

HETEROBICYCLIC INHIBITORS OF MAT2A AND METHODS OF USE FOR TREATING CANCER

BACKGROUND

[0001] Methionine adenosyltransferase (MAT), which is also known as S-adenosylmethionine synthetase, is a cellular enzyme that catalyzes the synthesis of S-adenosyl methionine (SAM or AdoMet) from methionine and ATP; the catalysis is considered to be rate-limiting step of the methionine cycle. SAM is the propylamino donor in polyamine biosynthesis, the principal methyl donor for DNA methylation, and is involved in gene transcription and cellular proliferation as well as the production of secondary metabolites.

[0002] Two genes designated as MAT1A and MAT2A encode two distinct catalytic MAT isoforms, respectively. A third gene, MAT2B, encodes a MAT2A regulatory subunit. MAT1A is specifically expressed in the adult liver, whereas MAT2A is widely distributed. Because MAT isoforms differ in catalytic kinetics and regulatory properties, MAT1A-expressing cells have considerably higher SAM levels than do MAT2A-expressing cells. It has been found that hypomethylation of the MAT2A promoter and histone acetylation causes upregulation of MAT2A expression.

[0003] In hepatocellular carcinoma (HCC), the downregulation of MAT1A and the up-regulation of MAT2A occur, which is known as the MAT1A:MAT2A switch. The switch, accompanied with up-regulation of MAT2B, results in lower SAM contents, which provide a growth advantage to hepatoma cells. Because MAT2A plays a crucial role in facilitating the growth of hepatoma cells, it is a target for antineoplastic therapy. Recent studies have shown that silencing by using small interfering RNA substantially suppresses growth and induces apoptosis in hepatoma cells. *See, e.g., T. Li et al., J. Cancer* 7(10) (2016) 1317-1327.

[0004] Some cancer cell lines that are MTAP deficient are particularly sensitive to inhibition of MAT2A. Marjon *et al.* (Cell Reports 15(3) (2016) 574–587). MTAP (methylthioadenosine phosphorylase) is an enzyme widely expressed in normal tissues that catalyzes the conversion of methylthioadenosine (MTA) into adenine and 5-methylthioribose-1-phosphate. The adenine is salvaged to

generate adenosine monophosphate, and the 5-methylthioribose-1-phosphate is converted to methionine and formate. Because of this salvage pathway, MTA can serve as an alternative purine source when de novo purine synthesis is blocked, e.g., with antimetabolites, such as L-alanosine.

[0005] MAT2A is dysregulated in additional cancers that lack MTAP-deletion, including hepatocellular carcinoma and leukemia. J. Cai *et al.*, *Cancer Res.* 58 (1998) 1444-1450; T. S. Jani *et al.*, *Cell. Res.* 19 (2009) 358-369. Silencing of MAT2A expression via RNA-interference results in anti-proliferative effects in several cancer models. H. Chen *et al.*, *Gastroenterology* 133 (2007) 207-218; Q. Liu *et al. Hepatol. Res.* 37 (2007) 376-388.

[0006] Many human and murine malignant cells lack MTAP activity. MTAP deficiency is found not only in tissue culture cells but the deficiency is also present in primary leukemias, gliomas, melanomas, pancreatic cancers, non-small cell lung cancers (NSCLC), bladder cancers, astrocytomas, osteosarcomas, head and neck cancers, myxoid chondrosarcomas, ovarian cancers, endometrial cancers, breast cancers, soft tissue sarcomas, non-Hodgkin lymphoma, and mesotheliomas. The gene encoding for human MTAP maps to region 9p21 on human chromosome 9p. This region also contains the tumor suppressor genes p16INK4A (also known as CDKN2A) and p15INK4B. These genes code for p16 and p15, which are inhibitors of the cyclin D-dependent kinases cdk4 and cdk6, respectively.

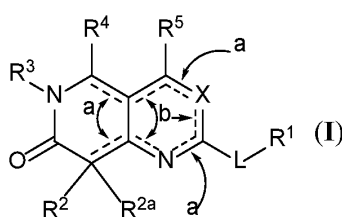
[0007] The p16INK4A transcript can alternatively be alternative reading frame (ARF) spliced into a transcript encoding p14ARF. p14ARF binds to MDM2 and prevents degradation of p53 (Pomerantz *et al.* (1998) *Cell* 92:713-723). The 9p21 chromosomal region is of interest because it is frequently homozygously deleted in a variety of cancers, including leukemias, NSLC, pancreatic cancers, gliomas, melanomas, and mesothelioma. The deletions often inactivate more than one gene. For example, Cairns *et al.* ((1995) *Nat. Gen.* 11:210-212) reported that after studying more than 500 primary tumors, almost all the deletions identified in such tumors involved a 170 kb region containing MTAP, p14ARF and P16INK4A. Carson *et al.* (WO 99/67634) reported that a correlation exists between the stage of tumor development and loss of homozygosity of the gene encoding MTAP and the gene encoding p16. For

example, deletion of the MTAP gene, but not p16INK4A was reported to be indicative of a cancer at an early stage of development, whereas deletion of the genes encoding for p16 and MTAP was reported to be indicative of a cancer at a more advanced stage of tumor development. In some osteosarcoma patients, the MTAP gene was present at diagnosis but was deleted at a later time point (Garcia-Castellano *et al.*, *Clin. Cancer Res.* 8(3) 2002 782-787).

SUMMARY

[0008] The present disclosure provides compounds that inhibit MAT2A. The compounds and their pharmaceutical compositions are useful in methods for treating various cancers, including those that are refractory to standard treatments, such as surgery, radiation therapy, chemotherapy, and hormonal therapy.

[0009] Thus, in accordance with some embodiments, the present disclosure provides compounds according to Formula I or pharmaceutically acceptable salts thereof:



[0010] In Formula I, X is N or CR⁶; L is O, S, NR, or a bond; and R is H or C₁-C₆-alkyl.

[0011] R¹ is selected from the group consisting of C₁-C₆-alkyl, C₃-C₆-carbocyclyl, -(C₁-C₆-alkyl)(C₃-C₆-carbocyclyl), and -(C₁-C₆-alkyl)(C₃-C₆-cycloalkenyl), wherein any alkyl in R¹ is straight or branched, and R¹ is optionally substituted by 1 – 6 halo.

[0012] Alternatively, when L is N, then R and R¹ in combination with L represent a 3- to 6-membered heterocycloalkyl (wherein 1-4 ring members are independently selected from N, O, and S) that is optionally substituted by one or more R^A.

[0013] R² and R³ are independently selected from the group consisting of C₆-C₁₀-aryl, 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are

independently selected from N, O, and S), and 3- to 14-membered heterocycloalkyl (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S). R^2 and R^3 are independently and optionally substituted by one or more substituents that are selected from the group consisting of R^A , OR^A , halo, $-N=N-R^A$, $NR^A R^B$, $-(C_1-C_6-alkyl)NR^A R^B$, $-C(O)OR^A$, $-C(O)NR^A R^B$, $-OC(O)R^A$, and $-CN$.

[0014] R^{2a} is absent or present and, if present, it is taken together with R^2 and the carbon atom to which they are attached to form a spiro-fused 5- to 6-membered carbocyclyl or heterocycloalkyl (wherein 1-4 ring members are independently selected from NR^A , O, and S), wherein the spiro-fused 5- to 6-membered carbocyclyl or heterocycloalkyl is optionally substituted by one or more R^A , and each bond $==$ (a) represents a single bond and each bond $==$ (b) represents a double bond.

[0015] When R^{2a} is absent, then each bond $==$ (a) represents a double bond and each bond $==$ (b) represents a single bond.

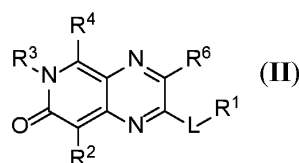
[0016] R^4 , R^5 , and R^6 are independently selected from the group consisting of R^A , OR^A , halo, $NR^A R^B$, $-(C_1-C_6-alkyl)NR^A R^B$, $-C(O)OR^A$, $-C(O)NR^A R^B$, and $-OC(O)R^A$;

[0017] R^A and R^B are independently selected from the group consisting of H, -CN, hydroxy, oxo, $C_1-C_6-alkyl$, $C_1-C_6-alkoxy$, $C_2-C_6-alkenyl$, $C_2-C_6-alkynyl$, NH_2 , $-S(O)_{0-2}-(C_1-C_6-alkyl)$, $-S(O)_{0-2}-(C_6-C_{10}-aryl)$, $-C(O)(C_1-C_6-alkyl)$, $-C(O)(C_3-C_{14}-carbocyclyl)$, $-C_3-C_{14}-carbocyclyl$, $-(C_1-C_6-alkyl)(C_3-C_{14}-carbocyclyl)$, $C_6-C_{10}-aryl$, 3- to 14-membered heterocycloalkyl, and $-(C_1-C_6-alkyl)-(3- to 14-membered heterocycloalkyl)$ (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S).

[0018] Each alkyl, alkoxy, alkenyl, alkynyl, aryl, carbocyclyl, heterocycloalkyl, and heteroaryl moiety of R^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, halo, $-NR'^2$ (wherein each R is independently selected from the group consisting of $C_1-C_6-alkyl$, $C_2-C_6-alkenyl$, $C_2-C_6-alkynyl$, $C_6-C_{10}-aryl$, 3- to 14-membered heterocycloalkyl and

-(C₁-C₆-alkyl)-(3- to 14-membered heterocycloalkyl) (wherein 1-4 ring members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4 ring members are independently selected from N, O, and S), -NHC(O)(OC₁-C₆-alkyl), -NO₂, -CN, oxo, -C(O)OH, -C(O)O(C₁-C₆-alkyl), -C₁-C₆-alkyl(C₁-C₆-alkoxy), -C(O)NH₂, C₁-C₆-alkyl, -C(O)C₁-C₆-alkyl, -OC₁-C₆-alkyl, -Si(C₁-C₆-alkyl)₃, -S(O)₀₋₂-(C₁-C₆-alkyl), C₆-C₁₀-aryl, -(C₁-C₆-alkyl)(C₆-C₁₀-aryl), 3- to 14-membered heterocycloalkyl, and -(C₁-C₆-alkyl)-(3- to 14-membered heterocycloalkyl) (wherein 1-4 ring members are independently selected from N, O, and S), and -O(C₆-C₁₄-aryl), wherein each alkyl, aryl, and heterocycloalkyl in R^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, -OC₁-C₆-alkyl, halo, -NH₂, -(C₁-C₆-alkyl)NH₂, -C(O)OH, CN, and oxo.

[0019] The present disclosure also provides, in accordance with additional embodiments, compounds according to Formula II or pharmaceutically acceptable salts thereof:



[0020] In Formula II, L is O, S, NR, or a bond; and R is H or C₁-C₆-alkyl.

[0021] R¹ is selected from the group consisting of C₁-C₆-alkyl, C₂-C₆-alkenyl, C₃-C₆-carbocyclyl, -(C₁-C₆-alkyl)(C₃-C₆-carbocyclyl), and -(C₁-C₆-alkyl)(C₃-C₆-cycloalkenyl) wherein any alkyl in R¹ is straight or branched, and R¹ is optionally substituted by 1 – 6 halo.

[0022] Alternatively, in some embodiments when L is NR, then R and R¹ in combination with L represent a 3- to 6-membered heterocycloalkyl (wherein 1-4 ring members are independently selected from N, O, and S) optionally substituted by one or more R^A.

[0023] R² and R³ are independently selected from the group consisting of C₆-C₁₀-aryl, 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S), and 3- to 14-membered heterocycloalkyl (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S), wherein R² and R³ are independently and optionally

substituted by one or more substituents that are selected from the group consisting of R^A , OR^A , halo, $-N=N-R^A$, $NR^A R^B$, $-(C_1-C_6-alkyl)NR^A R^B$, $-C(O)OR^A$, $-C(O)NR^A R^B$, $-OC(O)R^A$, and $-CN$.

[0024] R^4 and R^6 are independently selected from the group consisting of R^A , OR^A , halo, $NR^A R^B$, $-(C_1-C_6-alkyl)NR^A R^B$, $-C(O)OR^A$, $-C(O)NR^A R^B$, and $-OC(O)R^A$.

[0025] R^A and R^B are independently selected from the group consisting of H, $-CN$, $-hydroxy$, oxo , $C_1-C_6-alkyl$, $C_1-C_6-alkoxy$, $C_2-C_6-alkenyl$, $C_2-C_6-alkynyl$, NH_2 , $-S(O)_{0-2}-(C_1-C_6-alkyl)$, $-S(O)_{0-2}-(C_6-C_{10}-aryl)$, $-C(O)(C_1-C_6-alkyl)$, $-C(O)(C_3-C_{14}-carbocyclyl)$, $-C_3-C_{14}-carbocyclyl$, $-(C_1-C_6-alkyl)(C_3-C_{14}-carbocyclyl)$, $C_6-C_{10}-aryl$, 3- to 14-membered heterocycloalkyl and $-(C_1-C_6-alkyl)-(3- to 14-membered heterocycloalkyl)$ (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S);

[0026] In R^A and R^B , each alkyl, alkoxy, alkenyl, alkynyl, aryl, carbocyclyl, heterocycloalkyl, and heteroaryl moiety of R^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, halo, $-NR'^2$ (wherein each R' is independently selected from the group consisting of $C_1-C_6-alkyl$, $C_2-C_6-alkenyl$, $C_2-C_6-alkynyl$, $C_6-C_{10}-aryl$, 3- to 14-membered heterocycloalkyl and $-(C_1-C_6-alkyl)-(3- to 14-membered heterocycloalkyl)$ (wherein 1-4 ring members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S), $-NHC(O)(OC_1-C_6-alkyl)$, $-NO_2$, $-CN$, oxo , $-C(O)OH$, $-C(O)O(C_1-C_6-alkyl)$, $-C_1-C_6-alkyl(C_1-C_6-alkoxy)$, $-C(O)NH_2$, $C_1-C_6-alkyl$, $-C(O)C_1-C_6-alkyl$, $-OC_1-C_6-alkyl$, $-Si(C_1-C_6-alkyl)_3$, $-S(O)_{0-2}-(C_1-C_6-alkyl)$, $C_6-C_{10}-aryl$, $-(C_1-C_6-alkyl)(C_6-C_{10}-aryl)$, 3- to 14-membered heterocycloalkyl, and $-(C_1-C_6-alkyl)-(3- to 14-membered heterocycle)$ (wherein 1-4 heterocycle members are independently selected from N, O, and S), and $-O(C_6-C_{14}-aryl)$, and wherein each alkyl, alkenyl, aryl, and heterocycloalkyl in R^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, $-OC_1-C_6-alkyl$, halo, $-NH_2$, $-(C_1-C_6-alkyl)NH_2$, $-C(O)OH$, CN , and oxo .

[0027] In another embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0028] In yet another embodiment, the present disclosure provides a method for inhibiting the synthesis of SAM in a cell, comprising contacting the cell with an effective amount of a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof.

[0029] In yet another embodiment, the present disclosure provides a method for inhibiting the synthesis of SAM in a subject, comprising administering to the subject an effective amount of a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof.

[0030] Yet another embodiment is a method of treating a cancer in a subject suffering therefrom, comprising administering to the subject an effective amount of a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof. In some embodiments, the cancer is an MTAP-deleted cancer.

[0031] Also provided in an embodiment is a method for treating a cancer in a subject suffering therefrom, wherein the cancer is characterized by a reduction or absence of MTAP gene expression, or reduced or absent function of MTAP protein, as compared to cancers where the MTAP gene or protein is present and/or fully functioning, or as compared to cancers with wild type MTAP gene, comprising administering to the subject a therapeutically effective amount of a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof.

[0032] In another embodiment, optionally in combination with any other embodiment described herein, the present disclosure provides a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof, for use in inhibiting the synthesis of SAM in a cell. Alternatively, in accordance with some embodiments, optionally in combination with any other embodiment described herein, the compound is useful for inhibiting the synthesis of SAM in a subject. Another embodiment, optionally in combination with any other embodiment described herein, provides the use of a compound of Formula I or

Formula II or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inhibiting the synthesis of SAM in a subject.

[0033] Yet another embodiment, optionally in combination with any other embodiment described herein, provides a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof, for use in treating a cancer in a subject suffering therefrom. An embodiment, optionally in combination with any other embodiment described herein, is the use of a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a cancer in a subject suffering therefrom. In some embodiments, the cancer is an MTAP-deleted cancer, or is characterized by a reduction or absence of MTAP gene expression, or reduced function of MTAP protein, as compared to cancers with fully functional MTAP gene expression or function, or to cancers with fully functional MTAP protein function.

DETAILED DESCRIPTION

[0034] The compounds described herein are inhibitors of MAT2A. The present disclosure thus relates not only to such compounds having a structure according to Formula I or Formula II, but also to their pharmaceutical compositions. The compounds and compositions disclosed herein are useful in treating cancers. Some cancers include various MTAP-deleted cancers, i.e., those cancers characterized by the absence or deletion of the MTAP gene.

Definitions

[0035] "Alkyl" refers to straight, branched chain, or cyclic hydrocarbyl groups, e.g., "cycloalkyl," including from 1 to about 20 carbon atoms. For instance, an alkyl can have from 1 to 10 carbon atoms or 1 to 6 carbon atoms. Exemplary alkyl includes straight chain alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, and the like, and also includes branched chain isomers of straight chain alkyl groups, for example without limitation, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $-\text{CH}(\text{CH}_2\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, $-\text{C}(\text{CH}_2\text{CH}_3)_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $-\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$, $-\text{CH}_2\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{C}(\text{CH}_2\text{CH}_3)_3$, $-\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_2\text{CH}_3)_3$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)_2$, and the like. Thus, alkyl groups include primary

alkyl groups, secondary alkyl groups, and tertiary alkyl groups. An alkyl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0036] The phrase “substituted alkyl” refers to alkyl substituted at one or more positions, for example, 1, 2, 3, 4, 5, or even 6 positions, which substituents are attached at any available atom to produce a stable compound, with substitution as described herein. “Optionally substituted alkyl” refers to alkyl or substituted alkyl.

[0037] Each of the terms “halogen,” “halide,” and “halo” refers to -F, -Cl, -Br, or -I.

[0038] The term “alkenyl” refers to straight, branched chain, or cyclic hydrocarbyl groups, e.g., “cycloalkenyl,” including from 2 to about 20 carbon atoms having 1-3, 1-2, or at least one carbon to carbon double bond. The term “cycloalkenyl” refers specifically to cyclic alkenyl, such as C₃-C₆-cycloalkenyl. An alkenyl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0039] “Substituted alkenyl” refers to alkenyl substituted at 1 or more, *e.g.*, 1, 2, 3, 4, 5, or even 6 positions, which substituents are attached at any available atom to produce a stable compound, with substitution as described herein. “Optionally substituted alkenyl” refers to alkenyl or substituted alkenyl.

[0040] “Alkyne or “alkynyl” refers to a straight or branched chain unsaturated hydrocarbon having the indicated number of carbon atoms and at least one triple bond. Examples of a (C₂-C₈)alkynyl group include, but are not limited to, acetylene, propyne, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, 1-hexyne, 2-hexyne, 3-hexyne, 1-heptyne, 2-heptyne, 3-heptyne, 1-octyne, 2-octyne, 3-octyne and 4-octyne. An alkynyl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0041] “Substituted alkynyl” refers to an alkynyl substituted at 1 or more, *e.g.*, 1, 2, 3, 4, 5, or even 6 positions, which substituents are attached at any available atom to produce a stable compound, with substitution as described herein. “Optionally substituted alkynyl” refers to alkynyl or substituted alkynyl.

[0042] The term “alkoxy” refers to an -O-alkyl group having the indicated number of carbon atoms. For example, a (C₁-C₆)alkoxy group includes -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -O-butyl, -O-*sec*-butyl, -O-*tert*-butyl, -O-pentyl, -O-isopentyl, -O-neopentyl, -O-hexyl, -O-isohexyl, and -O-neohexyl.

[0043] The term “carbocyclyl” refers to a monocyclic, bicyclic, tricyclic, or polycyclic, 3- to 14-membered ring system, which is either saturated, such as “cycloalkyl,” or unsaturated, such as “cycloalkenyl.” The carbocyclyl may be attached via any atom. Carbocyclyl, for instance, also contemplates fused rings wherein, for instance, a carbocyclyl is fused to an aryl or heteroaryl ring as defined herein. Representative examples of carbocyclyl include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, phenyl, naphthyl, anthracyl, benzofuranyl, and benzothiophenyl. A carbocyclyl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0044] “Substituted carbocyclyl” refers to carbocyclyl substituted at 1 or more, *e.g.*, 1, 2, 3, 4, 5, or even 6 positions, which substituents are attached at any available atom to produce a stable compound, with substitution as described herein. “Optionally substituted carbocyclyl” refers to carbocyclyl or substituted carbocyclyl.

[0045] “Aryl” when used alone or as part of another term means a carbocyclic aromatic group whether or not fused having the number of carbon atoms designated or if no number is designated, up to 14 carbon atoms, such as a C₆-C₁₄-aryl. Particular aryl groups are phenyl, naphthyl, biphenyl, phenanthrenyl, naphthacenyl, and the like (see *e.g.*, *Lang’s Handbook of Chemistry* (Dean, J. A., ed) 13th ed. Table 7-2 [1985]). A particular aryl is phenyl. “Aryl” also includes aromatic ring systems that are optionally fused with a carbocyclyl ring, as herein defined. An aryl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0046] A “substituted aryl” is an aryl that is independently substituted with one or more substituents attached at any available atom to produce a stable compound, wherein the substituents are as described herein. “Optionally substituted aryl” refers to aryl or substituted aryl.

[0047] The term “heteroatom” refers to N, O, and S. Disclosed compounds that contain N or S atoms can be optionally oxidized to the corresponding N-oxide, sulfoxide, or sulfone compounds.

[0048] “Heteroaryl,” alone or in combination with any other moiety described herein, refers to a monocyclic aromatic ring structure containing 5 to 10, such as 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, such as 1-4, 1-3, or 1-2, heteroatoms independently selected from the group consisting of O, S, and N. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or heteroatom is the point of attachment of the heteroaryl ring structure such that a stable compound is produced. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrazinyl, quinoxalyl, indolizinyl, benzo[b]thienyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, pyrazolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazolyl, furanyl, benzofuryl, and indolyl. A heteroaryl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0049] A “substituted heteroaryl” is a heteroaryl that is independently substituted, unless indicated otherwise, with one or more, *e.g.*, 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, also 1 substituent, attached at any available atom to produce a stable compound, wherein the substituents are as described herein. “Optionally substituted heteroaryl” refers to heteroaryl or substituted heteroaryl.

[0050] “Heterocycloalkyl” means a saturated or unsaturated non-aromatic monocyclic, bicyclic, tricyclic or polycyclic ring system that has from 3 to 14, such as 3 to 6, atoms in which from 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N. A heterocycloalkyl is optionally fused with aryl or heteroaryl of 5-6 ring members, and includes oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. The point of attachment of the heterocycloalkyl ring is at a carbon or heteroatom such that a stable ring is retained. Examples of heterocycloalkyl groups include without limitation morpholino, tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, piperazinyl, dihydrobenzofuryl, and dihydroindolyl. A heterocycloalkyl group

can be unsubstituted or optionally substituted with one or more substituents as described herein below.

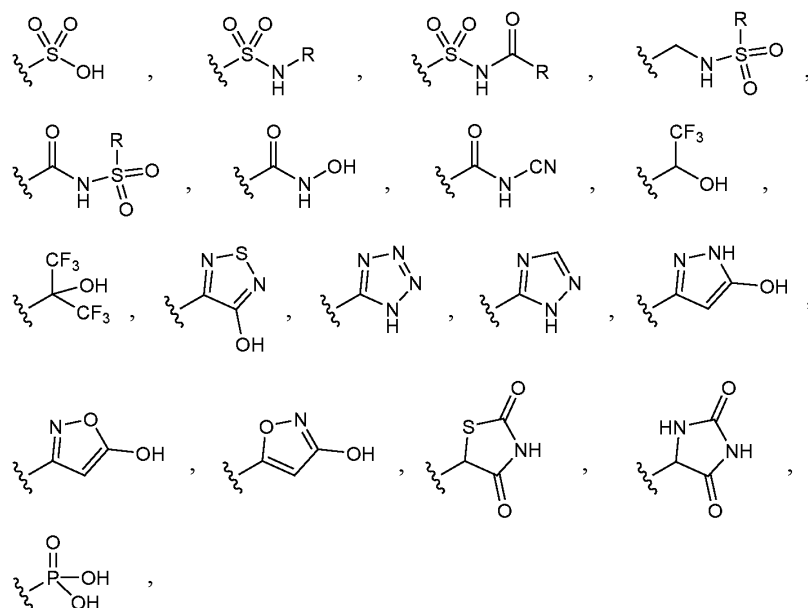
[0051] “Optionally substituted heterocycloalkyl” denotes a heterocycloalkyl that is substituted with 1 to 3 substituents, *e.g.*, 1, 2 or 3 substituents, attached at any available atom to produce a stable compound, wherein the substituents are as described herein.

[0052] The term “nitrile” or “cyano” can be used interchangeably and refer to a -CN group which is bound to a carbon atom of a heteroaryl ring, aryl ring and a heterocycloalkyl ring.

[0053] The term “oxo” refers to a =O atom attached to a saturated or unsaturated moiety. The =O atom can be attached to a carbon, sulfur, or nitrogen atom that is part of a cyclic or acyclic moiety.

[0054] A “hydroxyl” or “hydroxy” refers to an -OH group.

[0055] The substituent -CO₂H may be replaced with bioisosteric replacements such as:



and the like, wherein R has the same definition as R^A as defined herein. *See, e.g.*, THE PRACTICE OF MEDICINAL CHEMISTRY (Academic Press: New York, 1996), at page 203.

[0056] Compounds described herein can exist in various isomeric forms, including configurational, geometric, and conformational isomers, including, for example, *cis*- or *trans*- conformations. The compounds may also exist in one or more tautomeric forms, including both single tautomers and mixtures of tautomers. The term “isomer” is intended to encompass all isomeric forms of a compound of this disclosure, including tautomeric forms of the compound. The compounds of the present disclosure may also exist in open-chain or cyclized forms. In some cases, one or more of the cyclized forms may result from the loss of water. The specific composition of the open-chain and cyclized forms may be dependent on how the compound is isolated, stored or administered. For example, the compound may exist primarily in an open-chained form under acidic conditions but cyclize under neutral conditions. All forms are included in the present disclosure.

[0057] Some compounds described herein can have asymmetric centers and therefore exist in different enantiomeric and diastereomeric forms. A compound of the present disclosure can be in the form of an optical isomer or a diastereomer. Accordingly, the disclosure encompasses compounds and their uses as described herein in the form of their optical isomers, diastereoisomers and mixtures thereof, including a racemic mixture. Optical isomers of the compounds of the disclosure can be obtained by known techniques such as asymmetric synthesis, chiral chromatography, simulated moving bed technology or via chemical separation of stereoisomers through the employment of optically active resolving agents.

[0058] Unless otherwise indicated, the term “stereoisomer” means one stereoisomer of a compound that is substantially free of other stereoisomers of that compound. Thus, a stereomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, for example greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers

of the compound, or greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound, or greater than about 99% by weight of one stereoisomer of the compound and less than about 1% by weight of the other stereoisomers of the compound. The stereoisomer as described above can be viewed as composition comprising two stereoisomers that are present in their respective weight percentages described herein.

[0059] If there is a discrepancy between a depicted structure and a name given to that structure, then the depicted structure controls. Additionally, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it. In some cases, however, where more than one chiral center exists, the structures and names may be represented as single enantiomers to help describe the relative stereochemistry. Those skilled in the art of organic synthesis will know if the compounds are prepared as single enantiomers from the methods used to prepare them.

[0060] As used herein, and unless expressly and specifically stated to the contrary, the term “compound” is inclusive in that it encompasses a compound or a pharmaceutically acceptable salt, stereoisomer, and/or tautomer thereof. Thus, for instance, a compound of Formula I or Formula II includes a pharmaceutically acceptable salt of the compound. Similarly, a compound of Formula I or Formula II includes a pharmaceutically acceptable salt of a tautomer of the compound.

[0061] In this description, a “pharmaceutically acceptable salt” is a pharmaceutically acceptable, organic or inorganic acid or base salt of a compound of the present disclosure. Representative pharmaceutically acceptable salts include, *e.g.*, alkali metal salts, alkali earth salts, ammonium salts, water-soluble and water-insoluble salts, such as the acetate, mesonate (4,4-diaminostilbene-2, 2'-disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulinate, dihydrochloride, edetate,

edisylate, estolate, esylate, fiunarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts. A pharmaceutically acceptable salt can have more than one charged atom in its structure. In this instance the pharmaceutically acceptable salt can have multiple counterions. Thus, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counterions.

[0062] The terms “treat”, “treating” and “treatment” refer to the amelioration or eradication of a disease or symptoms associated with a disease. In certain embodiments, such terms refer to minimizing the spread or worsening of the disease resulting from the administration of one or more prophylactic or therapeutic agents to a patient or subject with such a disease.

[0063] The terms “prevent,” “preventing,” and “prevention” refer to the prevention of the onset, recurrence, or spread of the disease in a patient or subject resulting from the administration of a prophylactic or therapeutic agent.

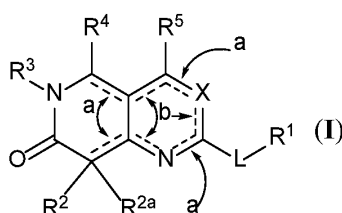
[0064] The term “effective amount” refers to an amount of a compound of the present disclosure or other active ingredient sufficient to provide a therapeutic or prophylactic benefit in the treatment or prevention of a disease or to delay or minimize symptoms associated with a disease. Further, a therapeutically effective amount with respect to a compound of the present disclosure means that amount of therapeutic agent alone, or in combination with other therapies, that provides a therapeutic benefit in the treatment or prevention of a disease. Used in connection with a compound of the present disclosure, the term can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease, or enhances the therapeutic efficacy of or is synergistic with another therapeutic agent.

[0065] A “patient” or “subject” includes an animal, such as a human, cow, horse, sheep, lamb, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit or guinea pig. In accordance with some embodiments, the animal is a mammal such as a non-primate and a primate (*e.g.*, monkey and human). In the present disclosure, the terms “patient” and “subject” are used interchangeably. In one embodiment, a patient or subject is a human, and in other embodiments a patient or subject is a human infant, child, adolescent or adult.

[0066] “Inhibitor” means a compound which prevents or reduces the amount of synthesis of SAM. In an embodiment, an inhibitor binds to MAT2A.

COMPOUNDS

[0067] As described generally above, the present disclosure provides compounds according to Formula I and pharmaceutically acceptable salts thereof:



[0068] In Formula I, X is N or CR⁶; L is O, S, NR, or a bond; and R is H or C₁-C₆-alkyl.

[0069] R¹ is selected from the group consisting of C₁-C₆-alkyl, C₂-C₆-alkenyl, C₃-C₆-carbocyclyl, -(C₁-C₆-alkyl)(C₃-C₆-carbocyclyl), and -(C₁-C₆-cycloalkenyl) wherein any alkyl in R¹ is straight or branched, and R¹ is optionally substituted by 1 – 6 halo.

[0070] In an embodiment when L is N, then R and R¹ in combination with L represent a 3- to 6-membered heterocycloalkyl (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S) that is optionally substituted by one or more R^A.

[0071] R² and R³ are independently selected from the group consisting of C₆-C₁₀-aryl, 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S), and 3- to 14-membered

heterocycloalkyl (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S), wherein R^2 and R^3 are independently and optionally substituted by one or more substituents that are selected from the group consisting of R^A , OR^A , halo, $-N=N-R^A$, $NR^A R^B$, $-(C_1-C_6-alkyl)NR^A R^B$, $-C(O)OR^A$, $-C(O)NR^A R^B$, $-OC(O)R^A$, and $-CN$.

[0072] R^{2a} is absent or present and, if present, it is taken together with R^2 and the carbon atom to which they are attached to form a spiro-fused 5- to 6-membered carbocyclyl or heterocycloalkyl (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S); and each bond $==$ (a) represents a single bond and each bond $==$ (b) represents a double bond, wherein the spiro-fused 5- to 6-membered carbocyclyl or heterocycloalkyl is optionally substituted by one or more R^A .

[0073] If R^{2a} is absent, then each bond $==$ (a) represents a double bond and each bond $==$ (b) represents a single bond.

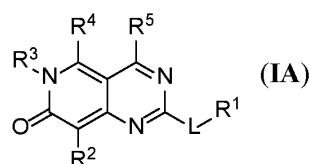
[0074] R^4 , R^5 , and R^6 are independently selected from the group consisting of R^A , OR^A , halo, $NR^A R^B$, $-(C_1-C_6-alkyl)NR^A R^B$, $-C(O)OR^A$, $-C(O)NR^A R^B$, and $-OC(O)R^A$.

[0075] R^A and R^B are independently selected from the group consisting of H, $-CN$, hydroxy, oxo, $C_1-C_6-alkyl$, $C_1-C_6-alkoxy$, $C_2-C_6-alkenyl$, $C_2-C_6-alkynyl$, NH_2 , $-S(O)_{0-2}-(C_1-C_6-alkyl)$, $-S(O)_{0-2}-(C_6-C_{10}-aryl)$, $-C(O)(C_1-C_6-alkyl)$, $-C(O)(C_3-C_{14}-carbocyclyl)$, $-C_3-C_{14}-carbocyclyl$, $-(C_1-C_6-alkyl)(C_3-C_{14}-carbocyclyl)$, $C_6-C_{10}-aryl$, 3- to 14-membered heterocycloalkyl, and $-(C_1-C_6-alkyl)-(3- to 14-membered heterocycloalkyl)$ (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S); wherein each alkyl, alkoxy, alkenyl, alkynyl, aryl, carbocyclyl, heterocycloalkyl, and heteroaryl moiety of R^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, halo, $-NR'^2$ (wherein each R' is independently selected from the group consisting of $C_1-C_6-alkyl$, $C_2-C_6-alkenyl$, $C_2-C_6-alkynyl$, $C_6-C_{10}-aryl$, 3- to 14-membered heterocycloalkyl and $-(C_1-C_6-alkyl)-(3- to 14-membered heterocycloalkyl)$ (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4

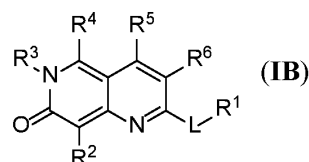
heteroaryl members are independently selected from N, O, and S), -NHC(O)(OC₁-C₆-alkyl), -NO₂, -CN, oxo, -C(O)OH, -C(O)O(C₁-C₆-alkyl), -C₁-C₆-alkyl(C₁-C₆-alkoxy), -C(O)NH₂, C₁-C₆-alkyl, -C(O)C₁-C₆-alkyl, -OC₁-C₆-alkyl, -Si(C₁-C₆-alkyl)₃, -S(O)₀₋₂-(C₁-C₆-alkyl), C₆-C₁₀-aryl, -(C₁-C₆-alkyl)(C₆-C₁₀-aryl), 3- to 14-membered heterocycloalkyl, and -(C₁-C₆-alkyl)-(3- to 14-membered heterocycloalkyl) (wherein 1-4 ring members are independently selected from N, O, and S), and -O(C₆-C₁₄-aryl), and wherein each alkyl, alkenyl, aryl, and heterocycloalkyl in R^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, -OC₁-C₆-alkyl, halo, -NH₂, -(C₁-C₆-alkyl)NH₂, -C(O)OH, CN, and oxo.

[0076] According to various embodiments, when R^{2a} is absent, each bond ===(a) represents a double bond and each bond ===(b) represents a single bond. In one embodiment, X is N. In another embodiment, X is CR⁶.

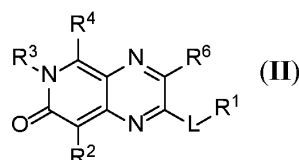
[0077] In accordance with various embodiments, compounds of Formula (I) have a structure according to Formula (IA):



[0078] Alternatively, compounds of Formula (I) have a structure according to Formula (IB):



[0079] The present disclosure also provides compounds according to Formula II and pharmaceutically acceptable salts thereof:



[0080] In Formula II, L is O, S, NR, or a bond; and R is H or C₁-C₆-alkyl.

[0081] R¹ is selected from the group consisting of C₁-C₆-alkyl, C₂-C₆-alkenyl, C₃-C₆-carbocyclyl, -(C₁-C₆-alkyl)(C₃-C₆-carbocyclyl), and -(C₁-C₆-alkyl)(C₃-C₆-cycloalkenyl) wherein any alkyl in R¹ is straight or branched, and R¹ is optionally substituted by 1 – 6 halo.

[0082] Alternatively, in some embodiments when L is NR, then R and R¹ in combination with L represent a 3- to 6-membered heterocycloalkyl (wherein 1-4 ring members are independently selected from N, O, and S) optionally substituted by one or more R^A.

[0083] R² and R³ are independently selected from the group consisting of C₆-C₁₀-aryl, 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S), and 3- to 14-membered heterocycloalkyl (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S), wherein R² and R³ are independently and optionally substituted by one or more substituents that are selected from the group consisting of R^A, OR^A, halo, -N=N- R^A, NR^AR^B, -(C₁-C₆-alkyl)NR^AR^B, -C(O)OR^A, -C(O)NR^AR^B, -OC(O)R^A, and -CN.

[0084] R⁴ and R⁶ are independently selected from the group consisting of R^A, OR^A, halo, NR^AR^B, -(C₁-C₆-alkyl)NR^AR^B, -C(O)OR^A, -C(O)NR^AR^B, and -OC(O)R^A.

[0085] R^A and R^B are independently selected from the group consisting of H, -CN, -hydroxy, oxo, C₁-C₆-alkyl, C₁-C₆-alkoxy, C₂-C₆-alkenyl, C₂-C₆-alkynyl, NH₂, -S(O)₀₋₂-(C₁-C₆-alkyl), -S(O)₀₋₂-(C₆-C₁₀-aryl), -C(O)(C₁-C₆-alkyl), -C(O)(C₃-C₁₄-carbocyclyl), -C₃-C₁₄-carbocyclyl, -(C₁-C₆-alkyl)(C₃-C₁₄-carbocyclyl), C₆-C₁₀-aryl, 3- to 14-membered heterocycloalkyl and -(C₁-C₆-alkyl)-(3- to 14-membered heterocycloalkyl) (wherein 1-4 heterocycloalkyl members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S);

[0086] In R^A and R^B, each alkyl, alkoxy, alkenyl, alkynyl, aryl, carbocyclyl, heterocycloalkyl, and heteroaryl moiety of R^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, halo, -NR'₂ (wherein each R' is independently selected from the group

consisting of C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₆-C₁₀-aryl, 3- to 14-membered heterocycloalkyl and -(C₁-C₆-alkyl)-(3- to 14-membered heterocycloalkyl) (wherein 1-4 ring members are independently selected from N, O, and S), and 5- to 10-membered heteroaryl (wherein 1-4 heteroaryl members are independently selected from N, O, and S), -NHC(O)(OC₁-C₆-alkyl), -NO₂, -CN, oxo, -C(O)OH, -C(O)O(C₁-C₆-alkyl), -C₁-C₆-alkyl(C₁-C₆-alkoxy), -C(O)NH₂, C₁-C₆-alkyl, -C(O)C₁-C₆-alkyl, -OC₁-C₆-alkyl, -Si(C₁-C₆-alkyl)₃, -S(O)₀₋₂-(C₁-C₆-alkyl), C₆-C₁₀-aryl, -(C₁-C₆-alkyl)(C₆-C₁₀-aryl), 3- to 14-membered heterocycloalkyl, and -(C₁-C₆-alkyl)-(3- to 14-membered heterocycle) (wherein 1-4 heterocycle members are independently selected from N, O, and S), and -O(C₆-C₁₄-aryl), and wherein each alkyl, alkenyl, aryl, and heterocycloalkyl in R^A and R^B is optionally substituted with one or more substituents selected from the group consisting of hydroxy, -OC₁-C₆-alkyl, halo, -NH₂, -(C₁-C₆-alkyl)NH₂, -C(O)OH, CN, and oxo.

[0087] In various embodiments, a compound of Formula (I), (II), (IA), or (IB) has substituents R⁴, R⁵, and R⁶ (if present) that are independently selected from the group consisting of H, C₁-C₆-alkyl, and C₁-C₆-alkoxy.

[0088] Optionally in combination with any other embodiment, another embodiment provides each of R⁴, R⁵, and R⁶ (if present) as H. Alternatively, according to various embodiments, one of R⁴, R⁵, and R⁶ is H. For instance, R⁴ is H. Another embodiment provides R⁵ as H. In still another embodiment, R⁶ is H. In additional embodiments, any two of R⁴, R⁵, and R⁶ are H. For example, R⁴ and R⁵ are H; R⁴ and R⁶ are H; or R⁵ and R⁶ are H.

[0089] In some compounds, according to another embodiment, R² is C₆-C₁₀-aryl or 5- to 10-membered heteroaryl. For instance, R² is C₆-C₁₀-aryl, such as phenyl.

[0090] In other compounds, according to another embodiment, R² is 5- to 10-membered heteroaryl that contains N as the only ring member heteroatom. Thus, for example, R² is pyridyl.

[0091] According to various embodiments, R³ is 3- to 14-membered heterocycloalkyl or 5- to 10-membered heteroaryl. Examples include compounds wherein R³ is a C₃-C₁₀-heteroaryl containing only 2 ring members as

heteroatoms independently selected from N, O, and S. Illustrative heteroaryl groups thus include benzothiazolyl, benzoisothiazolyl, benzoxazolyl, pyridinyl, pyridinonyl, benzimidazolyl, benzotriazolyl, indazolyl, quinoxaliny, quinolinyl, quinazolinyl, imidazopyridinyl, pyrazolopyridinyl, cinnolinyl, isoxazolyl, pyrazolyl, benzofuranyl, dihydrobenzofuranyl, and tetrahydrobenzodioxinyl.

[0092] Other embodiments, optionally in combination with any other embodiment described herein, provide a compound wherein L is O or NR. In these embodiments, R¹ can be C₁-C₆-alkyl or C₃-C₆-carbocyclyl. For example, R¹ is C₁-C₃-alkyl that is optionally substituted by 1 – 3 F.

[0093] In various embodiments, optionally in combination with any other embodiment, R³ is C₆-C₁₀-aryl.

[0094] Still further embodiments provide a compound of Formula I or Formula II wherein L is O or NR. Optionally in combination with this embodiment are embodiments wherein R¹ is C₁-C₆-alkyl or C₃-C₆-carbocyclyl. In other embodiments, R¹ is C₁-C₃-alkyl that is optionally substituted by 1 – 3 F.

[0095] Some compounds, in accordance with various embodiments, are those wherein L is O or NR and R is H; R¹ is C₁-C₃-alkyl that is optionally substituted by 1 – 3 F; R² is 3- to 14-membered heterocycloalkyl or 5- to 10-membered heteroaryl (wherein 1 ring member is N) or C₆-C₁₀-aryl; R³ is 5- to 10-membered heteroaryl wherein 1 to 3 ring members are independently selected from N, O, and S; and each of R⁴, R⁵, and R⁶ (if present) is H.

[0096] In various embodiments, optionally in combination with any other embodiment, L is NR. For example, in some embodiments, L is NH.

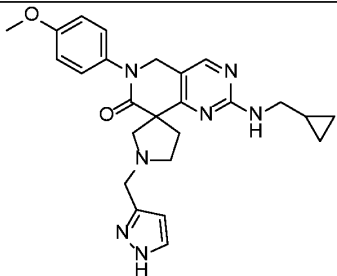
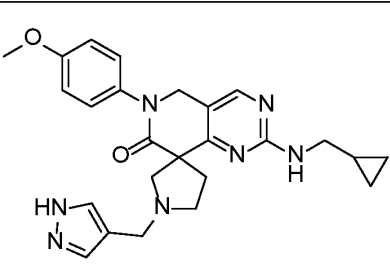
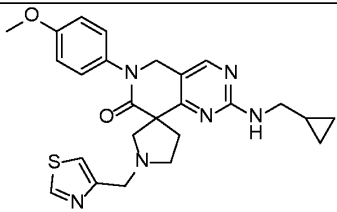
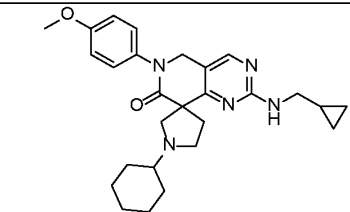
[0097] In other embodiments of the present disclosure, constituting a subgenus of Formula I, R^{2a} is present. In these embodiments, each bond == (a) represents a single bond and each bond == (b) represents a double bond. In addition, R^{2a} is present and is taken together with R² and the carbon atom to which these moieties are attached to form a spiro-fused 5- to 6-membered carbocyclyl or heterocycloalkyl (wherein 1-4 ring members are independently selected from N, O, and S), wherein the spiro-fused 5- to 6-membered carbocyclyl or heterocycloalkyl is optionally substituted by one or more R^A.

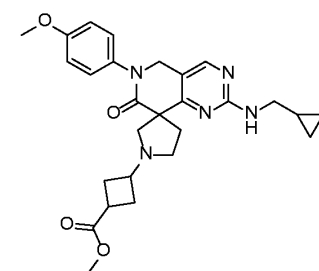
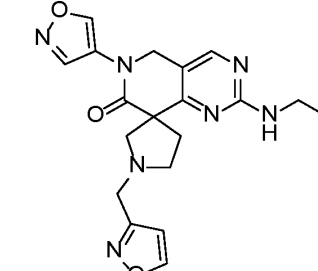
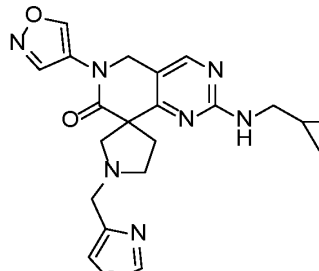
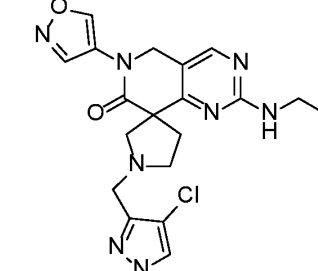
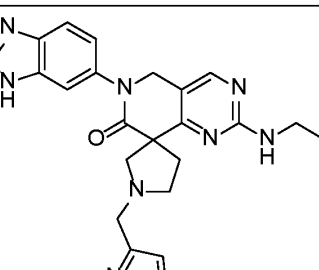
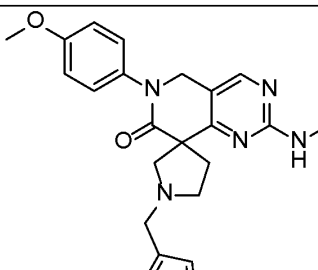
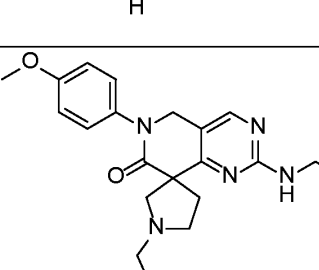
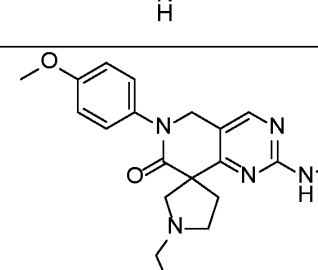
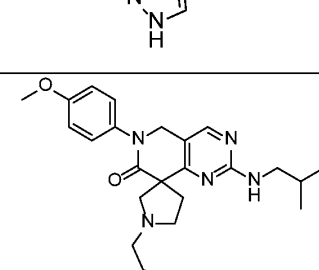
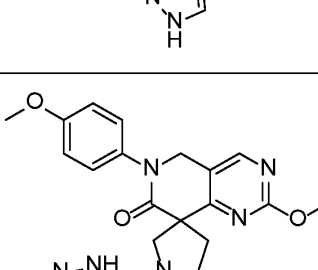
[0098] Examples of such spiro-fused compounds include those wherein R^{2a} , R^2 , and the carbon atom to which R^2 and R^{2a} are attached are taken to together to form a spiro-fused 5-membered heterocycloalkyl, wherein 1 ring member is N. Alternatively, R^{2a} , R^2 , and the carbon atom to which R^2 and R^{2a} are attached are taken together to form a spiro-fused 6-membered heterocycloalkyl, wherein 1 ring member is N. In still other embodiments, R^{2a} , R^2 , and the carbon atom to which R^2 and R^{2a} are attached are taken together to form a spiro-fused 6-membered carbocyclyl.

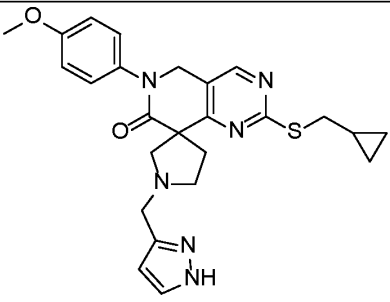
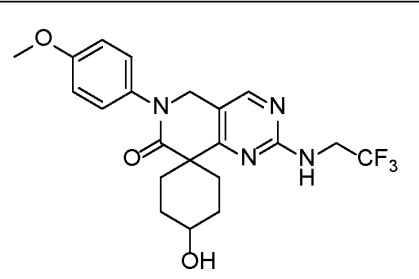
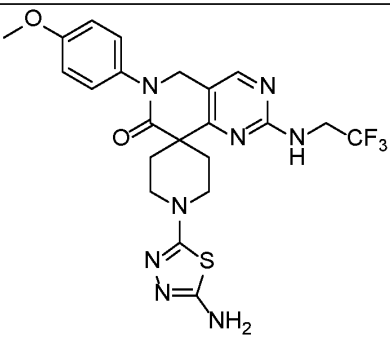
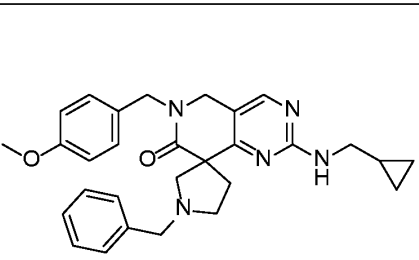
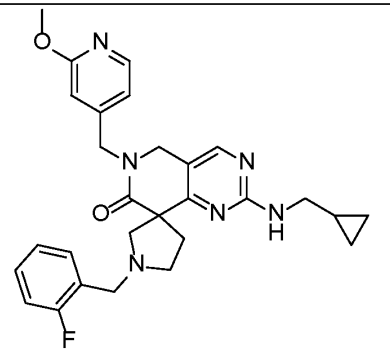
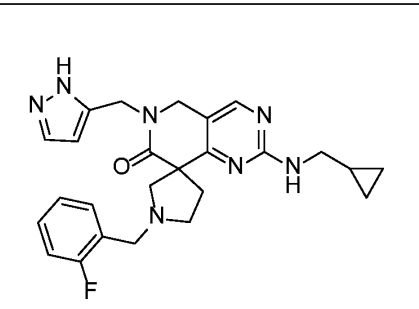
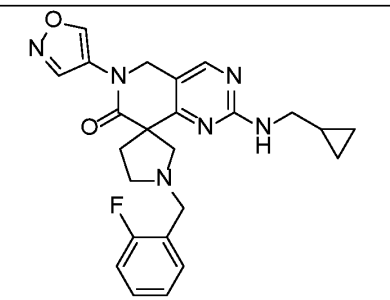
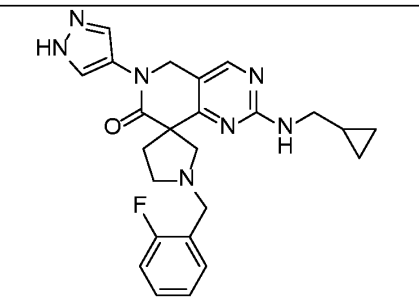
[0099] In this subgenus of Formula I, for instance, each of R^4 and R^5 is independently selected from the group consisting of H, C₁-C₆-alkyl, and C₁-C₆-alkoxy. Optionally, in addition, X is N. Further, in accordance with some embodiments, each of R^4 and R^5 is H. Alternatively, or in addition, R^3 is 5- to 10-membered heteroaryl having only 2 ring heteroatoms independently selected from N, O, and S. In other embodiments, R^3 is C₆-C₁₀-aryl.

[00100] In various embodiments, the present disclosure provides specific, illustrative examples of spiro-fused compounds of Formula I as set forth in Table 1 below:

[00101] **Table 1**

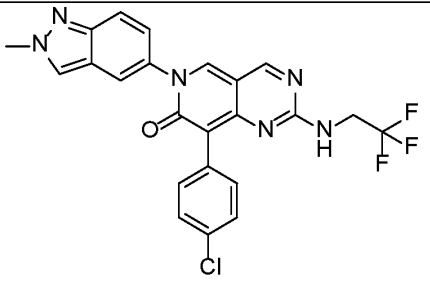
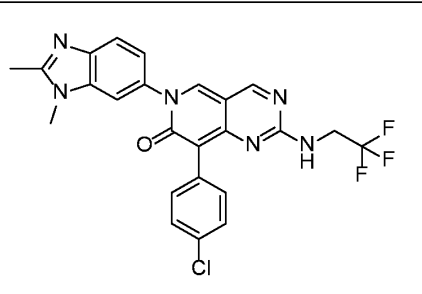
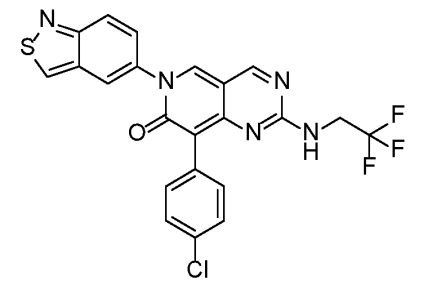
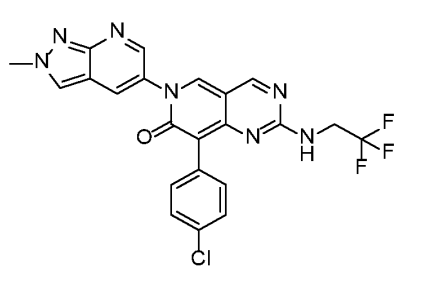
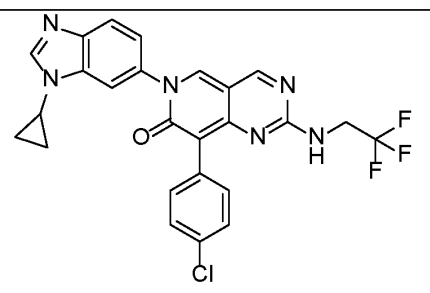
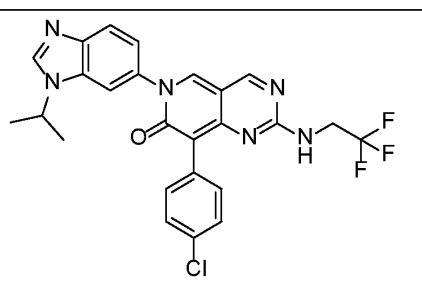
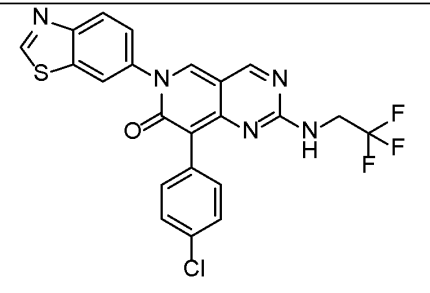
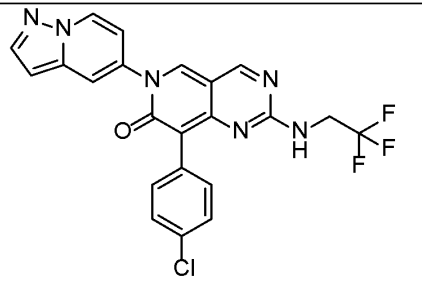
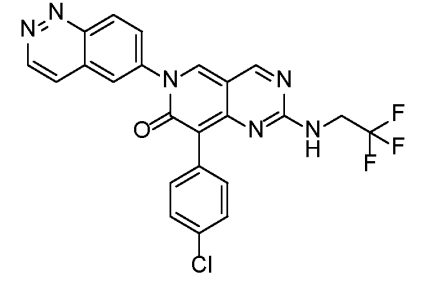
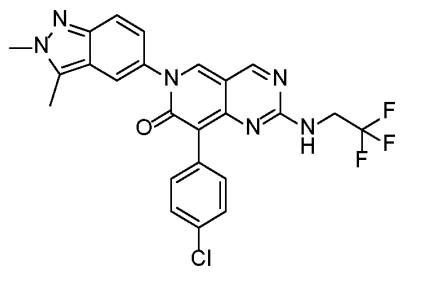
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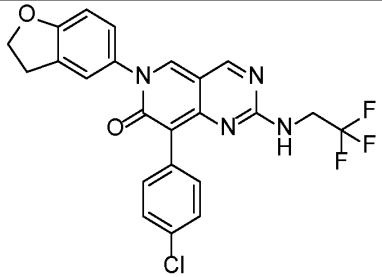
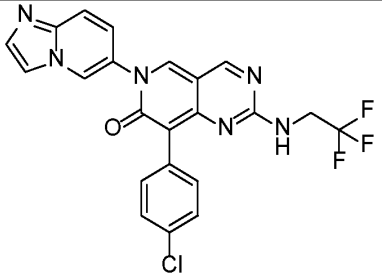
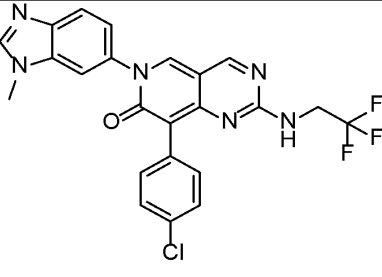
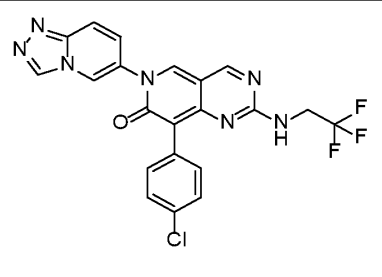
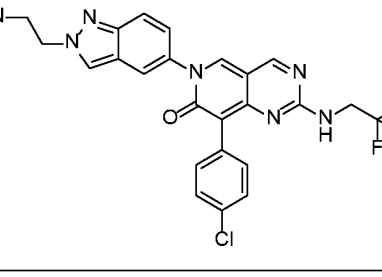
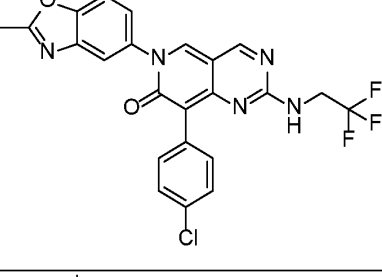
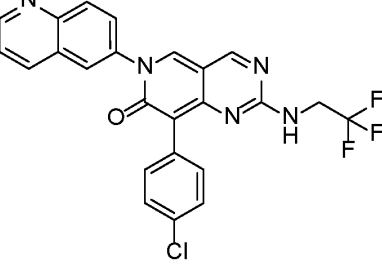
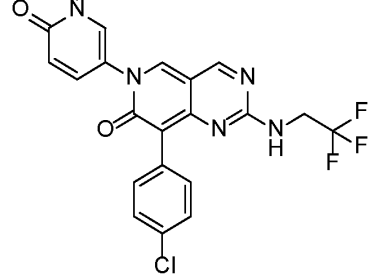
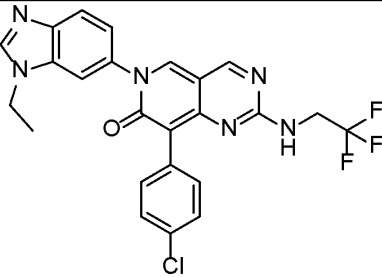
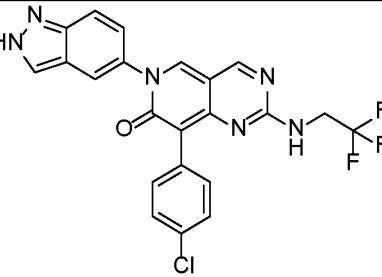
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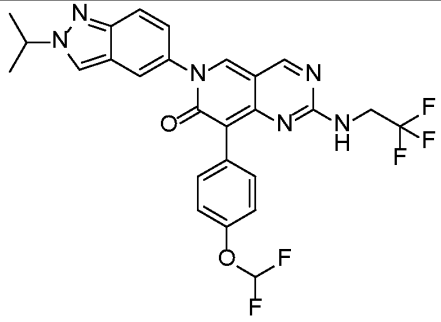
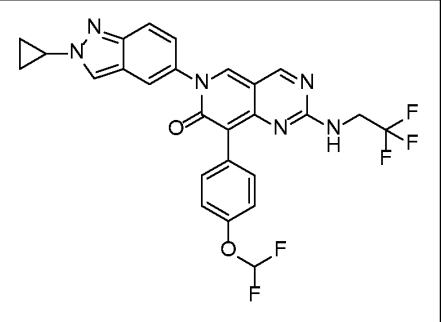
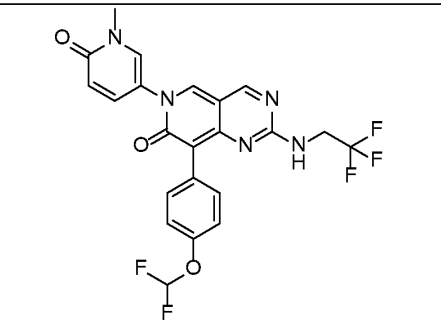
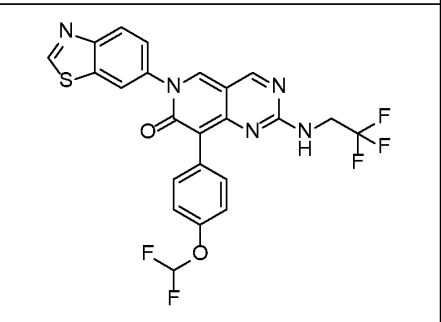
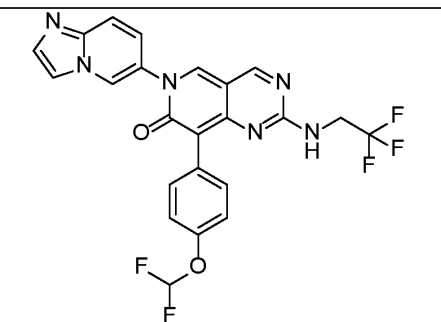
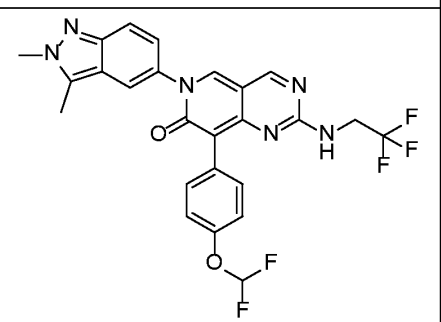
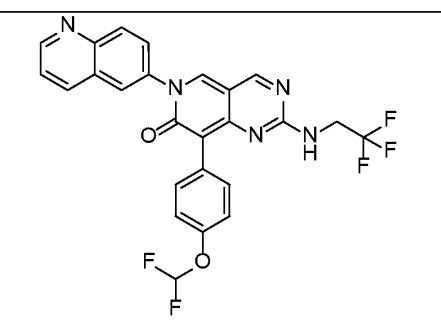
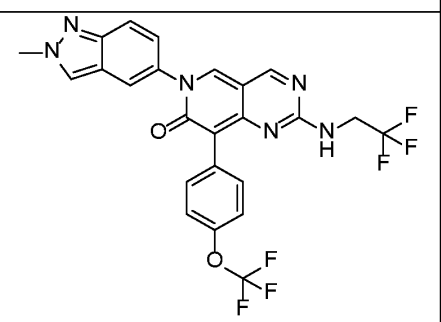
[00102] The present disclosure provides additional specific, illustrative examples of compounds of Formula I as set forth in Table 2 below.

