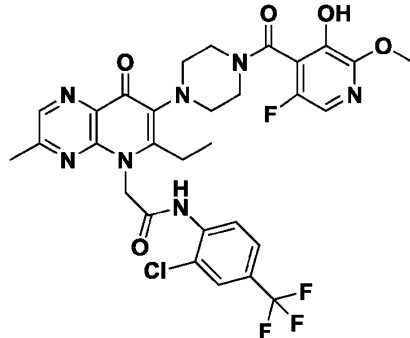
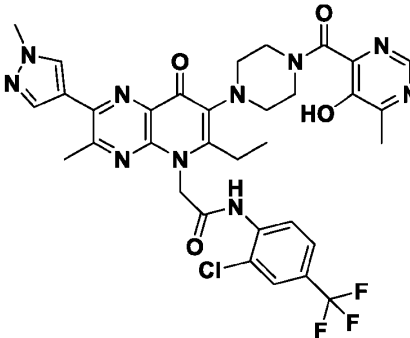
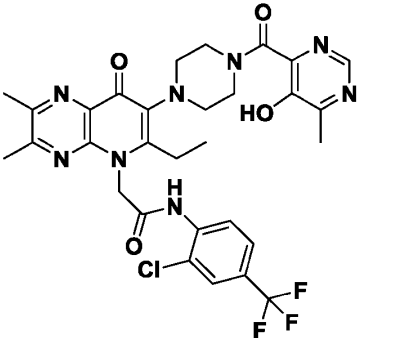
I-41		LCMS 1	675.2	0.532
I-42		LCMS 1	714.3	0.610
I-43		LCMS 1	665.1	0.562
I-44		LCMS 1	716.2	0.537

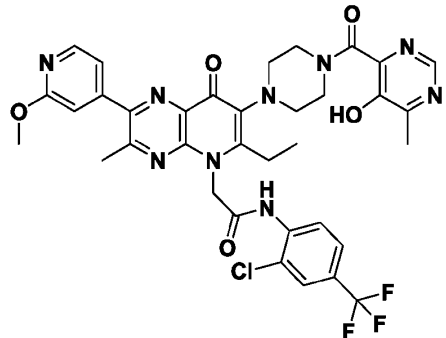
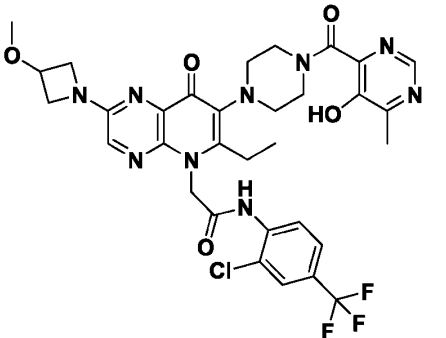
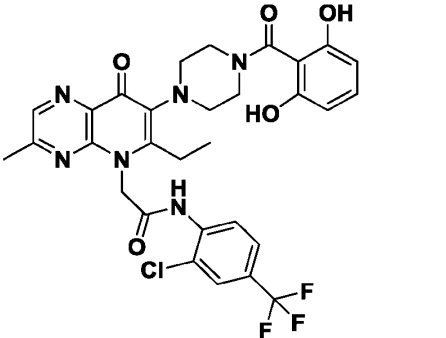
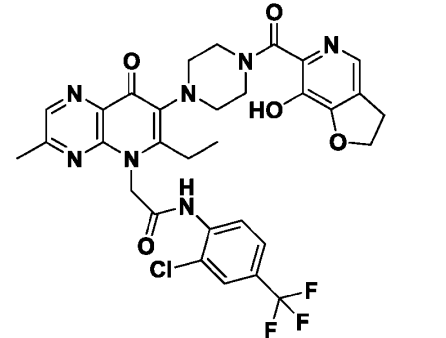
I-45		LCMS 1	702.2	0.530
I-46		LCMS 1	631.1	0.537
I-47		LCMS 1	730.2	0.538
I-48		LCMS 1	702.2	0.538

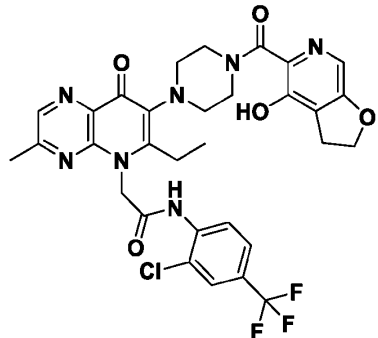
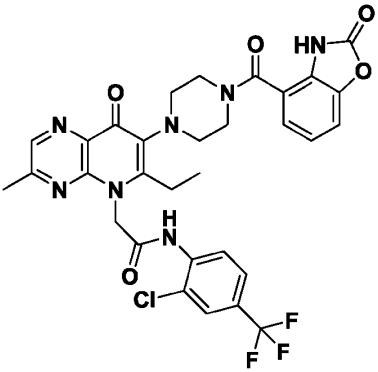
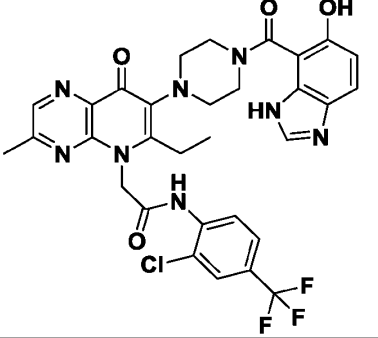
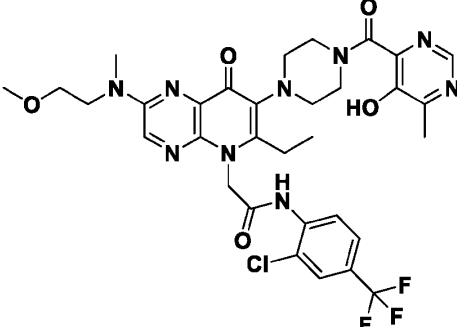
I-49		LCMS 1	730.2	0.509
I-50		LCMS 1	674.2	0.536
I-51		LCMS 1	689.2	0.536
I-52		LCMS 1	716.2	0.554

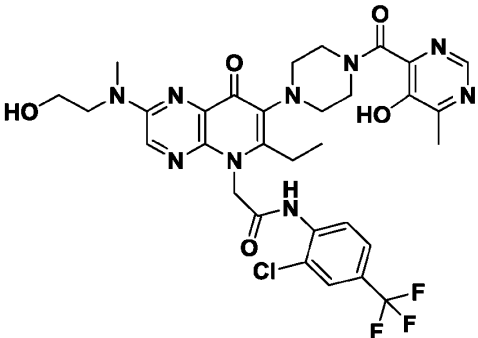
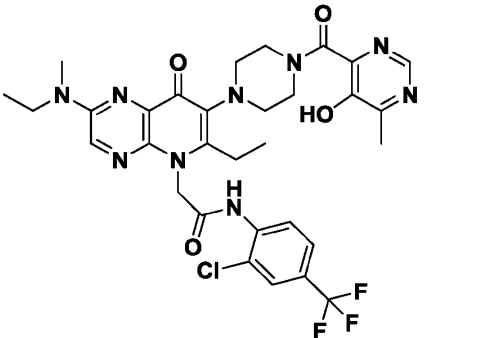
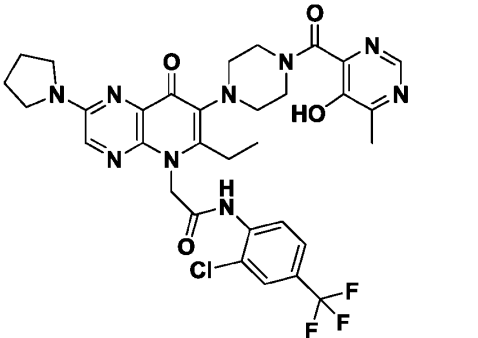
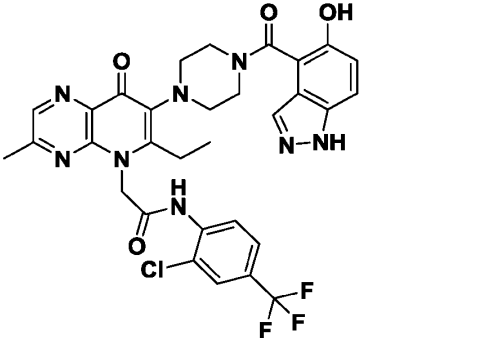
I-53		LCMS 1	686.2	0.561
I-54		LCMS 1	688.2	0.547
I-55		LCMS 1	701.2	0.573
I-56		LCMS 1	716.2	0.526

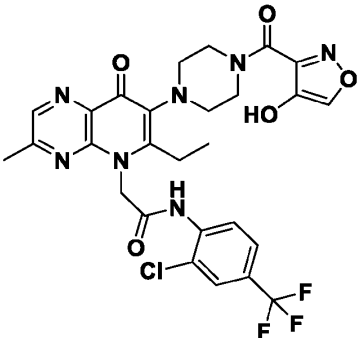
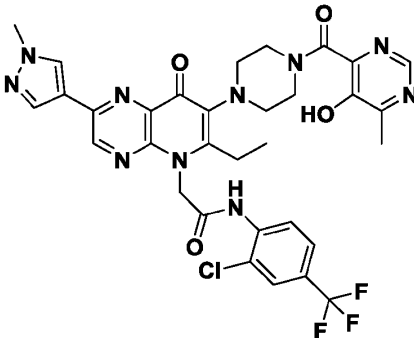
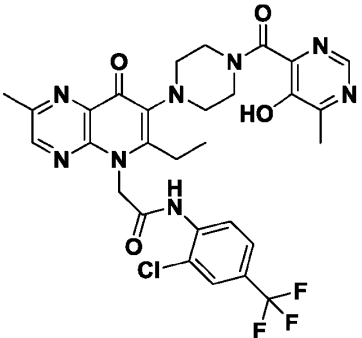
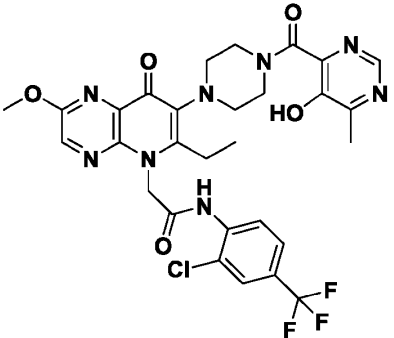
I-57		LCMS 1	688.2	0.559
I-58		LCMS 1	700.3	0.575
I-59		LCMS 1	744.4	0.561
I-60		LCMS 1	744.5	0.581

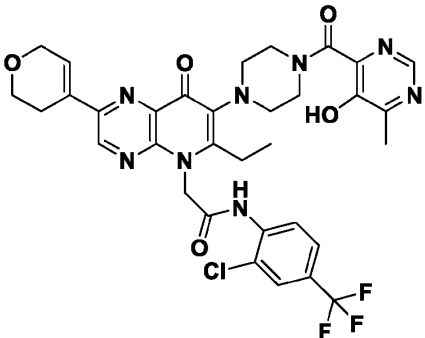
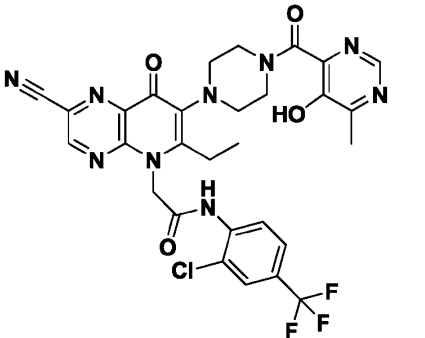
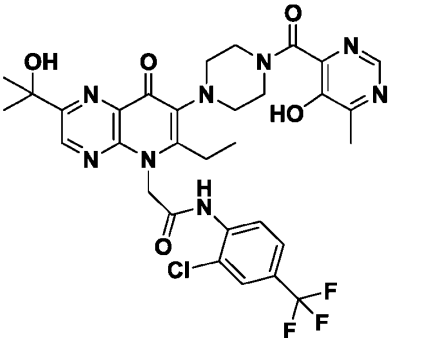
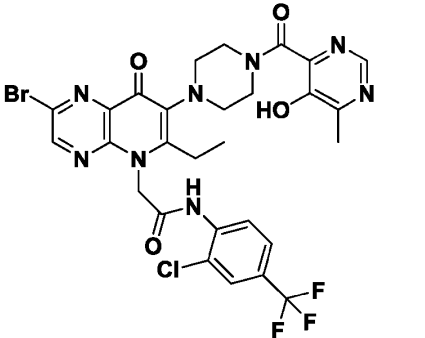
I-61		LCMS 4	701.2	0.432
I-62		LCMS 1	678.4	0.589
I-63		LCMS 1	725.4	0.590
I-64		LCMS 1	659.2	0.559

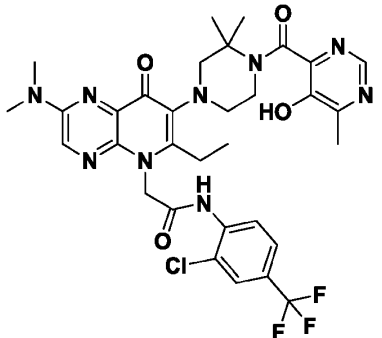
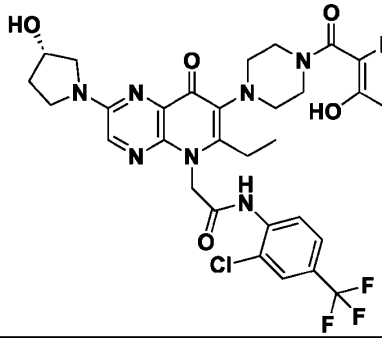
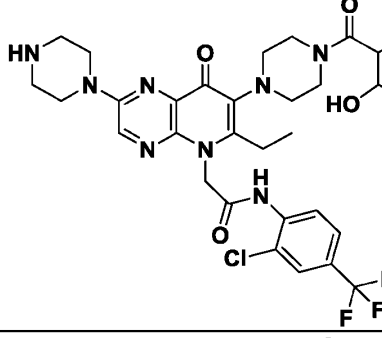
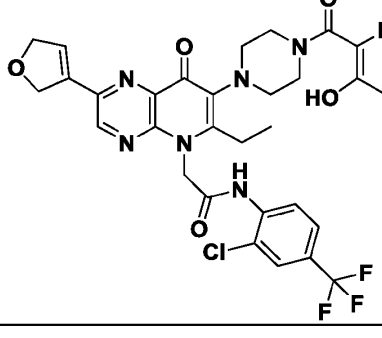
I-65		LCMS 1	752.2	0.871
I-66		LCMS 1	716.3	0.577
I-67		LCMS 1	645.4	0.563
I-68		LCMS 3	672.25	1.310

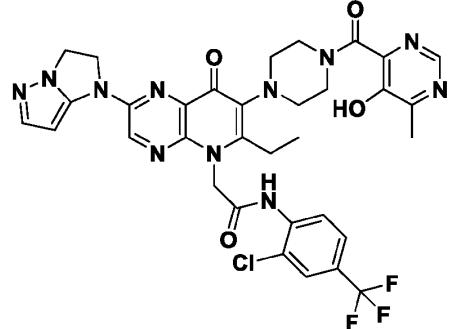
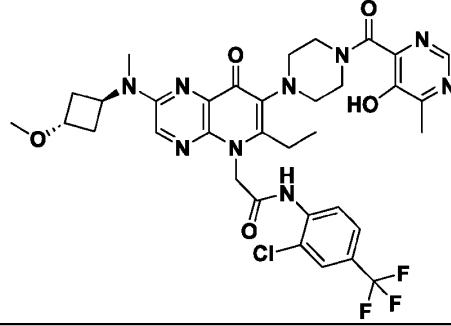
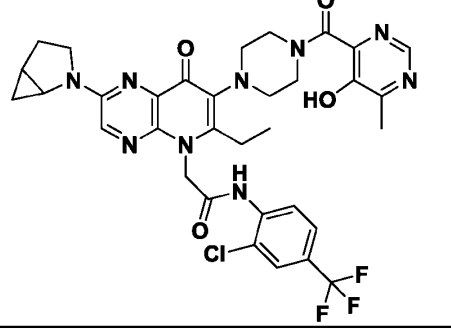
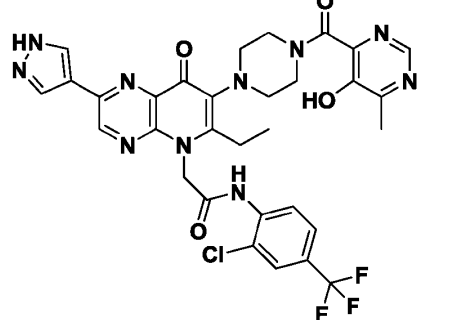
I-69		LCMS 2	672.25	0.840
I-70		LCMS 1	670.3	0.600
I-71		LCMS 1	669.3	0.536
I-72		LCMS 1	718.2	0.858

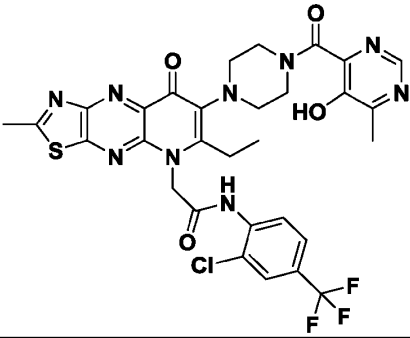
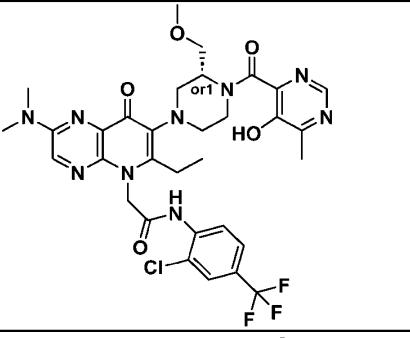
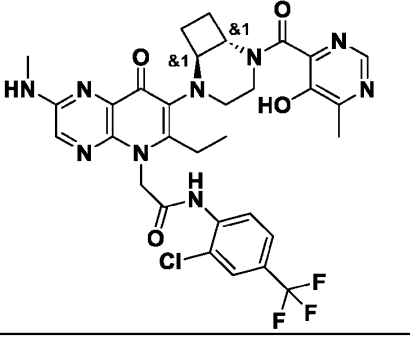
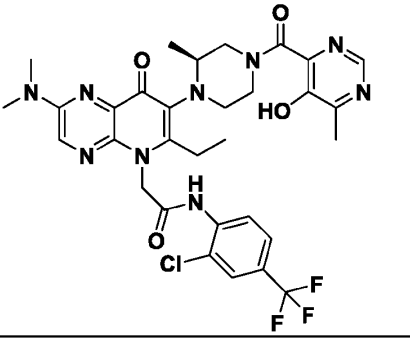
I-73		LCMS 1	704.2	0.828
I-74		LCMS 1	688.4	0.580
I-75		LCMS 1	700.4	0.583
I-76		LCMS 1	669.2	0.538

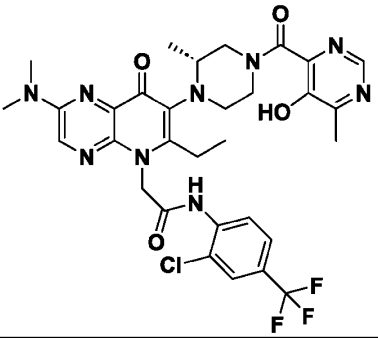
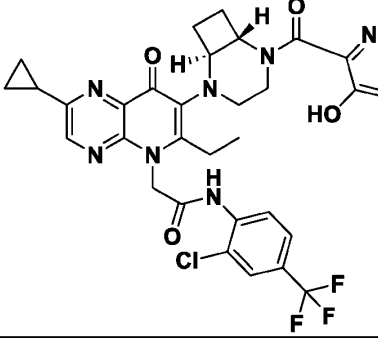
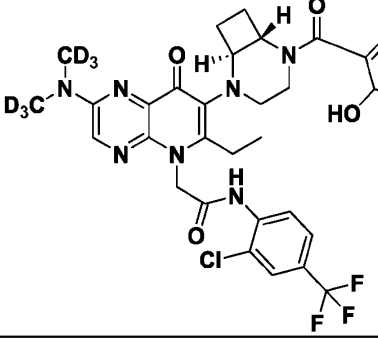
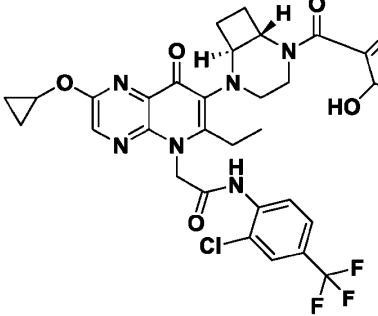
I-77		LCMS 1	620.1	0.550
I-79		LCMS 1	711.2	0.837
I-80		LCMS 1	645.2	0.550
I-81		LCMS 1	661.1	0.558

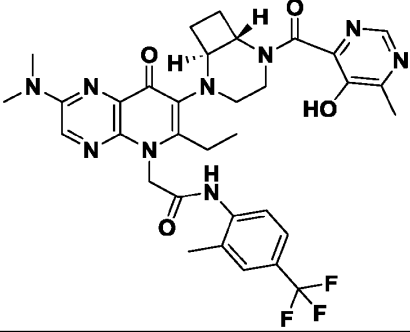
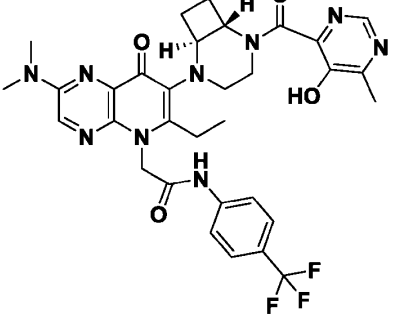
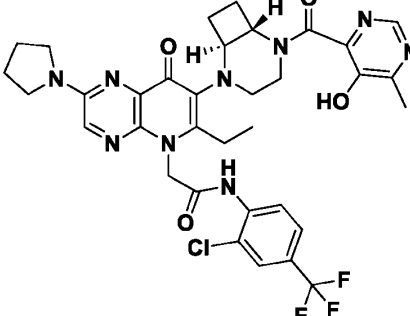
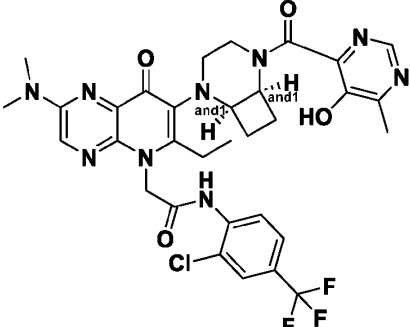
I-82		LCMS 1	713	0.889
I-83		LCMS 1	656.2	0.555
I-84		LCMS 1	689.2	0.550
I-86		LCMS 1	711.2	0.598

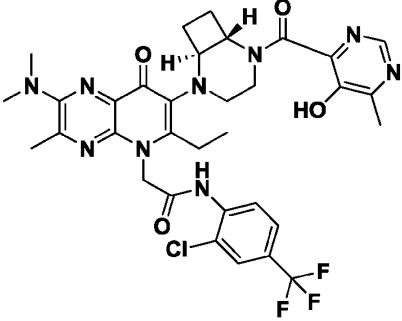
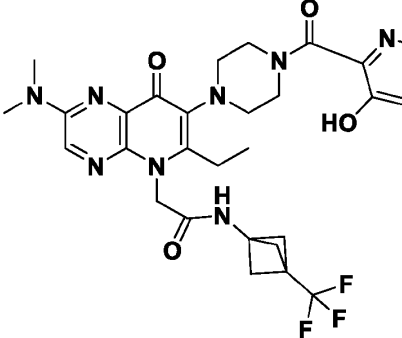
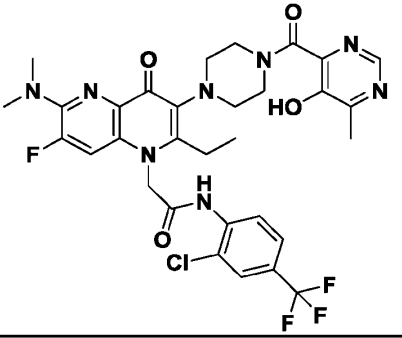
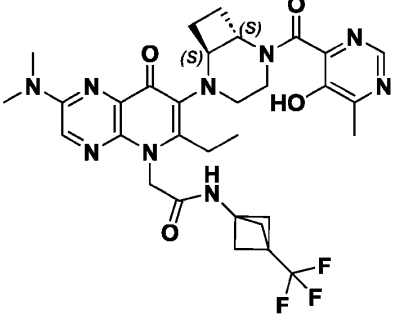
I-87		LCMS 1	702.5	0.590
I-88		LCMS 1	716.3	0.527
I-89		LCMS 1	715.3	0.498
I-90		LCMS 1	699.2	0.551

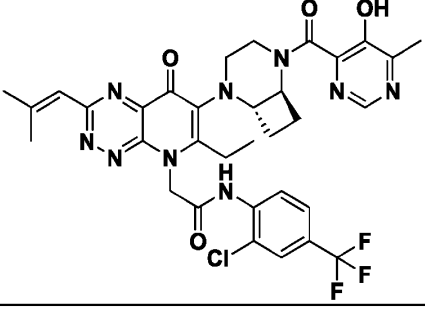
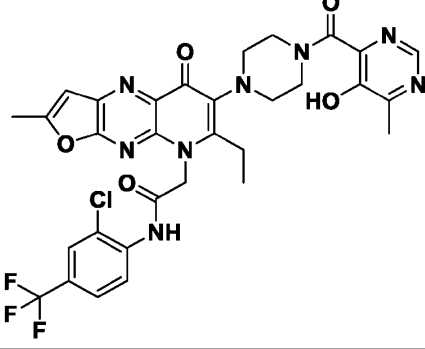
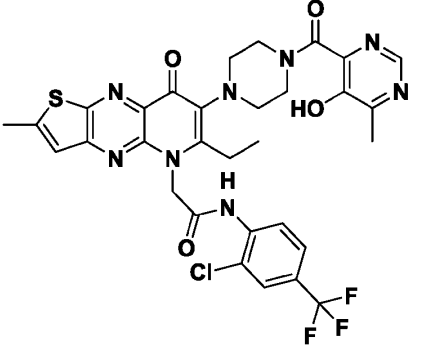
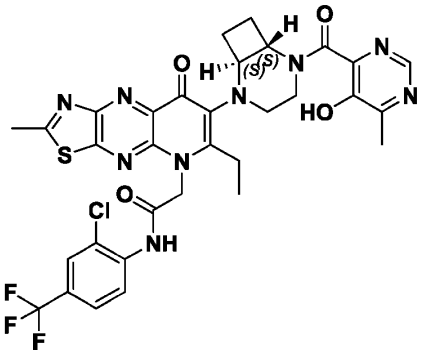
I-91		LCMS 1	738.2	0.553
I-92		LCMS 1	744.2	0.568
I-93		LCMS 1	712.2	0.571
I-94		LCMS 1	697.2	0.539

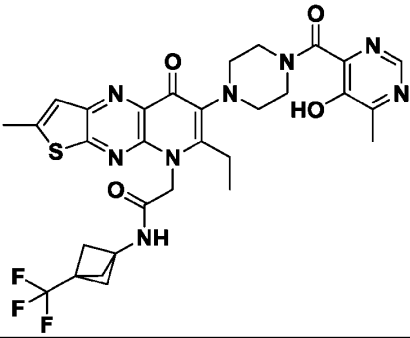
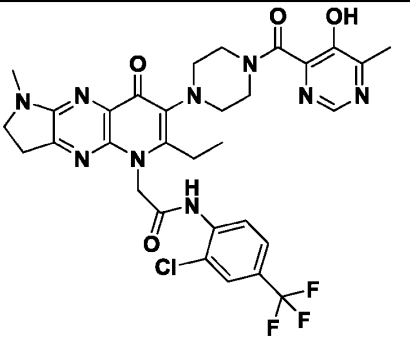
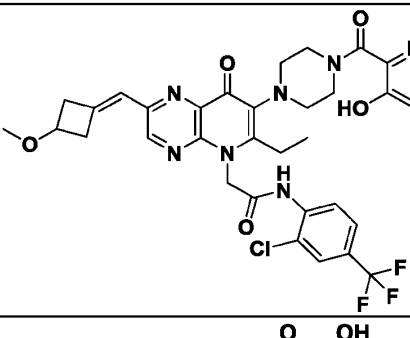
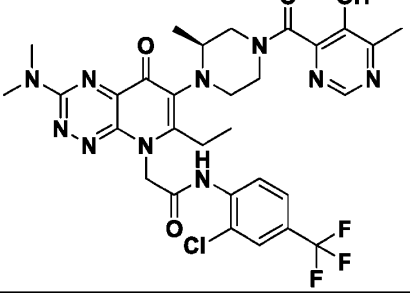
I-95		LCMS 1	702.3	0.542
I-96		LCMS 1	718.2	0.553
I-97		LCMS 1	686.2	0.543
I-98		LCMS 1	688.2	0.551

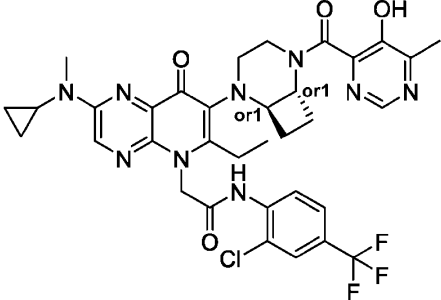
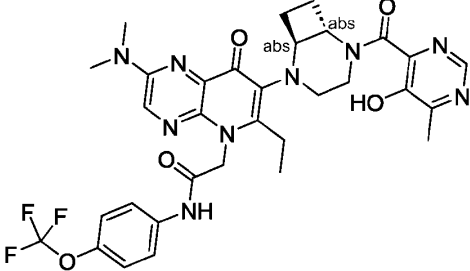
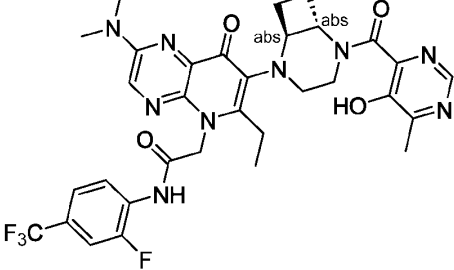
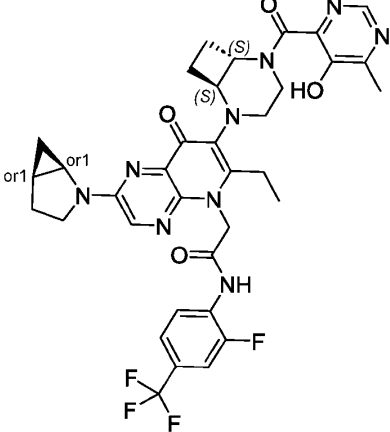
I-99		LCMS 1	688.2	0.544
I-100		LCMS 1	697.2	2.38
I-101		LCMS 1	706.5	0.59
I-102		LCMS 1	713.2	2.42

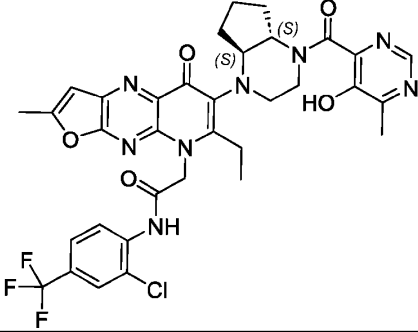
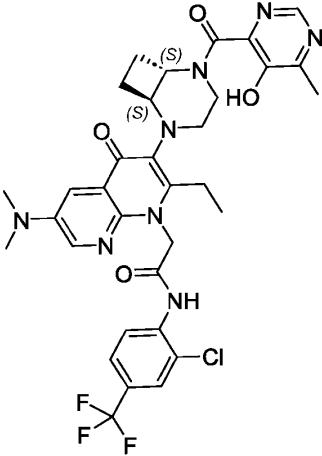
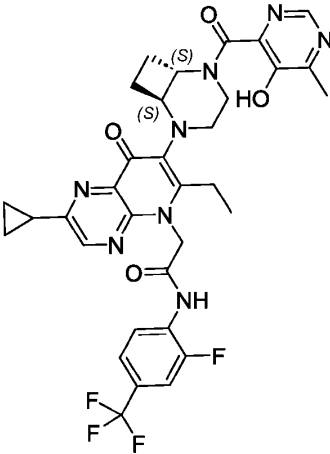
I-103		LCMS 1	680.3	2.17
I-104		LCMS 1	666.2	2.09
I-105		LCMS 1	726.2	2.31
I-106		LCMS 1	700.2	2.25

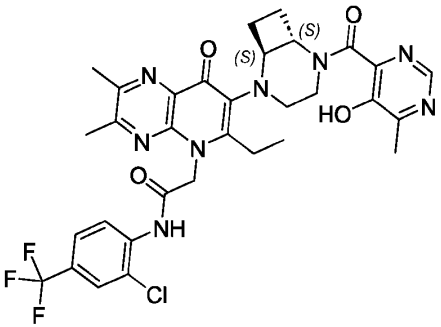
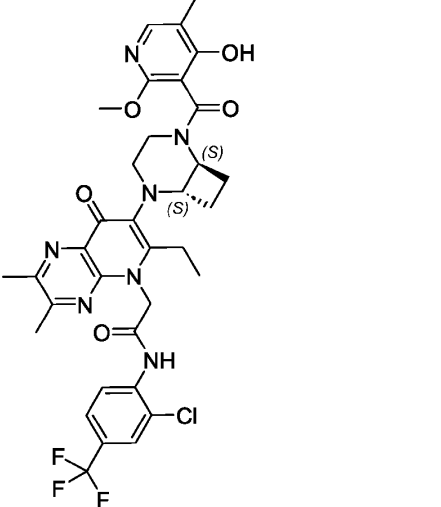
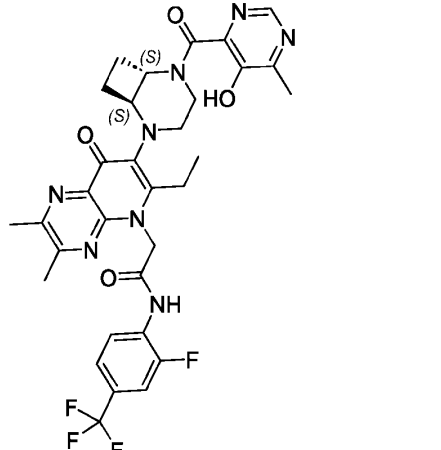
I-107		LCMS 1	714.3	2.31
I-108		LCMS 1	630.3	0.506
I-109		LCMS 1	691.3	0.53
I-110		LCMS 1	656.5	0.561

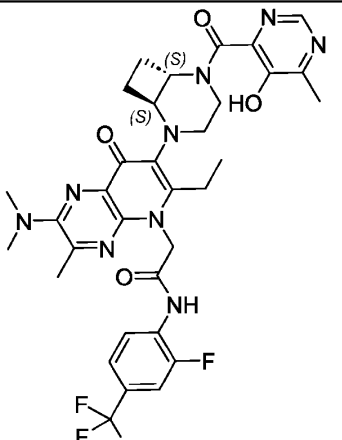
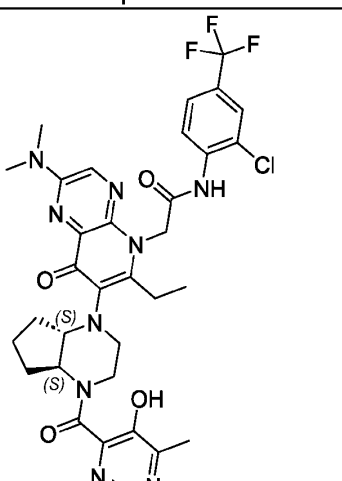
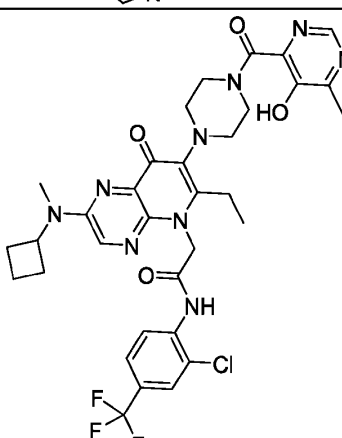
I-111		LCMS 1	712.2	2.47
I-112		LCMS 1	685.3	0.54
I-113		LCMS 1	701.3	0.558
I-114		LCMS 1	728.2	0.572