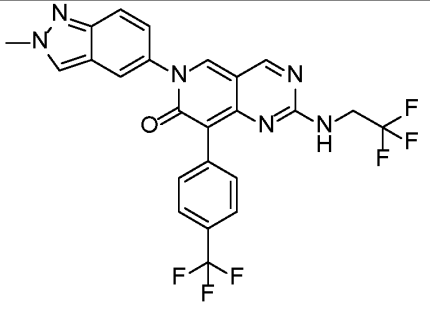
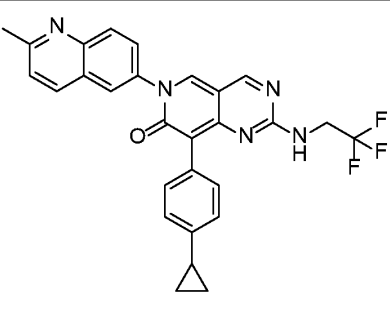
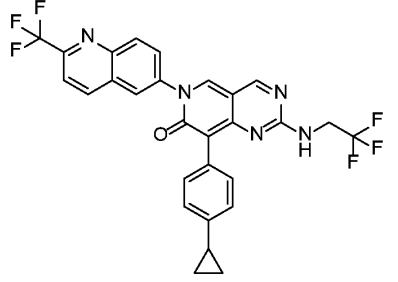
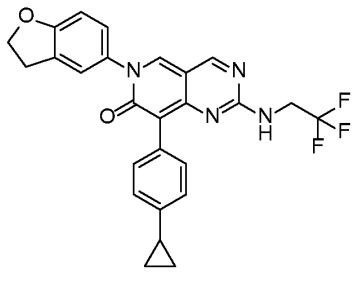
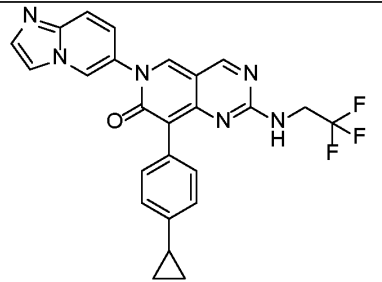
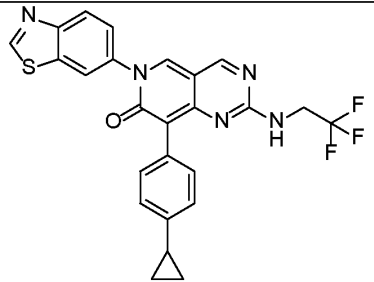
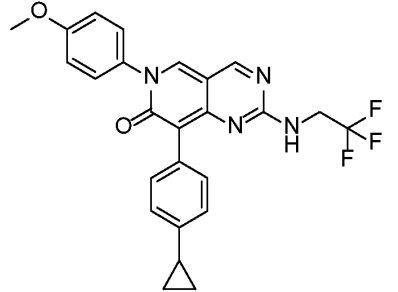
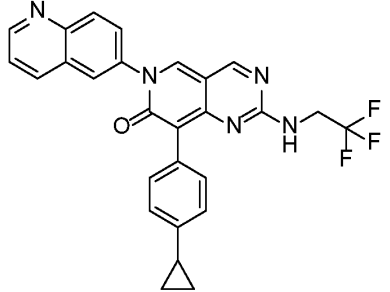
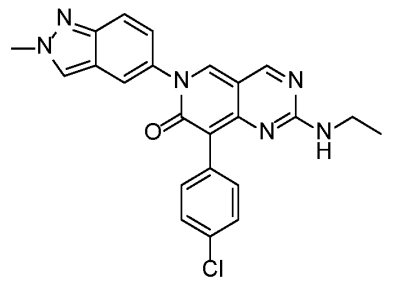
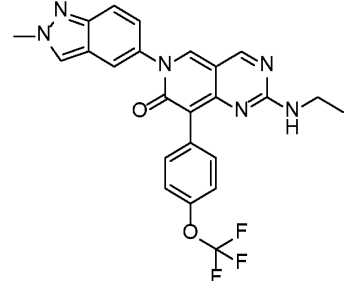
[00103] Table 2

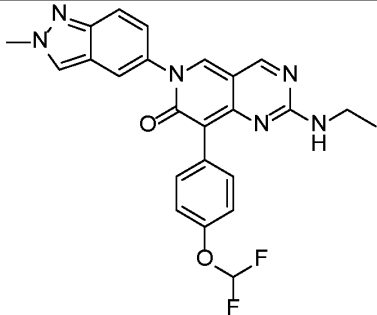
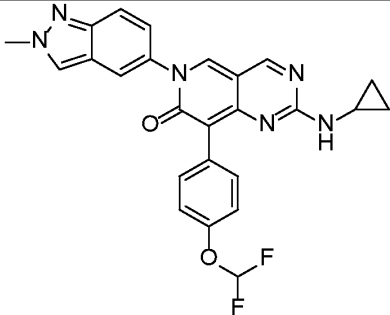
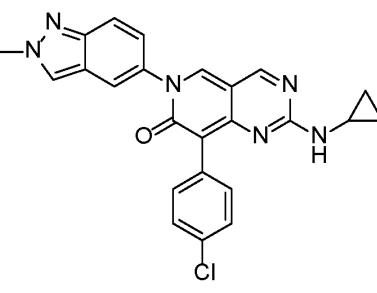
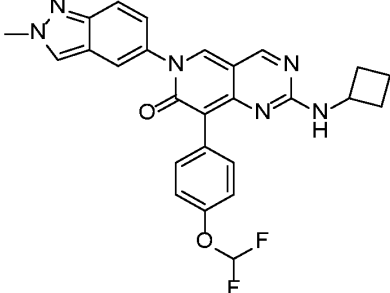
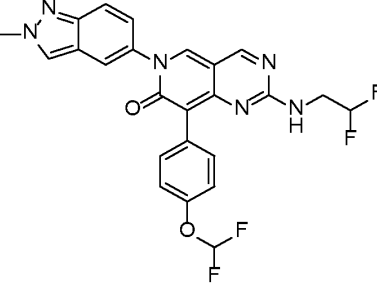
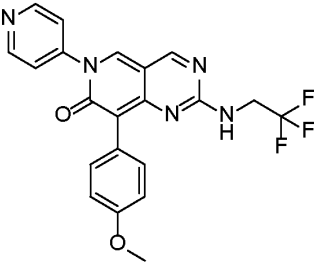
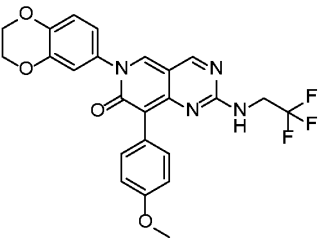
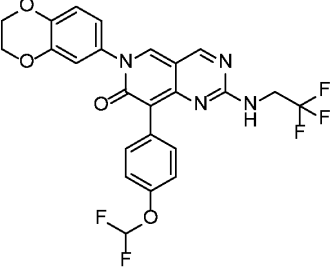
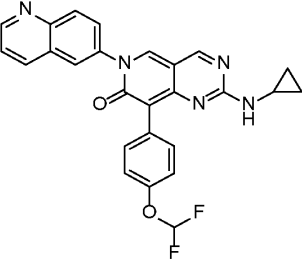
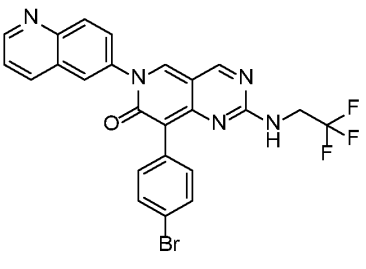
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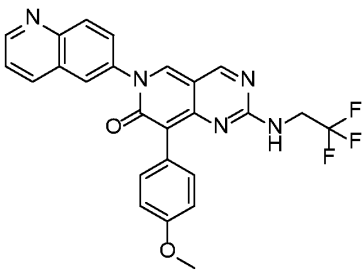
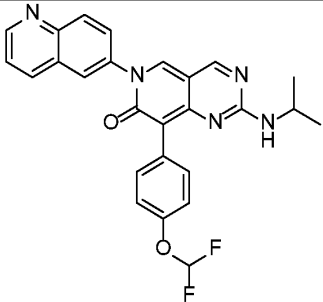
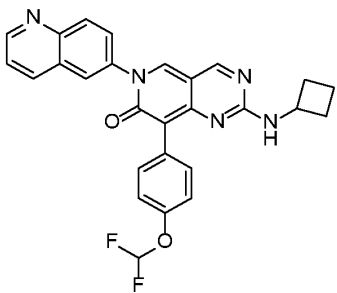
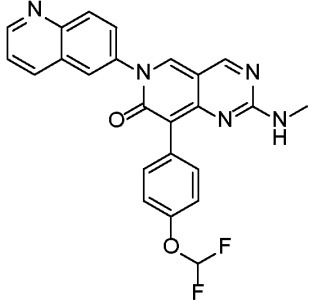
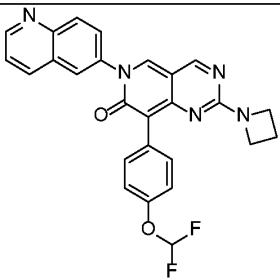
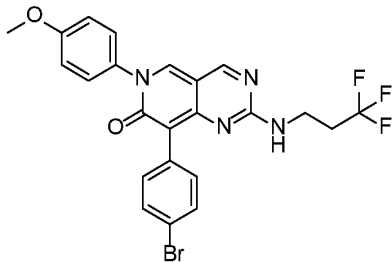
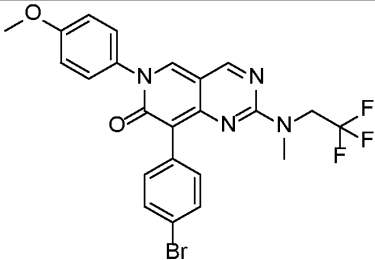
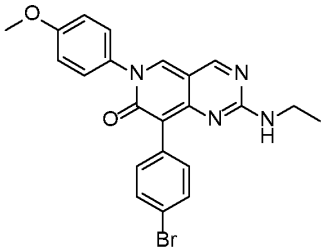
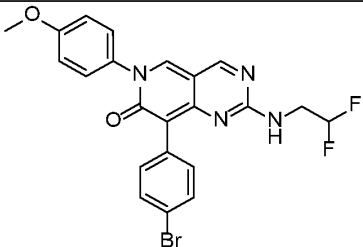
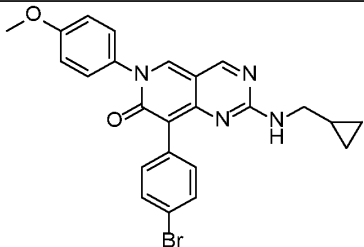
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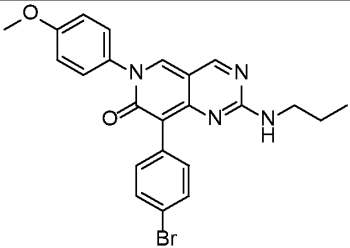
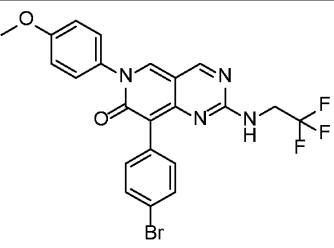
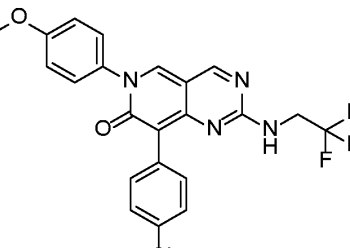
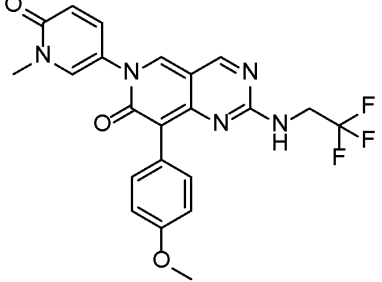
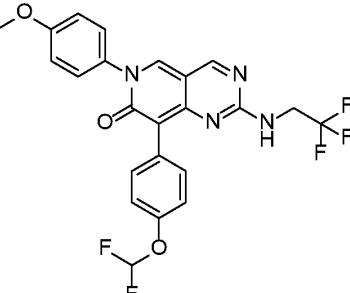
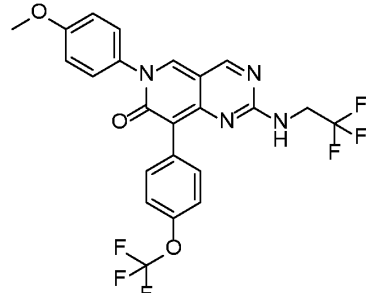
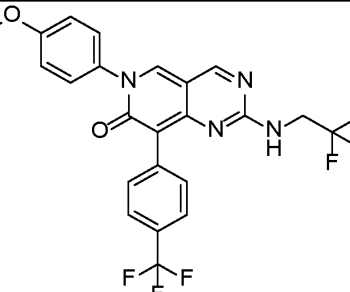
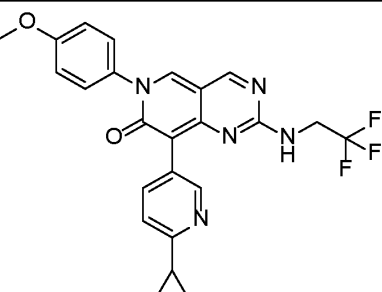
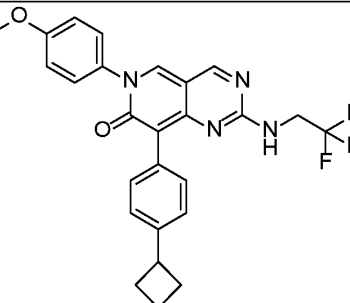
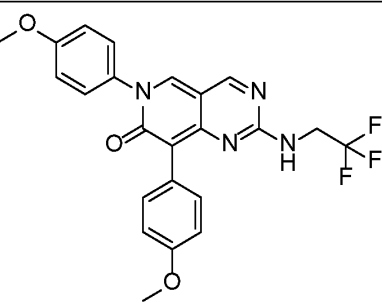
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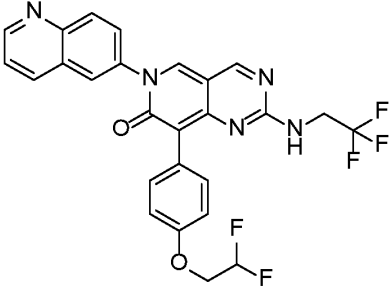
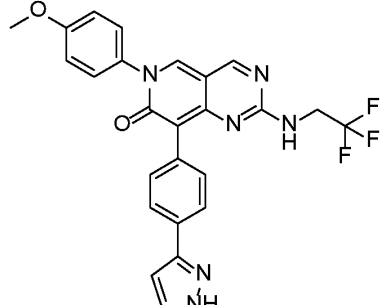
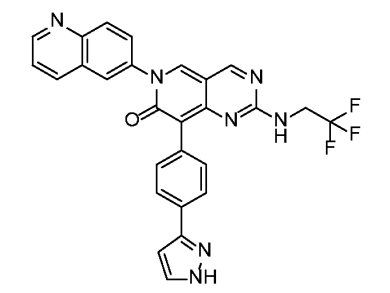
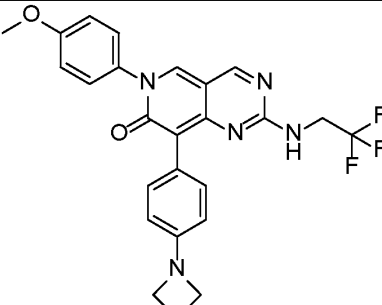
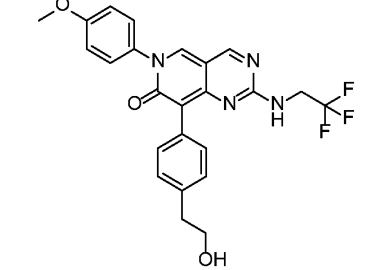
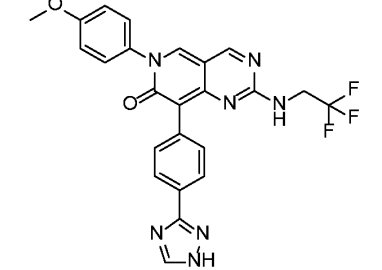
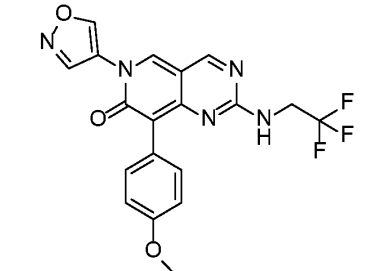
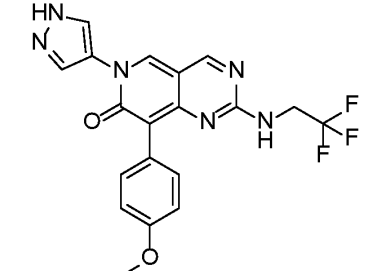
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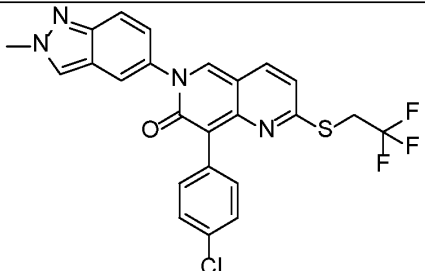
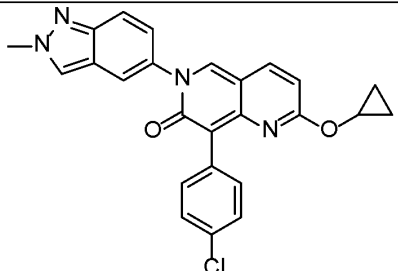
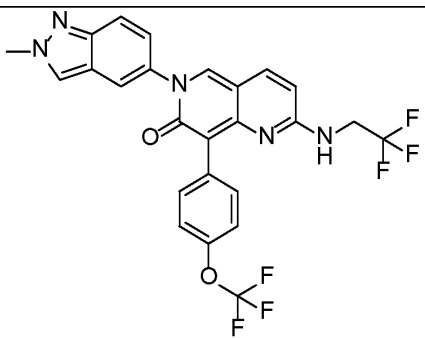
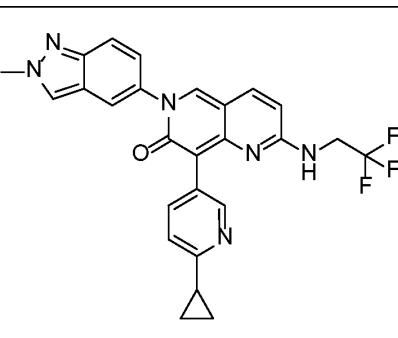
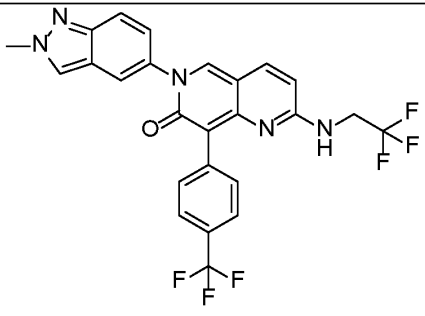
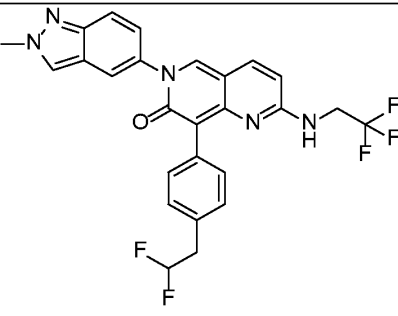
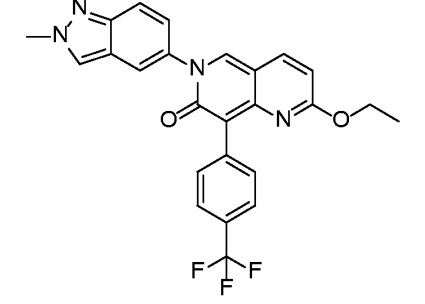
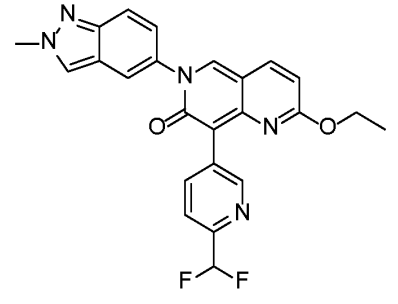
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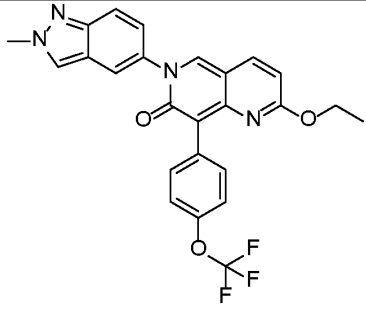
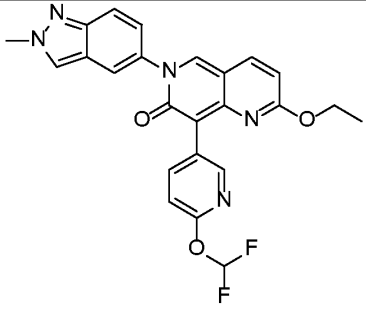
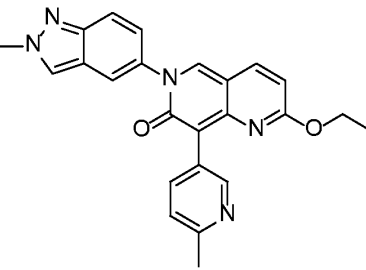
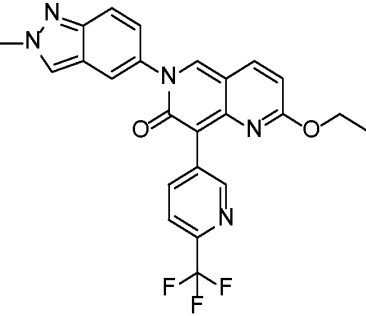
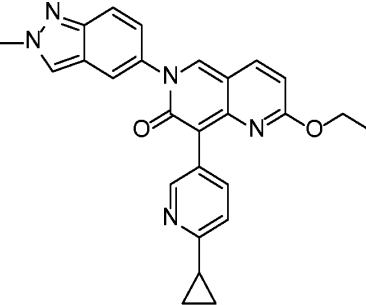
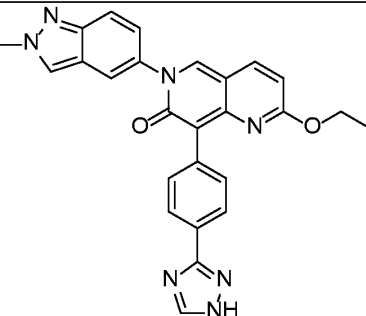
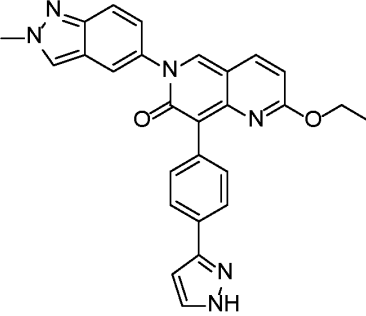
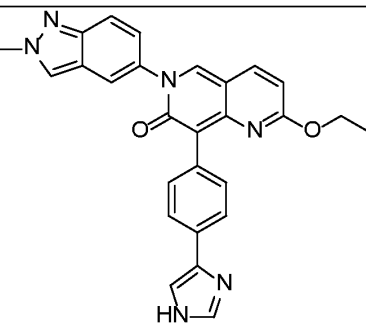
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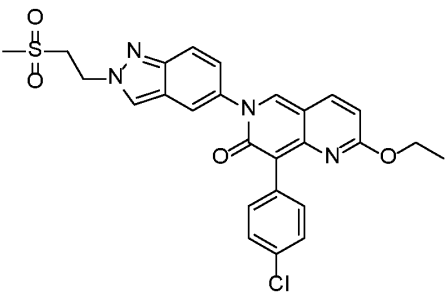
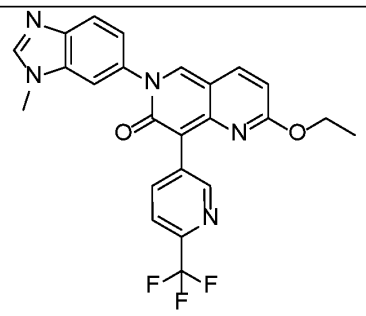
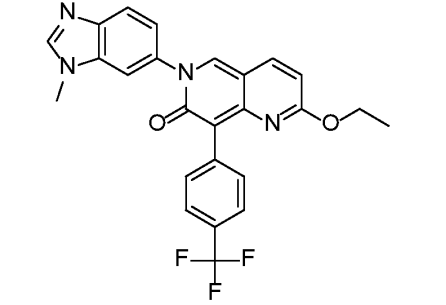
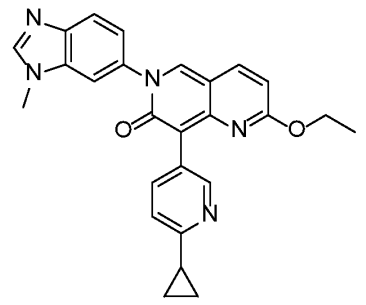
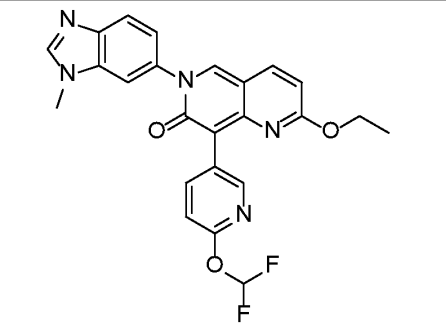
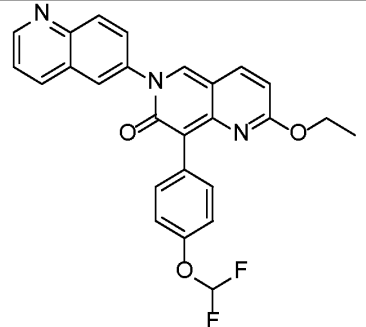
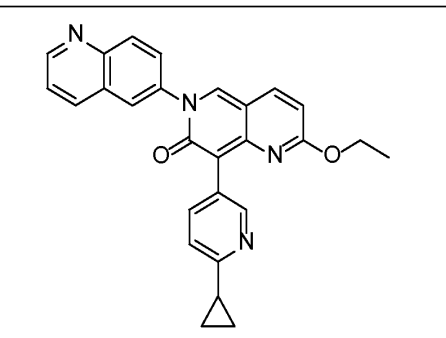
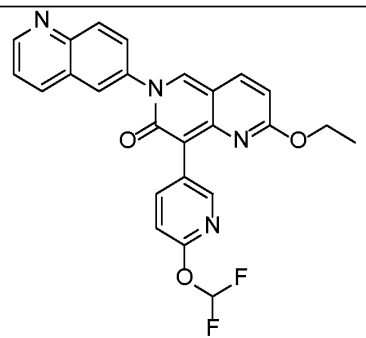
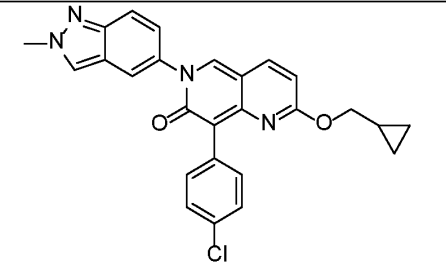
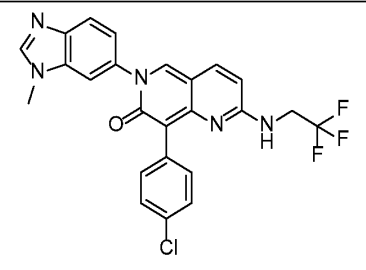
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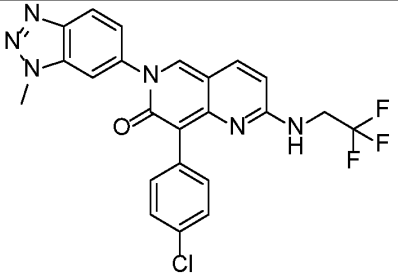
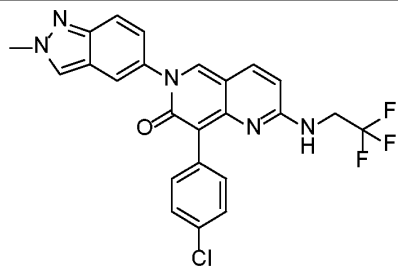
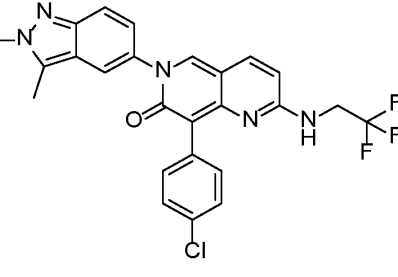
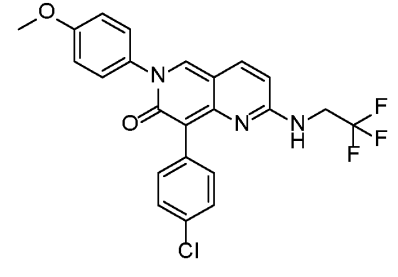
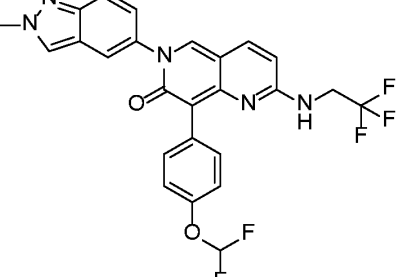
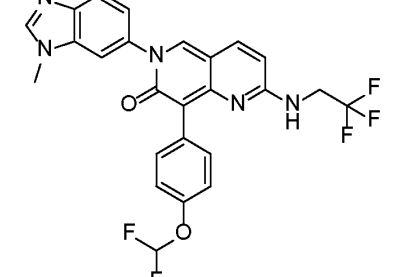
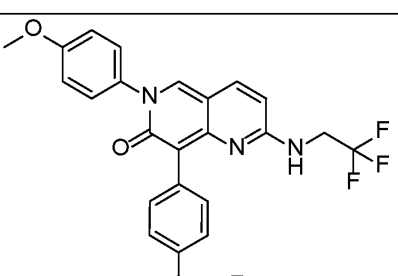
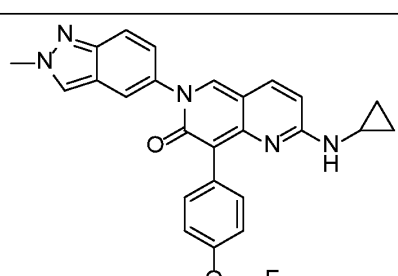
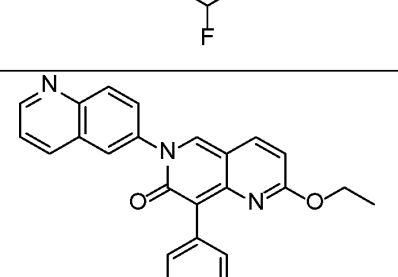
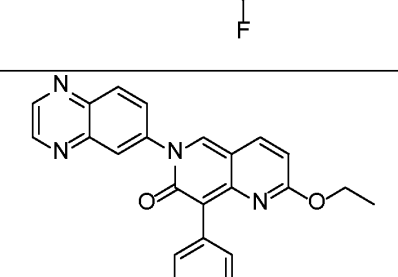
[00104] In still additional embodiments, the present disclosure provides the following specific, illustrative compounds as shown in Table 3.

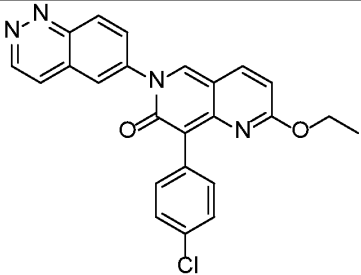
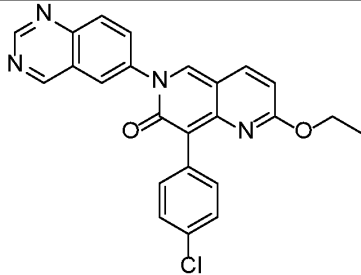
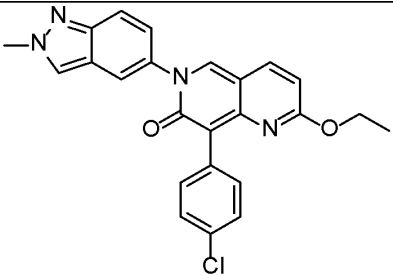
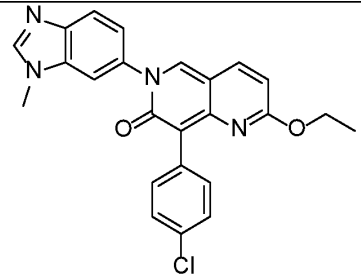
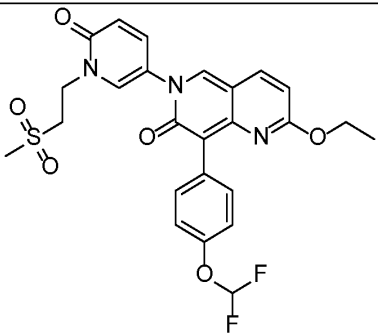
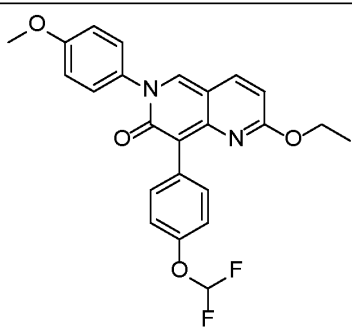
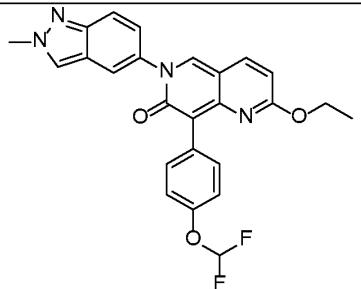
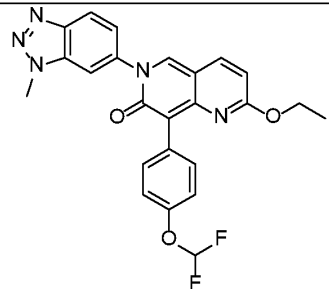
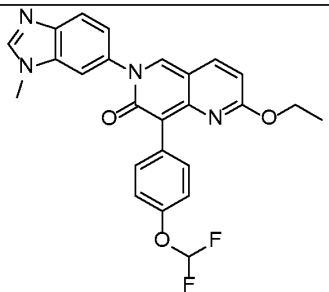
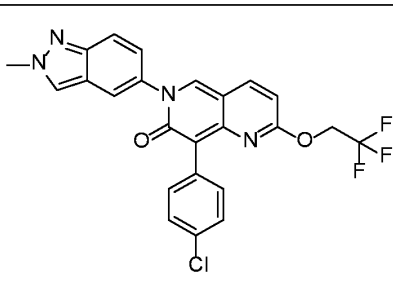
[00105] Table 3

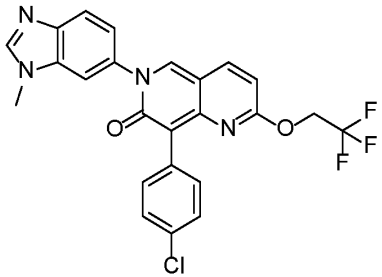
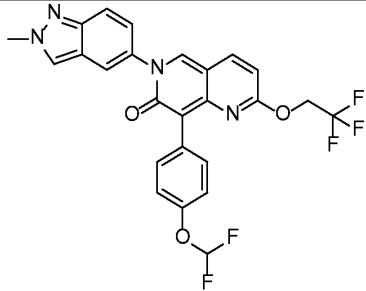
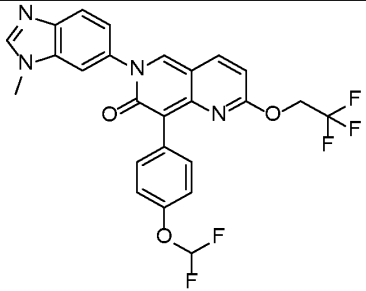
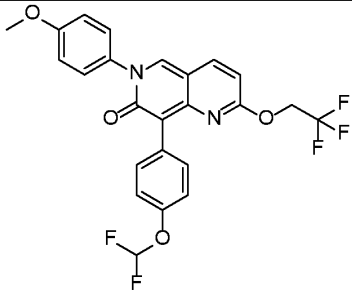
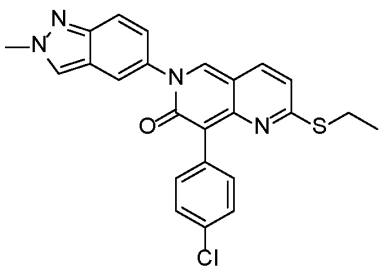
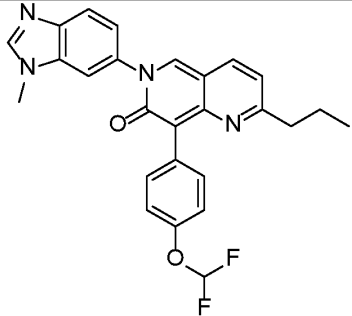
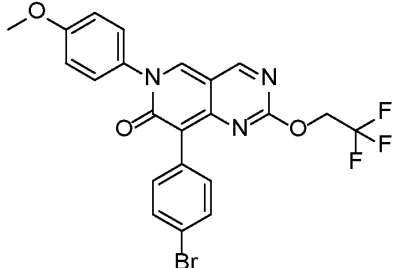
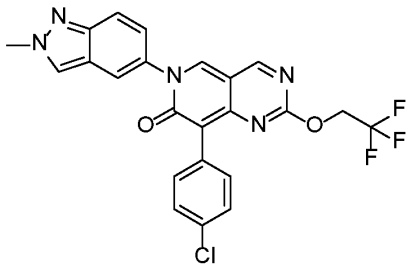
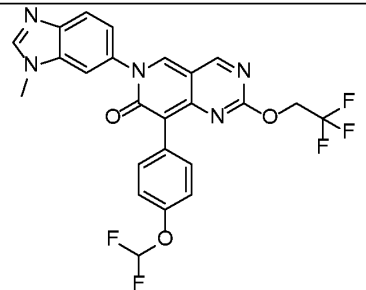
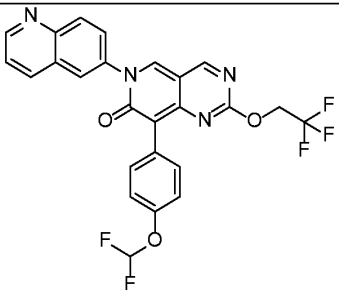
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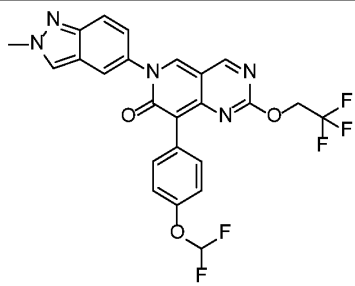
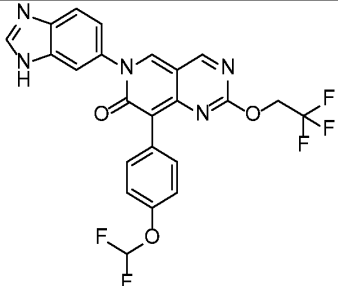
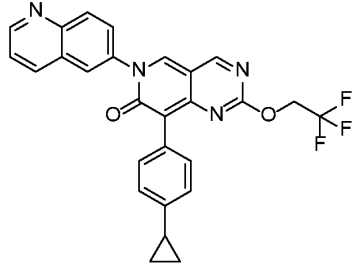
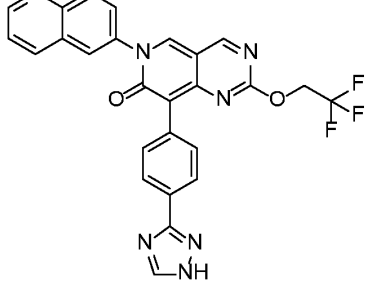
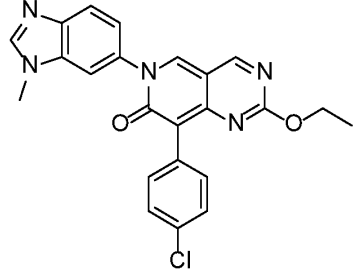
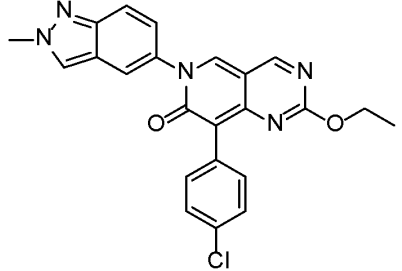
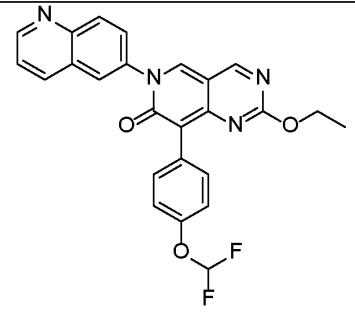
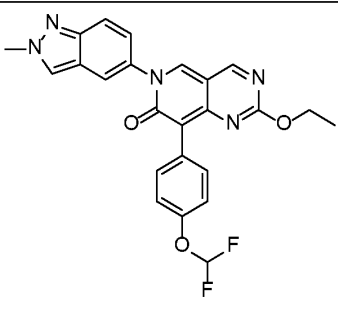
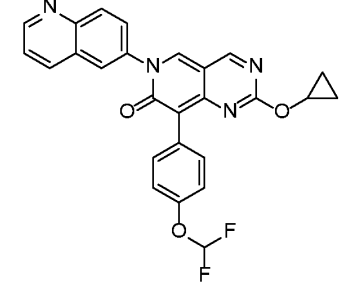
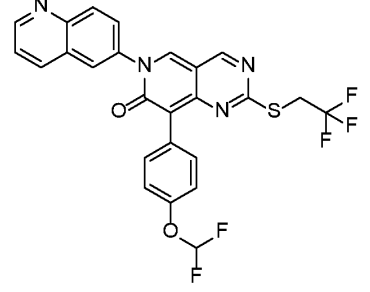
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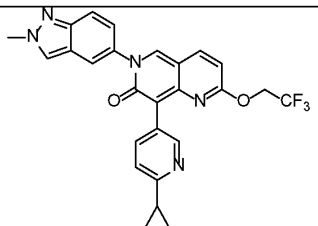
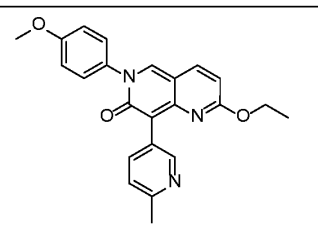
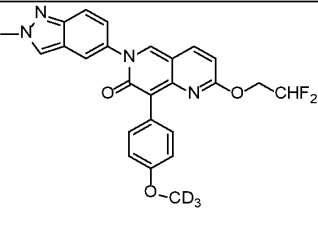
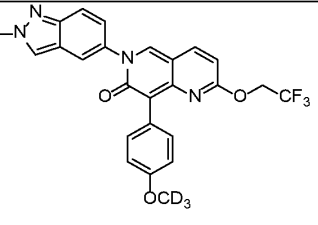
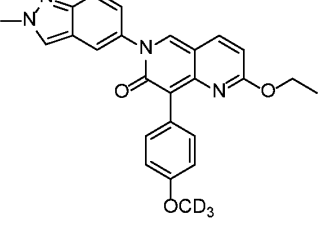
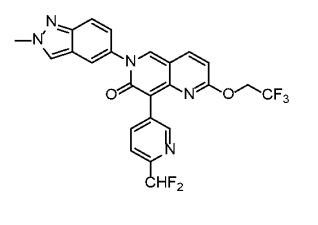
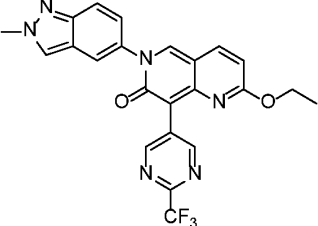
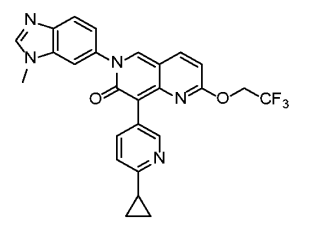
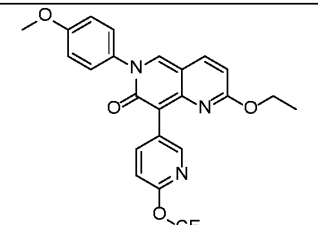
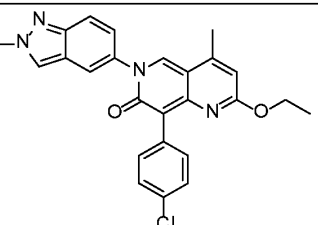
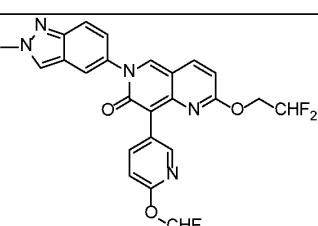
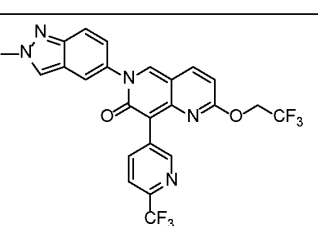
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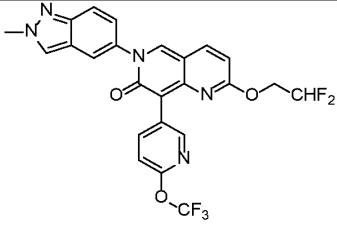
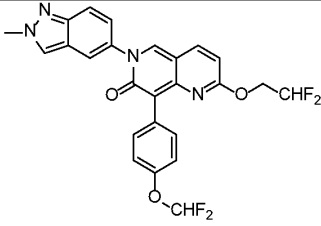
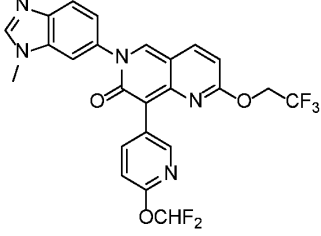
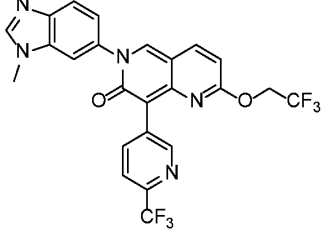
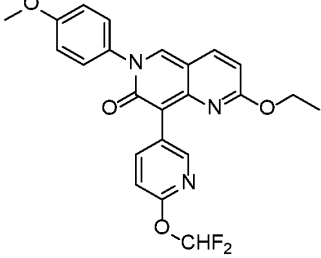
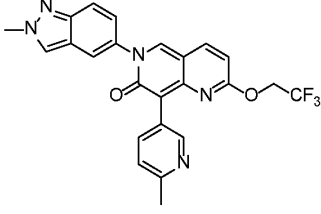
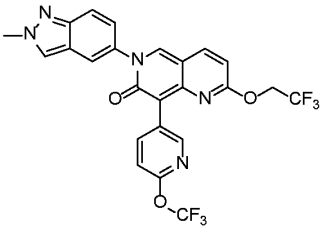
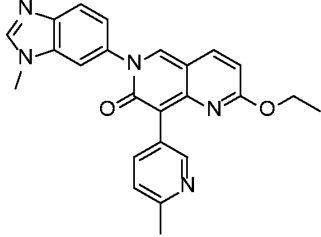
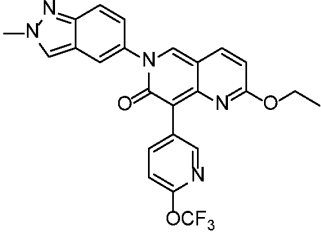
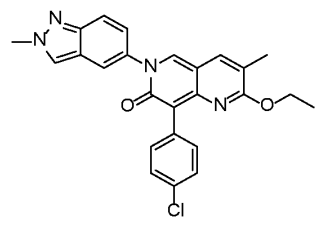
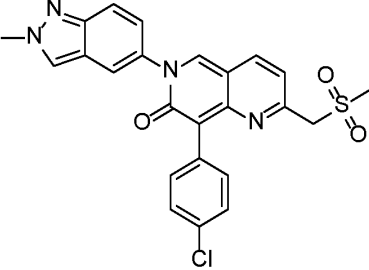
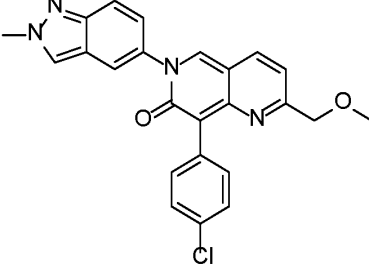
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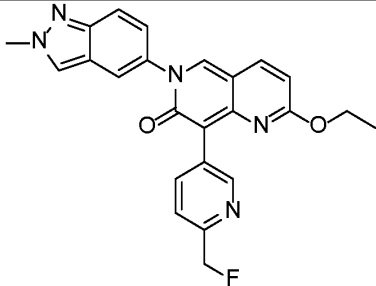
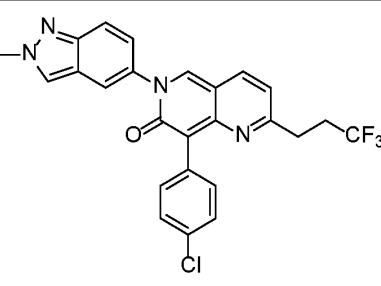
[00106] In still additional embodiments, the present disclosure provides the following specific, illustrative compounds of Formula I as set forth in Table 1-A below.

[00107] **Table 1-A**

101-A		102-A	
103-A		104-A	
105-A		106-A	
107-A		108-A	
109-A		110-A	
111-A		112-A	

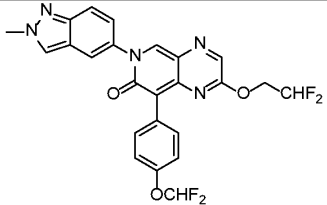
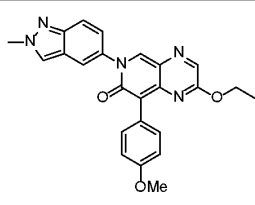
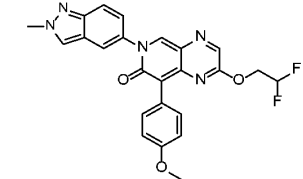
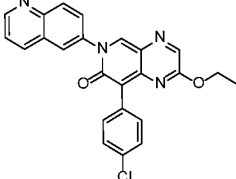
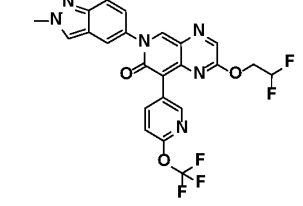
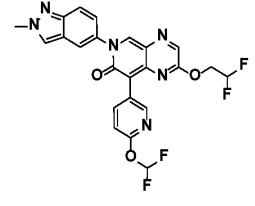
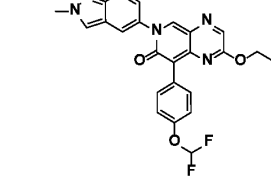
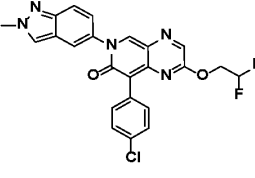
113-A		114-A	
115-A		116-A	
117-A		118-A	
119-A		120-A	
121-A		122-A	
123-A		124-A	

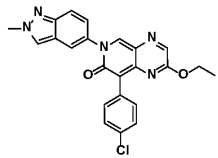
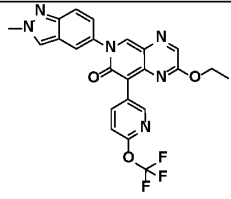
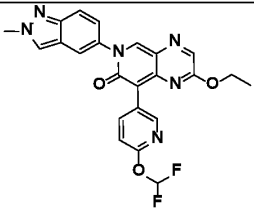
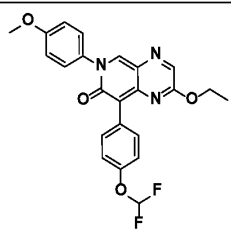
125-A		126-A	
127-A		128-A	
129-A		130-A	
131-A		132-A	
133-A		134-A	
135-A		136-A	

137-A		138-A	
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[00108] In various embodiments, the present disclosure provides specific, illustrative examples of compounds of Formula II, as set forth in Table 2-A below:

[00109] Table 2-A

139-A		140-A	
141-A		142-A	
143-A		144-A	
145-A		146-A	

147-A		148-A	
149-A		150-A	

Pharmaceutical Compositions

[00110] The present disclosure also provides a pharmaceutical composition comprising a therapeutically effective amount of one or more compounds according to Formula I or Formula II or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in admixture with a pharmaceutically acceptable carrier. In some embodiments, the composition further contains, in accordance with accepted practices of pharmaceutical compounding, one or more additional therapeutic agents, pharmaceutically acceptable excipients, diluents, adjuvants, stabilizers, emulsifiers, preservatives, colorants, buffers, flavor imparting agents.

[00111] In one embodiment, the pharmaceutical composition comprises a compound selected from those provided in Tables 1 – 3, 1-A, and 2-A, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[00112] The pharmaceutical composition of the present disclosure is formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular subject being treated, the clinical condition of the subject, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners.

[00113] The “therapeutically effective amount” of a compound (or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof) that is administered is governed by such considerations, and is the minimum amount necessary to exert a cytotoxic effect on a cancer, or to inhibit MAT2A activity, or both. Such amount may be below the amount that is toxic to normal cells, or the subject as a whole. Generally, in some embodiments a therapeutically effective amount of a compound (or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof) of the present disclosure that is administered is in the range of about 0.01 to about 200 mg/kg or about 0.1 to about 20 mg/kg of patient body weight per day, with the typical range being about 0.3 to about 15 mg/kg/day. Oral unit dosage forms, such as tablets and capsules, may contain from about 0.1 mg to about 1000 mg of a compound (or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof) of the present disclosure. In another embodiment, such dosage forms contain from about 50 mg to about 500 mg of a compound (or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof) of the present disclosure. In yet another embodiment, such dosage forms contain from about 25 mg to about 200 mg of a compound (or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof) of the present disclosure. In still another embodiment, such dosage forms contain from about 10 mg to about 100 mg of a compound (or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof) of the present disclosure. In a further embodiment, such dosage forms contain from about 5 mg to about 50 mg of a compound (or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof) of the present disclosure. In still other embodiments, such dosage forms contain from about 0.1 mg to about 10 mg of a compound (or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof) of the present disclosure. In any of the foregoing embodiments the dosage form can be administered once a day or twice a day.

[00114] The compositions of the present disclosure can be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

[00115] Suitable oral compositions in accordance with the present disclosure include without limitation tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, syrups or elixirs.

[00116] Encompassed within the scope of the present disclosure are pharmaceutical compositions suitable for single unit dosages that comprise a compound of the disclosure or its pharmaceutically acceptable stereoisomer, salt, or tautomer and a pharmaceutically acceptable carrier.

[00117] Compositions suitable for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. For instance, liquid formulations of the compounds of the present disclosure contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents.

[00118] For tablet compositions, a compound of the present disclosure in admixture with non-toxic pharmaceutically acceptable excipients is used for the manufacture of tablets. Examples of such excipients include without limitation inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known coating techniques to delay disintegration and absorption in the gastrointestinal tract and thereby to provide a sustained therapeutic action over a desired time period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

[00119] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

[00120] For aqueous suspensions, a compound of the present disclosure is admixed with excipients suitable for maintaining a stable suspension. Examples

of such excipients include without limitation are sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia.

[00121] Oral suspensions can also contain dispersing or wetting agents, such as naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[00122] Oily suspensions may be formulated by suspending a compound of the present disclosure in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

[00123] Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[00124] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water may be formulated by providing a compound of the present disclosure in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[00125] Pharmaceutical compositions of the present disclosure may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil,

for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensaturatedion products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

[00126] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable, an aqueous suspension or an oleaginous suspension. This suspension may be formulated according to techniques known in the art using one of more suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[00127] The compounds of general Formula I or Formula II may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[00128] Compositions for parenteral administrations are administered in a sterile medium. Depending on the vehicle used and concentration the concentration of the drug in the formulation, the parenteral formulation can either be a suspension or a solution containing dissolved drug. Adjuvants such

as local anesthetics, preservatives and buffering agents can also be added to parenteral compositions.

METHODS OF USE

[00129] The MAT2A enzyme catalyzes the synthesis of S-adenosyl methionine (SAM) from methionine and ATP in cells. Accordingly, in another embodiment of the present disclosure there is provided a method of inhibiting in a cell the synthesis of SAM comprising introducing into the cell an effective amount of a compound of Formula I or Formula II or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof. In some embodiments, a Formula I or Formula II compound is used to identify other compounds that are inhibitors of MAT2A, for example, in a competition assay for binding to MAT2A or for the inhibition of SAM production. Binding to MAT2A or the inhibition of SAM production by a test compound having a detectable label can be measured with and without the presence of an unlabeled compound of the present disclosure.

[00130] The present disclosure also provides a method for treating a cancer in a subject suffering therefrom, comprising administering to the subject an effective amount of a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof. In one embodiment, optionally in combination with any other embodiment disclosed herein, the subject is a mammal, such as a human.

[00131] The present disclosure additionally provides a method for treating a cancer in a subject suffering therefrom, comprising administering to the subject an effective amount of a MAT2A inhibitor. In some embodiments, the MAT2A inhibitor is a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof. In an embodiment, optionally in combination with any other embodiment disclosed herein, the subject is a mammal, such as a human.

[00132] In an embodiment, the cancer is an MTAP-deleted cancer. Alternatively, or in combination, other embodiments provide the cancer as one selected from the group consisting of mesothelioma, neuroblastoma, intestine carcinoma such as rectum carcinoma, colon carcinoma, familial adenomatous polyposis carcinoma and hereditary non-polyposis colorectal cancer, esophageal

carcinoma, labial carcinoma, larynx carcinoma, hypopharynx carcinoma, tongue carcinoma, salivary gland carcinoma, gastric carcinoma, adenocarcinoma, medullary thyroid carcinoma, papillary thyroid carcinoma, renal carcinoma, kidney parenchym carcinoma, ovarian carcinoma, cervix carcinoma, uterine corpus carcinoma, endometrium carcinoma, chorion carcinoma, pancreatic carcinoma, prostate carcinoma, bladder carcinoma, testis carcinoma, breast carcinoma, urinary carcinoma, melanoma, brain tumors, head and neck cancer, lymphoma, acute lymphatic leukemia (ALL), chronic lymphatic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), hepatocellular carcinoma, gall bladder carcinoma, bronchial carcinoma, small cell lung carcinoma (SCLC), non-small cell lung carcinoma (NSCLC), multiple myeloma (MM), basalioma, teratoma, retinoblastoma, choroidea melanoma, seminoma, rhabdomyo sarcoma, osteosarcoma, chondrosarcoma, myosarcoma, liposarcoma, fibrosarcoma, Ewing sarcoma, and plasmocytoma.

[00133] In other embodiments, the cancer is selected from lung cancer, non-small cell lung cancer, bronchioloalviolar cell lung cancer, bone cancer, pancreatic cancer, skin cancer, head and neck cancer, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, gastric cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, mesothelioma, hepatocellular cancer, biliary cancer, chronic or acute leukemia, lymphocytic lymphoma, neoplasms of the central nervous system (CNS), spinal axis tumors, brain stem glioma, glioblastoma multiforme, astrocytomas, schwannomas, ependymomas, medulloblastomas, meningiomas, squamous cell carcinomas, pituitary adenomas, including resistant and/or refractory versions of any of the above cancers, and a combination of one or more of the above cancers.

[00134] In some embodiments, the cancer is selected from the group consisting of B-cell acute lymphocytic leukemia (B-ALL), mesothelioma, lymphoma, pancreatic carcinoma, lung cancer, gastric cancer, esophageal cancer, bladder carcinoma, brain cancer, head and neck cancer, melanoma and breast cancer.

[00135] In other embodiments the lung cancer is non-small cell lung cancer, small cell lung cancer, adenocarcinoma of the lung, and squamous cell carcinoma of the lung.

[00136] In other embodiments the breast cancer is triple negative breast cancer (TNBC).

[00137] In other embodiments, the brain cancer is a brain tumor selected from the group consisting of glioma, glioblastoma, astrocytoma, meningioma, medulloblastoma, peripheral neuroectodermal tumors, and craniopharyngioma.

[00138] In still other embodiments, the cancer is a lymphoma selected from the group consisting of mantle cell lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), and adult T-cell leukemia/lymphoma (ATLL). As used herein, the expression adult T-cell leukemia/lymphoma refers to a rare and often aggressive T-cell lymphoma that can be found in the blood (leukemia), lymph nodes (lymphoma), skin, or multiple areas of the body.

[00139] As described generally above, methylthioadenosine phosphorylase (MTAP) is an enzyme found in all normal tissues that catalyzes the conversion of methylthioadenosine (MTA) into adenine and 5-methylthioribose-1-phosphate. The adenine is salvaged to generate adenosine monophosphate, and the 5-methylthioribose-1-phosphate is converted to methionine and formate. Because of this salvage pathway, MTA can serve as an alternative purine source when *de novo* purine synthesis is blocked, e.g., with antimetabolites, such as L-alanosine. Many human and murine malignant cells lack MTAP activity. MTAP deficiency is not only found in tissue culture cells but the deficiency is also present in primary leukemias, gliomas, melanomas, pancreatic cancers, non-small cell lung cancers (NSCLC), bladder cancers, astrocytomas, osteosarcomas, head and neck cancers, myxoid chondrosarcomas,

ovarian cancers, endometrial cancers, breast cancers, soft tissue sarcomas, non-Hodgkin lymphomas, and mesotheliomas. For example, proliferation of cancer cells that are MTAP null, i.e., MTAP-deleted, is inhibited by knocking down MAT2A expression with shRNA which was confirmed using small molecule inhibitors of MAT2A. K. Marjon *et al.*, *Cell Reports* 15 (2016) 574–587, incorporated herein by reference. An MTAP null or MTAP-deleted cancer is a cancer in which the MTAP gene has been deleted or lost or otherwise deactivated or a cancer in which the MTAP protein has a reduced or impaired function.

[00140] Accordingly, in an embodiment of the present disclosure there is provided a method for treating a cancer in a subject wherein the cancer is characterized by a reduction or absence of MTAP expression or absence of the MTAP gene or reduced function of MTAP protein as compared to cancers where the MTAP gene and/or protein is present and fully functioning, or as compared to cancers with the wild type MTAP gene. The method comprises administering to the subject a therapeutically effective amount of a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof.

[00141] In another embodiment, there is provided a method of treating an MTAP deleted cancer in a subject comprising administering to the subject an effective amount of a compound of Formula I or Formula II or a pharmaceutically acceptable salt thereof. In an embodiment, the MTAP deleted cancer is selected from leukemia, glioma, melanoma, pancreatic cancer, non-small cell lung cancer (NSCLC), bladder cancer, astrocytoma, osteosarcoma, head and neck cancer, myxoid chondrosarcoma, ovarian cancer, endometrial cancer, breast cancer, soft tissue sarcoma, lymphoma, and mesothelioma.

[00142] In an embodiment, the MTAP deleted cancer is pancreatic cancer. In another embodiment, the MTAP deleted cancer is selected from bladder cancer, melanoma, brain cancer, lung cancer, pancreatic cancer, breast cancer, liver cancer, esophageal cancer, gastric cancer, colon cancer, head and neck cancer, kidney cancer, colon cancer, diffuse large B cell lymphoma (DLBCL), acute lymphoblastic leukemia (ALL), mantle cell lymphoma (MCL), glioblastoma multiforme (GBM), and non-small cell lung cancer (NSCLC).

[00143] Genomic analysis of MTAP null cell lines revealed that cell lines incorporating a KRAS mutation or a p53 mutation were sensitive to MAT2A inhibition. Accordingly, an embodiment of the present disclosure provides a method for treating a cancer in a subject wherein the cancer is characterized by reduction or absence of MTAP expression or absence of the MTAP gene or reduced function of MTAP protein, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula I, wherein said cancer is further characterized by the presence of mutant KRAS or mutant p53. In an embodiment, there is provided a method of treating an MTAP null cancer having a mutant KRAS or mutant p53 in a subject, comprising administering to the subject an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. For example, the cancer is MTAP null and KRAS mutant, MTAP null and p53 mutant, or each of MTAP null, KRAS mutant and p53 mutant.

[00144] The term “mutant KRAS” or “KRAS mutation” refers to a KRAS protein incorporating an activating mutation that alters its normal function and the gene encoding such a protein. For example, a mutant KRAS protein may incorporate a single amino acid substitution at position 12 or 13. In a particular embodiment, the KRAS mutant incorporates a G12X or G13X substitution, wherein X represents any amino acid change at the indicated position. In a particular embodiment, the substitution is G12V, G12R, G12C or G13D. In another embodiment, the substitution is G13D. By “mutant p53” or “p53 mutation” is meant p53 protein (or gene encoding said protein) incorporating a mutation that inhibits or eliminates its tumor suppressor function. In an embodiment, said p53 mutation is, Y126_splice, K132Q, M133K, R174fs, R175H, R196*, C238S, C242Y, G245S, R248W, R248Q, I255T, D259V, S261_splice, R267P, R273C, R282W, A159V or R280K. In an embodiment, the foregoing cancer is non-small cell lung cancer (NSCLC), pancreatic cancer, head and neck cancer, gastric cancer, breast cancer, colon cancer or ovarian cancer.

[00145] In another embodiment, the compounds disclosed herein are useful as ligands for degradation of disease-associated proteins. An example of this approach is PROTACs (PROteolysis TArgeting Chimeras). PROTACs are bifunctional molecules that comprise both a ligand moiety selected from one of

the compounds disclosed herein, which is capable of binding the target protein, and a peptide portion (referred to as the degron) that is recognized and polyubiquitinated by E3 ligase. Thus, the PROTAC non-covalently binds to a target protein, and recruits E3 ligase via the degron peptide, which results in polyubiquitination and degradation of the bound target. A number of publications describe the pre-clinical use of PROTACs in a variety of therapeutic areas including oncology. *See, e.g., Lu et al. Chemistry & Biology 22 (2015) 755-763.*

EXAMPLES

[00146] The present disclosure will be more fully understood by reference to the following examples. The examples provided herein are illustrative and should not, however, be construed as limiting the scope of the present disclosure.

[00147] Abbreviations and terms list:

anhy.	anhydrous
aq.	aqueous
min	minute(s)
mL	milliliter
mmol	millimole(s)
mol	mole(s)
MS	mass spectrometry
NMR	nuclear magnetic resonance
TLC	thin layer chromatography
HPLC	high-performance liquid chromatography
RT(r.t.)	room temperature

[00148] -Spectrum

Hz	hertz
δ	chemical shift
J	coupling constant
s	singlet
d	doublet
t	triplet
q	quartet

m	multiplet
br	broad
qd	quartet of doublets
dquin	doublet of quintets
dd	doublet of doublets
dt	doublet of triplets

[00149] Solvents and Reagents:

CHCl ₃	chloroform
DCM	dichloromethane
DMF	dimethylformamide
Et ₂ O	diethyl ether
EtOH	ethyl alcohol
EtOAc	ethyl acetate
EA	ethyl acetate
MeOH	methyl alcohol
MeCN	acetonitrile
PE	petroleum ether
THF	tetrahydrofuran
AcOH	acetic acid
HCl	hydrochloric acid
H ₂ SO ₄	sulfuric acid
NH ₄ Cl	ammonium chloride
KOH	potassium hydroxide
NaOH	sodium hydroxide
K ₂ CO ₃	potassium carbonate
Na ₂ CO ₃	sodium carbonate
TFA	trifluoroacetic acid
Na ₂ SO ₄	sodium sulfate
NaBH ₄	sodium borohydride
NaHCO ₃	sodium bicarbonate
LiHMDS	lithium hexamethyldisilylamide
NaHMDS	sodium hexamethyldisilylamide
LAH	lithium aluminum hydride

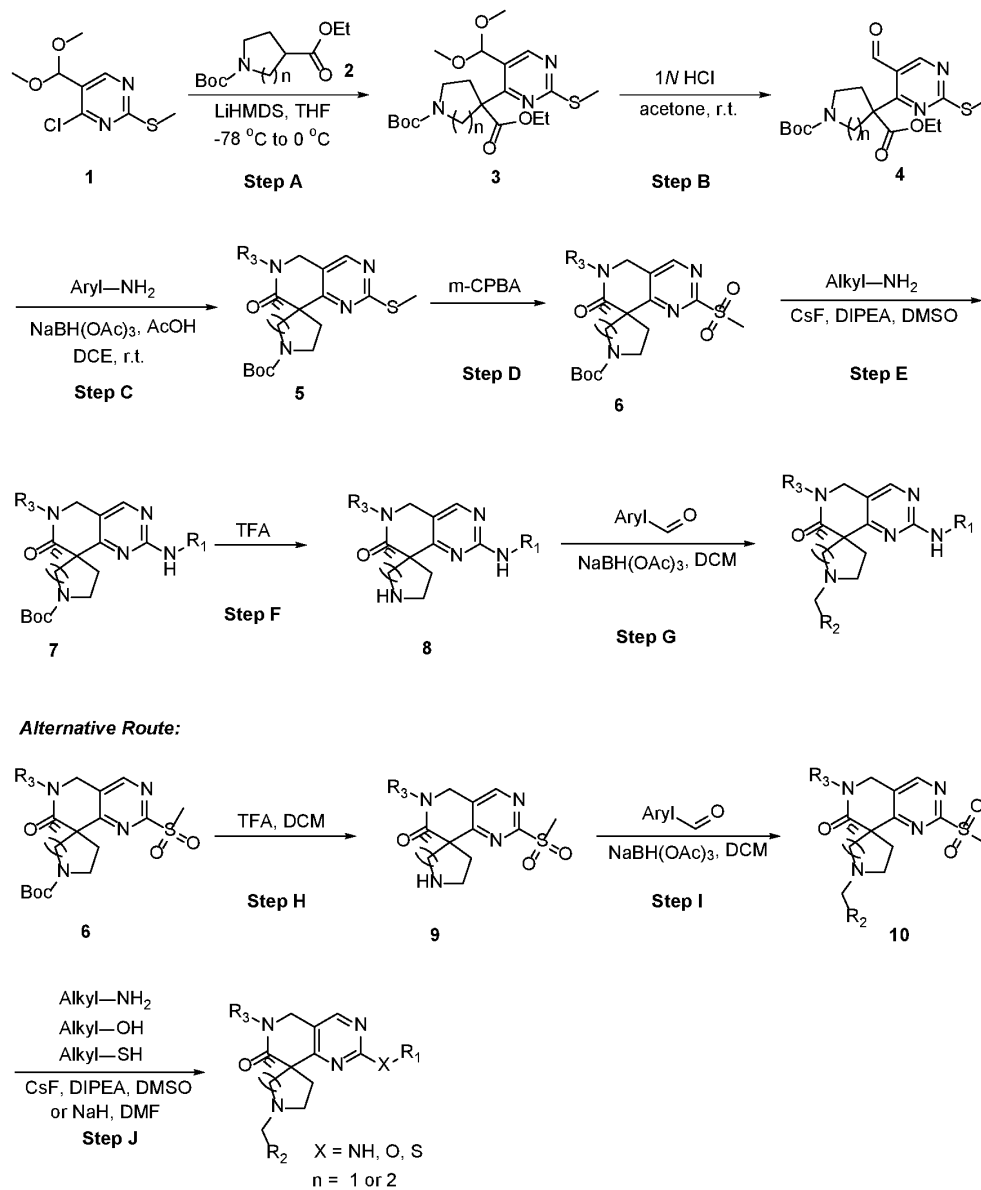
NaBH ₄	sodium borohydride
LDA	lithium diisopropylamide
Et ₃ N	triethylamine
DMAP	4-(dimethylamino)pyridine
DIPEA	<i>N,N</i> -diisopropylethylamine
NH ₄ OH	ammonium hydroxide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
HOBt	1-hydroxybenzotriazole
HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium
Xphos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
BINAP	2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl

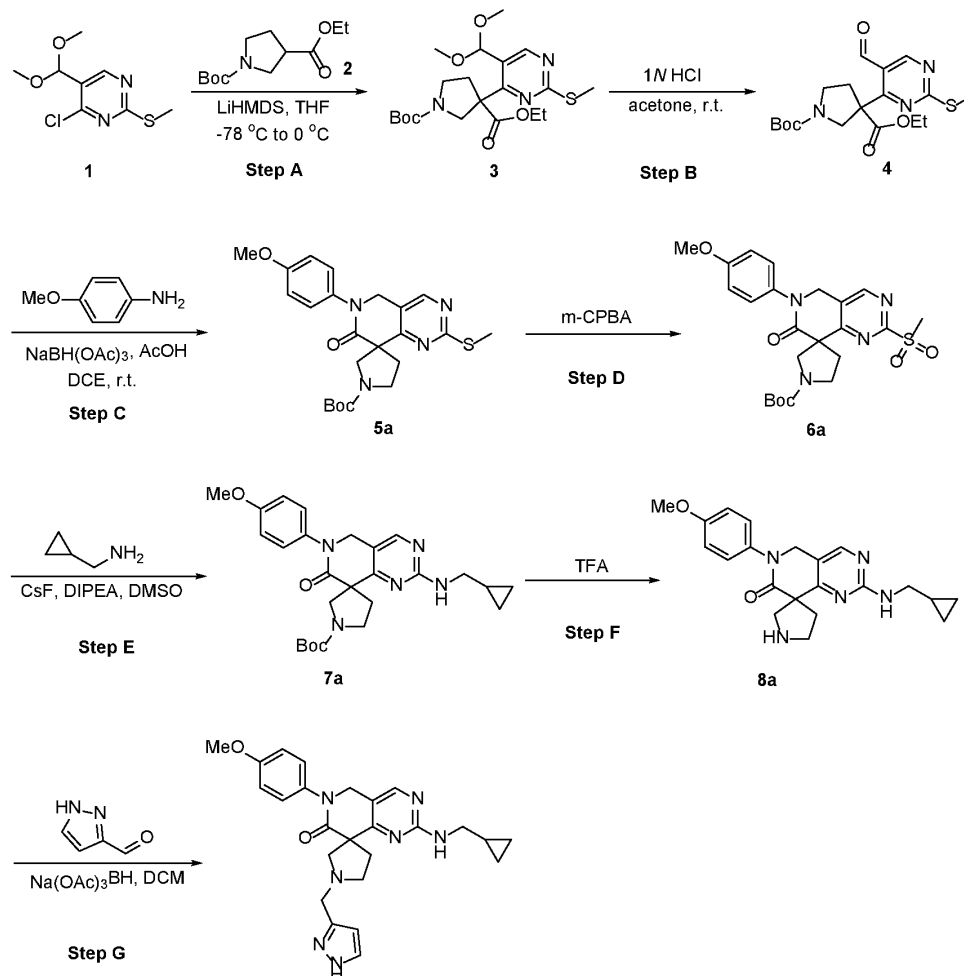
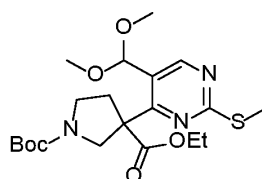
General Experimental

[00150] In the following examples, the reagents and solvents were purchased from commercial sources (such as Alfa, Acros, Sigma Aldrich, TCI and Shanghai Chemical Reagent Company), and used without further purification unless otherwise specified. Flash chromatography was performed on an Ez Purifier III using column with silica gel particles of 200-300 mesh. Analytical and preparative thin layer chromatography (TLC) plates were HSGF 254 (0.15-0.2 mm thickness, Shanghai Anbang Company, China). Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker AMX-400 NMR (Bruker, Switzerland). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Mass spectra were given with electrospray ionization (ESI) from a Waters LCT TOF Mass Spectrometer (Waters, USA). HPLC chromatographs were recorded on an Agilent 1200 Liquid Chromatography (Agilent, USA, column: Ultimate 4.6mmx50mm, 5 μ m, mobile phase A: 0.1% formic acid in water; mobile phase B: acetonitrile). Microwave reactions were run on an Initiator 2.5 Microwave Synthesizer (Biotage, Sweden).

[00151] General Procedure I:

General procedure I:

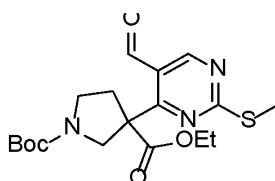


[00152] Preparation of **Example 101** via General Procedure I:**[00153]** **Step A:** 1-*tert*-butyl 3-ethyl 3-(5-(dimethoxymethyl)-2-(methylthio)pyrimidin-4-yl)pyrrolidine-1,3-dicarboxylate

[00154] To a solution of 1-*tert*-butyl 3-ethyl pyrrolidine-1,3-dicarboxylate (4.8 g, 19.8 mmol, 1.5 equiv.) in THF (30 mL) was added LiHMDS (1 M in THF, 26.4 mL, 26.4 mmol, 2.0 equiv.) at -78°C over 1h via the addition funnel. The mixture was stirred at -78°C for 4 h. Then a solution of 4-chloro-5-(dimethoxymethyl)-2-(methylthio)pyrimidine (3.1 g, 13.2 mmol, 1.0 equiv.) in THF (10 mL) was added. The reaction mixture was allowed to warm to room

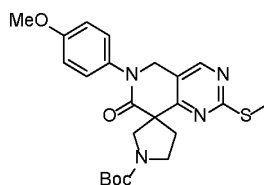
temperature and stirred for an additional 3 h. Then the reaction mixture was quenched with NH_4Cl (sat. aq.) (50 mL) and extracted with EtOAc (50 mL x 3). The organic layers were combined, dried over Na_2SO_4 , filtered, concentrated, and the resulting residue was purified by flash column chromatography on silica gel (PE/EtOAc = 20/1 to 4/1) to afford 1-*tert*-butyl 3-ethyl 3-(5-(dimethoxymethyl)-2-(methylthio)pyrimidin-4-yl)pyrrolidine-1,3-dicarboxylate (3.2 g, 55% yield) as a yellow oil. LC-MS: m/z 442 $[\text{M}+\text{H}]^+$.

[00155] Step B: 1-*tert*-butyl 3-ethyl 3-(5-formyl-2-(methylthio)pyrimidin-4-yl)pyrrolidine-1,3-dicarboxylate



[00156] To a solution of 1-*tert*-butyl 3-ethyl 3-(5-(dimethoxymethyl)-2-(methylthio)pyrimidin-4-yl)pyrrolidine-1,3-dicarboxylate (3.1 g, 7.0 mmol, 1.0 equiv.) in acetone (30 mL) was added dilute HCl solution (1N, aq) (56.0 mL, 56.0 mmol, 8.0 equiv.). The resulting mixture was stirred at room temperature for 6 h. The reaction was quenched by adding ice water (50 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, dried over Na_2SO_4 , filtered, concentrated, and the crude residue was used directly without further purification (2.8 g, crude) as a colorless oil. LC-MS: m/z 396 $[\text{M}+\text{H}]^+$.

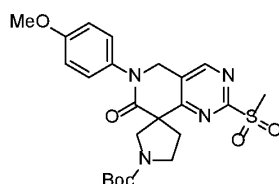
[00157] Step C: *tert*-butyl 6-(4-methoxyphenyl)-2-(methylthio)-7-oxo-6,7-dihydro-5H-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidine]-1'-carboxylate



[00158] To a solution of 1-*tert*-butyl 3-ethyl 3-(5-(dimethoxymethyl)-2-(methylthio)pyrimidin-4-yl)pyrrolidine-1,3-dicarboxylate (2.8 g, 7.0 mmol, 1.0 equiv.) and 4-methoxyaniline (1.9 g, 15.4 mmol, 2.2 equiv.) in DCE (18.0 mL) was added AcOH (1.4 mL, 24.5 mmol, 3.5 equiv.). The resulting solution was stirred at room temperature for 1 h. At this point, $\text{NaBH}(\text{AcO})_3$ (3.7 g, 17.5 mmol, 2.5 equiv.) was added in portions over the course of 0.5 h and the

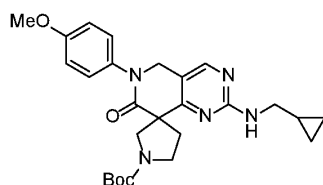
resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with ice water and extracted with EtOAc (30 mL x 3). All the organic layers were combined, dried over Na₂SO₄, filtered, concentrated under reduce pressure, and the residue was purified by flash column chromatography on silica gel (PE/EtOAc = 10/1 to 1/1) to give *tert*-butyl 6-(4-methoxyphenyl)-2-(methylthio)-7-oxo-6,7-dihydro-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidine]-1'-carboxylate (2.5 g, 79% yield) as a light brown solid. LC-MS: *m/z* 457 [M+H]⁺.

[00159] Step D: *tert*-butyl 6-(4-methoxyphenyl)-2-(methylsulfonyl)-7-oxo-6,7-dihydro-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidine]-1'-carboxylate



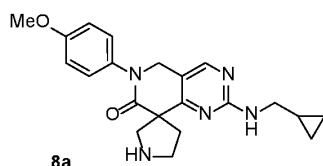
[00160] To a solution of *tert*-butyl 6-(4-methoxyphenyl)-2-(methylthio)-7-oxo-6,7-dihydro-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidine]-1'-carboxylate (500 mg, 1.1 mmol, 1.0 equiv.) in DCM (10.0 mL) was added *m*-CPBA (565 mg, 3.3 mmol, 3.0 equiv.) in small portions during 0.5 h. The resulting mixture was stirred at room temperature for an additional 2 h, before being quenched with ice water (20.0 mL) and extracted with DCM (20 mL x 3). The organic layers were combined, washed with brine (30 mL), dried over Na₂SO₄, filtered, concentrated under reduce pressure, and the residue was purified by flash column chromatography on silica gel (PE/EtOAc = 2/1 to 1/1) to afford *tert*-butyl 6-(4-methoxyphenyl)-2-(methylsulfonyl)-7-oxo-6,7-dihydro-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidine]-1'-carboxylate (500 mg, 94% yield) as a white solid. LCMS: *m/z* 489 [M+H]⁺.

[00161] Step E: *tert*-butyl 2-((cyclopropylmethyl)amino)-6-(4-methoxyphenyl)-7-oxo-6,7-dihydro-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidine]-1'-carboxylate



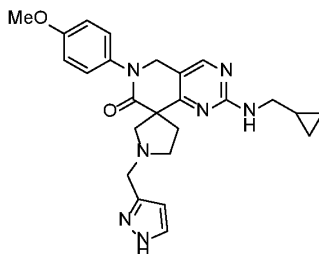
[00162] To a solution of *tert*-butyl 6-(4-methoxyphenyl)-2-(methylsulfonyl)-7-oxo-6,7-dihydro-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidine]-1'-carboxylate (1.2 g, 2.5 mmol, 1.0 equiv.) in DMSO (15.0 mL) was added CsF (380 mg, 2.5 mmol, 1.0 equiv.), DIPEA (967 mg, 7.5 mmol, 3.0 equiv.) and cyclopropylmethanamine (532 mg, 7.5 mmol, 3.0 equiv.) at room temperature. The resulting mixture was stirred at 80 °C overnight, then water (10 mL) was added. The reaction mixture was extracted with DCM (20 mL x 3), the organic layers were combined, washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduce pressure. The resulting residue was purified by flash column chromatography on silica gel to give *tert*-butyl 2-((cyclopropylmethyl)amino)-6-(4-methoxyphenyl)-7-oxo-6,7-dihydro-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidine]-1'-carboxylate (850 mg, 71% yield) as a white solid. LCMS: *m/z* 480 [M+H]⁺.

[00163] Step F: 2-((cyclopropylmethyl)amino)-6-(4-methoxyphenyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one



[00164] To a solution of *tert*-butyl 2-((cyclopropylmethyl)amino)-6-(4-methoxyphenyl)-7-oxo-6,7-dihydro-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidine]-1'-carboxylate (850 mg, 1.8 mmol, 1.0 equiv.) in DCM (10 mL) was added TFA (3 mL) at room temperature. The resulting mixture was stirred for 1 h, then the reaction was quenched with NaHCO₃ (sat. aq. 20 mL). The resulting mixture was extracted with DCM (20 mL x 3), the organic layers were combined, washed with brine (30.0 mL), dried over Na₂SO₄ and concentrated. The crude 2-((cyclopropylmethyl)amino)-6-(4-methoxyphenyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one (500 mg, crude) was used without further purification as a white solid. LCMS: *m/z* 380 [M+H]⁺.

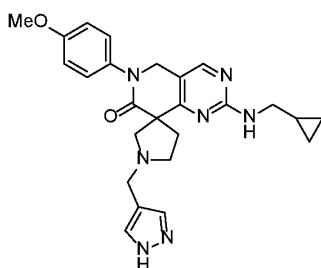
[00165] Step G: 1'-((1*H*-pyrazol-3-yl)methyl)-2-((cyclopropylmethyl)amino)-6-(4-methoxyphenyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one (**Example 101**)



[00166] To a solution of 6-(4-methoxyphenyl)-2-(methylsulfonyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one (56.0 mg, 0.15 mmol, 1.0 equiv.) in DCE (3 mL) was added 1*H*-pyrazole-3-carbaldehyde (28.0 mg, 0.29 mmol, 2.0 equiv.) and AcOH (60.0 μ L, catalytic amount) at room temperature. The resulting mixture was stirred for 1 h, after which NaBH₃CN (10.0 mg, 0.158 mmol, 1.1 equiv.) was added. The reaction mixture was stirred for an additional 0.5 h before being quenched with ice water (2.0 mL) and extracted with DCM (5 mL x 3). The organic layers were combined and washed with brine (10 mL), dried over Na₂SO₄ and concentrated under reduce pressure. The resulting residue was purified by RP-prep-HPLC to afford 1'-((1*H*-pyrazol-3-yl)methyl)-2-((cyclopropylmethyl)amino)-6-(4-methoxyphenyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one (**Example 101**).

[00167] ¹H NMR (400 MHz, CDCl₃) δ : 8.47 (br s, 1H), 8.13 (s, 1H), 7.54 (s, 1H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.34 (s, 1H), 4.79 (d, *J* = 15.4 Hz, 1H), 4.52 (d, *J* = 15.4 Hz, 1H), 4.38 (d, *J* = 13.2 Hz, 1H), 4.31 (d, *J* = 13.2 Hz, 1H), 4.11 (d, *J* = 10.8 Hz, 1H), 3.83 (s, 3H), 3.67 (d, *J* = 10.8 Hz, 1H), 3.65-3.47 (m, 1H), 3.35-3.28 (m, H), 3.26-3.16 (m, 1H), 2.61-2.51 (m, 1H), 2.48-2.37 (m, 1H), 1.15-1.04 (m, 1H), 0.60-0.50 (m, 2H), 0.32-0.23 (m, 2H) [one NH not observed underneath CDCl₃]. LCMS: *m/z* 460 [M+H]⁺.

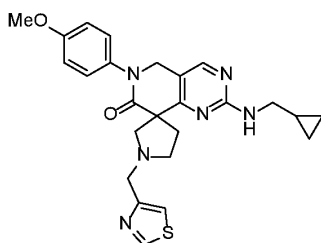
[00168] Example 102: 1'-((1*H*-pyrazol-4-yl)methyl)-2-((cyclopropylmethyl)amino)-6-(4-methoxyphenyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one



[00169] The title compound was synthesized from intermediate **8a** with 1*H*-pyrazole-4-carbaldehyde *via* general procedure *I*: (NaBH₃CN, HOAc, DCE).

[00170] ¹H NMR (400 MHz, CDCl₃)(HCO₂H salt) δ: 8.61 (s, 1H), 8.12 (s, 1H), 7.75 (s, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.81 (d, *J* = 15.2 Hz, 1H), 4.51 (d, *J* = 15.2 Hz, 1H), 4.44-4.30 (m, 2H), 4.22 (d, *J* = 13.2 Hz, 1H), 3.83 (s, 3H), 3.68 (d, *J* = 11.6 Hz, 1H), 3.38-3.18 (m, 5H), 2.60-2.37 (m, 2H), 1.17-1.04 (m, 1H), 0.57-0.48 (m, 2H), 0.29-0.22 (m, 2H). LC-MS: *m/z* 460 [M+H]⁺.

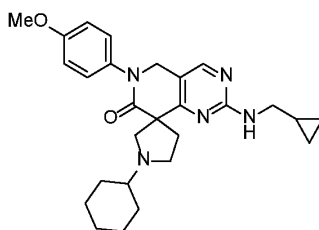
[00171] **Example 103:** 2-((cyclopropylmethyl)amino)-6-(4-methoxyphenyl)-1'-(thiazol-4-ylmethyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one



[00172] The title compound was synthesized from intermediate **8a** with thiazole-4-carbaldehyde *via* general procedure *I*: (NaBH₃CN, HOAc, DCE).

[00173] ¹H NMR (400 MHz, CDCl₃) δ: 8.76 (d, *J* = 2.0 Hz, 1H), 8.07 (s, 1H), 7.33 (d, *J* = 2.0 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.53 (br s, 1H), 4.65 (d, *J* = 15.2 Hz, 1H), 4.57 (d, *J* = 15.2 Hz, 1H), 4.06 (d, *J* = 14.0 Hz, 1H), 4.01 (d, *J* = 14.0 Hz, 1H), 3.81 (s, 3H), 3.51 (d, *J* = 9.6 Hz, 1H), 3.43 (d, *J* = 9.6 Hz, 1H), 3.29 (m, 2H), 3.13-3.05 (m, 1H), 3.02-2.92 (m, 1H), 2.55-2.49 (m, 1H), 2.46-2.39 (m, 1H), 1.17-1.07 (m, 1H), 0.59-0.49 (m, 2H), 0.30-0.23 (m, 2H). LC-MS: *m/z* 477 [M+H]⁺.

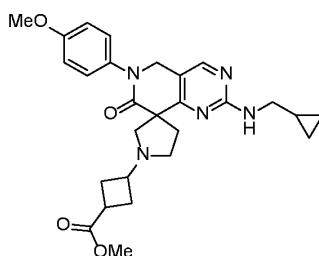
[00174] **Example 104:** 1'-cyclohexyl-2-((cyclopropylmethyl)amino)-6-(4-methoxyphenyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one



[00175] The title compound was synthesized from intermediate **8a** with cyclohexanone *via* General Procedure *I*: (NaBH₃CN, HOAc, DCE).

[00176] ¹H NMR (400 MHz, CDCl₃) δ : 8.09 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.54 (br s, 1H), 4.70 (d, *J* = 15.2 Hz, 1H), 4.55 (d, *J* = 15.2 Hz, 1H), 3.82 (s, 3H), 3.47 (d, *J* = 10.4 Hz, 1H), 3.36-3.29 (m, 3H), 2.98-2.92 (m, 1H), 2.58-2.38 (m, 4H), 1.77 (m, 2H), 1.63-1.56 (m, 1H), 1.47-1.34 (m, 2H), 1.30-1.04 (m, 6H), 0.60-0.50 (m, 2H), 0.30-0.24 (m, 2H). LC-MS: *m/z* 462 [M+H]⁺.

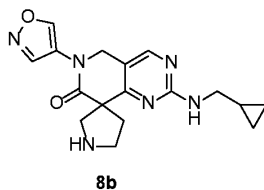
[00177] **Example 105:** methyl 3-(2-((cyclopropylmethyl)amino)-6-(4-methoxyphenyl)-7-oxo-6,7-dihydro-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-1'-yl)cyclobutanecarboxylate



[00178] The title compound was synthesized from intermediate **8a** with methyl 3-oxocyclobutanecarboxylate *via* general procedure *I*: (NaBH₃CN, HOAc, DCE).

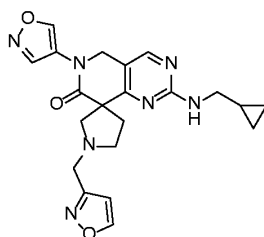
[00179] ¹H NMR (400 MHz, CDCl₃) δ : 8.08 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.45 (br s, 1H), 4.65 (d, *J* = 15.2 Hz, 1H), 4.59 (d, *J* = 15.2 Hz, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.41 (d, *J* = 9.6 Hz, 1H), 3.34-3.28 (m, 2H), 3.26-3.15 (m, 2H), 3.00-2.92 (m, 1H), 2.85-2.72 (m, 2H), 2.57-2.48 (m, 1H), 2.47-2.39 (m, 1H), 2.37-2.26 (m, 4H), 1.16-1.04 (m, 1H), 0.58-0.50 (m, 2H), 0.32-0.24 (m, 2H). LC-MS: *m/z* 492 [M+H]⁺.

[00180] Preparation of 2-((cyclopropylmethyl)amino)-6-(isoxazol-4-yl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one **8b**



[00181] 2-((cyclopropylmethyl)amino)-6-(isoxazol-4-yl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one **8b** was synthesized from isoxazol-4-amine *via* general procedure *I* (Step C-F). LC-MS: *m/z* 341 [M+H]⁺.

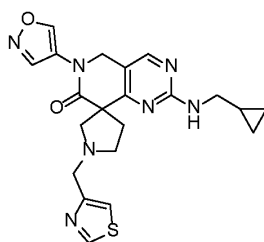
[00182] **Example 106:** Preparation of 2-((cyclopropylmethyl)amino)-1'-(isoxazol-3-ylmethyl)-6-(isoxazol-4-yl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one



[00183] The title compound was synthesized from intermediate **8b** with isoxazole-3-carbaldehyde *via* General Procedure *I*: (NaBH₃CN, HOAc, DCE).

[00184] ¹H NMR (400 MHz, CDCl₃) δ: 9.29 (s, 1H), 9.00 (s, 1H), 8.82 (s, 1H), 8.20 (s, 1H), 7.37 (t, *J* = 5.6 Hz, 1H), 6.52 (s, 1H), 4.79 (s, 2H), 3.77 (s, 2H), 3.17-3.05 (m, 4H), 2.87-2.74 (m, 2H), 2.53-2.35 (m, 2H), 1.13-1.01 (m, 1H), 0.43-0.33 (m, 2H), 0.25-0.16 (m, 2H). LC-MS: *m/z* 422 [M+H]⁺.

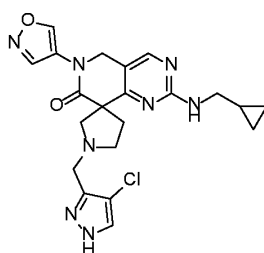
[00185] **Example 107:** 2-((cyclopropylmethyl)amino)-6-(isoxazol-4-yl)-1'-(thiazol-4-ylmethyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one



[00186] The title compound was synthesized from intermediate **8b** with thiazole-4-carbaldehyde *via* General Procedure I: (NaBH₃CN, HOAc, DCE).

[00187] ¹H NMR (400 MHz, MeOD-*d*₄) δ: 9.14 (s, 1H), 8.95 (d, *J* = 2.0 Hz, 1H), 8.88 (s, 1H), 8.19 (s, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 4.80 (d, *J* = 1.6 Hz, 2H), 4.59 (br s, 1H), 4.03 (s, 2H), 3.45 (d, *J* = 10.0 Hz, 1H), 3.41 (d, *J* = 10.0 Hz, 1H), 3.27 (d, *J* = 4.0 Hz, 1H), 3.26 (d, *J* = 4.0 Hz, 1H), 3.03 (t, *J* = 6.4 Hz, 2H), 2.60-2.43 (m, 2H), 1.18-1.05 (m, 1H), 0.54-0.45 (m, 2H), 0.29-0.22 (m, 2H). LC-MS: *m/z* 438 [M+H]⁺.

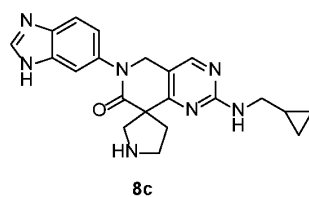
[00188] **Example 108:** 1'-((4-chloro-1H-pyrazol-3-yl)methyl)-2-((cyclopropylmethyl)amino)-6-(isoxazol-4-yl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one



[00189] The title compound was synthesized from intermediate **8b** with 4-chloro-1*H*-pyrazole-3-carbaldehyde *via* General Procedure I: (NaBH₃CN, HOAc, DCE).

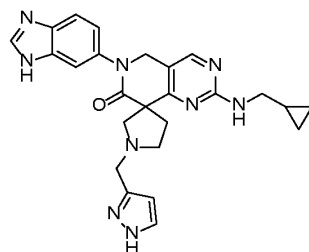
[00190] ¹H NMR (400 MHz, MeOD-*d*₄) δ: 9.19 (s, 1H), 8.92 (s, 1H), 8.27 (s, 1H), 7.76 (br s, 1H), 4.86 (s, 2H), 4.44-4.16 (m, 2H), 4.05-3.75 (m, 2H), 3.52-3.30 (m, 2H), 3.28 (dd, *J* = 6.8 Hz, 2.4 Hz, 2H), 2.67-2.57 (m, 1H), 2.51-2.41 (m, 1H), 1.19-1.07 (m, 1H), 0.56-0.50 (m, 2H), 0.30-0.25 (m, 2H). LC-MS: *m/z* 455 [M+H]⁺.

[00191] Preparation of 6-(1*H*-benzo[*d*]imidazol-6-yl)-2-((cyclopropylmethyl)amino)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one **8c**



[00192] 6-(1*H*-benzo[*d*]imidazol-6-yl)-2-((cyclopropylmethyl)amino)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one **8c** was synthesized from 1*H*-benzo[*d*]imidazol-6-amine *via* general procedure *I* (Step C-F). LC-MS: *m/z* 390 [M+H]⁺

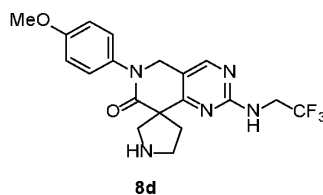
[00193] **Example 109:** Preparation of 1'-((1*H*-pyrazol-3-yl)methyl)-6-(1*H*-benzo[*d*]imidazol-6-yl)-2-((cyclopropylmethyl)amino)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one



[00194] The title compound was synthesized from intermediate **8c** with 1*H*-pyrazole-3-carbaldehyde *via* General Procedure *I*: (NaBH₃CN, HOAc, DCE).

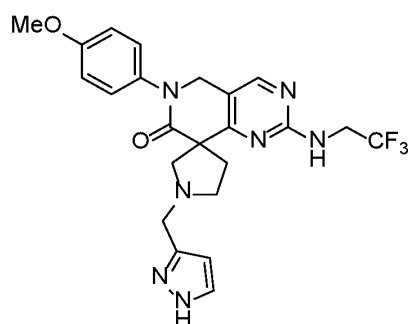
[00195] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 12.55 (br s, 2H), 8.26 (s, 1H), 8.21 (s, 1H), 7.69-7.42 (m, 3H), 7.31 (t, *J* = 5.6 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.17 (s, 1H), 4.77 (d, *J* = 15.6 Hz, 1H), 4.69 (d, *J* = 15.2 Hz, 1H), 3.85-3.67 (m, 2H), 3.29-3.09 (m, 4H), 2.69-2.71 (m, 2H), 2.61-2.53 (m, 2H), 1.17-1.03 (m, 1H), 0.46-0.36 (m, 2H), 0.27-0.17 (m, 2H). LC-MS: *m/z* 470 [M+H]⁺.

[00196] Preparation of 6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one **8d**



[00197] 6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)-5H-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one **8d** was synthesized from 2,2,2-trifluoroethanamine *via* general procedure I (Step E, F). LC-MS: *m/z* 408 [M+H]⁺

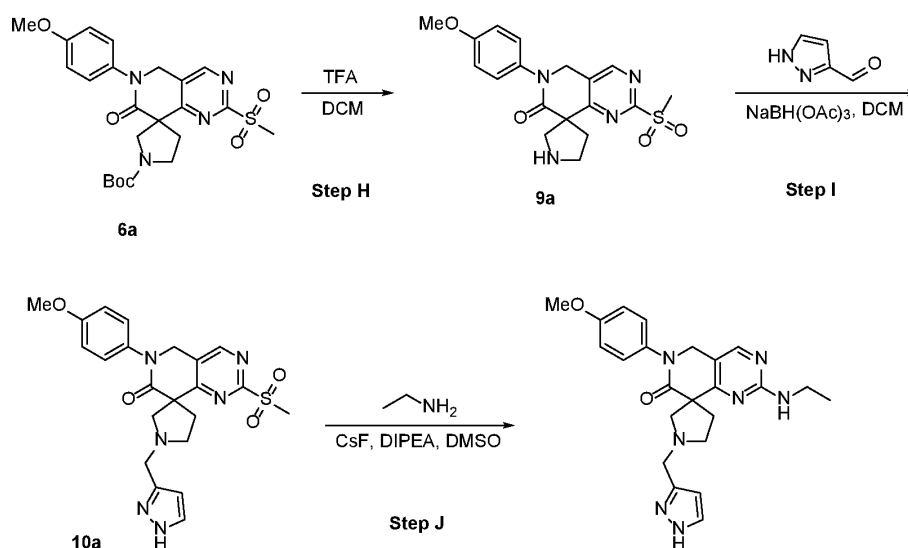
[00198] **Example 110:** Preparation of 1'-((1*H*-pyrazol-3-yl)methyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)-5H-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one



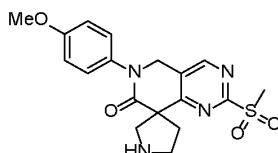
[00199] The title compound was synthesized from intermediate **8d** with 1*H*-pyrazole-3-carbaldehyde *via* General Procedure I: (NaBH₃CN, HOAc, DCE).

[00200] ¹H NMR (400 MHz, CDCl₃) δ: 8.17 (s, 1H), 7.52 (d, *J* = 1.2 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.19 (s, 1H), 4.73 (d, *J* = 15.6 Hz, 1H), 4.58 (d, *J* = 15.6 Hz, 1H), 4.31-4.13 (m, 2H), 3.99 (d, *J* = 14.0 Hz, 1H), 3.89 (d, *J* = 14.0 Hz, 1H), 3.82 (s, 3H), 3.53-3.34 (m, 2H), 3.16-3.05 (m, 1H), 3.04-2.94 (m, 1H), 2.68-2.55 (m, 1H), 2.48-2.35 (m, 1H) 2NH protons not shown. LC-MS: *m/z* 488 [M+H]⁺.

[00201] Preparation of **Example 111:**

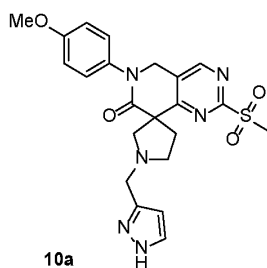


[00202] Step H: 6-(4-methoxyphenyl)-2-(methylsulfonyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one



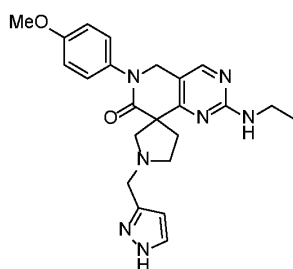
[00203] To a solution of *tert*-butyl 6-(4-methoxyphenyl)-2-(methylsulfonyl)-7-oxo-6,7-dihydro-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidine]-1'-carboxylate (500 mg, 1.0 mmol, 1.0 equiv) in DCM (5 mL) was added trifluoroacetic acid (1.5 mL) at room temperature. The resulting mixture was stirred for 1h, then the reaction mixture was quenched with cold NaHCO₃ (50 mL, sat. aq.) and extracted with DCM (50 mL x 2). The organic layers were combined and washed with brine (30 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE/EA = 3/1-1/1) to afford 6-(4-methoxyphenyl)-2-(methylsulfonyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one (340 mg, 85% yield) as a white solid. LC-MS: *m/z* 389 [M+H]⁺.

[00204] Step I: 1'-((1*H*-pyrazol-3-yl)methyl)-6-(4-methoxyphenyl)-2-(methylsulfonyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one



[00205] To a solution of 6-(4-methoxyphenyl)-2-(methylsulfonyl)-5H-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6H)-one (100 mg, 0.26 mmol, 1.0 equiv.) in DCM (5 mL) was added 1H-pyrazole-3-carbaldehyde (50 mg, 0.52 mmol, 2.0 equiv.) and AcOH (60.0 μ L, catalytic amount) at room temperature. The resulting mixture was stirred for 1h, and then NaBH₃CN (16.0 mg, 0.25 mmol, 1.0 equiv) was added. After 0.5 h, the reaction mixture was quenched with ice water (10 mL) and extracted with DCM (10 mL x 3). All the organic layers were combined and washed with brine (30 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by RP-prep-HPLC to afford 1'-((1H-pyrazol-3-yl)methyl)-6-(4-methoxyphenyl)-2-(methylsulfonyl)-5H-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6H)-one (60.0 mg, 49% yield) as a white solid. LC-MS: *m/z* 469 [M+H]⁺.

[00206] **Step J:** 1'-((1H-pyrazol-3-yl)methyl)-2-(ethylamino)-6-(4-methoxyphenyl)-5H-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6H)-one (**Example 111**)

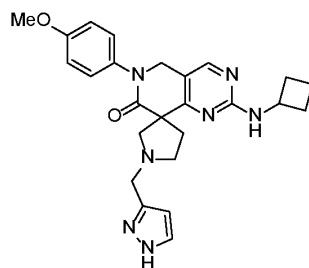


[00207] To a solution of 1'-((1H-pyrazol-3-yl)methyl)-6-(4-methoxyphenyl)-2-(methylsulfonyl)-5H-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6H)-one (60.0 mg, 0.13 mmol, 1.0 equiv.) in DMSO (1 mL) was added CsF (20.0 mg, 0.13 mmol, 1.0 equiv.), DIPEA (50.0 mg, 0.39 mmol, 3.0 equiv.) and ethanamine hydrochloride (30.0 mg, 0.37 mmol, 3.0 equiv.) at room temperature. The resulting mixture was stirred at 80 °C overnight. Then the reaction mixture was quenched with ice water (10 mL) and extracted with DCM

(10 mL x 3). All the organic layers were combined and washed with brine (30 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by RP-prep-HPLC to afford 1'-((1*H*-pyrazol-3-yl)methyl)-*N*-ethyl-6-(4-methoxyphenyl)-6,7-dihydro-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-2-amine (**Example 111**).

[00208] ¹H NMR (400 MHz, DMSO-*d*₆) (HCOOH salt) δ : 8.26 (br s, 1H), 8.19 (s, 1H), 7.51 (d, *J* = 1.2 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.18 (t, *J* = 6.0 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.14 (d, *J* = 1.6 Hz, 1H), 4.68 (d, *J* = 15.4 Hz, 1H), 4.58 (d, *J* = 15.4 Hz, 1H), 3.77 (s, 3H), 3.67 (s, 2H), 3.36-3.16 (m, 2H), 3.13-3.10 (m, 2H), 2.86-2.65 (m, 3H), 2.52-2.41 (m, 2H), 1.13 (t, *J* = 7.2 Hz, 3H). LC-MS: *m/z* 434 [M+H]⁺.

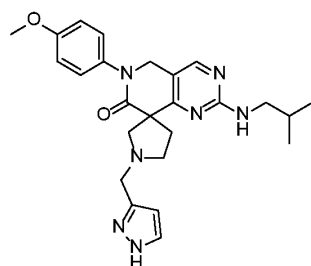
[00209] **Example 112:** 1'-((1*H*-pyrazol-3-yl)methyl)-2-(cyclobutylamino)-6-(4-methoxyphenyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one



[00210] The title compound was synthesized from intermediate **10a** with cyclobutanamine *via* general procedure *I*: (CsF, DIPEA, DMSO).

[00211] ¹H NMR (400 MHz, CDCl₃) δ : 8.11 (s, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.22 (s, 1H), 4.70 (d, *J* = 15.2 Hz, 1H), 4.53 (d, *J* = 15.2 Hz, 1H), 4.49 (d, *J* = 8.0 Hz, 1H), 4.45 (d, *J* = 8.0 Hz, 1H), 4.09-4.04 (m, 1H), 3.96 (d, *J* = 9.6 Hz, 1H), 3.82 (s, 3H), 3.57-3.48 (m, 1H), 3.43 (d, *J* = 9.6 Hz, 1H), 3.23-3.12 (m, 1H), 3.07-2.96 (m, 1H), 2.62-2.52 (m, 1H), 2.48-2.36 (m, 3H), 2.06-1.93 (m, 2H), 1.86-1.70 (m, 2H). LC-MS: *m/z* 460 [M+H]⁺.

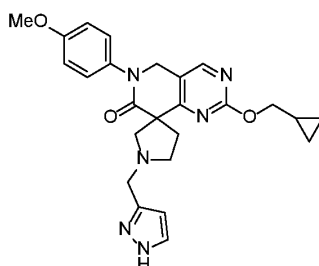
[00212] **Example 113:** 1'-((1*H*-pyrazol-3-yl)methyl)-2-(isobutylamino)-6-(4-methoxyphenyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one



[00213] The title compound was synthesized from intermediate **10a** with 2-methylpropan-1-amine *via* general procedure *I*: (CsF, DIPEA, DMSO).

[00214] ^1H NMR (400 MHz, DMSO- d_6) δ : 12.79-12.41 (br s, 1H), 8.18 (s, 1H), 7.69-7.35 (m, 1H), 7.29 (br s, 1H), 7.24 (d, $J = 8.8$ Hz, 2H), 6.97 (d, $J = 8.8$ Hz, 2H), 6.12 (s, 1H), 4.68 (d, $J = 15.2$ Hz, 1H), 4.58 (d, $J = 15.2$ Hz, 1H), 3.77 (s, 3H), 3.65 (s, 2H), 3.21-3.03 (m, 4H), 2.85-2.65 (m, 2H), 2.49-2.40 (m, 2H), 1.99-1.81 (m, 1H), 0.88 (dd, $J = 6.8$ Hz, 1.2 Hz, 6H). LC-MS: m/z 462 $[\text{M}+\text{H}]^+$.

[00215] **Example 114:** 1'-((1*H*-pyrazol-3-yl)methyl)-2-(cyclopropylmethoxy)-6-(4-methoxyphenyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one



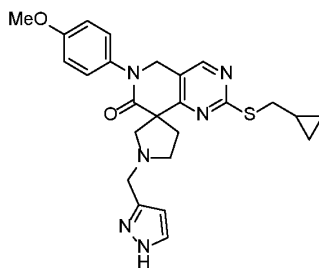
[00216] The title compound was synthesized from intermediate **10a** with cyclopropylmethanol *via* general procedure *I*: (Step J: alternative condition: NaH, DMF).

[00217] To a solution of cyclopropylmethanol (50 mg, 0.7 mmol, 4.0 equiv) in anhydrous DMF (2 mL) was added NaH (60% in mineral oil, 57 mg, 1.4 mmol, 8.0 equiv) at 0 °C. The resulting mixture was stirred at 0 °C for 1h. Then a solution of **10a** (82 mg, 0.18 mmol, 1.0 equiv) was added. The resulting mixture was stirred at room temperature for 1h. Then the reaction was quenched with ice NH_4Cl (Sat. aq., 10 mL) and extracted with DCM (10 mL x 3). The combined extracts were washed with brine (20 mL), dried over anhydrous

Na₂SO₄ and concentrated. The residue was purified by RP-prep-HPLC to afford 1'-((1*H*-pyrazol-3-yl)methyl)-2-(cyclopropylmethoxy)-6-(4-methoxyphenyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one.

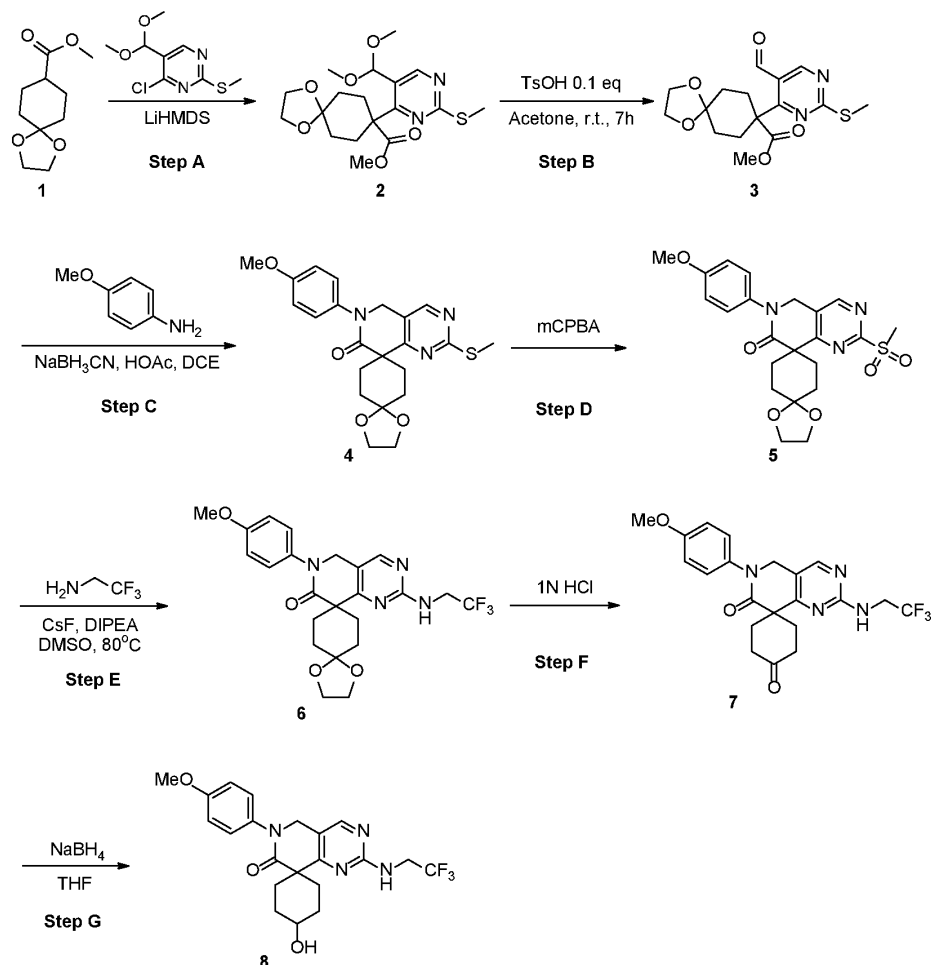
[00218] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 12.82-12.41 (m, 1H), 8.50 (s, 1H), 7.68-7.31 (m, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.13 (s, 1H), 4.84 (d, *J* = 15.6 Hz, 1H), 4.74 (d, *J* = 15.6 Hz, 1H), 4.24-4.11 (m, 2H), 3.77 (s, 3H), 3.65 (s, 2H), 3.20-3.05 (m, 2H), 2.90-2.81 (m, 1H), 2.76-2.66 (m, 1H), 2.98-2.53 (m, 2H), 1.37-1.24 (m, 1H), 0.61-0.52 (m, 2H), 0.39-0.33 (m, 2H). LC-MS: *m/z* 461 [M+H]⁺.

[00219] **Example 115:** 1'-((1*H*-pyrazol-3-yl)methyl)-2-((cyclopropylmethyl)thio)-6-(4-methoxyphenyl)-5*H*-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7(6*H*)-one

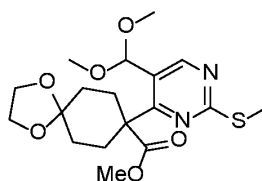


[00220] The title compound was synthesized from intermediate **10a** with cyclopropylmethanethiol *via* general procedure *I*: (Step J: alternative method, NaH, DMF, as prepared in **Example 114**).

[00221] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 12.56 (brs, 1H), 8.55 (s, 1H), 7.53 (br s, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.12 (d, *J* = 1.2 Hz, 1H), 4.86 (d, *J* = 16.4 Hz, 1H), 4.76 (d, *J* = 16.4 Hz, 1H), 3.78 (s, 3H), 3.65 (s, 2H), 3.20-3.12 (m, 3H), 3.03 (dd, *J* = 13.6 Hz, 7.2 Hz, 1H), 2.94-2.84 (m, 1H), 2.79-2.68 (m, 1H), 2.59-2.43 (m, 2H), 1.27-1.17 (m, 1H), 0.58-0.46 (m, 2H), 0.35-0.26 (m, 2H). LC-MS: *m/z* 477 [M+H]⁺.

[00222] Preparation of Example 116:

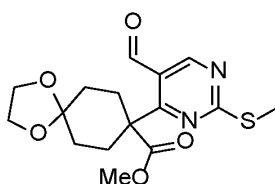
[00223] Step A: methyl 8-(5-(dimethoxymethyl)-2-(methylthio)pyrimidin-4-yl)-1,4-dioxaspiro[4.5]decane-8-carboxylate



[00224] To a solution of methyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (3.9 g, 19.8 mmol, 1.5 equiv.) in THF (30 mL) was added LiHMDS (1 M in THF, 26.4 mL, 26.4 mmol, 2.0 equiv.) at -78°C over 1 h via the addition funnel. The mixture was stirred at -78°C for 4 h. Then a solution of 4-chloro-5-(dimethoxymethyl)-2-(methylthio)pyrimidine (3.1 g, 13.2 mmol, 1.0 equiv.) in THF (10 mL) was added. The reaction mixture was allowed to warm to room

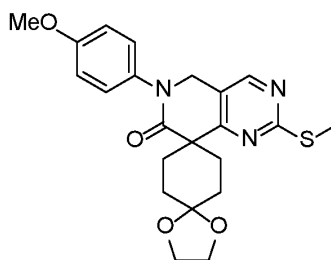
temperature and stirred for an additional 3 h. Then the reaction mixture was quenched with NH₄Cl (sat. aq., 50 mL) and extracted with EtOAc (50 mL x 3). The organic layers were combined, dried over Na₂SO₄, filtered, concentrated, and the resulting residue was purified by flash column chromatography on silica gel (PE/EtOAc = 20/1 to 4/1) to afford methyl 8-(5-(dimethoxymethyl)-2-(methylthio)pyrimidin-4-yl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (2.9 g, 55% yield) as a yellow oil. LC-MS: *m/z* 399 [M+H]⁺.

[00225] Step B: methyl 8-(5-formyl-2-(methylthio)pyrimidin-4-yl)-1,4-dioxaspiro[4.5]decane-8-carboxylate



[00226] To a solution of methyl 8-(5-(dimethoxymethyl)-2-(methylthio)pyrimidin-4-yl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (1.6 g, 4.1 mmol, 1.0 equiv.) in acetone (80 mL) was added *p*-TSA (68 mg, 0.4 mmol, 0.1 equiv.). The resulting mixture was stirred at room temperature for 4h. The reaction mixture was quenched by adding ice water (50 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, dried over Na₂SO₄, filtered, concentrated, and the crude residue was used directly without further purification (1.5 g, crude) as a colorless oil. LC-MS: *m/z* 353 [M+H]⁺

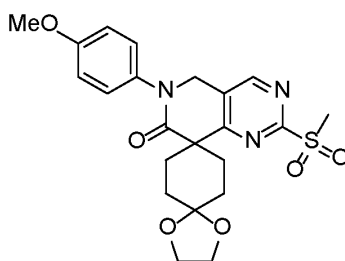
[00227] Step C: 6-(4-methoxyphenyl)-8-(1',4'-dioxaspiro[4.5]decane)-2-(methylthio)-5,6-dihydropyrido[4,3-*d*]pyrimidin-7(8*H*)-one



[00228] To a solution of methyl 8-(5-formyl-2-(methylthio)pyrimidin-4-yl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (1.5 g, 4.3 mmol, 1.0 equiv.) and 4-methoxyaniline (1.2 g, 9.5 mmol, 2.2 equiv.) in DCE (18 ml) was added AcOH (0.9 mL, 15.1 mmol, 3.5 equiv.). The resulting solution was stirred at room

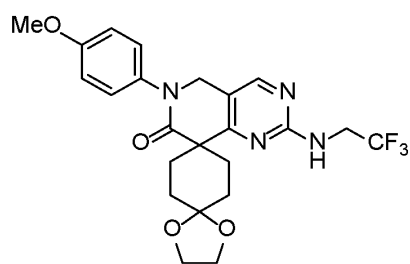
temperature for 1 h. after which NaBH_3CN (0.7 g, 10.8 mmol, 2.5 equiv.) was added in several portions over the course of 0.5h and the resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with ice water (10 mL) and extracted with EtOAc (30 mL x 3). All the organic layers were combined, dried over Na_2SO_4 , filtered, concentrated under reduce pressure, and the residue was purified by flash column chromatography on silica gel (PE/EtOAc = 10/1 to 1/1) to give 6-(4-methoxyphenyl)-8-(1',4'-dioxaspiro[4.5]decane)-2-(methylthio)-5,6-dihydropyrido[4,3-*d*]pyrimidin-7(8*H*)-one (1.4 g, 79% yield) as a light brown solid. LC-MS: m/z 428 $[\text{M}+\text{H}]^+$.

[00229] Step D: 6-(4-methoxyphenyl)-8-(1',4'-dioxaspiro[4.5]decane)-2-(methylsulfonyl)-5,6-dihydropyrido[4,3-*d*]pyrimidin-7(8*H*)-one



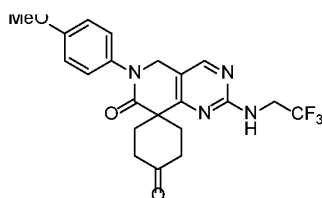
[00230] To a solution of 6-(4-methoxyphenyl)-8-(1',4'-dioxaspiro[4.5]decane)-2-(methylthio)-5,6-dihydropyrido[4,3-*d*]pyrimidin-7(8*H*)-one (470 mg, 1.1 mmol, 1.0 equiv.) in DCM (10 mL) was added *m*CPBA (565 mg, 3.3 mmol, 3.0 equiv.) in several portions during in the course of 0.5h. The resulting mixture was stirred at room temperature for an additional 2h, before being quenched with ice water (20 mL) and extracted with DCM (20 mL x 3). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4 , filtered, concentrated under reduce pressure, and the residue was purified by flash column chromatography on silica gel (PE/EtOAc = 2/1 to 1/1) to afford 6-(4-methoxyphenyl)-8-(1',4'-dioxaspiro[4.5]decane)-2-(methylsulfonyl)-5,6-dihydropyrido[4,3-*d*]pyrimidin-7(8*H*)-one (475 mg, 94% yield) as a white solid. LCMS: m/z 460 $[\text{M}+\text{H}]^+$.

[00231] Step E: 8-(1',4'-dioxaspiro[4.5]decane)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-7(8*H*)-one



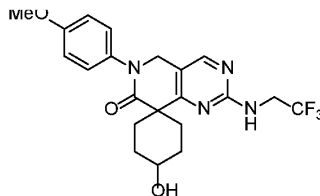
[00232] To a solution of 6-(4-methoxyphenyl)-8-(1',4'-dioxaspiro[4.5]decane)-2-(methylsulfonyl)-5,6-dihydropyrido[4,3-*d*]pyrimidin-7(8*H*)-one (1.1 g, 2.5 mmol, 1.0 equiv.) in DMSO (15 mL) was added CsF (380 mg, 2.5 mmol, 1.0 equiv.), DIPEA (967 mg, 7.5 mmol, 3.0 equiv.) and 2,2,2-trifluoroethanamine (740 mg, 7.5 mmol, 3.0 equiv.) at room temperature. The resulting mixture was stirred at 80 °C overnight, then water (10 mL) was added. The reaction mixture was extracted with DCM (20 mL x 3), the organic layers were combined, washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduce pressure. The resulting residue was purified by flash column chromatography on silica gel to give 8-(1',4'-dioxaspiro[4.5]decane)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-7(8*H*)-one (850 mg, 71% yield) as a white solid. LCMS: *m/z* 479 [M+H]⁺.

[00233] Step F: 6'-(4-methoxyphenyl)-2'-((2,2,2-trifluoroethyl)amino)-5'*H*-spiro[cyclohexane-1,8'-pyrido[4,3-*d*]pyrimidine]-4,7'-(6'*H*)-dione



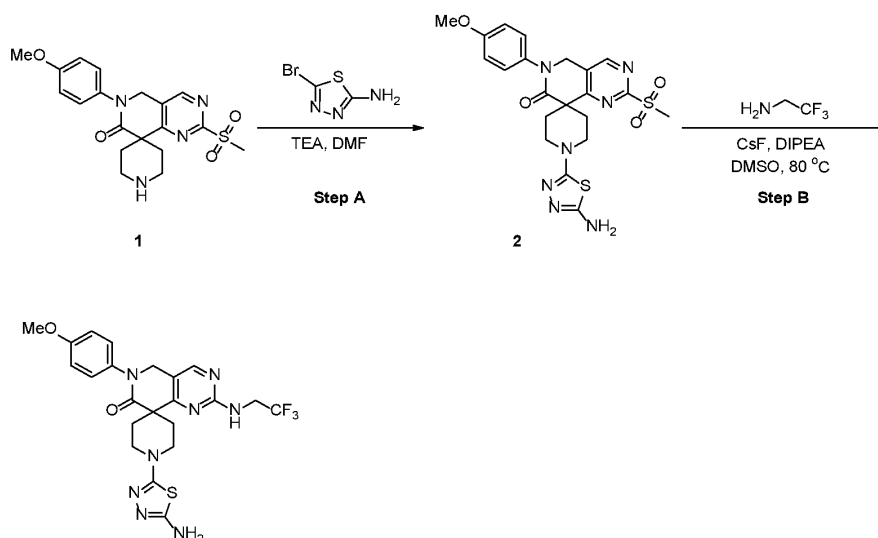
To a solution of 8-(1',4'-dioxaspiro[4.5]decane)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-7(8*H*)-one (50.0 mg, 0.1 mmol, 1.0 equiv.) in acetone (2.0 mL) was added 1N HCl (aq.) (0.5 mL, 0.5 mmol, 5.0 equiv.). The resulting solution was stirred at 80 °C for 2h. Then the reaction mixture was concentrated and purified by RP-prep-HPLC to afford the desired product (14 mg, 31% yield) as a white solid. LC-MS: *m/z* 435 [M+H]⁺.

[00234] Step G: 4-hydroxy-6'-(4-methoxyphenyl)-2'-((2,2,2-trifluoroethyl)amino)-5'*H*-spiro[cyclohexane-1,8'-pyrido[4,3-*d*]pyrimidin]-7'(6'*H*)-one (**Example 116**)

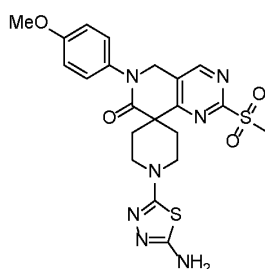


[00235] To a solution of 6'-(4-methoxyphenyl)-2'-((2,2,2-trifluoroethyl)amino)-5'*H*-spiro[cyclohexane-1,8'-pyrido[4,3-*d*]pyrimidine]-4,7'(6'*H*)-dione (10 mg, 0.023 mmol, 1.0 equiv) in THF (4 mL) was added NaBH₄ (3.8 mg, 0.10 mmol, 4.0 equiv) at -20 °C. The mixture was stirred at -20 °C for 1h. Then the reaction was quenched with NH₄Cl (sat. aq., 5 mL) and extracted with EtOAc (5 mL x 3). The organic layers were combined, washed with brine (30 mL), dried with Na₂SO₄, filtered and concentrated. The residue was purified by RP-prep-HPLC to afford 4-hydroxy-6'-(4-methoxyphenyl)-2'-((2,2,2-trifluoroethyl)amino)-5'*H*-spiro[cyclohexane-1,8'-pyrido[4,3-*d*]pyrimidin]-7'(6'*H*)-one (**Example 116**).

[00236] ¹H NMR (400 MHz, CDCl₃) δ: 8.14 (s, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 5.50-5.34 (m, 1H), 4.66 (s, 2H), 4.28-4.13 (m, 2H), 3.82 (s, 3H), 3.83-3.72 (m, 1H), 2.31-1.77 (m, 8H). LC-MS: *m/z* 437 [M+H]⁺.

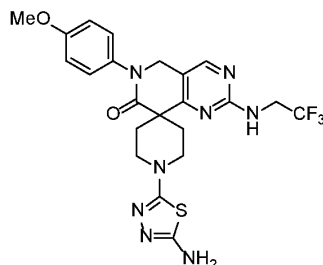
[00237] Preparation of Example 117:

[00238] Step A: 1-(5-amino-1,3,4-thiadiazol-2-yl)-6'-(4-methoxyphenyl)-2'-(methylsulfonyl)-5'H-spiro[piperidine-4,8'-pyrido[4,3-d]pyrimidin]-7'(6'H)-one



[00239] A mixture of 6'-(4-methoxyphenyl)-2'-(methylsulfonyl)-5'H-spiro[piperidine-4,8'-pyrido[4,3-d]pyrimidin]-7'(6'H)-one (prepared in the procedure for *General procedure I*, Step A-D and H, (n = 2) from 1-*tert*-butyl 4-ethyl piperidine-1,4-dicarboxylate. LC-MS: m/z 403 $[M+H]^+$) (150.0 mg, 0.37 mmol, 1.0 equiv), 5-bromo-1,3,4-thiadiazol-2-amine (80.0 mg, 0.45 mmol, 1.2 equiv), TEA (75.0 mg, 0.74 mmol, 2.0 equiv) and 3.0 mL of DMF was stirred at r.t. for 1h. Then the reaction mixture was concentrated under reduced pressure, and then purified by flash column chromatography on silica gel to afford 1-(5-amino-1,3,4-thiadiazol-2-yl)-6'-(4-methoxyphenyl)-2'-(methylsulfonyl)-5'H-spiro[piperidine-4,8'-pyrido[4,3-d]pyrimidin]-7'(6'H)-one (100.0 mg, 54% yield). LC-MS: m/z 502 $[M+H]^+$.

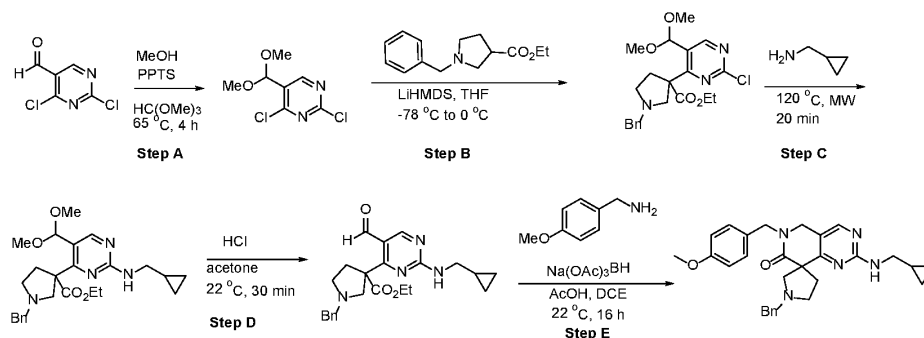
[00240] Step B: 1-(5-amino-1,3,4-thiadiazol-2-yl)-6'-(4-methoxyphenyl)-2'-((2,2,2-trifluoroethyl)amino)-5'*H*-spiro[piperidine-4,8'-pyrido[4,3-*d*]pyrimidin]-7'(6'*H*)-one (**Example 117**)

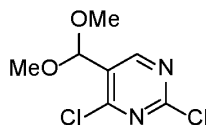


[00241] A mixture of 1-(5-amino-1,3,4-thiadiazol-2-yl)-6'-(4-methoxyphenyl)-2'-(methylsulfonyl)-5'*H*-spiro[piperidine-4,8'-pyrido[4,3-*d*]pyrimidin]-7'(6'*H*)-one (100.0 mg, 0.2 mmol, 1.0 equiv), CsF (30.0 mg, 0.2 mmol, 1.0 equiv), DIPEA (78.0 mg, 0.6 mmol, 3.0 equiv) and 2,2,2-trifluoroethanamine (60.0 mg, 0.6 mmol, 3.0 equiv) in 2.0 mL of DMSO was stirred at 80 °C for 3h. Then water (10.0 mL) was added and the resulting mixture was extracted with DCM (20 mL x 3). All the organic layers were combined and washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by RP-prep-HPLC to afford 1-(5-amino-1,3,4-thiadiazol-2-yl)-6'-(4-methoxyphenyl)-2'-((2,2,2-trifluoroethyl)amino)-5'*H*-spiro[piperidine-4,8'-pyrido[4,3-*d*]pyrimidin]-7'(6'*H*)-one (**Example 117**).