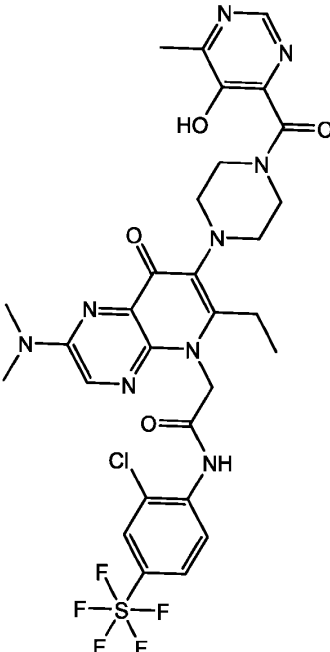
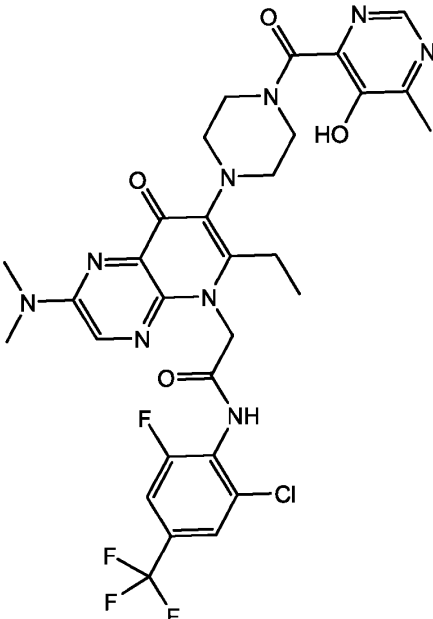
I-115		LCMS 1	657.3	0.519
I-116		LCMS 1	686.5	0.554
I-117		LCMS 1	727.2	0.585
I-118		LCMS 1	689.4	0.6

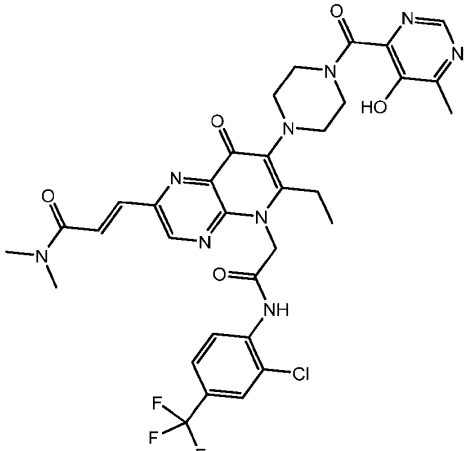
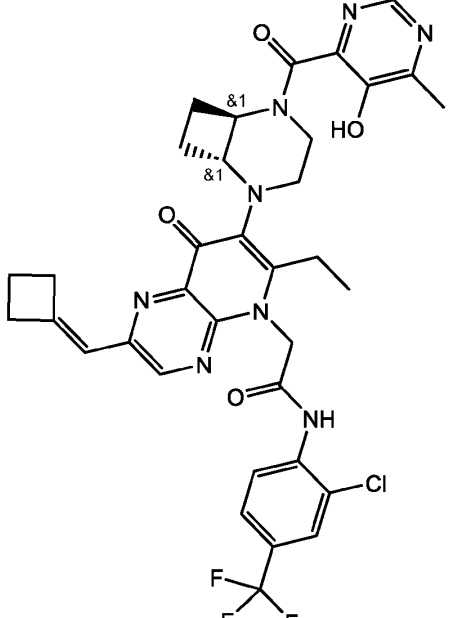
I-119		LCMS 1	726.2	0.586
I-120		LCMS 1	682.3	2.16
I-121		LCMS 1	684.3	2.18
I-122		LCMS 1	722.3	2.24

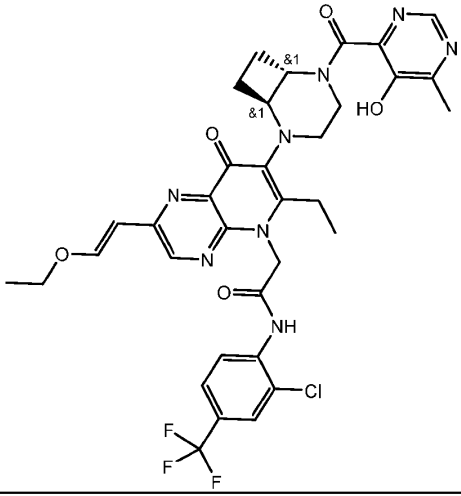
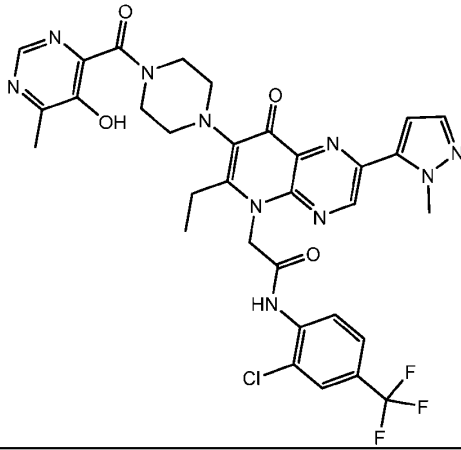
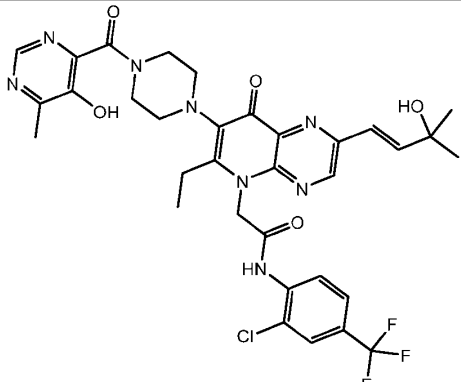
I-123		LCMS 4	725.3	0.41
I-124		LCMS 2	699.4	1.01
I-125		LCMS 1	681.3	2.28

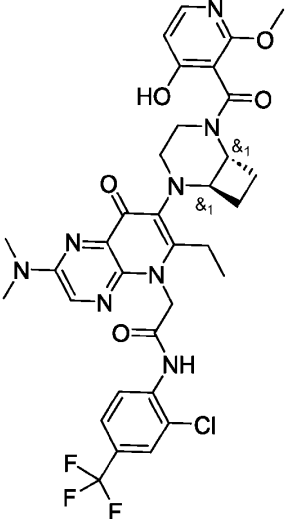
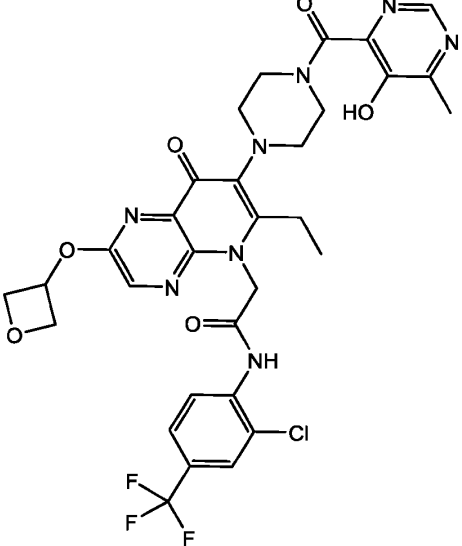
I-126		LCMS 1	685.3	2.28
I-127		LCMS 1	714.2	0.57
I-128		LCMS 1	699.3	2.18

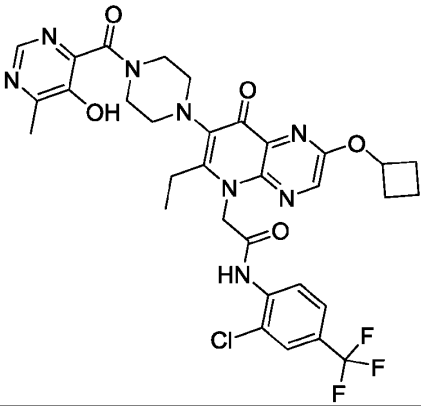
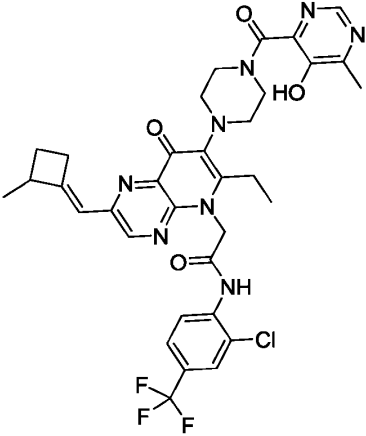
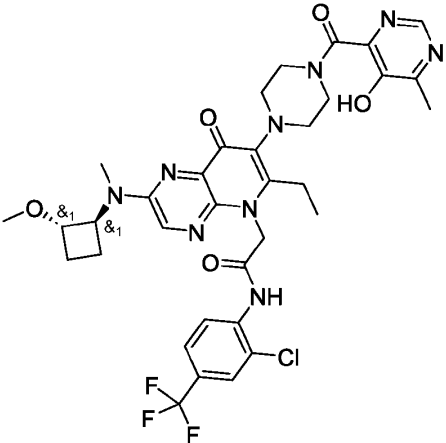
I-129		LCMS 1	698.3	2.21
I-130		LCMS 4	714.3	0.43
I-131		LCMS 1	714.4	0.60

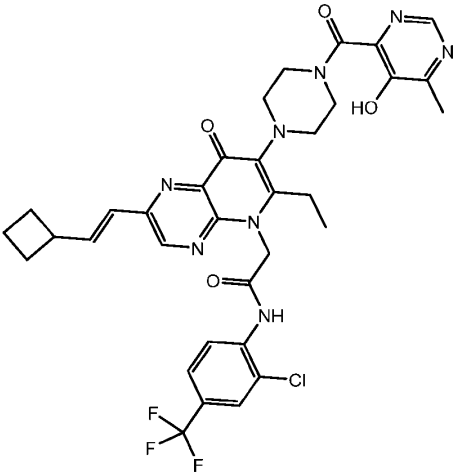
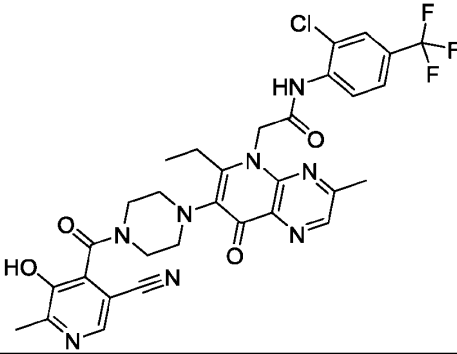
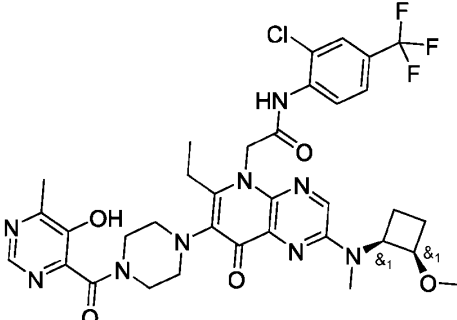
I-132		LCMS 1	732.1	0.56
I-133		LCMS 1	692.4	0.54

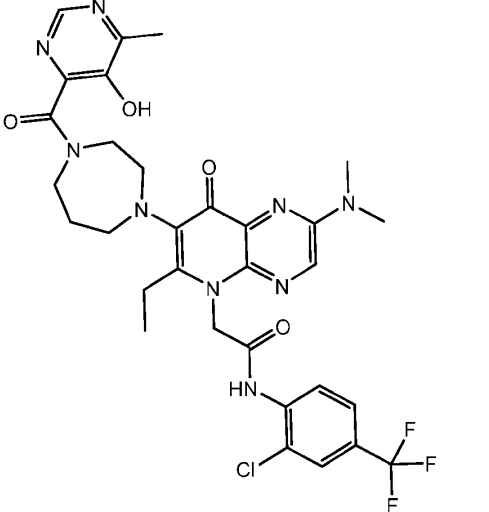
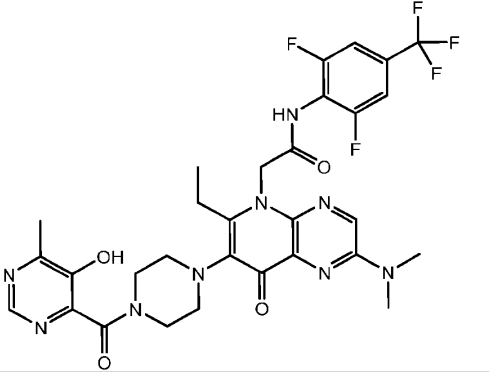
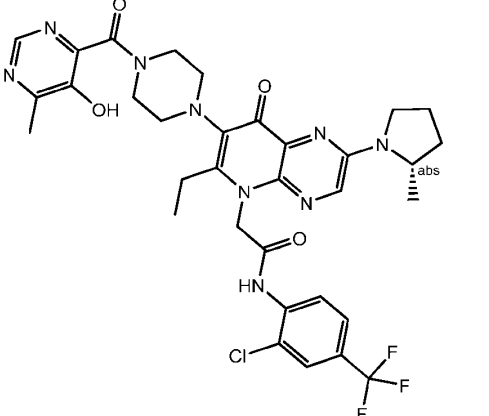
I-134		LCMS 1	728.4	0.57
I-135		LCMS 1	723.2	0.63

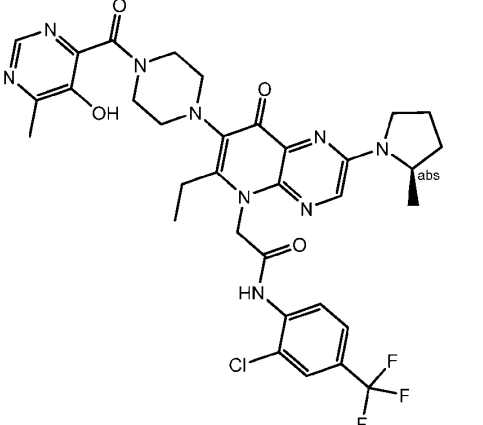
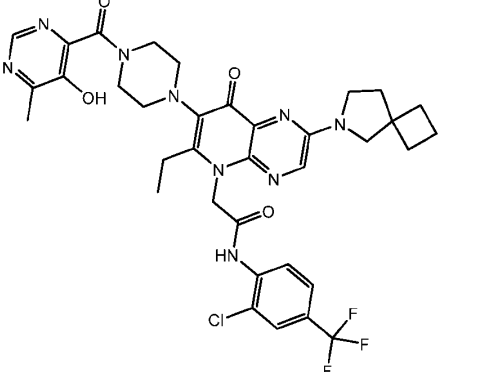
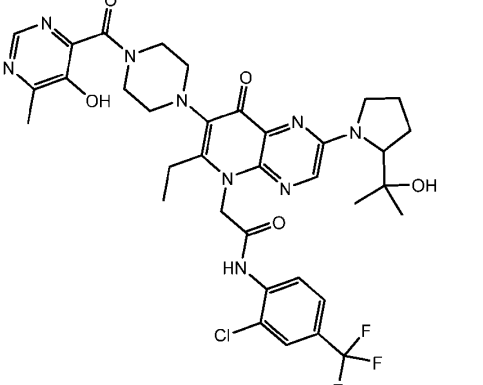
I-136		LCMS 1	727.2	0.61
I-137		LCMS 1	711.1	0.56
I-138		LCMS 1	715.2	0.55

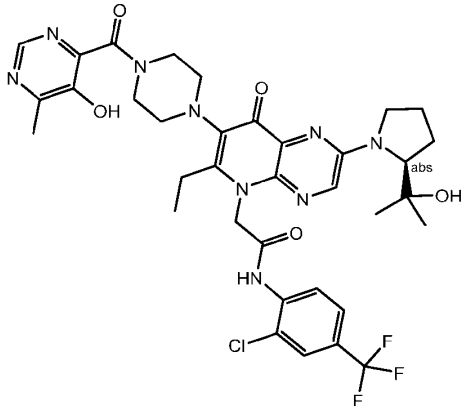
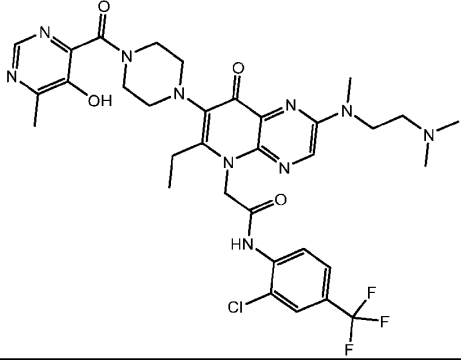
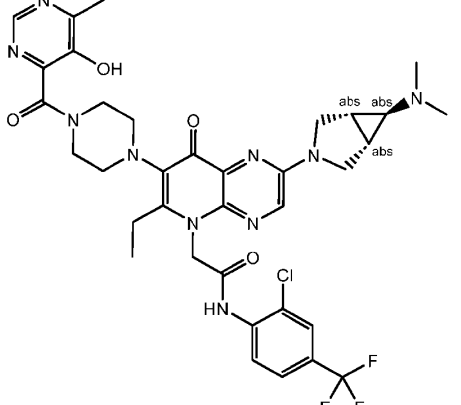
I-139		LCMS 1	715.4	0.57
I-140		LCMS 1	703.1	0.55

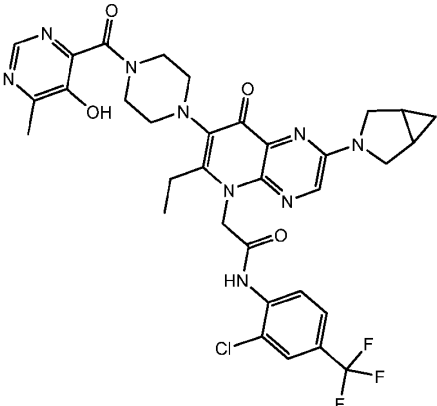
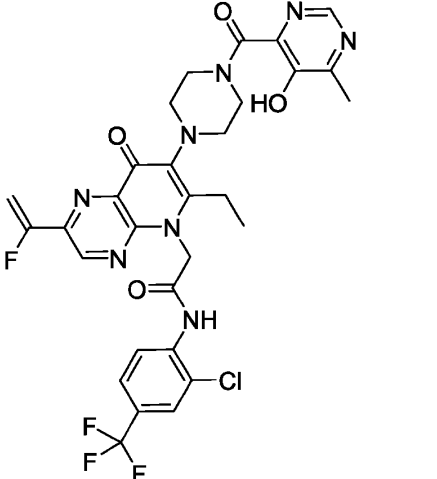
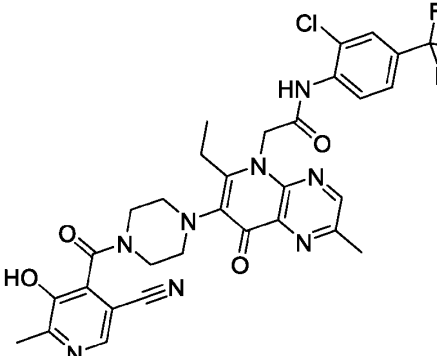
I-141		LCMS 1	701.2	0.60
I-142		LCMS 1	711.4	0.65
I-143		LCMS 1	744.4	0.59

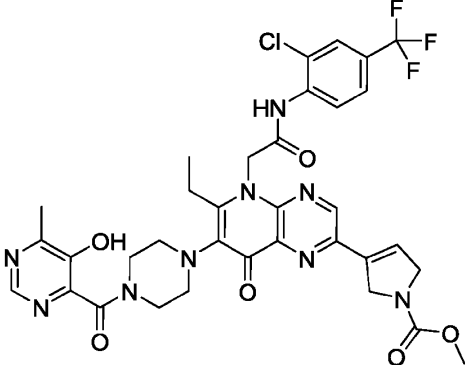
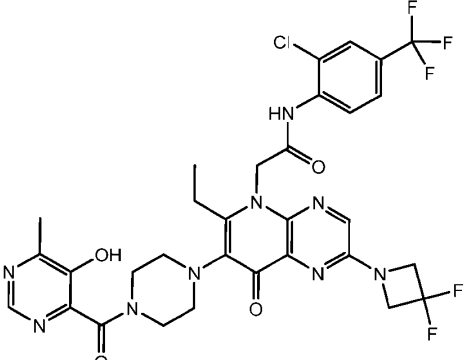
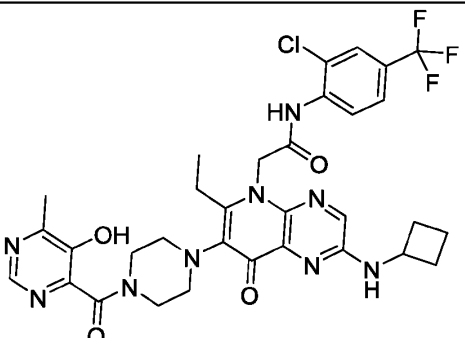
I-144		LCMS 1	711.2	0.62
I-145		LCMS 1	669.2	0.59
I-146		LCMS 1	744.2	0.61

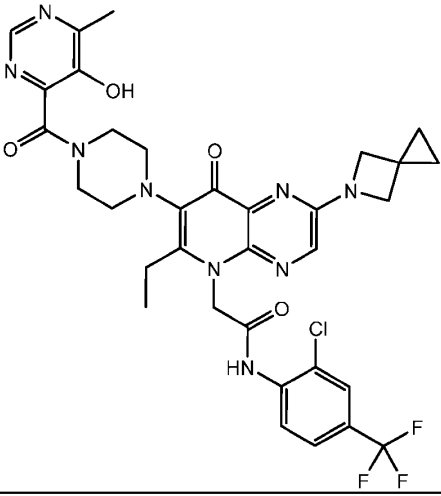
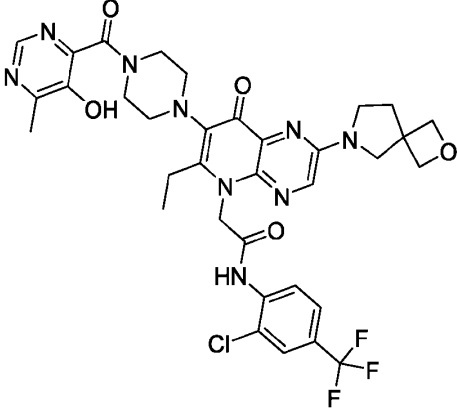
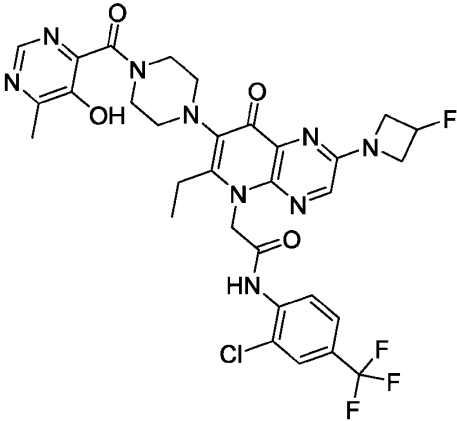
I-147		LCMS 1	688.4	0.57
I-148		LCMS 1	676.4	0.55
I-149		LCMS 1	714.2	0.57

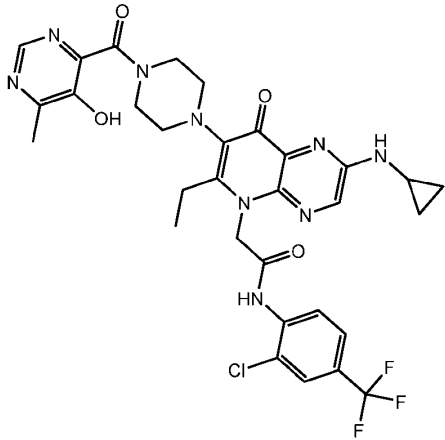
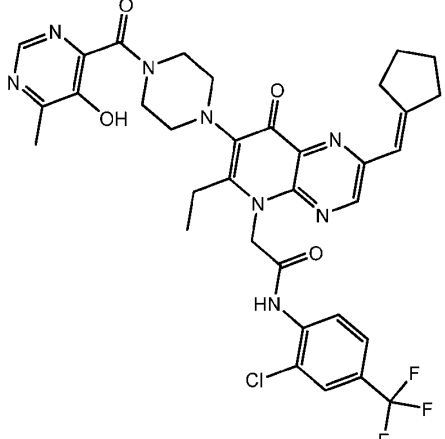
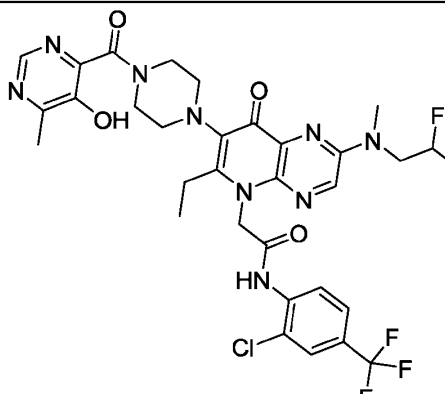
I-150		LCMS 1	714.2	0.57
I-151		LCMS 1	740.2	0.59
I-152		LCMS 1	758.5	0.58

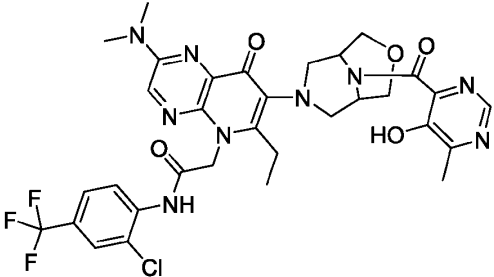
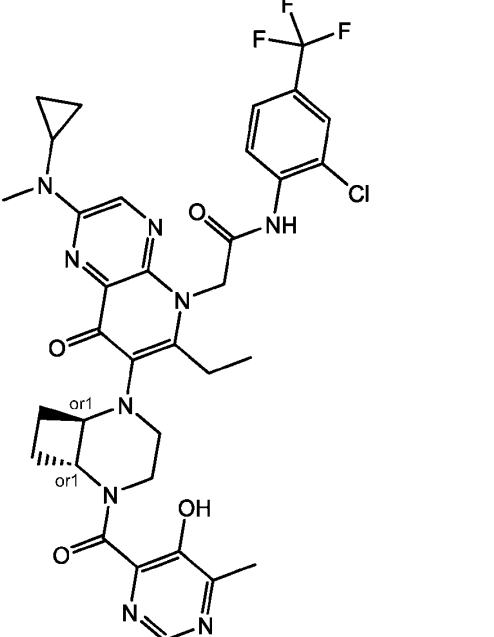
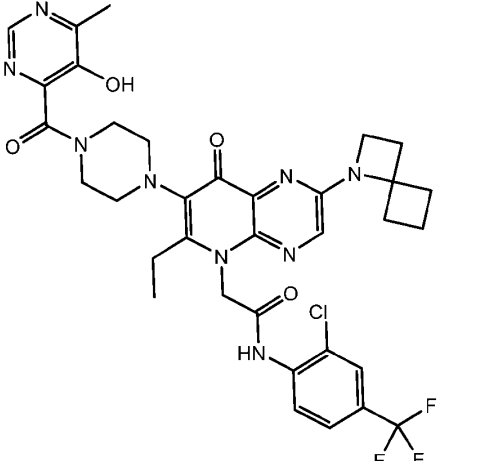
I-153		LCMS 1	758.5	0.58
I-154		LCMS 1	731.2	0.52
I-155		LCMS 1	755.2	0.50

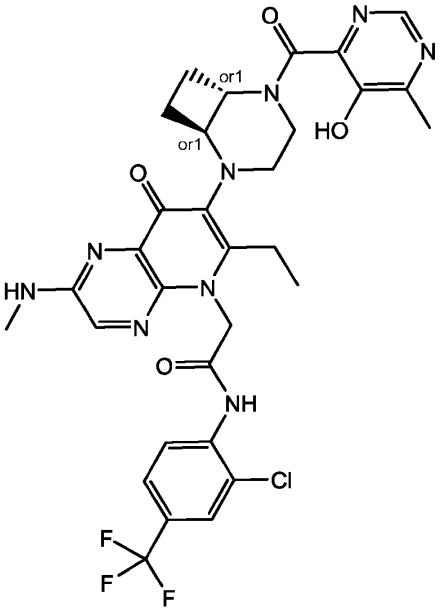
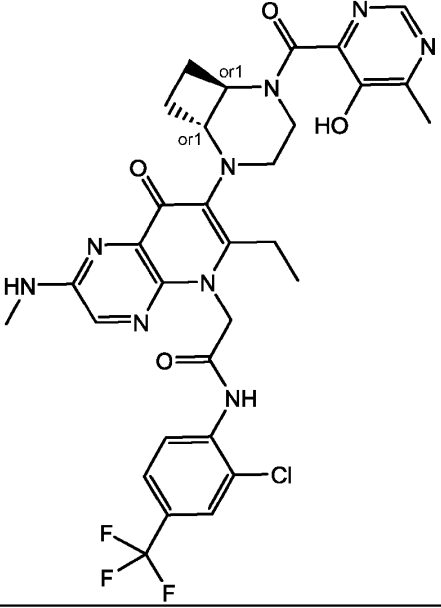
I-156		LCMS 1	712.2	0.57
I-157		LCMS 1	675.2	0.58
I-158		LCMS 1	669.4	0.57

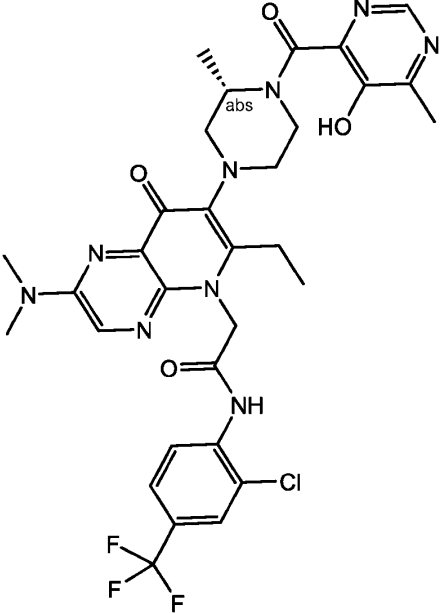
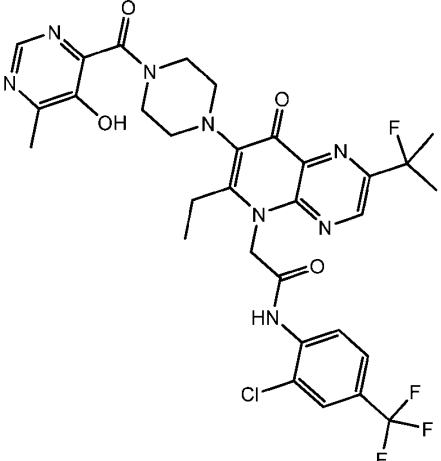
I-159		LCMS 1	756.4	0.59
I-160		LCMS 1	722.2	0.56
I-161		LCMS 1	700.2	0.56

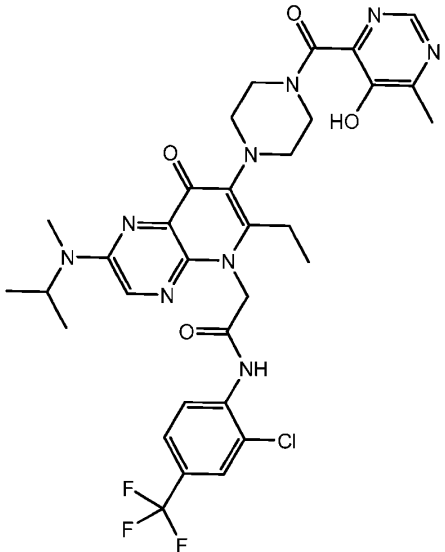
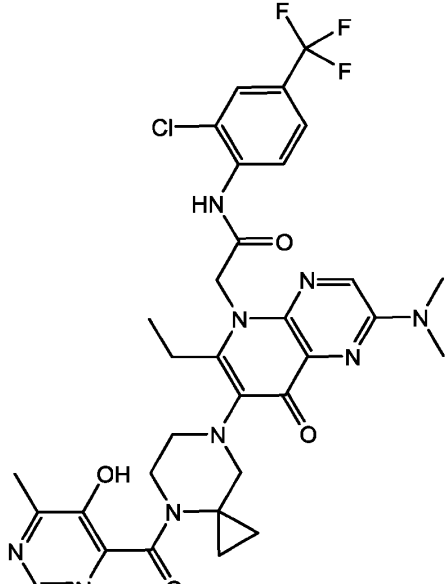
I-162		LCMS 1	712.2	0.57
I-163		LCMS 1	742.2	0.54
I-164		LCMS 1	704.4	0.58

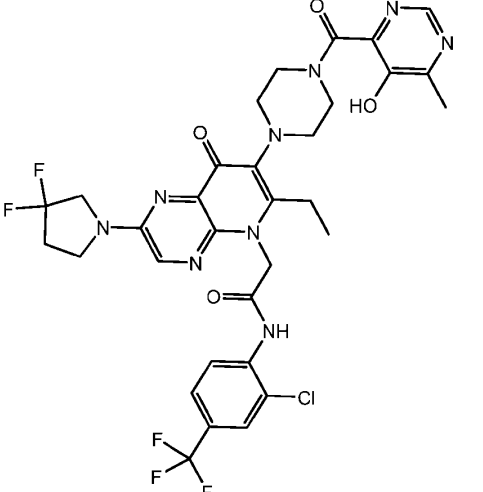
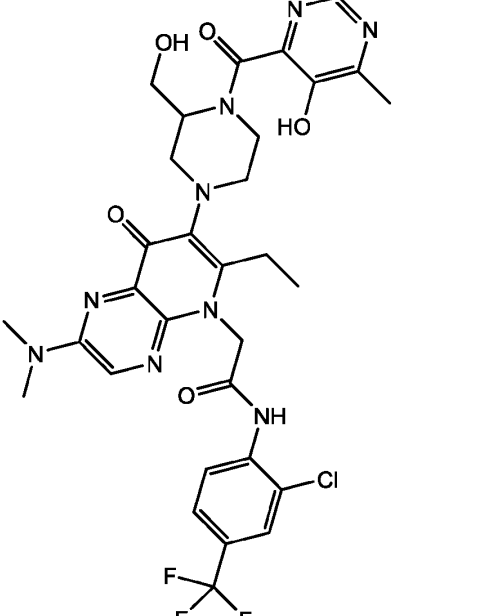
I-165		LCMS 1	686.2	0.56
I-166		LCMS 1	711.4	0.65
I-167		LCMS 1	724.4	0.60

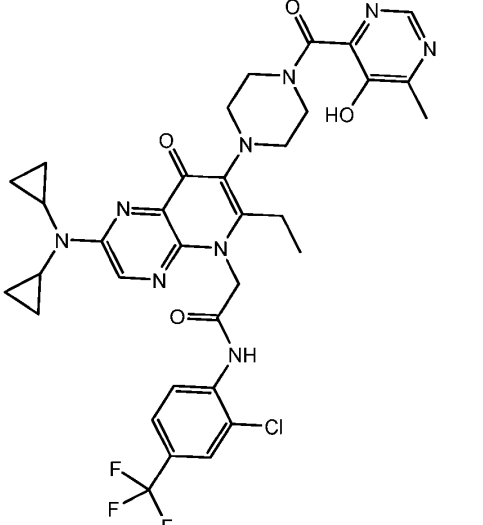
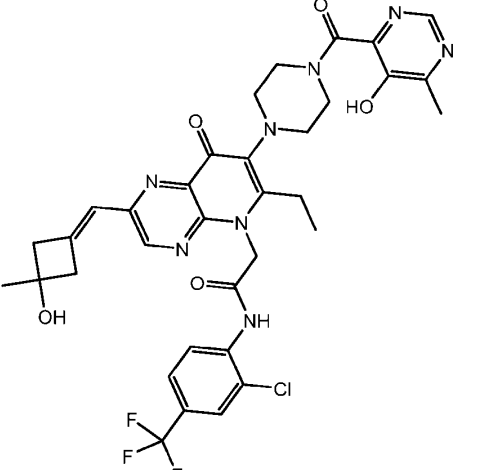
I-168		LCMS 1	716.4	0.57
I-169		LCMS 1	726.2	0.59
I-170		LCMS 1	726.5	0.61