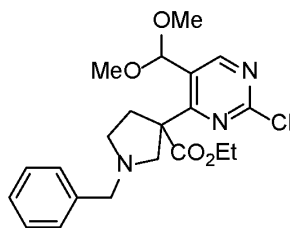
[00242] ¹H NMR (400 MHz, CDCl₃) δ: 8.18 (s, 1H), 7.17 (d, *J* = 9.2 Hz, 2H), 6.95 (d, *J* = 9.2 Hz, 2H), 5.45 (t, *J* = 6.4 Hz, 1H), 4.71-4.68 (br s, 2H), 4.69 (s, 2H), 4.23-4.10 (m, 2H), 3.82 (s, 3H), 3.81-3.71 (m, 4H), 2.35-2.29 (m, 2H), 2.25-2.17 (m, 2H). LC-MS: *m/z* 5

[00243] Preparation of Example 118



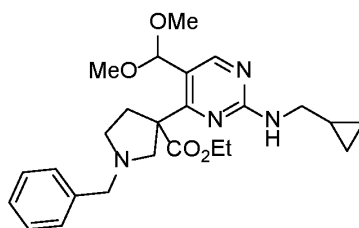
[00244] Step A: 2,4-dichloro-5-(dimethoxymethyl)pyrimidine

[00245] To a flask containing MeOH (24.0 mL), was added 2,4-dichloropyrimidine-5-carbaldehyde (1.5159 g, 1.0 equiv.), PPTS (215.0 mg, 0.1 equiv.) and trimethyl orthoformate (6.0 mL). The reaction mixture was stirred at 65 °C for 14 h, cooled to rt and concentrated. The resulting residue was purified via column chromatography to yield the title compound as an oil (1.4361 g, 75% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.73 (s, 1H), 5.54 (s, 1H), 3.38 (s, 7H). LC-MS: *m/z* 223, 225 [M+H]⁺.

[00246] Step B ethyl 1-benzyl-3-(2-chloro-5-(dimethoxymethyl)pyrimidin-4-yl)pyrrolidine-3-carboxylate

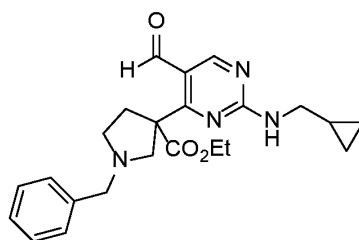
[00247] To a flask was added ethyl 1-benzylpyrrolidine-3-carboxylate (314.0 mg, 1.5 equiv.) and THF (10.0 mL). The mixture was cooled to -78 °C followed by the addition of LiHMDS (1.0 M in THF, 1.35 mL, 1.5 equiv.) and stirred at -78 °C for 30 min. To this mixture was added 2,4-dichloro-5-(dimethoxymethyl)pyrimidine (200.0 mg, 1.0 equiv.) at -78 °C. The reaction was stirred at -78 °C for 30 min, warmed to 0 °C and stirred for 1 h before it was quenched with silica gel. The resulting mixture was concentrated and purified via column chromatography to yield the title compound (269.7 mg, 72% yield). LC-MS: *m/z* 420 [M+H]⁺.

[00248] Step C: ethyl 1-benzyl-3-(2-((cyclopropylmethyl)amino)-5-(dimethoxymethyl)pyrimidin-4-yl)pyrrolidine-3-carboxylate



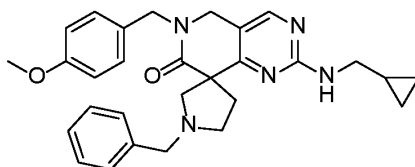
[00249] To a microwave reaction tube, was added ethyl 1-benzyl-3-(2-chloro-5-(dimethoxymethyl)pyrimidin-4-yl)pyrrolidine-3-carboxylate (269.7 mg, 1.0 equiv.) and cyclopropylmethanamine (2.5 mL). The reaction was stirred at 120 °C for 20 minutes using a Biotage microwave reactor and cooled to rt. The mixture was concentrated and purified via column chromatography to yield the title compound (201.8 mg, 69% yield). LC-MS: m/z 455 $[M+H]^+$.

[00250] Step D: ethyl 1-benzyl-3-(2-((cyclopropylmethyl)amino)-5-formylpyrimidin-4-yl)pyrrolidine-3-carboxylate



[00251] To a flask containing acetone, was added 1N HCl (0.4 mL) and ethyl 1-benzyl-3-(2-((cyclopropylmethyl)amino)-5-(dimethoxymethyl)pyrimidin-4-yl)pyrrolidine-3-carboxylate (201.8 mg, 1.0 equiv.). The reaction was stirred at 22 °C for 30 minutes and quenched with aq. NaHCO₃. The mixture was concentrated and purified via column chromatography to yield the title compound (165.7 mg, 91% yield). LC-MS: m/z 409 $[M+H]^+$.

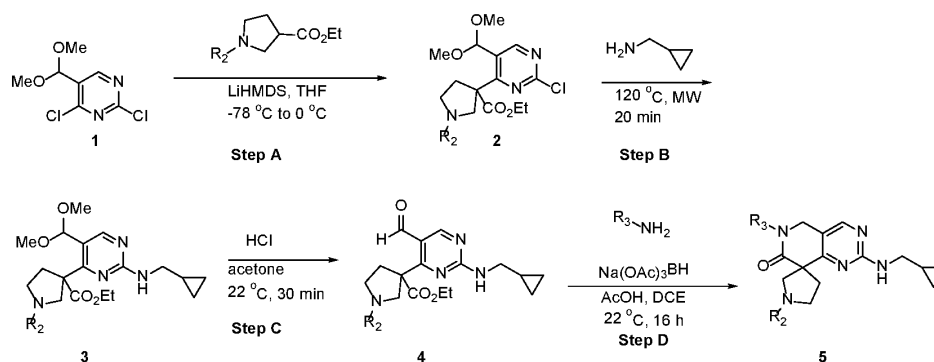
[00252] Step E: 1'-benzyl-2-((cyclopropylmethyl)amino)-6-(4-methoxybenzyl)-5,6-dihydro-7H-spiro[pyrido[4,3-d]pyrimidine-8,3'-pyrrolidin]-7-one (**Example 118**)

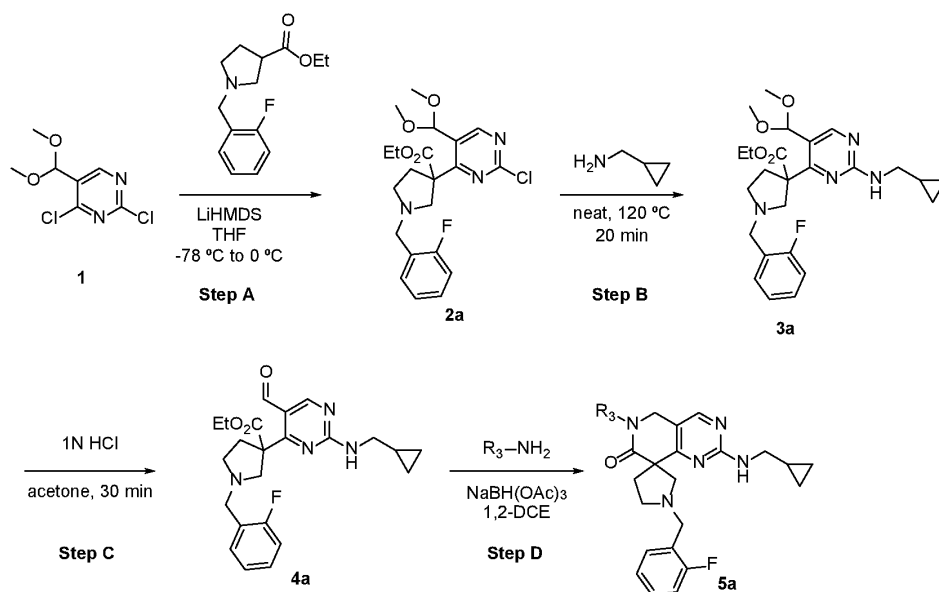


[00253] To a flask was added ethyl 1-benzyl-3-((cyclopropylmethyl)amino)-5-formylpyrimidin-4-yl)pyrrolidine-3-carboxylate (36.6 mg, 1.0 equiv.), (4-methoxyphenyl)methanamine (26 μ L, 2.2 equiv.), sodium triacetoxyborohydride (28.5 mg, 1.5 equiv.), dichloroethane (DCE, 2.0 mL) and acetic acid (15 μ L, 3.0 equiv.). The reaction was stirred at 22 °C for 16 h before it was quenched with aq. NaHCO₃. The mixture was concentrated and purified via column chromatography to yield the title compound (**Example 118**). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.93 (s, 1H), 7.46 – 7.39 (m, 2H), 7.35 – 7.29 (m, 2H), 7.27 (d, *J* = 7.1 Hz, 1H), 7.19 – 7.12 (m, 2H), 6.87 – 6.79 (m, 2H), 4.75 – 4.59 (m, 2H), 4.19 – 4.05 (m, 2H), 3.98 (s, 2H), 3.78 (s, 3H), 3.47 (d, *J* = 10.2 Hz, 1H), 3.34 (d, *J* = 10.2 Hz, 1H), 3.27 (t, *J* = 6.3 Hz, 2H), 3.20 (s, 1H), 3.05 (dt, *J* = 9.3, 7.1 Hz, 1H), 2.57 – 2.38 (m, 2H), 1.13–1.03 (m, 1H), 0.58 – 0.47 (m, 2H), 0.26 (dt, *J* = 6.0, 4.5 Hz, 2H). *m/z* 484 [M+H]⁺.

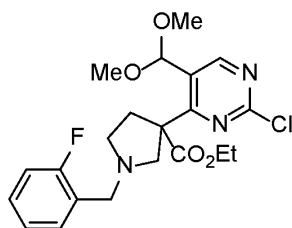
[00254] Preparation of **Example 119**, **Example 120**, **Example 121** and **Example 122** via General Procedure II:

General procedure II:



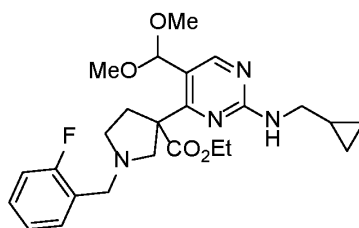


[00255] Step A: ethyl 3-(2-chloro-5-(dimethoxymethyl)pyrimidin-4-yl)-1-(2-fluorobenzyl)pyrrolidine-3-carboxylate



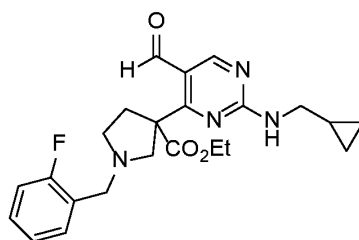
[00256] To a flask was added ethyl 1-(2-fluorobenzyl)pyrrolidine-3-carboxylate (2.02 g, 1.5 equiv., as prepared for **Example 118**) and THF (15.0 mL). The mixture was cooled to -78 °C followed by the addition of LiHMDS (1.0 M in THF, 8.1 mL, 1.5 equiv.). The reaction was stirred at -78 °C for 40 minutes and 2,4-dichloro-5-(dimethoxymethyl)pyrimidine (1.1965 g, 1.0 equiv.) was added dropwise at -78 °C. The reaction was stirred at -78 °C for 1 h, warmed to 0 °C and stirred for 45 minutes before it was quenched with silica gel. The resulting mixture was concentrated and purified via column chromatography to yield the title compound (1.30 g, 55% yield). LC-MS: *m/z* 438 [M+H]⁺.

[00257] Step B: ethyl 3-(2-((cyclopropylmethyl)amino)-5-(dimethoxymethyl)pyrimidin-4-yl)-1-(2-fluorobenzyl)pyrrolidine-3-carboxylate



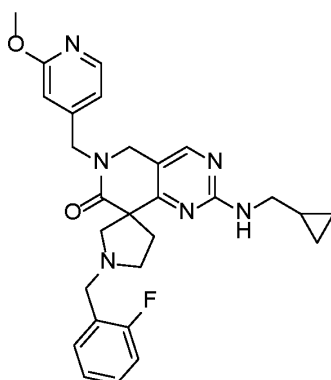
[00258] To a microwave reaction tube, was added ethyl 3-(2-chloro-5-(dimethoxymethyl)pyrimidin-4-yl)-1-(2-fluorobenzyl)pyrrolidine-3-carboxylate (398.8 mg, 1.0 equiv.) and cyclopropylmethanamine (2.5 mL). The reaction was stirred at 120 °C for 20 minutes using a Biotage microwave reactor and cooled to rt. The mixture was concentrated and purified via column chromatography to yield the title compound (312.3 mg, 73% yield). LC-MS: m/z 473 $[M+H]^+$.

[00259] **Step C:** ethyl 3-(2-((cyclopropylmethyl)amino)-5-formylpyrimidin-4-yl)-1-(2-fluorobenzyl)pyrrolidine-3-carboxylate



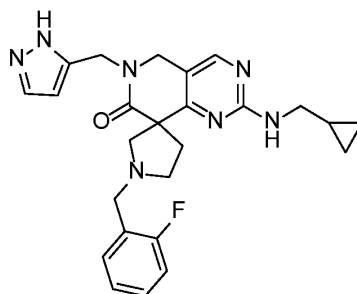
[00260] To a flask containing acetone, was added ethyl 3-(2-((cyclopropylmethyl)amino)-5-(dimethoxymethyl)pyrimidin-4-yl)-1-(2-fluorobenzyl)pyrrolidine-3-carboxylate (312.3 mg, 1.0 equiv.) and 1N HCl (0.7 mL). The reaction was stirred at 22 °C for 15 minutes and quenched with aq. NaHCO_3 . The mixture was concentrated and purified via column chromatography to yield the title compound (230.0 mg, 82% yield). LC-MS: m/z 427 $[M+H]^+$.

[00261] 2-((cyclopropylmethyl)amino)-1'-(2-fluorobenzyl)-6-((2-methoxy-4-pyridyl)methyl)-5,6-dihydro-7H-spiro[pyrido[4,3-d]pyrimidine-8,3'-pyrrolidin]-7-one (**Example 119**).



[00262] General procedure II (Step D): To a flask was added ethyl 3-(2-((cyclopropylmethyl)amino)-5-formylpyrimidin-4-yl)-1-(2-fluorobenzyl)pyrrolidine-3-carboxylate (30.0 mg, 1.0 equiv.), (6-methoxypyridin-3-yl)methanamine (21.4 mg, 2.2 equiv.), sodium triacetoxyborohydride (22.4 mg, 1.5 equiv.), dichloroethane (DCE, 2.0 mL) and acetic acid (14 μ L, 3.0 equiv.). The reaction was stirred at 22 °C for 16 h before it was quenched with aq. NaHCO_3 . The mixture was concentrated and purified via column chromatography to yield the title compound (**Example 119**). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.06 (d, J = 2.4 Hz, 1H), 7.96 (s, 1H), 7.52 (dd, J = 8.5, 2.5 Hz, 2H), 7.23 (s, 1H), 7.11 (t, J = 7.4 Hz, 1H), 7.01 (t, J = 9.1 Hz, 1H), 6.70 (d, J = 8.5 Hz, 1H), 4.73 – 4.58 (m, 2H), 4.15 (s, 2H), 3.92 (d, J = 0.8 Hz, 3H), 3.89 (s, 2H), 3.34 – 3.14 (m, 4H), 3.02 (s, 2H), 2.47 (ddt, J = 25.8, 12.6, 6.4 Hz, 2H), 1.13 – 1.03 (m, 1H), 0.62 – 0.44 (m, 2H), 0.25 (d, J = 5.0 Hz, 2H). LC-MS: m/z 503 $[\text{M}+\text{H}]^+$.

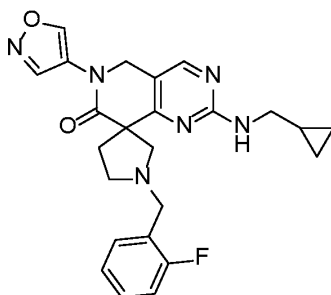
[00263] 6-((1H-pyrazol-5-yl)methyl)-2-((cyclopropylmethyl)amino)-1'-(2-fluorobenzyl)-5,6-dihydro-7H-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7-one (**Example 120**)



[00264] General procedure II (Step D): To a flask was added ethyl 3-(2-((cyclopropylmethyl)amino)-5-formylpyrimidin-4-yl)-1-(2-

fluorobenzyl)pyrrolidine-3-carboxylate (30.0 mg, 1.0 equiv.), (6-methoxypyridin-3-yl)methanamine (15.0 mg, 2.2 equiv.), sodium triacetoxyborohydride (22.4 mg, 1.5 equiv.), dichloroethane (DCE, 2.0 mL) and acetic acid (14 μ L, 3.0 equiv.). The reaction was stirred at 22 °C for 16 h before it was quenched with aq. NaHCO₃. The mixture was concentrated and purified via column chromatography to yield the title compound (**Example 120**). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.99 (s, 1H), 7.50 (t, *J* = 5.0 Hz, 2H), 7.21 (ddd, *J* = 7.4, 5.5, 1.9 Hz, 1H), 7.11 (td, *J* = 7.5, 1.3 Hz, 1H), 7.01 (ddd, *J* = 9.7, 8.1, 1.3 Hz, 1H), 6.25 (d, *J* = 2.1 Hz, 1H), 4.72 (s, 2H), 4.29 (s, 2H), 3.90 (s, 2H), 3.38 – 3.13 (m, 4H), 3.02 (d, *J* = 7.0 Hz, 2H), 2.51 (dt, *J* = 12.7, 6.5 Hz, 1H), 2.40 (dt, *J* = 12.6, 6.6 Hz, 1H), 1.13 – 1.01 (m, 1H), 0.59 – 0.47 (m, 2H), 0.25 (dt, *J* = 6.1, 4.5 Hz, 2H). LC-MS: *m/z* 462 [M+H]⁺.

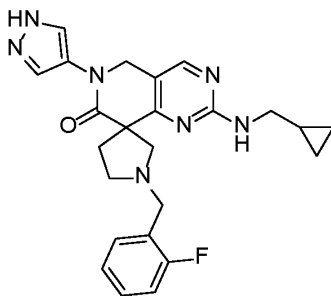
[00265] **Example 121:** 2-((cyclopropylmethyl)amino)-1'-(2-fluorobenzyl)-6-(isoxazol-4-yl)-5,6-dihydro-7H-spiro[pyrido[4,3-*d*]pyrimidine-8,3'-pyrrolidin]-7-one



[00266] General procedure II (Step D): To a solution of ethyl 3-((2-cyclopropylmethylamino)-5-formylpyrimidin-4-yl)-1-(2-fluorobenzyl)pyrrolidine-3-carboxylate (60 mg, 0.14 mmol, 1 equiv.) in 1,2-dichloroethane (0.7 ml) was added isoxazol-4-amine hydrochloride (25.4 mg, 0.21 mmol, 1.5 equiv.). The mixture was stirred at 75 °C for 1 h. The reaction was cooled to 60 °C before adding sodium triacetoxyborohydride (60 mg, 0.28 mmol, 2 equiv.) and stirring for another 3 h. The crude reaction mixture was purified via column chromatography (CombiFlash, 100:0 to 80:20 dichloromethane:methanol) to provide the title compound (**Example 121**). ¹H NMR (400 MHz, Chloroform-*d*) δ 9.01 (s, 1H), 8.66 (s, 1H), 8.15 (s, 1H), 7.50 – 7.44 (m, 1H), 7.21 (t, *J* = 6.6 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.01 (t, *J* = 9.1 Hz, 1H), 5.35 (s, 1H), 4.66 (s, 2H), 3.86 (s, 2H), 3.28 (td, *J* = 7.2, 6.4, 3.0 Hz,

3H), 3.20 (d, $J = 9.4$ Hz, 1H), 2.99 (t, $J = 6.6$ Hz, 2H), 2.56 (d, $J = 10.0$ Hz, 2H), 1.09 (s, 1H), 0.60 – 0.51 (m, 2H), 0.27 (d, $J = 5.0$ Hz, 2H). LC-MS: m/z 449 [M+H]⁺.

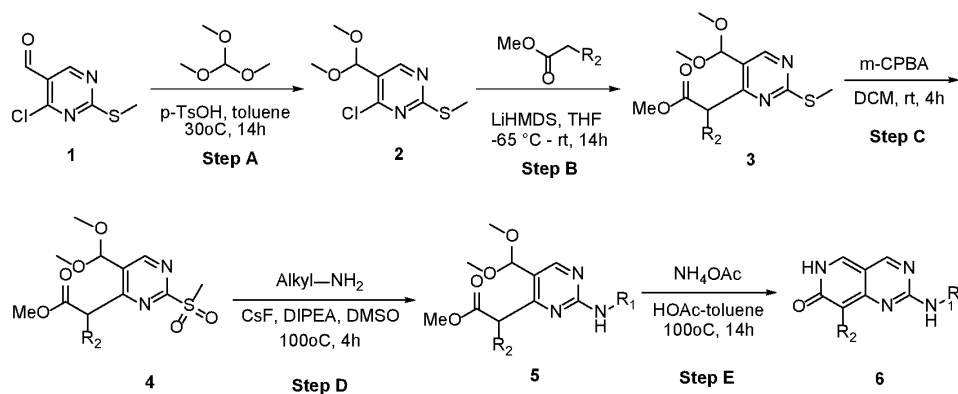
[00267] Example 122: 2-((cyclopropylmethyl)amino)-1'-(2-fluorobenzyl)-6-(1H-pyrazol-4-yl)-5,6-dihydro-7H-spiro[pyrido[4,3-d]pyrimidine-8,3'-pyrrolidin]-7-one



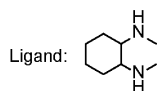
[00268] General procedure II (Step D): To a mixture of ethyl 3-((2-cyclopropylmethylamino)-5-formylpyrimidin-4-yl)-1-(2-fluorobenzyl)pyrrolidine-3-carboxylate (60 mg, 0.14 mmol, 1 equiv.) and acetic acid (0.025 mL, 0.42 mmol, 3 equiv.) in 1,2-dichloroethane (0.7 mL) was added isoxazol-4-amine hydrochloride (25.4 mg, 0.21 mmol, 1.5 equiv.). The mixture was stirred at room temperature for 2 h. The sodium triacetoxyborohydride (60 mg, 0.28 mmol, 2 equiv.) was added and the mixture was stirred for 48 h at room temperature. The crude reaction mixture was purified via column chromatography (CombiFlash, 100:0 to 80:20 dichloromethane:methanol). The appropriate fractions were pooled and concentrated and the residue was washed with saturated NaHCO₃ solution and extracted with dichloromethane (2 x 5 mL). The organic extracts were combined, dried over Na₂SO₄ and concentrated to provide the title compound (**Example 122**). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.12 (s, 1H), 7.96 (s, 2H), 7.46 (t, $J = 7.4$ Hz, 1H), 7.18 (d, $J = 7.0$ Hz, 1H), 7.10 – 7.04 (m, 1H), 6.98 (dd, $J = 9.9, 8.2$ Hz, 1H), 5.34 (s, 1H), 4.66 (s, 2H), 3.84 (d, $J = 2.5$ Hz, 2H), 3.32 – 3.18 (m, 4H), 2.97 (d, $J = 5.5$ Hz, 2H), 2.54 (d, $J = 19.0$ Hz, 3H), 1.07 (ddt, $J = 10.4, 7.4, 3.7$ Hz, 1H), 0.55 – 0.49 (m, 2H), 0.25 (q, $J = 5.1$ Hz, 2H). LC-MS: m/z 448 [M+H]⁺.

[00269] General Procedure III:

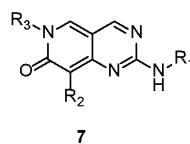
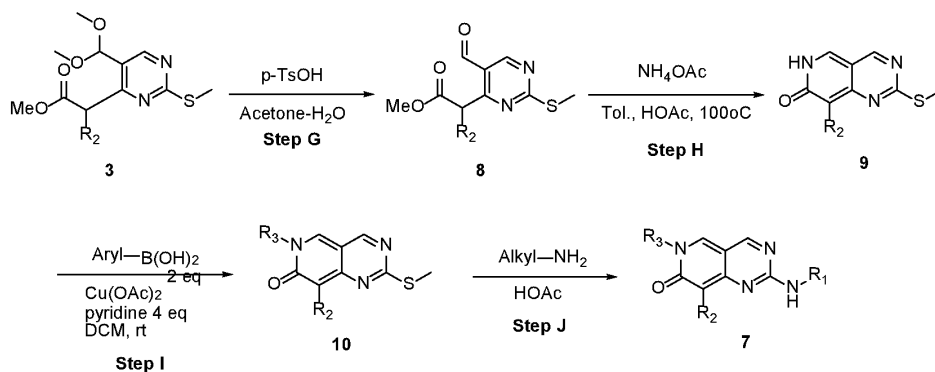
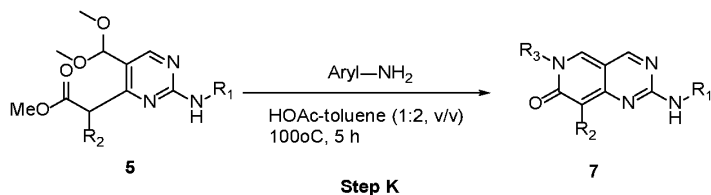
General procedure III:

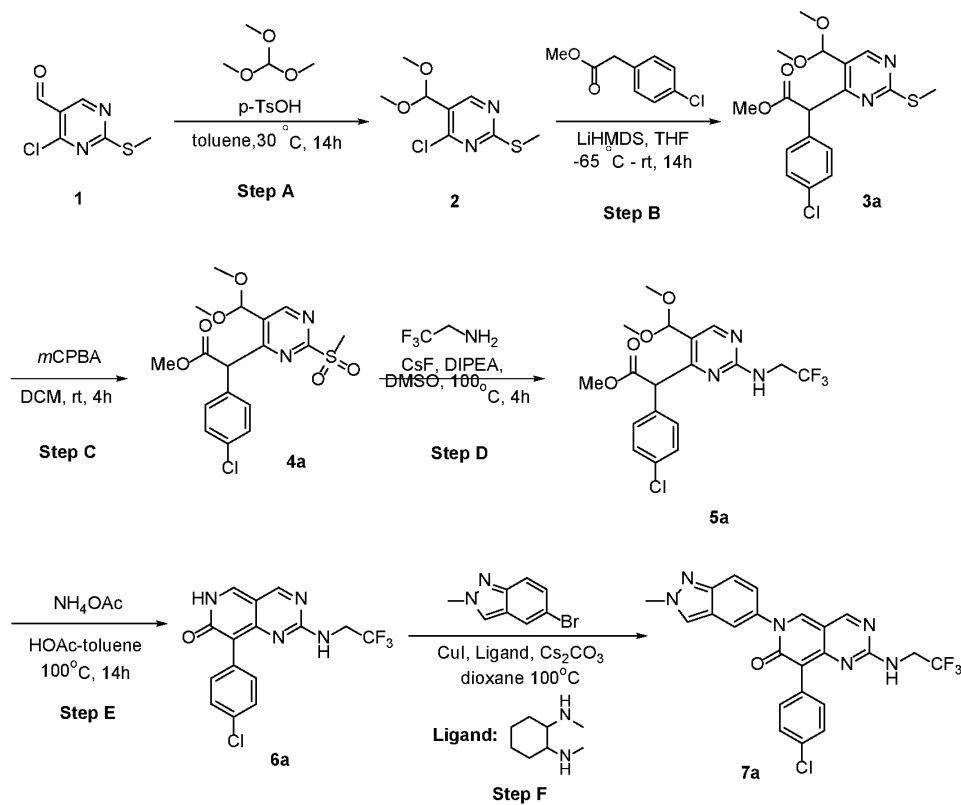
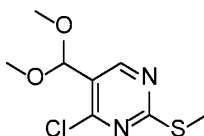
**Method A: Ullmann coupling**

CuI/Ligand , Cs_2CO_3 or CsF ,
dioxane or acetonitrile, 100°C

 R_3-Br **Method B: Chan-Lam coupling**

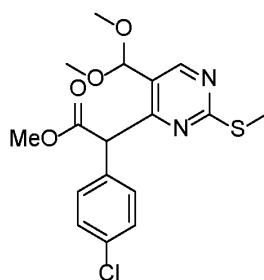
$\text{Cu}(\text{OAc})_2$, Pyridine
DCM, O_2 (1 atm), 40°C

 $\text{R}_3-\text{B}(\text{OH})_2$ **Step F****Alternative Route:****Alternative Route:**

[00270] Preparation of **Example 123** from General Procedure III:**[00271]** **Step A:** 4-chloro-5-(dimethoxymethyl)-2-(methylthio)pyrimidine

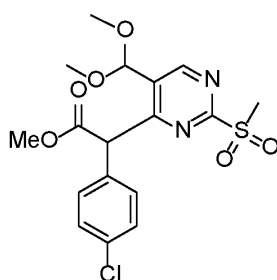
[00272] 4-chloro-2-(methylthio)pyrimidine-5-carbaldehyde (15.0 g, 79.8 mmol, 1.0 equiv.) and *p*-TsOH·H₂O (90.0 mg, 0.473 mmol, 0.006 equiv.) were dissolved in toluene (75.0 mL). Triethyl orthoformate (42.3 g, 399.0 mmol, 5.0 equiv) was added to the solution at 0°C. The resulting solution was stirred at 30°C for an additional 14h. Then the mixture was concentrated directly. The residue was re-dissolved in DCM (50.0 mL) and purified by flash chromatography on silica gel eluting with (PE/EA=10/1) to afford the desired product (18 g, 96% yield) as a colorless oil. LC-MS (ESI): *m/z* 235 [M+H]⁺.

Step B: methyl 2-(4-chlorophenyl)-2-(5-(dimethoxymethyl)-2-(methylthio)pyrimidin-4-yl)acetate



[00273] Methyl 2-(4-chlorophenyl)acetate (31.6 g, 170.9 mmol, 2.0 equiv.) was dissolved in anhydrous THF (200 mL), cooled to -65°C under N_2 atmosphere. LiHMDS (1N, in THF, 256 mL, 256.0 mmol, 3.0 equiv.) was added drop wise to the solution at -65°C . After addition, the resulting mixture was stirred at -65°C for 2h, then a solution of 4-chloro-5-(dimethoxymethyl)-2-(methylthio)pyrimidine (20 g, 85.4 mmol, 1.0 equiv) in anhydrous THF (80 mL) was added drop-wisely *via* an addition funnel into the reaction mixture. Following addition, the reaction mixture was slowly warmed to room temperature and stirred at room temperature for 14h. At this point, the mixture was quenched with NH_4Cl (Sat. aq., 500 mL) and extracted with EA (500 mL x 3). The organic layers were combined, washed with brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with (PE/EA=10:1~5:1) to afford the desired product (30 g, 93% yield) as a yellow solid. LC-MS: m/z 383 $[\text{M}+\text{H}]^+$.

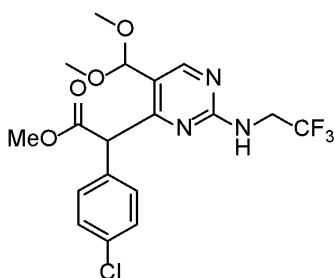
[00274] **Step C:** methyl 2-(4-chlorophenyl)-2-(5-(dimethoxymethyl)-2-(methylsulfonyl)pyrimidin-4-yl)acetate



[00275] To a solution of methyl 2-(4-chlorophenyl)-2-(5-(dimethoxymethyl)-2-(methylthio)pyrimidin-4-yl)acetate (30 g, 78.3 mmol, 1.0 equiv.) in DCM (500 mL) was added 3-Chloroperoxybenzoic acid (40.4 g, 235.1 mmol, 3.0 equiv.) in portions over 1h. The mixture was stirred at room

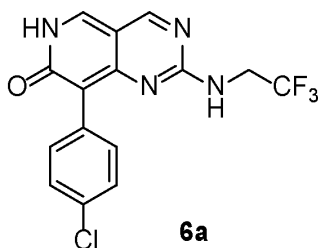
temperature for 4h. The reaction mixture was diluted with DCM (1 L) and washed with NaHCO₃ (Sat. aq., 1 L x 3), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with (PE/EA= 10:1~2:1) to afford the desired product (27 g, 83% yield) as a white solid. LC-MS: *m/z* 415 [M+H]⁺.

[00276] Step D: methyl 2-(4-chlorophenyl)-2-(5-(dimethoxymethyl)-2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)acetate



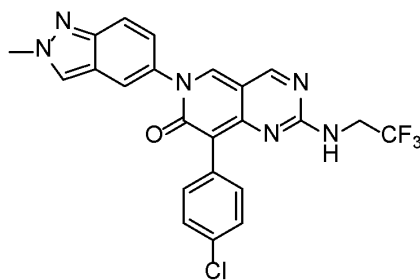
[00277] A mixture of methyl 2-(4-chlorophenyl)-2-(5-(dimethoxymethyl)-2-((2,2,2-trifluoro-ethyl)amino)pyrimidin-4-yl)acetate (15 g, 36.1 mmol, 1.0 equiv.), CsF (5.5 g, 36.1 mmol, 1.0 equiv.), DIPEA (23.3 g, 180.5 mmol, 5.0 equiv.), and 2,2,2-trifluoroethanamine (35.8 g, 361.5 mmol, 10 equiv.) in DMSO (150 mL) was stirred at 100°C overnight in a sealed tube. The reaction mixture was then concentrated to remove the excess 2,2,2-trifluoroethanamine. The resulting residue was poured into ice water (500 mL) and extracted with EA (500 mL x 3). The organic layers were combined, washed with brine (500 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with (PE/EA=5:1~3:1) to afford the desired product (10 g, 64% yield) as a yellow solid. LC-MS: *m/z* 434 [M+H]⁺.

[00278] Step E: 8-(4-chlorophenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00279] A mixture of methyl 2-(4-chlorophenyl)-2-(5-(dimethoxymethyl)-2-((2,2,2-trifluoro-ethyl)amino)pyrimidin-4-yl)acetate (30 g, 69.1 mmol, 1.0 equiv.), NH_4OAc (180 g, 779 mmol, 11.3 equiv.), AcOH (75 mL) and toluene (150 mL) was stirred at 100°C for an additional 14 h. Then the mixture was concentrated under reduced pressure, and the residue was poured into ice water (500 mL). This mixture was filtered and the collected precipitate was washed with NaHCO_3 (Sat, aq., 500 mL) followed by water (1 L). The obtained solid was dried in vacuo to afford the desired product (21 g, 85 % yield) as a yellow solid. LC-MS: m/z 355 $[\text{M}+\text{H}]^+$.

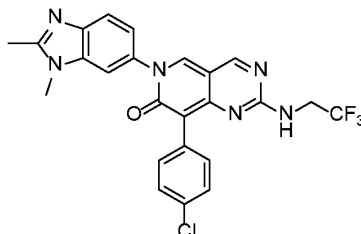
[00280] Step F: (Method A: Ullmann coupling). 8-(4-chlorophenyl)-6-(2-methyl-2H-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6H)-one (Example 123)



[00281] A mixture of 8-(4-chlorophenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6H)-one (100 mg, 0.28 mmol, 1.0 equiv), 5-bromo-2-methyl-2H-indazole (119 mg, 0.56 mmol, 2.0 equiv.), CuI (5.4 mg, 0.028 mmol, 0.1 equiv.), N,N' -dimethylcyclohexane-1,2-diamine (8.1 mg, 0.056 mmol, 0.2 equiv.), Cs_2CO_3 (276 mg, 0.847 mmol, 3.0 equiv.) and dioxane (2 mL) was stirred at 100°C under N_2 atmosphere for 16h. The crude mixture was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography on silica gel to yield 8-(4-chlorophenyl)-6-(2-methyl-2H-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6H)-one (Example 123).

[00282] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.97 (s, 1H), 8.91 (s, 1H), 8.59 (t, $J = 6.4$ Hz, 1H), 8.51 (s, 1H), 7.89 (d, $J = 1.6$ Hz, 1H), 7.72-7.64 (m, 3H), 7.38-7.28 (m, 3H), 4.22 (s, 3H), 4.12-4.03 (m, 2H). LC-MS: m/z 485 $[\text{M}+\text{H}]^+$.

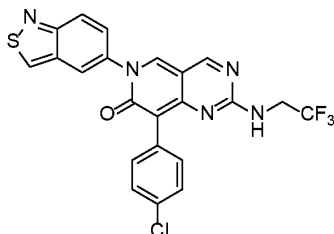
[00283] Example 124: 8-(4-chlorophenyl)-6-(1,2-dimethyl-1*H*-benzo[*d*]imidazol-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00284] The title compound was synthesized from intermediate **6a** with 6-bromo-1,2-dimethyl-1*H*-benzo[*d*]imidazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

[00285] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (s, 1H), 8.89 (s, 1H), 8.59 (t, *J* = 6.4 Hz, 1H), 7.74 (d, *J* = 2.0 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.26 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.15-4.01 (m, 2H), 3.75 (s, 3H), 2.57 (s, 3H). LC-MS: *m/z* 499 [M+H]⁺.

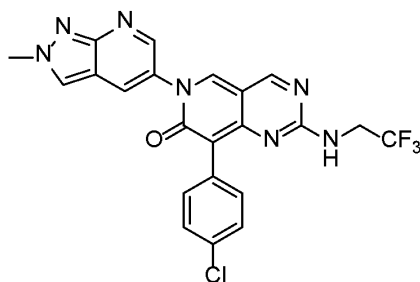
[00286] Example 125: 6-(benzo[*c*]isothiazol-5-yl)-8-(4-chlorophenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00287] The title compound was synthesized from intermediate **6a** with 5-bromobenzo[*c*]isothiazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

[00288] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.94 (s, 1H), 8.99 (s, 1H), 8.98 (s, 1H), 8.65 (t, *J* = 6.4 Hz, 1H), 8.15 (d, *J* = 1.2 Hz, 1H), 7.91 (d, *J* = 9.2 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.63 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 4.16-4.03 (m, 2H). LC-MS: *m/z* 488 [M+H]⁺.

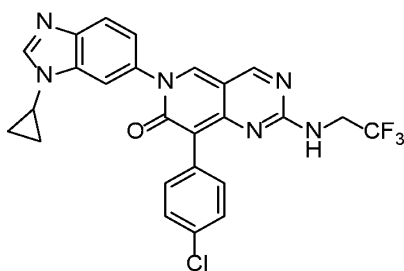
[00289] Example 126: 8-(4-chlorophenyl)-6-(2-methyl-2*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00290] The title compound was synthesized from intermediate **6a** with 5-bromo-2-methyl-2H-pyrazolo[3,4-*b*]pyridine *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

[00291] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (s, 1H), 8.97 (s, 1H), 8.67 (d, *J* = 2.4 Hz, 1H), 8.65 (t, *J* = 6.4 Hz, 1H), 8.60 (s, 1H), 8.45 (d, *J* = 2.4 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 4.26 (s, 3H), 4.15-4.03 (m, 2H). LC-MS: *m/z* 486 [M+H]⁺.

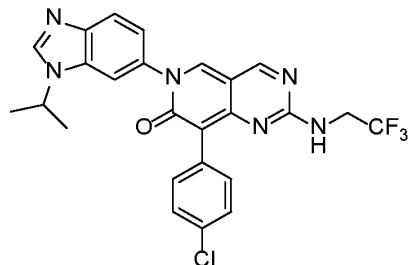
[00292] **Example 127:** 8-(4-chlorophenyl)-6-(1-cyclopropyl-1H-benzo[*d*]imidazol-6-yl)-2-(2,2,2-trifluoroethylamino)pyrido[4,3-*d*]pyrimidin-7(6H)-one



[00293] The title compound was synthesized from intermediate **6a** with 6-bromo-1-cyclopropyl-1H-benzo[*d*]imidazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

[00294] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.99 (s, 1H), 8.91 (s, 1H), 8.60 (t, *J* = 6.8 Hz, 1H), 8.38 (s, 1H), 7.87 (d, *J* = 1.6 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 4.16-4.02 (m, 2H), 3.57-3.48 (m, 1H), 1.13-1.04 (m, 4H). LC-MS: *m/z* 511 [M+H]⁺.

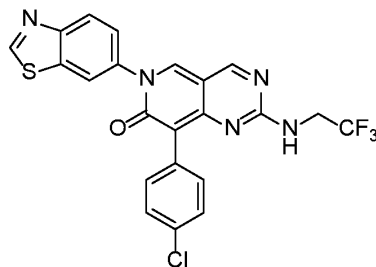
[00295] Example 128: 8-(4-chlorophenyl)-6-(1-isopropyl-1*H*-benzo[*d*]imidazol-6-yl)-2-(2,2,2-trifluoroethylamino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00296] The title compound was synthesized from intermediate **6a** with 6-bromo-1-isopropyl-1*H*-benzo[*d*]imidazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

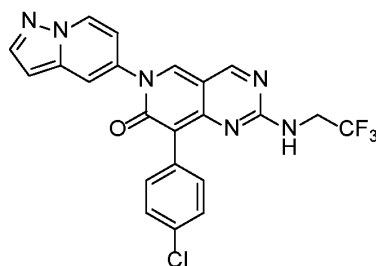
[00297] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.00 (s, 1H), 8.94 (s, 1H), 8.62 (t, *J* = 6.4 Hz, 1H), 8.51 (s, 1H), 7.93 (d, *J* = 1.6 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.34 (dd, *J* = 8.4, 1.6 Hz, 1H), 4.84-4.74 (m, 1H), 4.16-4.03 (m, 2H), 1.55 (d, *J* = 6.8 Hz, 6H). LC-MS: *m/z* 513 [M+H]⁺.

[00298] Example 129: 6-(benzo[*d*]thiazol-6-yl)-8-(4-chlorophenyl)-2-(2,2,2-trifluoroethylamino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00299] The title compound was synthesized from intermediate **6a** with 6-bromobenzo[*d*]thiazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C). LC-MS: *m/z* 488 [M+H]⁺.

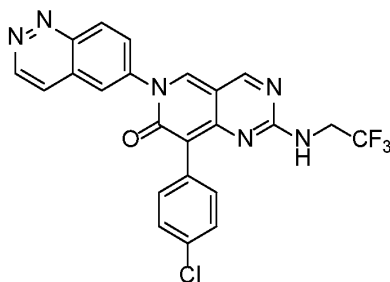
[00300] Example 130: 8-(4-chlorophenyl)-6-(pyrazolo[1,5-*a*]pyridin-5-yl)-2-(2,2,2-trifluoroethylamino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00301] The title compound was synthesized from intermediate **6a** with 5-bromopyrazolo[1,5-*a*]pyridine *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

[00302] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.98 (s, 1H), 8.96 (s, 1H), 8.83 (d, *J* = 7.6 Hz, 1H), 8.67 (t, *J* = 6.4 Hz, 1H), 8.13 (d, *J* = 2.0 Hz, 1H), 7.99 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.09 (dd, *J* = 7.2 Hz, 2.0 Hz, 1H), 6.79 (d, *J* = 1.2 Hz, 1H), 4.19-4.01 (m, 2H). LC-MS: *m/z* 471 [M+H]⁺.

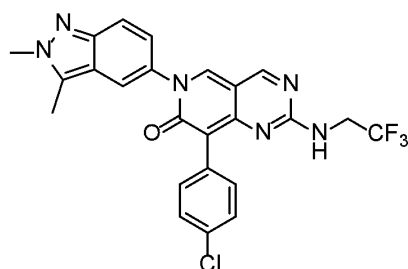
[00303] **Example 131:** 8-(4-chlorophenyl)-6-(cinnolin-6-yl)-2-(2,2,2-trifluoroethylamino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00304] The title compound was synthesized from intermediate **6a** with 6-bromocinnoline *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

[00305] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.51 (d, *J* = 6.0 Hz, 1H), 9.05 (s, 1H), 9.02 (s, 1H), 8.73 (d, *J* = 6.4 Hz, 1H), 8.63 (d, *J* = 8.8 Hz, 1H), 8.37 (d, *J* = 2.0 Hz, 1H), 8.36 (d, *J* = 5.6 Hz, 1H), 8.16 (dd, *J* = 9.2 Hz, 2.4 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 4.18-4.03 (m, 2H). LC-MS: *m/z* 483 [M+H]⁺.

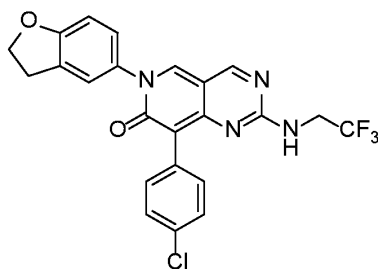
[00306] **Example 132:** 8-(4-chlorophenyl)-6-(2,3-dimethyl-2H-indazol-5-yl)-2-(2,2,2-trifluoroethylamino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00307] The title compound was synthesized from intermediate **6a** with 5-bromo-2,3-dimethyl-2H-indazole via *general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

[00308] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.99 (s, 1H), 8.92 (s, 1H), 8.59 (t, *J* = 6.4 Hz, 1H), 7.89 (d, *J* = 1.2 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.29 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 4.15-4.02 (m, 2H), 4.11 (s, 3H), 2.64 (s, 3H). LC-MS: *m/z* 499 [M+H]⁺.

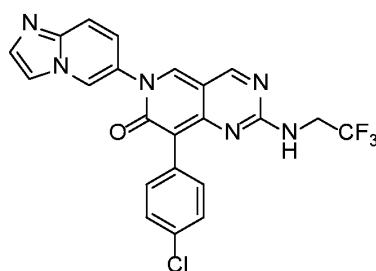
[00309] **Example 133:** 8-(4-chlorophenyl)-6-(2,3-dihydrobenzofuran-5-yl)-2-(2,2,2-trifluoroethylamino)pyrido[4,3-*d*]pyrimidin-7(6H)-one



[00310] The title compound was synthesized from intermediate **6a** with 5-bromo-2,3-dihydrobenzofuran via *general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

[00311] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.96 (s, 1H), 8.82 (s, 1H), 8.58 (t, *J* = 6.4 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.04 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 4.63 (d, *J* = 8.8 Hz, 2H), 2.82 (d, *J* = 8.8 Hz, 2H), 4.15-4.03 (m, 2H), 3.26 (t, *J* = 8.8 Hz, 2H). LC-MS: *m/z* 473 [M+H]⁺.

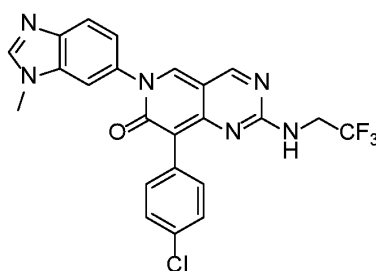
[00312] **Example 134:** 8-(4-chlorophenyl)-6-(imidazo[1,2-*a*]pyridin-6-yl)-2-(2,2,2-trifluoroethylamino)pyrido[4,3-*d*]pyrimidin-7(6H)-one



[00313] The title compound was synthesized from intermediate **6a** with 6-bromoimidazo[1,2-*a*]pyridine *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

[00314] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (s, 1H), 8.97 (s, 1H), 8.69 (t, *J* = 6.4 Hz, 1H), 8.08 (s, 1H), 8.17 (d, *J* = 9.2 Hz, 1H), 8.12 (s, 1H), 7.77 - 7.63 (m, 3H), 7.43 (dd, *J* = 9.2 Hz, 1.6 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 4.17-4.03 (m, 2H). LC-MS: *m/z* 471 [M+H]⁺.

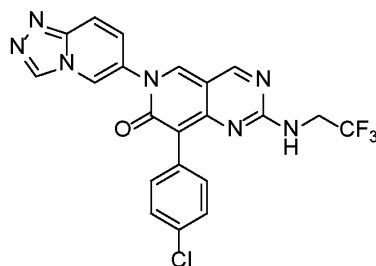
[00315] **Example 135:** 8-(4-chlorophenyl)-6-(1-methyl-1H-benzo[*d*]imidazol-6-yl)-2-((2,2,2-trifluoroethylamino)pyrido[4,3-*d*]pyrimidin-7(6H)-one



[00316] The title compound was synthesized from intermediate **6a** with 6-bromo-1-methyl-1H-benzo[*d*]imidazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

[00317] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.99 (s, 1H), 8.91 (s, 1H), 8.61 (t, *J* = 6.4 Hz, 1H), 8.34 (s, 1H), 7.85 (d, *J* = 2.0 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.35 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 4.15-4.02 (m, 2H), 3.87 (s, 3H). LC-MS: *m/z* 485 [M+H]⁺.

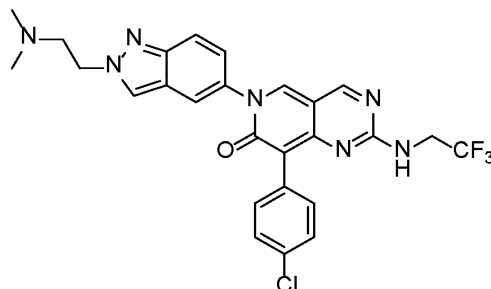
[00318] **Example 136:** 6-([1,2,4]triazolo[4,3-*a*]pyridin-6-yl)-8-(4-chlorophenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6H)-one



[00319] The title compound was synthesized from intermediate **6a** with 6-bromo-[1,2,4]triazolo[4,3-*a*]pyridine *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

[00320] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.41 (s, 1H), 9.00 (s, 1H), 8.98 (s, 1H), 8.95 (s, 1H), 8.72 (t, *J* = 6.4 Hz, 1H), 7.92 (d, *J* = 9.6 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.58 (dd, *J* = 9.6 Hz, 1.6 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 4.17-4.03 (m, 2H). LC-MS: *m/z* 472 [M+H]⁺.

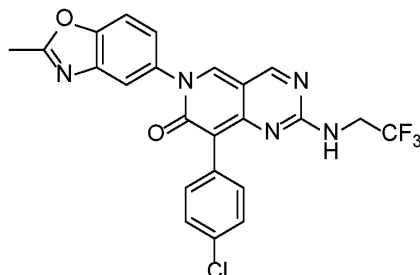
[00321] **Example 137:** 8-(4-chlorophenyl)-6-(2-(2-(dimethylamino)ethyl)-2H-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6H)-one



[00322] The title compound was synthesized from intermediate **6a** with 2-(5-bromo-2H-indazol-2-yl)-N,N-dimethylethanamine *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

[00323] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.97 (s, 1H), 8.92 (s, 1H), 8.59 (t, *J* = 6.4 Hz, 1H), 8.55 (s, 1H), 7.90 (d, *J* = 1.2 Hz, 1H), 7.71 (d, *J* = 9.2 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.33 (dd, *J* = 9.2 Hz, 2.0 H, 1H), 4.56 (t, *J* = 6.4 Hz, 2H), 4.14-4.03 (m, 2H), 2.81 (t, *J* = 6.4 Hz, 1H), 2.18 (s, 6H). LC-MS: *m/z* 542 [M+H]⁺.

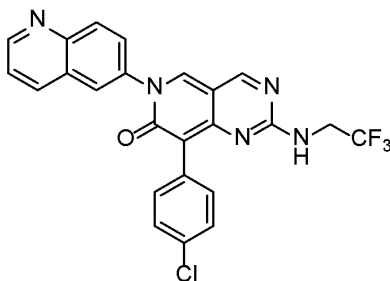
[00324] **Example 138:** 8-(4-chlorophenyl)-6-(2-methylbenzo[d]oxazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00325] The title compound was synthesized from intermediate **6a** with 5-bromo-2-methylbenzo[d]oxazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

[00326] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.97 (s, 1H), 8.90 (s, 1H), 8.61 (t, *J* = 6.4 Hz, 1H), 7.91 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 4.16-4.01 (m, 2H), 2.67 (s, 3H). LC-MS: *m/z* 486 [M+H]⁺.

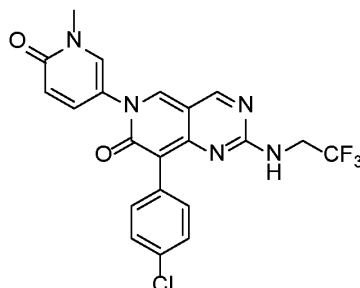
[00327] **Example 139:** 8-(4-chlorophenyl)-6-(quinolin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00328] The title compound was synthesized from intermediate **6a** with 6-bromoquinoline *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

[00329] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.03 (d, *J* = 4.0 Hz, 1.6 Hz, 1H), 9.02 (s, 1H), 9.00 (s, 1H), 8.67 (t, *J* = 6.4 Hz, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 8.24 (d, *J* = 2.0 Hz, 1H), 8.17 (d, *J* = 9.2 Hz, 1H), 7.94 (dd, *J* = 9.2 Hz, 2.4 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.66 (dd, *J* = 8.4 Hz, 4.0 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 4.17-4.03 (m, 2H). LC-MS: *m/z* 482 [M+H]⁺.

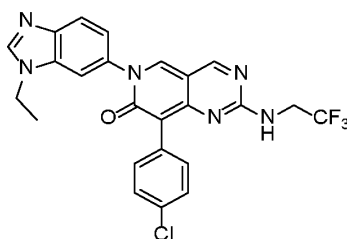
[00330] Example 140: 8-(4-chlorophenyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00331] The title compound was synthesized from intermediate **6a** with 5-bromo-1-methylpyridin-2(1*H*)-one *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

[00332] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.95 (s, 1H), 8.86 (s, 1H), 8.65 (t, *J* = 6.4 Hz, 1H), 8.14 (d, *J* = 2.8 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.63 (dd, *J* = 9.6 Hz, 2.8 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 9.6 Hz, 1H), 4.14-4.00 (m, 2H), 3.48 (s, 3H). LC-MS: *m/z* 462 [M+H]⁺.

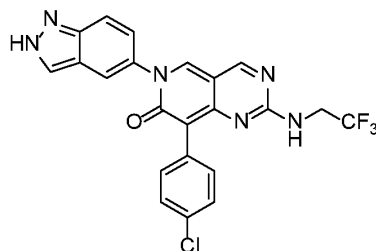
[00333] Example 141: 8-(4-chlorophenyl)-6-(1-ethyl-1*H*-benzo[*d*]imidazol-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00334] The title compound was synthesized from intermediate **6a** with 6-bromo-1-ethyl-1*H*-benzo[*d*]imidazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

[00335] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (s, 1H), 8.92 (s, 1H), 8.60 (t, *J* = 6.4, 1H), 8.41 (s, 1H), 7.90 (d, *J* = 1.6 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.34 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.15-4.02 (m, 2H), 1.43 (t, *J* = 7.2 Hz, 3H). LC-MS: *m/z* 499 [M+H]⁺.

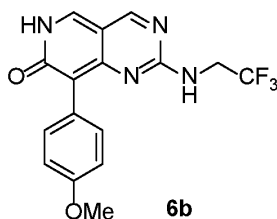
[00336] Example 142: 8-(4-chlorophenyl)-6-(2*H*-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00337] The title compound was synthesized from intermediate **6a** with 5-bromo-2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazole *via* general procedure III method A (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C), and then de-protection with TFA *via* general procedure I (Step F).

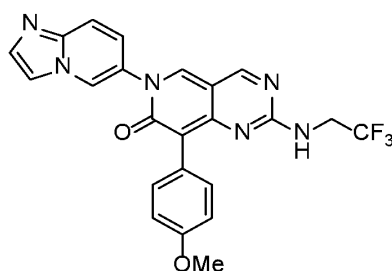
[00338] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 13.37 (s, 1H), 8.97 (s, 1H), 8.92 (s, 1H), 8.60 (t, *J* = 6.4 Hz, 1H), 8.21 (s, 1H), 7.95 (d, *J* = 1.6 Hz, 1H), 7.72-7.65 (m, 3H), 7.48 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 4.16-4.02 (m, 2H). LC-MS: *m/z* 471 [M+H]⁺.

[00339] Preparation of 8-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6b**



[00340] 8-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6b** was synthesized from methyl 2-(4-methoxyphenyl)acetate *via* general procedure III (Step B-E). LC-MS: *m/z* 351 [M+H]⁺.

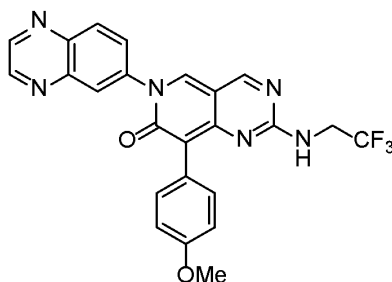
[00341] Example 143: 6-(imidazo[1,2-*a*]pyridin-6-yl)-8-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00342] The title compound was synthesized from intermediate **6b** with 6-bromoimidazo[1,2-*a*]pyridine via *general procedure III* method A (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00343] ¹H NMR (400 MHz, CDCl₃) δ 8.75 (s, 1H), 8.45 (s, 1H), 8.16 (s, 1H), 7.78 (d, *J* = 10.0 Hz, 1H), 7.76 (s, 1H), 7.71-7.65 (m, 3H), 7.25 (dd, *J* = 10.0, 2.0 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 5.81 (t, *J* = 6.4 Hz, 1H), 4.21-4.07 (m, 2H), 3.86 (s, 3H). LC-MS: *m/z* 467 [M+H]⁺.

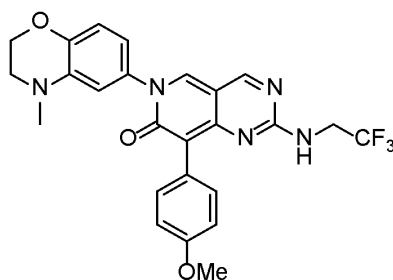
[00344] **Example 144:** 8-(4-methoxyphenyl)-6-(quinoxalin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00345] The title compound was synthesized from intermediate **6b** with 6-bromoquinoxaline via *general procedure III* method A (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00346] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.88 (d, *J* = 2.0 Hz, 1H), 8.86 (d, *J* = 2.0 Hz, 1H), 8.70 (s, 1H), 8.19 (s, 1H), 8.18 (d, *J* = 8.8 Hz, 1H), 8.11 (d, *J* = 2.4 Hz, 1H), 7.91 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.71 (t, *J* = 6.4 Hz, 1H), 4.14-4.03 (m, 2H), 3.79 (s, 3H). LC-MS: *m/z* 479 [M+H]⁺.

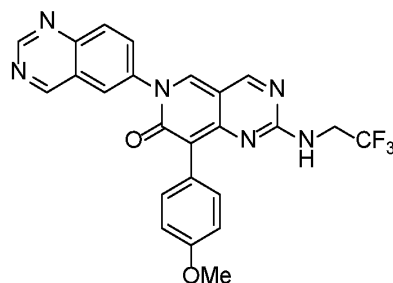
[00347] **Example 145:** 8-(4-methoxyphenyl)-6-(4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00348] The title compound was synthesized from intermediate **6b** with 6-bromo-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00349] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.69 (s, 1H), 8.13 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 1H), 6.61 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 5.72 (t, *J* = 6.4 Hz, 1H), 4.32 (t, *J* = 4.4 Hz, 2H), 4.18-4.06 (m, 2H), 3.84 (s, 3H), 3.31 (t, *J* = 4.4 Hz, 2H), 2.88 (s, 3H). LC-MS: *m/z* 498 [M+H]⁺.

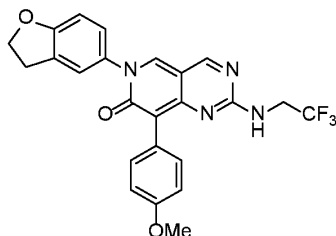
[00350] **Example 146:** 8-(4-methoxyphenyl)-6-(quinazolin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00351] The title compound was synthesized from intermediate **6b** with 6-bromoquinazoline *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00352] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.73 (s, 1H), 9.43 (s, 1H), 9.00 (s, 1H), 8.97 (s, 1H), 8.61 (t, *J* = 6.4 Hz, 1H), 8.44 (d, *J* = 2.0 Hz, 1H), 8.23 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 8.18 (d, *J* = 8.8 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.18-4.04 (m, 2H), 3.78 (s, 3H). LC-MS: *m/z* 479 [M+H]⁺.

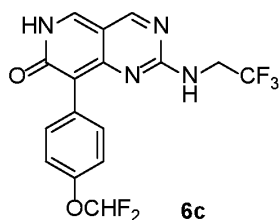
[00353] Example 147: 6-(2,3-dihydrobenzofuran-5-yl)-8-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00354] The title compound was synthesized from intermediate **6b** with 5-bromo-2,3-dihydrobenzofuran *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

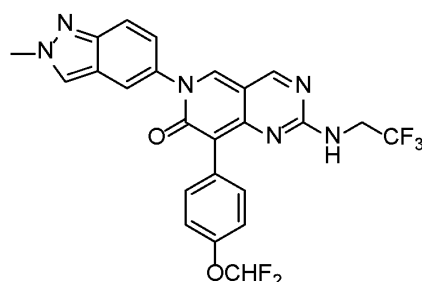
[00355] ¹H NMR (400 MHz, CDCl₃) δ 8.70 (s, 1H), 8.13 (s, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.31 (s, 1H), 7.11 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.69 (t, *J* = 5.6 Hz, 1H), 4.66 (t, *J* = 8.8 Hz, 2H), 4.21-4.07 (m, 2H), 3.85 (s, 3H), 3.27 (t, *J* = 8.8 Hz, 2H). LC-MS: *m/z* 469 [M+H]⁺.

[00356] Preparation of 8-(4-(difluoromethoxy)phenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6c**



[00357] 8-(4-(difluoromethoxy)phenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6c** was synthesized from methyl 2-(4-(difluoromethoxy)phenyl)acetate *via general procedure III* (Step B-E). LC-MS: *m/z* 387 [M+H]⁺.

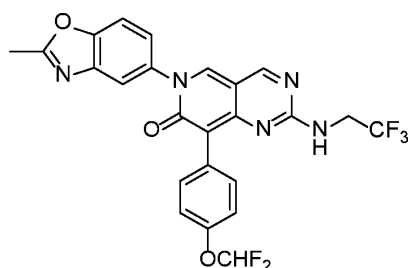
[00358] Example 148: 8-(4-(difluoromethoxy)phenyl)-6-(2-methyl-2*H*-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00359] The title compound was synthesized from intermediate **6c** with 5-bromo-2-methyl-2H-indazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00360] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.97 (s, 1H), 8.90 (s, 1H), 8.57 (t, *J* = 6.4 Hz, 1H), 8.51 (s, 1H), 7.90 (d, *J* = 1.2 Hz, 1H), 7.72-7.69 (m, 3H), 7.34 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 7.26 (t, *J*_{HF} = 74.4 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 2H), 4.22 (s, 3H), 4.15-4.02 (m, 2H). LC-MS: *m/z* 517 [M+H]⁺.

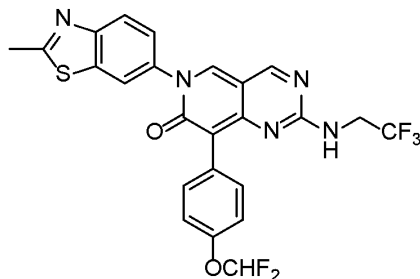
[00361] **Example 149:** 8-(4-(difluoromethoxy)phenyl)-6-(2-methylbenzo[*d*]oxazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00362] The title compound was synthesized from intermediate **6c** with 5-bromo-2-methylbenzo[*d*]oxazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00363] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.97 (s, 1H), 8.89 (s, 1H), 8.59 (t, *J* = 6.0 Hz, 1H), 7.91 (d, *J* = 2.0 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.52 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.26 (t, *J*_{HF} = 74.4 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 2H), 4.15-4.01 (m, 2H), 2.67 (s, 3H). LC-MS: *m/z* 518 [M+H]⁺.

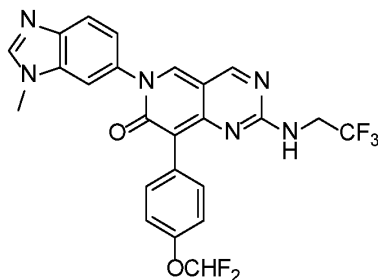
[00364] Example 150: 8-(4-(difluoromethoxy)phenyl)-6-(2-methylbenzo[*d*]thiazol-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00365] The title compound was synthesized from intermediate **6c** with 6-bromo-2-methylbenzo[*d*]thiazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00366] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (s, 1H), 8.94 (s, 1H), 8.63 (t, *J* = 6.4 Hz, 1H), 8.29 (d, *J* = 2.0 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.65 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.27 (t, *J*_{HF} = 74.4 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 2H), 4.15-4.03 (m, 2H), 2.87 (s, 3H). LC-MS: *m/z* 534 [M+H]⁺.

[00367] Example 151: 8-(4-(difluoromethoxy)phenyl)-6-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one

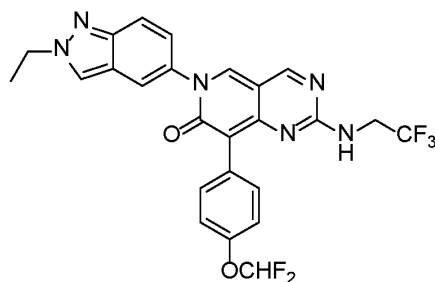


[00368] The title compound was synthesized from intermediate **6c** with 6-bromo-1-methyl-1*H*-benzo[*d*]imidazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00369] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.98 (s, 1H), 8.70 (s, 1H), 8.59 (t, *J* = 6.4 Hz, 1H), 8.35 (br s, 1H), 7.86 (d, *J* = 1.2 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.28 (t, *J*_{HF} =

74.4 Hz, 1H), 7.11 (d, $J = 8.8$ Hz, 2H), 4.15-4.02 (m, 2H), 3.87 (s, 3H). LC-MS: m/z 517 $[M+H]^+$.

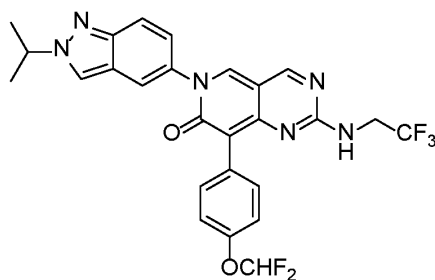
[00370] Example 152: 8-(4-(difluoromethoxy)phenyl)-6-(2-ethyl-2H-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6H)-one



[00371] The title compound was synthesized from intermediate **6c** with 5-bromo-2-ethyl-2H-indazole *via general procedure III* method **A** (CuI, N^1,N^2 -dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00372] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.97 (s, 1H), 8.89 (s, 1H), 8.57 (t, $J = 6.4$ Hz, 1H), 8.56 (s, 1H), 7.90 (d, $J = 1.2$ Hz, 1H), 7.75-7.67 (m, 3H), 7.33 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 7.26 (t, $J_{\text{HF}} = 74.4$ Hz, 1H), 7.11 (d, $J = 8.4$ Hz, 2H), 4.51 (q, $J = 7.2$ Hz, 2H), 4.17-4.02 (m, 2H), 1.54 (t, $J = 7.2$ Hz, 3H). LC-MS: m/z 531 $[M+H]^+$.