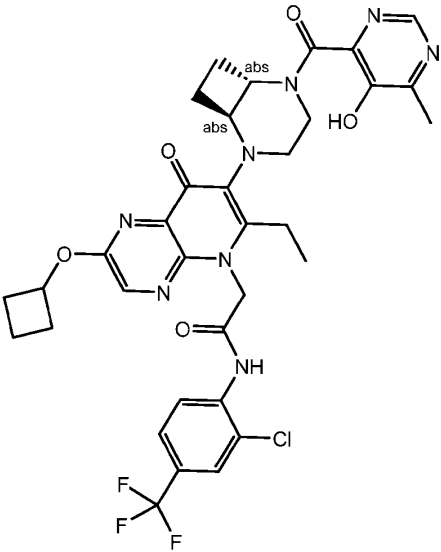
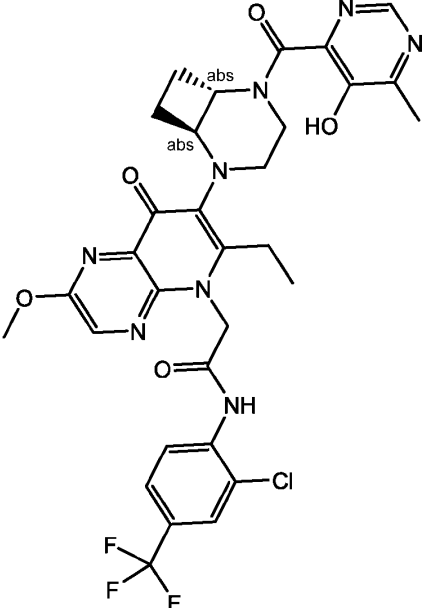
I-171		LCMS 9	686.2	1.49
I-172		LCMS 9	686.2	1.49

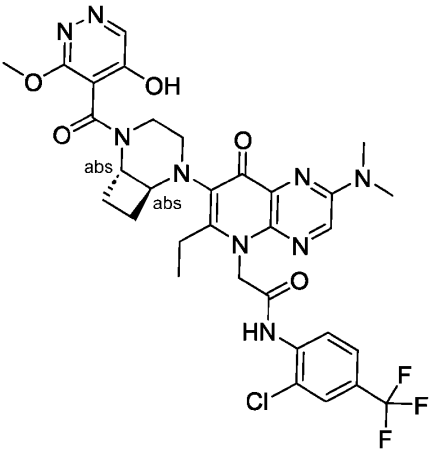
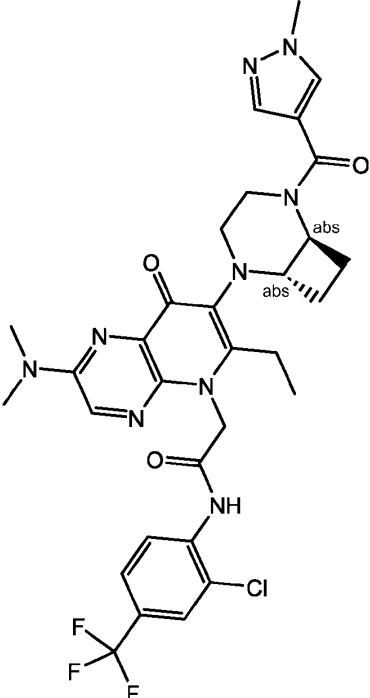
I-173		LCMS 2	688.4	0.81
I-174		LCMS 1	691.1	0.88

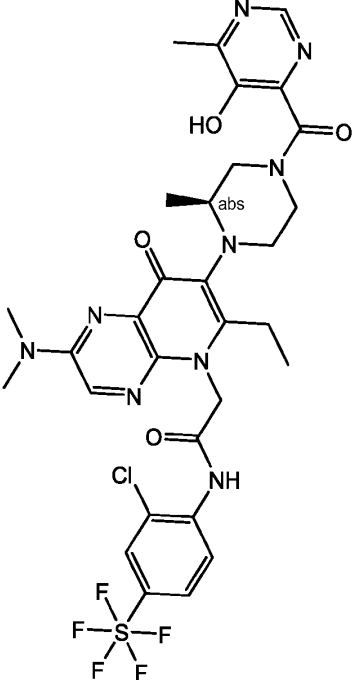
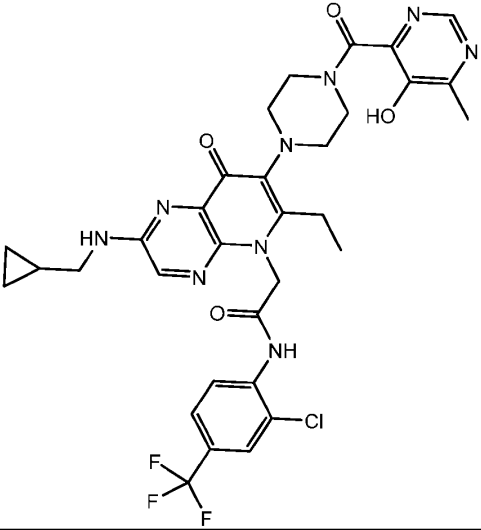
I-175		LCMS 1	702.2	0.56
I-176		LCMS 1	700.5	0.58

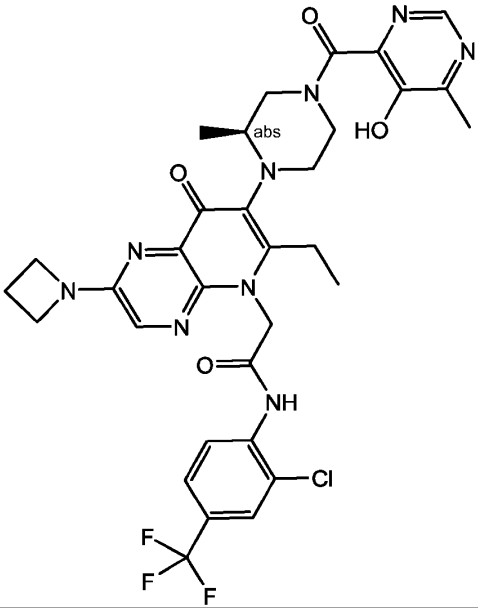
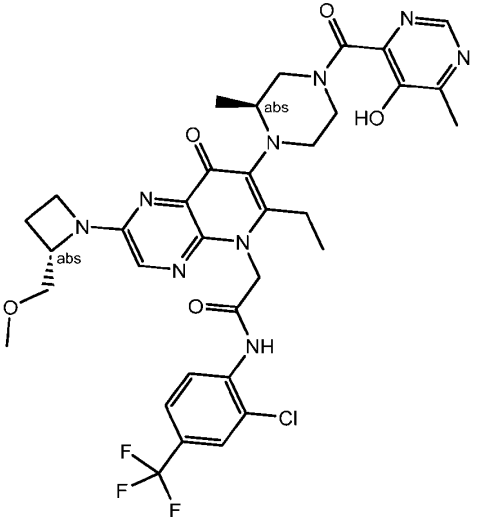
I-177		LCMS 1	736.4	0.60
I-178		LCMS 1	704.4	0.54

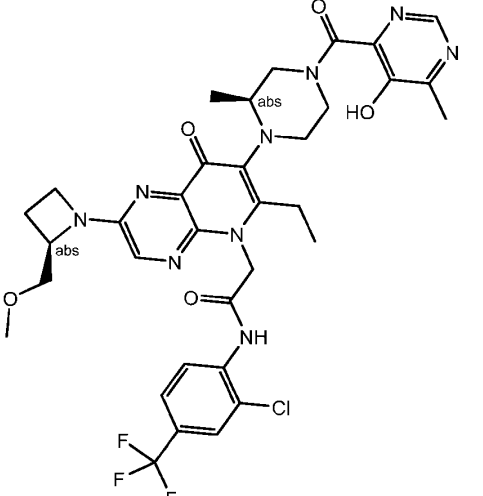
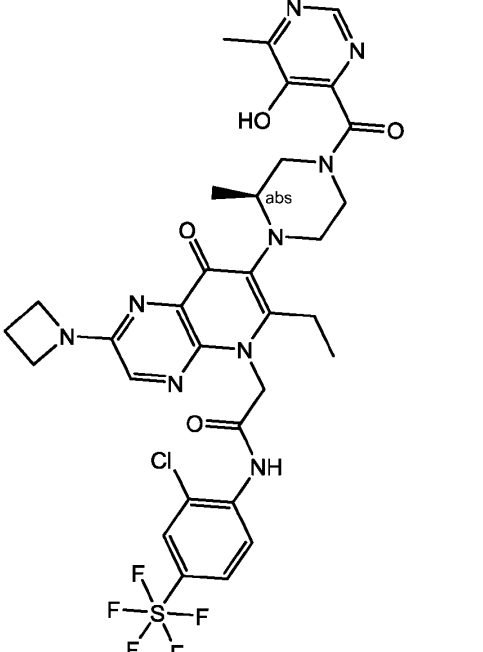
I-179		LCMS 1	726.2	0.58
I-180		LCMS 1	727.2	0.55

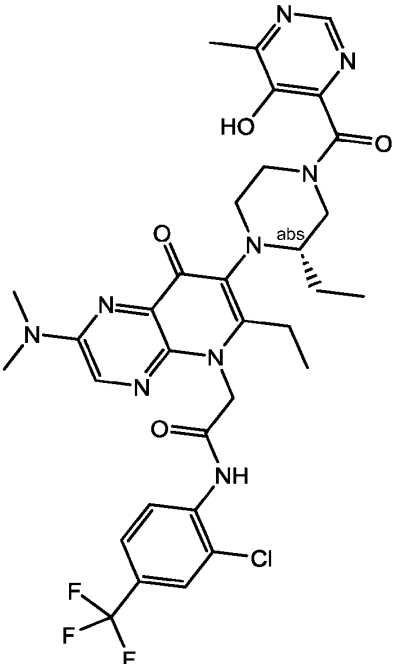
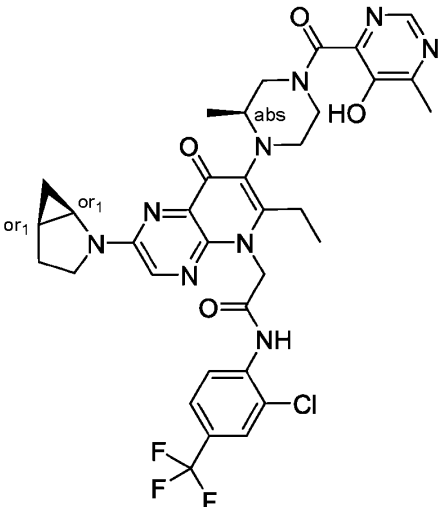
I-181		LCMS 1	727.3	2.52
I-182		LCMS 1	687.2	2.32

I-183		LCMS 1	716.2	2.10
I-184		LCMS 1	672.2	2.10

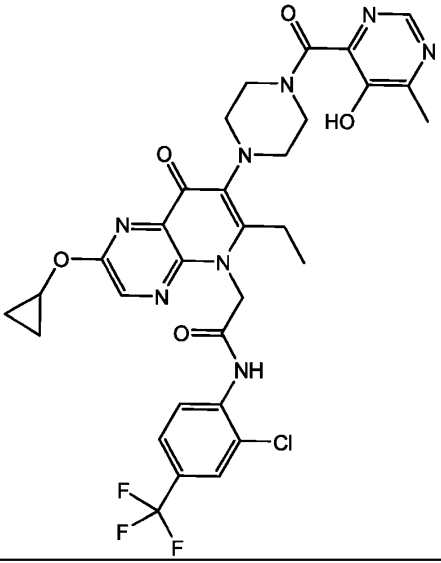
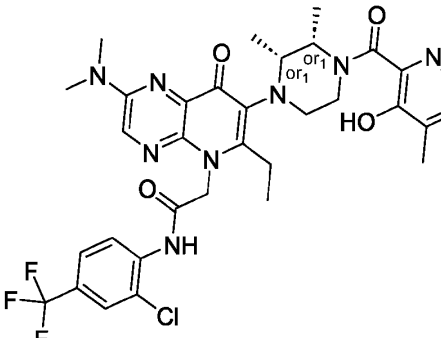
I-185		LCMS 1	746.2	2.25
I-186		LCMS 1	700.2	0.54

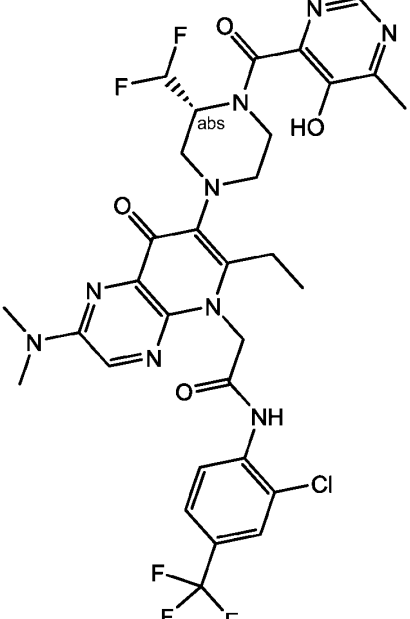
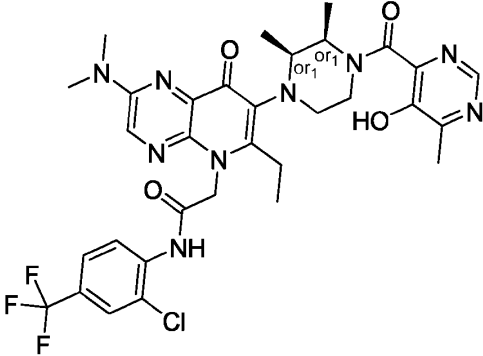
I-187		LCMS 1	700.3	2.20
I-188		LCMS 1	744.2	2.22

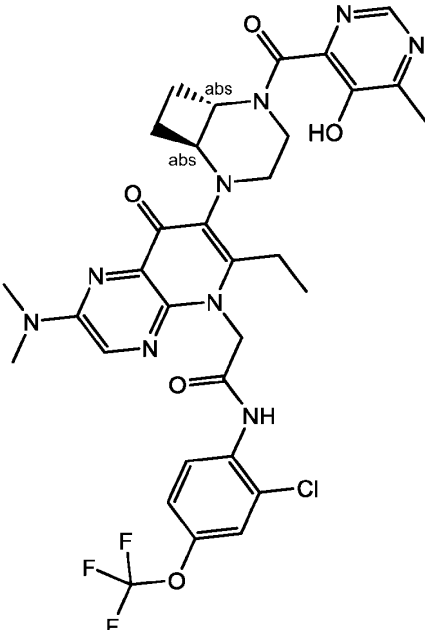
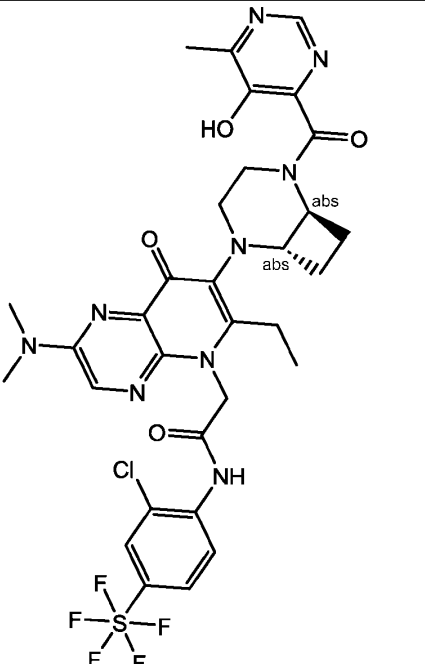
I-189	 Chemical structure of I-189: A complex molecule featuring a central pyrimidine ring system. It includes a 4-chloro-2-(trifluoromethyl)phenyl group, a 4-methoxyphenyl group, and a 4-methyl-2-pyrimidinyl group. Stereochemistry is indicated with 'abs' labels.	LCMS 1	744.3	2.21
I-190	 Chemical structure of I-190: A complex molecule featuring a central pyrimidine ring system. It includes a 4-chloro-2-(trifluoromethyl)phenyl group, a 4-methyl-2-pyrimidinyl group, and a 4-methyl-2-pyrimidinyl group. Stereochemistry is indicated with 'abs' labels.	LCMS 1	758.2	2.29

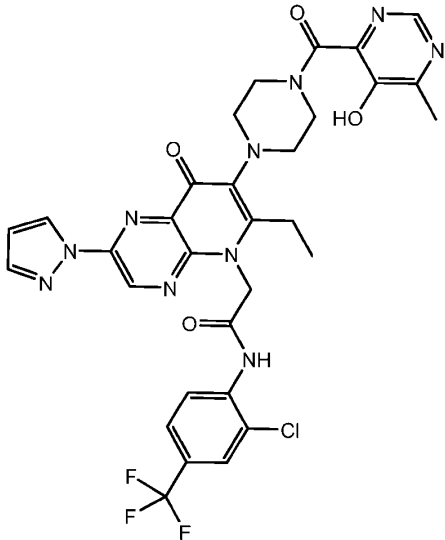
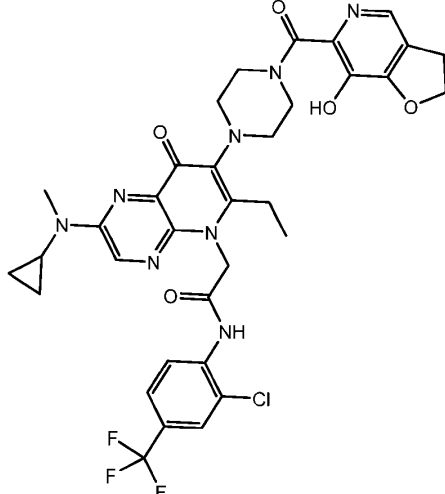
I-191		LCMS 1	702.2	0.56
I-192		LCMS 1	726.2	0.86

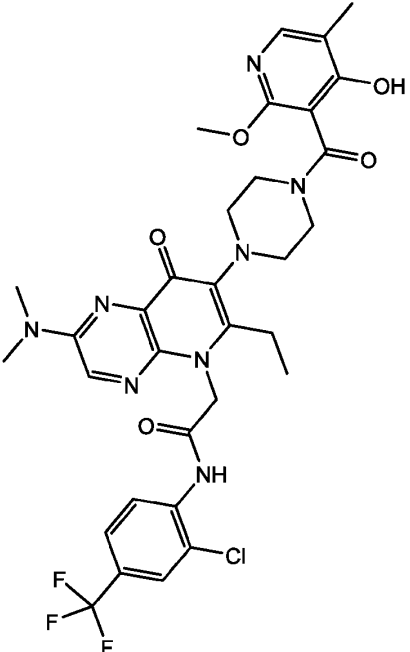
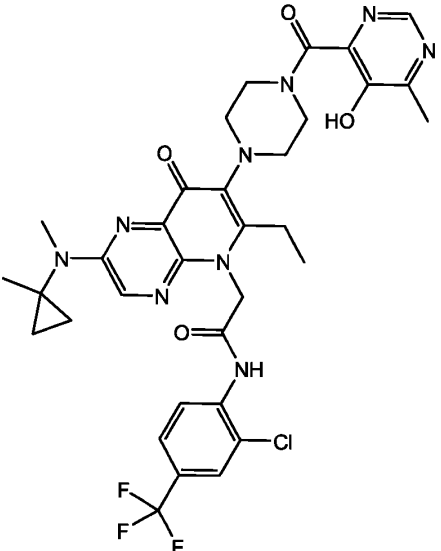
I-193	 <chem>CC1=CN(C(=O)NCC2=CN(C(=O)NCC3=CN(C(=O)NCC4=CN(C(=O)NCC5=CC(=CC=C5)C(F)(F)F)Cl)C)C)C(=O)NCC6=CC=NC(=C6)C</chem>	LCMS 1	726.2	0.87
I-194	 <chem>CC1=CN(C(=O)NCC2=CN(C(=O)NCC3=CN(C(=O)NCC4=CC5=CC(=CC=C5)C(F)(F)F)Cl)C)C(=O)NCC6=CC=NC(=C6)C7=CC=CC=C7O</chem>	LCMS 1	727.4	0.60

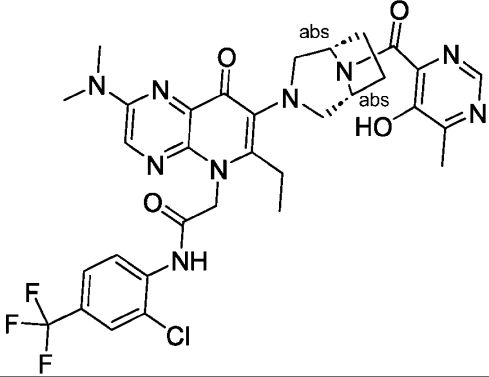
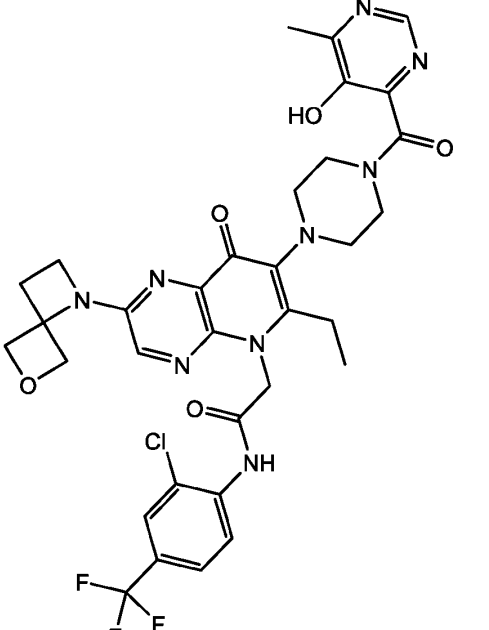
I-195		LCMS 1	687.2	0.58
I-196		LCMS 1	702.3	0.92

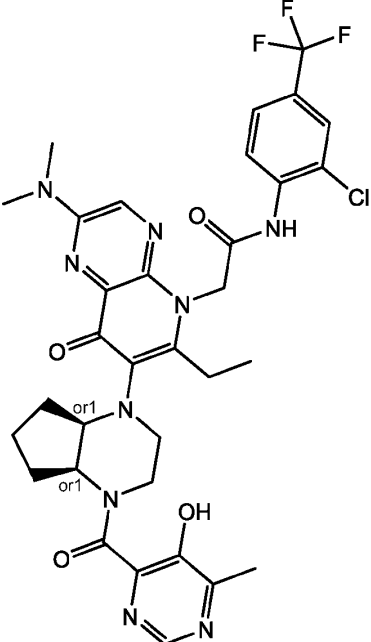
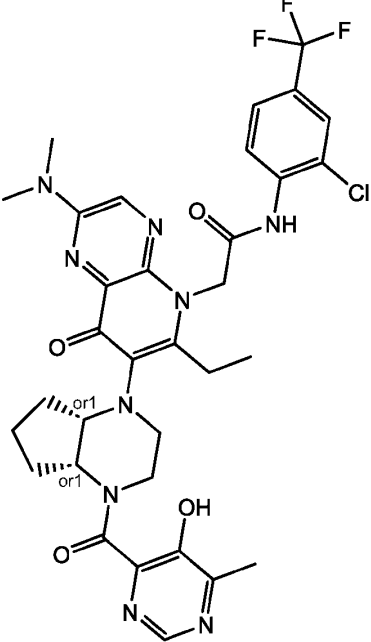
I-197		LCMS 1	724.2	0.57
I-198		LCMS 1	702.3	0.92

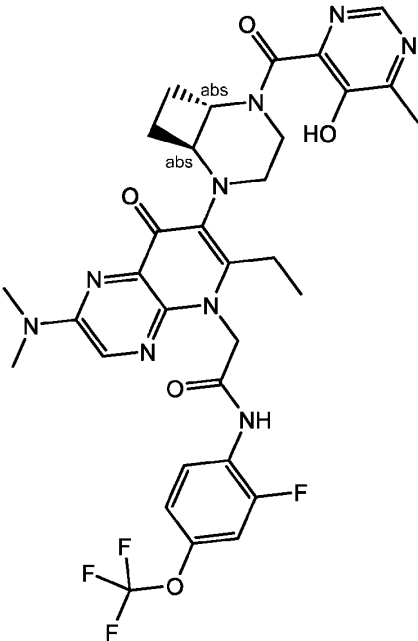
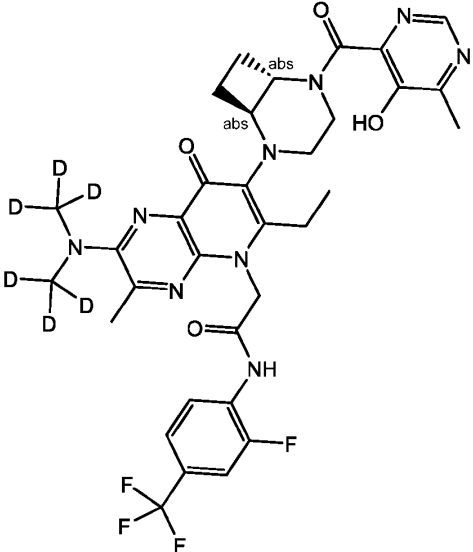
I-199		LCMS 1	716.3	2.23
I-200		LCMS 1	758.2	2.29

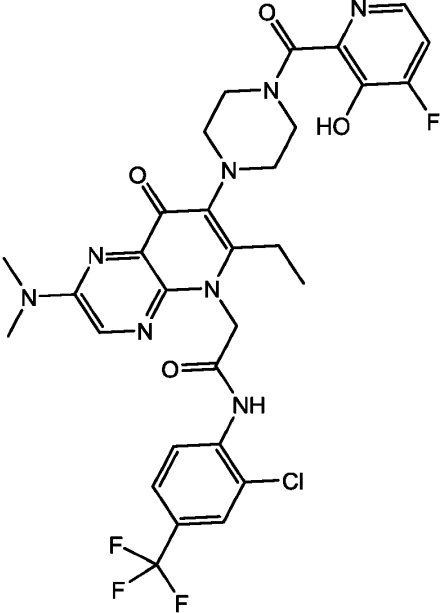
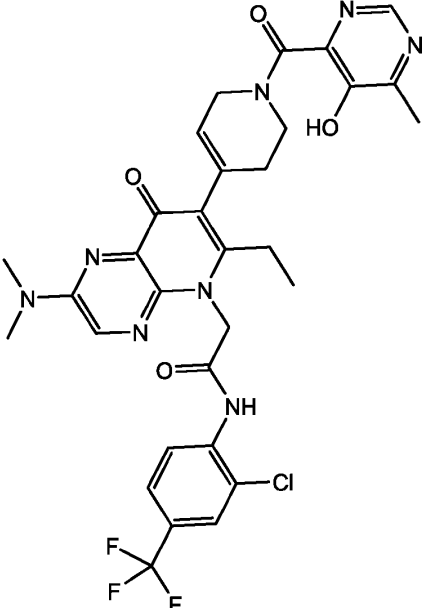
I-201	 Chemical structure of compound I-201: A complex molecule featuring a central pyrimidine ring system. The pyrimidine ring is substituted with a 1H-imidazo[4,5-b]pyridine group at position 2, an ethyl group at position 4, and a 2-chloro-4-(trifluoromethyl)phenyl group at position 6. The pyrimidine ring is also substituted with a 2-hydroxy-4-methyl-6-methyl-1,2,3,4-tetrahydropyrimidin-5(1H)-one group at position 1. The pyrimidine ring is further substituted with a 2-chloro-4-(trifluoromethyl)phenyl group at position 6.	LCMS 11	697.3	0.57
I-203	 Chemical structure of compound I-203: A complex molecule featuring a central pyrimidine ring system. The pyrimidine ring is substituted with a 1H-imidazo[4,5-b]pyridine group at position 2, an ethyl group at position 4, and a 2-chloro-4-(trifluoromethyl)phenyl group at position 6. The pyrimidine ring is also substituted with a 2-hydroxy-4-methyl-6-methyl-1,2,3,4-tetrahydropyrimidin-5(1H)-one group at position 1. The pyrimidine ring is further substituted with a 2-chloro-4-(trifluoromethyl)phenyl group at position 6.	LCMS 1	727.4	0.56

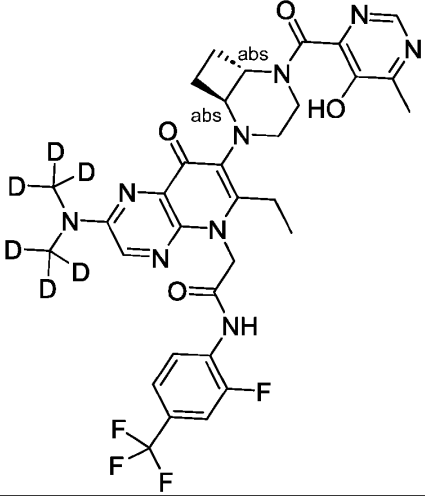
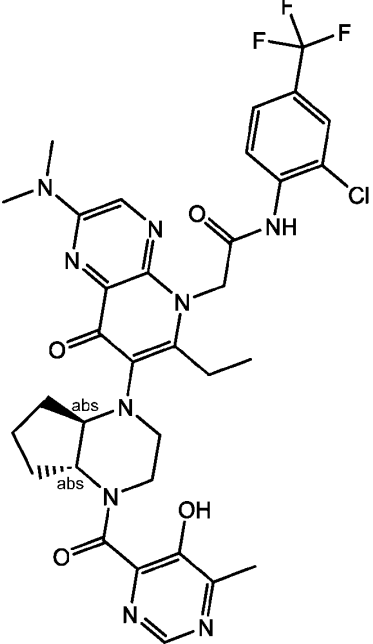
I-204		LCMS 1	703.2	0.53
I-205		LCMS 1	714.2	0.58

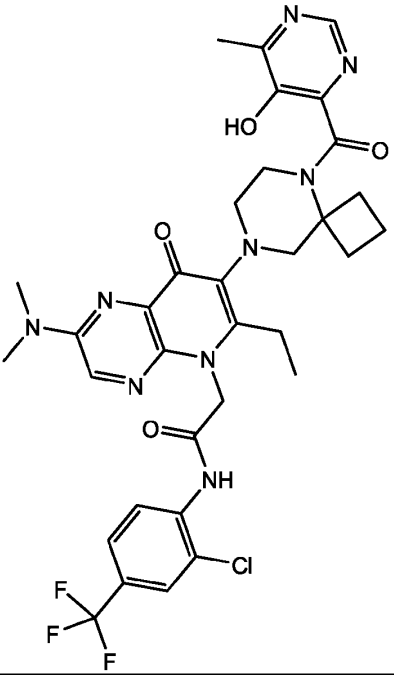
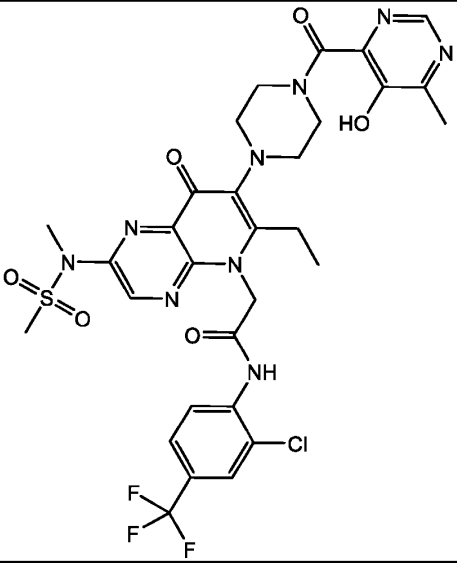
I-206		LCMS 1	700.3	0.58
I-207		LCMS 1	728.3	0.50

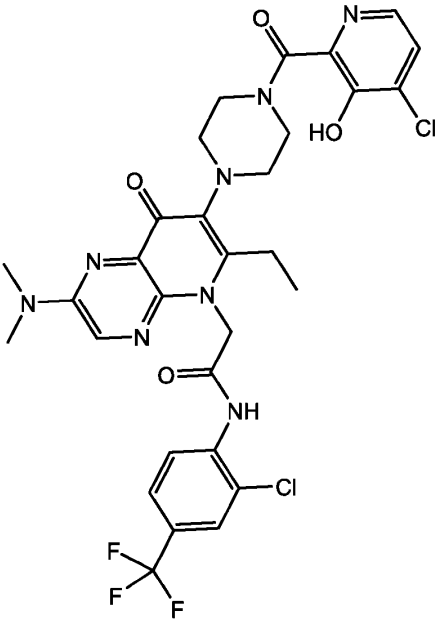
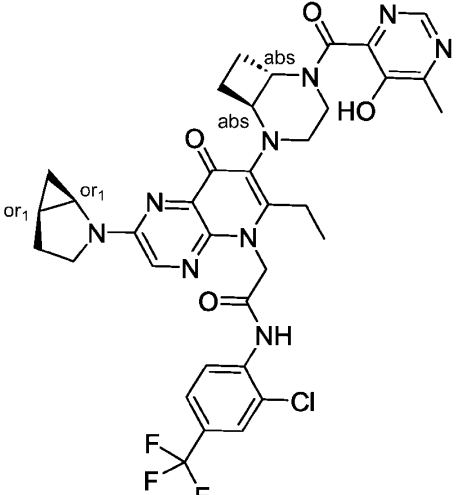
I-208	 Chemical structure of I-208: A complex molecule featuring a pyrimidine ring system. The pyrimidine ring is substituted with a methyl group at position 2, a carbonyl group at position 4, and a 4-chloro-3-(trifluoromethyl)phenylamino group at position 6. The pyrimidine ring is also substituted with a 4-hydroxy-2-methylpyrimidin-5-yl group at position 5. The pyrimidine ring is further substituted with a 4-chloro-3-(trifluoromethyl)phenylamino group at position 6. The pyrimidine ring is also substituted with a 4-hydroxy-2-methylpyrimidin-5-yl group at position 5. The pyrimidine ring is further substituted with a 4-chloro-3-(trifluoromethyl)phenylamino group at position 6. The pyrimidine ring is also substituted with a 4-hydroxy-2-methylpyrimidin-5-yl group at position 5.	LCMS 1	714.3	0.55
I-209	 Chemical structure of I-209: A complex molecule featuring a pyrimidine ring system. The pyrimidine ring is substituted with a methyl group at position 2, a carbonyl group at position 4, and a 4-chloro-3-(trifluoromethyl)phenylamino group at position 6. The pyrimidine ring is also substituted with a 4-hydroxy-2-methylpyrimidin-5-yl group at position 5. The pyrimidine ring is further substituted with a 4-chloro-3-(trifluoromethyl)phenylamino group at position 6. The pyrimidine ring is also substituted with a 4-hydroxy-2-methylpyrimidin-5-yl group at position 5. The pyrimidine ring is further substituted with a 4-chloro-3-(trifluoromethyl)phenylamino group at position 6. The pyrimidine ring is also substituted with a 4-hydroxy-2-methylpyrimidin-5-yl group at position 5.	LCMS 1	714.3	0.56

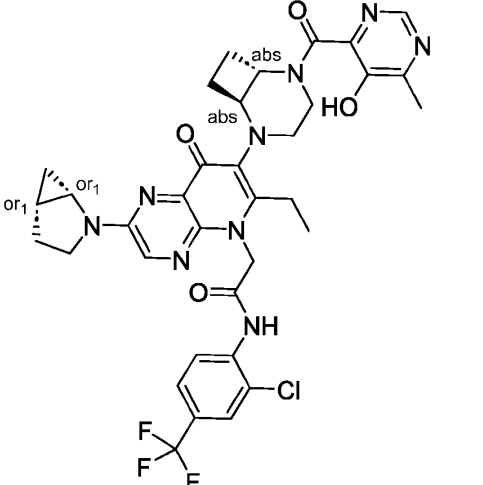
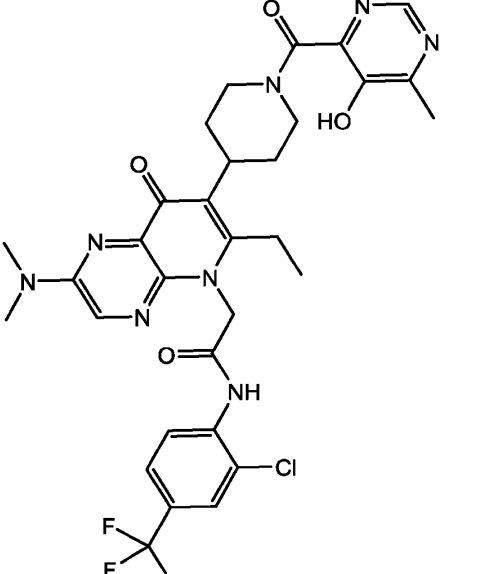
I-210		LCMS 1	700.3	2.15
I-211		LCMS 1	704.3	2.21

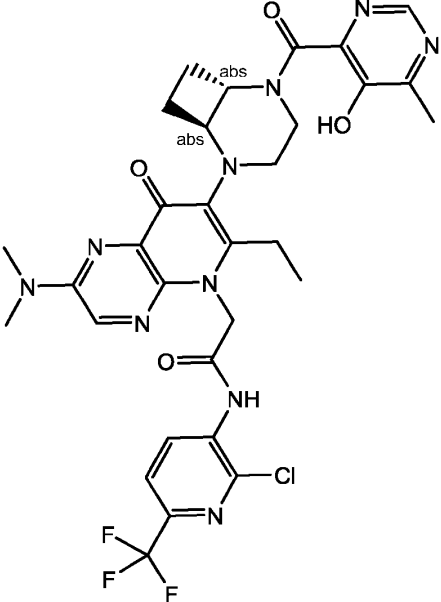
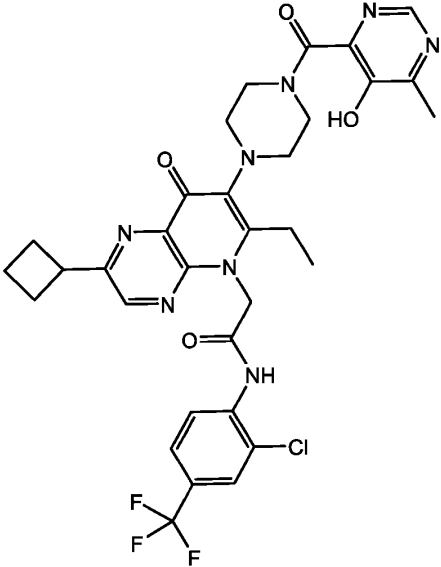
I-212		LCMS 1	677.4	0.52
I-213		LCMS 1	671.2	2.07

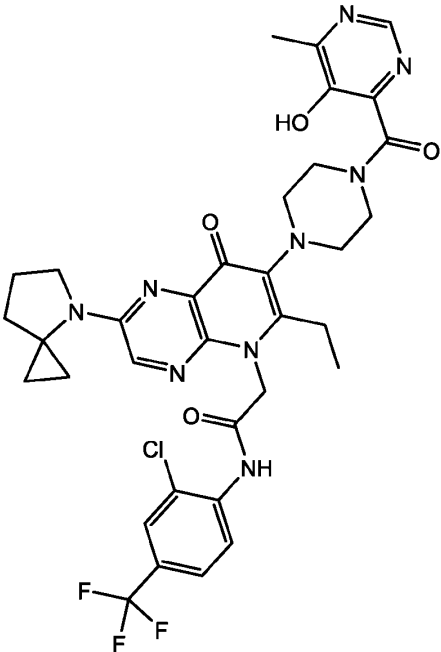
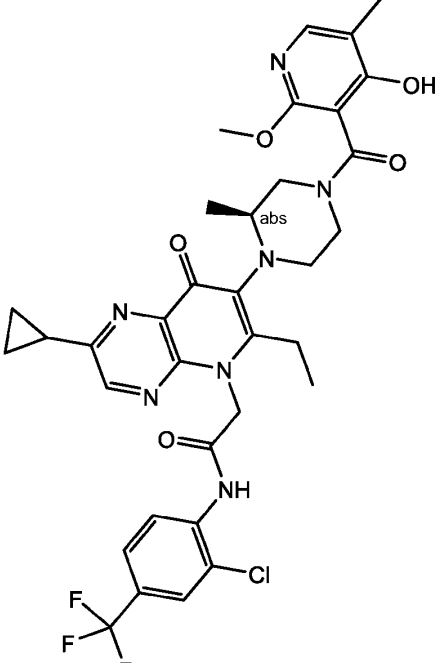
I-214		LCMS 1	690.3	0.55
I-215		LCMS 4	714.3	0.43

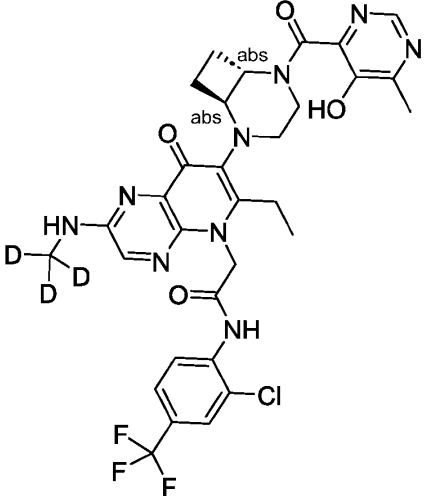
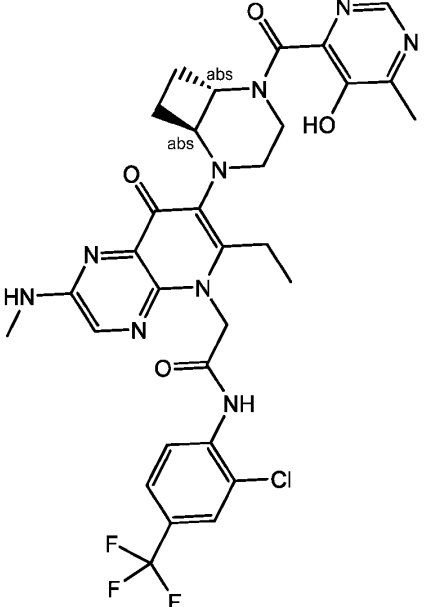
I-216		LCMS 10	714.4	1.76
I-217		LCMS 1	738.1	0.55

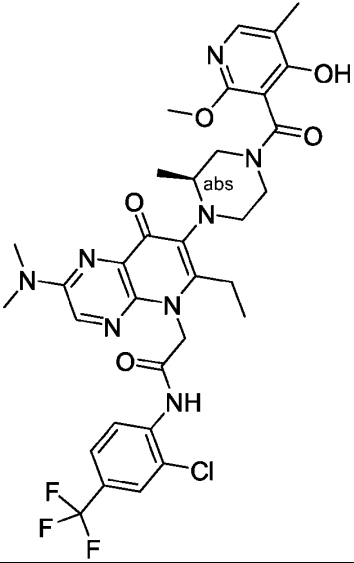
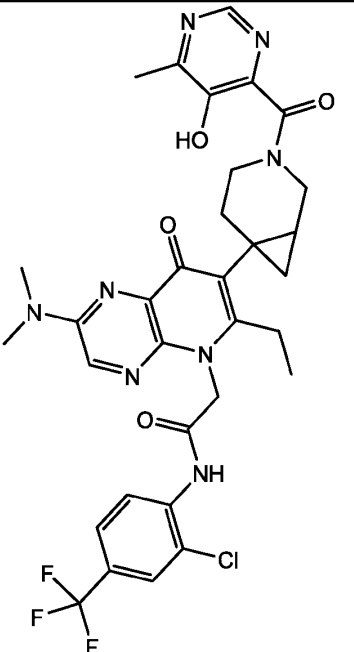
I-218		LCMS 1	693.2	2.16
I-219		LCMS 1	738.4	0.62

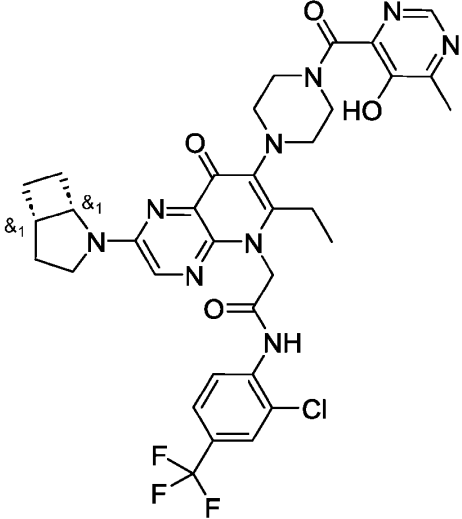
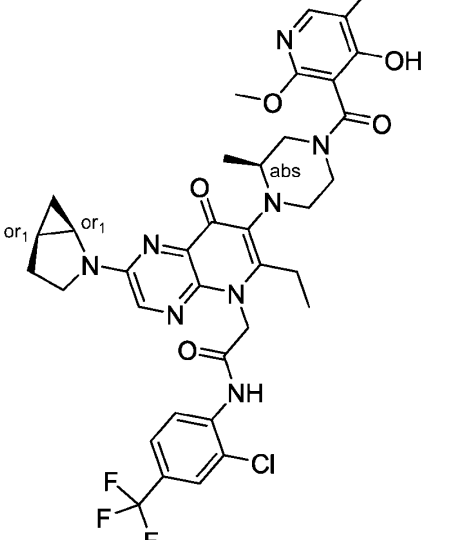
I-220		LCMS 1	738.4	0.62
I-221		LCMS 1	673.2	0.53

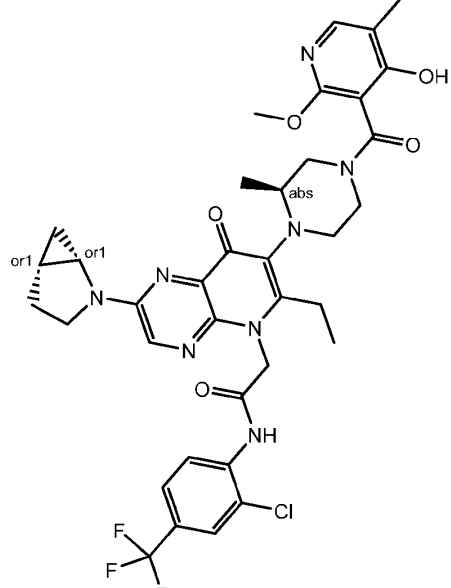
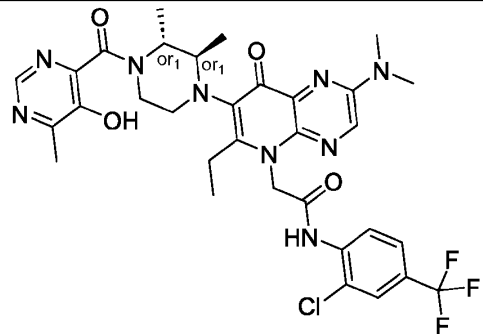
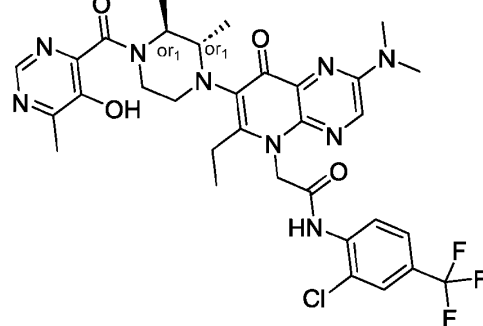
I-222		LCMS 1	701.4	0.52
I-223		LCMS 1	685.4	0.62

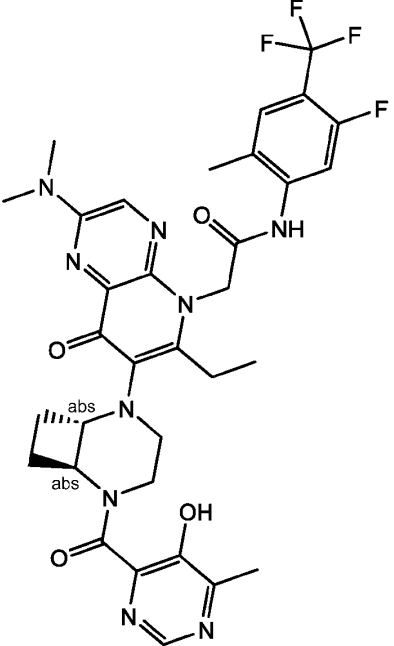
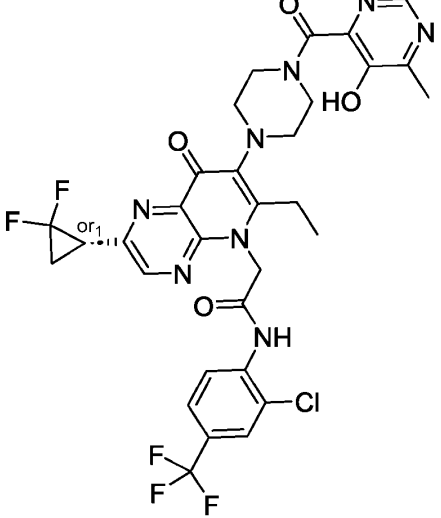
I-224		LCMS 1	726.2	0.60
I-225		LCMS 1	714.2	0.57

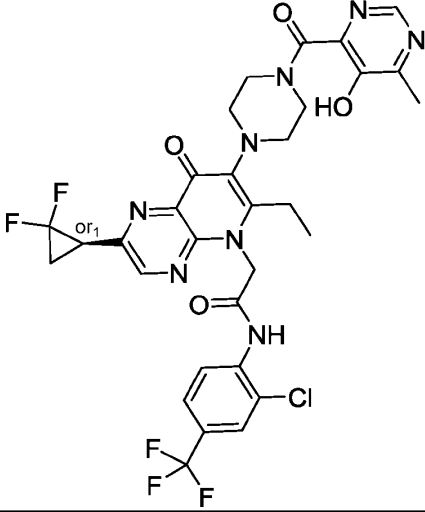
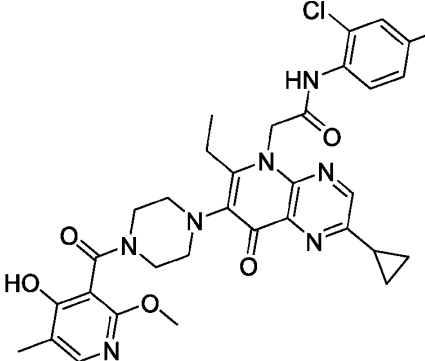
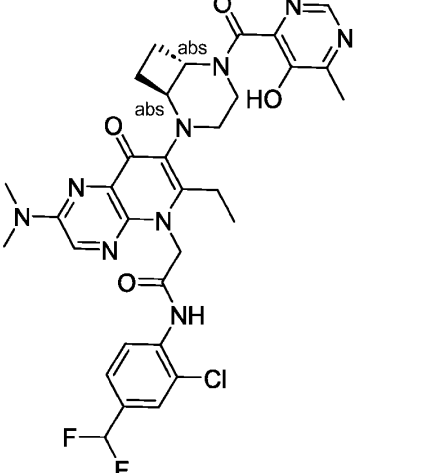
I-226		LCMS 1	689.3	2.15
I-227		LCMS 1	686.2	2.09

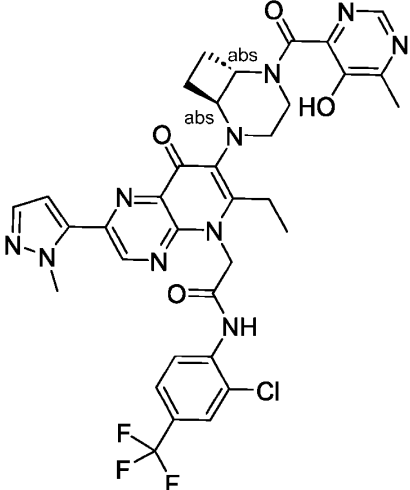
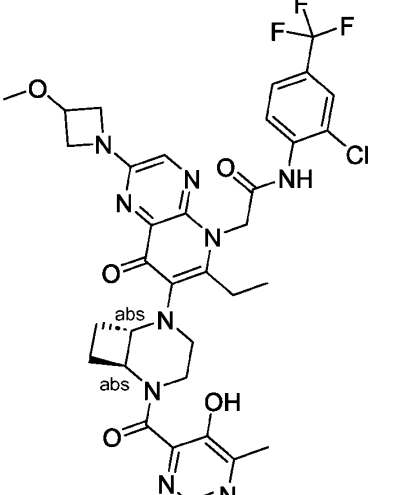
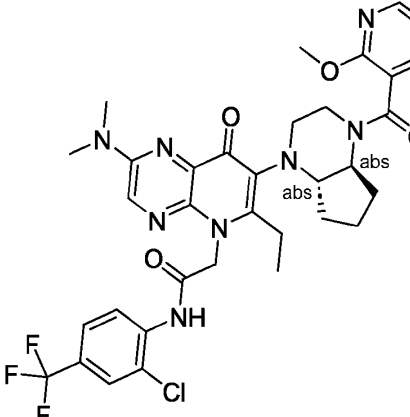
I-228		LCMS 1	717.5	0.57
I-229		LCMS 1	685.4	0.56

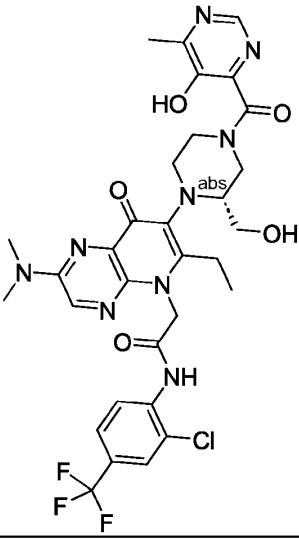
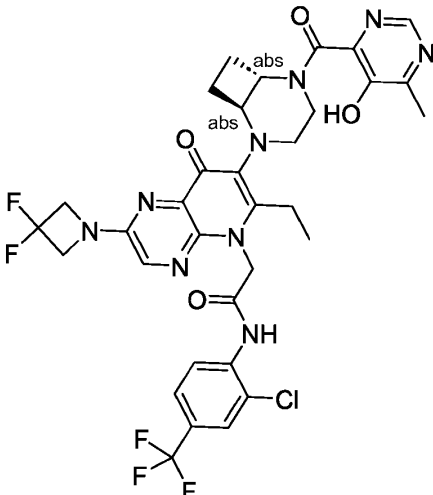
I-230		LCMS 4	726.4	0.45
I-231		LCMS 1	755.5	0.60

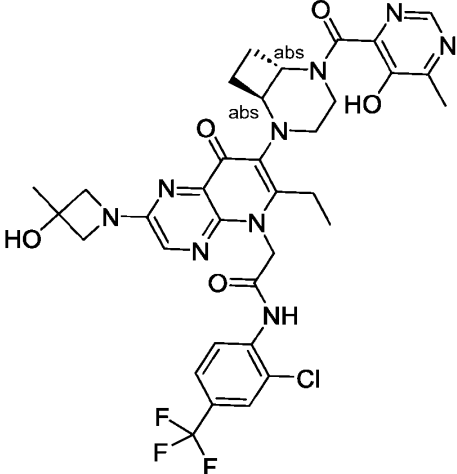
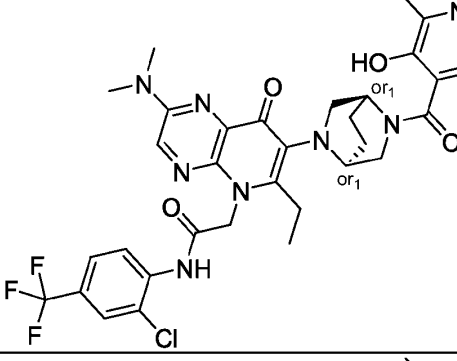
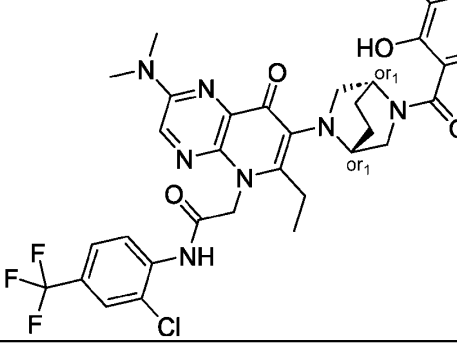
I-232		LCMS 1	755.5	0.59
I-233		LCMS 1	702.3	2.15
I-234		LCMS 1	702.3	2.14

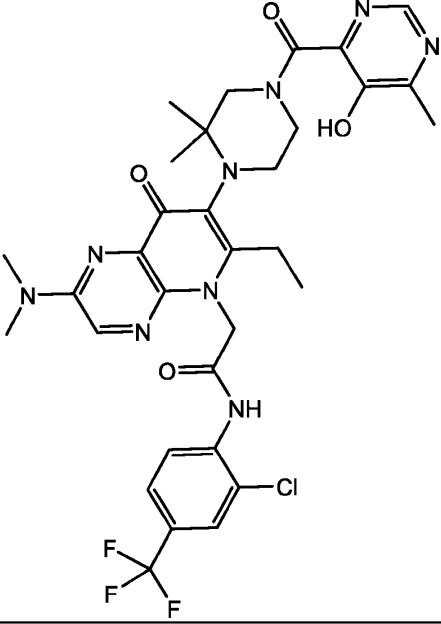
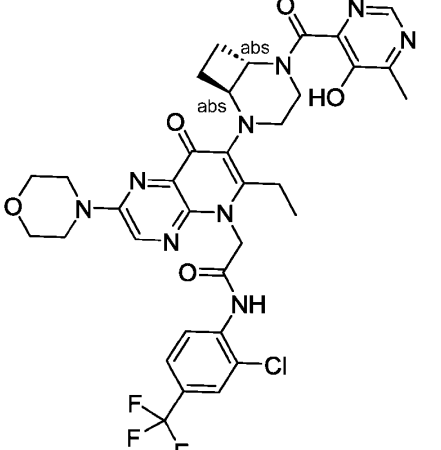
I-236		LCMS 1	698.4	0.54
I-237		LCMS 11	707.2	0.57

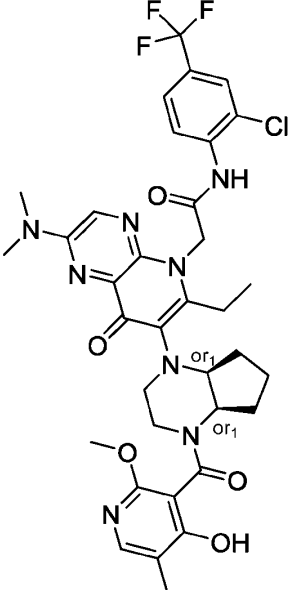
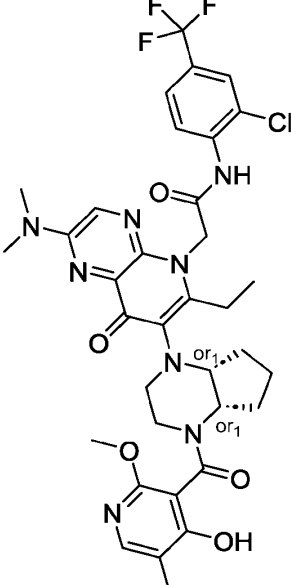
I-238		LCMS 11	707.3	0.57
I-239		LCMS 1	700.3	0.55
I-240		LCMS 1	682.2	0.51

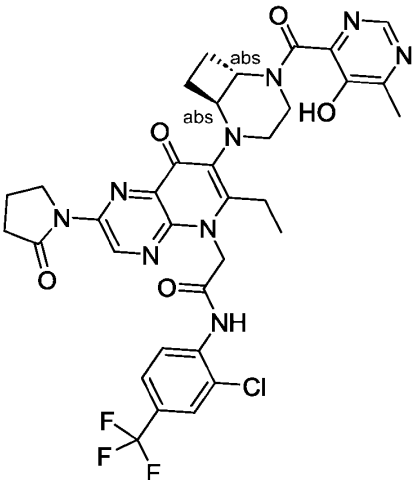
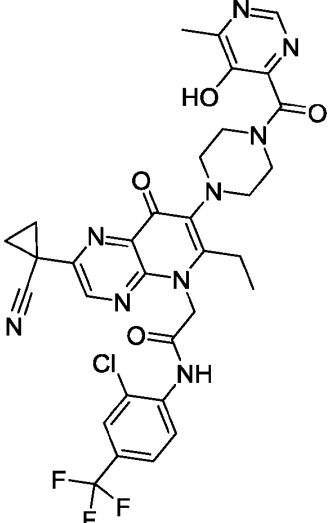
I-241		LCMS 1	737.3	2.31
I-242		LCMS 1	742.3	2.22
I-243		LCMS 4	743.3	0.46

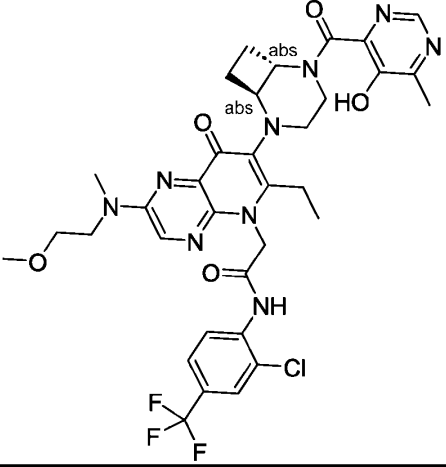
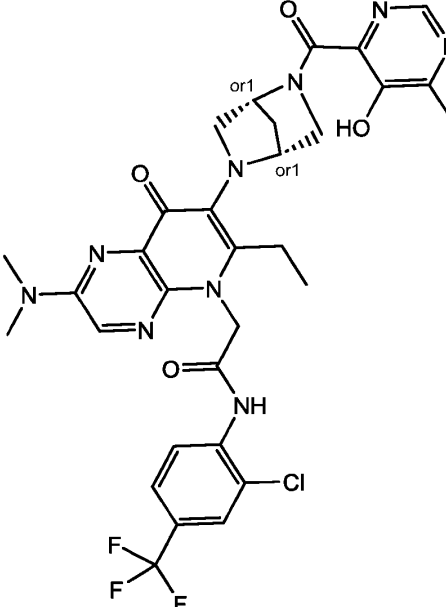
I-244		LCMS 1	704.3	0.51
I-245		LCMS 1	748.2	2.29

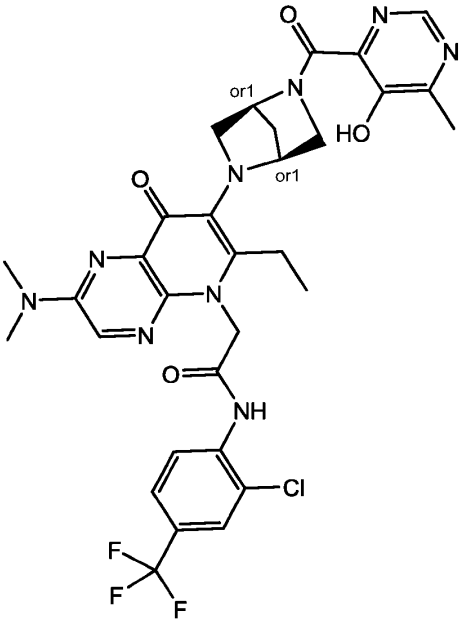
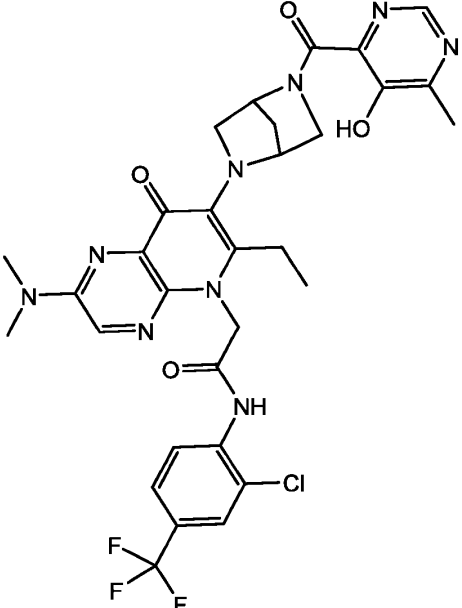
I-246		LCMS 1	742.2	2.15
I-247		LCMS 1	700.2	0.57
I-248		LCMS 1	700.2	0.57

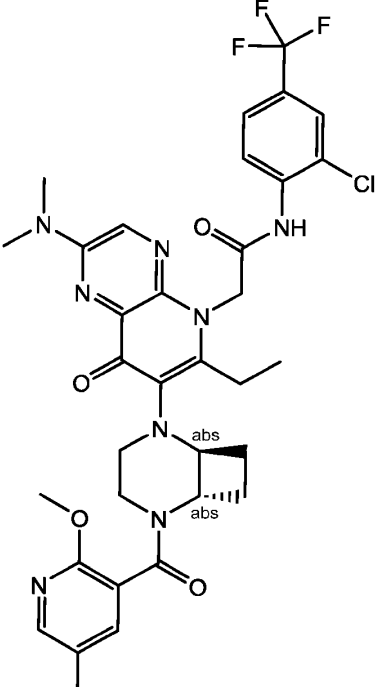
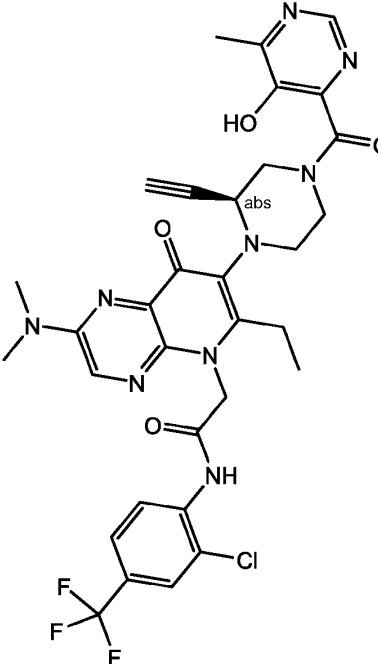
I-249		LCMS 1	702.5	0.58
I-250		LCMS 1	742.2	2.21

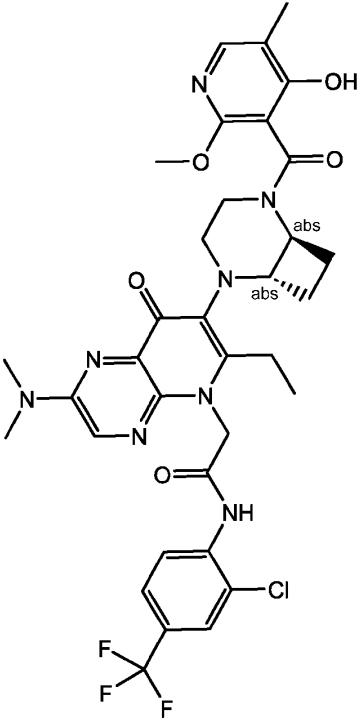
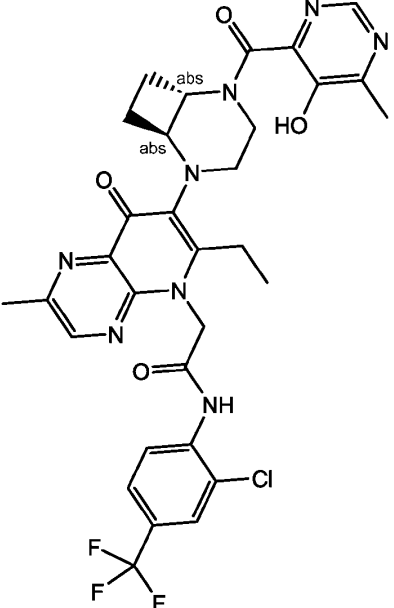
I-251		LCMS 4	743.4	0.46
I-252		LCMS 4	743.4	0.46

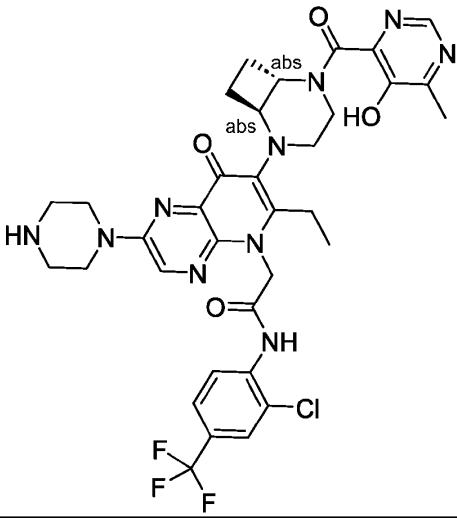
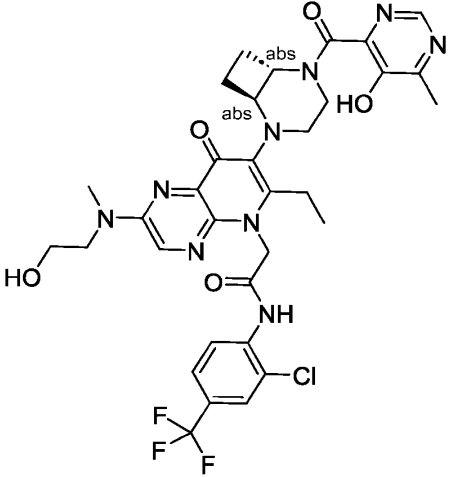
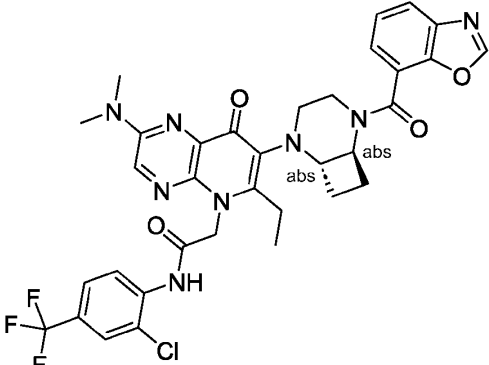
I-253		LCMS 1	740.3	2.28
I-254		LCMS 1	696.3	0.54

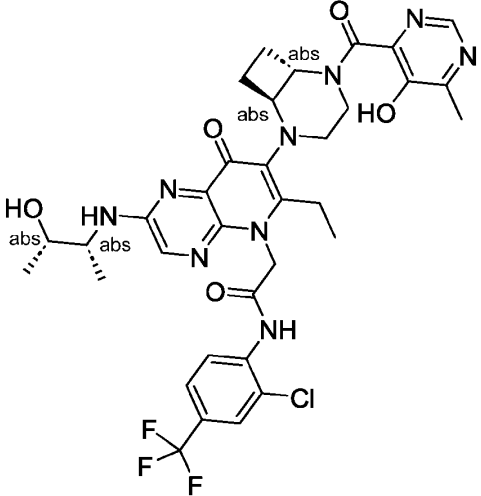
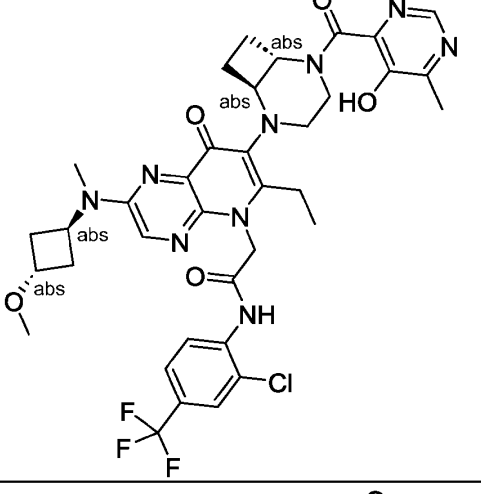
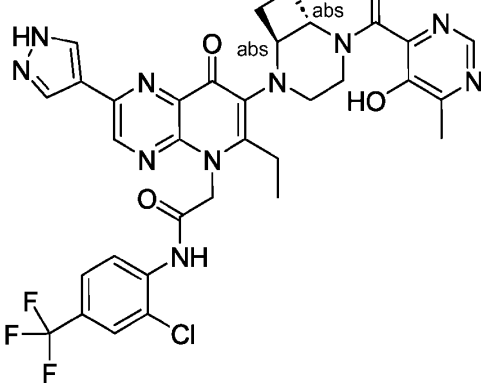
I-255		LCMS 1	744.3	0.57
I-256		LCMS 1	686.2	0.55

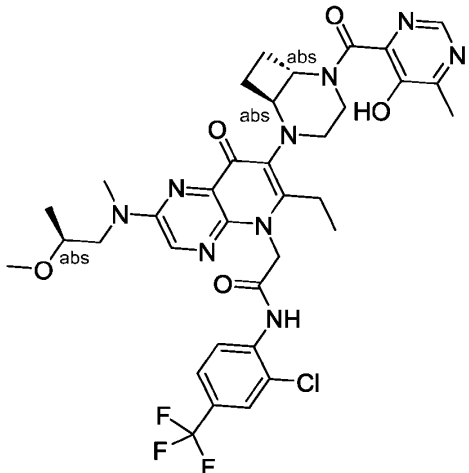
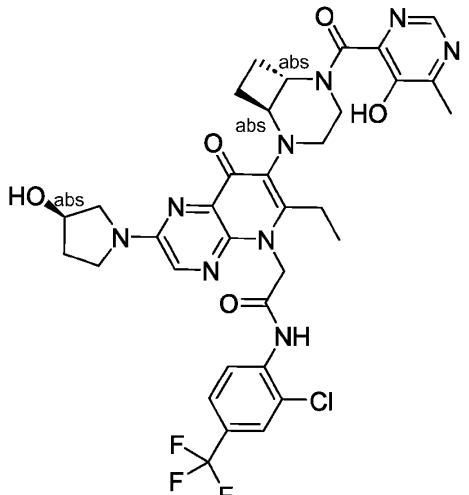
I-257		LCMS 1	686.2	0.55
I-258		LCMS 1	686.3	0.56