[00373] Example 153: 8-(4-(difluoromethoxy)phenyl)-6-(2-isopropyl-2H-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6H)-one

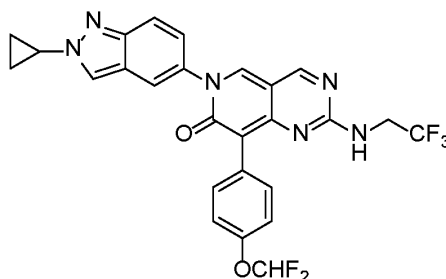


[00374] The title compound was synthesized from intermediate **6c** with 5-bromo-2-isopropyl-2H-indazole *via general procedure III* method **A** (CuI, N^1,N^2 -dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00375] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.97 (s, 1H), 8.88 (s, 1H), 8.58 (s, 1H), 8.57 (t, $J = 6.4$ Hz, 1H), 7.88 (d, $J = 1.6$ Hz, 1H), 7.75-7.67 (m, 3H),

7.32 (dd, $J = 8.8$ Hz, 2.0 Hz, 1H), 7.26 (t, $J_{HF} = 74.4$ Hz, 1H), 7.11 (d, $J = 8.8$ Hz, 2H), 4.89 (hept, $J = 6.8$ Hz, 1H), 4.15-4.02 (m, 2H), 1.58 (d, $J = 6.8$ Hz, 6H). LC-MS: m/z 545 $[M+H]^+$.

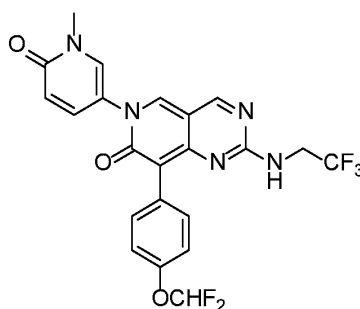
[00376] Example 154: 6-(2-cyclopropyl-2H-indazol-5-yl)-8-(4-(difluoromethoxy)phenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6H)-one



[00377] The title compound was synthesized from intermediate **6c** with 5-bromo-2-cyclopropyl-2H-indazole *via general procedure III* method **A** (CuI, N^1,N^2 -dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00378] ^1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.89 (s, 1H), 8.65 (s, 1H), 8.57 (t, $J = 6.4$ Hz, 1H), 7.87 (d, $J = 1.6$ Hz, 1H), 7.73-7.66 (m, 3H), 7.33 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 7.26 (t, $J_{HF} = 74.4$ Hz, 1H), 7.11 (d, $J = 8.4$ Hz, 2H), 4.27-4.17 (m, 1H), 4.15-4.01 (m, 2H), 1.37-1.28 (m, 2H), 1.19-1.10 (m, 2H). LC-MS: m/z 543 $[M+H]^+$.

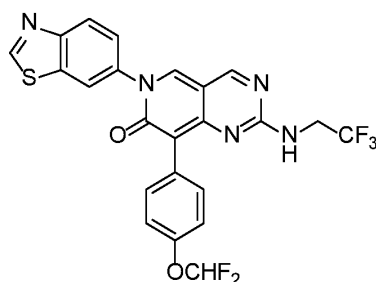
[00379] Example 155: 8-(4-(difluoromethoxy)phenyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6H)-one



The title compound was synthesized from intermediate **6c** with 5-bromo-1-methylpyridin-2(1H)-one *via general procedure III* method **A** (CuI, N^1,N^2 -dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00380] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.95 (s, 1H), 8.86 (s, 1H), 8.66 (t, *J* = 6.4 Hz, 1H), 8.16 (d, *J* = 2.0 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.63 (dd, *J* = 10.0 Hz, 2.8 Hz, 1H), 7.28 (t, *J*_{HF} = 74.4 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 9.2 Hz, 1H), 4.14-4.02 (m, 2H), 3.48 (s, 3H). LC-MS: *m/z* 494 [M+H]⁺.

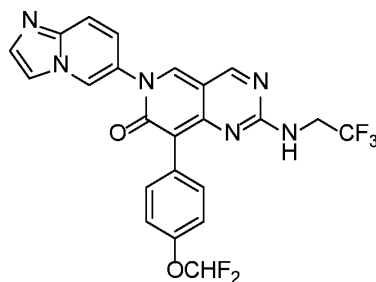
[00381] **Example 156:** 6-(benzo[*d*]thiazol-6-yl)-8-(4-(difluoromethoxy)phenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00382] The title compound was synthesized from intermediate **6c** with 6-bromobenzo[*d*]thiazole *via general procedure III* method **A** (CuI, *N*^l,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00383] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.55 (s, 1H), 8.98 (s, 1H), 8.96 (s, 1H), 8.64 (t, *J* = 6.0 Hz, 1H), 8.44 (d, *J* = 1.2 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 7.78-7.66 (m, 3H), 7.27 (t, *J*_{HF} = 74.4 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 4.18-4.02 (m, 2H). LC-MS: *m/z* 520 [M+H]⁺.

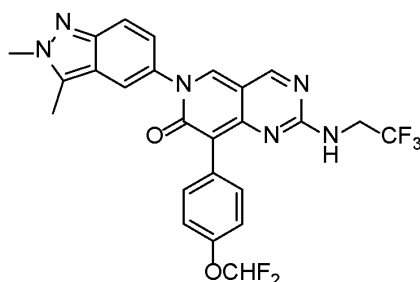
[00384] **Example 157:** 8-(4-(difluoromethoxy)phenyl)-6-(imidazo[1,2-*a*]pyridin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00385] The title compound was synthesized from intermediate **6c** with 6-bromoimidazo[1,2-*a*]pyridine *via general procedure III* method **A** (CuI, *N*^l,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00386] ^1H NMR (400 MHz, DMSO- d_6) δ 9.16 (s, 1H), 9.00 (s, 1H), 8.95 (s, 1H), 8.70 (t, $J = 6.4$ Hz, 1H), 8.27 (s, 1H), 7.91 (s, 1H), 7.90 (d, $J = 9.6$ Hz, 1H), 7.77 (d, $J = 9.2$ Hz, 1H), 7.70 (d, $J = 8.8$ Hz, 2H), 7.27 (t, $J_{\text{HF}} = 74.4$ Hz, 1H), 7.13 (d, $J = 8.8$ Hz, 2H), 4.17-4.03 (m, 2H). LC-MS: m/z 503 $[\text{M}+\text{H}]^+$.

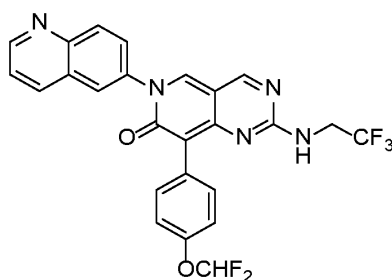
[00387] **Example 158:** 8-(4-(difluoromethoxy)phenyl)-6-(2,3-dimethyl-2H-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3- d]pyrimidin-7(6H)-one



[00388] The title compound was synthesized from intermediate **6c** with 5-bromo-2,3-dimethyl-2H-indazole via *general procedure III* method **A** (CuI, N^1,N^2 -dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00389] ^1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.90 (s, 1H), 8.56 (t, $J = 6.4$ Hz, 1H), 7.89 (d, $J = 1.6$ Hz, 1H), 7.70 (d, $J = 8.8$ Hz, 2H), 7.60 (d, $J = 9.2$ Hz, 1H), 7.29 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 7.27 (t, $J_{\text{HF}} = 74.4$ Hz, 1H), 7.11 (d, $J = 8.8$ Hz, 2H), 4.10 (s, 3H), 4.15-4.02 (m, 2H), 2.64 (s, 3H). LC-MS: m/z 531 $[\text{M}+\text{H}]^+$.

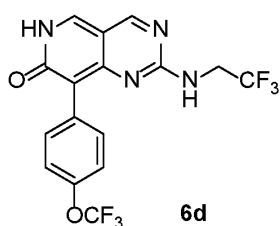
[00390] **Example 159:** 8-(4-(difluoromethoxy)phenyl)-6-(quinolin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3- d]pyrimidin-7(6H)-one



[00391] The title compound was synthesized from intermediate **6c** with 6-bromoquinoline via *general procedure III* method **A** (CuI, N^1,N^2 -dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

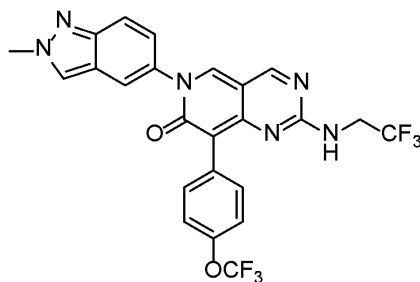
[00392] ^1H NMR (400 MHz, DMSO- d_6) δ 9.03 (s, 1H), 9.01 (s, 1H), 9.00 (s, 1H), 8.85 (t, $J = 6.4$ Hz, 1H), 8.49 (d, $J = 8.0$ Hz, 1H), 8.25 (d, $J = 2.4$ Hz, 1H), 8.17 (d, $J = 8.8$ Hz, 1H), 7.95 (dd, $J = 8.8$ Hz, 2.4 Hz, 1H), 7.73 (d, $J = 8.8$ Hz, 2H), 7.67 (dd, $J = 8.4$ Hz, 4.4 Hz, 1H), 7.27 (t, $J_{\text{HF}} = 74.4$ Hz, 1H), 7.13 (d, $J = 8.8$ Hz, 2H), 4.17-4.03 (m, 2H). LC-MS: m/z 514 $[\text{M}+\text{H}]^+$.

[00393] Preparation of 2-((2,2,2-trifluoroethyl)amino)-8-(4-(trifluoromethoxy)phenyl)pyrido[4,3- d]pyrimidin-7(6H)-one **6d**



[00394] 8-(4-(difluoromethoxy)phenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3- d]pyrimidin-7(6H)-one **6d** was synthesized from methyl 2-(4-(trifluoromethoxy)phenyl)acetate via *general procedure III* (Step B-E). LC-MS: m/z 405 $[\text{M}+\text{H}]^+$.

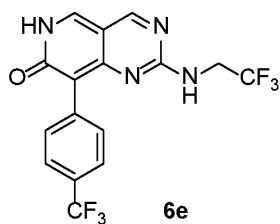
[00395] **Example 160:** Preparation of 6-(2-methyl-2H-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)-8-(4-(trifluoromethoxy)phenyl)pyrido[4,3- d]pyrimidin-7(6H)-one



[00396] The title compound was synthesized from intermediate **6d** with 5-bromo-2-methyl-2H-indazole via *general procedure III* method **A** (CuI, N^1,N^2 -dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

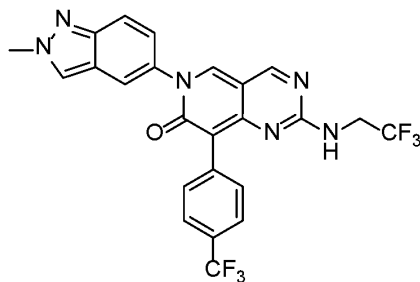
[00397] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.98 (s, 1H), 8.93 (s, 1H), 8.60 (t, $J = 6.0$ Hz, 1H), 8.51 (s, 1H), 7.91 (d, $J = 1.2$ Hz, 1H), 7.76 (d, $J = 8.8$ Hz, 2H), 7.71 (d, $J = 9.1$ Hz, 1H), 7.34 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 7.29 (d, $J = 8.4$ Hz, 2H), 4.22 (s, 3H), 4.14-4.00 (m, 2H). LC-MS: m/z 535 $[\text{M}+\text{H}]^+$.

[00398] Preparation of 2-((2,2,2-trifluoroethyl)amino)-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6e**



[00399] 2-((2,2,2-trifluoroethyl)amino)-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6e** was synthesized from methyl 2-(4-(trifluoromethyl)phenyl)acetate *via general procedure III* (Step B-E). LC-MS: *m/z* 389 [M+H]⁺.

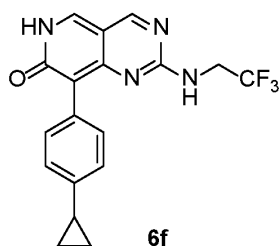
[00400] **Example 161:** Preparation of 6-(2-methyl-2*H*-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00401] The title compound was synthesized from intermediate **6e** with 5-bromo-2-methyl-2*H*-indazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

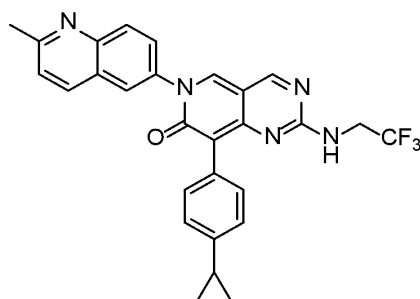
[00402] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.00 (s, 1H), 8.97 (s, 1H), 8.65 (t, *J* = 6.4 Hz, 1H), 8.52 (s, 1H), 7.92 (d, *J* = 1.2 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 9.2 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.35 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 4.23 (s, 3H), 4.13-4.00 (m, 2H). LC-MS: *m/z* 519 [M+H]⁺.

[00403] Preparation of 8-(4-cyclopropylphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6f**



[00404] 8-(4-cyclopropylphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6f** was synthesized from methyl 2-(4-cyclopropylphenyl)acetate *via general procedure III* (Step B-E). LC-MS: *m/z* 361 [M+H]⁺.

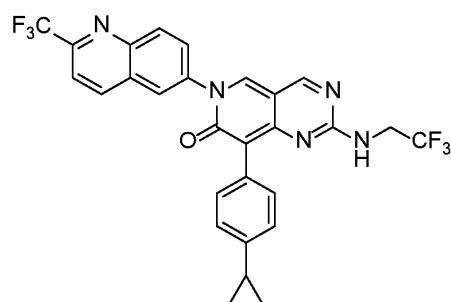
[00405] **Example 162:** Preparation of 8-(4-cyclopropylphenyl)-6-(2-methylquinolin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00406] The title compound was synthesized from intermediate **6f** with 6-bromo-2-methylquinoline *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00407] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.97 (s, 1H), 8.94 (s, 1H), 8.56 (t, *J* = 6.4 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 2.4 Hz, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.86 (dd, *J* = 8.8 Hz, 2.4Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 2H), 4.16-4.03 (m, 2H), 2.71 (s, 3H), 1.98-1.86 (m, 1H), 0.99-0.91 (m, 2H), 0.71-0.63 (m, 2H). LC-MS: *m/z* 520 [M+H]⁺.

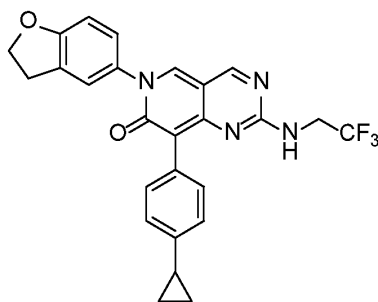
[00408] **Example 163:** 8-(4-cyclopropylphenyl)-2-((2,2,2-trifluoroethyl)amino)-6-(2-(trifluoromethyl)quinolin-6-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00409] The title compound was synthesized from intermediate **6f** with 6-bromo-2-(trifluoromethyl)quinoline *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00410] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.99 (s, 1H), 8.98 (s, 1H), 8.83 (d, *J* = 8.4 Hz, 1H), 8.60 (t, *J* = 6.4 Hz, 1H), 8.43 (d, *J* = 2.0 Hz, 1H), 8.33 (d, *J* = 9.2 Hz, 1H), 8.14-8.07 (m, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 4.17-4.04 (m, 2H), 1.97-1.88 (m, 1H), 0.99-0.92 (m, 2H), 0.70-0.63 (m, 2H). LC-MS: *m/z* 556 [M+H]⁺.

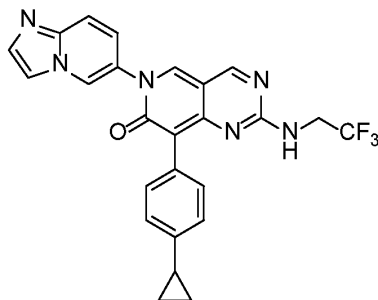
[00411] **Example 164:** 8-(4-cyclopropylphenyl)-6-(2,3-dihydrobenzofuran-5-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00412] The title compound was synthesized from intermediate **6f** with 5-bromo-2,3-dihydrobenzofuran *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00413] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.99 (s, 1H), 8.82 (s, 1H), 8.54 (t, *J* = 6.4 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.45 (s, 1H), 7.28 (dd, *J* = 8.5 Hz, 2.4 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 1H), 4.69 (t, *J* = 8.8 Hz, 2H), 4.21-4.06 (m, 2H), 3.31 (t, *J* = 8.8 Hz, 2H), 2.03-1.93 (m, 1H), 1.05-0.97 (m, 2H), 0.77-0.66 (m, 2H). LC-MS: *m/z* 479 [M+H]⁺.

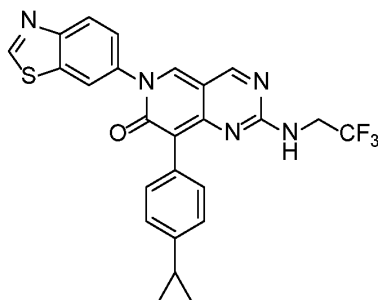
[00414] Example 165: 8-(4-cyclopropylphenyl)-6-(imidazo[1,2-*a*]pyridin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00415] The title compound was synthesized from intermediate **6f** with 6-bromoimidazo[1,2-*a*]pyridine *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00416] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.96 (d, *J* = 1.2 Hz, 1H), 8.95 (s, 1H), 8.92 (s, 1H), 8.59 (t, *J* = 6.4 Hz, 1H), 8.06 (s, 1H), 7.71 (s, 1H) 7.69 (d, *J* = 9.2 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.41 (dd, *J* = 9.6 Hz, 2.0 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 2H), 4.17-4.03 (m, 2H), 1.98-1.88 (m, 1H), 0.99-0.91 (m, 2H), 0.71-0.62 (m, 2H). LC-MS: *m/z* 477 [M+H]⁺.

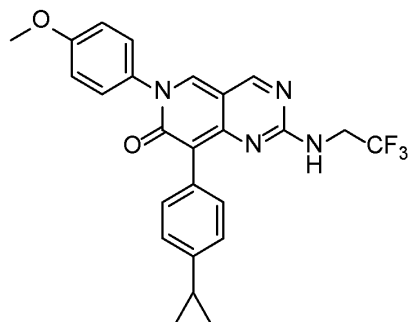
[00417] Example 166: 6-(benzo[*d*]thiazol-6-yl)-8-(4-cyclopropylphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00418] The title compound was synthesized from intermediate **6f** with 6-bromobenzo[*d*]thiazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00419] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.54 (s, 1H), 8.95 (s, 1H), 8.90 (s, 1H), 8.56 (t, *J* = 6.4 Hz, 1H), 8.42 (d, *J* = 2.0 Hz, 1H), 8.24 (d, *J* = 8.8 Hz, 1H), 7.71 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 4.18-4.01 (m, 2H), 1.98-1.86 (m, 1H), 0.99-0.89 (m, 2H), 0.71-0.63 (m, 2H). LC-MS: *m/z* 494 [M+H]⁺.

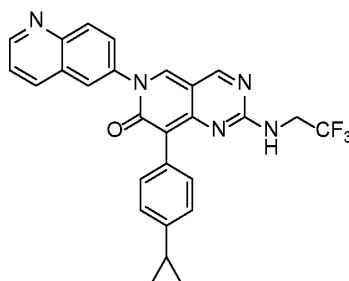
[00420] **Example 167:** 8-(4-cyclopropylphenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00421] The title compound was synthesized from intermediate **6f** with 1-bromo-4-methoxybenzene *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00422] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.94 (s, 1H), 8.77 (s, 1H), 8.49 (t, *J* = 6.4 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 4.14-4.00 (m, 2H), 3.83 (s, 3H), 1.97-1.87 (m, 1H), 0.99-0.91 (m, 2H), 0.70-0.63 (m, 2H). LC-MS: *m/z* 467 [M+H]⁺.

[00423] **Example 168:** 8-(4-cyclopropylphenyl)-6-(quinolin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one

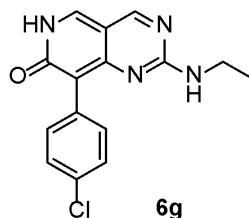


[00424] The title compound was synthesized from intermediate **6f** with 6-bromoquinoline *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00425] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.03 (dd, *J* = 4.4 Hz, 1.6 Hz, 1H), 8.98 (s, 1H), 8.96 (s, 1H), 8.58 (t, *J* = 6.4 Hz, 1H), 8.48 (dd, *J* = 8.4, 1.7 Hz, 1H), 8.24 (d, *J* = 2.0 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 7.93 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.66 (dd, *J* = 8.4 Hz, 4.4 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* =

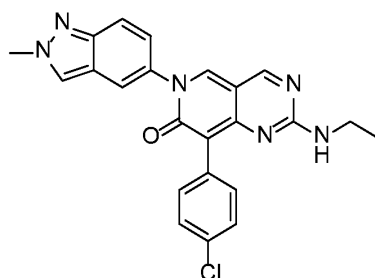
8.4 Hz, 2H), 4.17-4.04 (m, 2H), 1.98-1.89 (m, 1H), 1.00-0.91 (m, 2H), 0.72-0.63 (m, 2H). LC-MS: m/z 488 $[M+H]^+$.

[00426] Preparation of 8-(4-chlorophenyl)-2-(ethylamino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6g**



[00427] 8-(4-chlorophenyl)-2-(ethylamino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6g** was synthesized from ethanamine *via general procedure III* (Step D, E). LC-MS: m/z 301 $[M+H]^+$.

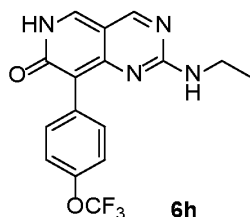
[00428] **Example 169:** Preparation of 8-(4-chlorophenyl)-2-(ethylamino)-6-(2-methyl-2*H*-indazol-5-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00429] The title compound was synthesized from intermediate **6g** with 5-bromo-2-methyl-2*H*-indazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, Cs₂CO₃, 1,4-dioxane, 100°C).

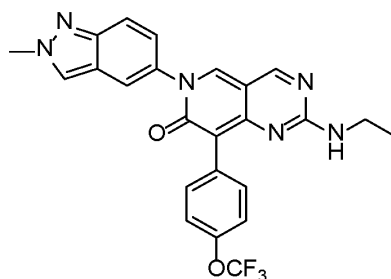
[00430] ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.86 (s, 1H), 8.77 (s, 1H), 8.49 (s, 1H), 8.07 (t, J = 5.6 Hz, 1H), 7.87 (d, J = 1.2 Hz, 1H), 7.71 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 9.2 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.31 (dd, J = 9.2 Hz, 2.0 Hz, 1H), 4.22 (s, 3H), 3.30-3.20 (m, 2H), 1.11 (t, J = 7.2 Hz, 1H) LC-MS: m/z 431 $[M+H]^+$.

[00431] Preparation of 2-(ethylamino)-8-(4-(trifluoromethoxy)phenyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6h**



[00432] 2-(ethylamino)-8-(4-(trifluoromethoxy)phenyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6h** was synthesized from methyl 2-(4-(trifluoromethoxy)phenyl)acetate *via general procedure III* (Step B-E). LC-MS: *m/z* 351 [M+H]⁺.

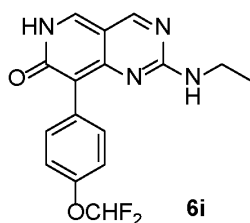
[00433] **Example 170:** Preparation of 2-(ethylamino)-6-(2-methyl-2*H*-indazol-5-yl)-8-(4-(trifluoromethoxy)phenyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00434] The title compound was synthesized from intermediate **6h** with 5-bromo-2-methyl-2*H*-indazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

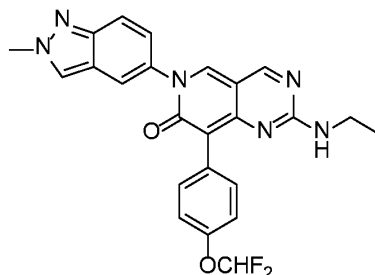
[00435] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.86 (s, 1H), 8.78 (s, 1H), 8.50 (s, 1H), 8.09 (t, *J* = 5.6 Hz, 1H), 7.88 (d, *J* = 1.2 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 9.2 Hz, 1H), 7.32 (dd, *J* = 9.2 Hz, 1.2 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 4.22 (s, 3H), 3.30-3.20 (m, 2H), 1.10 (t, *J* = 6.8 Hz, 3H). LC-MS: *m/z* 481 [M+H]⁺.

[00436] Preparation of 8-(4-(difluoromethoxy)phenyl)-2-(ethylamino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6i**



[00437] 8-(4-(difluoromethoxy)phenyl)-2-(ethylamino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6i** was synthesized from methyl 2-(4-(difluoromethoxy)phenyl)acetate *via general procedure III* (Step B-E). LC-MS: *m/z* 333 [M+H]⁺.

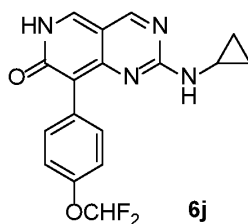
[00438] Preparation of 8-(4-(difluoromethoxy)phenyl)-2-(ethylamino)-6-(2-methyl-2H-indazol-5-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 171**)



[00439] The title compound was synthesized from intermediate **6i** with 5-bromo-2-methyl-2*H*-indazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

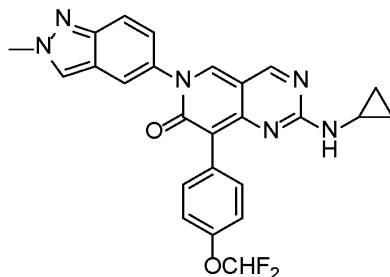
[00440] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.85 (s, 1H), 8.76 (s, 1H), 8.49 (s, 1H), 8.04 (t, *J* = 5.6 Hz, 1H), 7.87 (d, *J* = 1.2 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 9.2 Hz, 1H), 7.31 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.26 (t, *J*_{HF} = 74.4 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 4.22 (s, 3H), 3.31-3.15 (m, 2H), 1.11 (t, *J* = 7.2 Hz, 3H). LC-MS: *m/z* 463 [M+H]⁺.

[00441] Preparation of 2-(cyclopropylamino)-8-(4-(difluoromethoxy)phenyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6j**



[00442] 2-(cyclopropylamino)-8-(4-(difluoromethoxy)phenyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6j** was synthesized from cyclopropanamine *via general procedure III* (Step D, E). LC-MS: *m/z* 345 [M+H]⁺.

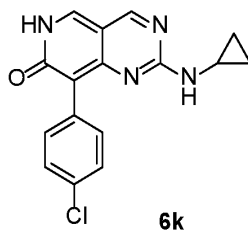
[00443] Example 172: Preparation of 2-(cyclopropylamino)-8-(4-(difluoromethoxy)phenyl)-6-(2-methyl-2H-indazol-5-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00444] The title compound was synthesized from intermediate **6j** with 5-bromo-2-methyl-2*H*-indazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

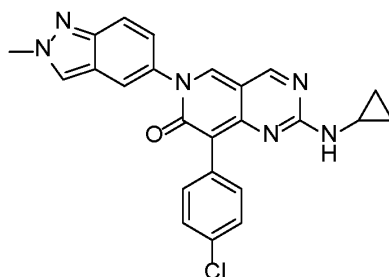
[00445] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.90 (s, 1H), 8.83 (s, 1H), 8.55 (s, 1H), 8.25 (d, *J* = 4.0 Hz, 1H), 7.97-7.87 (m, 3H), 7.76 (d, *J* = 9.2 Hz, 1H), 7.38 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 7.30 (t, *J*_{HF} = 74.4 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 4.18 (s, 3H), 2.87-2.76 (m, 1H), 0.77-0.70 (m, 2H), 0.66-0.58 (m, 2H). LC-MS: *m/z* 475 [M+H]⁺.

[00446] Preparation of 8-(4-chlorophenyl)-2-(cyclopropylamino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6k**



[00447] 8-(4-chlorophenyl)-2-(cyclopropylamino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6k** was synthesized from cyclopropanamine *via general procedure III* (Step D, E). LC-MS: *m/z* 313 [M+H]⁺.

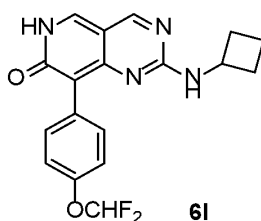
[00448] Example 173: Preparation of 8-(4-chlorophenyl)-2-(cyclopropylamino)-6-(2-methyl-2*H*-indazol-5-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00449] The title compound was synthesized from intermediate **6k** with 5-bromo-2-methyl-2H-indazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

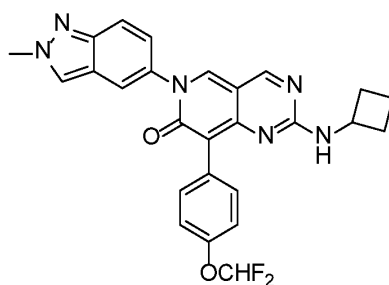
[00450] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.85 (s, 1H), 8.79 (s, 1H), 8.50 (s, 1H), 8.22 (d, *J* = 4.0 Hz, 1H), 7.88 (d, *J* = 1.6 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 9.2 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.33 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 4.23 (s, 3H), 2.82-2.73 (m, 1H), 0.73-0.64 (m, 2H), 0.59-0.53 (m, 2H). LC-MS: *m/z* 443 [M+H]⁺.

[00451] Preparation of 2-(cyclobutylamino)-8-(4-(difluoromethoxy)phenyl)pyrido[4,3-*d*]pyrimidin-7(6H)-one **6l**



[00452] 2-(cyclobutylamino)-8-(4-(difluoromethoxy)phenyl)pyrido[4,3-*d*]pyrimidin-7(6H)-one **6l** was synthesized from cyclobutanamine *via general procedure III* (Step D, E). LC-MS: *m/z* 359 [M+H]⁺.

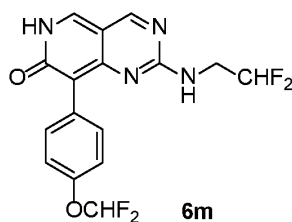
[00453] **Example 174:** Preparation of 2-(cyclobutylamino)-8-(4-(difluoromethoxy)phenyl)-6-(2-methyl-2H-indazol-5-yl)pyrido[4,3-*d*]pyrimidin-7(6H)-one



[00454] The title compound was synthesized from intermediate **6l** with 5-bromo-2-methyl-2H-indazole *via general procedure III* method **A** (CuI, *N*^l,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

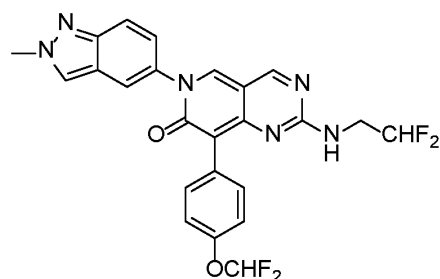
[00455] ¹HNMR (400 MHz, DMSO-*d*₆) δ: 8.86 (s, 1H), 8.76 (s, 1H), 8.49 (s, 1H), 8.33 (d, *J* = 6.8 Hz, 1H), 7.82 (d, *J* = 1.2 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 9.2 Hz, 1H), 7.31 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 7.27 (t, *J*_{HF} = 74.4 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 4.22 (s, 3H), 4.23-4.11 (m, 1H), 2.23-2.11 (m, 2H), 2.09-1.93 (m, 2H). LC-MS: *m/z* 489 [M+H]⁺.

[00456] Preparation of 2-((2,2-difluoroethyl)amino)-8-(4-(difluoromethoxy)phenyl)pyrido[4,3-*d*]pyrimidin-7(6H)-one **6m**



[00457] 2-((2,2-difluoroethyl)amino)-8-(4-(difluoromethoxy)phenyl)pyrido[4,3-*d*]pyrimidin-7(6H)-one **6m** was synthesized from 2,2-difluoroethanamine *via general procedure III* (Step D, E). LC-MS: *m/z* 369 [M+H]⁺.

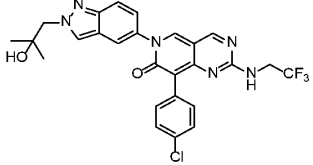
[00458] **Example 175:** Preparation of 2-((2,2-difluoroethyl)amino)-8-(4-(difluoromethoxy)phenyl)-6-(2-methyl-2H-indazol-5-yl)pyrido[4,3-*d*]pyrimidin-7(6H)-one

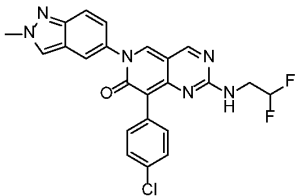


[00459] The title compound was synthesized from intermediate **6m** with 5-bromo-2-methyl-2*H*-indazole *via general procedure III* method **A** (CuI, *N*¹,*N*²-dimethylcyclohexane-1,2-diamine, CsF, 1,4-dioxane, 100°C).

[00460] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.94 (s, 1H), 8.87 (s, 1H), 8.51 (s, 1H), 7.89 (d, *J* = 1.2 Hz, 1H), 7.70 (d, *J* = 9.2 Hz, 3H), 7.32 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 7.25 (t, *J*_{HF} = 74.4 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.12 (tt, *J*_{HF} = 56.4 Hz, 4.0 Hz, 1H), 4.22 (s, 3H), 3.60 (dt, *J*_{HF} = 14.8 Hz, 4.0 Hz, 2H). LC-MS: *m/z* 499 [M+H]⁺.

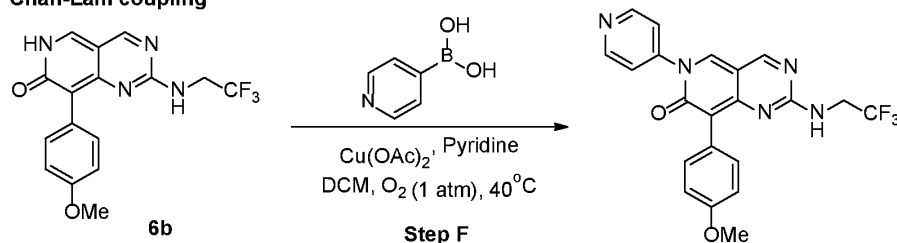
[00461] The following compounds were synthesized via general procedure III method **A**:

101-A	 8-(4-chlorophenyl)-6-(2-(2-hydroxy-2-methylpropyl)-2<i>H</i>-indazol-5-yl)-2-(2,2,2-trifluoroethylamino)pyrido[4,3-<i>d</i>]pyrimidin-7(6<i>H</i>)-one (synthesized from 8-(4-chlorophenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-<i>d</i>]pyrimidin-7(6<i>H</i>)-one & 1-(5-bromo-2<i>H</i>-indazol-2-yl)-2-methylpropan-2-ol	LC-MS (ESI) : <i>m/z</i> 543 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) (ratio of tautomers 7:1) δ 9.05 (s, 0.15H), 8.99 (s, 0.15H), 8.97 (s, 0.85H), 8.93 (s, 0.85H), 8.59 (t, <i>J</i> = 6.5 Hz, 1H), 8.46 (d, <i>J</i> = 1.0 Hz, 1H), 7.92 (dd, <i>J</i> = 2.0, 0.8 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.70 – 7.66 (m, 1.75H), 7.55 (d, <i>J</i> = 8.3 Hz, 0.25H), 7.40 (d, <i>J</i> = 8.2 Hz, 0.25H), 7.36 (dd, <i>J</i> = 8.2, 1.6 Hz, 1.75H), 7.34 – 7.31 (m, 1H), 4.89 (s, 1H), 4.39 (s, 2H), 4.23 (s, 0.25H),
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	(Ref: <i>Organic Letters</i> , 16 (11), 3114-3117; 2014))	4.08 (p, J = 9.3 Hz, 1.75H), 1.13 (s, 6H).
102-A	 8-(4-chlorophenyl)-2-(2,2-difluoroethylamino)-6-(2-methyl-2H-indazol-5-yl)pyrido[4,3-d]pyrimidin-7(6H)-one	LC-MS (ESI) : m/z 467 $[M+H]^+$. ¹ H NMR (400 MHz,) δ 8.94 (s, 1H), 8.88 (s, 1H), 8.50 (s, 1H), 8.38 (t, J = 6.0 Hz, 1H), 7.89 (d, J = 1.9 Hz, 1H), 7.70 (dd, J = 8.8, 6.8 Hz, 3H), 7.41 – 7.27 (m, 3H), 6.12 (tt, JHF = 56.3, J = 4.1 Hz, 1H), 4.22 (s, 3H), 3.70 – 3.54 (m, 2H). (Tautomer Ratio 10:1. Only major peaks reported)

[00462] Step F: (Method B: Chan-Lam coupling). 8-(4-methoxyphenyl)-6-(pyridin-4-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 176**)

Method B:
Chan-Lam coupling

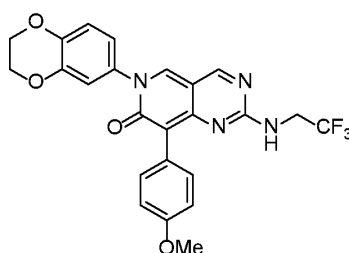


[00463] **Example 176:** A mixture of 8-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (70.0 mg, 0.2 mmol, 1.0 equiv), pyridin-4-ylboronic acid (50.0 mg, 0.4 mmol, 2.0 equiv), copper acetate (73.0 mg, 0.4 mmol, 2.0 equiv) and pyridine (63.0 mg, 0.8 mmol, 4.0 equiv) in DCM (3.0 mL) was stirred at 40°C overnight under an atmosphere of O₂. After this time, the reaction mixture was diluted with DCM (10.0 mL), washed with H₂O (10 mL x 3), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by Prep-HPLC to yield 8-(4-methoxyphenyl)-

6-(pyridin-4-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one

[00464] ^1H NMR (400 MHz, CDCl_3) δ : 8.82 (d, $J = 6.0$ Hz, 2H), 8.75 (s, 1H), 8.08 (s, 1H), 7.68 (d, $J = 9.2$ Hz, 2H), 7.48 (d, $J = 6.4$ Hz, 2H), 6.96 (d, $J = 8.8$ Hz, 2H), 5.81 (t, $J = 6.8$ Hz, 1H), 4.19-4.08 (m, 2H), 3.82 (s, 3H). LC-MS: m/z 428 $[\text{M}+\text{H}]^+$.

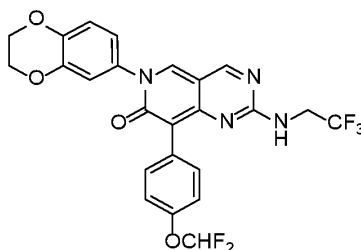
[00465] **Example 177:** Preparation of 6-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-8-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00466] The title compound was synthesized from intermediate **6b** with (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid *via general procedure III* method **B** ($\text{Cu}(\text{OAc})_2$, Pyridine, DCM, O_2 (1 atm), 40°C).

[00467] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.93 (s, 1H), 8.74 (s, 1H), 8.49 (t, $J = 6.4$ Hz, 1H), 7.58 (t, $J = 8.8$ Hz, 2H), 7.10 (d, $J = 2.0$ Hz, 1H), 7.01 (s, 1H), 7.00 (d, $J = 2.4$ Hz, 1H), 6.87 (d, $J = 8.8$ Hz, 2H), 4.32 (s, 4H), 4.15-4.01 (m, 2H), 3.78 (s, 3H). LC-MS: m/z 485 $[\text{M}+\text{H}]^+$.

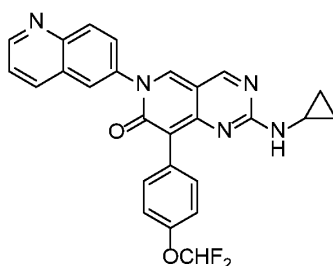
[00468] **Example 178:** 8-(4-(difluoromethoxy)phenyl)-6-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00469] The title compound was synthesized from intermediate **6c** with (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid *via general procedure III* method **B** (Cu(OAc)₂, Pyridine, DCM, O₂ (1 atm), 40°C).

[00470] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.94 (s, 1H), 8.79 (s, 1H), 8.56 (t, *J* = 6.4 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.26 (t, *J*_{HF} = 74.4 Hz, 1H), 7.11 (d, *J* = 2.8 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.12-7.01 (m, 2H), 4.31 (s, 4H), 4.12-4.03 (m, 2H). LC-MS: *m/z* 521 [M+H]⁺.

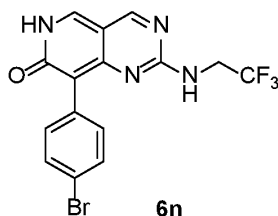
[00471] **Example 179:** 2-(cyclopropylamino)-8-(4-(difluoromethoxy)phenyl)-6-(quinolin-6-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00472] The title compound was synthesized from intermediate **6j** with quinolin-6-ylboronic acid *via general procedure III* method **B** (Cu(OAc)₂, Pyridine, DCM, O₂ (1 atm), 40°C).

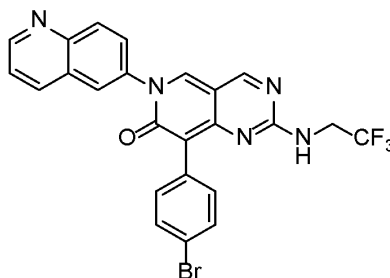
[00473] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.02 (dd, *J* = 4.0 Hz, 1.6 Hz, 1H), 8.88 (s, 1H), 8.87 (s, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 8.27 (d, *J* = 4.4 Hz, 1H), 8.23 (d, *J* = 2.4 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 7.93 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.66 (dd, *J* = 8.8 Hz, 4.4 Hz, 1H), 7.26 (t, *J*_{HF} = 74.4 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 2.83-2.74 (m, 1H), 0.74-0.65 (m, 2H), 0.62-0.53 (m, 2H). LC-MS: *m/z* 472 [M+H]⁺.

[00474] Preparation of 8-(4-bromophenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6n**



[00475] 8-(4-bromophenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **6n** was synthesized from methyl 2-(4-bromophenyl)acetate *via general procedure III* (Step B-E). LC-MS: *m/z* 399, 401 [M+H]⁺.

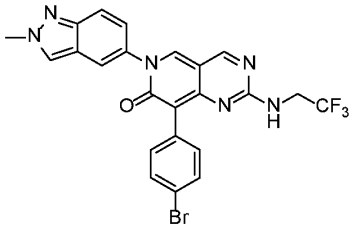
[00476] **Example 180:** Preparation of 8-(4-bromophenyl)-6-(quinolin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00477] The title compound was synthesized from intermediate **6n** with quinolin-6-ylboronic acid *via general procedure III* method **B** (Cu(OAc)₂, Pyridine, DCM, O₂ (1 atm), 40°C).

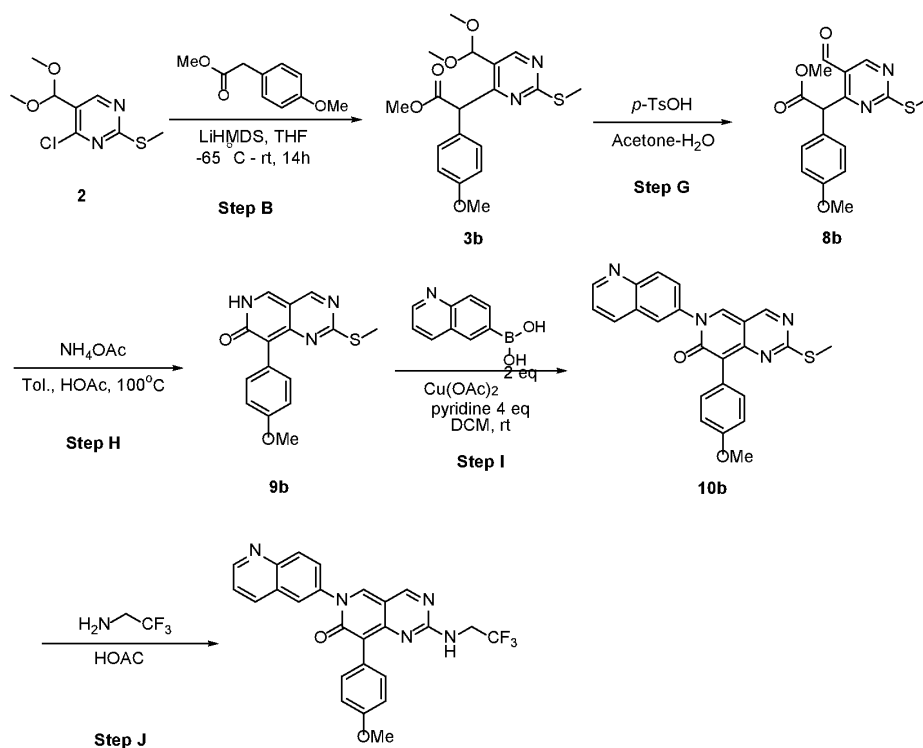
[00478] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.03 (d, *J* = 4.0 Hz, 1H), 9.02 (s, 1H), 9.00 (s, 1H), 8.68 (t, *J* = 6.0 Hz, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 2.0 Hz, 1H), 8.17 (d, *J* = 9.2 Hz, 1H), 7.94 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 7.69-7.61 (m, 3H), 7.51 (d, *J* = 8.8 Hz, 2H), 4.17-4.03 (m, 2H). LC-MS: *m/z* 526, 528 [M+H]⁺.

[00479] The following compound was synthesized via general procedure III (alternate route; steps G – J):

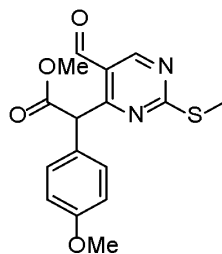
103-A	 8-(4-bromophenyl)-6-(2-methyl-2H-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-<i>d</i>]pyrimidin-7(6<i>H</i>)-one	LC-MS (ESI) : <i>m/z</i> 529 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.96 (s, 1H), 8.82 (d, <i>J</i> = 2.5 Hz, 1H), 8.45 (s, 1H), 7.86 (s, 1H), 7.69 (d, <i>J</i> = 9.1 Hz, 1H), 7.58 (d, <i>J</i> = 8.1 Hz, 2H), 7.48 (d, <i>J</i> = 8.3 Hz,
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		2H), 7.31 (dd, J = 9.1, 2.0 Hz, 1H), 4.19 (s, 3H), 4.05 (q, J = 9.6 Hz, 2H). (Tautomer Ratio 6:1. Only major peaks reported)
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[00480] Preparation of **Example 181**:

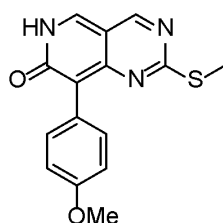


[00481] **Step G:** methyl 2-(5-formyl-2-(methylthio)pyrimidin-4-yl)-2-(4-methoxyphenyl)acetate



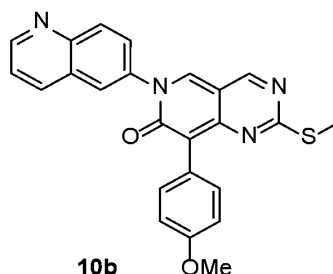
[00482] To a solution of methyl 2-(5-(dimethoxymethyl)-2-(methylthio)pyrimidin-4-yl)-2-(4-methoxyphenyl)acetate (570 mg, 1.5 mmol 1.0 equiv) in Acetone/H₂O (5.0 / 5.0 mL) was added *p*-TsOH (77 mg, 0.45 mmol 0.3 equiv). The mixture was then stirred at 70°C for 2h. The resulting mixture was extracted with DCM. The organic layer was dried over Na₂SO₄, filtered and concentrated under vacuum to give the desired product (450 mg, 90% yield) as a yellow oil. LC-MS (ESI): *m/z* 333 [M+H]⁺.

[00483] Step H: 8-(4-methoxyphenyl)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



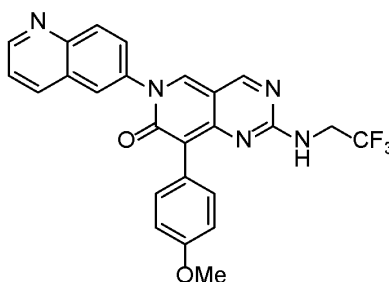
[00484] To a mixture of 2-(5-formyl-2-(methylthio)pyrimidin-4-yl)-2-(4-methoxyphenyl)acetate (450 mg, 1.35 mmol 1.0 equiv) in toluene/HOAc (5.0 / 5.0 mL) was added NH₄OAc (2.7 g, 350.6 mmol 26.0 equiv). The resulting mixture was stirred at 100°C for 5h. At this point, the mixture was concentrated under vacuum and diluted with DCM and H₂O. The aqueous layer was extracted with DCM (10.0 mL x 2), and the combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel eluting with (DCM/MeOH=150:1~50:1) to afford the desired product (180 mg, 44% yield) as a brown solid. LC-MS (ESI): *m/z* 300 [M+H]⁺.

[00485] Step I: 8-(4-methoxyphenyl)-2-(methylthio)-6-(quinolin-6-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00486] To a solution of 8-(4-methoxyphenyl)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (210.0 mg, 0.7 mmol, 1.0 equiv) in DCM (5.0 mL) was added quinolin-6-ylboronic acid (240 mg, 1.4 mmol, 2.0 equiv), Cu(OAc)₂ (250 mg, 1.4 mmol, 2.0 equiv) and pyridine (221 mg, 2.8 mmol 4.0 equiv). The mixture was stirred at 40°C under O₂ (1 atm) overnight. The solvent was removed under vacuum, and the residue was diluted with DCM and H₂O. The aqueous layer was extracted with DCM (10.0 mL x 2), and the combined organic layers were dried over Na₂SO₄ and concentrated to give a brown oil. The residue was purified by flash chromatography on silica gel eluting with (DCM/MeOH=200:1~50:1) to afford the desired product (250 mg, 83% yield) as a brown solid. LC-MS (ESI): *m/z* 427 [M+H]⁺.

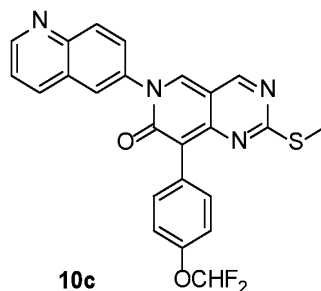
[00487] Step J: 8-(4-methoxyphenyl)-6-(quinolin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 181**)



[00488] To a solution of 8-(4-methoxyphenyl)-2-(methylthio)-6-(quinolin-6-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (63 mg, 0.15 mmol, 1.0 equiv) in HOAc (1.0 mL) was added 2,2,2-trifluoroethanamine (300 mg, 3.0 mmol, 20.0 equiv). Then the mixture was sealed and stirred at 100°C overnight. The resulting mixture was concentrated to give a brown oil and purified by flash column chromatography on silica gel to yield 8-(4-methoxyphenyl)-6-(quinolin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 181**)

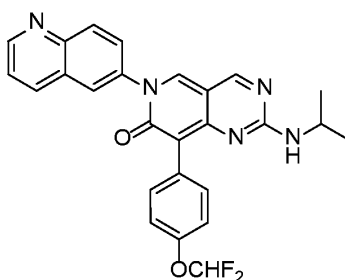
[00489] ¹H NMR (400 MHz, CDCl₃) δ 9.02 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.76 (s, 1H), 8.28 – 8.16 (m, 3H), 7.95 (d, *J* = 2.4 Hz, 1H), 7.82 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.51 (dd, *J* = 8.3, 4.3 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 2H), 5.74 (t, *J* = 6.4 Hz, 1H), 4.16 (q, *J* = 8.3 Hz, 2H), 3.85 (s, 3H). LC-MS: *m/z* 478 [M+H]⁺.

[00490] Preparation of 8-(4-(difluoromethoxy)phenyl)-2-(methylthio)-6-(quinolin-6-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **10c**



[00491] 8-(4-(difluoromethoxy)phenyl)-2-(methylthio)-6-(quinolin-6-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **10c** was synthesized from methyl 2-(4-(difluoromethoxy)phenyl)acetate *via general procedure III* (Step B, G-J). LC-MS: *m/z* 463 [M+H]⁺

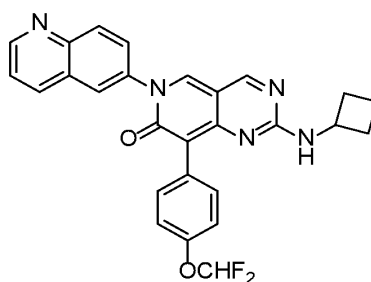
[00492] **Example 182:** Preparation of 8-(4-(difluoromethoxy)phenyl)-2-(isopropylamino)-6-(quinolin-6-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00493] The title compound was synthesized from intermediate **10c** with propan-2-amine in the procedure for **Example 181** Step J (HOAc, 100°C).

[00494] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.02 (dd, *J* = 4.4 Hz, 2.0 Hz, 1H), 8.88 (s, 1H), 8.86 (s, 1H), 8.48 (d, *J* = 7.6 Hz, 1H), 8.22 (d, *J* = 2.4 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 1H), 7.93 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.66 (dd, *J* = 8.4 Hz, 4.4 Hz, 1H) 7.27 (t, *J*_{HF} = 74.4 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 4.00-3.90 (m, 1H), 1.16 (d, *J* = 6.4 Hz, 6H). LC-MS: *m/z* 474 [M+H]⁺.

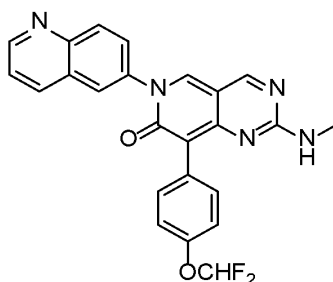
[00495] **Example 183:** 2-(cyclobutylamino)-8-(4-(difluoromethoxy)phenyl)-6-(quinolin-6-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00496] The title compound was synthesized from intermediate **10c** with cyclobutanamine in the procedure for **Example 181** Step J (HOAc, 100°C).

[00497] ^1H NMR (400 MHz, DMSO- d_6) δ : 9.02 (dd, $J = 4.0$ Hz, 1.6 Hz, 1H), 8.88 (s, 1H), 8.86 (s, 1H), 8.47 (d, $J = 8.4$ Hz, 1H), 8.42 (d, $J = 6.4$ Hz, 1H), 8.22 (d, $J = 2.0$ Hz, 1H), 8.15 (d, $J = 8.4$ Hz, 1H), 7.92 (dd, $J = 9.2$ Hz, 2.4 Hz, 1H), 7.74 (d, $J = 8.8$ Hz, 2H), 7.65 (dd, $J = 8.4$ Hz, 4.0 Hz, 1H), 7.27 (t, $J_{\text{HF}} = 74.4$ Hz, 1H), 7.15 (d, $J = 8.8$ Hz, 2H), 4.25-4.12 (m, 1H), 2.23-2.12 (m, 2H), 2.09-1.92 (m, 2H), 1.71-1.54 (m, 2H). LC-MS: m/z 486 $[\text{M}+\text{H}]^+$.

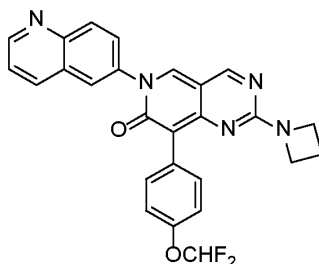
[00498] **Example 184:** 8-(4-(difluoromethoxy)phenyl)-2-(methylamino)-6-(quinolin-6-yl)pyrido[4,3-*d*]pyrimidin-7(6H)-one



[00499] The title compound was synthesized from intermediate **10c** with methylamine hydrochloride in the procedure for **Example 181** Step J (HOAc, 100°C).

[00500] ^1H NMR (400 MHz, DMSO- d_6) δ : 9.02 (dd, $J = 4.0$ Hz, 1.6 Hz, 1H), 8.88 (s, 1H), 8.87 (s, 1H), 8.47 (d, $J = 8.0$ Hz, 1H), 8.23 (d, $J = 2.0$ Hz, 1H), 8.15 (d, $J = 9.2$ Hz, 1H), 8.07-8.02 (m, 1H), 7.93 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 7.79 (d, $J = 8.8$ Hz, 2H), 7.66 (dd, $J = 8.4$ Hz, 4.0 Hz, 1H), 7.27 (t, $J_{\text{HF}} = 74.6$ Hz, 1H), 7.14 (d, $J = 8.8$ Hz, 2H), 2.82 (d, $J = 5.6$ Hz, 3H). LC-MS: m/z 446 $[\text{M}+\text{H}]^+$.

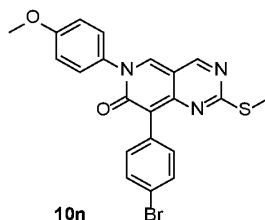
[00501] Example 185: 2-(azetidin-1-yl)-8-(4-(difluoromethoxy)phenyl)-6-(quinolin-6-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00502] The title compound was synthesized from intermediate **10c** with azetidine in the procedure for **Example 181** Step J (HOAc, 100°C).

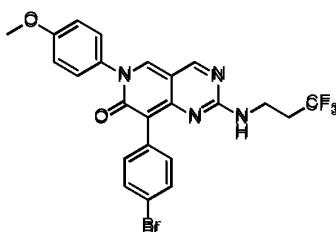
[00503] ^1H NMR (400 MHz, DMSO-*d*₆) δ : 9.02 (dd, $J = 4.4$ Hz, 1.6Hz, 1H), 8.945 (s, 1H), 8.944 (s, 1H), 8.47 (d, $J = 7.6$ Hz, 1H), 8.23 (d, $J = 2.0$ Hz, 1H), 8.14 (d, $J = 8.8$ Hz, 1H), 7.93 (dd, $J = 8.4$ Hz, 2.0 Hz, 1H), 7.76 (d, $J = 8.8$ Hz, 2H), 7.65 (dd, $J = 8.4$ Hz, 4.4 Hz, 1H), 7.26 (t, $J_{\text{HF}} = 74.4$ Hz, 1H), 7.11 (d, $J = 8.8$ Hz, 2H), 4.24 (t, $J = 6.4$ Hz, 2H), 4.06 (t, $J = 5.2$ Hz, 2H), 2.36-2.25 (m, 2H). LC-MS: m/z 472 $[\text{M}+\text{H}]^+$.

[00504] Preparation of 8-(4-bromophenyl)-6-(4-methoxyphenyl)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **10n**



[00505] 8-(4-bromophenyl)-6-(4-methoxyphenyl)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **10n** was synthesized from methyl 2-(4-bromophenyl)acetate *via general procedure III* (Step B, G-J). LC-MS: m/z 454, 456 $[\text{M}+\text{H}]^+$

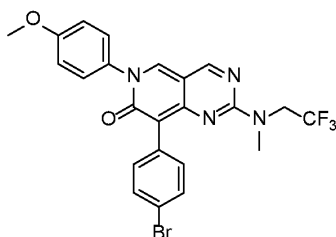
[00506] Example 186: Preparation of 8-(4-bromophenyl)-6-(4-methoxyphenyl)-2-((3,3,3-trifluoropropyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00507] The title compound was synthesized from intermediate **10n** with 3,3,3-Trifluoropropan-1-amine hydrochloride in the procedure for **Example 181** Step J (HOAc, 100°C).

[00508] ¹H NMR (400 MHz, CDCl₃) δ 8.66 (s, 1H), 8.11 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 5.74 (t, *J* = 6.0 Hz, 1H), 3.86 (s, 3H), 3.65 (q, *J* = 6.4 Hz, 2H), 2.50-2.36 (m, 2H). LC-MS: *m/z* 519, 521 [M+H]⁺.

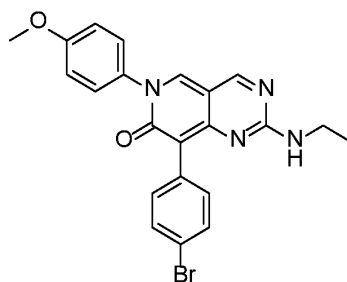
[00509] **Example 187:** 8-(4-bromophenyl)-6-(4-methoxyphenyl)-2-(methyl(2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00510] The title compound was synthesized from intermediate **10n** with 2,2,2-trifluoro-*N*-methylethanamine in the procedure for **Example 181** Step J (HOAc, 100°C).

[00511] ¹H NMR (400 MHz, DMSO-*d*₆) δ major isomer: 9.01 (s, 1H), 8.89 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 4.66 (q, *J* = 9.2 Hz, 2H), 3.83 (s, 3H), 3.15 (s, 3H). minor isomer: 9.07 (s, 1H), 8.92 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 4H), 7.09 (d, *J* = 8.8 Hz, 2H), 4.46 (q, *J* = 9.2 Hz, 2H), 3.83 (s, 3H), 3.33 (s, 3H). Ratio of two isomers is 2:1. LC-MS: *m/z* 519, 521 [M+H]⁺.

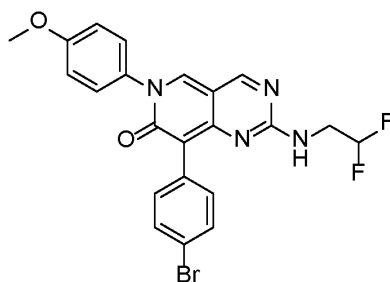
[00512] **Example 188:** 8-(4-bromophenyl)-2-(ethylamino)-6-(4-methoxyphenyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00513] The title compound was synthesized from intermediate **10n** with ethylamine hydrochloride in the procedure for **Example 181** Step J (HOAc, 100°C).

[00514] ^1H NMR (400 MHz, DMSO- d_6) δ 8.84 (s, 1H), 8.68 (s, 1H), 8.06 (t, J = 6.0 Hz, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H), 3.29-3.17 (m, 2H), 1.10 (t, J = 7.2 Hz, 3H). LC-MS: m/z 451, 453 $[\text{M}+\text{H}]^+$.

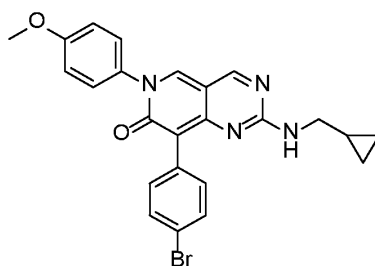
[00515] **Example 189:** 8-(4-bromophenyl)-2-((2,2-difluoroethyl)amino)-6-(4-methoxyphenyl)pyrido[4,3- d]pyrimidin-7(6H)-one



[00516] The title compound was synthesized from intermediate **10n** with 2,2-difluoroethanamine in the procedure for **Example 181** Step J (HOAc, 100°C).

[00517] ^1H NMR (400 MHz, DMSO- d_6) δ 8.92 (s, 1H), 8.79 (s, 1H), 8.37 (t, J = 6.0 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 6.11 (tt, J_{HF} = 56.2 Hz, 4.4 Hz, 1H), 3.83 (s, 3H), 3.60 (tt, J = 14.4 Hz, 4.4 Hz, 2H). LC-MS: m/z 487, 489 $[\text{M}+\text{H}]^+$.

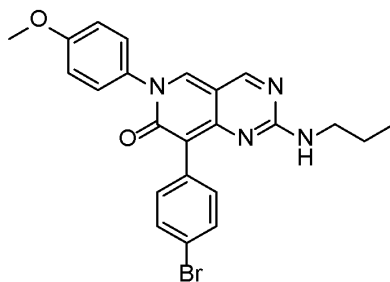
[00518] **Example 190:** 8-(4-bromophenyl)-2-((cyclopropylmethyl)amino)-6-(4-methoxyphenyl)pyrido[4,3- d]pyrimidin-7(6H)-one



[00519] The title compound was synthesized from intermediate **10n** with cyclopropylmethanamine in the procedure for **Example 181** Step J (HOAc, 100°C).

[00520] ^1H NMR (400 MHz, DMSO- d_6) δ 8.84 (s, 1H), 8.67 (s, 1H), 8.16 (t, J = 6.0 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 3.82 (s, 3H), 3.11 (t, J = 6.4 Hz, 2H), 1.10-0.95 (m, 1H), 0.44-0.32 (m, 2H), 0.18-0.07 (m, 2H). LC-MS: m/z 477, 479 $[\text{M}+\text{H}]^+$.

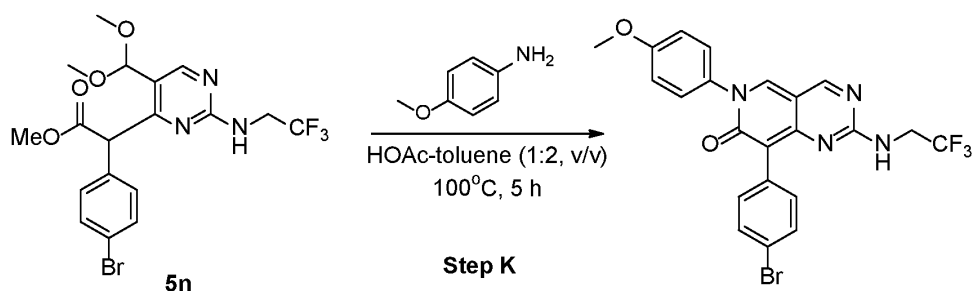
[00521] **Example 191:** 8-(4-bromophenyl)-6-(4-methoxyphenyl)-2-(propylamino)pyrido[4,3-d]pyrimidin-7(6H)-one



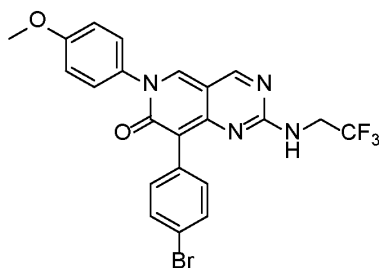
[00522] The title compound was synthesized from intermediate **10n** with 1-aminopropane Hydrochloride in the procedure for **Example 181** Step J (HOAc, 100°C).