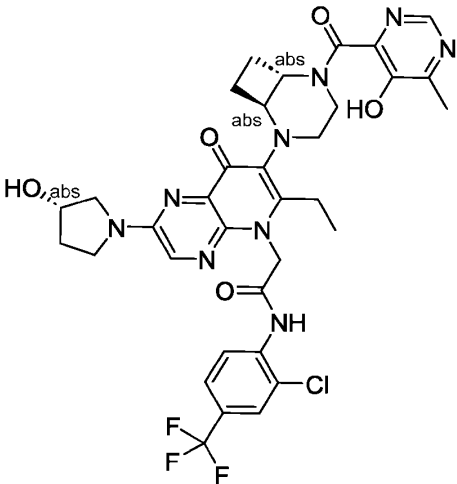
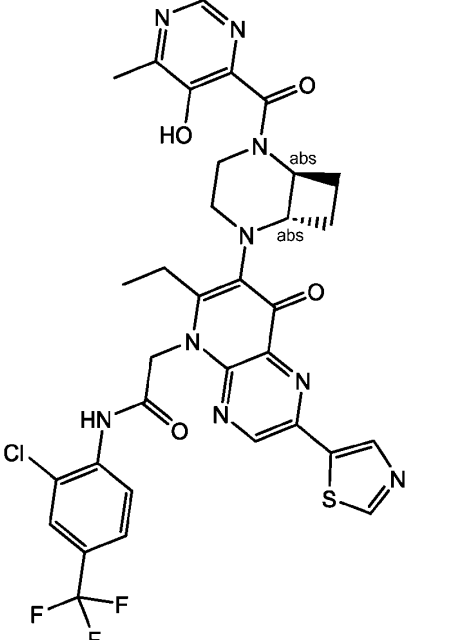
I-259		LCMS 1	713.2	0.55
I-260		LCMS 1	698.3	0.53

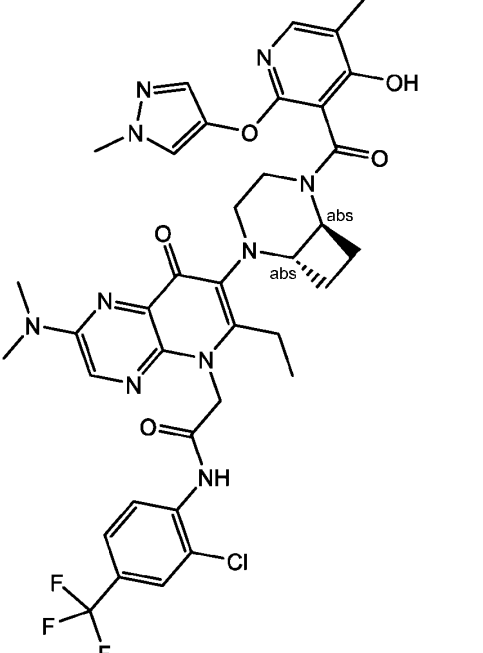
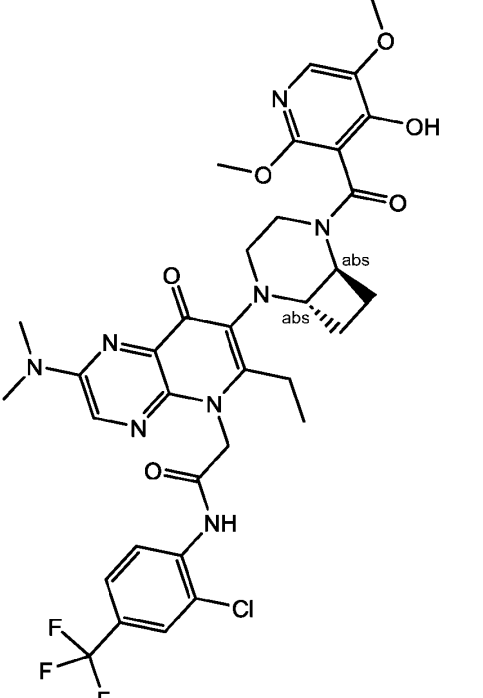
I-261		LCMS 1	729.2	2.05
I-262		LCMS 1	671.3	1.28

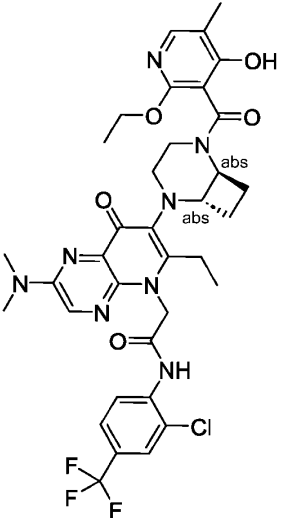
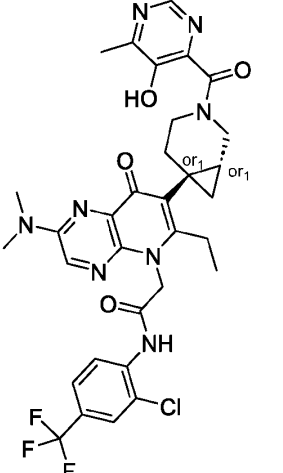
I-263		LCMS 1	741.3	1.93
I-264		LCMS 1	730.3	2.13
I-265		LCMS 4	709.3	0.67

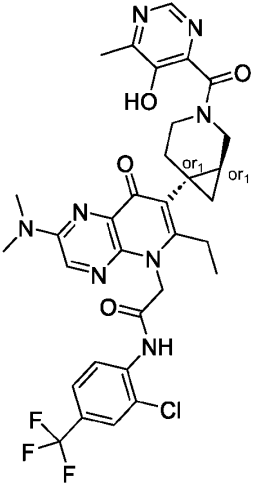
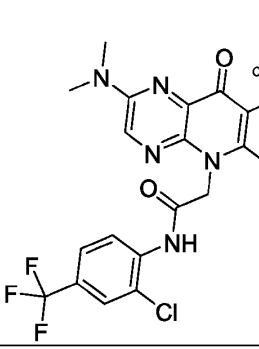
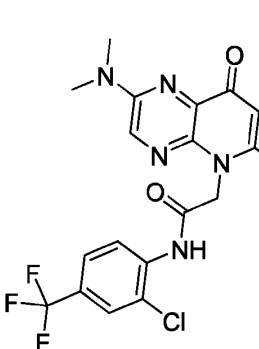
I-266		LCMS 1	744.4	0.52
I-267		LCMS 1	770.5	0.56
I-268		LCMS 4	723.3	0.41

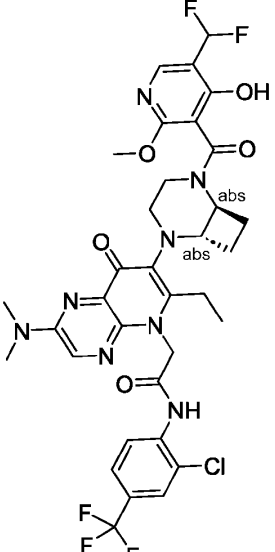
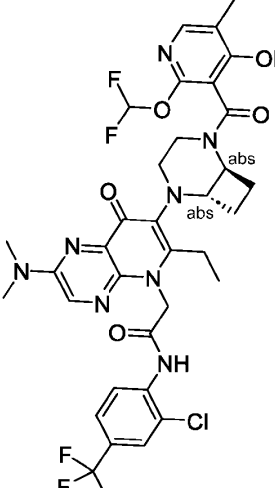
I-269		LCMS 1	758.4	0.57
I-270		LCMS 1	742.3	2.10

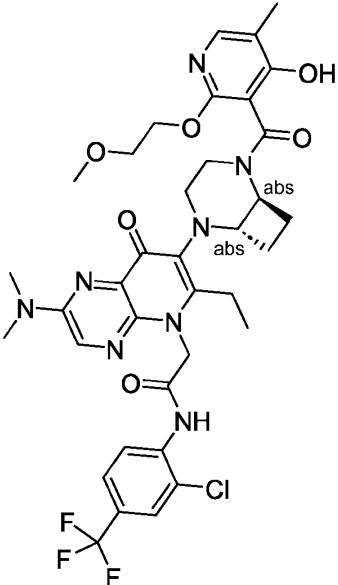
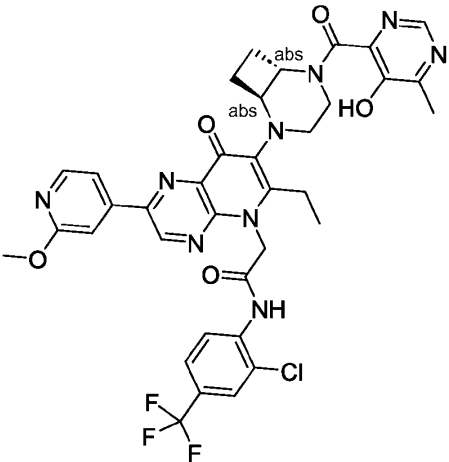
I-271		LCMS 1	742.3	2.12
I-272		LCMS 1	740.3	0.56

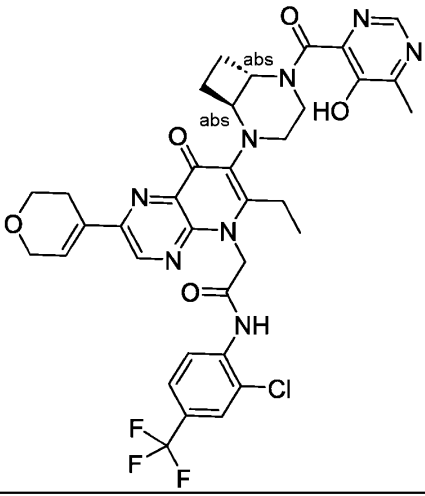
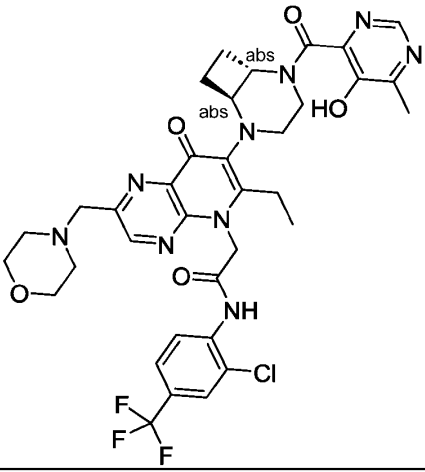
I-273	 Chemical structure of I-273: A complex molecule featuring a central pyrimidine ring system. The pyrimidine ring is substituted with a dimethylamino group (N(CH₃)₂) at position 2, an ethyl group at position 4, and a carbonyl group at position 6. The carbonyl group is linked to a piperidine ring via a carbonyl bridge. The piperidine ring is substituted with a 4-chloro-3-(trifluoromethyl)phenyl group at position 2 and a 4-methoxy-3-hydroxyphenyl group at position 6. The piperidine ring is also substituted with a 4-methoxy-3-hydroxyphenyl group at position 4. The piperidine ring is further substituted with a 4-methoxy-3-hydroxyphenyl group at position 6. The piperidine ring is also substituted with a 4-methoxy-3-hydroxyphenyl group at position 6.	LCMS 1	795.3	0.54
I-274	 Chemical structure of I-274: A complex molecule featuring a central pyrimidine ring system. The pyrimidine ring is substituted with a dimethylamino group (N(CH₃)₂) at position 2, an ethyl group at position 4, and a carbonyl group at position 6. The carbonyl group is linked to a piperidine ring via a carbonyl bridge. The piperidine ring is substituted with a 4-chloro-3-(trifluoromethyl)phenyl group at position 2 and a 4-methoxy-3-hydroxyphenyl group at position 6. The piperidine ring is also substituted with a 4-methoxy-3-hydroxyphenyl group at position 4. The piperidine ring is further substituted with a 4-methoxy-3-hydroxyphenyl group at position 6. The piperidine ring is also substituted with a 4-methoxy-3-hydroxyphenyl group at position 6.	LCMS 1	745.3	2.12

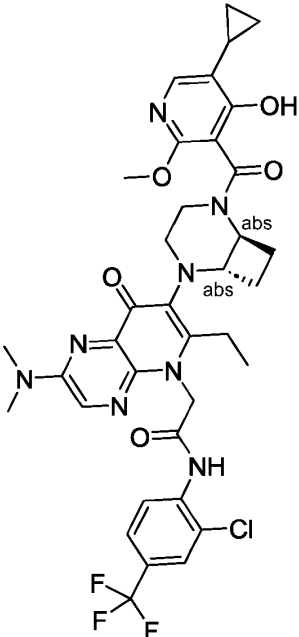
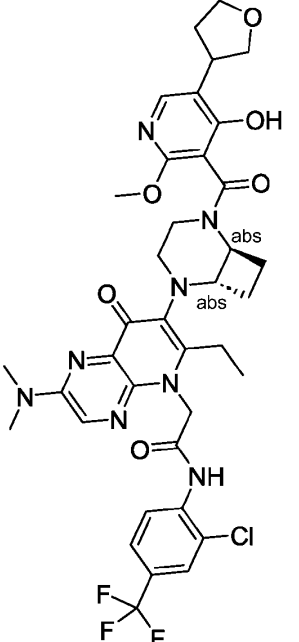
I-275		LCMS 1	743.3	2.16
I-276		LCMS 1	685.3	0.88

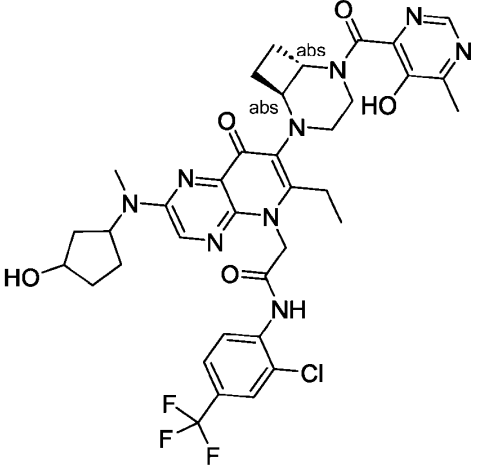
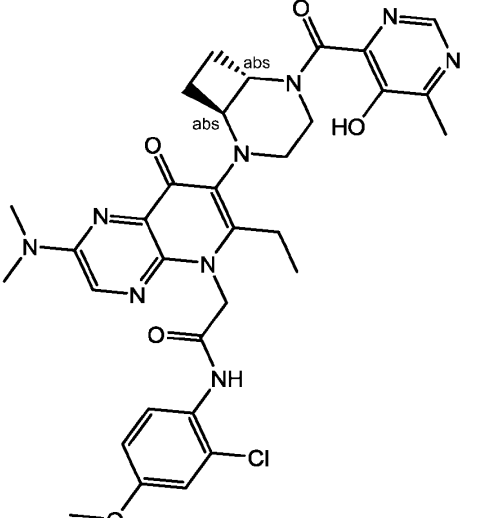
I-277		LCMS 1	685.3	0.88
I-278		LCMS 1	716.3	2.09
I-279		LCMS 1	716.3	2.09

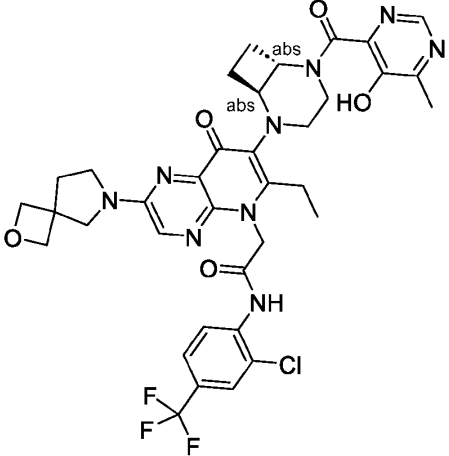
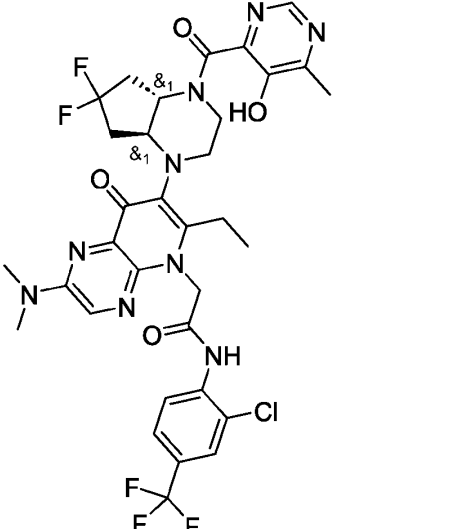
I-280	 Chemical structure of I-280: A complex molecule featuring a central pyrimidine ring system. The pyrimidine ring is substituted with a dimethylamino group (N(CH₃)₂) at position 2, an ethyl group at position 4, and a carbonyl group at position 6. The carbonyl group is part of a side chain that includes a secondary amide (NH) and a 4-chloro-3-(trifluoromethyl)phenyl group. The pyrimidine ring is also substituted with a 4-(2,6-difluorophenyl)-2-methoxyphenyl group at position 5. The 2,6-difluorophenyl group is further substituted with a hydroxyl group (OH) and a carbonyl group (C=O). The carbonyl group is part of a side chain that includes a secondary amide (NH) and a 4-chloro-3-(trifluoromethyl)phenyl group. The pyrimidine ring is also substituted with a 4-(2,6-difluorophenyl)-2-methoxyphenyl group at position 5. The 2,6-difluorophenyl group is further substituted with a hydroxyl group (OH) and a carbonyl group (C=O). The carbonyl group is part of a side chain that includes a secondary amide (NH) and a 4-chloro-3-(trifluoromethyl)phenyl group.	LCMS 1	765.2	2.24
I-281	 Chemical structure of I-281: A complex molecule featuring a central pyrimidine ring system. The pyrimidine ring is substituted with a dimethylamino group (N(CH₃)₂) at position 2, an ethyl group at position 4, and a carbonyl group at position 6. The carbonyl group is part of a side chain that includes a secondary amide (NH) and a 4-chloro-3-(trifluoromethyl)phenyl group. The pyrimidine ring is also substituted with a 4-(2,6-difluorophenyl)-2-methoxyphenyl group at position 5. The 2,6-difluorophenyl group is further substituted with a hydroxyl group (OH) and a carbonyl group (C=O). The carbonyl group is part of a side chain that includes a secondary amide (NH) and a 4-chloro-3-(trifluoromethyl)phenyl group.	LCMS 1	765.3	2.30

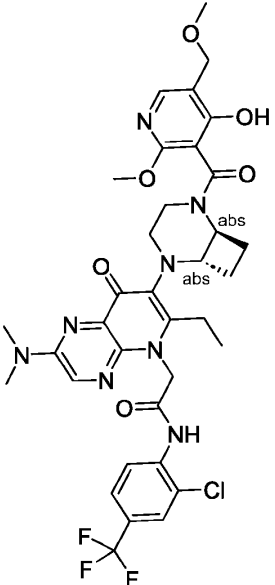
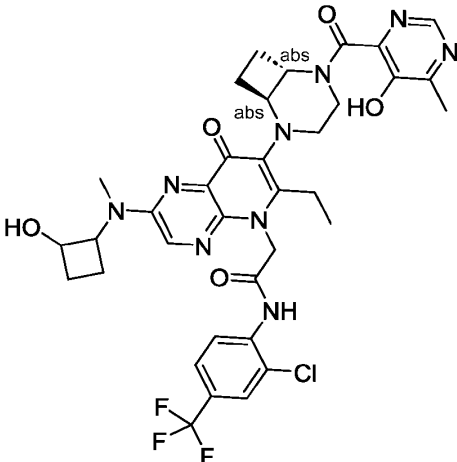
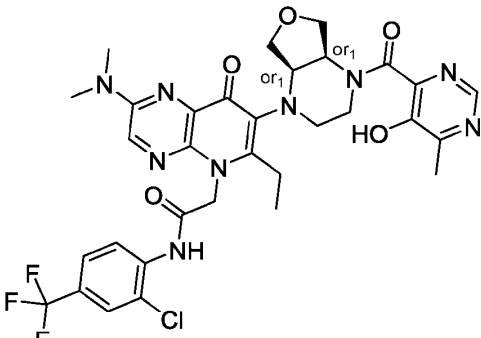
I-282		LCMS 1	773.3	0.54
I-283		LCMS 1	764.3	2.42

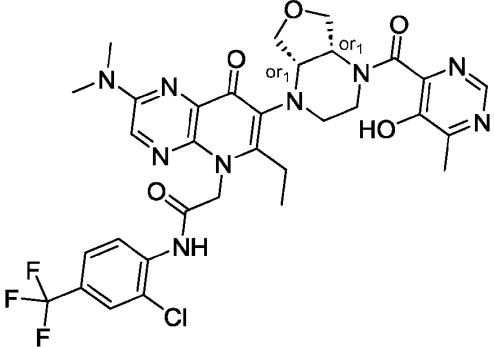
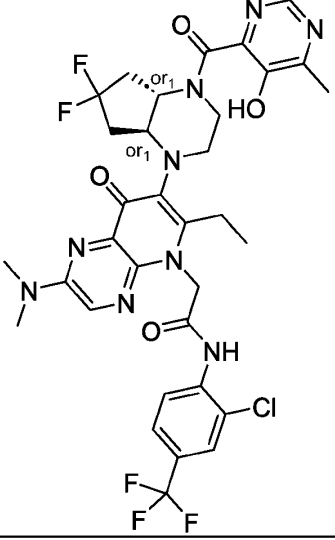
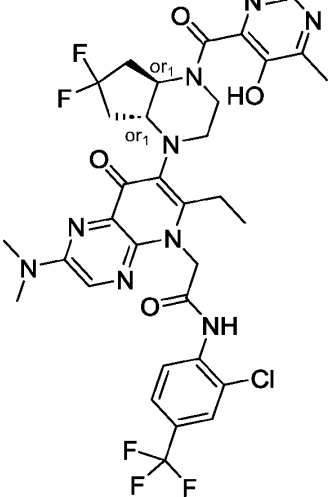
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I-285		LCMS 1	756.3	1.94

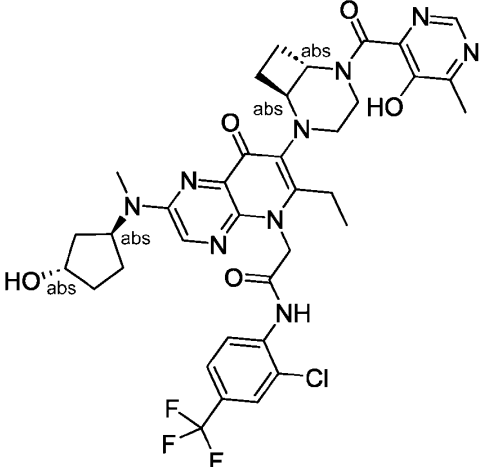
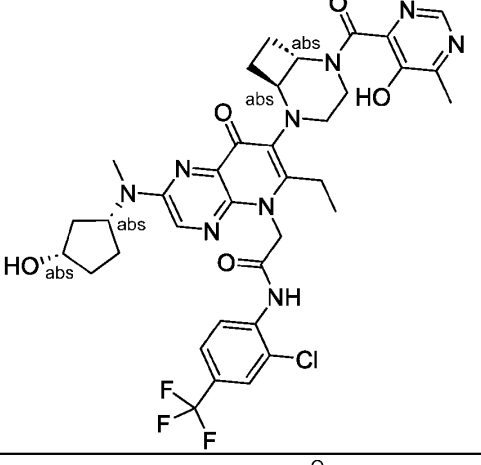
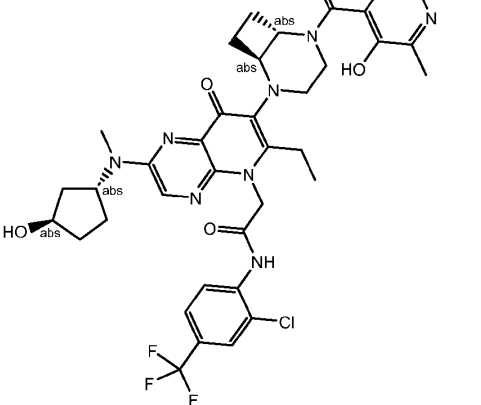
I-286		LCMS 1	755.3	2.23
I-287		LCMS 1	785.3	2.15

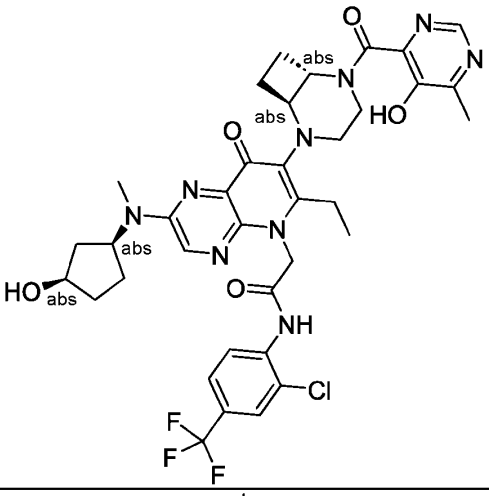
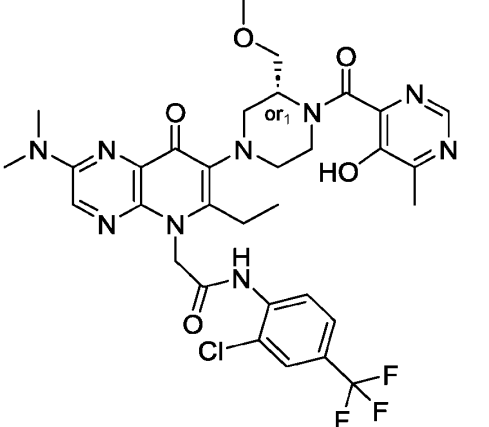
I-288		LCMS 1	770.3	2.19
I-289		LCMS 1	662.3	1.96

I-290		LCMS 1	768.3	2.19
I-291		LCMS 1	750.3	2.47

I-292		LCMS 1	759.4	0.57
I-293		LCMS 1	756.3	2.55
I-294		LCMS 8	716.2	4.04

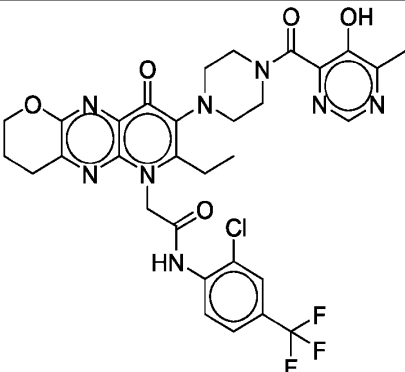
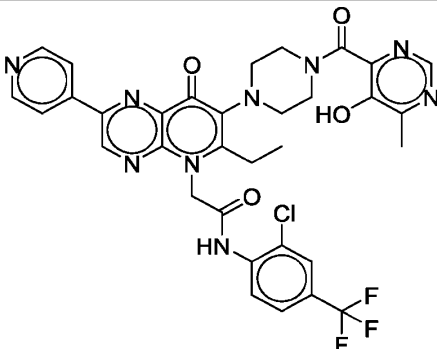
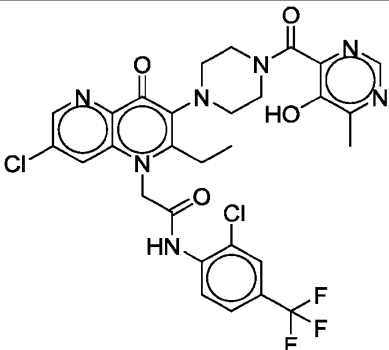
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I-296		LCMS 1	750.3	2.44
I-297		LCMS 1	750.3	2.44

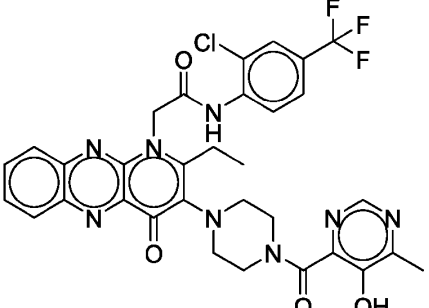
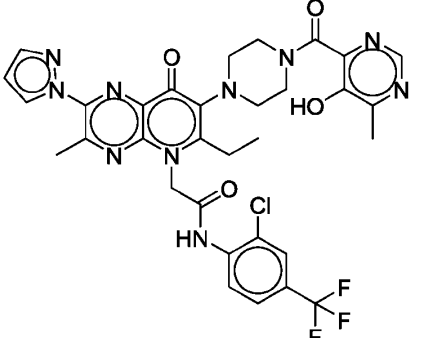
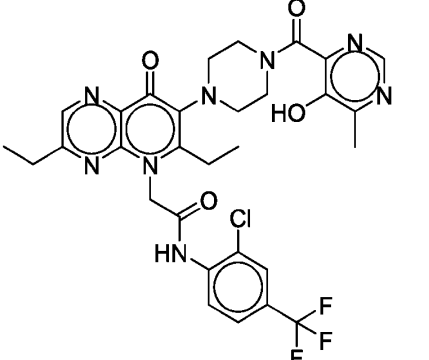
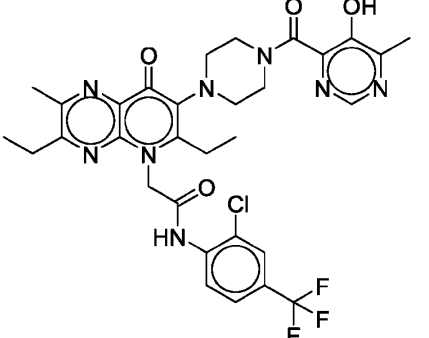
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I-300		LCMS 1	770.3	2.34
I-301		LCMS 1	770.3	2.35

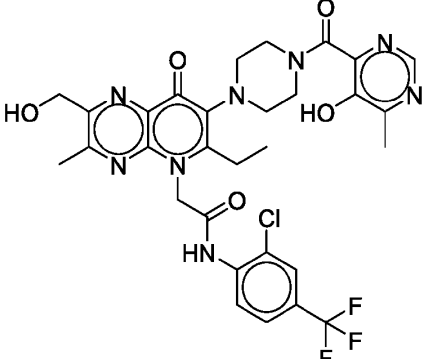
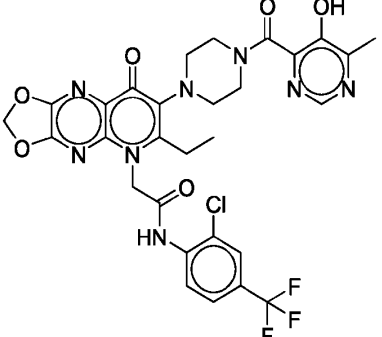
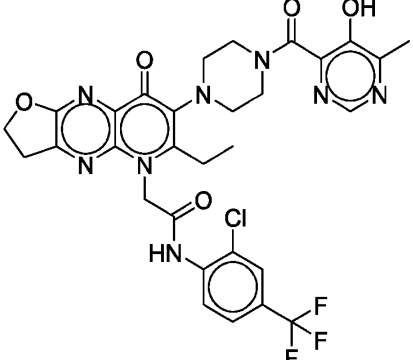
I-302		LCMS 1	770.3	2.33
I-303		LCMS 1	718.2	0.55

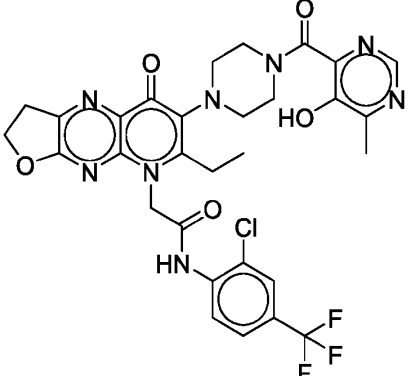
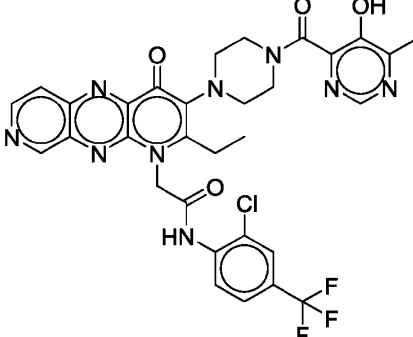
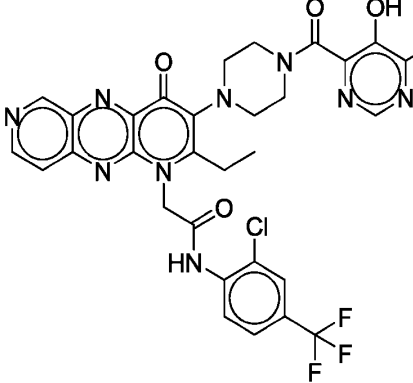
[001514] Further compounds of the disclosure are shown below in Table 2a.