[00523] ^1H NMR (400 MHz, DMSO- d_6) δ 8.84 (s, 1H), 8.68 (s, 1H), 8.11 (t, J = 6.4 Hz, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 3.82 (s, 3H), 3.22-3.12 (m, 2H), 1.59-1.44 (m, 2H), 0.84 (t, J = 7.2 Hz, 3H). LC-MS: m/z 465, 467 $[\text{M}+\text{H}]^+$.

[00524] Preparation of **Example 192**



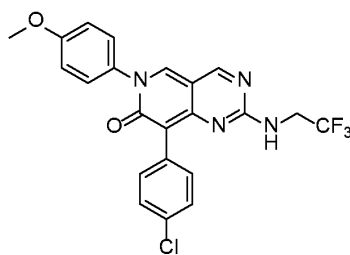
[00525] **Step K:** 8-(4-bromophenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 192**)



[00526] A mixture of Methyl 2-(4-bromophenyl)-2-(5-(dimethoxymethyl)-2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)acetate (800 mg, 1.67 mmol, 1.0 equiv.; prepared as in the procedure for **Example 123** Step B-D), 4-methoxyaniline (410 mg, 3.34 mmol, 2.0 equiv.), AcOH (4.0 mL), toluene (8.0 mL) and 0.8 ml of water was stirred at 100°C for 5h. The mixture was concentrated under reduced pressure, the residue was purified by flash chromatography on silica gel to yield 8-(4-bromophenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 192**)

[00527] ^1H NMR (400 MHz, DMSO-*d*₆) δ 8.96 (s, 1H), 8.83 (s, 1H), 8.59 (t, *J* = 6.0 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 4.16-4.00 (m, 2H), 3.84 (s, 3H). LC-MS (ESI): *m/z* 505, 507 [*M*+H]⁺.

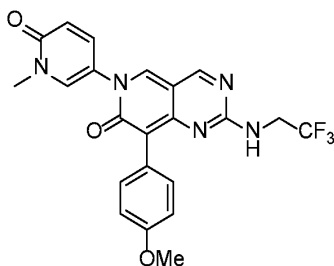
[00528] **Example 193:** 8-(4-chlorophenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00529] The title compound was synthesized from intermediate **5a** with 4-methoxyaniline in the procedure for **Example 192** Step K (HOAc-toluene, 100°C).

[00530] ¹H NMR (400 MHz, CDCl₃) δ 8.72 (s, 1H), 8.16 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.41-7.32 (m, 4H), 7.02 (d, *J* = 8.8 Hz, 2H), 5.76 (t, *J* = 6.4 Hz, 1H), 4.18-4.05 (m, 2H), 3.87 (s, 3H). LC-MS: *m/z* 461 [M+H]⁺.

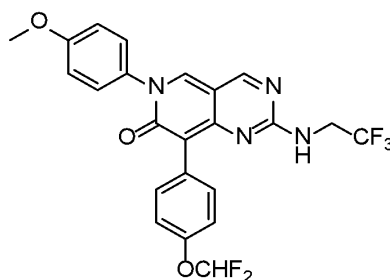
[00531] **Example 194:** 8-(4-methoxyphenyl)-6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6H)-one



[00532] The title compound was synthesized from intermediate **5b** with 5-amino-1-methylpyridin-2(1H)-one in the procedure for **Example 192** Step K (HOAc-toluene, 100°C).

[00533] ¹H NMR (400 MHz, CDCl₃) δ 8.73 (s, 1H), 8.07 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.45 (dd, *J* = 9.6 Hz, 2.4 Hz, 1H), 6.95 (dd, *J* = 8.4 Hz, 2H), 6.68 (d, *J* = 10.0 Hz, 1H), 5.75 (t, *J* = 5.6 Hz, 1H), 4.18-4.06 (m, 2H), 3.86 (s, 3H), 3.60 (s, 3H). LC-MS: *m/z* 458 [M+H]⁺.

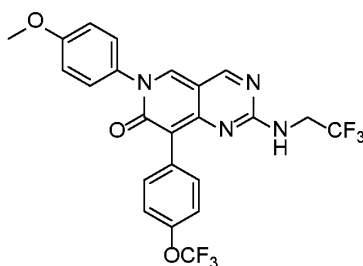
[00534] **Example 195:** 8-(4-(difluoromethoxy)phenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6H)-one



[00535] The title compound was synthesized from intermediate **5c** with 4-methoxyaniline in the procedure for **Example 192** Step K (HOAc-toluene, 100°C).

[00536] ^1H NMR (400 MHz, CDCl_3) δ 8.71 (s, 1H), 8.17 (s, 1H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.36 (d, $J = 8.8$ Hz, 2H), 7.13 (d, $J = 8.4$ Hz, 2H), 7.01 (d, $J = 8.8$ Hz, 2H), 6.54 (t, $J_{\text{HF}} = 74.6$ Hz, 1H), 5.95 (t, $J = 5.6$ Hz, 1H), 4.17-4.02 (m, 2H), 3.86 (s, 3H). LC-MS: m/z 493 $[\text{M}+\text{H}]^+$.

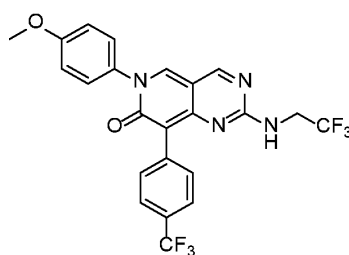
[00537] **Example 196:** 6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)-8-(4-(trifluoromethoxy)phenyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00538] The title compound was synthesized from intermediate **5d** with 4-methoxyaniline in the procedure for **Example 192** Step K (HOAc-toluene, 100°C).

[00539] ^1H NMR (400 MHz, CDCl_3) δ 8.73 (s, 1H), 8.18 (s, 1H), 7.78 (d, $J = 8.0$ Hz, 2H), 7.37 (d, $J = 8.8$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 2H), 7.02 (d, $J = 8.8$ Hz, 2H), 5.76 (t, $J = 6.4$ Hz, 1H), 4.17-4.05 (m, 2H), 3.87 (s, 3H). LC-MS: m/z 511 $[\text{M}+\text{H}]^+$.

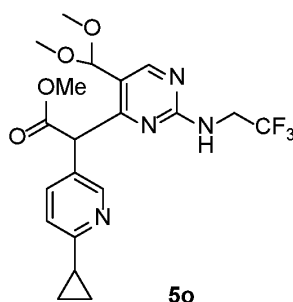
[00540] **Example 197:** 6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00541] The title compound was synthesized from intermediate **5e** with 4-methoxyaniline in the procedure for **Example 192** Step K (HOAc-toluene, 100°C).

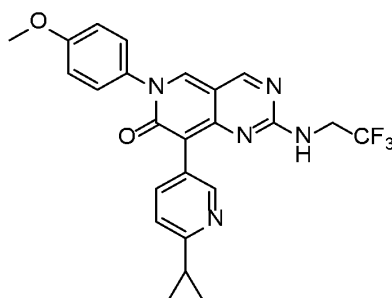
[00542] ^1H NMR (400 MHz, CDCl_3) δ 8.93 (s, 1H), 8.20 (s, 1H), 7.86 (d, $J = 8.4$ Hz, 2H), 7.63 (d, $J = 8.4$ Hz, 2H), 7.37 (d, $J = 8.8$ Hz, 2H), 7.03 (d, $J = 8.8$ Hz, 2H), 5.76 (t, $J = 6.0$ Hz, 1H), 4.16-4.04 (m, 2H), 3.87 (s, 3H). LC-MS: m/z 495 $[\text{M}+\text{H}]^+$.

[00543] Preparation of methyl 2-(6-cyclopropylpyridin-3-yl)-2-(5-(dimethoxymethyl)-2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)acetate **5o**



[00544] methyl 2-(6-cyclopropylpyridin-3-yl)-2-(5-(dimethoxymethyl)-2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)acetate **5o** was synthesized from methyl 2-(6-cyclopropylpyridin-3-yl)acetate *via general procedure III* (Step B-D). LC-MS: m/z 441 $[\text{M}+\text{H}]^+$

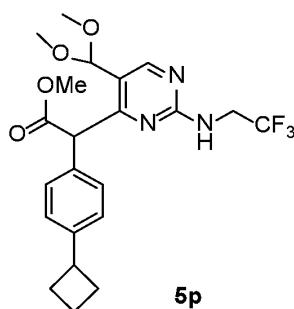
[00545] **Example 198:** 8-(6-cyclopropylpyridin-3-yl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00546] The title compound was synthesized from intermediate **5o** with 4-methoxyaniline in the procedure for **Example 192** Step K (HOAc-toluene, 100°C).

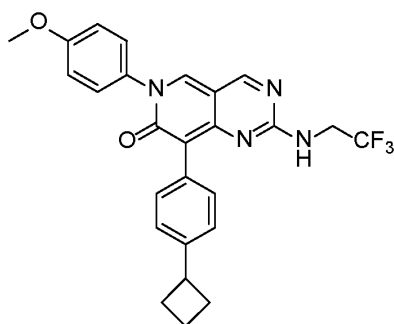
[00547] ^1H NMR (400 MHz, DMSO- d_6) δ 8.96 (s, 1H), 8.82 (s, 1H), 8.62 (d, $J = 2.0$ Hz, 1H), 8.58 (t, $J = 6.4$ Hz, 1H), 7.84 (dd, $J = 8.0$ Hz, 2.4 Hz, 1H), 7.47 (d, $J = 8.8$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 1H), 7.09 (d, $J = 8.8$ Hz, 2H), 4.14-4.00 (m, 2H), 3.83 (s, 3H), 2.14-2.05 (m, 1H), 0.97-0.90 (m, 4H). LC-MS: m/z 468 $[\text{M}+\text{H}]^+$.

[00548] Preparation of methyl 2-(4-cyclobutylphenyl)-2-(5-(dimethoxymethyl)-2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)acetate **5p**



[00549] methyl 2-(4-cyclobutylphenyl)-2-(5-(dimethoxymethyl)-2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)acetate **5p** was synthesized from methyl 2-(4-cyclobutylphenyl)acetate *via general procedure III* (Step B-D). LC-MS: m/z 454 $[\text{M}+\text{H}]^+$

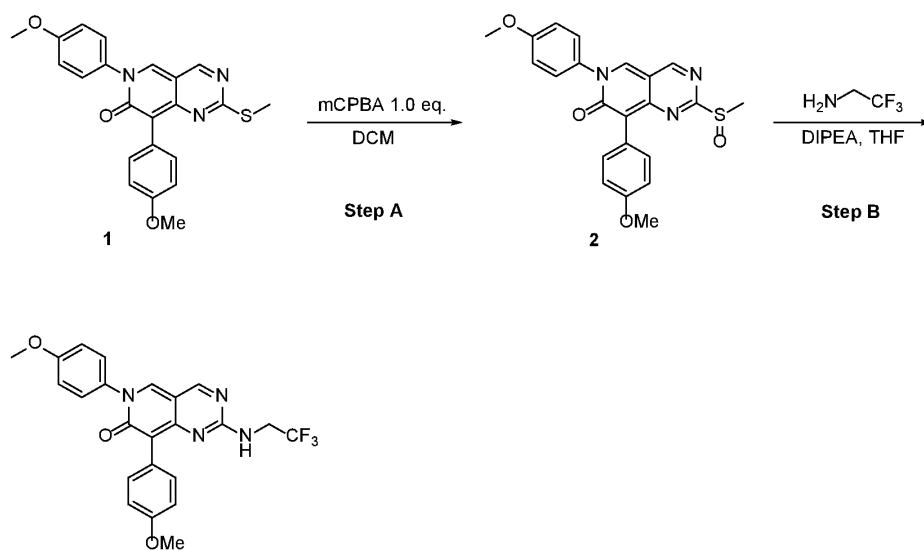
[00550] 8-(4-cyclobutylphenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3- d]pyrimidin-7(6H)-one (**Example 199**)



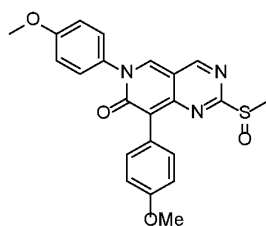
[00551] The title compound was synthesized from intermediate **5p** with 4-methoxyaniline in the procedure for **Example 192** Step K (HOAc-toluene, 100°C).

[00552] ^1H NMR (400 MHz, DMSO- d_6) δ 8.94 (s, 1H), 8.77 (s, 1H), 8.49 (t, $J = 6.4$ Hz, 1H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.46 (d, $J = 8.8$ Hz, 2H), 7.16 (d, $J = 8.4$ Hz, 2H), 7.09 (d, $J = 8.8$ Hz, 2H), 4.15-4.00 (m, 2H), 3.59-3.48 (m, 1H), 2.37-2.24 (m, 2H), 2.19-2.04 (m, 2H), 2.03-1.90 (m, 1H), 1.88-1.76 (m, 1H). LC-MS: m/z 481 $[\text{M}+\text{H}]^+$.

[00553] Preparation of **Example 200**

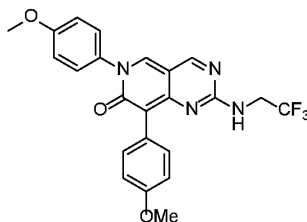


[00554] **Step A:** 6,8-bis(4-methoxyphenyl)-2-(methylsulfinyl)pyrido[4,3- d]pyrimidin-7(6H)-one



[00555] To a solution of 6,8-bis(4-methoxyphenyl)-2-(methylthio)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (180 mg, 0.4 mmol, 1.0 equiv) in DCM (15 mL) was added *m*CPBA (76 mg, 0.4 mmol, 1.0 equiv) at -5 °C. Then the mixture was stirred at -5 °C for 3h. The solvent was removed under vacuum and the resulting mixture was purified by prep-TLC (PE : EA =1: 4) to give 6,8-bis(4-methoxyphenyl)-2-(methylsulfinyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (65 mg, 35% yield) as a yellow solid. LC-MS: *m/z* 422 [M+H]⁺.

[00556] **Step B:** 6,8-bis(4-methoxyphenyl)-2-(2,2,2-trifluoroethylamino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 200**)

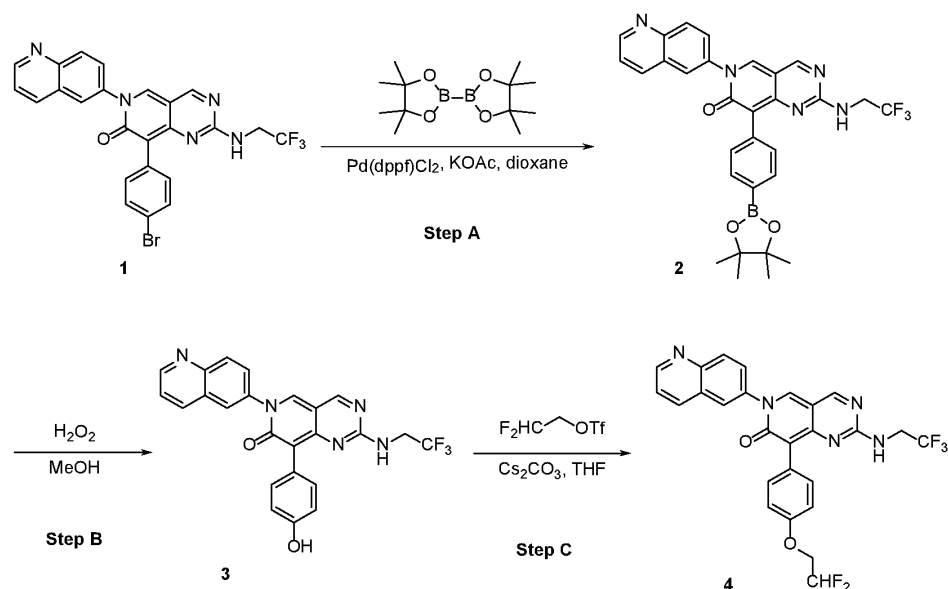


[00557] To a solution of 6,8-bis(4-methoxyphenyl)-2-(methylsulfinyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (65 mg, 0.15 mmol, 1.0 equiv), DIPEA (10.0 mg, 0.75 mmol, 5 equiv) in THF (3.0 mL) was added 2,2,2-trifluoroethanamine (75 mg, 0.75 mmol, 5 equiv). The mixture was then stirred at 25 °C overnight, and the resulting mixture was concentrated under vacuum before being diluted with DCM (10 mL) and H₂O (10 mL). The aqueous layer was extracted with DCM (10.0 mL x 2), and the combined organic layers were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel to yield 6,8-bis(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 200**).

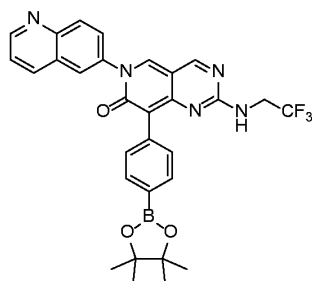
[00558] ¹H NMR (400 MHz, CDCl₃) δ 8.69 (s, 1H), 8.12 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 9.2 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* =

8.8 Hz, 2H), 5.84 (t, $J = 6.4$ Hz, 1H), 4.19-4.06 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H). LC-MS: m/z 457 $[M+H]^+$.

[00559] Preparation of Example 201



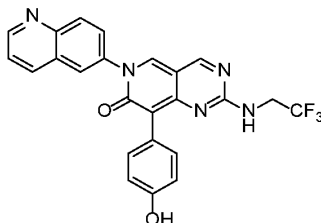
[00560] Step A: 6-(quinolin-6-yl)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00561] A mixture of 8-(4-bromophenyl)-6-(quinolin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 180**, 160 mg, 0.3 mmol, 1.0 equiv), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (116 mg, 0.46 mmol, 1.5 equiv), Pd(dppf)Cl₂ (22 mg, 0.03 mmol, 0.1 equiv) and KOAc (90 mg, 0.91 mmol, 3.0 equiv) in 1,4-dioxane (5.0 mL) was stirred at 80 °C overnight under an atmosphere of N₂. The mixture was filtered through a short pad of Celite[®] and the filtrate was concentrated under reduced pressure. Then the residue was further purified by flash column chromatography on silica

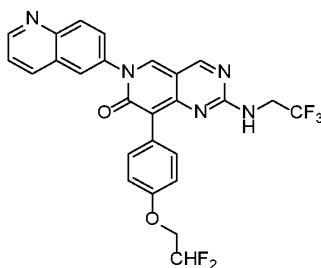
gel to afford the desired product (110 mg, 63% yield) as a yellow solid. LC-MS (ESI): m/z 574 $[M+H]^+$.

[00562] Step B: 8-(4-hydroxyphenyl)-6-(quinolin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00563] A mixture of 6-(quinolin-6-yl)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (100 mg, 0.17 mmol, 1.0 equiv) and H_2O_2 (30% aq., 350 mg, 3.49 mmol, 20.0 equiv) in MeOH (4.0 ml) was stirred at 0 °C for 1h. The mixture was diluted with EtOAc (10.0 mL), and washed with NaS_2O_3 (sat. aq., 10.0 mL). The organic layer was concentrated under reduced pressure to afford 8-(4-hydroxyphenyl)-6-(quinolin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (75.0 mg, 95% yield) as a yellow solid, which was taken forward without further purification. LC-MS: m/z 464 $[M+H]^+$.

[00564] Step C: 8-(4-(2,2-difluoroethoxy)phenyl)-6-(quinolin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 201**)

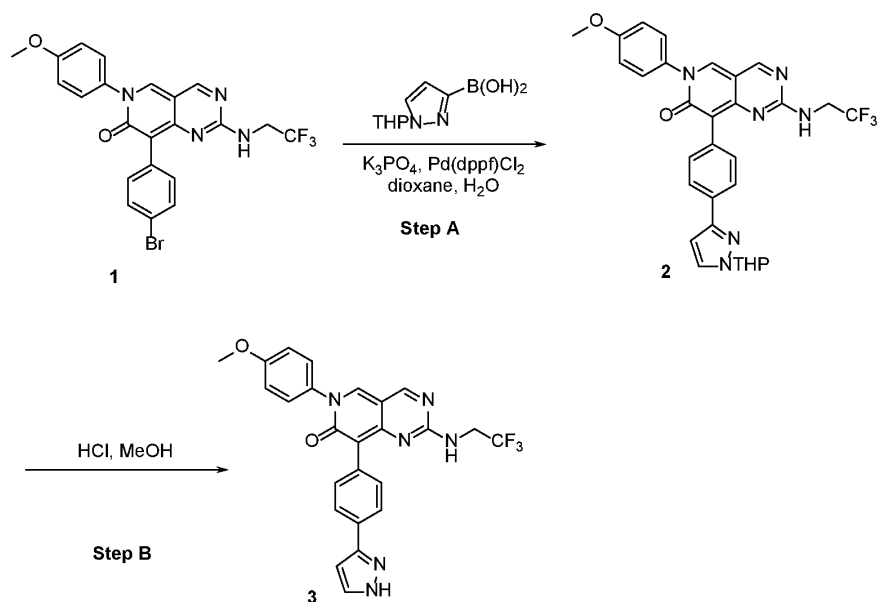


[00565] To a mixture of 8-(4-hydroxyphenyl)-6-(quinolin-6-yl)-2-((2,2,2-trifluoroethyl)amino) pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (50.0 mg, 0.11 mmol, 1.0 equiv) in THF (3.0 mL), was added 2,2-difluoroethyl trifluoromethanesulfonate (25.0 mg, 0.12 mmol, 1.1 equiv) and Cs_2CO_3 (70.0 mg, 0.22 mmol, 2.0 equiv) at 0°C, after which the resulting mixture was allowed to warm to room temperature and stirred for an additional 3h. The mixture was

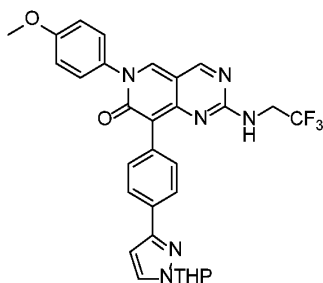
concentrated under reduced pressure, and the resulting residue was purified by RP-prep-HPLC to yield 8-(4-(2,2-difluoroethoxy)phenyl)-6-(quinolin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 201**).

[00566] ^1H NMR (400 MHz, DMSO-*d*₆) δ 9.03 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 8.99 (s, 1H), 8.97 (s, 1H), 8.59 (t, *J* = 6.4 Hz, 1H), 8.48 (d, *J* = 7.6 Hz, 1H), 8.24 (d, *J* = 2.0 Hz, 1H), 8.17 (d, *J* = 9.2 Hz, 1H), 7.94 (dd, *J* = 9.2 Hz, 2.4 Hz, 1H), 7.69-7.61 (m, 3H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.41 (tt, *J*_{HF} = 56.2 Hz, 3.6 Hz, 1H), 4.34 (tq, *J* = 14.8 Hz, 3.6 Hz, 2H), 4.18-4.04 (m, 2H). LC-MS (ESI): *m/z* 528 [M+H]⁺.

[00567] Preparation of **Example 202**

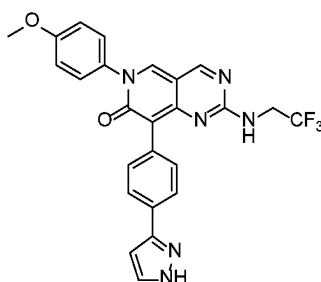


[00568] **Step A:** 6-(4-methoxyphenyl)-8-(4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)phenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00569] A mixture of 8-(4-bromophenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 192**, 70.0 mg, 0.1 mmol, 1.0 equiv), (1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)boronic acid (77.0 mg, 0.3 mmol, 3.0 equiv), Pd(dppf)Cl₂ (8.0 mg, 0.01 mmol, 0.1 equiv) and K₃PO₄ (88.0 mg, 0.4 mmol, 4.0 equiv) in dioxane/H₂O (4/1, 5.0 mL) was stirred at 100 °C overnight under nitrogen atmosphere. The mixture was cooled to r.t., diluted with water (10.0 mL), extracted with EtOAc (20.0 mL x 2), washed with brine (10.0 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (PE : EA = 5 : 1) to give the desired product (70.0 mg, 88% yield) as a yellow solid. LC-MS: *m/z* 577 [M+H]⁺.

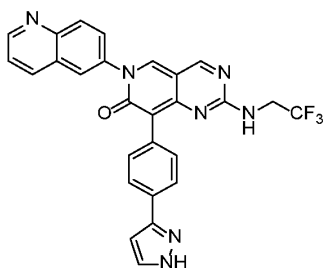
[00570] **Step B:** 8-(4-(1*H*-pyrazol-3-yl)phenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 202**)



[00571] A mixture of 6-(4-methoxyphenyl)-8-(4-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)phenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (50.0 mg, 0.1 mmol, 1.0 equiv) and HCl (1 M aq., 0.3 mL, 3.0 equiv.) in MeOH (1.0 mL) was stirred at r.t. for 30 minutes. The solution was then concentrated and the resulting residue was purified by RP-prep-HPLC to give 8-(4-(1*H*-pyrazol-3-yl)phenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 202**).

[00572] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.97 (s, 1H), 8.81 (s, 1H), 8.55 (t, *J* = 6.4 Hz, 1H), 7.81-7.66 (m, 4H), 7.48 (d, *J* = 9.2 Hz, 2H), 7.40-7.16 (m, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.72 (s, 1H), 4.15-4.03 (m, 2H), 3.83 (s, 3H). LC-MS: *m/z* 493 [M+H]⁺.

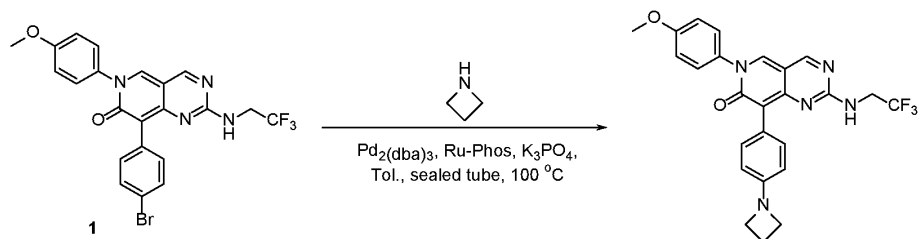
[00573] **Example 203:** 8-(4-(1*H*-pyrazol-3-yl)phenyl)-6-(quinolin-6-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00574] The title compound was synthesized from **Example 180** with 1-(tetrahydro-2*H*-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole as prepared in the procedure for **Example 202** (Step A-B).

[00575] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.03 (dd, *J* = 4.4 Hz, 1.6 Hz, 1H), 9.01 (s, 1H), 9.00 (s, 1H), 8.63 (t, *J* = 6.4 Hz, 1H), 8.49 (d, *J* = 7.2 Hz, 1H), 8.26 (d, *J* = 2.0 Hz, 1H), 8.17 (d, *J* = 8.8 Hz, 1H), 8.16 (s, 1H), 7.96 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.71 (br s, 1H), 7.66 (dd, *J* = 8.4 Hz, 4.4 Hz, 1H), 6.73 (d, *J* = 2.0 Hz, 1H), 4.20-4.04 (m, 2H). LC-MS: *m/z* 514 [M+H]⁺.

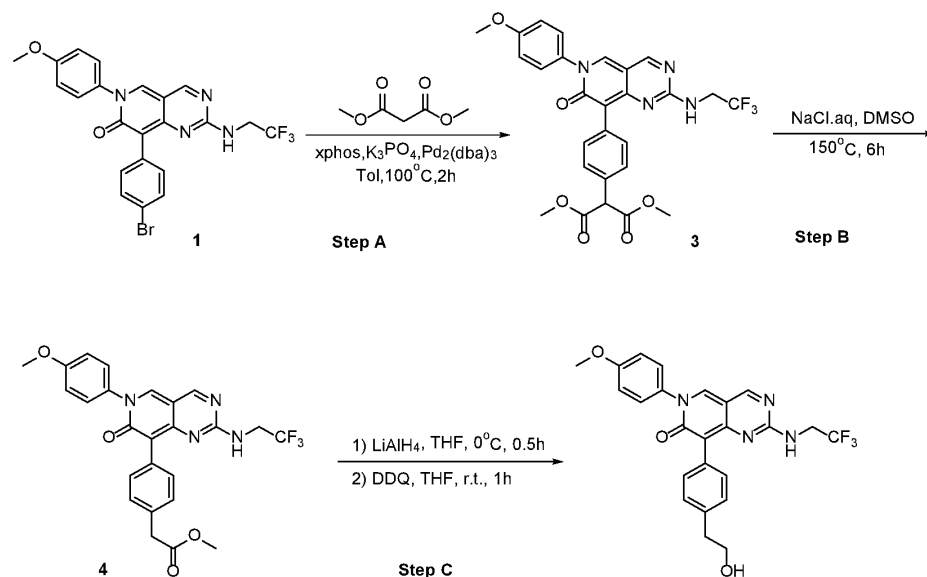
[00576] **Example 204:** Preparation of 8-(4-(azetidin-1-yl)phenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



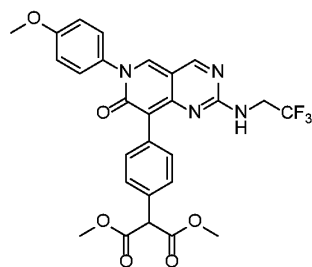
[00577] A mixture of 8-(4-bromophenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 192**, 100 mg, 0.2 mmol, 1.0 equiv), azetidine (114.0 mg, 2.0 mmol, 10.0 equiv), Pd₂(dba)₃ (18.0 mg, 0.02 mmol, 0.1 equiv), Ru-Phos (18.0 mg, 0.04 mmol, 0.2 equiv) and K₃PO₄ (127 mg, 0.6 mmol, 3.0 equiv) in toluene (2.0 mL) was stirred at 100 °C in a sealed tube overnight under nitrogen atmosphere. The mixture was concentrated and the residue was purified by RP-prep-HPLC to give 8-(4-(azetidin-1-yl)phenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 204**).

[00578] ^1H NMR (400 MHz, DMSO- d_6) δ 8.93 (s, 1H), 8.70 (s, 1H), 8.43 (t, $J = 6.4$ Hz, 1H), 7.51 (d, $J = 8.4$ Hz, 2H), 7.45 (d, $J = 8.8$ Hz, 2H), 7.09 (d, $J = 8.8$ Hz, 2H), 6.35 (d, $J = 8.4$ Hz, 2H), 4.18-4.04 (m, 2H), 3.84 (s, 3H), 3.82 (t, $J = 7.2$ Hz, 4H), 2.36-2.26 (m, 2H). LC-MS: m/z 482 $[\text{M}+\text{H}]^+$.

[00579] Preparation of Example 205



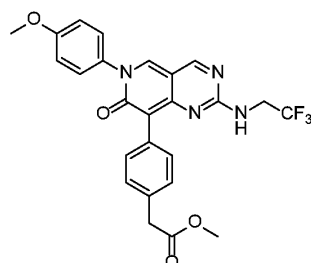
[00580] **Step A:** dimethyl 2-(4-(6-(4-methoxyphenyl)-7-oxo-2-((2,2,2-trifluoroethyl)amino)-6,7-dihydropyrido[4,3- d]pyrimidin-8-yl)phenyl)malonate



[00581] To a solution of 8-(4-bromophenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3- d]pyrimidin-7(6H)-one (200.0 mg, 0.396 mmol, 1.0 equiv) in toluene (5.0 mL) was added K_3PO_4 (168.0 mg, 0.792 mmol, 2.0 equiv), X-Phos (40.0 mg, 0.084 mmol, 0.2 equiv) and $\text{Pd}_2(\text{dba})_3$ (38.0 mg, 0.045 mmol, 0.1 equiv). Then the resulting mixture was stirred at 100 °C for 2h under N_2 . The reaction mixture was diluted with EtOAc (10.0 mL) and washed with H_2O (10 mL x 3), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE

/ EA = 3/1–1/1) to afford the desired product (130 mg, 59% yield) as a yellow solid. LC-MS: m/z 557 $[M+H]^+$.

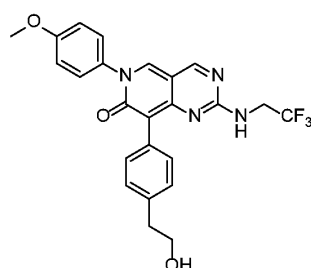
[00582] Step B: methyl 2-(4-(6-(4-methoxyphenyl)-7-oxo-2-((2,2,2-trifluoroethyl)amino)-6,7-dihydropyrido[4,3-*d*]pyrimidin-8-yl)phenyl)acetate



To a solution of 2-(4-(6-(4-methoxyphenyl)-7-oxo-2-(2,2,2-trifluoroethylamino)-6,7-dihydropyrido[4,3-*d*]pyrimidin-8-yl)phenyl)malonate (130.0 mg, 0.234 mmol, 1.0 equiv) in DMSO (2.0 mL) was added NaCl aq. (0.55 M, 2.0 mL, 5.0 equiv). The resulting mixture was stirred at 150 °C for 6h. The reaction mixture was then diluted with ethyl acetate (10.0 mL) and washed with H₂O (10.0 mL x 3), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE/EA = 1/1) to afford 2-(4-(6-(4-methoxyphenyl)-7-oxo-2-((2,2,2-trifluoroethyl)

[00583] amino)-6,7-dihydropyrido[4,3-*d*]pyrimidin-8-yl)phenyl)acetate (85.0 mg, 73% yield) as a yellow solid. LC-MS: m/z 499 $[M+H]^+$.

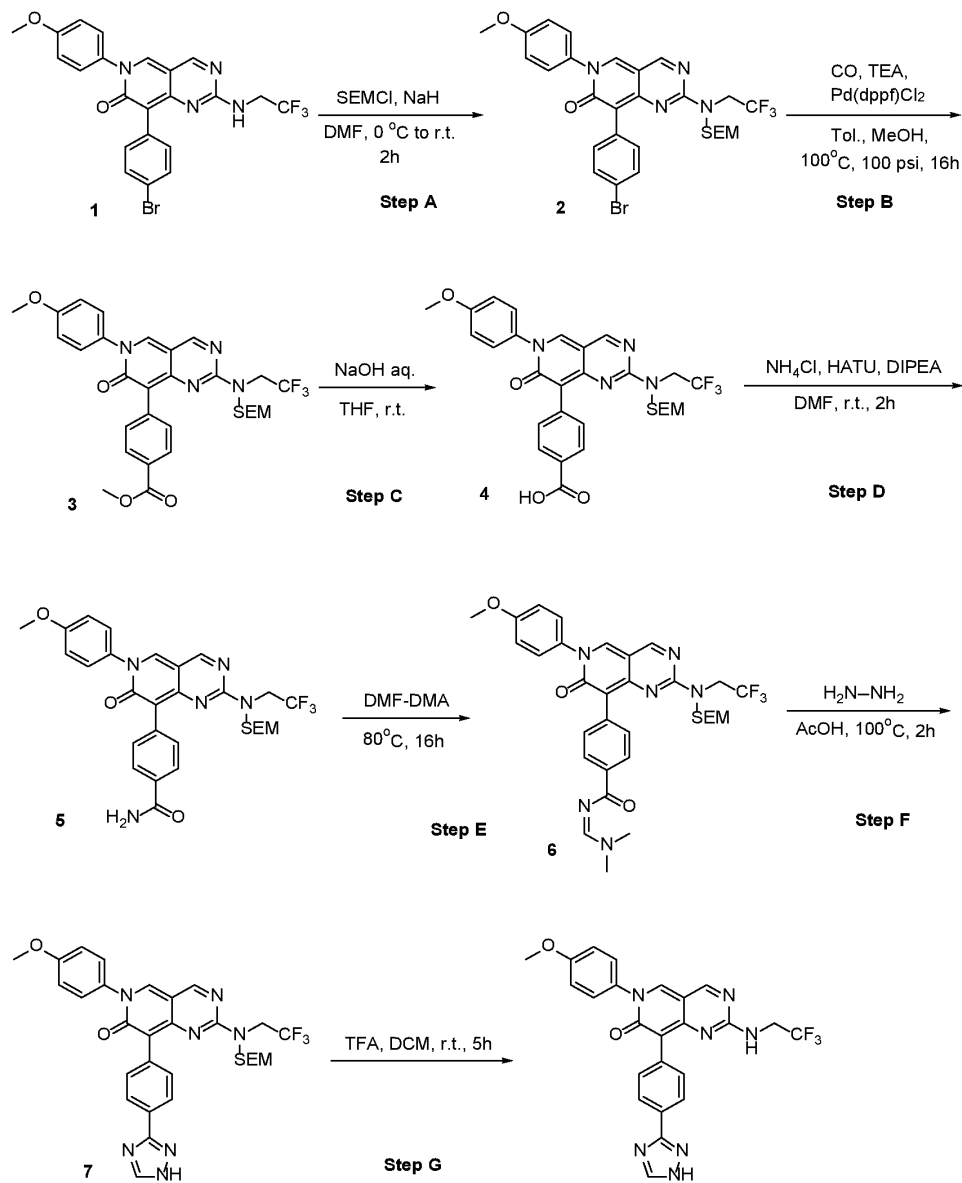
[00584] Step C: 8-(4-(2-hydroxyethyl)phenyl)-6-(4-methoxyphenyl)-2-(2,2,2-trifluoroethylamino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 205**)



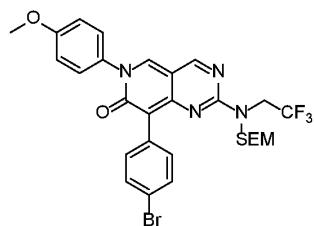
[00585] To a solution of methyl 2-(4-(6-(4-methoxyphenyl)-7-oxo-2-(2,2,2-trifluoroethylamino)-6,7-dihydropyrido[4,3-*d*]pyrimidin-8-yl)phenyl)acetate (85.0 mg, 0.170 mmol, 1.0 equiv) in THF (3.0 mL) was added LiAlH₄ (32.0 mg, 0.842 mmol, 5.0 equiv) at 0 °C. The resulting mixture was stirred at 0 °C for 30 minutes. The reaction mixture was then quenched with

sodium sulfate decahydrate (100 mg), filtered and concentrated. Then a mixture of the residue and DDQ (57.0 mg, 0.251 mmol, 1.5 equiv) in THF (3.0 mL) was stirred at r.t. for 1h and then concentrated under reduced pressure. The residue was purified by Prep-HPLC to afford 8-(4-(2-hydroxyethyl)phenyl)-6-(4-methoxyphenyl)-2-(2,2,2-trifluoroethylamino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 205**).

[00586] ^1H NMR (400 MHz, DMSO-*d*₆) δ 8.94 (s, 1H), 8.77 (s, 1H), 8.50 (t, *J* = 6.4 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 9.2 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 9.2 Hz, 2H), 4.64 (t, *J* = 5.2 Hz, 1H), 4.18-4.04 (m, 2H), 4.15-4.02 (m, 2 H), 3.83 (s, 3H), 3.67-3.58 (m, 2H), 2.74 (t, *J* = 7.2 Hz, 2H). LC-MS: *m/z* 471 [M+H]⁺.

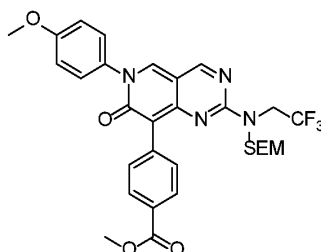
[00587] Preparation of Example 206

[00588] Step A: 8-(4-bromophenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



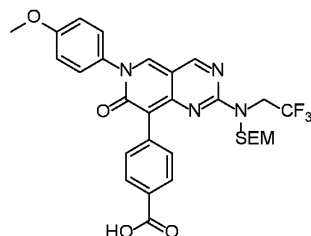
[00589] To a solution of 8-(4-bromophenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethylamino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 192**, 350.0 mg, 0.7 mmol, 1.0 equiv) in anhydrous DMF (5.0 mL) was added NaH (60% in oil, 57.0 mg, 1.4 mmol, 2.0 equiv) at 0 °C. The mixture was stirred at 0 °C for 1h, and then SEMCl (141.0 mg, 0.86 mmol, 1.2 equiv) was added. The resulting mixture was stirred at r.t. for 1h. Then the reaction was quenched with ice NH₄Cl aq. (10.0 mL) and extracted with DCM (10.0 mL x 2). The combined extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by flash column chromatography to afford 8-(4-bromophenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (350.0 mg, 77% yield) as a yellow solid. LC-MS: *m/z* 635 [M+H]⁺.

[00590] **Step B:** methyl 4-(6-(4-methoxyphenyl)-7-oxo-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-6,7-dihydropyrido[4,3-*d*]pyrimidin-8-yl)benzoate



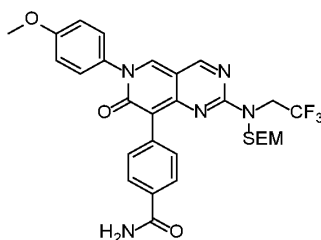
[00591] To a solution of 8-(4-bromophenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (350.0 mg, 0.55 mmol, 1.0 equiv) in toluene/MeOH (1/1, v/v, 10.0 mL) was added TEA (167.0 mg, 1.65 mmol, 3.0 equiv) and Pd(dppf)Cl₂ (37.0 mg, 0.05 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred at 100 °C under CO (1atm) overnight. The resulting mixture was diluted with water (20.0 mL) and extracted with EtOAc (20.0 mL x 3). The organic layers were combined and washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (PE/EA = 3/1-1/2) to afford methyl 4-(6-(4-methoxyphenyl)-7-oxo-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-6,7-dihydropyrido[4,3-*d*]pyrimidin-8-yl)benzoate (280.0 mg, 83% yield) as a yellow solid. LC-MS: *m/z* 615 [M+H]⁺.

[00592] Step C: 4-(6-(4-methoxyphenyl)-7-oxo-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-6,7-dihydropyrido[4,3-*d*]pyrimidin-8-yl)benzoic acid



[00593] To a solution of methyl 4-(6-(4-methoxyphenyl)-7-oxo-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-6,7-dihydropyrido[4,3-*d*]pyrimidin-8-yl)benzoate (280.0 mg, 0.46 mmol, 1.0 equiv) in THF (5.0 mL) was added LiOH (1N, aq., 4.6 mL, 4.6 mmol, 10.0 equiv) at room temperature. The resulting mixture was stirred overnight. Then the reaction mixture was poured into water (20.0 mL) and adjusted the pH to 6.0 with dilute HCl solution (1N). The mixture was extracted with EtOAc (20.0 mL x 3), dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (PE / EA = 2: 1 to 0:1) to afford 4-(6-(4-methoxyphenyl)-7-oxo-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-6,7-dihydropyrido[4,3-*d*]pyrimidin-8-yl)benzoic acid (250.0 mg, 91% yield) as a yellow solid. LC-MS: *m/z* 601 [M+H]⁺.

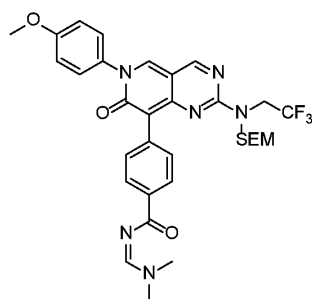
[00594] Step D: 4-(6-(4-methoxyphenyl)-7-oxo-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-6,7-dihydropyrido[4,3-*d*]pyrimidin-8-yl)benzamide



[00595] To a solution of 4-(6-(4-methoxyphenyl)-7-oxo-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-6,7-dihydropyrido[4,3-*d*]pyrimidin-8-yl)benzoic acid (250.0 mg, 0.42 mmol, 1.0 equiv) in DMF (5 mL) was added NH₄Cl (133.0 mg, 2.08 mmol, 5.0 equiv), DIPEA (268.0 mg, 2.08 mmol, 5.0 equiv) and HATU (316.0 mg, 0.83 mmol, 2.0 equiv). The resulting

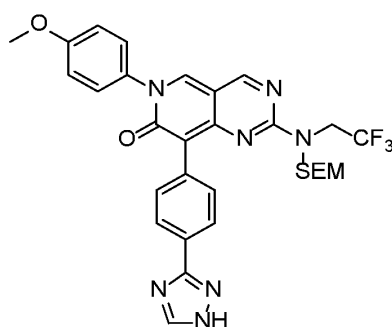
mixture was stirred at room temperature for 2h. Then the reaction mixture was diluted with water (20 mL) and extracted with DCM (20 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (PE/EA = 1/1) to afford 4-(6-(4-methoxyphenyl)-7-oxo-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-6,7-dihydropyrido[4,3-*d*]pyrimidin-8-yl)benzamide (200. mg, 80% yield) as a yellow solid. LC-MS: *m/z* 600 [M+H]⁺.

[00596] Step E: (Z)-N-((dimethylamino)methylene)-4-(6-(4-methoxyphenyl)-7-oxo-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-6,7-dihydropyrido[4,3-*d*]pyrimidin-8-yl)benzamide



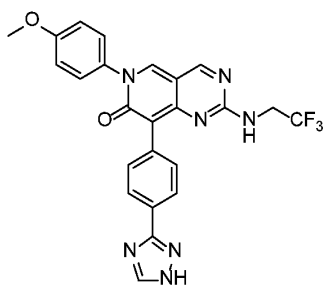
[00597] A mixture of 4-(6-(4-methoxyphenyl)-7-oxo-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-6,7-dihydropyrido[4,3-*d*]pyrimidin-8-yl)benzamide (100.0 mg, 0.17 mmol, 1.0 equiv) and DMF-DMA (2.0 mL) was stirred at 80 °C for overnight. Then the reaction mixture was concentrated to afford the crude product as a yellow oil. LC-MS: *m/z* 655 [M+H]⁺.

[00598] Step F: 8-(4-(1H-1,2,4-triazol-3-yl)phenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00599] To a solution of (Z)-N-((dimethylamino)methylene)-4-(6-(4-methoxyphenyl)-7-oxo-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-6,7-dihydropyrido[4,3-d]pyrimidin-8-yl)benzamide (120 mg, 0.17 mmol, 1.0 equiv) in AcOH (2 mL) was added hydrazine monohydrate (27.0 mg, 0.84 mmol, 5.0 equiv) at room temperature. The resulting mixture was stirred at 100 °C for 2h. Then the reaction was diluted with NaHCO₃ (sat. aq., 20 mL) and extracted with EtOAc (20 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (PE/EA = 1/1) to afford 8-(4-(1H-1,2,4-triazol-3-yl)phenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)pyrido[4,3-d]pyrimidin-7(6H)-one (80 mg, 76% yield) as a yellow solid. LC-MS: *m/z* 624 [M+H]⁺.

[00600] **Step G:** 8-(4-(1H-1,2,4-triazol-3-yl)phenyl)-6-(4-methoxyphenyl)-2-(2,2,2-trifluoroethylamino)pyrido[4,3-d]pyrimidin-7(6H)-one

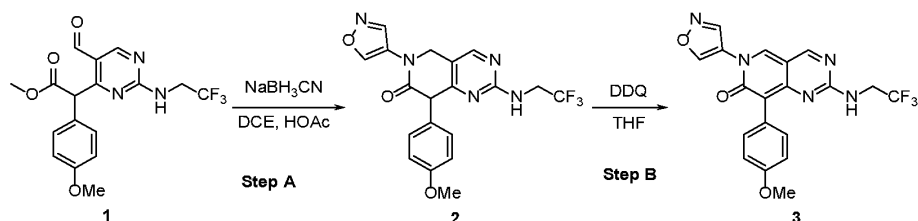


[00601] To a solution of 8-(4-(1H-1,2,4-triazol-3-yl)phenyl)-6-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)((2-(trimethylsilyl)ethoxy)methyl)amino)pyrido[4,3-d]pyrimidin-7(6H)-one (80 mg, 0.13 mmol, 1.0 equiv) in DCM (3.0 mL) was added trifluoroacetic acid (1.0 mL) at room temperature. The resulting mixture was stirred for 5h before being

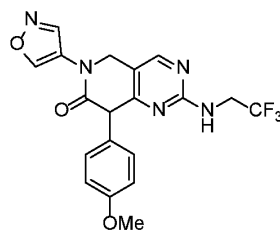
concentrated and purified by RP-prep-HPLC to afford 8-(4-(1*H*-1,2,4-triazol-3-yl)phenyl)-6-(4-methoxyphenyl)-2-(2,2,2-trifluoroethylamino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (Example 206).

[00602] ^1H NMR (400 MHz, DMSO-*d*₆) δ 8.97 (s, 1H), 8.84 (s, 1H), 8.58 (t, *J* = 6.4 Hz, 1H), 8.43 (br s, 1H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 4.16-4.02 (m, 2H), 3.81 (s, 3H). LC-MS: *m/z* 494 [M+H]⁺.

[00603] Preparation of **Example 207**



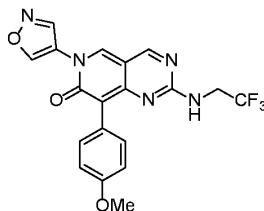
[00604] **Step A:** 6-(isoxazol-4-yl)-8-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-7(4*aH*)-one



[00605] To a solution of methyl 2-(5-formyl-2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)-2-(4-methoxyphenyl)acetate (as prepared in *General procedure III*, Step G) (76 mg, 0.2 mmol, 1.0 equiv), isoxazol-4-amine (42 mg, 0.5 mmol, 2.5 equiv) in DCE/MeOH (3/0.5 mL) was added HOAc (42 mg, 0.7 mmol, 3.5 equiv). The mixture was stirred at 45 °C overnight, then the mixture was cooled down to 0°C, NaBH₃CN (12 mg, 0.2 mmol, 1.0 equiv) was added to the reaction mixture in one portion, after which the resulting mixture was allowed to warm to room temperature and stirred for an additional 12h before being quenched with DCM (10 mL) and H₂O (10 mL). The aqueous layer was extracted with DCM (10 mL x 3). The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by Prep-TLC (PE:EA = 1/2) to give 6-(isoxazol-4-yl)-8-(4-methoxyphenyl)-2-((2,2,2-

trifluoroethyl)amino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-7(4*aH*)-one (51 mg, 44% yield) as a white solid. LC-MS: *m/z* 420 [M+H]⁺.

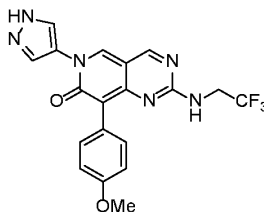
[00606] Step B: 6-(isoxazol-4-yl)-8-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00607] A mixture of 6-(isoxazol-4-yl)-8-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)-5,6-dihydropyrido[4,3-*d*]pyrimidin-7(4*aH*)-one (51.0 mg, 0.12 mmol, 1.0 equiv) and DDQ (40.0 mg, 0.18 mmol, 1.5 equiv) in THF (3.0 mL) was stirred at r.t. for 3h. The reaction mixture was concentrated under vacuum and the residue was purified by RP-prep-HPLC to give 6-(isoxazol-4-yl)-8-(4-methoxyphenyl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 207**).

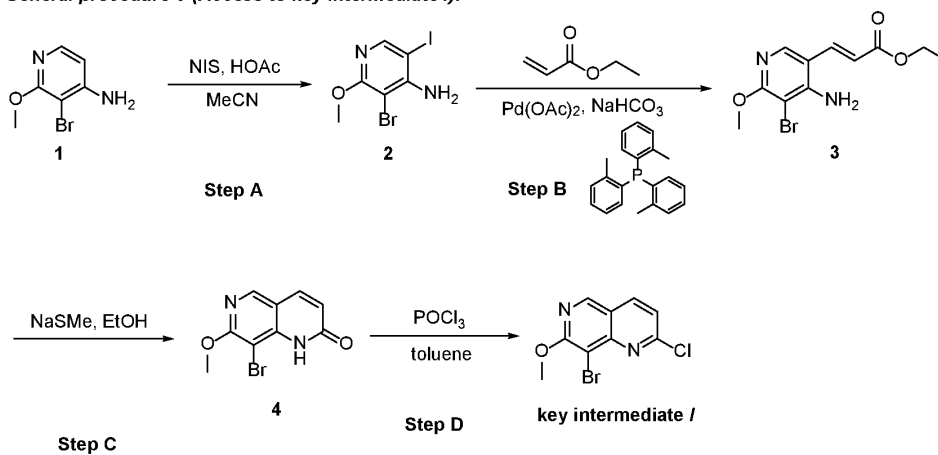
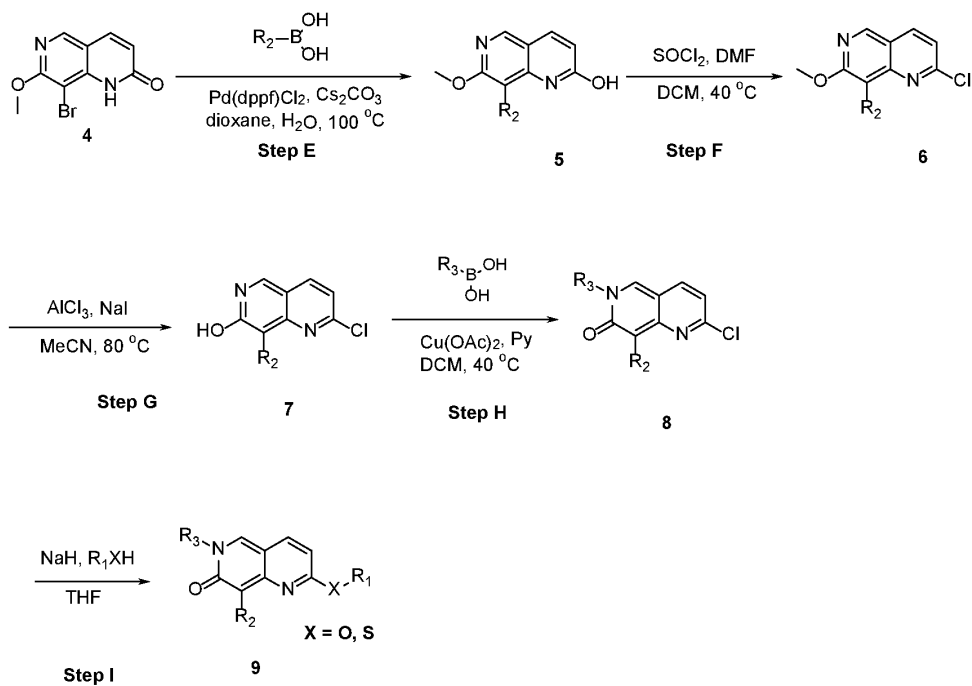
[00608] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.62 (s, 1H), 9.20 (s, 1H), 9.00 (s, 1H), 8.97 (s, 1H), 8.66 (t, *J* = 6.4 Hz, 1H) 7.57 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.15-4.03 (m, 2H), 3.79 (s, 3H). LC-MS: *m/z* 418 [M+H]⁺.

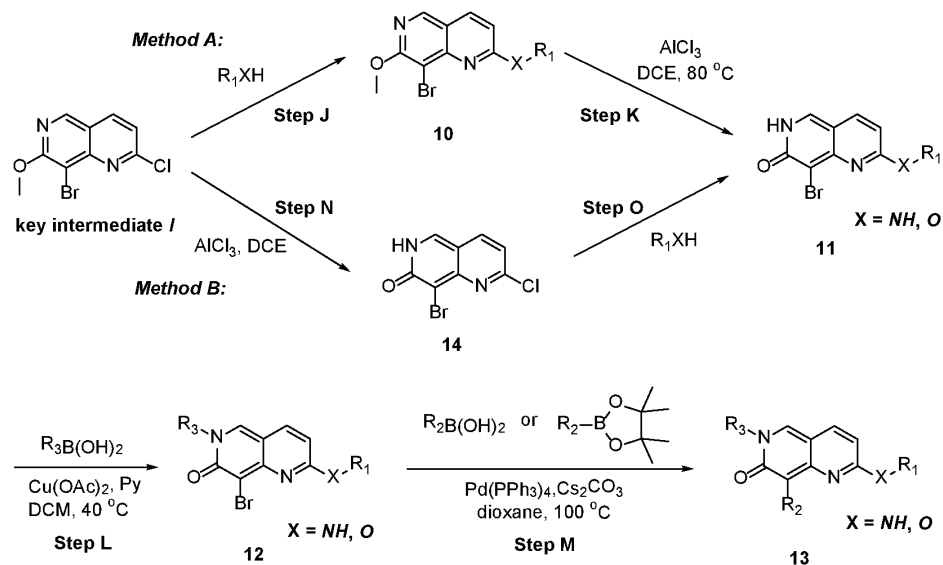
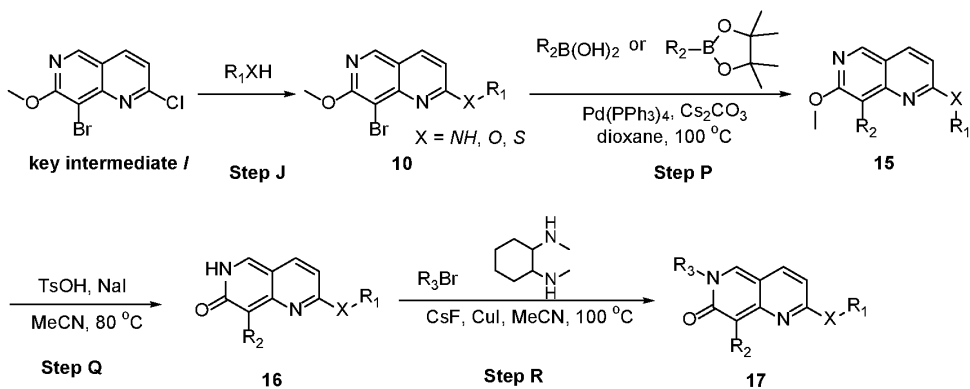
[00609] Example 208: 8-(4-methoxyphenyl)-6-(1*H*-pyrazol-4-yl)-2-((2,2,2-trifluoroethyl)amino)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



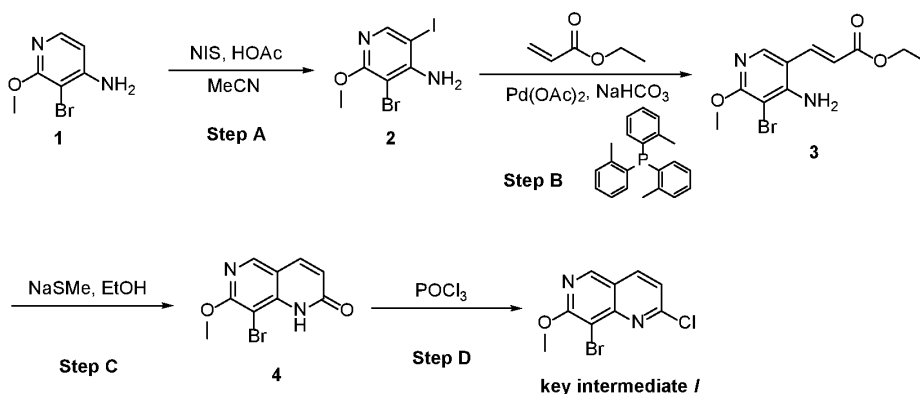
[00610] The title compound was synthesized from intermediate **1** with 1*H*-pyrazol-4-amine as prepared in the procedure for **Example 207** (Step A-B).

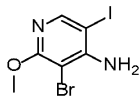
[00611] ¹HNMR (600 MHz, DMSO-*d*₆) δ 8.95 (s, 1H), 8.93 (s, 1H), 8.51 (br s, 1H), 8.13 (s, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.13-4.03 (q, *J* = 9.6 Hz, 2H), 3.78 (s, 3H). LC-MS: *m/z* 417 [M+H]⁺.

[00612] General Procedure V:*General procedure V (Access to key intermediate I):**General Procedure V (R2-R3-R1 sequence):*

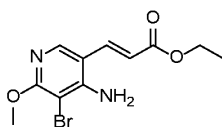
General Procedure V (R1-R3-R2 sequence):**General Procedure V (R1-R2-R3 sequence):**

[00613] Preparation of 8-bromo-2-chloro-7-methoxy-1,6-naphthyridine (key intermediate I)

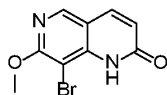


[00614] Step A: 3-bromo-5-iodo-2-methoxypyridin-4-amine

[00615] To a solution of 3-bromo-2-methoxypyridin-4-amine (4.0 g, 19.8 mmol, 1.0 equiv.) in acetonitrile (30 mL) and acetic acid (4.1 mL) was added NIS (4.9 g, 21.7 mmol, 1.1 equiv.), and the reaction mixture was stirred at room temperature for 16 h. Then the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with water (50 mL x 2). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent: PE/EtOAc = 4/1) to afford 3-bromo-5-iodo-2-methoxypyridin-4-amine (6.0 g, 92% yield) as a white solid. LC-MS: *m/z* 329 [M+H]⁺.

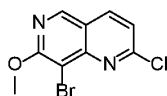
[00616] Step B: (*E*)-ethyl 3-(4-amino-5-bromo-6-methoxypyridin-3-yl)acrylate

[00617] A mixture of 3-bromo-5-iodo-2-methoxypyridin-4-amine (6 g, 18.3 mmol, 1.0 equiv.), trio-tolylphosphine (553 mg, 1.8 mmol, 0.1 equiv.), NaHCO₃ (2.7 g, 32.1 mmol, 1.8 equiv.), ethyl acrylate (2 g, 20.1 mmol, 1.1 equiv.) and Pd(OAc)₂ (205 mg, 0.9 mmol, 0.05 equiv.) in DMF (30 mL) was stirred at 70 °C under N₂ for 16 h. Then the reaction was diluted with 10% aq. LiCl (50 mL) and extracted with EtOAc (50 mL x 3). All the organic layers were combined and washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel (eluent: PE/EtOAc = 3/1) to afford (*E*)-ethyl 3-(4-amino-5-bromo-6-methoxypyridin-3-yl)acrylate (4.5 g, 82% yield) as a white solid. LC-MS: *m/z* 301 [M+H]⁺.

[00618] Step C: 8-bromo-7-methoxy-1,6-naphthyridin-2(1*H*)-one

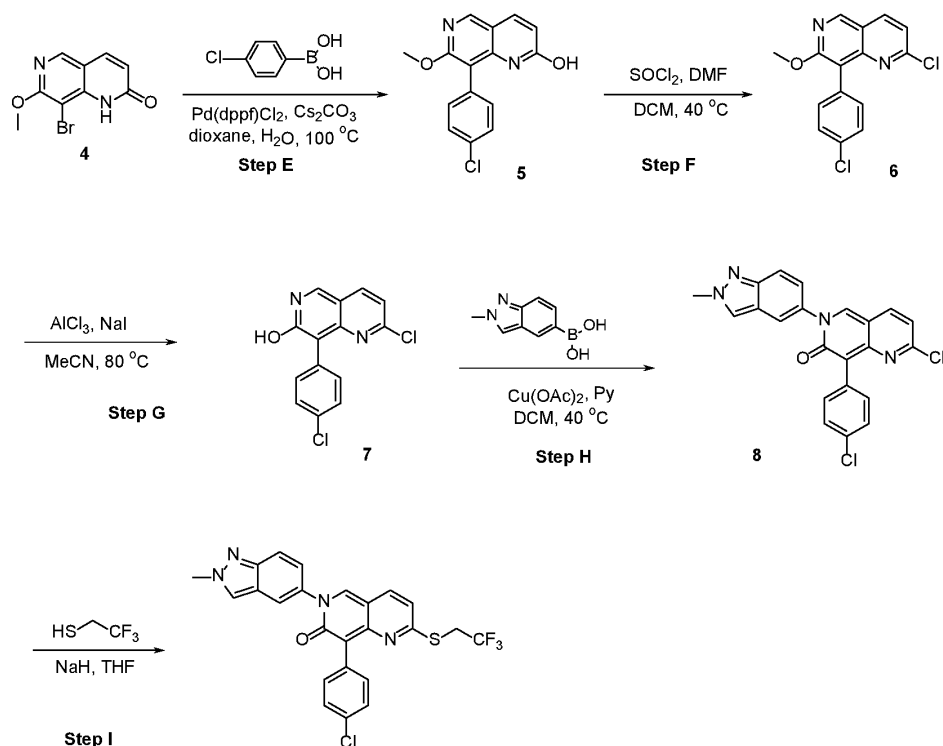
[00619] To a solution of (*E*)-ethyl 3-(4-amino-5-bromo-6-methoxypyridin-3-yl)acrylate (1.5 g, 5.0 mmol, 1.0 equiv.) in EtOH (10 mL) was added 15% aq. NaSMe (2.6 g, 5.5 mmol, 1.1 equiv.). The resulting mixture was stirred at room temperature overnight. The precipitate was collected by filtration and the filter cake was washed with EtOAc (10 mL) then dried to afford 8-bromo-7-methoxy-1,6-naphthyridin-2(1*H*)-one (1.0 g, 79% yield) as a yellow solid. LC-MS: m/z 255 [M+H]⁺.

[00620] **Step D:** 8-bromo-2-chloro-7-methoxy-1,6-naphthyridine (*key intermediate I*)

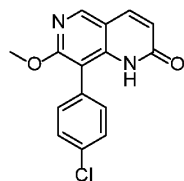


[00621] A mixture of 8-bromo-7-methoxy-1,6-naphthyridin-2(1*H*)-one (2.3 g, 9.0 mmol, 1.0 equiv.) and POCl₃ (12.0 mL) was stirred at 80 °C for 2 h. Then the reaction was poured into cooled NaHCO₃ (Sat. aq., 150 mL) and extracted with EtOAc (50 mL x 4). All the organic layers were combined and washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel (eluent: PE/EtOAc = 3/1) to afford 8-bromo-2-chloro-7-methoxy-1,6-naphthyridine (1.9 g, 77% yield) as an off-white solid. LC-MS: m/z 273 [M+H]⁺.

[00622] Preparation of 8-(4-chlorophenyl)-6-(2-methyl-2*H*-indazol-5-yl)-2-(2,2,2-trifluoroethylthio)-1,6-naphthyridin-7(6*H*)-one (**Example 209**)

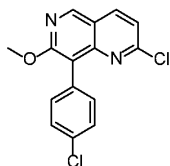


[00623] **Step E:** 8-(4-chlorophenyl)-7-methoxy-1,6-naphthyridin-2(1H)-one



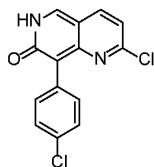
[00624] A mixture of 8-bromo-7-methoxy-1,6-naphthyridin-2(1H)-one (10 g, 39.4 mmol, 1.0 equiv.), Pd(dppf)Cl_2 (1.4 g, 1.9 mmol, 0.05 equiv.), Cs_2CO_3 (25.6 g, 78.5 mmol, 2.0 equiv.) and 4-chlorophenylboronic acid (9.2 g, 59.0 mmol, 1.5 equiv.) in dioxane/water (200 mL, 9/1, v/v) was stirred at 100°C under N_2 atmosphere for 16 h. Then the reaction mixture was diluted with water (100 mL) and extracted with EtOAc (50 mL x 5). All the organic layers were combined and washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: PE/EtOAc = 2/1) to afford 8-(4-chlorophenyl)-7-methoxy-1,6-naphthyridin-2(1H)-one (10.0 g, 89% yield) as a white solid. LC-MS: m/z 287 $[\text{M}+\text{H}]^+$.

[00625] Step F: 2-chloro-8-(4-chlorophenyl)-7-methoxy-1,6-naphthyridine



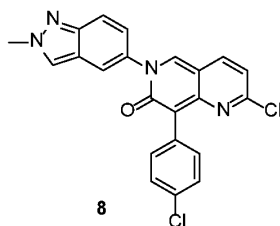
[00626] To a solution of 8-(4-chlorophenyl)-7-methoxy-1,6-naphthyridin-2(1*H*)-one (8 g, 27.9 mmol, 1.0 equiv.) in DCM (100 mL) was added DMF (6.1 g, 83.6 mmol, 3.0 equiv.) and SOCl₂ (8.2 g, 83.6 mmol, 3.0 equiv.). Then the reaction was stirred at 80 °C for 16 h. The resulting mixture was cooled to room temperature, concentrated, quenched with ice cooled NaHCO₃ (Sat. aq., 50 mL) and extracted with EtOAc (50 mL x 2). All the organic layers were combined and washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: PE/EtOAc = 5/1) to afford 2-chloro-8-(4-chlorophenyl)-7-methoxy-1,6-naphthyridine (7.0 g, 83% yield) as a white solid. LC-MS: *m/z* 305 [M+H]⁺.

[00627] Step G: 2-chloro-8-(4-chlorophenyl)-1,6-naphthyridin-7(6*H*)-one



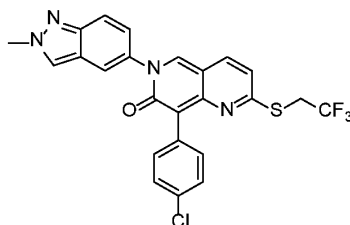
[00628] To a solution of 2-chloro-8-(4-chlorophenyl)-7-methoxy-1,6-naphthyridine (2.0 g, 6.6 mmol, 1.0 equiv.) in MeCN (40.0 mL) was added AlCl₃ (1.8 g, 13.5 mmol, 2.0 equiv.) and NaI (2.2 g, 13.3 mmol, 2.0 equiv.). The resulting mixture was stirred at 80 °C for 8h. Then the reaction mixture was quenched with ice water (20 mL) and extracted with EtOAc (20 mL x 3). All the organic layers were combined and washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (eluent: DCM/acetone = 2/1) to afford 2-chloro-8-(4-chlorophenyl)-1,6-naphthyridin-7(6*H*)-one (1.5 g, 79% yield) as a white solid. LC-MS: *m/z* 291 [M+H]⁺.

[00629] Step H: 2-chloro-8-(4-chlorophenyl)-6-(2-methyl-2*H*-indazol-5-yl)-1,6-naphthyridin-7(6*H*)-one



[00630] To a solution of 2-chloro-8-(4-chlorophenyl)-1,6-naphthyridin-7(6*H*)-one (1.5 g, 5.2 mmol, 1.0 equiv.) in DCM (20.0 mL) was added Cu(OAc)₂ (1.2 g, 5.6 mmol, 1.1 equiv.), pyridine (1.2 g, 15.2 mmol, 3.0 equiv.) and 2-methyl-2*H*-indazol-5-ylboronic acid (1.4 g, 8.0 mmol, 1.5 equiv.). The reaction mixture was stirred at 40 °C under O₂ atmosphere for 16 h, then concentrated under reduced pressure and purified by flash chromatography on silica gel (eluent: PE/EtOAc = 1/1) to afford 2-chloro-8-(4-chlorophenyl)-6-(2-methyl-2*H*-indazol-5-yl)-1,6-naphthyridin-7(6*H*)-one (1.4 g, 65% yield) as an orange solid. LC-MS: *m/z* 421 [M+H]⁺.

[00631] Step I: 8-(4-chlorophenyl)-6-(2-methyl-2*H*-indazol-5-yl)-2-((2,2,2-trifluoroethyl)thio)-1,6-naphthyridin-7(6*H*)-one (Example 209)

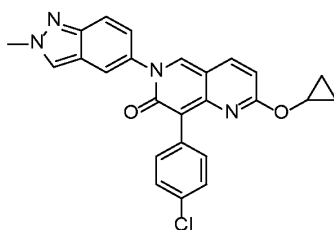


[00632] To a solution of 2,2,2-trifluoroethanethiol (124.0 mg, 1.1 mmol, 3.0 equiv.) in 2.0 mL of anhydrous THF was added NaH (60% suspend in mineral oil, 43.0 mg, 1.1 mmol, 3.0 equiv.) in portions at 0 °C. The mixture was stirred at 0 °C for 0.5 h. Then a solution of 2-chloro-8-(4-chlorophenyl)-6-(2-methyl-2*H*-indazol-5-yl)-1,6-naphthyridin-7(6*H*)-one (150.0 mg, 0.36 mmol, 1.0 equiv.) in THF (1 mL) was added. The reaction mixture was stirred at room temperature for an additional 2 h. The reaction mixture was quenched with NH₄Cl (Sat. aq., 10 mL) and extracted with EtOAc (10 mL x 3). All the organic layers were combined and washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was

purified by RP-prep-HPLC to afford 8-(4-chlorophenyl)-6-(2-methyl-2*H*-indazol-5-yl)-2-((2,2,2-trifluoroethyl)thio)-1,6-naphthyridin-7(6*H*)-one (Example 209).

[00633] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.92 (s, 1H), 8.51 (s, 1H), 7.98 (d, *J* = 8.8 Hz, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.72 (d, *J* = 9.2 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.37 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 4.23 (s, 3H), 4.21-4.08 (m, 2H). LC-MS: *m/z* 501 (M+H)⁺.

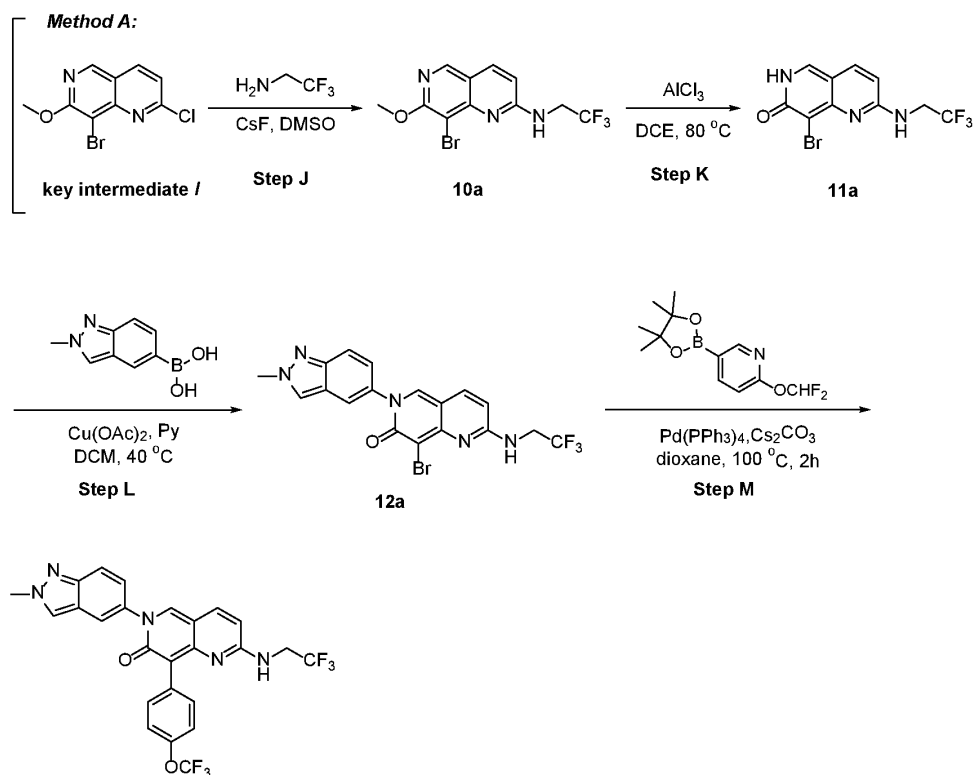
[00634] **Example 210:** 8-(4-chlorophenyl)-2-cyclopropoxy-6-(2-methyl-2*H*-indazol-5-yl)-1,6-naphthyridin-7(6*H*)-one



[00635] The title compound was synthesized from intermediate **8** with cyclopropanol *via* general procedure V (Step I) (NaH, anhydrous THF, 0 °C to r.t.).

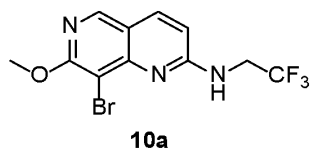
[00636] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.78 (s, 1H), 8.50 (s, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.70 (d, *J* = 2.4 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.34 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 6.53 (d, *J* = 9.2 Hz, 1H), 4.23 (s, 3H), 4.21-4.14 (m, 2H), 0.74-0.72 (m, 4H). LC-MS: *m/z* 443 [M+H]⁺.

[00637] Preparation of 6-(2-methyl-2*H*-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)-8-(4-(trifluoromethoxy)phenyl)-1,6-naphthyridin-7(6*H*)-one (Example 211)



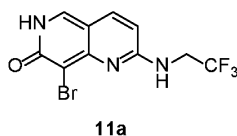
[00638] Method A

[00639] **Step J:** 8-bromo-7-methoxy-*N*-(2,2,2-trifluoroethyl)-1,6-naphthyridin-2-amine 10a



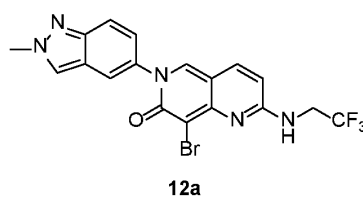
[00640] A mixture of 8-bromo-2-chloro-7-methoxy-1,6-naphthyridine (1.0 g, 3.8 mmol, 1.0 equiv.), CsF (860.0 mg, 5.7 mmol, 1.5 equiv.), and 2,2,2-trifluoroethanamine (1.9 g, 18.8 mmol, 5.0 equiv.) in DMSO (10.0 mL) was stirred at 100 °C for 2 h. Then the mixture was poured into ice water (100 mL), and extracted with EtOAc (50 mL x 4). All the organic layers were combined, washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: PE/EtOAc = 2/1) to afford 8-bromo-7-methoxy-*N*-(2,2,2-trifluoroethyl)-1,6-naphthyridin-2-amine (900 mg, 71% yield) as a white solid. LC-MS: *m/z* 336 [M+H]⁺.

[00641] **Step K:** 8-bromo-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6*H*)-one **11a**



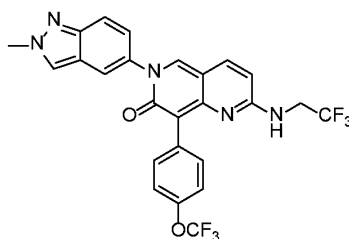
[00642] A mixture of 8-bromo-7-methoxy-*N*-(2,2,2-trifluoroethyl)-1,6-naphthyridin-2-amine (300.0 mg, 0.8 mmol, 1.0 equiv.) and AlCl₃ (301.5 mg, 2.2 mmol, 3.0 equiv.) in DCE (10 mL) was stirred at 80 °C for 2h. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel (eluent: DCM/MeOH = 10/1) to afford 8-bromo-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6*H*)-one (220.0 mg, 92% yield) as a yellow solid. LC-MS: *m/z* 322 [M+H]⁺.

[00643] **Step L:** 8-bromo-6-(2-methyl-2*H*-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)-1,6-naphthyridin-7(6*H*)-one **12a**



[00644] 8-bromo-6-(2-methyl-2*H*-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)-1,6-naphthyridin-7(6*H*)-one **12a** was synthesized from intermediate **11a** with (2-methyl-2*H*-indazol-5-yl)boronic acid *via* general procedure V (Step H). LC-MS: *m/z* 452 [M+H]⁺.

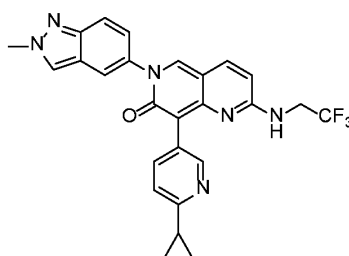
[00645] **Step M:** 6-(2-methyl-2*H*-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)-8-(4-(trifluoromethoxy)phenyl)-1,6-naphthyridin-7(6*H*)-one (**Example 211**)



[00646] The title compound was synthesized from intermediate **12a** with (4-(trifluoromethoxy)phenyl)boronic acid *via* general procedure V (Step M).

[00647] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.52 (s, 1H), 8.48 (s, 1H), 8.34 (t, *J* = 6.4 Hz, 1H), 7.85 (dd, *J* = 2.0 Hz, 0.4 Hz, 1H), 7.76 (d, *J* = 9.2 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.31 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 6.49 (d, *J* = 8.8 Hz, 1H), 4.22 (s, 3H), 4.18-4.07 (m, 2H). LC-MS: *m/z* 534 [M+H]⁺.

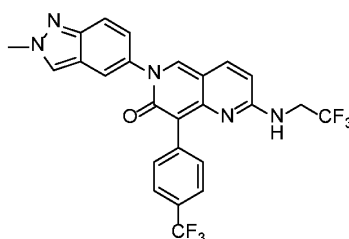
[00648] **Example 212:** 8-(6-cyclopropylpyridin-3-yl)-6-(2-methyl-2*H*-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)-1,6-naphthyridin-7(6*H*)-one



[00649] The title compound was synthesized from intermediate **12a** with (6-cyclopropylpyridin-3-yl)boronic acid *via* general procedure V (Step M).

[00650] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.61 (d, *J* = 1.2 Hz, 1H), 8.50 (s, 1H), 8.48 (s, 1H), 8.34 (t, *J* = 6.4 Hz, 1H), 7.87-7.80 (m, 2H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.32 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 8.8 Hz, 1H), 4.22 (s, 3H), 4.21-4.10 (m, 2H), 2.14-2.05 (m, 1H), 0.98-0.88 (m, 4H). LC-MS: *m/z* 491 [M+H]⁺.

[00651] **Example 213:** 6-(2-methyl-2*H*-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)-8-(4-(trifluoromethyl)phenyl)-1,6-naphthyridin-7(6*H*)-one

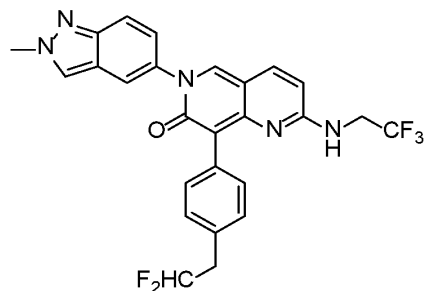


[00652] The title compound was synthesized from intermediate **12a** with (4-(trifluoromethyl)phenyl)boronic acid *via* general procedure V (Step M).

[00653] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.56 (s, 1H), 8.48 (s, 1H), 8.40 (t, *J* = 6.4 Hz, 1H), 7.89-7.80 (m, 3H), 7.78 (d, *J* = 9.2 Hz, 1H), 7.69 (d, *J* = 9.2

Hz, 1H), 7.63 (d, $J = 8.4$ Hz, 2H), 7.33 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 6.52 (d, $J = 9.2$ Hz, 1H), 4.22 (s, 3H), 4.21-4.06 (m, 2H). LC-MS: m/z 518 $[M+H]^+$.

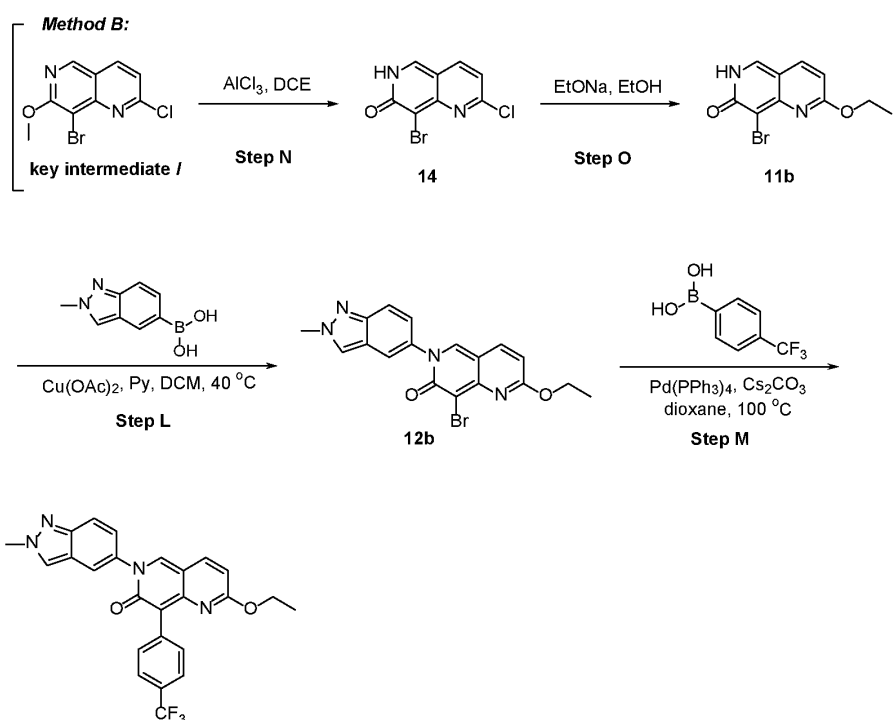
[00654] Example 214: 8-(4-(2,2-difluoroethyl)phenyl)-6-(2-methyl-2H-indazol-5-yl)-2-((2,2,2-trifluoroethyl)amino)-1,6-naphthyridin-7(6H)-one



[00655] The title compound was synthesized from intermediate **12a** with (4-(2,2-difluoroethyl)phenyl)boronic acid *via* general procedure V (Step M).

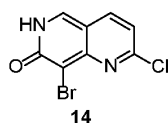
[00656] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.47 (s, 2H), 8.31 (br s, 1H), 7.84 (d, $J = 1.6$ Hz, 1H), 7.74 (d, $J = 9.2$ Hz, 1H), 7.67 (d, $J = 8.8$ Hz, 1H), 7.58 (d, $J = 8.0$ Hz, 2H), 7.30 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 7.22 (d, $J = 8.0$ Hz, 2H), 6.49 (d, $J = 8.8$ Hz, 1H), 6.24 (tt, $J_{\text{HF}} = 56.6$ Hz, 4.8 Hz, 1H), 4.22 (s, 3H), 4.23-4.10 (m, 2H), 3.18 (dt, $J_{\text{HF}} = 18.2$ Hz, 4.8 Hz, 2H). LC-MS: m/z 514 $[M+H]^+$.

[00657] Preparation of 2-ethoxy-6-(2-methyl-2H-indazol-5-yl)-8-(4-(trifluoromethyl)phenyl)-1,6-naphthyridin-7(6H)-one (**Example 215**)



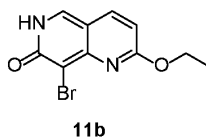
[00658] Method B

[00659] **Step N:** 8-bromo-2-chloro-1,6-naphthyridin-7(6H)-one



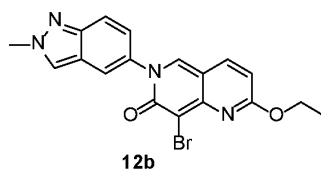
[00660] To a solution of 8-bromo-2-chloro-7-methoxy-1,6-naphthyridine (10.1 g, 40.0 mmol 1.0 equiv.) in DCE (180 mL) was added AlCl_3 (15.9 g, 120.0 mmol, 3.0 equiv.) at 10 °C. The resulting mixture was then stirred at 80 °C for 2h and quenched by water (19.4 mL, 1.1 mol, 27.0 equiv.) at 10°C. This quenched mixture was stirred at room temperature for 0.5h and then filtered. The filter cake was washed with DCM/EtOH (200 mL, 10/1, v/v), and the filtrate was concentrated to give 8-bromo-2-chloro-1,6-naphthyridin-7(6H)-one (9.8 g, crude) as a yellow solid, which was used directly in the next step. LC-MS: m/z 261 $[\text{M}+\text{H}]^+$.

[00661] **Step O:** 8-bromo-2-ethoxy-1,6-naphthyridin-7(6H)-one



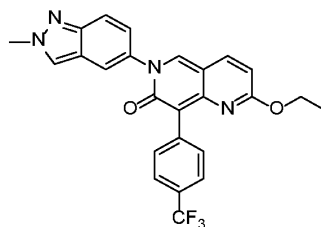
[00662] To a solution of 8-bromo-2-chloro-7-methoxy-1,6-naphthyridine (9.5 g, 40.0 mmol, 1.0 equiv.) in EtOH (220.0 mL) was added NaOEt (27.2 g, 400.0 mmol, 10.0 equiv.). The resulting solution was stirred at 100 °C for 5 h. Then the mixture was poured into ice cooled NH₄Cl (Sat. aq., 200 mL) and adjusted to pH = 6 with 1N HCl (aq.). The mixture was extracted with EtOAc (100 mL x 4) and the organic layers were combined, washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: DCM/EtOH = 50/ to 10/1) to give 8-bromo-2-ethoxy-1,6-naphthyridin-7(6H)-one (5.3 g, 49% yield) as a brown solid. LC-MS: *m/z* 271, 273 [M+H]⁺.

[00663] Preparation of 8-bromo-2-ethoxy-6-(2-methyl-2*H*-indazol-5-yl)-1,6-naphthyridin-7(6*H*)-one



[00664] 8-bromo-2-ethoxy-6-(2-methyl-2*H*-indazol-5-yl)-1,6-naphthyridin-7(6*H*)-one was synthesized from intermediate **11b** with 2-methyl-2*H*-indazol-5-ylboronic acid as in the procedure for **Example 209** (Step H). LC-MS: *m/z* 399, 401 [M+H]⁺.

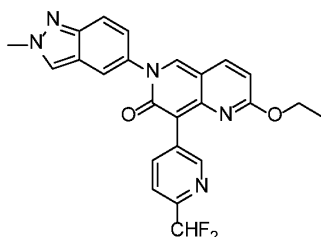
[00665] **Example 215:** Preparation of 2-ethoxy-6-(2-methyl-2*H*-indazol-5-yl)-8-(4-(trifluoromethyl)phenyl)-1,6-naphthyridin-7(6*H*)-one



[00666] The title compound was synthesized from intermediate **12b** with 4-(trifluoromethyl)phenylboronic acid *via* general procedure V (Step M) (Pd(PPh₃)₄, Cs₂CO₃, dioxane, 100°C).

[00667] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.81 (s, 1H), 8.50 (s, 1H), 7.99 (d, $J = 9.2$ Hz, 1H), 7.91 (d, $J = 1.6$ Hz, 1H), 7.88 (d, $J = 8.0$ Hz, 2H), 7.74-7.67 (m, 3H), 7.35 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 6.57 (d, $J = 8.8$ Hz, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 4.23 (s, 3H), 1.26 (t, $J = 7.2$ Hz, 3H). LC-MS: m/z 465 $[\text{M}+\text{H}]^+$.

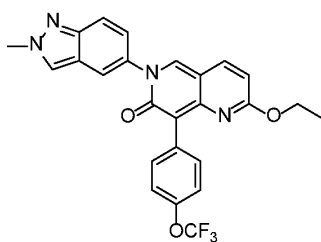
[00668] **Example 216:** 8-(6-(difluoromethyl)pyridin-3-yl)-2-ethoxy-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one



[00669] The title compound was synthesized from intermediate **12b** with 2-(difluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine *via* general procedure V (Step M).

[00670] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.95 (d, $J = 1.2$ Hz, 1H), 8.85 (s, 1H), 8.51 (s, 1H), 8.27 (dd, $J = 8.4$ Hz, 2.0 Hz, 1H), 8.02 (d, $J = 9.2$ Hz, 6H), 7.92 (d, $J = 1.2$ Hz, 1H), 7.72 (d, $J = 3.6$ Hz, 1H), 7.70 (d, $J = 2.8$ Hz, 1H), 7.36 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 6.98 (t, $J_{\text{HF}} = 55.2$ Hz, 1H), 6.59 (d, $J = 9.2$ Hz, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 4.23 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H). LC-MS: m/z 448 $[\text{M}+\text{H}]^+$.

Example 217: 2-ethoxy-6-(2-methyl-2H-indazol-5-yl)-8-(4-(trifluoromethoxy)phenyl)-1,6-naphthyridin-7(6H)-one

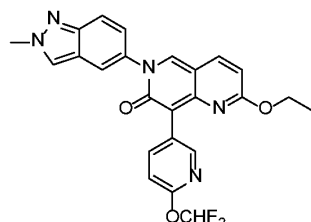


[00671] The title compound was synthesized from intermediate **12b** with (4-(trifluoromethoxy)phenyl)boronic acid *via* general procedure V (Step M).

[00672] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.77 (s, 1H), 8.50 (s, 1H), 7.98 (d, $J = 9.0$ Hz, 1H), 7.89 (d, $J = 2.0$ Hz, 1H), 7.75 (d, $J = 8.8$ Hz, 2H), 7.70 (d, J

= 9.0 Hz, 1H), 7.37-7.30 (m, 3H), 6.55 (d, J = 9.0 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.22 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H). LC-MS: m/z 481 [M+H]⁺.

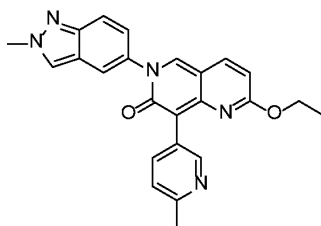
[00673] Example 218: 8-(6-(difluoromethoxy)pyridin-3-yl)-2-ethoxy-6-(2-methyl-2*H*-indazol-5-yl)-1,6-naphthyridin-7(6*H*)-one



[00674] The title compound was synthesized from intermediate **12b** with 2-(difluoromethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine *via* general procedure V (Step M).

[00675] ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.77 (s, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.49 (s, 1H), 8.18 (dd, J = 4.4 Hz, 2.0 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.74 (t, J_{HF} = 73.2 Hz, 1H), 7.71 (d, J = 9.2 Hz, 1H), 7.35 (dd, J = 9.2 Hz, 2.0 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 9.2 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 4.22 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H). LC-MS: m/z 464 [M+H]⁺.

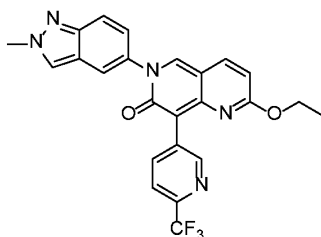
[00676] Example 219: 2-ethoxy-6-(2-methyl-2*H*-indazol-5-yl)-8-(6-methylpyridin-3-yl)-1,6-naphthyridin-7(6*H*)-one



[00677] The title compound was synthesized from intermediate **12b** with (6-methylpyridin-3-yl)boronic acid *via* general procedure V (Step M).

[00678] ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.75 (s, 1H), 8.70 (br s, 1H), 8.50 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.93 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.89 (d, J = 1.6 Hz, 1H), 7.71 (d, J = 9.2 Hz, 1H), 7.35 (dd, J = 9.2 Hz, 2.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 8.8 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 4.23 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). LC-MS: m/z 412 [M+H]⁺.

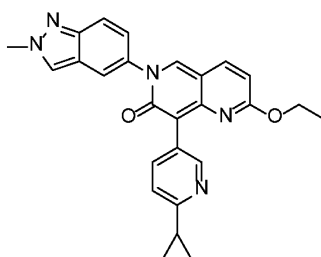
[00679] Example 220: 2-ethoxy-6-(2-methyl-2*H*-indazol-5-yl)-8-(6-(trifluoromethyl)pyridin-3-yl)-1,6-naphthyridin-7(6*H*)-one



[00680] The title compound was synthesized from intermediate **12b** with (6-(trifluoromethyl)pyridin-3-yl)boronic acid *via* general procedure V (Step M).

[00681] ^1H NMR (400 MHz, DMSO-*d*₆) δ : 9.05 (d, J = 7.8 Hz, 1H), 8.88 (s, 1H), 8.51 (s, 1H), 8.37 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 8.04 (d, J = 9.2 Hz, 1H), 7.93 (d, J = 2.0 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 9.2 Hz, 1H), 7.37 (dd, J = 9.6 Hz, 2.0 Hz, 1H), 6.61 (d, J = 9.2 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 4.23 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). LC-MS: m/z 466 [M+H]⁺.

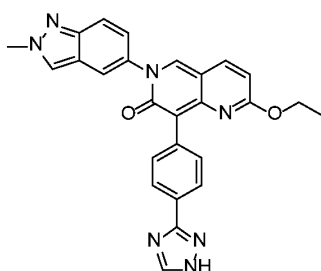
[00682] Example 221: 8-(6-cyclopropylpyridin-3-yl)-2-ethoxy-6-(2-methyl-2*H*-indazol-5-yl)-1,6-naphthyridin-7(6*H*)-one



[00683] The title compound was synthesized from intermediate **12b** with (6-cyclopropylpyridin-3-yl)boronic acid *via* general procedure V (Step M).

[00684] ^1H NMR (400 MHz, DMSO-*d*₆) δ : 8.93 (s, 1H), 8.89 (s, 1H), 8.51 (s, 1H), 8.04 (d, J = 9.2 Hz, 1H), 7.91 (d, J = 1.2 Hz, 1H), 7.72 (d, J = 9.2 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.35 (dd, J = 9.2 Hz, 2.0 Hz, 1H), 6.63 (d, J = 9.2 Hz, 1H), 4.31 (q, J = 6.8 Hz, 2H), 4.23 (s, 3H), 2.36-2.25 (m, 1H), 1.31 (t, J = 6.8 Hz, 3H), 1.27-1.20 (m, 2H), 1.17-1.09 (m, 2H). LC-MS: m/z 437 [M+H]⁺.

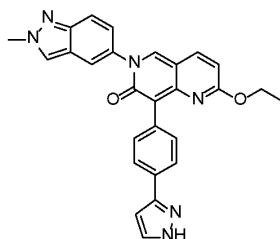
[00685] Example 222: 8-(4-(1*H*-1,2,4-triazol-3-yl)phenyl)-2-ethoxy-6-(2-methyl-2*H*-indazol-5-yl)-1,6-naphthyridin-7(6*H*)-one



[00686] The title compound was synthesized from intermediate **12b** with 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazole *via* general procedure V (Step M) and then de-protection with TFA *via* general procedure I (Step F).

[00687] ^1H NMR (400 MHz, DMSO- d_6) δ : 14.05 (br.s, 1H), 8.75 (s, 1H), 8.50 (s, 1H), 8.39 (br.s, 1H), 8.01 (d, $J = 8.4$ Hz, 2H), 7.98 (d, $J = 9.2$ Hz, 1H), 7.90 (d, $J = 1.6$ Hz, 1H), 7.77 (d, $J = 8.4$ Hz, 2H), 7.71 (d, $J = 8.8$ Hz, 1H), 7.35 (dd, $J = 8.8$ Hz, 2.0 Hz, 1H), 6.55 (d, $J = 9.2$ Hz, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 4.23 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H). LC-MS: m/z 464 $[\text{M}+\text{H}]^+$.

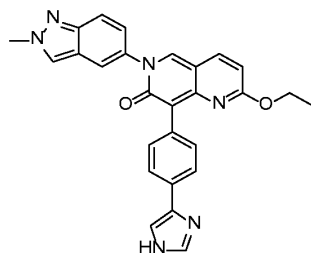
[00688] **Example 223:** 8-(4-(1H-pyrazol-3-yl)phenyl)-2-ethoxy-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one



[00689] The title compound was synthesized from intermediate **12b** with 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole *via* general procedure V (Step M) and then de-protection with TFA *via* general procedure I (Step F).

[00690] ^1H NMR (400 MHz, DMSO- d_6) δ : 12.87 (br.s, 1H), 8.70 (s, 1H), 8.49 (s, 1H), 7.97 (d, $J = 9.2$ Hz, 1H), 7.89 (d, $J = 1.2$ Hz, 1H), 7.85-7.69 (m, 6H), 7.35 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 6.73 (s, 1H), 6.54 (d, $J = 8.8$ Hz, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 4.22 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H). LC-MS: m/z 463 $[\text{M}+\text{H}]^+$.

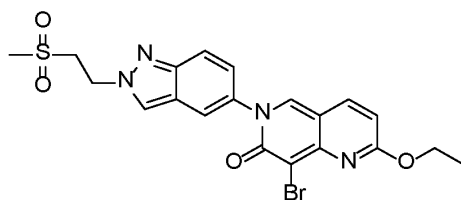
[00691] Example 224: 8-(4-(1*H*-imidazol-4-yl)phenyl)-2-ethoxy-6-(2-methyl-2*H*-indazol-5-yl)-1,6-naphthyridin-7(6*H*)-one



[00692] The title compound was synthesized from intermediate **12b** with 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole *via* general procedure V (Step M) and then de-protection with TFA *via* general procedure I (Step F).

[00693] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 12.14 (br s, 1H), 8.70 (s, 1H), 8.50 (s, 1H), 7.96 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 1.6 Hz, 1H), 7.78-7.58 (m, 7H), 7.35 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 6.53 (d, *J* = 9.2 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 4.23 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H). LC-MS: *m/z* 463 [M+H]⁺.

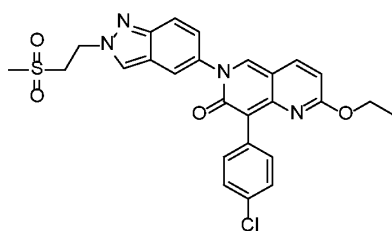
[00694] Preparation of 8-bromo-2-ethoxy-6-(2-(2-(methylsulfonyl)ethyl)-2*H*-indazol-5-yl)-1,6-naphthyridin-7(6*H*)-one **12c**



12c

[00695] 8-bromo-2-ethoxy-6-(2-(2-(methylsulfonyl)ethyl)-2*H*-indazol-5-yl)-1,6-naphthyridin-7(6*H*)-one **12c** was synthesized from intermediate **11b** with 2-(2-(methylsulfonyl)ethyl)-2*H*-indazol-5-ylboronic acid *via* general procedure V (Step L). LC-MS: *m/z* 491, 493 [M+H]⁺.

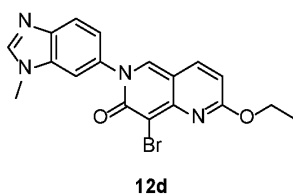
[00696] Example 225: Preparation of 8-(4-chlorophenyl)-2-ethoxy-6-(2-(2-(methylsulfonyl)ethyl)-2*H*-indazol-5-yl)-1,6-naphthyridin-7(6*H*)-one



[00697] The title compound was synthesized from intermediate **12c** with 4-chlorophenylboronic acid *via* general procedure V (Step M).

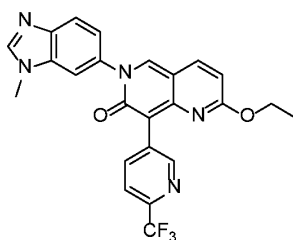
¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.76 (s, 1H), 8.62 (s, 1H), 8.00-7.93 (m, 2H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.42-7.36 (m, 3H), 6.54 (d, *J* = 9.2 Hz, 1H), 4.91 (t, *J* = 6.8 Hz, 2H), 4.26 (q, *J* = 6.8 Hz, 2H), 3.80 (t, *J* = 6.8 Hz, 2H), 2.94 (s, 3H), 1.27 (t, *J* = 6.8 Hz, 3H). LC-MS: *m/z* 523 [M+H]⁺.

[00698] Preparation of 8-bromo-2-ethoxy-6-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)-1,6-naphthyridin-7(6*H*)-one **12d**



[00699] 8-bromo-2-ethoxy-6-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)-1,6-naphthyridin-7(6*H*)-one **12d** was synthesized from intermediate **11b** with (1-methyl-1*H*-benzo[*d*]imidazol-6-yl)boronic acid *via* general procedure V (Step L). LC-MS: *m/z* 399 [M+H]⁺.

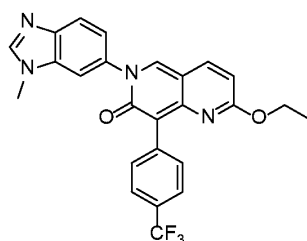
[00700] **Example 226:** Preparation of 2-ethoxy-6-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)-8-(6-(trifluoromethyl)pyridin-3-yl)-1,6-naphthyridin-7(6*H*)-one



[00701] The title compound was synthesized from intermediate **12d** with (6-(trifluoromethyl)pyridin-3-yl)boronic acid *via* general procedure V (Step M).

[00702] ^1H NMR (400 MHz, DMSO- d_6) δ : 9.05 (d, J =1.6 Hz, 1H), 8.88 (s, 1H), 8.37 (dd, J =8.4 Hz, 2.0 Hz, 1H), 8.35 (s, 1H), 8.03 (d, J =9.0 Hz, 1H), 7.89 (d, J =2.0 Hz, 1H), 7.80 (d, J =8.4 Hz, 1H), 7.38 (dd, J =8.4 Hz, 2.0 Hz, 1H), 6.62 (d, J =8.8 Hz, 1H), 4.28 (q, J =7.2 Hz, 2H), 3.88 (s, 3H), 1.28 (t, J =7.2 Hz, 3H). LC-MS: m/z 466 $[\text{M}+\text{H}]^+$.

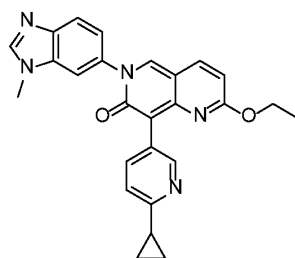
[00703] **Example 227:** 2-ethoxy-6-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)-8-(4-(trifluoromethyl)phenyl)-1,6-naphthyridin-7(6*H*)-one



[00704] The title compound was synthesized from intermediate **12d** with (4-(trifluoromethyl)phenyl)boronic acid *via* general procedure V (Step M).

[00705] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.80 (s, 1H), 8.34 (s, 1H), 8.00 (d, J =8.8 Hz, 1H), 7.90-7.84 (m, 3H), 7.79 (d, J =8.4 Hz, 1H), 7.71 (d, J =8.0 Hz, 2H), 7.36 (dd, J =8.8 Hz, 2.4 Hz, 1H), 6.57 (d, J =8.8 Hz, 1H), 4.25 (q, J =7.2 Hz, 2H), 3.88 (s, 3H), 1.26 (t, J =7.2 Hz, 3H). LC-MS: m/z 465 $[\text{M}+\text{H}]^+$.

[00706] **Example 228:** 8-(6-cyclopropylpyridin-3-yl)-2-ethoxy-6-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)-1,6-naphthyridin-7(6*H*)-one

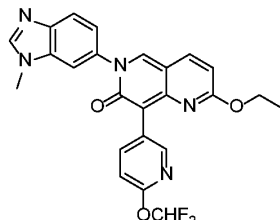


[00707] The title compound was synthesized from intermediate **12d** with (6-cyclopropylpyridin-3-yl)boronic acid *via* general procedure V (Step M).

[00708] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.74 (s, 1H), 8.64 (d, J =1.6 Hz, 1H), 8.34 (s, 1H), 7.97 (d, J =9.2 Hz, 1H), 7.89 (dd, J =8.0 Hz, 2.4 Hz, 1H), 7.85 (d, J =2.4 Hz, 1H), 7.78 (d, J =8.4 Hz, 1H), 7.35 (dd, J =8.8 Hz, 2.0 Hz, 1H), 7.28 (d, J =8.0 Hz, 1H), 6.56 (d, J =9.2 Hz, 1H), 4.26 (q, J =7.2 Hz,

2H), 3.88 (s, 3H), 2.16-2.06 (m, 1H), 1.28 (t, $J = 7.2$ Hz, 3H), 0.99-0.88 (m, 4H). LC-MS: m/z 438 $[M+H]^+$.

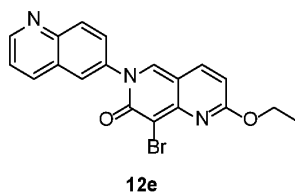
[00709] Example 229: 8-(6-(difluoromethoxy)pyridin-3-yl)-2-ethoxy-6-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)-1,6-naphthyridin-7(6*H*)-one



[00710] The title compound was synthesized from intermediate **12d** with 2-(difluoromethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine *via* general procedure V (Step M).

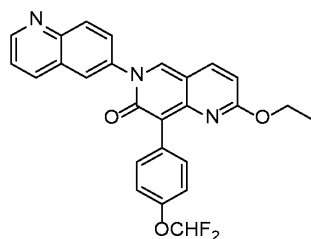
[00711] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.77 (s, 1H), 8.51 (d, $J = 1.6$ Hz, 1H), 8.34 (s, 1H), 8.19 (dd, $J = 8.8$ Hz, 2.0 Hz, 1H), 8.00 (d, $J = 9.2$ Hz, 1H), 7.86 (d, $J = 2.0$ Hz, 1H), 7.79 (d, $J = 8.4$ Hz, 1H), 7.75 (t, $J_{\text{HF}} = 73.2$ Hz, 1H), 7.36 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 7.10 (d, $J = 9.2$ Hz, 1H), 6.58 (d, $J = 9.2$ Hz, 1H), 4.28 (q, $J = 7.2$ Hz, 2H), 3.88 (s, 3H), 1.28 (t, $J = 7.2$ Hz, 3H). LC-MS: m/z 464 $[M+H]^+$.

[00712] Preparation of 8-bromo-2-ethoxy-6-(quinolin-6-yl)-1,6-naphthyridin-7(6*H*)-one **12e**



[00713] 8-bromo-2-ethoxy-6-(quinolin-6-yl)-1,6-naphthyridin-7(6*H*)-one **12e** was synthesized from intermediate **11b** with quinolin-6-ylboronic acid *via* general procedure V (Step L). LC-MS: m/z 396 $(M+H)^+$.

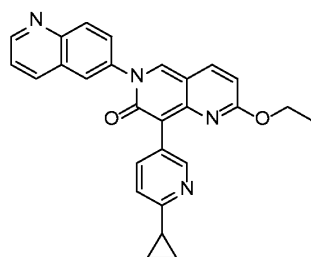
[00714] Example 230: Preparation of 8-(4-(difluoromethoxy)phenyl)-2-ethoxy-6-(quinolin-6-yl)-1,6-naphthyridin-7(6*H*)-one



[00715] The title compound was synthesized from intermediate **12e** with 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane *via* general procedure V (Step M).

[00716] ^1H NMR (400 MHz, DMSO- d_6) δ : 9.02 (dd, $J = 4.4$ Hz, 2.0 Hz, 1H), 8.83 (s, 1H), 8.48 (dd, $J = 8.8$ Hz, 1.2 Hz, 1H), 8.24 (d, $J = 2.4$ Hz, 1H), 8.16 (d, $J = 8.8$ Hz, 1H), 7.97 (d, $J = 9.2$ Hz, 1H), 7.94 (dd, $J = 8.8$ Hz, 2.0 Hz, 1H), 7.71 (d, $J = 8.8$ Hz, 2H), 7.65 (dd, $J = 8.4$ Hz, 4.0 Hz, 1H), 7.28 (t, $J_{\text{HF}} = 74.4$ Hz, 1H), 7.16 (d, $J = 8.8$ Hz, 2H), 6.57 (d, $J = 8.8$ Hz, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 1.28 (t, $J = 7.2$ Hz, 3H). LC-MS: m/z 460 $[\text{M}+\text{H}]^+$.

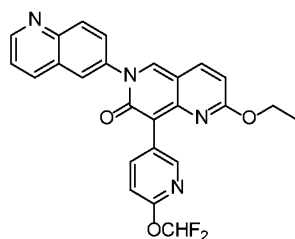
[00717] **Example 231:** 8-(6-cyclopropylpyridin-3-yl)-2-ethoxy-6-(quinolin-6-yl)-1,6-naphthyridin-7(6H)-one



[00718] The title compound was synthesized from intermediate **12e** with (6-cyclopropylpyridin-3-yl)boronic acid *via* general procedure V (Step M).

[00719] ^1H NMR (400 MHz, DMSO- d_6) δ : 9.02 (dd, $J = 4.0$ Hz, 2.0 Hz, 1H), 8.84 (s, 1H), 8.65 (d, $J = 2.0$ Hz, 1H), 8.47 (dd, $J = 8.8$ Hz, 2.0 Hz, 1H), 8.24 (d, $J = 2.4$ Hz, 1H), 8.16 (d, $J = 9.2$ Hz, 1H), 7.98 (d, $J = 9.2$ Hz, 1H), 7.94 (dd, $J = 9.2$ Hz, 2.4 Hz, 1H), 7.90 (dd, $J = 8.0$ Hz, 2.0 Hz, 1H), 7.65 (dd, $J = 8.4$ Hz, 4.4 Hz, 1H), 7.28 (d, $J = 8.0$ Hz, 1H), 6.58 (d, $J = 9.2$ Hz, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 2.16-2.06 (m, 1H), 1.28 (t, $J = 7.2$ Hz, 3H), 0.98-0.91 (m, 4H). LC-MS: m/z 435 $[\text{M}+\text{H}]^+$.

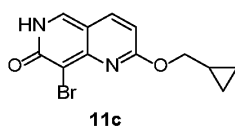
[00720] **Example 232:** 8-(6-(difluoromethoxy)pyridin-3-yl)-2-ethoxy-6-(quinolin-6-yl)-1,6-naphthyridin-7(6H)-one



[00721] The title compound was synthesized from intermediate **12e** with 2-(difluoromethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine *via* general procedure V (Step M).

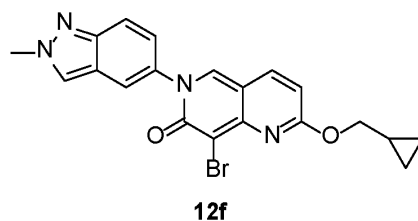
[00722] ^1H NMR (400 MHz, DMSO- d_6) δ : 9.02 (dd, $J = 4.2$ Hz, 2.0 Hz, 1H), 8.89 (s, 1H), 8.53 (d, $J = 2.0$ Hz, 1H), 8.48 (dd, $J = 8.4$ Hz, 1.2 Hz, 1H), 8.25 (d, $J = 2.4$ Hz, 1H), 8.21 (dd, $J = 8.4$ Hz, 2.4 Hz, 1H), 8.17 (d, $J = 9.0$ Hz, 1H), 8.00 (d, $J = 9.0$ Hz, 1H), 7.96 (dd, $J = 9.0$ Hz, 2.0 Hz, 1H), 7.76 (t, $J_{\text{HF}} = 73.2$ Hz, 1H), 7.66 (dd, $J = 8.4$ Hz, 4.2 Hz, 1H), 7.11 (dd, $J = 8.4$ Hz, 0.4 Hz, 1H), 6.61 (d, $J = 9.0$ Hz, 1H), 4.28 (q, $J = 7.2$ Hz, 2H), 1.28 (t, $J = 7.2$ Hz, 3H). LC-MS: m/z 461 ($\text{M}+\text{H}$) $^+$.

[00723] Preparation of 8-bromo-2-(cyclopropylmethoxy)-1,6-naphthyridin-7(6H)-one **11c**



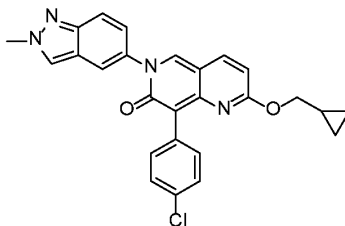
[00724] 8-bromo-2-(cyclopropylmethoxy)-1,6-naphthyridin-7(6H)-one **11c** was synthesized from intermediate **14** with cyclopropylmethanol *via* general procedure V (Step O). LC-MS: m/z 295 [$\text{M}+\text{H}$] $^+$.

[00725] Preparation of 8-bromo-2-(cyclopropylmethoxy)-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one **12f**



[00726] 8-bromo-2-(cyclopropylmethoxy)-6-(2-methyl-2*H*-indazol-5-yl)-1,6-naphthyridin-7(6*H*)-one **12f** was synthesized from intermediate **11c** with 2-methyl-2*H*-indazol-5-ylboronic acid *via* general procedure V (Step L). LC-MS: m/z 425, 427 $[M+H]^+$.

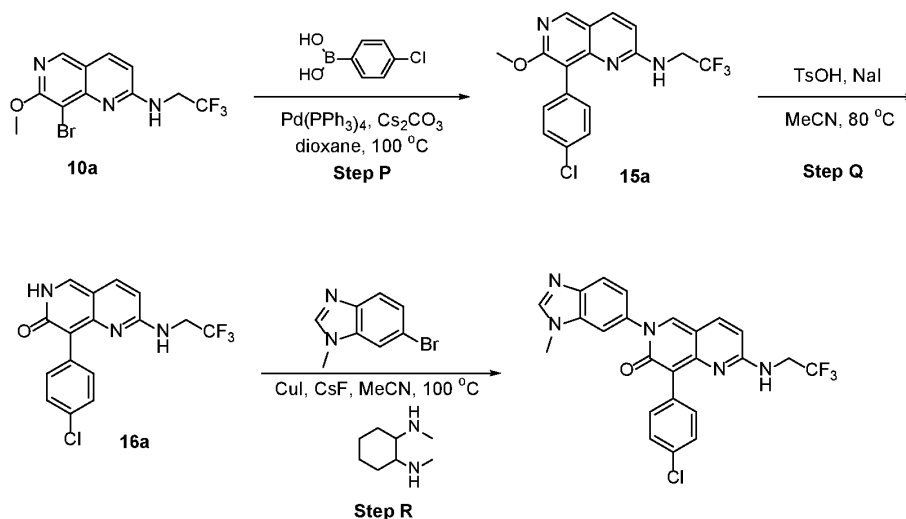
Example 233: Preparation of 8-(4-chlorophenyl)-2-(cyclopropylmethoxy)-6-(2-methyl-2*H*-indazol-5-yl)-1,6-naphthyridin-7(6*H*)-one



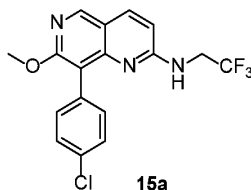
[00727] The title compound was synthesized from intermediate **12f** with 4-chlorophenylboronic acid *via* general procedure V (Step M).

[00728] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.75 (s, 1H), 8.49 (s, 1H), 7.97 (d, $J = 9.2$ Hz, 1H), 7.89 (dd, $J = 2.0$ Hz, 0.4 Hz, 1H), 7.70 (d, $J = 9.2$ Hz, 1H), 7.65 (d, $J = 8.8$ Hz, 2H), 7.39 (d, $J = 8.8$ Hz, 2H), 7.33 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 6.57 (d, $J = 9.2$ Hz, 1H), 4.22 (s, 3H), 4.08 (d, $J = 7.6$ Hz, 2H), 1.23-1.11 (m, 1H), 0.53-0.46 (m, 2H), 0.26-0.20 (m, 2H). LC-MS: m/z 457 $[M+H]^+$.

[00729] **Example 234:** Preparation of 8-(4-chlorophenyl)-6-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6*H*)-one

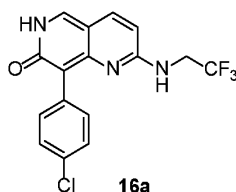


[00730] Step P: 8-(4-chlorophenyl)-7-methoxy-*N*-(2,2,2-trifluoroethyl)-1,6-naphthyridin-2-amine **15a**



[00731] A mixture of 8-bromo-7-methoxy-*N*-(2,2,2-trifluoroethyl)-1,6-naphthyridin-2-amine (300.0 mg, 0.9 mmol, 1.0 equiv.), Pd(PPh₃)₄ (52.0 mg, 0.05 mmol, 0.05 equiv.), Cs₂CO₃ (580.0 mg, 1.8 mmol, 2.0 equiv.) and 4-chlorophenylboronic acid (208.0 mg, 1.3 mmol, 1.5 equiv.) in dioxane-water (5.0 mL, 9/1, v/v) was stirred at 100°C under N₂ atmosphere for 16h. Then the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). All the organic layers were combined and washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: PE/EA = 2/1) to afford 8-(4-chlorophenyl)-7-methoxy-*N*-(2,2,2-trifluoroethyl)-1,6-naphthyridin-2-amine (300 mg, 92% yield) as a white solid. LC-MS: *m/z* 368 [M+H]⁺.

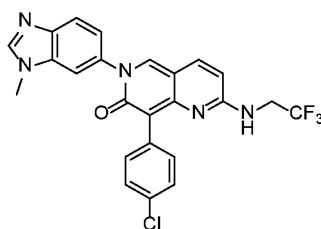
[00732] Step Q: 8-(4-chlorophenyl)-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6*H*)-one **16a**



[00733] A mixture of 8-(4-chlorophenyl)-7-methoxy-*N*-(2,2,2-trifluoroethyl)-1,6-naphthyridin-2-amine (300 mg, 0.8 mmol, 1.0 equiv.), TsOH (422 mg, 2.5 mmol, 3.0 equiv.), NaI (407.0 mg, 2.5 mmol, 3.0 equiv.) in MeCN (10 mL) was stirred at 80 °C for 2h. Then the reaction mixture was quenched with ice water (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (DCM/MeOH = 20/1) to afford 8-

(4-chlorophenyl)-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6*H*)-one (280 mg, 97% yield) as a white solid. LC-MS: m/z 354 $[M+H]^+$.

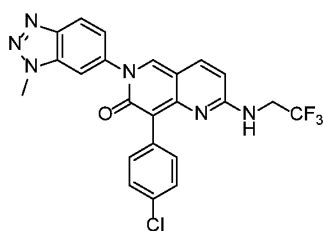
[00734] Example 234, Step R: 8-(4-chlorophenyl)-6-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6*H*)-one



[00735] A mixture of 8-(4-chlorophenyl)-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6*H*)-one (50.0 mg, 0.14 mmol, 1.0 equiv.), CuI (26.6 mg, 0.14 mmol, 1.0 equiv.), CsF (63.8 mg, 0.4 mmol, 3.0 equiv.), *N*₁,*N*₂-dimethylcyclohexane-1,2-diamine (29.8 mg, 0.2 mmol, 1.5 equiv.), and 6-bromo-1-methyl-1*H*-benzo[*d*]imidazole (44.3 mg, 0.2 mmol, 1.5 equiv.) in MeCN (3 mL) was stirred at 100 °C under N₂ atmosphere for 3h. Then the reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by RP-prep-HPLC to afford 8-(4-chlorophenyl)-6-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6*H*)-one (**Example 234**).

[00736] ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.50 (s, 1H), 8.40-8.28 (m, 2H), 7.82 (s, 1H), 7.75 (d, J = 9.2 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.37-7.28 (m, 3H), 6.51 (d, J = 8.8 Hz, 1H), 4.22-4.10 (m, 2H), 3.87 (s, 3H). LC-MS: m/z 484 $[M+H]^+$.

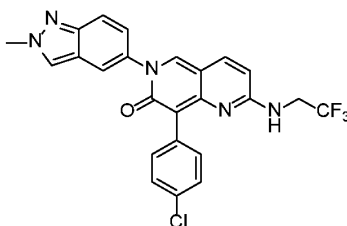
[00737] Example 235: 8-(4-chlorophenyl)-6-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-6-yl)-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6*H*)-one



[00738] The title compound was synthesized from intermediate **16a** with 6-bromo-1-methyl-1*H*-benzo[*d*][1,2,3]triazole *via* general procedure V (Step R).

[00739] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.53 (s, 1H), 8.41 (t, *J* = 6.0 Hz, 1H), 8.17 (d, *J* = 3.6 Hz, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.54 (dd, *J* = 9.2 Hz, 1.6 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.52 (d, *J* = 9.2 Hz, 1H), 4.35 (s, 3H), 4.23-4.10 (m, 2H). LC-MS: *m/z* 485 [M+H]⁺.

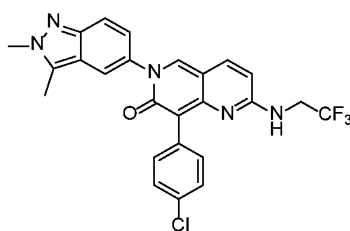
[00740] **Example 236:** 8-(4-chlorophenyl)-6-(2-methyl-2*H*-indazol-5-yl)-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6*H*)-one



[00741] The title compound was synthesized from intermediate **16a** with 5-bromo-2-methyl-2*H*-indazole *via* general procedure V (Step R).

[00742] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.51 (s, 1H), 8.47 (s, 1H), 8.36 (t, *J* = 6.4 Hz, 1H), 7.84 (d, *J* = 1.2 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 9.2 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.31 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 6.50 (d, *J* = 9.2 Hz, 1H), 4.22 (s, 3H), 4.09-4.06 (m, 2H). LC-MS: *m/z* 484 [M+H]⁺.

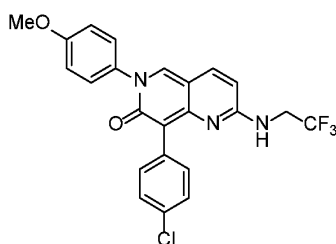
[00743] **Example 237:** 8-(4-chlorophenyl)-6-(2,3-dimethyl-2*H*-indazol-5-yl)-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6*H*)-one



[00744] The title compound was synthesized from intermediate **16a** with 5-bromo-2,3-dimethyl-2*H*-indazole *via* general procedure V (Step R).

[00745] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.50 (s, 1H), 8.34 (br s, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 1H), 6.50 (d, *J* = 8.8 Hz, 1H), 4.18-4.03 (m, 2H), 4.10 (s, 3H), 2.64 (s, 3H). LC-MS: *m/z* 498 [M+H]⁺.

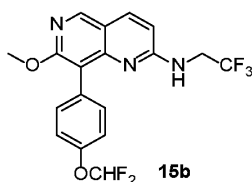
Example 238: 8-(4-chlorophenyl)-6-(4-methoxyphenyl)-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6H)-one



[00746] The title compound was synthesized from intermediate **16a** with 1-bromo-4-methoxybenzene *via* general procedure V (Step R).

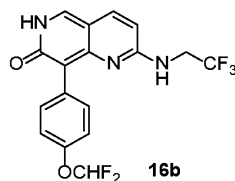
[00747] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.41 (s, 1H), 8.34 (t, *J* = 6.0 Hz, 1H), 7.74 (d, *J* = 9.2 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 9.2 Hz, 1H), 4.20-4.07 (m, 2H), 3.83 (s, 3H). LC-MS: *m/z* 460 [M+H]⁺.

[00748] Preparation of 8-(4-(difluoromethoxy)phenyl)-7-methoxy-*N*-(2,2,2-trifluoroethyl)-1,6-naphthyridin-2-amine **15b**



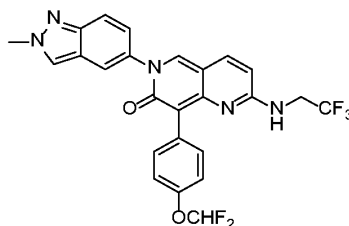
[00749] 8-(4-(difluoromethoxy)phenyl)-7-methoxy-*N*-(2,2,2-trifluoroethyl)-1,6-naphthyridin-2-amine **15b** was synthesized from intermediate **10a** with 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane *via* general procedure V (Step P). LC-MS: m/z 400 $[M+H]^+$.

[00750] Preparation of 8-(4-(difluoromethoxy)phenyl)-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6*H*)-one **16b**



[00751] 8-(4-(difluoromethoxy)phenyl)-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6*H*)-one **16b** was synthesized from intermediate **15b** *via* general procedure V (Step Q). LC-MS: m/z 386 $[M+H]^+$.

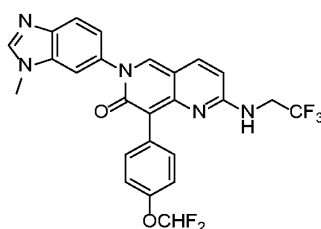
[00752] **Example 239:** 8-(4-(difluoromethoxy)phenyl)-6-(2-methyl-2*H*-indazol-5-yl)-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6*H*)-one



[00753] The title compound was synthesized from intermediate **16b** with 5-bromo-2-methyl-2*H*-indazole *via* general procedure V (Step R).

[00754] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.49 (s, 1H), 8.48 (s, 1H), 8.31 (t, $J = 6.0$ Hz, 1H), 7.84 (d, $J = 1.6$ Hz, 1H), 7.75 (d, $J = 9.2$ Hz, 1H), 7.71-7.64 (m, 3H), 7.31 (dd, $J = 9.2$ Hz, 1.6 Hz, 1H), 7.25 (t, $J_{\text{HF}} = 74.4$ Hz, 1H), 7.09 (d, $J = 8.8$ Hz, 2H), 6.49 (d, $J = 9.2$ Hz, 1H), 4.22 (s, 3H), 4.21-4.09 (m, 2H). LC-MS: m/z 516 $[M+H]^+$.

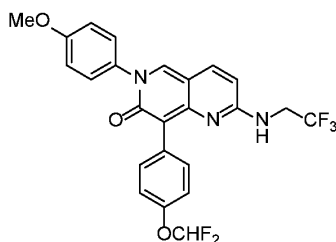
[00755] **Example 240:** 8-(4-(difluoromethoxy)phenyl)-6-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6*H*)-one



[00756] The title compound was synthesized from intermediate **16b** with 6-bromo-1-methyl-1*H*-benzo[*d*]imidazole *via* general procedure V (Step R).

[00757] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.49 (s, 1H), 8.33 (br s, 1H), 8.32 (s, 1H), 7.81 (d, *J* = 1.6 Hz, 1H), 7.78-7.72 (m, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.31 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.25 (t, *J*_{HF} = 74.4 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.51 (d, *J* = 9.2 Hz, 1H), 4.22-4.10 (m, 2H), 3.87 (s, 3H). LC-MS: *m/z* 516 [M+H]⁺.

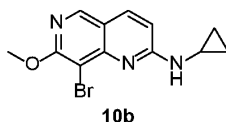
[00758] **Example 241:** 8-(4-(difluoromethoxy)phenyl)-6-(4-methoxyphenyl)-2-(2,2,2-trifluoroethylamino)-1,6-naphthyridin-7(6*H*)-one



[00759] The title compound was synthesized from intermediate **16b** with 1-bromo-4-methoxybenzene *via* general procedure V (Step R).

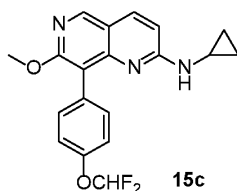
[00760] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.40 (s, 1H), 8.30 (t, *J* = 5.6 Hz, 1H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 9.2 Hz, 2H), 7.24 (t, *J*_{HF} = 74.4 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.07 (d, *J* = 9.2 Hz, 2H), 6.48 (d, *J* = 9.2 Hz, 1H), 4.20-4.07 (m, 2H), 3.82 (s, 3H). LC-MS: *m/z* 492 [M+H]⁺.

[00761] Preparation of 8-bromo-*N*-cyclopropyl-7-methoxy-1,6-naphthyridin-2-amine **10b**



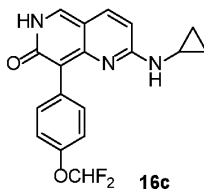
[00762] 8-bromo-*N*-cyclopropyl-7-methoxy-1,6-naphthyridin-2-amine **10b** was synthesized from **key intermediate I** with cyclopropanamine *via* general procedure V (Step J). LC-MS: m/z 294 $[M+H]^+$.

[00763] Preparation of *N*-cyclopropyl-8-(4-(difluoromethoxy)phenyl)-7-methoxy-1,6-naphthyridin-2-amine **15c**



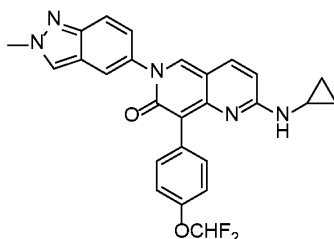
[00764] *N*-cyclopropyl-8-(4-(difluoromethoxy)phenyl)-7-methoxy-1,6-naphthyridin-2-amine **15c** was synthesized from intermediate **10b** with 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane *via* general procedure V (Step P). LC-MS: m/z 358 $[M+H]^+$.

[00765] Preparation of 2-(cyclopropylamino)-8-(4-(difluoromethoxy)phenyl)-1,6-naphthyridin-7(6*H*)-one **16c**



[00766] 2-(cyclopropylamino)-8-(4-(difluoromethoxy)phenyl)-1,6-naphthyridin-7(6*H*)-one **16c** was synthesized from intermediate **15c** *via* general procedure V (Step Q). LC-MS: m/z 344 $[M+H]^+$.