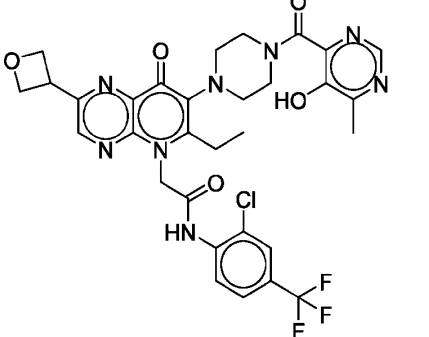
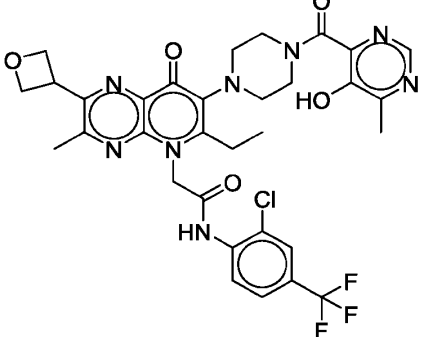
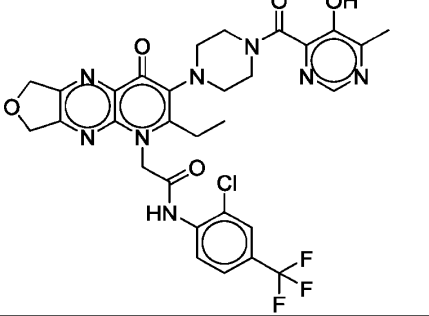
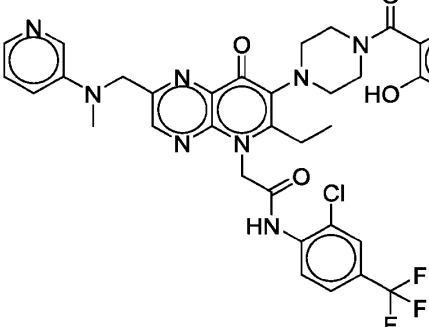
Table 2a

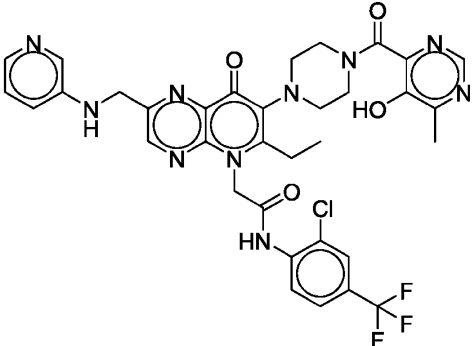
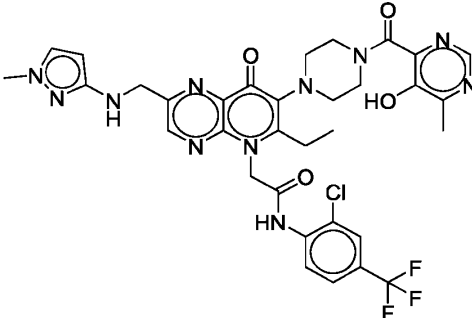
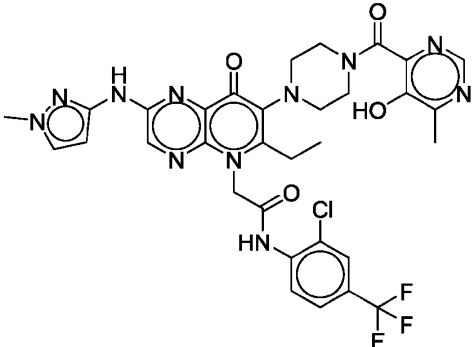
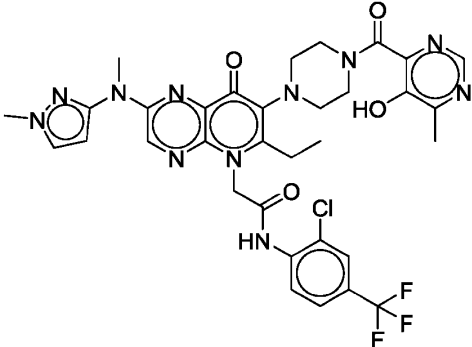
Compound No.	
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I-4a	
I-5a	

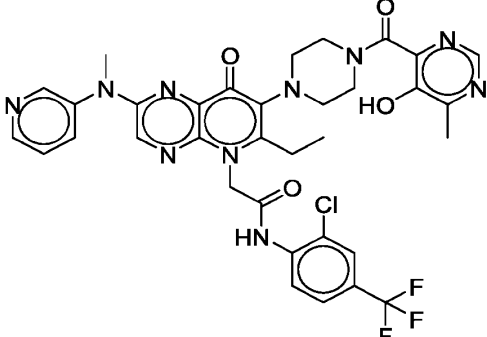
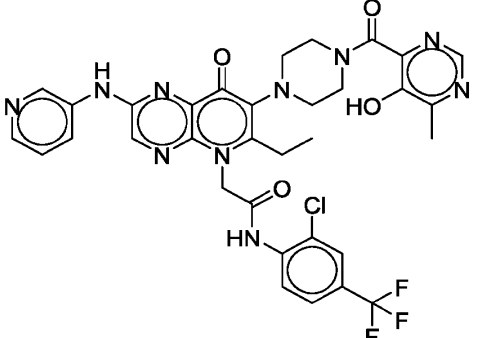
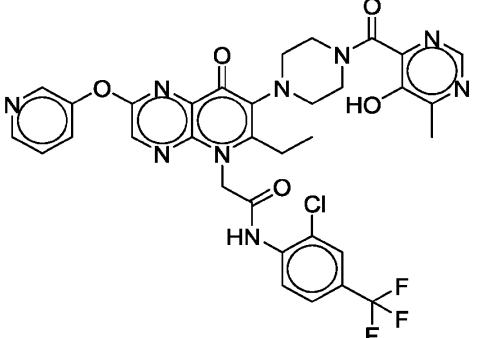
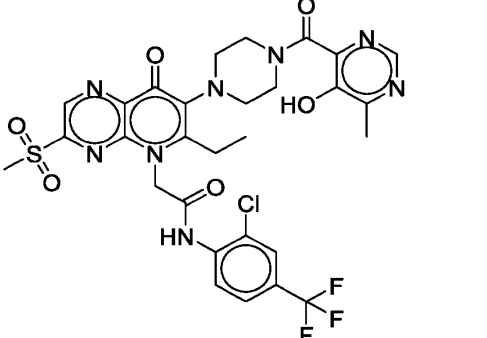
Compound No.	
I-14a	
I-15a	
I-16a	
I-17a	

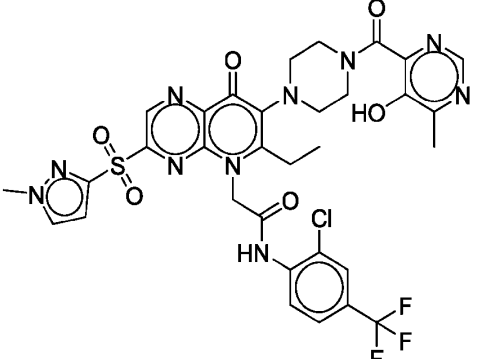
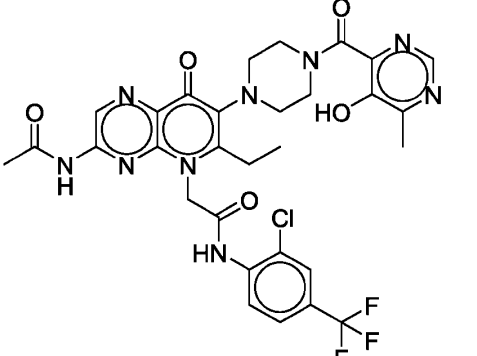
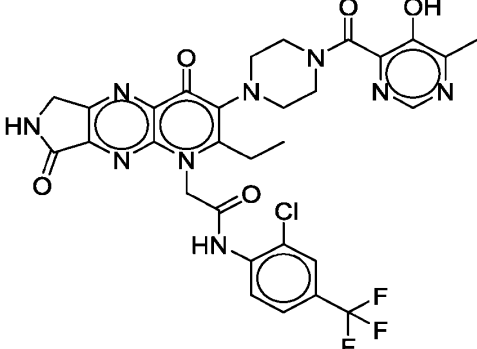
Compound No.	
I-18a	 Chemical structure of I-18a: A complex molecule featuring a quinoline core. The quinoline has a hydroxymethyl group at position 6, an ethyl group at position 8, and a piperazine ring at position 4. The piperazine ring is connected to a pyrimidine-2-carboxamide group. The pyrimidine ring has a hydroxyl group at position 6 and a methyl group at position 5. The quinoline core is also connected to a 4-chloro-2-(trifluoromethyl)phenyl group via an amide linkage.
I-23a	 Chemical structure of I-23a: A complex molecule featuring a quinoline core. The quinoline has a 1,3-dioxolane ring at position 6, an ethyl group at position 8, and a piperazine ring at position 4. The piperazine ring is connected to a pyrimidine-2-carboxamide group. The pyrimidine ring has a hydroxyl group at position 6 and a methyl group at position 5. The quinoline core is also connected to a 4-chloro-2-(trifluoromethyl)phenyl group via an amide linkage.
I-24a	 Chemical structure of I-24a: A complex molecule featuring a quinoline core. The quinoline has a 1,3-dioxolane ring at position 6, an ethyl group at position 8, and a piperazine ring at position 4. The piperazine ring is connected to a pyrimidine-2-carboxamide group. The pyrimidine ring has a hydroxyl group at position 6 and a methyl group at position 5. The quinoline core is also connected to a 4-chloro-2-(trifluoromethyl)phenyl group via an amide linkage.

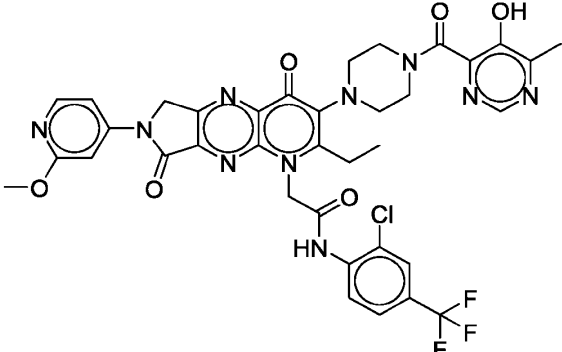
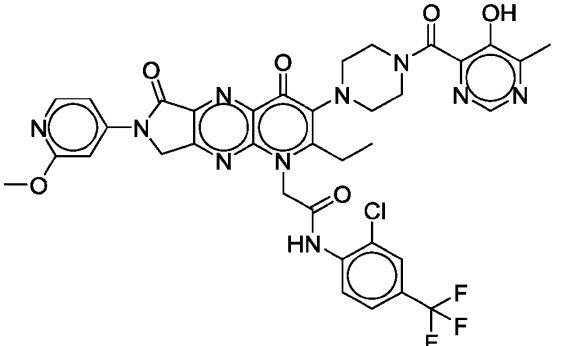
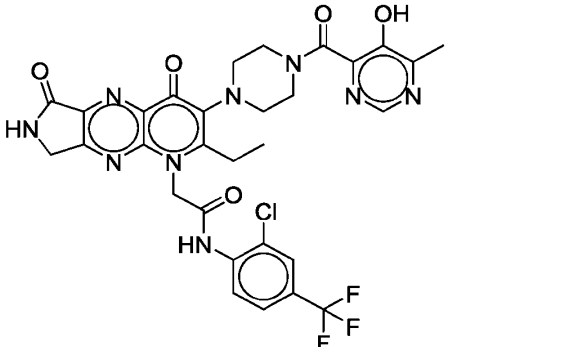
Compound No.	
I-25a	 Chemical structure of I-25a: A complex molecule featuring a 4,5,6,7-tetrahydro-1H-benzofuro[2,3-b]pyridine-2-carboxamide core. The core is substituted with an ethyl group at position 3, a piperidine ring at position 4, and a 2-hydroxy-4-methyl-1H-pyridin-3-yl group at position 5. The amide group is further substituted with a 4-chloro-2-(trifluoromethyl)phenyl group.
I-28a	 Chemical structure of I-28a: A complex molecule featuring a 4,5,6,7-tetrahydro-1H-benzofuro[2,3-b]pyridine-2-carboxamide core. The core is substituted with an ethyl group at position 3, a piperidine ring at position 4, and a 2-hydroxy-4-methyl-1H-pyridin-3-yl group at position 5. The amide group is further substituted with a 4-chloro-2-(trifluoromethyl)phenyl group.
I-29a	 Chemical structure of I-29a: A complex molecule featuring a 4,5,6,7-tetrahydro-1H-benzofuro[2,3-b]pyridine-2-carboxamide core. The core is substituted with an ethyl group at position 3, a piperidine ring at position 4, and a 2-hydroxy-4-methyl-1H-pyridin-3-yl group at position 5. The amide group is further substituted with a 4-chloro-2-(trifluoromethyl)phenyl group.

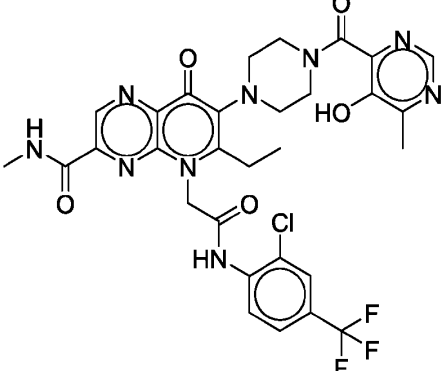
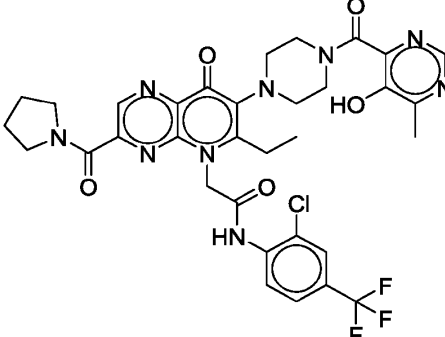
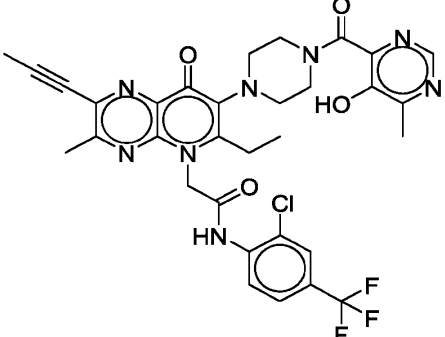
Compound No.	
I-31a	
I-32a	
I-33a	
I-34a	

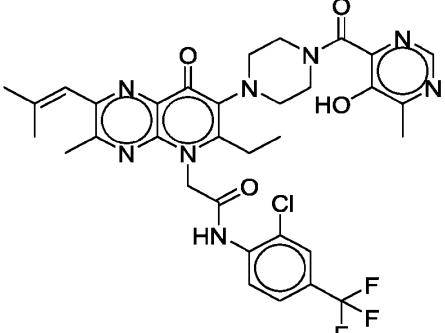
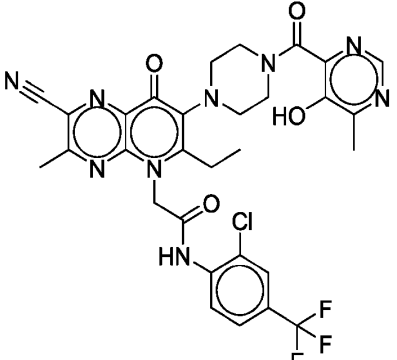
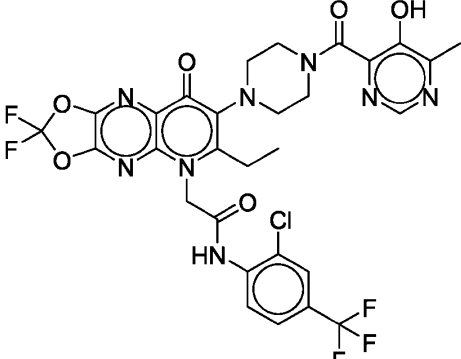
Compound No.	
I-35a	
I-36a	
I-37a	
I-38a	

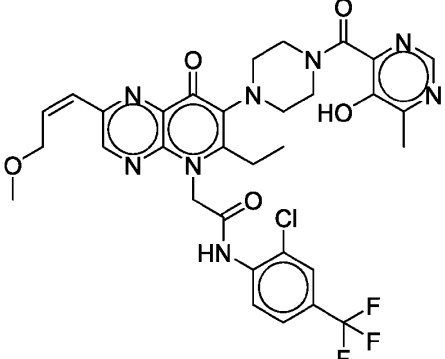
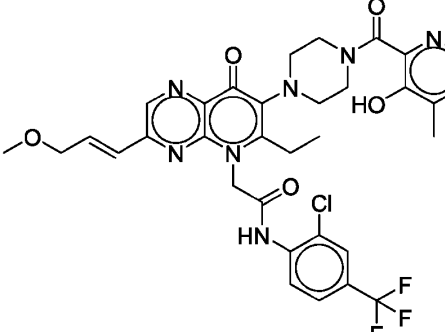
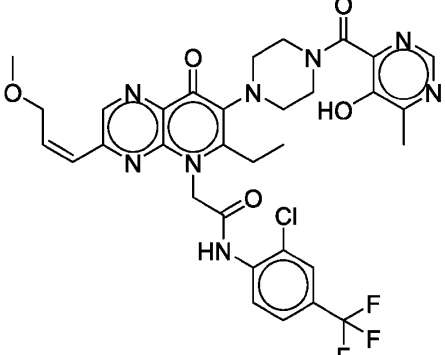
Compound No.	
I-39a	
I-40a	
I-41a	
I-42a	

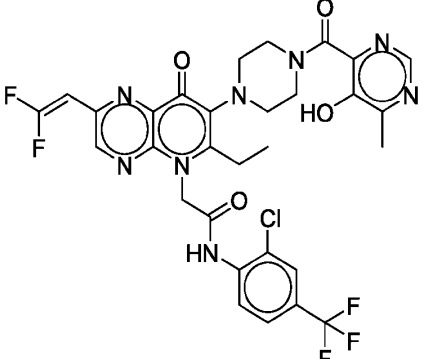
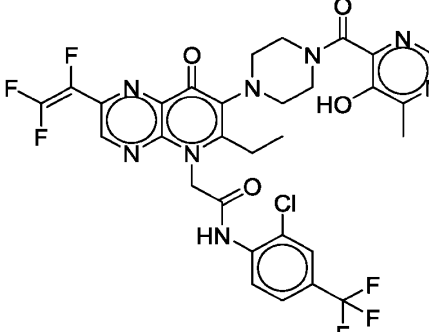
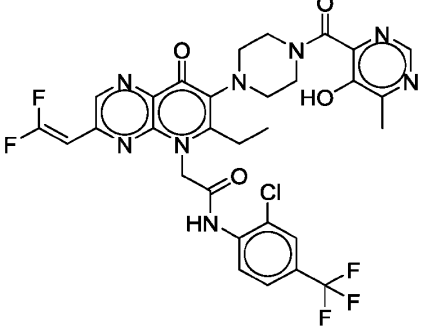
Compound No.	
I-43a	 Chemical structure of I-43a: A complex molecule featuring a central quinazolinone core. The core is substituted with a 4-ethyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl group, a 4-chloro-2-(trifluoromethyl)phenyl group, and a 4-(trifluoromethyl)phenyl group. The quinazolinone core is also substituted with a 4-(trifluoromethyl)phenyl group and a 4-chloro-2-(trifluoromethyl)phenyl group. The quinazolinone core is also substituted with a 4-(trifluoromethyl)phenyl group and a 4-chloro-2-(trifluoromethyl)phenyl group.
I-44a	 Chemical structure of I-44a: A complex molecule featuring a central quinazolinone core. The core is substituted with a 4-ethyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl group, a 4-chloro-2-(trifluoromethyl)phenyl group, and a 4-(trifluoromethyl)phenyl group. The quinazolinone core is also substituted with a 4-(trifluoromethyl)phenyl group and a 4-chloro-2-(trifluoromethyl)phenyl group. The quinazolinone core is also substituted with a 4-(trifluoromethyl)phenyl group and a 4-chloro-2-(trifluoromethyl)phenyl group.
I-45a	 Chemical structure of I-45a: A complex molecule featuring a central quinazolinone core. The core is substituted with a 4-ethyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl group, a 4-chloro-2-(trifluoromethyl)phenyl group, and a 4-(trifluoromethyl)phenyl group. The quinazolinone core is also substituted with a 4-(trifluoromethyl)phenyl group and a 4-chloro-2-(trifluoromethyl)phenyl group. The quinazolinone core is also substituted with a 4-(trifluoromethyl)phenyl group and a 4-chloro-2-(trifluoromethyl)phenyl group.

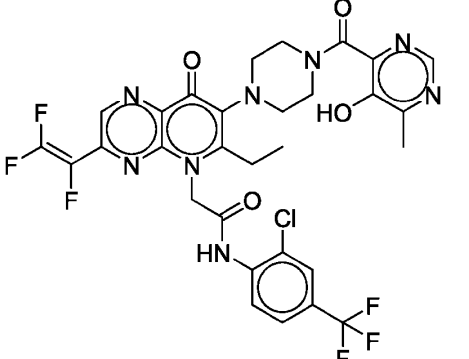
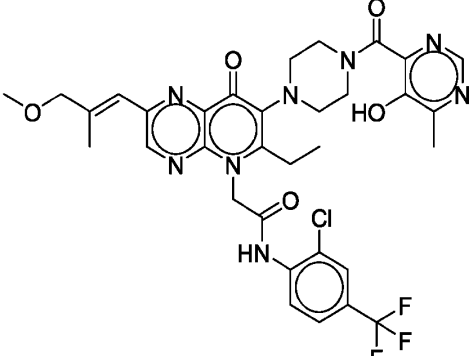
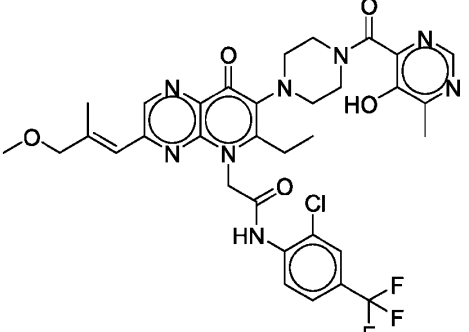
Compound No.	
I-46a	 Chemical structure of I-46a: A complex molecule featuring a central pyrazolo[1,5-a]pyridine core. The core is substituted with a 4-methoxyphenyl group, a 4-chlorophenyl group, and a 4-(trifluoromethyl)phenyl group. The core is also linked to a piperazine ring, which is further substituted with a 4-hydroxyphenyl group.
I-47a	 Chemical structure of I-47a: A complex molecule featuring a central pyrazolo[1,5-a]pyridine core. The core is substituted with a 4-methoxyphenyl group, a 4-chlorophenyl group, and a 4-(trifluoromethyl)phenyl group. The core is also linked to a piperazine ring, which is further substituted with a 4-hydroxyphenyl group.
I-48a	 Chemical structure of I-48a: A complex molecule featuring a central pyrazolo[1,5-a]pyridine core. The core is substituted with a 4-methoxyphenyl group, a 4-chlorophenyl group, and a 4-(trifluoromethyl)phenyl group. The core is also linked to a piperazine ring, which is further substituted with a 4-hydroxyphenyl group.

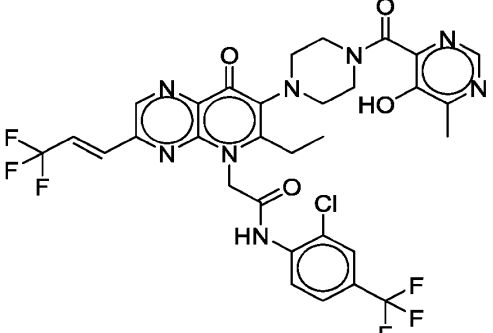
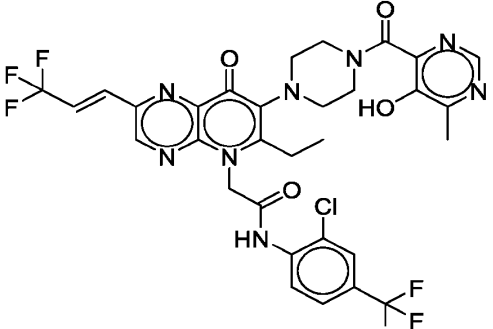
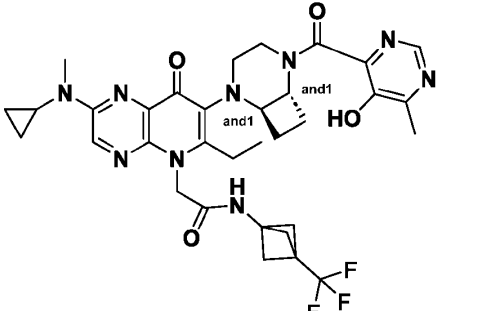
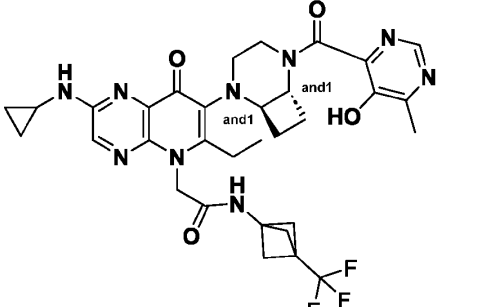
Compound No.	
I-49a	 Chemical structure of I-49a: A complex molecule featuring a quinazolinone core. The quinazolinone has a methylamino group at position 2, an ethyl group at position 4, and a (2-chloro-4-(trifluoromethyl)phenyl)amino group at position 6. It is linked via a methylene group to a piperazine ring, which is further connected to a pyrimidin-2(1H)-one moiety with a methyl group at position 6.
I-50a	 Chemical structure of I-50a: Similar to I-49a, but the methylamino group at position 2 of the quinazolinone is replaced by a pyrrolidin-1-yl group.
I-55a	 Chemical structure of I-55a: Similar to I-49a, but the quinazolinone core is substituted with an ethynyl group at position 8 and a methyl group at position 9.

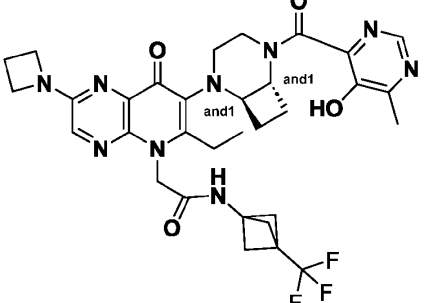
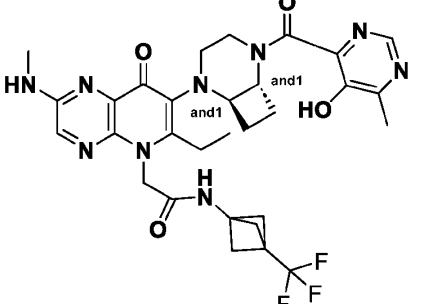
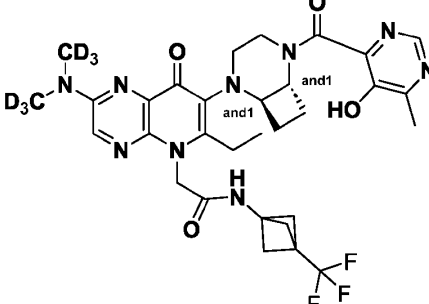
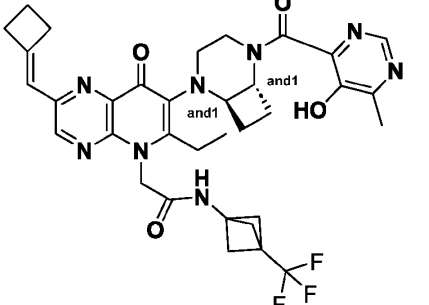
Compound No.	
I-56a	
I-58a	
I-59a	

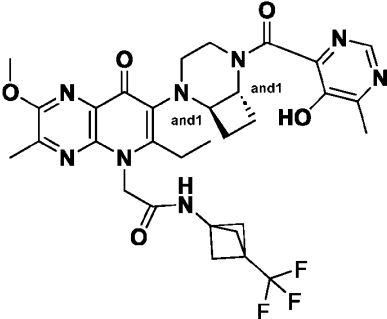
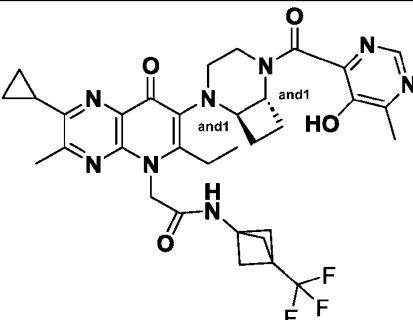
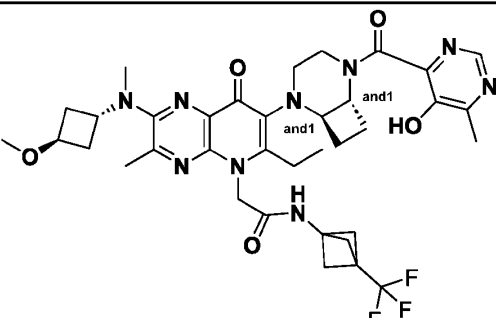
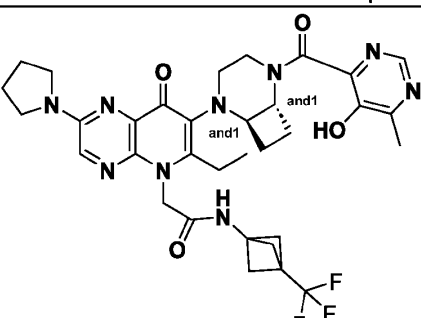
Compound No.	
I-60a	 Chemical structure of I-60a: A complex molecule featuring a quinazolinone core. The quinazolinone has a 4-methoxy-3-vinyl group at position 6, an ethyl group at position 4, and a (2-chloro-4-(trifluoromethyl)phenyl)amino group at position 2. The nitrogen at position 1 is connected via a methylene group to a piperazine ring. The piperazine ring is further connected to a pyrimidin-2(1H)-one moiety, which has a methyl group at position 5 and a hydroxyl group at position 4.
I-61a	 Chemical structure of I-61a: A complex molecule featuring a quinazolinone core. The quinazolinone has a 4-methoxy-3-vinyl group at position 6, an ethyl group at position 4, and a (2-chloro-4-(trifluoromethyl)phenyl)amino group at position 2. The nitrogen at position 1 is connected via a methylene group to a piperazine ring. The piperazine ring is further connected to a pyrimidin-2(1H)-one moiety, which has a methyl group at position 5 and a hydroxyl group at position 4.
I-62a	 Chemical structure of I-62a: A complex molecule featuring a quinazolinone core. The quinazolinone has a 4-methoxy-3-vinyl group at position 6, an ethyl group at position 4, and a (2-chloro-4-(trifluoromethyl)phenyl)amino group at position 2. The nitrogen at position 1 is connected via a methylene group to a piperazine ring. The piperazine ring is further connected to a pyrimidin-2(1H)-one moiety, which has a methyl group at position 5 and a hydroxyl group at position 4.

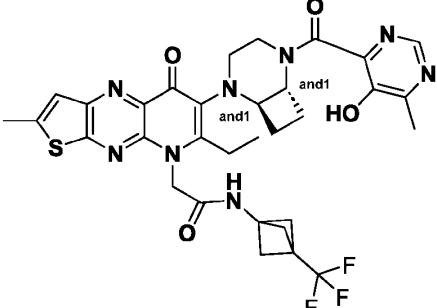
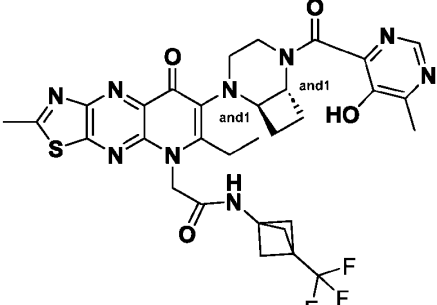
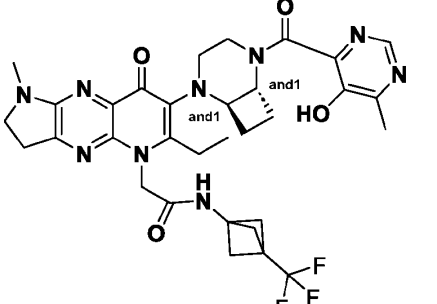
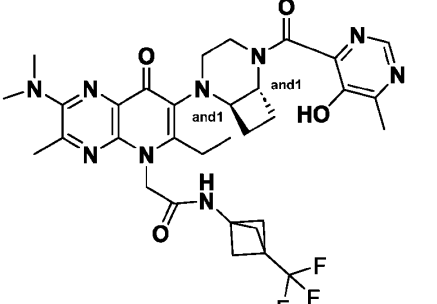
Compound No.	
I-64a	 Chemical structure of I-64a: A complex molecule featuring a quinazolinone core. The quinazolinone has a 2,2-difluoroethyl group at position 4 and a 2-chloro-4-(trifluoromethyl)phenyl group at position 2. The quinazolinone is linked via a piperazine ring to a pyrimidin-2(1H)-one moiety. The pyrimidin-2(1H)-one has a methyl group at position 6 and a hydroxyl group at position 4.
I-65a	 Chemical structure of I-65a: A complex molecule featuring a quinazolinone core. The quinazolinone has a 2,2-difluoroethyl group at position 4 and a 2-chloro-4-(trifluoromethyl)phenyl group at position 2. The quinazolinone is linked via a piperazine ring to a pyrimidin-2(1H)-one moiety. The pyrimidin-2(1H)-one has a methyl group at position 6 and a hydroxyl group at position 4.
I-66a	 Chemical structure of I-66a: A complex molecule featuring a quinazolinone core. The quinazolinone has a 2,2-difluoroethyl group at position 4 and a 2-chloro-4-(trifluoromethyl)phenyl group at position 2. The quinazolinone is linked via a piperazine ring to a pyrimidin-2(1H)-one moiety. The pyrimidin-2(1H)-one has a methyl group at position 6 and a hydroxyl group at position 4.

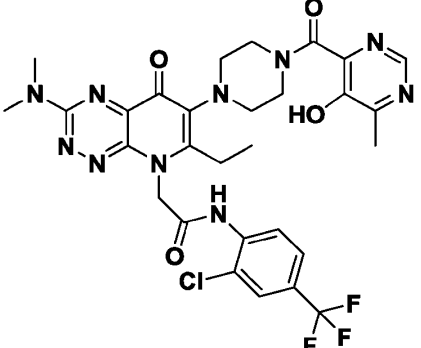
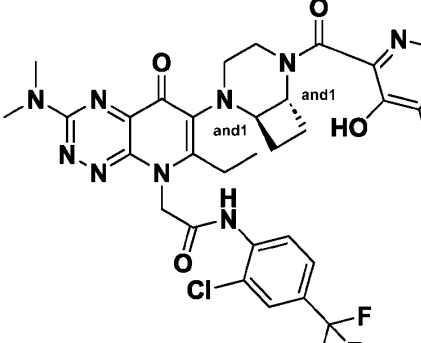
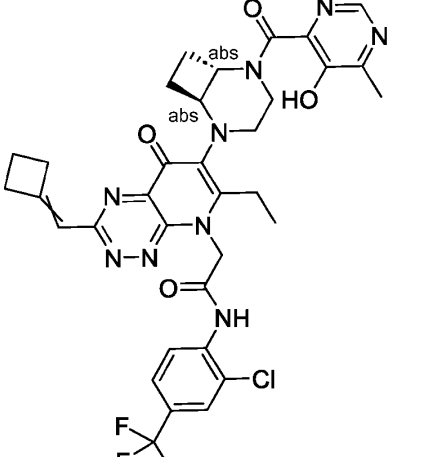
Compound No.	
I-67a	 Chemical structure of I-67a: A complex molecule featuring a quinazolinone core. The quinazolinone has a 2,2-difluoroethyl group at position 4 and a 2-ethyl-2-oxo-1-(4-chloro-3-(trifluoromethyl)phenyl)ethyl group at position 3. The quinazolinone is linked via a piperazine ring to a pyrimidin-2(1H)-one moiety, which has a methyl group at position 6 and a hydroxyl group at position 4.
I-68a	 Chemical structure of I-68a: A complex molecule featuring a quinazolinone core. The quinazolinone has a 2-methoxy-2-methylprop-1-en-1-yl group at position 4 and a 2-ethyl-2-oxo-1-(4-chloro-3-(trifluoromethyl)phenyl)ethyl group at position 3. The quinazolinone is linked via a piperazine ring to a pyrimidin-2(1H)-one moiety, which has a methyl group at position 6 and a hydroxyl group at position 4.
I-69a	 Chemical structure of I-69a: A complex molecule featuring a quinazolinone core. The quinazolinone has a 2-methoxy-2-methylprop-1-en-1-yl group at position 4 and a 2-ethyl-2-oxo-1-(4-chloro-3-(trifluoromethyl)phenyl)ethyl group at position 3. The quinazolinone is linked via a piperazine ring to a pyrimidin-2(1H)-one moiety, which has a methyl group at position 6 and a hydroxyl group at position 4.

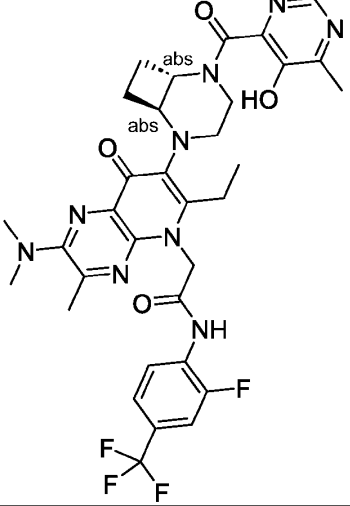
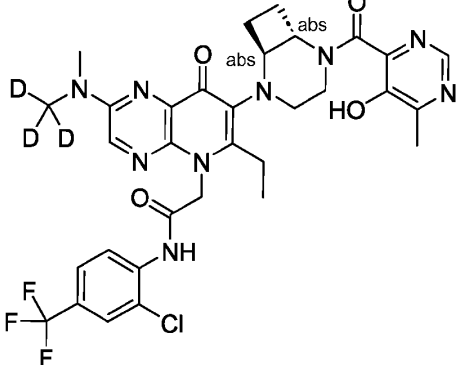
Compound No.	
I-70a	
I-71a	
I-72a	
I-73a	

Compound No.	
I-74a	
I-75a	
I-76a	
I-77a	

Compound No.	
I-78a	
I-79a	
I-80a	
I-81a	

Compound No.	
I-82a	 Chemical structure of I-82a: A complex molecule featuring a thienopyrimidine core. The thienopyrimidine ring is substituted with a methyl group at the 2-position and a carbonyl group at the 4-position. The nitrogen at the 1-position is linked via a methylene group to a carbonyl group, which is further linked to a cyclobutyl ring. The cyclobutyl ring is substituted with a trifluoromethyl group. The thienopyrimidine ring is also linked via a methylene group to a carbonyl group, which is further linked to a cyclobutyl ring. The cyclobutyl ring is substituted with a trifluoromethyl group. The thienopyrimidine ring is also linked via a methylene group to a carbonyl group, which is further linked to a cyclobutyl ring. The cyclobutyl ring is substituted with a trifluoromethyl group.
I-83a	 Chemical structure of I-83a: A complex molecule featuring a thienopyrimidine core. The thienopyrimidine ring is substituted with a methyl group at the 2-position and a carbonyl group at the 4-position. The nitrogen at the 1-position is linked via a methylene group to a carbonyl group, which is further linked to a cyclobutyl ring. The cyclobutyl ring is substituted with a trifluoromethyl group. The thienopyrimidine ring is also linked via a methylene group to a carbonyl group, which is further linked to a cyclobutyl ring. The cyclobutyl ring is substituted with a trifluoromethyl group. The thienopyrimidine ring is also linked via a methylene group to a carbonyl group, which is further linked to a cyclobutyl ring. The cyclobutyl ring is substituted with a trifluoromethyl group.
I-84a	 Chemical structure of I-84a: A complex molecule featuring a thienopyrimidine core. The thienopyrimidine ring is substituted with a methyl group at the 2-position and a carbonyl group at the 4-position. The nitrogen at the 1-position is linked via a methylene group to a carbonyl group, which is further linked to a cyclobutyl ring. The cyclobutyl ring is substituted with a trifluoromethyl group. The thienopyrimidine ring is also linked via a methylene group to a carbonyl group, which is further linked to a cyclobutyl ring. The cyclobutyl ring is substituted with a trifluoromethyl group. The thienopyrimidine ring is also linked via a methylene group to a carbonyl group, which is further linked to a cyclobutyl ring. The cyclobutyl ring is substituted with a trifluoromethyl group.
I-85a	 Chemical structure of I-85a: A complex molecule featuring a thienopyrimidine core. The thienopyrimidine ring is substituted with a methyl group at the 2-position and a carbonyl group at the 4-position. The nitrogen at the 1-position is linked via a methylene group to a carbonyl group, which is further linked to a cyclobutyl ring. The cyclobutyl ring is substituted with a trifluoromethyl group. The thienopyrimidine ring is also linked via a methylene group to a carbonyl group, which is further linked to a cyclobutyl ring. The cyclobutyl ring is substituted with a trifluoromethyl group. The thienopyrimidine ring is also linked via a methylene group to a carbonyl group, which is further linked to a cyclobutyl ring. The cyclobutyl ring is substituted with a trifluoromethyl group.

Compound No.	
I-86a	 Chemical structure of I-86a: A complex molecule featuring a 1,2,4-triazole ring system. The triazole is substituted with a methyl group at position 4 and a 1-ethyl-2-((2-chloro-4-(trifluoromethyl)phenyl)amino)ethyl group at position 5. The triazole is also connected to a 1,2,4-triazole-5-carboxamide derivative, which is further substituted with a methyl group at position 6 and a hydroxyl group at position 7. The amide group is connected to a 1,2,4-triazole ring system, which is substituted with a methyl group at position 4 and a hydroxyl group at position 5. The amide group is also connected to a 1,2,4-triazole ring system, which is substituted with a methyl group at position 4 and a hydroxyl group at position 5.
I-87a	 Chemical structure of I-87a: A complex molecule featuring a 1,2,4-triazole ring system. The triazole is substituted with a methyl group at position 4 and a 1-ethyl-2-((2-chloro-4-(trifluoromethyl)phenyl)amino)ethyl group at position 5. The triazole is also connected to a 1,2,4-triazole-5-carboxamide derivative, which is further substituted with a methyl group at position 6 and a hydroxyl group at position 7. The amide group is connected to a 1,2,4-triazole ring system, which is substituted with a methyl group at position 4 and a hydroxyl group at position 5. The amide group is also connected to a 1,2,4-triazole ring system, which is substituted with a methyl group at position 4 and a hydroxyl group at position 5.
I-89a	 Chemical structure of I-89a: A complex molecule featuring a 1,2,4-triazole ring system. The triazole is substituted with a methyl group at position 4 and a 1-ethyl-2-((2-chloro-4-(trifluoromethyl)phenyl)amino)ethyl group at position 5. The triazole is also connected to a 1,2,4-triazole-5-carboxamide derivative, which is further substituted with a methyl group at position 6 and a hydroxyl group at position 7. The amide group is connected to a 1,2,4-triazole ring system, which is substituted with a methyl group at position 4 and a hydroxyl group at position 5. The amide group is also connected to a 1,2,4-triazole ring system, which is substituted with a methyl group at position 4 and a hydroxyl group at position 5.

Compound No.	
I-91a	
I-95a	

LCMS methods

LCMS 1

Instrument	Shimadzu LCMS-2020
Stationary Phase	HALO C18 3.0X30mm, 5.0μm
Mode	Binary Gradient
Mobile Phase A	0.0375% TFA in water (v/v)
Mobile Phase B	0.01875% TFA in Acetonitrile (v/v)
Gradient	5 to 95% B in 0.5min, 95% B for 0.3min, 95 to 5% B in 0.25min
Flow Rate	1.5 mL/min
Column Temperature	50 °C

Column 3.0X30mm, 5.0µm

LCMS 2

Instrument Shimadzu LCMS-2020
Stationary Phase HALO C18
Mode Binary Gradient
Mobile Phase A water/0.05%TFA
Mobile Phase B ACN/0.05%TFA
Gradient 5% to 100% B in 1.2 min, hold 100% B in 0.6 min
Flow Rate (mL/min) 1.5
Column Temperature (°C) 40
Column Dimensions 30x3.0mm, 2.0µm

LCMS 3

Instrument Shimadzu LCMS-2020
Stationary Phase HALO C18
Mode Binary Gradient
Mobile Phase A water/0.05%TFA
Mobile Phase B ACN/0.05%TFA
Gradient 5% to 60% B in 1.7 min, 60% to 100% B in 0.6 min, hold
100% B in 0.5 min
Flow Rate (mL/min) 1.5
Column Temperature (°C) 40
Column Dimensions 30x3.0mm, 2.0µm

LCMS 4

Instrument Shimadzu LCMS-2020
Mode Binary Gradient
Stationary Phase Kinetex EVO C18 2.1X30mm, 5µm
Mobile Phase A 0.025% NH₃·H₂O in water (v/v)
Mobile Phase B Acetonitrile
Column Dimensions 2.1X30mm, 5µm
Flow Rate (mL/min) 1.5
Column Temperature (°C) 40
Gradient 5% to 95% B in 0.8min, hold 95%B for 0.4min, 95% to 5%B in

0.01min, hold 5%B for 0.34min

LCMS 8

Instrument	Shimadzu LCMS-2020
Mode	Binary gradient
Stationary Phase	CORTECS C18
Mobile Phase A	water/0.1%FA
Mobile Phase B	ACN/0.07%FA
Column Dimensions	30x2.1mm, 2.7µm
Flow Rate (mL/min)	1.2
Column Temperature (°C)	40
Gradient	5% to 100% B in 1.2 min, hold 100% B in 0.6 min

LCMS 9

Instrument	Shimadzu LCMS-2020
Mode	Binary gradient
Stationary Phase	Luna Omega PS C18
Mobile Phase A	water/0.1%FA
Mobile Phase B	ACN/0.07%FA
Column Dimensions	30x2.1mm, 3.0µm
Flow Rate (mL/min)	1.2
Column Temperature (°C)	40
Gradient	5% to 60% B in 1.7 min, 60% to 100% B in 0.6 min, hold 100% B in 0.5 min

LCMS 10

Instrument	Shimadzu LCMS-2020
Mode	Binary gradient
Stationary Phase	HALO C18
Mobile Phase A	water/0.05%TFA
Mobile Phase B	ACN/0.05%TFA
Column Dimensions	30x3.0mm, 2.0µm

Flow Rate (mL/min)	1.5
Column Temperature (°C)	40
Gradient	20% to 50% B in 1.7 min, 50% to 95% B in 0.6 min, hold 100% B in 0.5 min

LCMS 11

Instrument	Shimadzu LCMS-2020
Mode	Binary Gradient
Stationary Phase	Kinetex EVO C18 2.1X30mm, 5µm
Mobile Phase A	0.025% NH ₃ ·H ₂ O in water (v/v)
Mobile Phase B	Acetonitrile
Column Dimensions	2.1X30mm, 5µm
Flow Rate (mL/min)	1.5
Column Temperature (°C)	40
Gradient	0% to 60% B in 0.8min, hold 60%B for 0.4min, 60% to 0%B in 0.01min, hold 0%B for 0.34min

Example 2: WRN (BV08) ADP-Glo assay protocol

[001515] Bovine skin gelatin (BSG), dimethyl sulfoxide (DMSO), Pluronic F-127 and tris(2-carboxyethyl)phosphine hydrochloride solution (TCEP) were purchased from Sigma-Aldrich (St. Louis, MO) at the highest level of purity possible. Bicine buffer solution was purchased from Alfa Aesar (Tewksbury, MA) and compound NSC-617145 was purchased from Tocris (Minneapolis, MN). DNA duplex was synthesized at BGI (Shenzhen, China) and was composed of strand 1 with the sequence 5'-GCACTGGCCGTCGTTTTACGGTCG-3' (SEQ ID NO.: 1) and strand 2 with the sequence 5'-TCCAAGTAAACGACGGCCAGTGC-3' (SEQ ID NO.: 2). DNA strands were annealed by heating to 95°C for 5 minutes followed by slow cooling to room temperature. Compounds in 100% DMSO (0.1 µl) were spotted into a 384-well white polystyrene Optiplate-384 (Perkin Elmer; Waltham, MA) assay plate using a LabCyte Echo 550 (Agilent; Santa Clara, CA). DMSO (0.1 µl) was added to columns 12, rows A-H and column 24, rows I-P for the maximum signal control. Compound NSC-617145 (0.1 µl) was added to columns 12, rows I-P and 24, rows A-H for the minimum signal control (100% inhibition). Compounds/DMSO were

preincubated for 15 minutes at 25°C with 5 µl 2X WRN (BV08), prepared as described below, in assay buffer containing 20 mM Bicine (pH = 7.5), 1 mM MgCl₂, 10 mM KCl, 0.1% Pluronic F-127, 0.005% BSG, 1 mM TCEP. The reaction was initiated by the addition of 5 µl 2X substrate mixture in assay buffer and incubated for 60 minutes at 25°C. The final concentrations of the assay components were 0.15 nM WRN, 5 µM ATP, and 0.1 nM DNA duplex. The final DMSO concentration was 1% and the reference compound concentration (NSC-617145) used for the minimal signal control was 20 µM. The reaction was stopped by the addition of the ADP-Glo Kit components (Promega; Madison, WI) as directed and the relative luminescence units (RLU) were read on an Envision 2104 (Perkin Elmer; Waltham, MA).

% inhibition calculation:

$$\%INH = (RLU\ MAX - RLU\ sample) / (RLU\ MAX - RLU\ MIN) \times 100$$

Where RLU = relative luminescence units, sample = signal in sample well, and MIN and MAX are the respective minimum and maximum signal controls.

Four-parameter IC₅₀ fit equation:

$$Y = Bottom + (Top - Bottom) / (1 + (IC50/X)^{Hill\ Slope})$$

Where top and bottom are normally allowed to float but may be fixed at 100 or 0 respectively in a 3-parameter fit. Y is the % inhibition and X is the compound concentration.

WRN protein production

[001516] Molecular Biology and virus production. The DNA encoding human Werner helicase (Uniprot Q14191, amino acids 517-1235 with L1074F point mutation) was generated with codon-optimization for *E.coli* expression and subcloned into the pFastBac vector with a TEV cleavable 8xHis tag (WRN-BV08). The baculovirus from the expression plasmid WRN-BV08 was generated from transfection and amplification following the manufacturer's instructions.

[001517] Gene sequence of WRN-BV08 [pFastBac1-WRN-(517-1235 L1074F)-TEV-8His] (SEQ ID NO.: 3)

ATGAACGAGGGCGAAGAAGACGACGACAAGGACTTCCTGTGGCCTGCCCCTAACGA
AGAACAAGTGACATGCCTGAAGATGTACTTCGGACACAGTAGCTTCAAGCCTGTGC
AATGGAAGGTCATCCACTCCGTGCTGGAAGAAAGAAGGGACAACGTGGCTGTGATG
GCTACCGGATACGGTAAGTCCCTGTGCTTCCAGTACCCTCCCGTGTACGTGGGCAAG
ATCGGTCTGGTGATCTCCCCTCTGATCTCTCTGATGGAGGACCAGGTGCTGCAATTG
AAGATGTCCAACATCCCCGCTTGCTTCCTGGGTTCGGCTCAAAGTGAGAACGTGCTG

ACAGACATCAAGCTGGGCAAGTACCGCATCGTGTACGTGACCCCTGAGTACTGCTCC
GGTAACATGGGTCTGCTGCAACAGCTGGAGGCTGACATCGGAATCACCTGATCGCT
GTGGACGAGGCTCACTGCATCTCCGAGTGGGGACACGACTTCCGCGACTCCTTCCGT
AAGCTGGGATCCTTGAAGACCGCTCTCCCTATGGTGCCTATCGTGGCCCTGACCGCC
ACTGCTTCCTCCTCCATCCGCGAGGACATCGTGC GTTGCCTGAACCTGCGCAACCCT
CAGATCACTTGCACCGGTTTCGACCGCCCTAACTTGTACCTCGAGGTGCGTCGCAAG
ACCGGTAACATCCTCCAGGACCTGCAGCCTTTCCTGGTCAAGACCTCCTCCCACTGG
GAATTTGAGGGCCCTACCATCATCTACTGCCCTTCCCGCAAGATGACCCAGCAAGTC
ACCGGCGAGCTGCGCAAGCTCAACCTCTCCTGCGGTACCTACCACGCTGGTATGTCC
TTCTCCACCCGCAAGGACATCCACCACCGCTTCGTCCGTGACGAAATCCAATGCGTC
ATCGCTACCATCGCTTTCGGAATGGGCATCAACAAGGCTGACATCCGCCAGGTGATC
CACTACGGCGCCCCCAAGGACATGGAATCCTACTACCAGGAAATCGGTGCGCGCCGG
TCGCGACGGTCTGCAGTCTTCCTGTCACGTGCTGTGGGCCCCCGCTGACATCAACCT
GAACCGCCACCTGCTGACCGAAATCCGCAACGAGAAGTTCCGCCTGTACAAGCTCA
AGATGATGGCTAAGATGGAGAAGTACCTGCACTCCTCCCGCTGTGCGCCGTCAGATCA
TCCTCTCCCACTTCGAGGACAAGCAAGTGCAAAAGGCTAGCCTGGGTATCATGGGC
ACCGAAAAGTGTTGTGACAACCTGCCGCTCCCGCCTCGACCACTGCTACTCCATGGAC
GACAGCGAGGACACCTCCTGGGACTTCGGTCTCTCAAGCTTTCAGCTCTTGTCCGCT
GTGGACATCCTGGGCGAGAAGTTCGGTATCGGTCTCCCCATCCTCTTCCTGCGTGGT
AGCAACTCCCAACGCCTGGCTGACCAGTACCGCCGCCACTCCCTCTTCGGTACCGGT
AAGGACCAGACCGAGTCCTGGTGGAAAGGCTTTCCTCTCGCCAACTGATCACCGAAGG
TTTCCTGGTGGAGGTGTCCCGCTACAACAAGTTCATGAAGATCTGCGCTCTCACTAA
GAAGGGAAGGAACCTGGCTGCACAAGGCTAACACTGAGTCCCAATCCCTCATCCTGC
AGGCTAACGAGGAGCTGTGCCCTAAGAAGTTCCTGCTGCCTTCCTCCAAGACCGTGT
CCTCCGGAACAAAGGAACACTGCTACAACCAAGTCCCTGTGGAGCTCTCCACCGAG
AAGAAGTCCAACCTGGAGAAGCTGTACAGCTACAAGCCTTGCGACAAGATCAGCTC
CGGTTCCAACATCAGCAAGAAGTCCATCATGGTGCAATCCCCTGAAAAGGCCTACTC
CAGCTCCCAACCTGTCATCTCCGCTCAAGAGCAAGAGACCCAGATCGTGCTGTACGG
TAAGCTGGTGAAGCCCGCCAAAAGCACGCTAACAAGATGGACGTCCCTCCCGCTA
TCCTCGCCACCAACAAGATCCTCGTGGATATGGCTAAGATGCGCCCCACCACCGTCG
AGAACGTGAAGCGCATCGACGGTGTCTCCGAGGGTAAGGCCGCTATGCTGGCTCCT

CTGCTGGAAGTGATCAAGCACTTCTGCCAGACCAACTCCGTGCAGACCGACCTGTTC
AGTAGTGAGAACCTGTACTTCCAAGGCCACCATCATCATCATCACCCTAA

[001518] Protein sequence of WRN-BV08 [pFastBac1-WRN-(517-1235 L1074F)-TEV-8His] (SEQ ID NO.: 4)

MNEGEEDDDKDFLWPAPNEEQVTCLKMYFGHSSFKPVQWKVIHSVLEERRDNVAVMA
TGYGKSLCFQYPPVYVGKIGLVISPLISLMEDQVLQLKMSNIPACFLGSAQSENVLTDIKL
GKYRIVYVTPEYCSGNMGLLQQLEADIGITLIAVDEAHCISEWGHDFRDSFRKLGSLKTA
LPMVPIVALTATASSIREDIVRCLNLRNPQITCTGFDRPNLYLEVRRKTGNILQDLQPFL
VKTSSHWEFEGPTIIYCPSRKMTQQVTGELRKLNLSCGTYHAGMSFSTRKDIHHRFVRD
EIQCVIATIAFGMGINKADIRQVIHYGAPKDMESYYQEIGRAGRDLQSSCHVLWAPADI
NLNRHLLTEIRNEKFRLYKMKMAKMEKYLHSSRCRRQIILSHFEDKQVQKASLGIMGT
EKCCDNCRSRLDHCYSMDDESDTSWDFGPQAFKLLSAVDILGEKFGIGLPILFLRGSNSQ
RLADQYRRHSLFGTGKDQTESWWKAFSRQLITEGFLVEVSRYNKFMKICALTKKGRNW
LHKANTESQSLILQANEELCPKKFLLPSSKTVSSGTEHCYNQVPVELSTEKKSNEKLY
SYKPCDKISSGSNISKKSIMVQSPEKAYSSSQPVISAQEETQIVLYGKLVEARQKHANK
MDVPPAILATNKILVDMAMRPTTVENVKRIDGVSEGKAAMLAPLLEVIKHFCQTNSV
QTDLFSSENLYFQGHHHHHHHH

[001519] Sf9 cells grown in SF900II media were infected with 1:200 WRN-BV08 P2 virus and incubated for protein expression for 72 h at 27°C. The WRN protein was purified using the following protocol. The cell pellets were thawed and resuspended in buffer A (50 mM Tris, pH 7.5, 500 mM NaCl, 1 mM TCEP, 10% Glycerol) supplemented with 0.5% CHAPS, 1mM PMSF, 1µg/ml Leupeptin, 1µg/ml Pepstatin, and the Pierce Universal Nuclease and cocktail tablet. Cleared lysates were loaded onto a Ni Sepharose™ excel column and washed with buffer A and bound protein was eluted with buffer A supplemented with 300 mM imidazole. The eluted protein was dialyzed against buffer A and digested by His-tagged TEV (1:5 ratio) overnight at 4°C. ZnCl₂ was added into the sample at final 15µM before loading onto a second Ni Sepharose™ excel column. Untagged WRN protein was eluted from the column with buffer A supplemented with 20 mM imidazole, dialyzed overnight into buffer B (50 mM Tris, pH 7.5, 1 mM TCEP, 10% Glycerol) supplemented with 150 mM NaCl and loaded onto a Heparin column. Proteins were eluted with a step gradient of buffer B supplemented with 150 mM, 200 mM, 300 mM and 500 mM NaCl. WRN containing fractions were pooled and concentrated prior to loading on to size exclusion

chromatography using a HiLoad 16/600 Superdex TM 200 pg column (GE Healthcare) in buffer C (20 mM HEPES, pH 7.5, 250 mM NaCl, 0.25 mM TCEP, 2.5% Glycerol).

[001520] The resultant IC₅₀ results obtained for the tested compounds are shown below in Table 3. Compounds with an IC₅₀ less than or equal to 0.005 μ M are designated as “A.” Compounds with an IC₅₀ greater than 0.005 μ M and less than or equal to 0.05 μ M are designated as “B.” Compounds with an IC₅₀ greater than 0.05 μ M and less than or equal to 0.1 μ M are designated as “C.” Compounds with an IC₅₀ greater than 0.1 μ M or equal to 0.5 μ M are designated as “D.” Compounds with an IC₅₀ greater than 0.5 μ M are designated as “E.”

Table 3

Compound No.	ADP-Glo_hWRN_IC50 [mM]
I-1	B
I-2	C
I-3	B
I-4	B
I-5	D
I-6	B
I-7	B
I-8	B
I-9	B
I-10	B
I-11	B
I-12	B
I-13	C
I-14	B
I-15	B
I-16	B
I-17	B
I-18	B
I-19	B
I-20	B

Compound No.	ADP-Glo_hWRN_IC50 [mM]
I-21	B
I-22	C
I-23	B
I-24	B
I-25	C
I-26	D
I-27	B
I-28	B
I-29	B
I-30	C
I-31	B
I-32	C
I-33	B
I-34	B
I-35	B
I-36	B
I-37	A
I-38	A
I-39	C
I-40	B
I-41	D
I-42	B
I-43	D
I-44	B
I-45	B
I-46	B
I-47	B
I-48	D
I-49	C

Compound No.	ADP-Glo_hWRN_IC50 [mM]
I-50	C
I-51	B
I-52	B
I-53	B
I-54	D
I-55	B
I-56	B
I-57	B
I-58	B
I-59	B
I-60	B
I-61	B
I-62	B
I-63	B
I-64	B
I-65	B
I-66	B
I-67	B
I-68	B
I-69	B
I-70	B
I-71	B
I-72	B
I-73	B
I-74	B
I-75	B
I-76	B
I-77	B
I-79	B

Compound No.	ADP-Glo_hWRN_IC50 [mM]
I-80	B
I-81	C
I-82	B
I-83	B
I-84	C
I-86	B
I-87	B
I-88	B
I-89	D
I-90	B
I-91	B
I-92	B
I-93	B
I-94	B
I-95	B
I-96	B
I-97	B
I-98	B
I-99	B
I-100	A
I-101	B
I-102	A
I-103	B
I-104	B
I-105	B
I-106	B
I-107	A
I-108	D
I-109	B

Compound No.	ADP-Glo_hWRN_IC50 [mM]
I-110	D
I-111	A
I-112	B
I-113	A
I-114	B
I-115	B
I-116	B
I-117	B
I-118	B
I-119	B
I-120	B
I-121	B
I-122	A
I-123	B
I-124	B
I-125	A
I-126	B
I-127	B
I-128	B
I-129	B
I-130	B
I-131	B
I-132	B
I-133	B
I-134	C
I-135	B
I-136	B
I-137	B
I-138	B

Compound No.	ADP-Glo_hWRN_IC50 [mM]
I-139	B
I-140	E
I-141	B
I-142	A
I-143	B
I-144	A
I-145	B
I-146	B
I-147	B
I-148	B
I-149	B
I-150	B
I-151	B
I-152	B
I-153	B
I-154	E
I-155	C
I-156	B
I-157	B
I-158	B
I-159	B
I-160	B
I-161	B
I-162	B
I-163	B
I-164	B
I-165	B
I-166	A
I-167	B

Compound No.	ADP-Glo_hWRN_IC50 [mM]
I-168	D
I-169	B
I-170	B
I-171	C
I-172	A
I-173	B
I-174	B
I-175	B
I-176	C
I-177	B
I-178	B
I-179	B
I-180	B
I-181	B
I-182	A
I-183	B
I-184	B
I-185	B
I-186	B
I-187	B
I-188	B
I-189	B
I-190	B
I-191	B
I-192	A
I-193	A
I-194	A
I-195	B
I-196	B

Compound No.	ADP-Glo_hWRN_IC50 [mM]
I-197	C
I-198	B
I-199	B
I-200	B
I-201	B
I-203	A
I-204	B
I-205	B
I-206	B
I-207	B
I-208	D
I-209	B
I-210	B
I-211	B
I-212	B
I-213	B
I-214	B
I-215	D
I-216	C
I-217	D
I-218	A
I-219	A
I-220	A
I-221	B
I-222	B
I-223	B
I-224	B
I-225	B
I-226	A

Compound No.	ADP-Glo_hWRN_IC50 [mM]
I-227	A
I-228	B
I-229	B
I-230	B
I-231	B
I-232	B
I-233	B
I-234	B
I-236	B
I-237	B
I-238	B
I-239	B
I-240	B
I-241	A
I-242	B
I-243	B
I-244	B
I-245	B
I-246	B
I-247	D
I-248	C
I-249	B
I-250	B
I-251	B
I-252	D
I-253	B
I-254	B
I-255	B
I-256	D

Compound No.	ADP-Glo_hWRN_IC50 [mM]
I-257	E
I-258	D
I-259	B
I-260	B
I-261	B
I-262	B
I-263	B
I-264	B
I-265	B
I-266	B
I-267	B
I-268	A
I-269	B
I-270	B
I-271	B
I-272	B
I-273	B
I-274	B
I-275	B
I-276	B
I-277	B
I-278	B
I-279	D
I-280	B
I-281	B
I-282	B
I-283	A
I-284	B
I-285	B

Compound No.	ADP-Glo_hWRN_IC50 [mM]
I-286	B
I-287	B
I-288	B
I-289	B
I-290	B
I-291	B
I-292	B
I-293	B
I-294	E
I-295	B
I-296	B
I-297	D
I-299	B
I-300	B
I-301	B
I-302	B
I-303	C

Example 3: Method for determining effect on p21 induction in cells.

[001521] The colon carcinoma cell line HCT116 was obtained from ATCC and cultured in growth medium consisting of Mccoy's 5A Medium (Gibco 16600108) supplemented with 10% FBS (Transgene FS201-02) and 100 units/mL penicillin-streptomycin (Gibco 15140122) and maintained at 37 °C under 5% CO₂. On the day of seeding, 2,000 cells in 30μL of culture media were plated per well to Poly-D-Lysine 384 Well Black Clear Plates (Biocoat 356663) and incubated overnight at 37 °C under 5% CO₂. The following day, compounds were serially diluted in DMSO for a total of 11 test concentrations. The typical starting concentration of compounds was 10μM with 2-fold dilutions. Next, 150nL of diluted compound was added in duplicate to the assay plate, using an Echo 655 (Labcyte). The plate was centrifuged at 500 RPM for 1 min and then incubated at 37 °C under 5% CO₂ for 24h. After 24h, medium was removed, and cells were

fixed by adding 40µL of 4% paraformaldehyde solution to each well and incubated for 20 min at room temperature. The plate was then washed 4 times with 100µL per well of wash buffer (PBS with 0.1% Tween-20) using a microplate washer. Next, 30µL of ice-cold methanol was added to each well and the plate was incubated at -20 °C for 10 min. The plate was washed 4 times with 100µL per well of wash buffer by a microplate washer, then 30µL per well of blocking buffer (Intercept PBS blocking buffer (LI-COR 927-70001) with 0.05% Tween-20) was added and the plate was incubated at room temperature with shaking for 2h. Next, to each test well, 20µL of primary antibody solution (p21 Waf1/CIP (12D1) Rabbit mAb (Cell Signaling Technologies 2947) diluted 1:1000 and GAPDH (D4C6R) Mouse mAb (Cell Signaling Technologies 97166) diluted 1:2000 in blocking buffer) was added and the plate was placed at 4 °C, overnight. The following day, the plate was washed 5 times with 100µL per well of wash buffer using a microplate washer for 5 min. 20µL per well of secondary antibody (IRDye 680CW Goat anti-Mouse IgG (H+L) (LI-COR 926-68070) diluted 1: 2000 in Blocking Buffer and IRDye 800CW Goat anti-Rabbit IgG (H+L) (LI-COR 926-32211) diluted 1: 2000 in Blocking Buffer) was then added and the plate was stored for 2h in the dark at room temperature with shaking. The plate was then washed 4 times with 100µL per well of wash buffer again using a microplate washer. Finally, the p21 signal and the GAPDH signal were quantified using a LI-COR Odyssey CLx Imager machine reading at 800nm and 700nm, respectively. Each plate contained DMSO control (low control) and an internal reference WRN inhibitor (high control) respectively. For quantitation, the 800nm/700nm ratio was calculated for each well to give fold p21 induction and then percent activation for each compound well was calculated as follows $(100 \times (\text{ratio cpd well} - \text{ratio low control}) / (\text{ratio high control} - \text{ratio low control}))$. EC₅₀ values for each compound were generated after non-linear regression curve fitting using commercially available software. The resultant EC₅₀ results obtained for the tested compounds are shown below in Table 4. Compounds with an EC₅₀ less than or equal to 0.50 µM are designated as “A.” Compounds with an EC₅₀ greater than 0.50 µM and less than or equal to 2.00 µM are designated as “B.” Compounds with an EC₅₀ greater than 2.00 µM and less than or equal to 5.00 µM are designated as “C.” Compounds with an EC₅₀ greater than 5.00 µM are designated as “D.”

Table 4

Compound No.	P21_EC ₅₀ [mM]
I-1	C

Compound No.	P21_EC ₅₀ [mM]
I-2	D
I-3	D
I-4	D
I-5	D
I-6	C
I-7	D
I-8	B
I-9	B
I-10	C
I-11	C
I-12	D
I-13	D
I-14	B
I-15	A
I-16	B
I-17	B
I-18	B
I-19	D
I-20	D
I-21	B
I-22	D
I-23	B
I-24	D
I-25	D
I-26	D
I-27	D
I-28	D
I-29	B
I-30	D

Compound No.	P21_EC ₅₀ [mM]
I-31	D
I-32	D
I-33	D
I-34	A
I-35	C
I-36	C
I-37	A
I-38	A
I-39	C
I-40	A
I-41	D
I-42	C
I-43	D
I-44	D
I-45	D
I-46	D
I-47	D
I-48	D
I-49	D
I-50	D
I-51	A
I-52	D
I-53	B
I-54	D
I-55	B
I-56	D
I-57	B
I-58	A
I-59	C

Compound No.	P21_EC ₅₀ [mM]
I-60	B
I-61	A
I-62	D
I-63	D
I-64	B
I-65	D
I-66	C
I-67	D
I-68	D
I-69	D
I-70	D
I-71	D
I-72	D
I-73	D
I-74	B
I-75	B
I-76	D
I-77	D
I-79	D
I-80	D
I-81	D
I-82	D
I-83	D
I-84	D
I-86	C
I-87	B
I-88	D
I-89	D
I-90	D

Compound No.	P21_EC ₅₀ [mM]
I-91	D
I-92	B
I-93	B
I-94	D
I-95	B
I-96	D
I-97	A
I-98	A
I-99	D
I-100	A
I-101	A
I-102	A
I-103	A
I-104	A
I-105	A
I-106	B
I-107	A
I-108	D
I-109	B
I-110	D
I-111	A
I-112	A
I-113	A
I-114	A
I-115	D
I-116	B
I-117	A
I-118	B
I-119	A

Compound No.	P21_EC ₅₀ [mM]
I-120	A
I-121	A
I-122	A
I-123	A
I-124	A
I-125	A
I-126	A
I-127	A
I-128	A
I-129	A
I-130	A
I-131	B
I-132	A
I-133	D
I-134	D
I-135	A
I-136	A
I-137	D
I-138	D
I-139	B
I-140	D
I-141	D
I-142	B
I-143	C
I-144	B
I-145	D
I-146	C
I-147	D
I-148	D

Compound No.	P21_EC ₅₀ [mM]
I-149	B
I-150	B
I-151	C
I-152	D
I-153	C
I-154	D
I-155	D
I-156	B
I-157	B
I-158	D
I-159	D
I-160	D
I-161	C
I-162	B
I-163	D
I-164	C
I-165	B
I-166	B
I-167	C
I-168	D
I-169	B
I-170	A
I-171	D
I-172	A
I-173	NA*
I-174	C
I-175	C
I-176	D
I-177	D

Compound No.	P21_EC ₅₀ [mM]
I-178	D
I-179	C
I-180	B
I-181	A
I-182	A
I-183	D
I-184	C
I-185	A
I-186	C
I-187	B
I-188	B
I-189	B
I-190	A
I-191	B
I-192	A
I-193	NA*
I-194	A
I-195	C
I-196	B
I-197	D
I-198	NA*
I-199	A
I-200	A
I-201	C
I-203	B
I-204	A
I-205	A
I-206	D

Compound No.	P21_EC ₅₀ [mM]
I-207	C
I-208	D
I-209	A
I-210	A
I-211	A
I-212	B
I-213	B
I-214	A
I-215	D
I-216	D
I-217	D
I-218	B
I-219	A
I-220	A
I-221	D
I-222	A
I-223	B
I-224	C
I-225	A
I-226	A
I-227	A
I-228	A
I-229	B
I-230	A
I-231	A
I-232	A
I-233	D
I-234	B

Compound No.	P21_EC ₅₀ [mM]
I-236	A
I-237	D
I-238	D
I-239	A
I-240	A
I-241	A
I-242	A
I-243	A
I-244	D
I-245	A
I-246	B
I-247	D
I-248	NA*
I-249	A
I-250	A
I-251	A
I-252	C
I-253	A
I-254	B
I-255	A
I-256	D
I-257	D
I-258	D
I-259	B
I-260	NA*
I-261	A
I-262	A
I-263	D
I-264	A

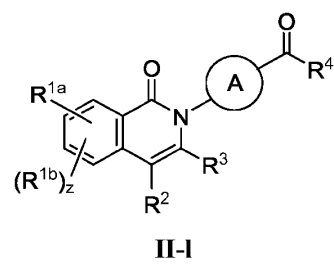
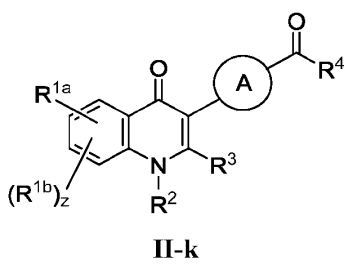
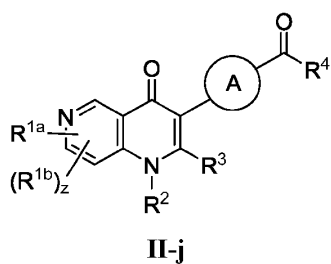
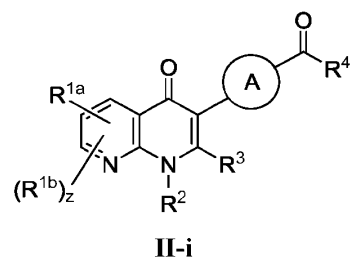
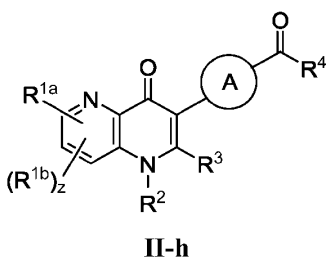
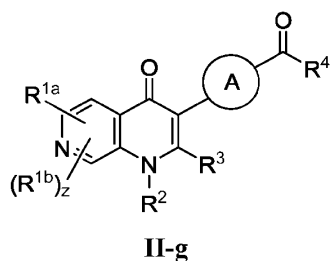
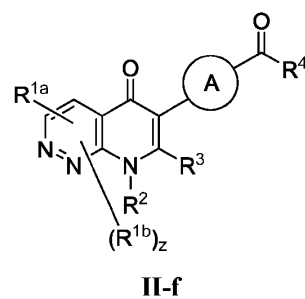
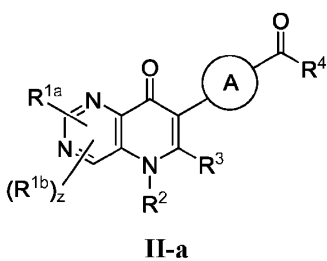
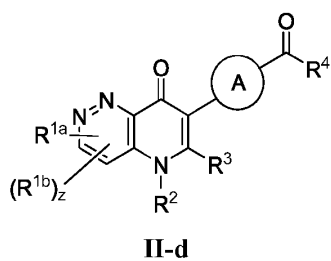
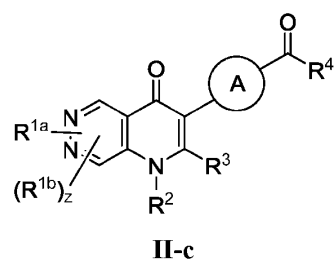
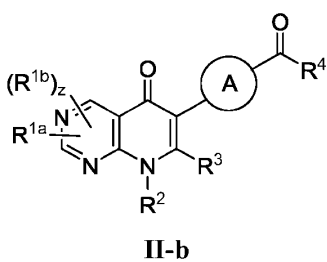
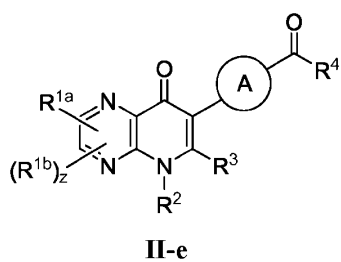
Compound No.	P21_EC ₅₀ [mM]
I-265	C
I-266	B
I-267	A
I-268	A
I-269	A
I-270	B
I-271	B
I-272	A
I-273	A
I-274	A
I-275	A
I-276	B
I-277	B
I-278	C
I-279	D
I-280	D
I-281	A
I-282	A
I-283	A
I-284	A
I-285	B
I-286	A
I-287	A
I-288	A
I-289	B
I-290	A
I-291	C
I-292	D
I-293	A

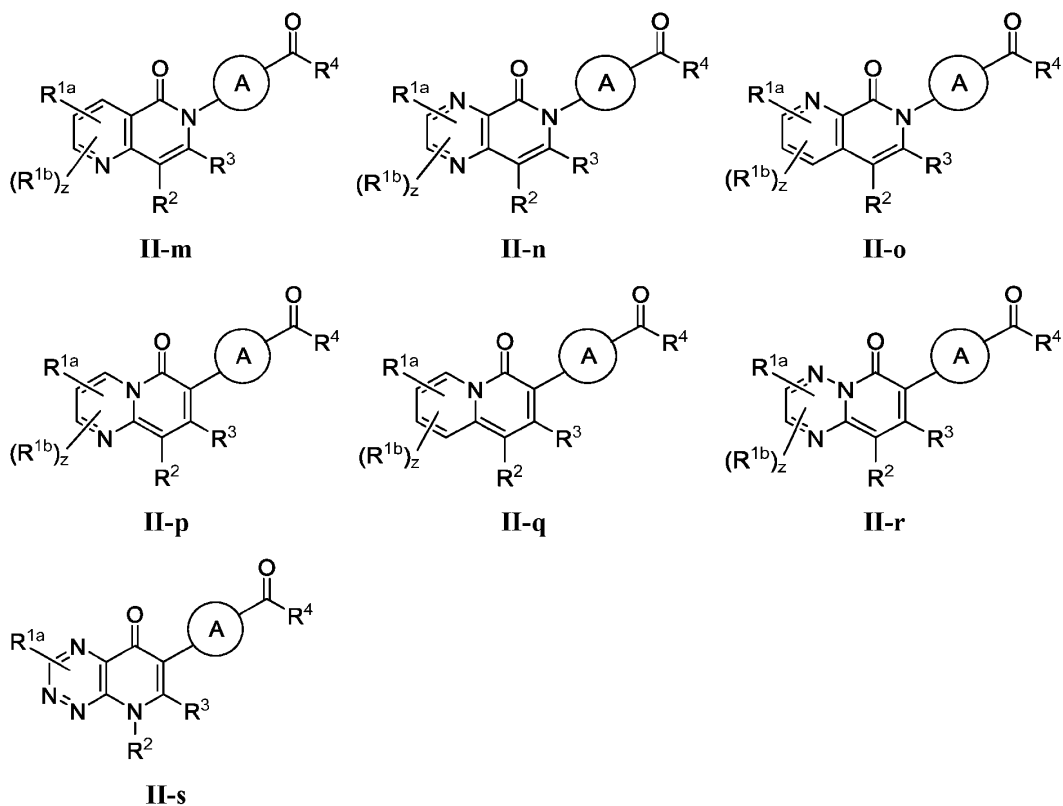
Compound No.	P21_EC ₅₀ [mM]
I-294	D
I-295	NA*
I-296	B
I-297	D
I-299	A
I-300	A
I-301	A
I-302	A
I-303	D

NA* = not available

We claim:

1. A compound of one of formulas **II-a** to **II-s**:





or a pharmaceutically acceptable salt thereof;

wherein R^{1a} is selected from groups a)-d):

- a) a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with 1 or 2 groups independently selected from C_3 - C_6 cycloalkyl and C_3 - C_6 cycloalkoxy, wherein said 5-6 membered heteroaryl is further substituted with 0-3 independently selected R^B ;
- b) a 4-6 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), said heterocyclyl substituted with 0-2 R^B groups independently selected from halogen, oxo, NR_2 , optionally substituted C_1 - C_4 aliphatic, -OR, azetidiny optionally substituted with 1 or 2 independently selected halogen, and pyrrolidinyl optionally substituted with 1 or 2 independently selected halogen;

- c) a 6-8 membered saturated or partially unsaturated bridged bicyclic heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), said heterocyclyl substituted with 0-2 R^B groups independently selected from halogen, oxo, NR_2 , optionally substituted C_1 - C_4 aliphatic, -OR, azetidiny optionally substituted with 1 or 2 independently selected halogen, and pyrrolidiny optionally substituted with 1 or 2 independently selected halogen; and
- d) H, halogen, C_1 - C_6 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, CN, $-OR^{10}$, $-NR^{10}R^{11}$, $-C(O)NR^{10}R^{11}$, $-CH_2NR^{10}R^{11}$, $-SO_2R^{12}$, or a 3-7 membered carbocyclyl, wherein said C_1 - C_6 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, or 3-7 membered carbocyclyl is substituted with 0-3 independently selected R^B ;
- and wherein each R^{1b} group is independently selected from H, halogen, CN, OH, C_1 - C_6 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, C_1 - C_6 alkylene-O- C_1 - C_6 alkyl, and C_3 - C_6 cycloalkoxy, wherein said C_1 - C_6 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, C_1 - C_6 alkylene-O- C_1 - C_6 alkyl, and C_3 - C_6 cycloalkoxy are each independently optionally substituted with 1-5 halogen, OH, CN, C_1 - C_6 alkyl, and C_3 - C_6 cycloalkyl; wherein z is 0, 1, or 2;

Ring A is:

- a 4-7 membered saturated or partially unsaturated bivalent monocyclic carbocyclylene or 4-7 membered saturated or partially unsaturated bivalent heterocyclylene ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 0 or 1 nitrogen atoms in addition to the 1-4 heteroatoms); or
- a 4-12 membered saturated or partially unsaturated bivalent bicyclic ring system that is fused, bridged, or spirocyclic selected from carbocyclylene or heterocyclylene (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

wherein Ring A is substituted with 0-4 independently selected R^B substituents;

R^2 is $C(R^C)_2C(O)N(R)R^{2A}$;

R^{2A} is phenyl or pyridyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1 - C_4 aliphatic, halo C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, halo C_3 - C_6 cycloalkyl, -OH, -CN, C_1 - C_4 alkoxy, halo C_1 - C_4 alkoxy, and $-SF_5$, and wherein two substituents on adjacent atoms of the phenyl or pyridyl, together with said adjacent atoms, form

- a 4-7 membered carbocyclyl fused to the phenyl or pyridyl, and wherein two substituents on adjacent atoms of the phenyl or pyridyl together with said adjacent atoms form a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) fused to the phenyl or pyridyl, wherein said fused 4-7 membered carbocyclyl or fused 4-7 membered heterocyclyl is substituted with 0-5 independently selected halogen; or
- R^{2A} is 2-benzimidazolyl, 2-naphthyl, or 3-quinoliny, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C₁₋₄alkyl, and -OH;
- R³ is hydrogen, C₁-C₄aliphatic, C₃-C₅cycloalkyl, C₁-C₄alkoxy, -NHR^{3A}, -N(R^{3A})₂, or C₁-C₄alkylthio, each of which, besides hydrogen, is optionally substituted with -OH, 1-5 independently selected halogen, OR, -C(O)NR¹⁰R¹¹, or N(R)C(O)R;
- each R^{3A} is independently selected from C₁-C₄alkyl;
- R⁴ is phenyl or a first 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) wherein said phenyl or first 5-6 membered heteroaryl is substituted with 0-5 R^B; and optionally two adjacent atoms of said phenyl or first 5-6 membered heteroaryl have two substituents that together with said adjacent atoms form a cyclic group fused to the phenyl or first 5-6 membered heteroaryl selected from a 4-7 membered carbocyclyl, a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or a second 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said fused cyclic group is substituted with 0-3 independently selected R^B; or
- R⁴ is a C₁-C₄aliphatic, C₁-C₄alkoxy, or C₃-C₆cycloalkyl, each of which is substituted with 0-3 groups independently selected from halogen, -CN, -OH, C₁-C₄alkyl, C₁-C₄alkoxy, optionally substituted 5-6 membered heterocyclyl, and optionally substituted 5-6 membered heterocycloxy;
- R¹⁰ is H, C₁-C₆aliphatic, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, -C(O)C₁-C₆alkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R¹⁰ except H being optionally substituted with 1 or 2 independently selected R^B;

R¹¹ is H, C₁-C₆aliphatic, or C₃-C₆cycloalkyl, or R¹⁰ and R¹¹ are taken together with the nitrogen atom to which they are attached to form a 5-6 membered ring optionally substituted with 1, 2, or 3 substituents independently selected from halogen, -OH, -CN, C₁-C₄alkoxy, and haloC₁-C₄alkoxy;

R¹² is C₁-C₆aliphatic, C₃-C₆cycloalkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R¹² optionally substituted with 1 or 2 groups independently selected from halogen, C₁-C₆aliphatic, haloC₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, and C₃-C₆cycloalkoxy;

R^B is independently selected at each occurrence from the group consisting of optionally substituted phenyl, optionally substituted 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), halogen, optionally substituted C₁-C₆aliphatic, haloC₁-C₆alkyl, C₃-C₆cycloalkyl, haloC₃-C₆cycloalkyl, C₁-C₆alkoxy, haloC₁-C₆alkoxy, C₃-C₆cycloalkoxy, haloC₃-C₆cycloalkoxy, C₁-C₆alkylene-O-C₁-C₆alkyl, -CN, -NO₂, oxo, -OR, -SR, NR₂, S(O)₂R, S(O)₂NR₂, S(O)R, S(O)NR₂, C(O)R, C(O)OR, -C(O)NR₂, C(O)N(R)OR, OC(O)R, OC(O)NR₂, -N(R)C(O)OR, N(R)C(O)R, N(R)C(O)NR₂, N(R)C(NR)NR₂, N(R)S(O)₂NR₂, and -N(R)S(O)₂R;

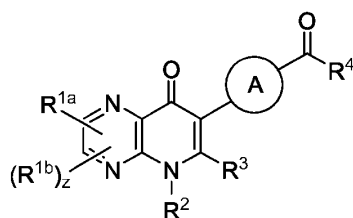
R^C is independently selected at each occurrence from hydrogen, -CH₃, or -CH₂CH₃, or two R^C taken together with the carbon to which they are attached form a cyclopropyl ring;

each R is independently hydrogen, or an optionally substituted C₁-C₆aliphatic group, an optionally substituted phenyl, an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or an optionally substituted 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); or

two R groups on the same atom are taken together with the same atom to form a cyclic group selected from an optionally substituted 4-7 membered saturated ring, a 4-7 membered partially unsaturated ring, or a 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said 4-7 membered saturated ring or 4-7

membered partially unsaturated ring has 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

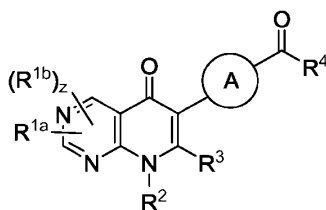
2. The compound of claim 1, wherein the compound is of formula **II-e**:



II-e

or a pharmaceutically acceptable salt thereof.

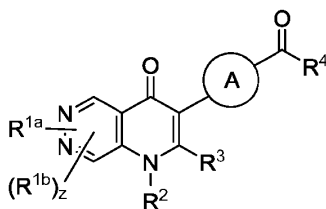
3. The compound of claim 1, wherein the compound is of formula **II-b**:



II-b

or a pharmaceutically acceptable salt thereof.

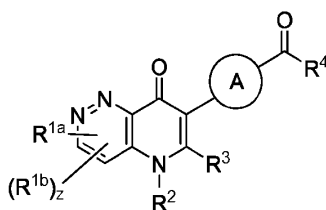
4. The compound of claim 1, wherein the compound is of formula **II-c**:



II-c

or a pharmaceutically acceptable salt thereof.

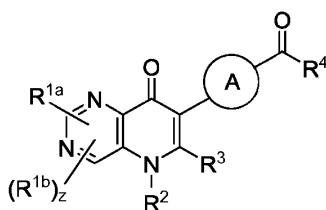
5. The compound of claim 1, wherein the compound is of formula **II-d**:



II-d

or a pharmaceutically acceptable salt thereof.

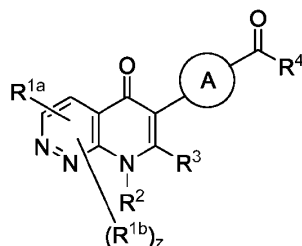
6. The compound of claim 1, wherein the compound is of formula **II-a**:



II-a

or a pharmaceutically acceptable salt thereof.

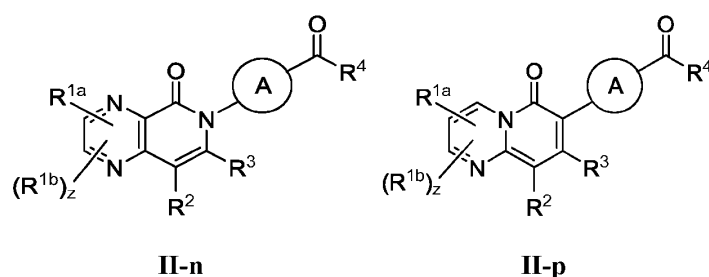
7. The compound of claim 1, wherein the compound is of formula **II-f**:



II-f

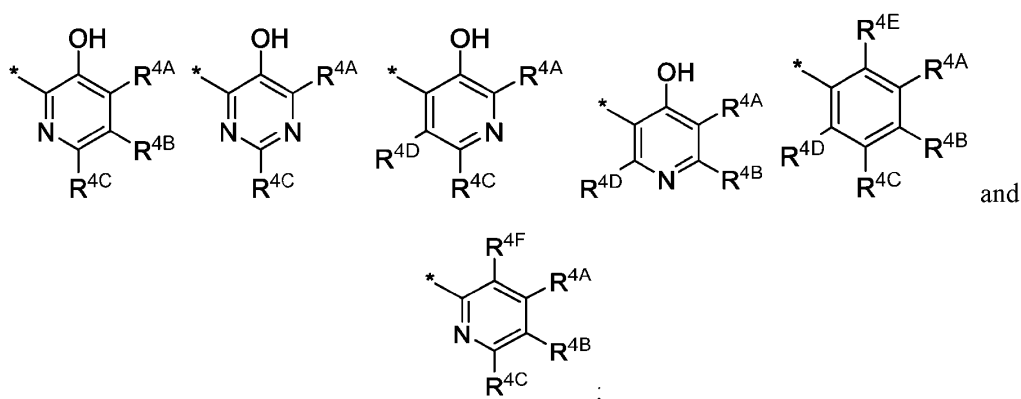
or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1, wherein the compound is of formula **II-n** or **II-p**:



or a pharmaceutically acceptable salt thereof.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^4 is a Ring E that is selected from the group consisting of:



wherein * is a point of attachment to $-C(O)-$;

and:

any substituents that are present on Ring E selected from R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^{4E} , and R^{4F} are each independently selected from hydrogen; halogen; $-CN$; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; C_1 - C_4 alkoxy; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with $-OH$, $-OCH_3$, or $-OCH_2CH_3$; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and $NR^{13}R^{14}$, or

R^{4A} and R^{4B} , along with their intervening atoms, join to form a 4-7 membered carbocyclyl substituted with 0-3 independently selected R^B , a 4-7 membered heterocyclyl substituted with 0-3 independently selected R^B , or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) substituted with 0-3 independently selected R^B ; that is fused to Ring E; and any substituents that are present on Ring E selected from R^{4C} , R^{4D} , R^{4E} , and R^{4F} are each independently selected from hydrogen; halogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and $NR^{13}R^{14}$; or

R^{4B} and R^{4C} , along with their intervening atoms, join to form a 4-7 membered carbocyclyl substituted with 0-3 independently selected R^B , a 4-7 membered heterocyclyl substituted with 0-3 independently selected R^B , or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) substituted with 0-3 independently selected R^B ; that is fused to Ring E; and any substituents that are present on Ring E selected from R^{4A} , R^{4D} , R^{4E} , and R^{4F} are each independently selected from hydrogen; halogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and $NR^{13}R^{14}$; or

R^{4C} and R^{4D} , along with their intervening atoms, join to form a 4-7 membered carbocyclyl substituted with 0-3 independently selected R^B , a 4-7 membered heterocyclyl substituted with 0-3 independently selected R^B , or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) substituted with 0-3 independently selected R^B ; that is fused to Ring E; and any substituents that are present on Ring E selected from R^{4A} , R^{4B} , R^{4E} and R^{4F} are each independently selected from hydrogen; halogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; halo C_1 - C_4 alkyl; C_1 - C_3 alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; halo C_1 - C_4 alkoxy; C_3 - C_6 cycloalkyl; C_3 - C_6 cycloalkoxy; and $NR^{13}R^{14}$; or

R^{4E} is halogen or -OH, and R^{4A} , R^{4B} , R^{4C} , and R^{4D} are each independently selected from hydrogen; halogen; -CN; C_1 - C_4 alkyl; C_2 - C_4 alkenyl; C_2 - C_4 alkynyl; halo C_1 - C_4 alkyl; C_1 -

C₃alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; haloC₁-C₄alkoxy; C₃-C₆cycloalkyl; C₃-C₆cycloalkoxy; and NR¹³R¹⁴; or

R^{4E} and R^{4A}, along with their intervening atoms, join to form a 5-6 membered optionally substituted heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) substituted with 0-3 independently selected R^B; that is fused to Ring E; and R^{4B}, R^{4C}, and R^{4D} are each independently selected from hydrogen; halogen; -CN; C₁-C₄alkyl; C₂-C₄alkenyl; C₂-C₄alkynyl; haloC₁-C₄alkyl; C₁-C₃alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; haloC₁-C₄alkoxy; C₃-C₆cycloalkyl; C₃-C₆cycloalkoxy; and NR¹³R¹⁴; or

R^{4F} and R^{4A}, along with their intervening atoms, join to form a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) substituted with 0-3 independently selected R^B; that is fused to Ring E; and R^{4B} and R^{4C} are each independently selected from hydrogen; halogen; -CN; C₁-C₄alkyl; C₂-C₄alkenyl; C₂-C₄alkynyl; haloC₁-C₄alkyl; C₁-C₃alkyl substituted with -OH, -OCH₃, or -OCH₂CH₃; haloC₁-C₄alkoxy; C₃-C₆cycloalkyl; C₃-C₆cycloalkoxy; and NR¹³R¹⁴;

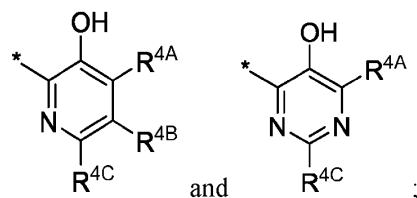
R¹³ is independently selected at each occurrence from hydrogen and C₁-C₄alkyl optionally substituted with -OH, -OCH₃, or -OCH₂CH₃; and

R¹⁴ is hydrogen, or R¹³ and R¹⁴ combine with the nitrogen atom to which they are attached to form a heterocyclic ring selected from azetidiny, pyrrolidinyl, or piperidinyl, said heterocyclic ring optionally substituted with -CH₃; or

R⁴ is a 5-membered heteroaryl (having 1 heteroatom independently selected from nitrogen, oxygen, and sulfur and 0, 1, 2, or 3 additional ring nitrogen atoms), wherein said heteroaryl is substituted with 0-4 groups independently selected from halogen, -OH, -CN, C₁-C₄alkyl, haloC₁-C₄alkyl, C₃-C₆cycloalkyl, and C₁-C₄alkoxy; or

R⁴ is a C₁-C₄alkyl, C₁-C₄alkoxy, or C₃-C₆cycloalkyl, each of which is substituted with 0-3 groups independently selected from halogen, -CN, -OH, C₁-C₄alkyl, C₁-C₄alkoxy, optionally substituted 5-6 membered heterocyclyl, and optionally substituted 5-6 membered heterocyclyloxy.

10. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^4 is a Ring E that is selected from the group consisting of:



wherein * is a point of attachment to $-C(O)-$;

R^{4A} is hydrogen, halogen, $-CH_3$, $-CH_2CH_3$, $-F$, $-CF_2H$, $-CF_3$, $-OCH_3$, $-OCF_3$, $-OCH_2CH_3$, or $-OCHF_2$;

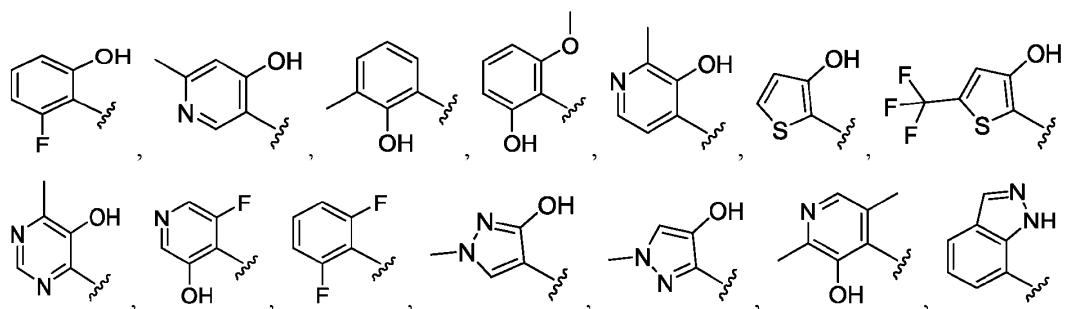
R^{4B} and R^{4C} are each independently selected from hydrogen, $-CN$, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, halo C_1 - C_4 alkyl, C_1 - C_3 alkyl substituted with $-OH$, $-OCH_3$, or $-OCH_2CH_3$, halo C_1 - C_4 alkoxy, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkoxy, and $NR^{13}R^{14}$; and

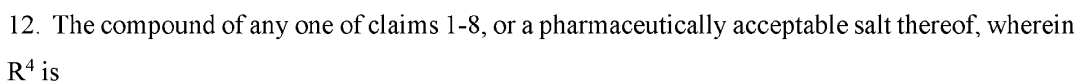
R^{13} is independently selected at each occurrence from hydrogen or C_1 - C_4 alkyl optionally substituted with $-OH$, $-OCH_3$, or $-OCH_2CH_3$; and

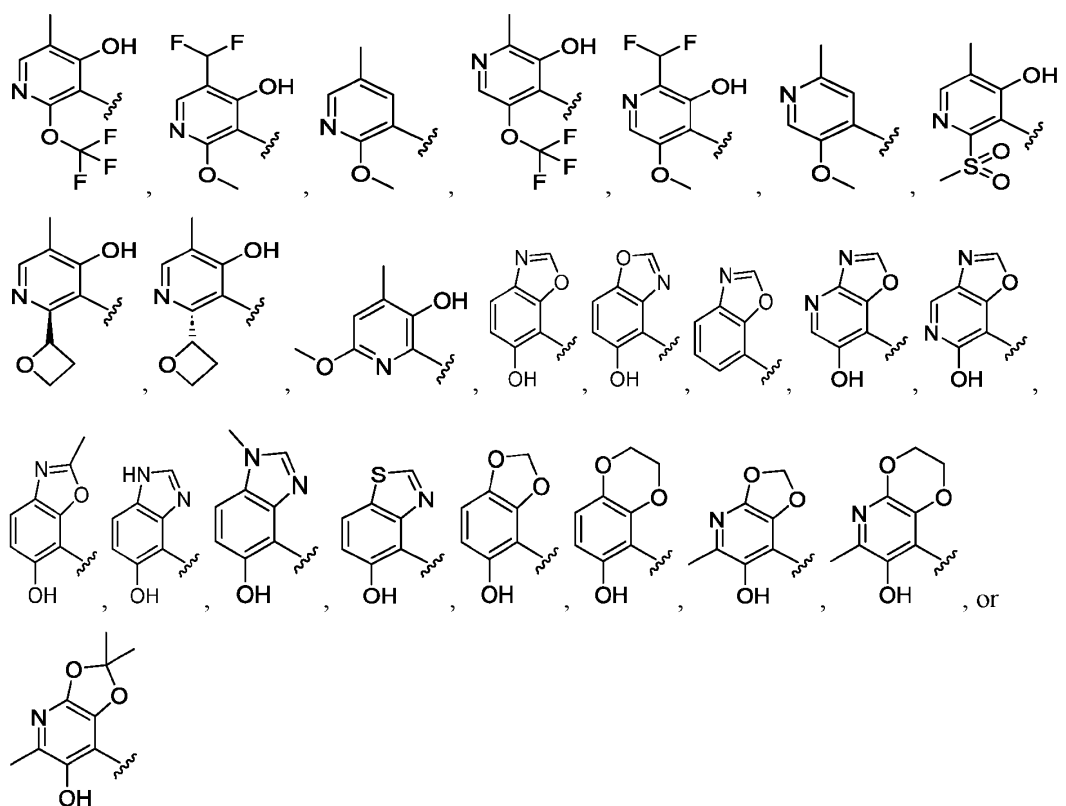
R^{14} is H; or

$NR^{13}R^{14}$, taken in combination, form a heterocyclic ring selected from azetidiny, pyrrolidinyl, and piperidinyl; wherein said heterocyclic ring is optionally substituted with one or more $-CH_3$ groups.

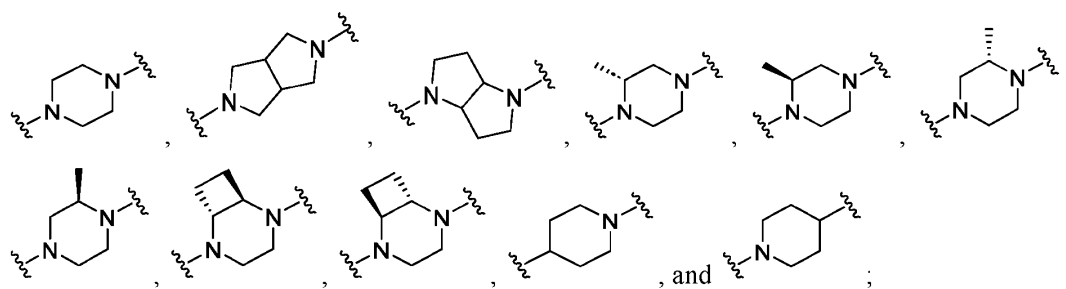
11. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^4 is





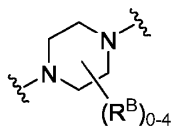


13. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein Ring A is selected from

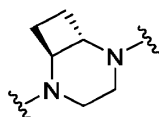


wherein Ring A is substituted with 0-4 independently selected R^B substituents.

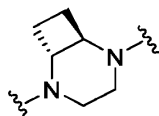
14. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein Ring A and the 0-4 independently selected R^B substituents with which Ring A is substituted, is:



15. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein Ring A is:



16. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein Ring A is:



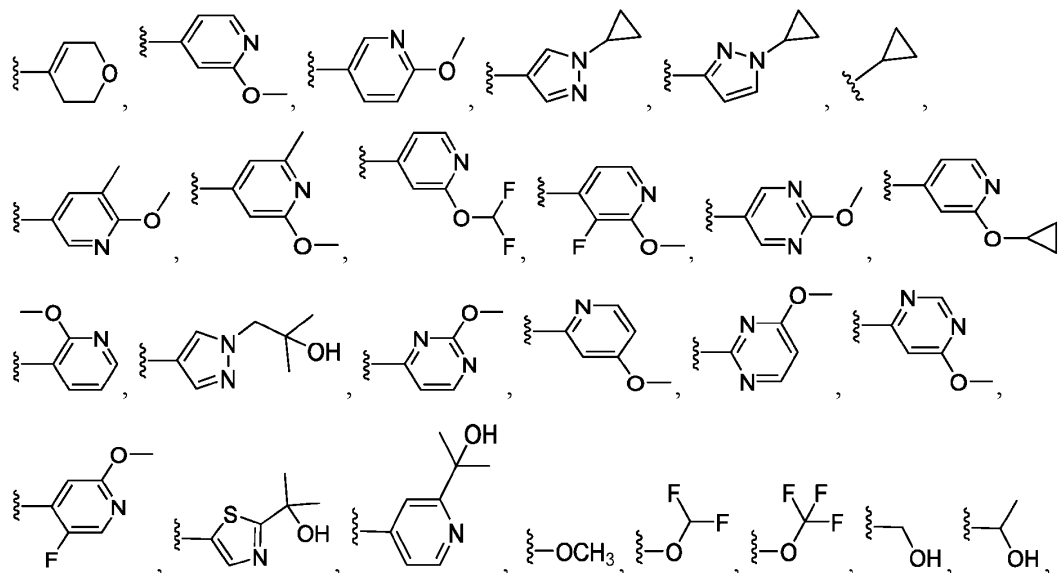
17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with 1-3 groups selected from halogen, C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and C_3 - C_6 cycloalkyl, wherein said 5-6 membered heteroaryl is further substituted with 0-3 independently selected R^B groups; and R^{1b} is selected from H, halogen, C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and halo C_1 - C_6 alkoxy.

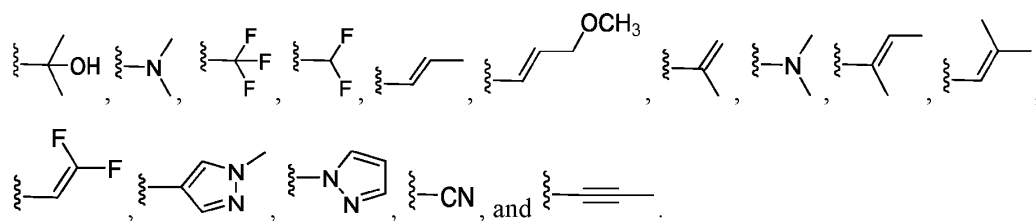
18. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is a 4-6 membered saturated or partially unsaturated heterocyclyl (having 1-2

heteroatoms independently selected from nitrogen, oxygen, and sulfur), said heterocyclyl substituted with 0-2 R^B groups independently selected from halogen, oxo, NR_2 , optionally substituted C_{1-4} aliphatic, -OR, azetidynyl optionally substituted with 1 or 2 independently selected halogen, and pyrrolidinyl optionally substituted with 1 or 2 independently selected halogen; and R^{1b} is selected from H, halogen, C_{1-6} alkyl, halo C_{1-6} alkyl, C_{1-6} alkoxy, and halo C_{1-6} alkoxy.

19. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is halogen, C_{1-6} alkyl, C_2-C_4 alkene, C_2-C_4 alkyne, CN, $-OR^{10}$, $-NR^{10}R^{11}$, $-C(O)NR^{10}R^{11}$, $-CH_2NR^{10}R^{11}$, $-SO_2R^{12}$, or a C_3-C_7 cycloalkyl, wherein said C_{1-6} alkyl, C_2-C_4 alkene, C_2-C_4 alkyne, and C_3-C_7 cycloalkyl is substituted with 0-3 R^B groups independently selected from halogen, C_3-C_6 cycloalkyl, halo C_3-C_6 cycloalkyl, -OH, -CN, C_{1-4} alkoxy, and halo C_{1-4} alkoxy; and R^{1b} is selected from H, halogen, C_{1-6} alkyl, halo C_{1-6} alkyl, C_{1-6} alkoxy, and halo C_{1-6} alkoxy.

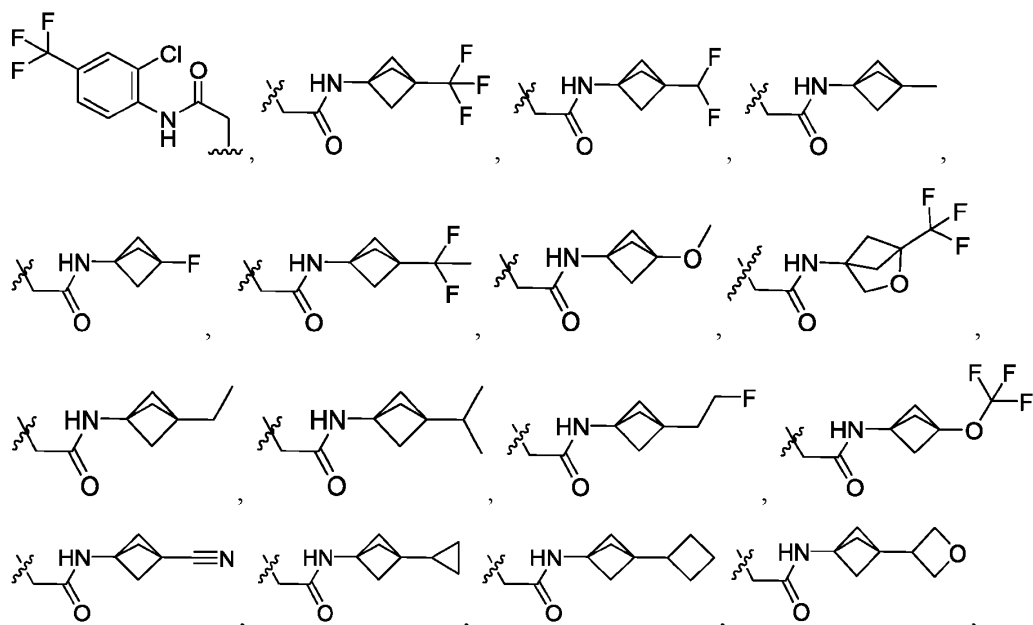
20. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is selected from the group consisting of:

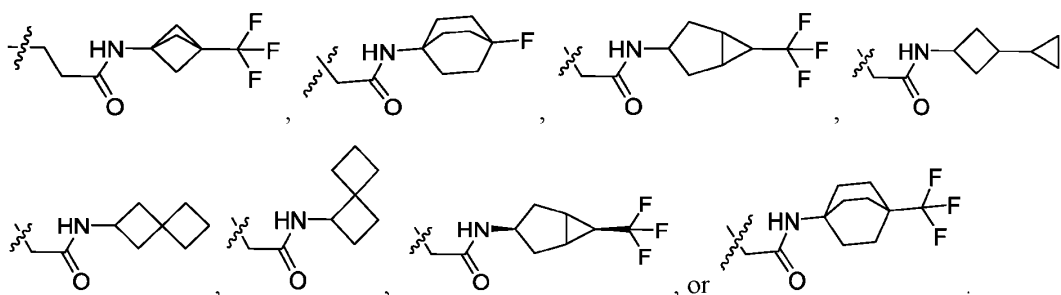




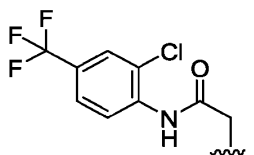
21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein R^{2A} is phenyl comprising a -CF₃ substituent or pyridyl comprising a -CF₃ substituent.

22. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein R² is





23. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein R² is:



24. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein R³ is C₁-C₄alkyl or C₃-C₅cycloalkyl.

25. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein R³ is C₁-C₄alkyl optionally substituted with -OH, 1-5 independently selected halogen, or C₁-C₄alkoxy.

26. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein R³ is C₁-C₄alkyl.

27. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein R³ is -CH₂CH₃.

28. A compound selected from one of those shown in Table 1, Table 1a, Table 2, or Table 2a; or a pharmaceutically acceptable salt thereof.
29. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof of any one of claims 1-28, and one or more pharmaceutically acceptable carriers.
30. A method of treating cancer in a subject, wherein the cancer is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof.
31. A method of modulating WRN activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof.
32. A method of treating a disorder or disease which can be treated by WRN inhibition in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of one of claims 1-28, or a pharmaceutically acceptable salt thereof.
33. A method of inhibiting WRN in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof.
34. The method of claim 33, wherein the disorder or disease is a cancer characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

35. The method of claim 34, wherein the cancer characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) is selected from colorectal, gastric, prostate, endometrial, adrenocortical, uterine, cervical, esophageal, breast, kidney and ovarian cancer.