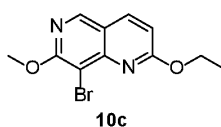
[00767] **Example 242:** Preparation of 2-(cyclopropylamino)-8-(4-(difluoromethoxy)phenyl)-6-(2-methyl-2*H*-indazol-5-yl)-1,6-naphthyridin-7(6*H*)-one



[00768] The title compound was synthesized from intermediate **16c** with 5-bromo-2-methyl-2H-indazole *via* general procedure V (Step R).

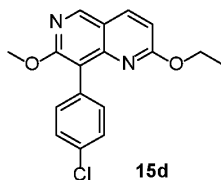
[00769] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.46 (s, 1H), 8.37 (br s, 1H), 7.90 (br s, 1H), 7.84-7.81 (m, 2H), 7.87 (d, $J = 9.2$ Hz, 1H), 7.59 (d, $J = 8.4$ Hz, 1H), 7.29 (dd, $J = 9.2, 2.0$ Hz, 1H), 7.23 (t, $J_{\text{HF}} = 74.6$ Hz, 1H), 7.08 (d, $J = 8.4$ Hz, 2H), 6.31 (t, $J = 8.8$ Hz, 1H), 4.22 (s, 3H), 2.80-2.70 (m, 1H), 0.80-0.61 (m, 2H), 0.55-0.42 (m, 2H). LC-MS: m/z 474 $[\text{M}+\text{H}]^+$.

[00770] Preparation of 8-bromo-2-ethoxy-7-methoxy-1,6-naphthyridine **10c**



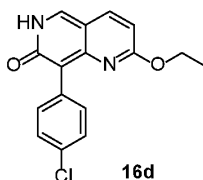
[00771] 8-bromo-2-ethoxy-7-methoxy-1,6-naphthyridine **10c** was synthesized from **key intermediate I** with EtONa/EtOH *via* general procedure V (Step J). LC-MS: m/z 283 $[\text{M}+\text{H}]^+$.

[00772] Preparation of 8-(4-chlorophenyl)-2-ethoxy-7-methoxy-1,6-naphthyridine **15d**



[00773] 8-(4-chlorophenyl)-2-ethoxy-7-methoxy-1,6-naphthyridine **15d** was synthesized from **10c** with 4-chlorophenylboronic acid *via* general procedure V (Step P). LC-MS: m/z 315 $[\text{M}+\text{H}]^+$.

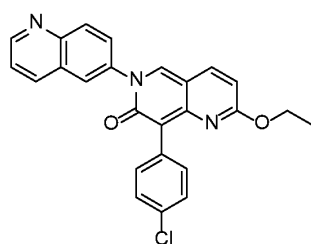
[00774] Preparation of 8-(4-chlorophenyl)-2-ethoxy-1,6-naphthyridin-7(6H)-one **16d**



[00775] A mixture of 8-(4-chlorophenyl)-2-ethoxy-7-methoxy-1,6-naphthyridine (550.0 mg, 1.8 mmol, 1.0 equiv.), TsOH (958.0 mg, 5.3 mmol, 3.0

equiv), LiCl (115.0 mg, 5.3 mmol, 3.0 equiv) in DMF (12.0 mL) was stirred at 120 °C for 5 h. The mixture was poured into ice NH₄Cl aq. (10 mL). The mixture was extracted with EA (10 mL x 3), and the combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel (PE : EA = 4 : 1 to 0 : 1) to afford 8-(4-chlorophenyl)-2-ethoxy-1,6-naphthyridin-7(6*H*)-one (180 mg, 34% yield) as a yellow solid. LC-MS: *m/z* 301 [M+H]⁺.

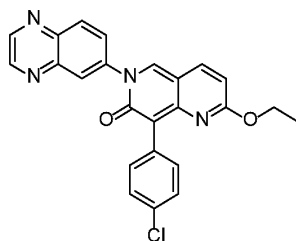
[00776] **Example 243:** Preparation of 8-(4-chlorophenyl)-2-ethoxy-6-(quinolin-6-yl)-1,6-naphthyridin-7(6*H*)-one



[00777] The title compound was synthesized from intermediate **16d** with 6-bromoquinoline *via* general procedure V (Step R).

[00778] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.02 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.85 (s, 1H), 8.48 (d, *J* = 7.2 Hz 1H), 8.24 (d, *J* = 2.4 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.95 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.65 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 6.57 (d, *J* = 9.2 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H). LC-MS: *m/z* 428 [M+H]⁺.

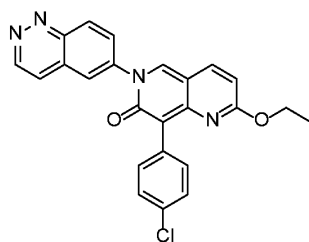
[00779] **Example 244:** 8-(4-chlorophenyl)-2-ethoxy-6-(quinoxalin-6-yl)-1,6-naphthyridin-7(6*H*)-one



[00780] The title compound was synthesized from intermediate **16d** with 6-bromoquinoxaline *via* general procedure V (Step R).

[00781] ^1H NMR (400 MHz, DMSO- d_6) δ : 9.06 (dd, J = 4.4 Hz, 2.0 Hz, 2H), 8.88 (s, 1H), 8.38 (d, J = 2.4 Hz, 1H), 8.25 (d, J = 8.8 Hz, 1H), 8.09 (dd, J = 9.0 Hz, 2.0 Hz, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 9.0 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H). LC-MS: m/z 429 $[\text{M}+\text{H}]^+$.

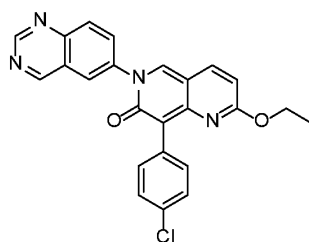
[00782] **Example 245:** 8-(4-chlorophenyl)-6-(cinnolin-6-yl)-2-ethoxy-1,6-naphthyridin-7(6H)-one



[00783] The title compound was synthesized from intermediate **16d** with 6-bromocinnoline *via* general procedure V (Step R).

[00784] ^1H NMR (400 MHz, DMSO- d_6) δ : 9.49 (d, J = 6.0 Hz, 1H), 8.87 (s, 1H), 8.62 (d, J = 9.2 Hz, 1H), 8.37 (d, J = 2.0 Hz, 1H), 8.33 (d, J = 6.0 Hz, 1H), 8.18 (d, J = 6.4 Hz, 1H), 8.16 (d, J = 2.0 Hz, 1H), 7.98 (d, J = 9.2 Hz, 1H), 7.69 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 6.59 (d, J = 9.2 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H). LC-MS: m/z 429 $[\text{M}+\text{H}]^+$.

[00785] **Example 246:** 8-(4-chlorophenyl)-2-ethoxy-6-(quinazolin-6-yl)-1,6-naphthyridin-7(6H)-one

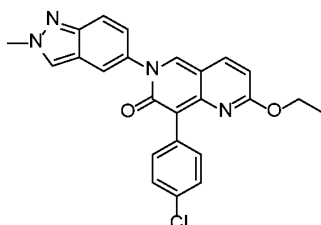


[00786] The title compound was synthesized from intermediate **16d** with 6-bromoquinazoline *via* general procedure V (Step R).

[00787] ^1H NMR (400 MHz, DMSO- d_6) δ : 9.71 (s, 1H), 9.42 (s, 1H), 8.86 (s, 1H), 8.44 (d, J = 2.0 Hz, 1H), 8.24 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 8.17 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.41 (d, J =

8.4 Hz, 2H), 6.59 (d, $J = 8.8$ Hz, 1H), 4.27 (d, $J = 7.2$ Hz, 2H), 1.28 (t, $J = 7.2$ Hz, 3H). LC-MS: m/z 429 $[M+H]^+$.

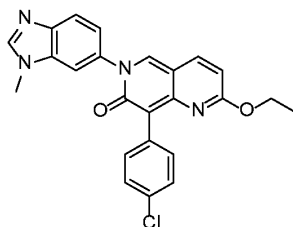
[00788] Example 247: 8-(4-chlorophenyl)-2-ethoxy-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one



[00789] The title compound was synthesized from intermediate **16d** with 5-bromo-2-methyl-2H-indazole *via* general procedure V (Step R).

[00790] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.75 (s, 1H), 8.50 (s, 1H), 7.97 (d, $J = 9.1$ Hz, 1H), 7.89 (d, $J = 2.0$ Hz, 1H), 7.70 (d, $J = 9.1$ Hz, 1H), 7.66 (d, $J = 8.6$ Hz, 2H), 7.40 (d, $J = 8.6$ Hz, 2H), 7.33 (dd, $J = 9.2$ Hz, 2.4 Hz, 1H), 6.54 (d, $J = 9.2$ Hz, 1H), 4.25 (q, $J = 6.8$ Hz, 2H), 4.22 (s, 3H), 1.27 (t, $J = 6.8$ Hz, 3H). LC-MS: m/z 431 $[M+H]^+$.

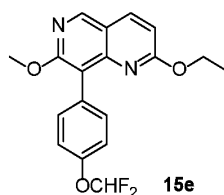
[00791] Example 248: 8-(4-chlorophenyl)-2-ethoxy-6-(1-methyl-1H-benzo[d]imidazol-6-yl)-1,6-naphthyridin-7(6H)-one



[00792] The title compound was synthesized from intermediate **16d** with 6-bromo-1-methyl-1H-benzo[d]imidazole *via* general procedure V (Step R).

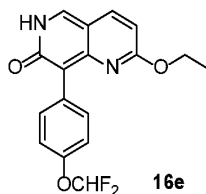
[00793] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.74 (s, 1H), 8.34 (s, 1H), 7.97 (d, $J = 9.0$ Hz, 1H), 7.85 (d, $J = 2.0$ Hz, 1H), 7.78 (d, $J = 8.5$ Hz, 1H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.34 (dd, $J = 8.5$ Hz, 2.0 Hz, 1H), 6.55 (d, $J = 9.0$ Hz, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 3.87 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H). LC-MS: m/z 431 $[M+H]^+$.

[00794] Preparation of 8-(4-(difluoromethoxy)phenyl)-2-ethoxy-7-methoxy-1,6-naphthyridine **15e**



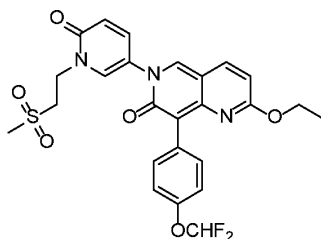
[00795] 8-(4-(difluoromethoxy)phenyl)-2-ethoxy-7-methoxy-1,6-naphthyridine **15e** was synthesized from intermediate **10c** with 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane *via* general procedure V (Step P). LC-MS: m/z 347 $[M+H]^+$.

[00796] Preparation of 8-(4-(difluoromethoxy)phenyl)-2-ethoxy-1,6-naphthyridin-7(6H)-one **16e**



[00797] 8-(4-(difluoromethoxy)phenyl)-2-ethoxy-1,6-naphthyridin-7(6H)-one **16e** was prepared from intermediate **16d** *via* the general procedure V (Step Q). LC-MS: m/z 333 $[M+H]^+$.

[00798] **Example 249:** Preparation of 8-(4-(difluoromethoxy)phenyl)-2-ethoxy-6-(1-(2-(methylsulfonyl)ethyl)-6-oxo-1,6-dihydropyridin-3-yl)-1,6-naphthyridin-7(6H)-one

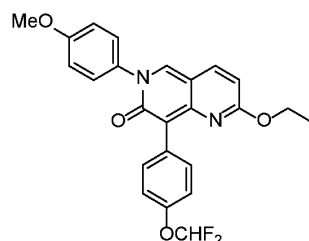


[00799] The title compound was synthesized from intermediate **16e** with 5-bromo-1-(2-(methylsulfonyl)ethyl)pyridin-2(1H)-one *via* general procedure V (Step R).

[00800] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.61 (s, 1H), 8.17 (d, J = 2.8 Hz, 1H), 7.93 (d, J = 9.2 Hz, 1H), 7.69 (dd, J = 9.6 Hz, 2.8 Hz, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.28 (t, J_{HF} = 74.4 Hz, 1H), 6.55 (d, J = 9.2 Hz, 1H), 6.52 (d, J =

9.6 Hz, 1H), 4.34 (t, $J = 7.2$ Hz, 2H), 4.24 (q, $J = 7.2$ Hz, 2H), 3.61 (t, $J = 7.2$ Hz, 2H), 3.08 (s, 3H), 1.26 (t, $J = 7.2$ Hz, 3H). LC-MS: m/z 532 $[M+H]^+$.

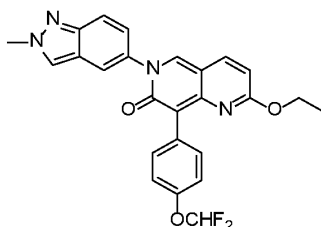
[00801] Example 250: 8-(4-(difluoromethoxy)phenyl)-2-ethoxy-6-(4-methoxyphenyl)-1,6-naphthyridin-7(6H)-one



[00802] The title compound was synthesized from intermediate **16e** with 1-bromo-4-methoxybenzene *via* general procedure V (Step R).

[00803] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.64 (s, 1H), 7.94 (d, $J = 9.2$ Hz, 1H), 7.67 (d, $J = 8.8$ Hz, 2H), 7.46 (d, $J = 8.8$ Hz, 2H), 7.27 (t, $J_{\text{HF}} = 74.4$ Hz, 1H), 7.15 (d, $J = 8.8$ Hz, 2H), 7.09 (d, $J = 8.8$ Hz, 2H), 6.52 (d, $J = 9.2$ Hz, 1H), 4.24 (q, $J = 7.2$ Hz, 2H), 3.83 (s, 3H), 1.26 (t, $J = 7.2$ Hz, 3H). LC-MS: m/z 439 $[M+H]^+$.

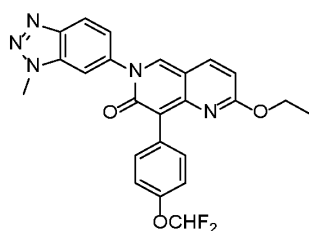
[00804] Example 251: 8-(4-(difluoromethoxy)phenyl)-2-ethoxy-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one



[00805] The title compound was synthesized from intermediate **16e** with 1-bromo-4-methoxybenzene *via* general procedure V (Step R).

[00806] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.73 (s, 1H), 8.50 (s, 1H), 7.96 (d, $J = 9.2$ Hz, 1H), 7.89 (d, $J = 1.6$ Hz, 1H), 7.73-7.65 (m, 3H), 7.34 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 7.28 (t, $J_{\text{HF}} = 74.4$ Hz, 1H), 7.15 (d, $J = 8.8$ Hz, 2H), 6.54 (d, $J = 8.8$ Hz, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 4.22 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H). LC-MS: m/z 463 $[M+H]^+$.

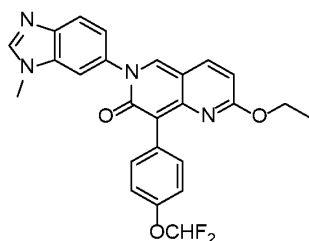
[00807] Example 252: 8-(4-(difluoromethoxy)phenyl)-2-ethoxy-6-(1-methyl-1H-benzo[*d*][1,2,3]triazol-6-yl)-1,6-naphthyridin-7(6H)-one



[00808] The title compound was synthesized from intermediate **16e** with 6-bromo-1-methyl-1*H*-benzo[*d*][1,2,3]triazole *via* general procedure V (Step R).

[00809] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.76 (s, 1H), 8.22-8.17 (m, 2H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.58 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 8.28 (t, *J*_{HF} = 74.4 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 2H), 6.57 (d, *J* = 9.2 Hz, 1H), 4.35 (s, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H). LC-MS: *m/z* 464 [M+H]⁺.

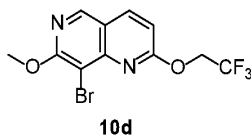
[00810] **Example 253:** 8-(4-(difluoromethoxy)phenyl)-2-ethoxy-6-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)-1,6-naphthyridin-7(6*H*)-one



[00811] The title compound was synthesized from intermediate **16e** with 6-bromo-1-methyl-1*H*-benzo[*d*]imidazole *via* general procedure V (Step R).

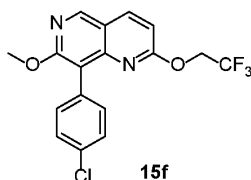
[00812] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.79 (s, 1H), 8.45 (br s, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.94 (br s, 1H), 7.88 (br s, 1H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 6.0 Hz, 1H), 7.34 (t, *J*_{HF} = 74.4 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.60 (d, *J* = 8.8 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.94 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H). LC-MS: *m/z* 463 [M+H]⁺.

[00813] Preparation of 8-bromo-7-methoxy-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridine **10d**



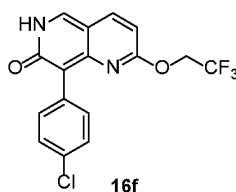
[00814] 8-bromo-7-methoxy-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridine **10d** was synthesized from **key intermediate I** with 2,2,2-trifluoroethanol *via* general procedure V (Step J). LC-MS: m/z 337 $[M+H]^+$.

[00815] Preparation of 8-(4-chlorophenyl)-7-methoxy-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridine **15f**



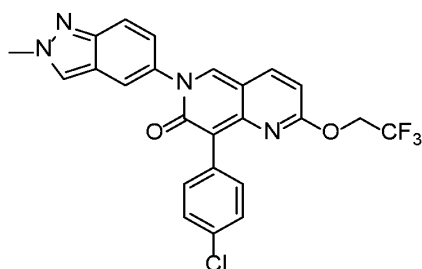
[00816] 8-(4-chlorophenyl)-7-methoxy-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridine **15f** was synthesized from **10d** with 4-chlorophenylboronic acid *via* general procedure V (Step P). LC-MS: m/z 369 $[M+H]^+$.

[00817] Preparation of 8-(4-chlorophenyl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6H)-one **16f**



[00818] 8-(4-chlorophenyl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6H)-one **16f** was synthesized from **15f** *via* general procedure V (Step Q). LC-MS: m/z 355 $[M+H]^+$.

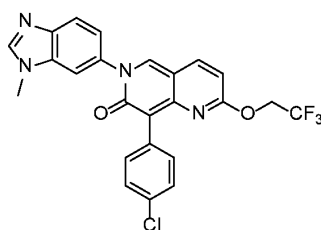
[00819] **Example 254:** Preparation of 8-(4-chlorophenyl)-6-(2-methyl-2H-indazol-5-yl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6H)-one



[00820] The title compound was synthesized from intermediate **16f** with 5-bromo-2-methyl-2H-indazole *via* general procedure V (Step R).

[00821] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.86 (s, 1H), 8.50 (s, 1H), 8.10 (d, $J = 9.2$ Hz, 1H), 7.91 (d, $J = 2.0$ Hz, 1H), 7.71 (d, $J = 9.2$ Hz, 1H), 7.68 (d, $J = 8.8$ Hz, 2H), 7.41 (d, $J = 8.8$ Hz, 2H), 7.35 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 6.71 (d, $J = 9.2$ Hz, 1H), 4.93 (q, $J = 9.2$ Hz, 2H), 4.23 (s, 3H). LC-MS: m/z 485 $[\text{M}+\text{H}]^+$.

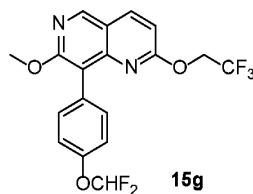
[00822] **Example 255:** 8-(4-chlorophenyl)-6-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6*H*)-one



[00823] The title compound was synthesized from intermediate **16f** with 6-bromo-1-methyl-1*H*-benzo[*d*]imidazole *via* general procedure V (Step R).

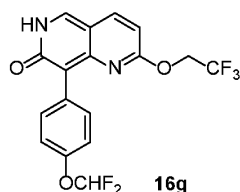
[00824] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.85 (s, 1H), 8.34 (s, 1H), 8.10 (d, $J = 9.2$ Hz, 1H), 7.87 (d, $J = 2.0$ Hz, 1H), 7.79 (d, $J = 8.4$ Hz, 1H), 7.68 (d, $J = 8.8$ Hz, 2H), 7.42 (d, $J = 8.8$ Hz, 2H), 7.35 (dd, $J = 8.8$ Hz, 2.0 Hz, 1H), 6.71 (d, $J = 8.8$ Hz, 1H), 4.93 (q, $J = 9.2$ Hz, 2H), 3.87 (s, 3H). LC-MS: m/z 485 $[\text{M}+\text{H}]^+$.

[00825] Preparation of 8-(4-(difluoromethoxy)phenyl)-7-methoxy-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridine **15g**



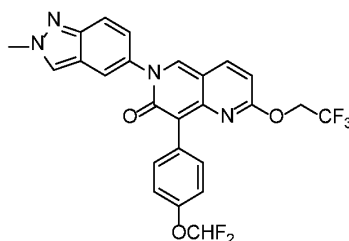
[00826] 8-(4-(difluoromethoxy)phenyl)-7-methoxy-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridine **15g** was synthesized from **10d** with 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane *via* general procedure V (Step P). LC-MS: m/z 401 $[\text{M}+\text{H}]^+$.

[00827] Preparation of 8-(4-(difluoromethoxy)phenyl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6*H*)-one **16g**



[00828] 8-(4-(difluoromethoxy)phenyl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6H)-one **16g** was synthesized from **15g** *via* general procedure V (Step Q). LC-MS: m/z 387 $[M+H]^+$.

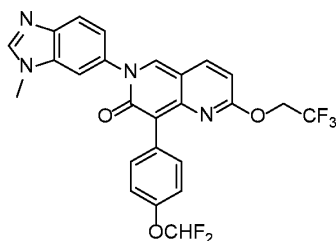
[00829] **Example 256:** Preparation of 8-(4-(difluoromethoxy)phenyl)-6-(2-methyl-2H-indazol-5-yl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6H)-one



[00830] The title compound was synthesized from intermediate **16g** with 5-bromo-2-methyl-2H-indazole *via* general procedure V (Step R).

[00831] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.85 (s, 1H), 8.51 (s, 1H), 8.10 (d, $J = 9.2$ Hz, 1H), 7.91 (d, $J = 2.0$ Hz, 1H), 7.73-7.67(m, 3H), 7.35 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 7.28 (t, $J_{\text{HF}} = 74.4$ Hz, 1H), 7.17 (d, $J = 8.8$ Hz, 2H), 6.70 (d, $J = 9.2$ Hz, 1H), 4.92 (q, $J = 8.8$ Hz, 2H), 4.23 (s, 3H). LC-MS: m/z 517 $[M+H]^+$.

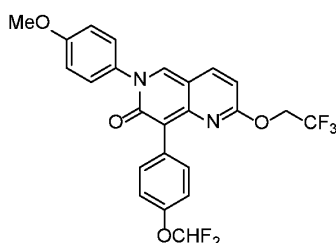
[00832] **Example 257:** 8-(4-(difluoromethoxy)phenyl)-6-(1-methyl-1H-benzo[d]imidazol-6-yl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6H)-one



[00833] The title compound was synthesized from intermediate **16g** with 6-bromo-1-methyl-1H-benzo[d]imidazole *via* general procedure V (Step R).

[00834] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.84 (s, 1H), 8.34 (s, 1H), 8.10 (d, $J = 9.2$ Hz, 1H), 7.87 (d, $J = 2.0$ Hz, 1H), 7.79 (d, $J = 8.8$ Hz, 1H), 7.71 (d, $J = 8.8$ Hz, 2H), 7.36 (dd, $J = 8.8$ Hz, 2.0 Hz, 1H), 7.28 (t, $J_{\text{HF}} = 74.4$ Hz, 1H), 7.17 (d, $J = 8.8$ Hz, 2H), 6.71 (d, $J = 9.2$ Hz, 1H), 4.93 (q, $J = 8.8$ Hz, 2H), 3.88 (s, 3H). LC-MS: m/z 517 $[\text{M}+\text{H}]^+$.

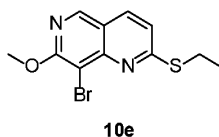
[00835] **Example 258:** 8-(4-(difluoromethoxy)phenyl)-6-(4-methoxyphenyl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6H)-one



[00836] The title compound was synthesized from intermediate **16g** with 1-bromo-4-methoxybenzene *via* general procedure V (Step R).

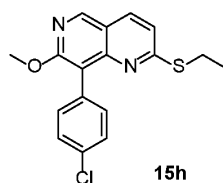
[00837] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.81 (s, 1H), 8.13 (d, $J = 9.2$ Hz, 1H), 7.74 (d, $J = 8.8$ Hz, 2H), 7.54 (d, $J = 8.8$ Hz, 2H), 7.34 (t, $J_{\text{HF}} = 74.4$ Hz, 1H), 7.22 (d, $J = 8.8$ Hz, 2H), 7.16 (d, $J = 8.8$ Hz, 2H), 6.74 (d, $J = 8.8$ Hz, 1H), 4.97 (q, $J = 8.8$ Hz, 2H), 3.89 (s, 3H). LC-MS: m/z 493 $[\text{M}+\text{H}]^+$.

[00838] Preparation of 8-bromo-2-(ethylthio)-7-methoxy-1,6-naphthyridine **10e**



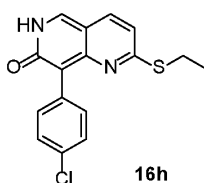
[00839] 8-bromo-2-(ethylthio)-7-methoxy-1,6-naphthyridine **10e** was synthesized from **key intermediate I** with sodium ethanethiolate *via* general procedure V (Step J). LC-MS: m/z 299, 301 $[\text{M}+\text{H}]^+$.

[00840] Preparation of 8-(4-chlorophenyl)-2-(ethylthio)-7-methoxy-1,6-naphthyridine **15h**



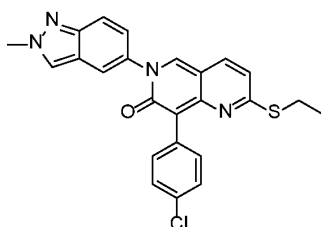
[00841] 8-(4-chlorophenyl)-2-(ethylthio)-7-methoxy-1,6-naphthyridine **15h** was synthesized from **10e** with 4-chlorophenylboronic acid *via* general procedure V (Step P). LC-MS: m/z 331 $[M+H]^+$.

[00842] Preparation of 8-(4-chlorophenyl)-2-(ethylthio)-1,6-naphthyridin-7(6H)-one **16h**



[00843] 8-(4-chlorophenyl)-2-(ethylthio)-1,6-naphthyridin-7(6H)-one **16h** was synthesized from **15h** *via* general procedure V (Step Q). LC-MS: m/z 317 $[M+H]^+$.

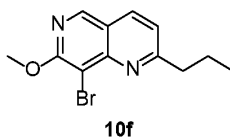
[00844] **Example 259:** Preparation of 8-(4-chlorophenyl)-2-(ethylthio)-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one



[00845] The title compound was synthesized from intermediate **16h** with 5-bromo-2-methyl-2H-indazole *via* general procedure V (Step R).

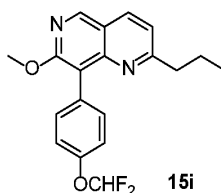
[00846] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.82 (s, 1H), 8.50 (s, 1H), 7.91 (d, $J = 2.0$ Hz, 1H), 7.84 (d, $J = 8.8$ Hz, 1H), 7.71 (d, $J = 9.2$ Hz, 1H), 7.64 (d, $J = 8.6$ Hz, 2H), 7.42 (d, $J = 8.6$ Hz, 2H), 7.35 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 6.84 (d, $J = 8.8$ Hz, 1H), 4.23 (s, 3H), 2.99 (q, $J = 7.2$ Hz, 2H), 1.16 (t, $J = 7.2$ Hz, 3H). LC-MS: m/z 447 $[M+H]^+$.

[00847] Preparation of 8-bromo-7-methoxy-2-propyl-1,6-naphthyridine **10f**



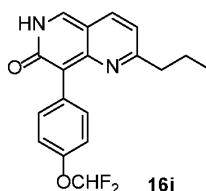
[00848] To a mixture of 8-bromo-2-chloro-7-methoxy-1,6-naphthyridine (300.0 mg, 1.1 mmol, 1.0 equiv.) and Fe(acac)₃ (387.0 mg, 1.1 mmol, 1.0 equiv.) in THF/NMP (5.0 mL/0.5 mL) was added 11.0 mL of propylmagnesium bromide (1M solution in diethyl ether, 11.0 mmol, 10.0 equiv.) slowly at r.t.. The mixture was stirred at r.t. for 1 h, and quenched carefully with water. The mixture was diluted with EtOAc, washed with water followed by brine (30 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EtOAc = 5/1) to give 8-bromo-7-methoxy-2-propyl-1,6-naphthyridine (180 mg, 59% yield) as a yellow solid. LC-MS: *m/z* 281, 283 [M+H]⁺.

[00849] Preparation of 8-(4-(difluoromethoxy)phenyl)-7-methoxy-2-propyl-1,6-naphthyridine **15i**



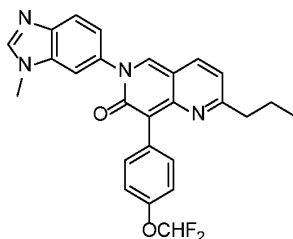
[00850] 8-(4-(difluoromethoxy)phenyl)-7-methoxy-2-propyl-1,6-naphthyridine **15i** was synthesized from **10f** with 2-(4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane *via* general procedure V (Step P). LC-MS: *m/z* 345 [M+H]⁺.

[00851] Preparation of 8-(4-(difluoromethoxy)phenyl)-2-propyl-1,6-naphthyridin-7(6*H*)-one **16i**



[00852] 8-(4-(difluoromethoxy)phenyl)-2-propyl-1,6-naphthyridin-7(6*H*)-one **16i** was synthesized from **15i** *via* general procedure V (Step Q). LC-MS: *m/z* 331 (M+H)⁺.

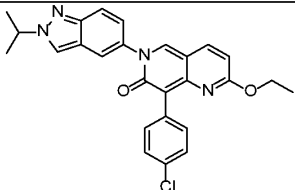
[00853] Example 260: Preparation of 8-(4-(difluoromethoxy)phenyl)-6-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)-2-propyl-1,6-naphthyridin-7(6*H*)-one

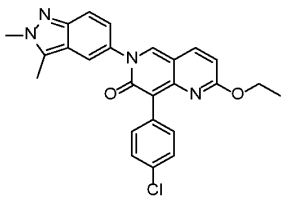
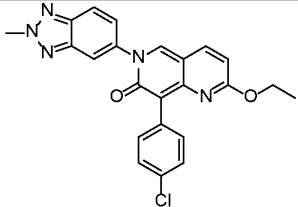
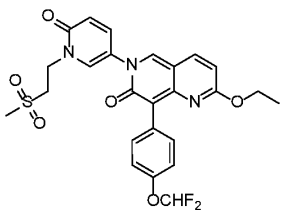


[00854] The title compound was synthesized from intermediate **16i** with 6-bromo-1-methyl-1*H*-benzo[*d*]imidazole *via* general procedure V (Step R).

[00855] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.87 (s, 1H), 8.34 (s, 1H), 7.99 (d, $J = 8.8$ Hz, 1H), 7.87 (d, $J = 2.0$ Hz, 1H), 7.79 (d, $J = 8.8$ Hz, 1H), 7.65 (d, $J = 8.6$ Hz, 2H), 7.36 (dd, $J = 8.8$ Hz, 2.0 Hz, 1H), 7.29 (t, $J_{\text{HF}} = 74.4$ Hz, 1H), 7.16 (d, $J = 8.6$ Hz, 2H), 6.93 (d, $J = 8.8$ Hz, 1H), 3.88 (s, 3H), 2.70-2.66 (m, 2H), 1.73-1.62 (m, 2H), 0.92 (t, $J = 7.2$ Hz, 3H). LC-MS: m/z 461 $[\text{M}+\text{H}]^+$.

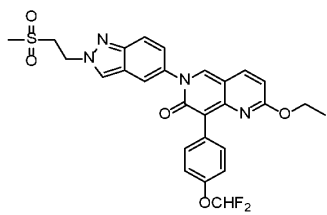
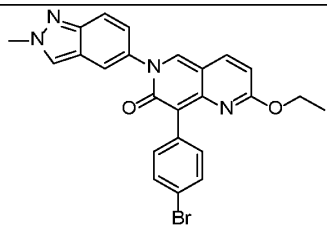
[00856] The following compounds were synthesized via General Procedure V (steps J, P, Q, and R):

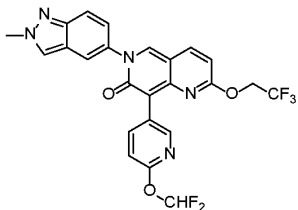
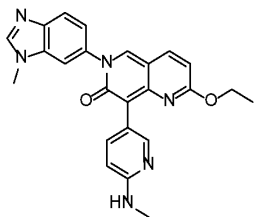
104-A	 8-(4-chlorophenyl)-2-ethoxy-6-(2-isopropyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one (synthesized from 8-(4-chlorophenyl)-2-ethoxy-1,6-naphthyridin-7(6H)-one & 5-bromo-2-isopropyl-2H-indazole (Ref: <i>Organic Letters</i>, 16 (11), 3114-3117; 2014))	LC-MS (ESI) : m/z 459 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.57 (d, $J = 0.9$ Hz, 1H), 7.96 (d, $J = 9.1$ Hz, 1H), 7.87 (dd, $J = 2.1, 0.8$ Hz, 1H), 7.72 (dt, $J = 9.1, 0.9$ Hz, 1H), 7.70 – 7.64 (m, 2H), 7.43 – 7.38 (m, 2H), 7.33 (dd, $J = 9.1, 2.1$ Hz, 1H), 6.54 (d, $J = 9.0$ Hz, 1H), 4.89 (hept, $J = 6.6$ Hz, 1H), 4.26 (q, $J = 7.0$ Hz, 2H), 1.58 (d, $J = 6.6$ Hz, 6H), 1.27 (t, $J = 7.1$ Hz, 3H).
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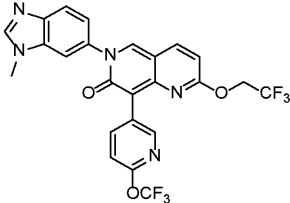
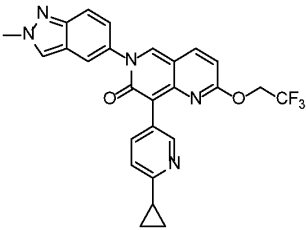
105-A	 8-(4-chlorophenyl)-6-(2,3-dimethyl-2H-indazol-5-yl)-2-ethoxy-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 445 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.74 (s, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.88 (d, J = 1.9 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.60 (d, J = 9.1 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.29 (dd, J = 9.1, 2.0 Hz, 1H), 6.54 (d, J = 9.0 Hz, 1H), 4.25 (q, J = 7.0 Hz, 2H), 4.10 (s, 3H), 2.64 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H).
106-A	 8-(4-chlorophenyl)-2-ethoxy-6-(2-methyl-2H-benzo[d][1,2,3]triazol-5-yl)-1,6-naphthyridin-7(6H)-one (synthesized from 8-(4-chlorophenyl)-2-ethoxy-1,6-naphthyridin-7(6H)-one & 5-bromo-2-methyl-2H-benzo[d][1,2,3]triazole (Ref: WO 2007/84451))	LC-MS (ESI) : m/z 432 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.79 (s, 1H), 8.20 (dd, J = 2.0, 0.7 Hz, 1H), 8.05 (d, J = 9.0 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.58 (dd, J = 9.0, 2.0 Hz, 1H), 7.41 (d, J = 8.6 Hz, 2H), 6.56 (d, J = 9.0 Hz, 1H), 4.56 (s, 3H), 4.26 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.0 Hz, 3H).
107-A		LC-MS (ESI) : m/z 532 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.62 (s, 1H), 8.17 (d, J = 2.9 Hz, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.69 (dd, J = 9.7, 2.9

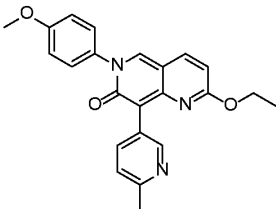
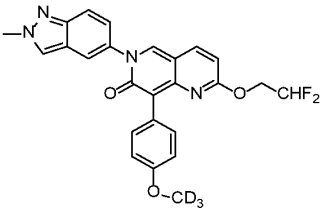
	8-(4-(difluoromethoxy)phenyl)-2-ethoxy-6-(1-(2-(methylsulfonyl)ethyl)-6-oxo-1,6-dihydropyridin-3-yl)-1,6-naphthyridin-7(6H)-one	Hz, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 8.6 Hz, 2H), 6.56 (d, J = 9.0 Hz, 1H), 6.52 (d, J = 9.7 Hz, 1H), 4.34 (t, J = 7.1 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H), 3.61 (t, J = 7.1 Hz, 2H), 3.08 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).
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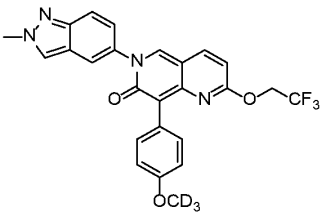
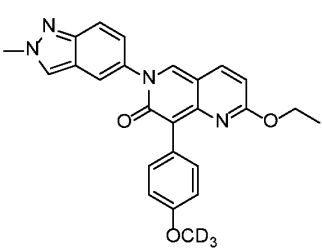
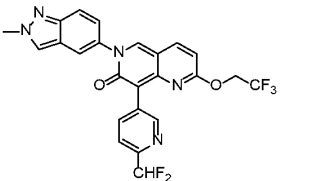
[00857] The following compounds were synthesized via General Procedure V (Method B):

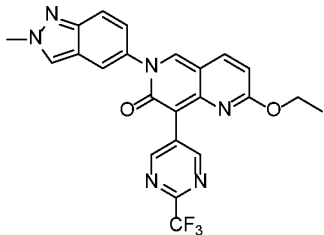
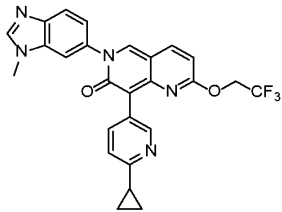
108-A	 8-(4-(difluoromethoxy)phenyl)-2-ethoxy-6-(2-(2-(methylsulfonyl)ethyl)-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 555 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 8.73 (s, 1H), 8.63 (d, J = 0.9 Hz, 1H), 7.96 (d, J = 9.1 Hz, 1H), 7.93 (dd, J = 2.1, 0.8 Hz, 1H), 7.74 (dt, J = 9.2, 0.9 Hz, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.38 (dd, J = 9.1, 2.1 Hz, 1H), 7.27 (t, JHF = 74.4 Hz, 1H), 7.16 (d, J = 8.8 Hz, 2H), 6.54 (d, J = 9.0 Hz, 1H), 4.94 (t, J = 6.8 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.91 (t, J = 6.8 Hz, 2H), 2.95 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H).
109-A	 8-(4-(difluoromethoxy)phenyl)-2-ethoxy-6-(2-(2-(methylsulfonyl)ethyl)-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 475 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 8.75 (s, 1H), 8.50 (s, 1H), 7.97 (d, J = 9.1

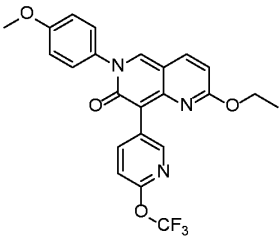
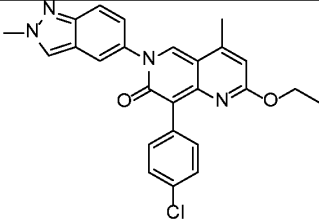
	8-(4-bromophenyl)-2-ethoxy-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one	Hz, 1H), 7.92 – 7.87 (m, 1H), 7.70 (d, J = 9.1 Hz, 1H), 7.61 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 8.6 Hz, 2H), 7.34 (dd, J = 9.1, 2.0 Hz, 1H), 6.54 (d, J = 8.9 Hz, 1H), 4.30 – 4.21 (m, 5H), 1.27 (t, J = 7.1 Hz, 3H).
110-A	 8-(6-(difluoromethoxy)pyridin-3-yl)-6-(2-methyl-2H-indazol-5-yl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 518 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.91 (s, 1H), 8.57 – 8.47 (m, 2H), 8.20 (dd, J = 8.6, 2.4 Hz, 1H), 8.13 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 2.0 Hz, 1H), 7.76 (t, JHF = 73.1 Hz, 1H), 7.72 (d, J = 9.1 Hz, 1H), 7.37 (dd, J = 9.1, 2.0 Hz, 1H), 7.11 (d, J = 8.6 Hz, 1H), 6.74 (d, J = 9.0 Hz, 1H), 4.94 (q, J = 9.0 Hz, 2H), 4.23 (s, 3H).
111-A	 2-ethoxy-6-(1-methyl-1H-benzo[d]imidazol-6-yl)-8-(6-(methylamino)pyridin-3-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 427 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.61 (s, 1H), 8.37 – 8.29 (m, 2H), 8.19 (s, 1H), 7.93 (d, J = 9.1 Hz, 1H), 7.83 (d, J = 1.9 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.71 (dd, J = 8.7, 2.4 Hz, 1H), 7.32 (dd, J = 8.5, 2.0 Hz, 1H), 6.52 (d, J = 8.9

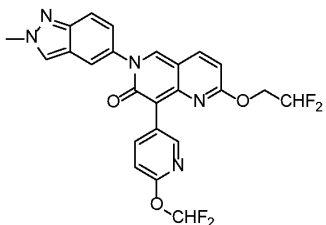
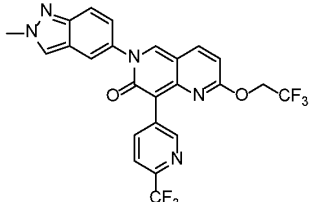
		Hz, 1H), 6.44 (d, J = 8.7 Hz, 1H), 6.39 (t, J = 4.9 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 2.79 (d, J = 4.5 Hz, 3H), 1.30 (t, J = 7.0 Hz, 3H).
112-A	 6-(1-methyl-1H-benzo[d]imidazol-6-yl)-2-(2,2,2-trifluoroethoxy)-8-(6-(trifluoromethoxy)pyridin-3-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 536 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.64 (d, J = 2.3 Hz, 1H), 8.36 (s, 1H), 8.29 (dd, J = 8.5, 2.4 Hz, 1H), 8.14 (d, J = 9.0 Hz, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.39 (dd, J = 8.5, 2.1 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 6.76 (d, J = 9.0 Hz, 1H), 4.95 (q, J = 9.0 Hz, 2H), 3.88 (s, 3H).
113-A	 8-(6-cyclopropylpyridin-3-yl)-6-(2-methyl-2H-indazol-5-yl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 492 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.65 (dd, J = 2.2, 0.8 Hz, 1H), 8.51 (s, 1H), 8.10 (d, J = 9.0 Hz, 1H), 7.93 – 7.87 (m, 2H), 7.72 (dt, J = 9.2, 0.9 Hz, 1H), 7.35 (dd, J = 9.1, 2.0 Hz, 1H), 7.30 (dd, J = 8.1, 0.8 Hz, 1H), 6.71 (d, J = 9.0 Hz, 1H), 4.93 (q, J = 9.1 Hz, 2H), 4.23 (s, 3H), 2.12 (tt, J = 7.6, 5.2 Hz, 1H), 0.95

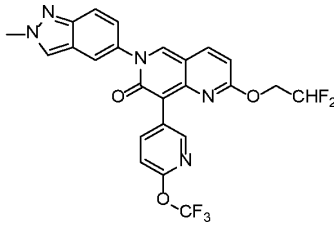
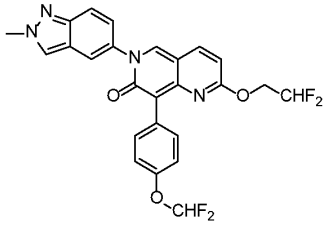
		(ddd, J = 7.3, 5.5, 2.3 Hz, 4H).
114-A	 2-ethoxy-6-(4-methoxyphenyl)-8-(6-methylpyridin-3-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 388 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.68 (dd, J = 2.2, 0.8 Hz, 1H), 8.66 (s, 1H), 7.95 (d, J = 9.1 Hz, 1H), 7.90 (dd, J = 8.0, 2.3 Hz, 1H), 7.47 (d, J = 8.9 Hz, 2H), 7.24 (d, J = 8.1 Hz, 1H), 7.09 (d, J = 9.0 Hz, 2H), 6.54 (d, J = 9.0 Hz, 1H), 4.25 (q, J = 7.0 Hz, 2H), 3.83 (s, 3H), 2.48 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H).
115-A	 2-(2,2-difluoroethoxy)-8-(4-(methoxy-d₃)phenyl)-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 466 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.74 (s, 1H), 8.50 (s, 1H), 8.03 (d, J = 9.0 Hz, 1H), 7.89 (s, 1H), 7.71 (d, J = 9.2 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.34 (dd, J = 9.1, 2.1 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.63 (d, J = 9.0 Hz, 1H), 6.35 (t, JHF = 54.7 Hz, 1H), 4.50 (td, JHF = 15.0, J = 3.6 Hz, 2H), 4.23 (s, 3H).

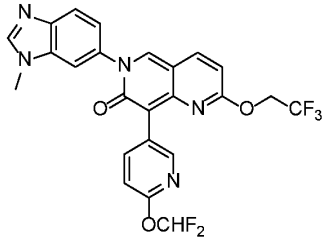
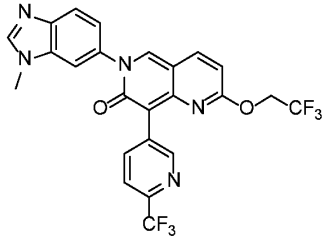
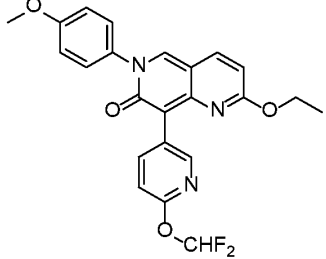
116-A	 8-(4-(methoxy-d₃)phenyl)-6-(2-methyl-2H-indazol-5-yl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 484 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 8.77 (s, 1H), 8.50 (s, 1H), 8.07 (d, J = 9.0 Hz, 1H), 7.90 (s, 1H), 7.71 (d, J = 9.1 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.34 (dd, J = 9.1, 2.1 Hz, 1H), 6.92 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.9 Hz, 1H), 4.94 (q, J = 9.1 Hz, 2H), 4.22 (s, 3H).
117-A	 2-ethoxy-8-(4-(methoxy-d₃)phenyl)-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 430 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 8.66 (s, 1H), 8.49 (s, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.87 (s, 1H), 7.70 (d, J = 9.1 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 9.3 Hz, 1H), 6.91 (d, J = 8.2 Hz, 2H), 6.51 (d, J = 9.0 Hz, 1H), 4.35 – 4.08 (m, 5H), 1.26 (q, J = 7.4 Hz, 3H).
118-A	 8-(6-(difluoromethyl)pyridin-3-yl)-6-(2-methyl-2H-indazol-5-yl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 502 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 8.96 (br s, 2H), 8.52 (s, 1H), 8.29 (dd, J = 8.1, 2.1 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.94 (dd, J = 2.1, 0.8 Hz, 1H), 7.75 – 7.73 (m, 1H), 7.71 (dd, J = 2.2,

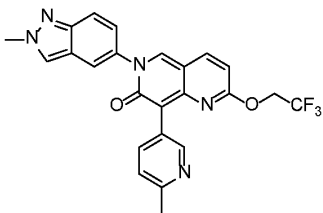
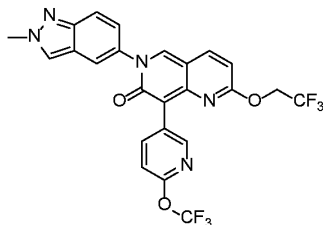
	trifluoroethoxy)-1,6-naphthyridin-7(6H)-one	1.3 Hz, 1H), 7.38 (dd, J = 9.1, 2.1 Hz, 1H), 6.99 (t, JHF = 55.1 Hz, 1H), 6.76 (d, J = 9.0 Hz, 1H), 4.94 (q, J = 9.0 Hz, 2H), 4.23 (s, 3H).
119-A	 2-ethoxy-6-(2-methyl-2H-indazol-5-yl)-8-(2-(trifluoromethyl)pyrimidin-5-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 467 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 9.41 (s, 2H), 8.96 (s, 1H), 8.52 (s, 1H), 8.07 (d, J = 9.1 Hz, 1H), 7.94 (dd, J = 2.0, 0.8 Hz, 1H), 7.77 – 7.69 (m, 1H), 7.38 (dd, J = 9.1, 2.1 Hz, 1H), 6.66 (d, J = 9.0 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 4.23 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H).
120-A	 8-(6-cyclopropylpyridin-3-yl)-6-(1-methyl-1H-benzo[d]imidazol-6-yl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 492 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.85 (s, 1H), 8.65 (d, J = 2.1 Hz, 1H), 8.34 (s, 1H), 8.10 (d, J = 9.0 Hz, 1H), 7.94 – 7.88 (m, 1H), 7.87 (d, J = 2.0 Hz, 1H), 7.79 (d, J = 8.6 Hz, 1H), 7.36 (dd, J = 8.6, 2.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 9.0 Hz, 1H), 4.94 (q, J = 9.0 Hz, 2H), 3.87 (s, 3H), 2.12 (dq, J = 12.8, 7.9, 6.7 Hz, 1H), 0.96 (dt, J = 10.0, 3.3 Hz, 4H).

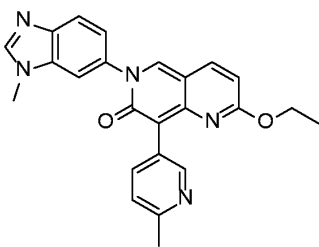
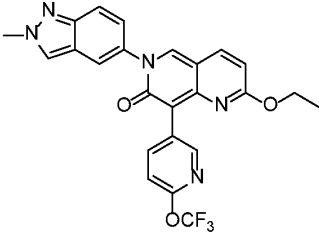
121-A	 2-ethoxy-6-(4-methoxyphenyl)-8-(6-(trifluoromethoxy)pyridin-3-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 458 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 8.74 (s, 1H), 8.60 (dd, J = 2.4, 0.7 Hz, 1H), 8.26 (dd, J = 8.5, 2.4 Hz, 1H), 7.99 (d, J = 9.1 Hz, 1H), 7.49 (d, J = 8.9 Hz, 2H), 7.30 (dd, J = 8.5, 0.7 Hz, 1H), 7.10 (d, J = 9.0 Hz, 2H), 6.57 (d, J = 9.0 Hz, 1H), 4.26 (q, J = 7.0 Hz, 2H), 3.84 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).
122-A	 8-(4-chlorophenyl)-2-ethoxy-4-methyl-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one (synthesized from 3-bromo-5-iodo-2-methoxypyridin-4-amine & ethyl (E)-but-2-enoate <i>via</i> general procedure V (R1-R3-R2 sequence, Method B, Step B-D & L-O))	LC-MS (ESI) : m/z 445 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 8.56 (s, 1H), 8.49 (s, 1H), 7.89 (d, J = 1.9 Hz, 1H), 7.69 (d, J = 9.1 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.43 – 7.37 (m, 2H), 7.34 (dd, J = 9.1, 2.0 Hz, 1H), 6.42 (d, J = 1.3 Hz, 1H), 4.28 – 4.16 (m, 5H), 2.43 (s, 3H), 1.25 (t, J = 7.0 Hz, 3H).

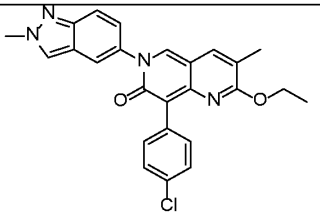
123-A	 2-(2,2-difluoroethoxy)-8-(6-(difluoromethoxy)pyridin-3-yl)-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 500 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 8.87 (s, 1H), 8.55 – 8.49 (m, 2H), 8.19 (dd, J = 8.5, 2.4 Hz, 1H), 8.08 (d, J = 9.1 Hz, 1H), 7.92 (dd, J = 2.1, 0.8 Hz, 1H), 7.76 (t, JHF = 73.1 Hz, 1H), 7.72 (dt, J = 9.2, 0.9 Hz, 1H), 7.36 (dd, J = 9.1, 2.0 Hz, 1H), 7.10 (dd, J = 8.6, 0.7 Hz, 1H), 6.69 (d, J = 9.0 Hz, 1H), 6.36 (tt, JHF = 54.6, J = 3.4 Hz, 1H), 4.53 (td, JHF = 15.1, J = 3.4 Hz, 2H), 4.23 (s, 3H).
124-A	 6-(2-methyl-2H-indazol-5-yl)-2-(2,2,2-trifluoroethoxy)-8-(6-(trifluoromethyl)pyridin-3-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 520 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 9.06 (d, J = 2.0 Hz, 1H), 9.00 (s, 1H), 8.53 (s, 1H), 8.39 (dd, J = 8.2, 2.0 Hz, 1H), 8.17 (d, J = 9.1 Hz, 1H), 7.96 (dd, J = 2.1, 0.8 Hz, 1H), 7.92 (dd, J = 8.3, 0.8 Hz, 1H), 7.73 (dd, J = 9.2, 0.9 Hz, 1H), 7.39 (dd, J = 9.1, 2.0 Hz, 1H), 6.78 (d, J = 9.0 Hz, 1H), 4.95 (q, J = 9.0 Hz, 2H), 4.24 (s, 3H).

125-A	 2-(2,2-difluoroethoxy)-6-(2-methyl-2H-indazol-5-yl)-8-(6-(trifluoromethoxy)pyridin-3-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 518 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 8.91 (s, 1H), 8.63 (dd, J = 2.4, 0.6 Hz, 1H), 8.52 (s, 1H), 8.29 (dd, J = 8.5, 2.4 Hz, 1H), 8.10 (d, J = 9.1 Hz, 1H), 7.93 (dd, J = 2.0, 0.8 Hz, 1H), 7.72 (dt, J = 9.1, 0.9 Hz, 1H), 7.37 (dd, J = 9.1, 2.1 Hz, 1H), 7.31 (dd, J = 8.4, 0.7 Hz, 1H), 6.70 (d, J = 9.0 Hz, 1H), 6.35 (tt, JHF = 54.6, J = 3.5 Hz, 1H), 4.52 (td, JHF = 15.0, J = 3.6 Hz, 2H), 4.23 (s, 3H).
126-A	 2-(2,2-difluoroethoxy)-8-(4-(difluoromethoxy)phenyl)-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 499 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 8.82 (s, 1H), 8.51 (s, 1H), 8.06 (d, J = 9.1 Hz, 1H), 7.91 (dd, J = 2.1, 0.8 Hz, 1H), 7.78 – 7.63 (m, 3H), 7.35 (dd, J = 9.1, 2.0 Hz, 1H), 7.28 (t, JHF = 74.3 Hz, 1H), 7.17 (d, J = 8.7 Hz, 2H), 6.66 (d, J = 9.0 Hz, 1H), 6.35 (tt, JHF = 54.7, J = 3.5 Hz, 1H), 4.51 (td, J = 15.0, 3.5 Hz, 2H), 4.23 (s, 3H).

127-A	 8-(6-(difluoromethoxy)pyridin-3-yl)-6-(1-methyl-1H-benzo[d]imidazol-6-yl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 518 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 8.90 (s, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.35 (s, 1H), 8.20 (dd, J = 8.5, 2.4 Hz, 1H), 8.13 (d, J = 9.0 Hz, 1H), 7.89 (t, J = 2.0 Hz, 1H), 7.76 (t, JHF = 73.1 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.38 (dd, J = 8.5, 2.1 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H), 6.75 (d, J = 9.0 Hz, 1H), 4.94 (q, J = 9.0 Hz, 2H), 3.88 (s, 3H).
128-A	 6-(1-methyl-1H-benzo[d]imidazol-6-yl)-2-(2,2,2-trifluoroethoxy)-8-(6-(trifluoromethyl)pyridin-3-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 520 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 9.06 (s, 1H), 8.99 (s, 1H), 8.39 (d, J = 8.7 Hz, 1H), 8.36 (s, 1H), 8.17 (d, J = 9.0 Hz, 1H), 7.96 – 7.89 (m, 2H), 7.81 (d, J = 8.5 Hz, 1H), 7.40 (dd, J = 8.7, 2.0 Hz, 1H), 6.79 (d, J = 9.0 Hz, 1H), 4.95 (q, J = 9.0 Hz, 2H), 3.88 (s, 3H).
129-A	 8-(6-(difluoromethoxy)pyridin-3-yl)-6-(1-methyl-1H-benzo[d]imidazol-6-yl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 440 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 8.70 (s, 1H), 8.50 (dd, J = 2.3, 0.7 Hz, 1H), 8.16 (dd, J = 8.5, 2.4 Hz, 1H), 7.98 (d, J = 9.1 Hz,

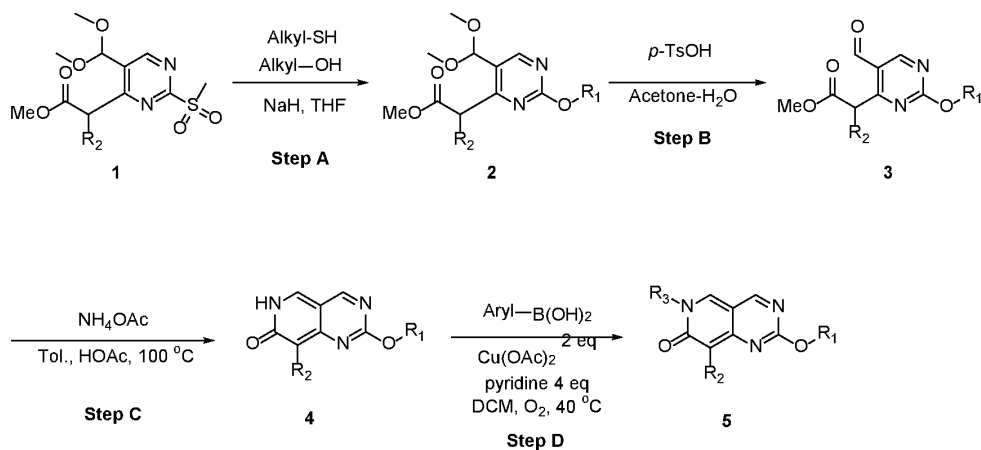
	yl)-2-ethoxy-6-(4-methoxyphenyl)-1,6-naphthyridin-7(6H)-one	1H), 7.76 (t, JHF = 73.1 Hz, 1H), 7.48 (d, J = 8.9 Hz, 2H), 7.13 – 7.07 (m, 3H), 6.56 (d, J = 9.0 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H).
130-A	 6-(2-methyl-2H-indazol-5-yl)-8-(6-methylpyridin-3-yl)-2-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 466 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.87 (s, 1H), 8.71 (d, J = 2.2 Hz, 1H), 8.52 (s, 1H), 8.12 (d, J = 9.0 Hz, 1H), 7.98 – 7.90 (m, 2H), 7.72 (d, J = 9.1 Hz, 1H), 7.37 (dd, J = 9.1, 2.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 9.0 Hz, 1H), 4.94 (q, J = 9.0 Hz, 2H), 4.23 (s, 3H), 2.51 (s, 3H - buried).
131-A	 6-(2-methyl-2H-indazol-5-yl)-2-(2,2,2-trifluoroethoxy)-8-(6-(trifluoromethoxy)pyridin-3-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 536 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.95 (s, 1H), 8.64 (d, J = 2.4 Hz, 1H), 8.52 (s, 1H), 8.29 (dd, J = 8.5, 2.4 Hz, 1H), 8.14 (d, J = 9.0 Hz, 1H), 7.94 (dd, J = 2.1, 0.8 Hz, 1H), 7.76 – 7.69 (m, 1H), 7.37 (dd, J = 9.1, 2.0 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 6.75 (d, J = 9.0 Hz, 1H), 4.94 (q, J = 9.1 Hz, 2H), 4.23 (s, 3H).

132-A	 2-ethoxy-6-(1-methyl-1H-benzo[d]imidazol-6-yl)-8-(6-methylpyridin-3-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 412 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 8.75 (s, 1H), 8.70 (d, J = 2.2 Hz, 1H), 8.34 (s, 1H), 7.98 (d, J = 9.1 Hz, 1H), 7.93 (dd, J = 8.0, 2.3 Hz, 1H), 7.86 (d, J = 2.0 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.35 (dd, J = 8.5, 2.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 6.56 (d, J = 9.0 Hz, 1H), 4.27 (q, J = 7.0 Hz, 2H), 3.88 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H).
133-A	 2-ethoxy-6-(2-methyl-2H-indazol-5-yl)-8-(6-(trifluoromethoxy)pyridin-3-yl)-1,6-naphthyridin-7(6H)-one	LC-MS (ESI) : m/z 482 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 8.83 (s, 1H), 8.62 (d, J = 2.3 Hz, 1H), 8.51 (s, 1H), 8.28 (dd, J = 8.5, 2.4 Hz, 1H), 8.01 (d, J = 9.0 Hz, 1H), 7.91 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 9.1 Hz, 1H), 7.36 (dd, J = 9.1, 2.0 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 6.59 (d, J = 9.0 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 4.23 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H).

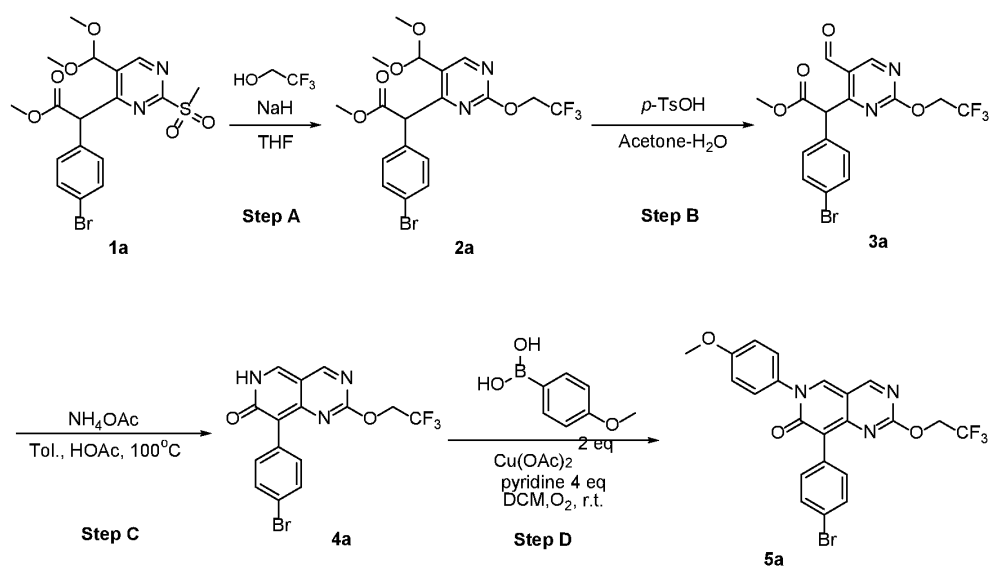
134-A	 8-(4-chlorophenyl)-2-ethoxy-3-methyl-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one (synthesized from 3-bromo-5-iodo-2-methoxypyridin-4-amine & ethyl methacrylate <i>via</i> general procedure V (R1-R3-R2 sequence, Method B, Step B-D & L-O))	LC-MS (ESI) : m/z 445 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.49 (s, 1H), 7.86 (dd, $J = 2.0, 0.8$ Hz, 1H), 7.72 (d, $J = 1.4$ Hz, 1H), 7.71 – 7.65 (m, 3H), 7.39 (d, $J = 8.5$ Hz, 2H), 7.32 (dd, $J = 9.1, 2.1$ Hz, 1H), 4.28 (q, $J = 7.0$ Hz, 2H), 4.22 (s, 3H), 2.12 (d, $J = 1.2$ Hz, 3H), 1.29 (t, $J = 7.0$ Hz, 3H).
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[00858] General Procedure VI:

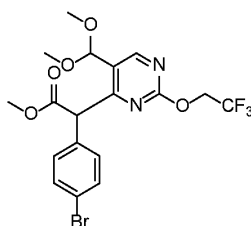
General procedure VI:



[00859] Preparation of **Example 261**:

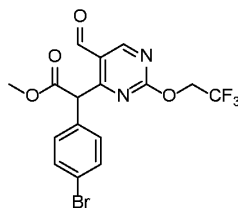


[00860] Step A: methyl 2-(4-bromophenyl)-2-(5-(dimethoxymethyl)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)acetate



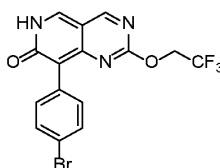
[00861] To a solution of 2,2,2-trifluoroethanol (150 mg, 1.5 mmol, 3 equiv) in THF (3 mL) was added NaH (60% in mineral oil, 60 mg, 1.5 mmol, 3 equiv) at 0 °C. The mixture was stirred at 0 °C for 30 min. Then methyl 2-(4-bromophenyl)-2-(5-(dimethoxymethyl)-2-(methylsulfonyl)pyrimidin-4-yl)acetate (**1a**) (prepared *via* General Procedure III using methyl 2-(4-bromophenyl)acetate (Steps A-C)) (230 mg, 0.5 mmol, 1.0 equiv) was added, and then the mixture was stirred at room temperature (25 °C) for an additional 3h. The reaction mixture was then poured into cooled NH₄Cl (Sat. aq.), and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were dried over Na₂SO₄ and concentrated to give a brown oil, which was purified by silica gel chromatography (PE : EA = 20: 1 ~ 10: 1) to give the methyl 2-(4-bromophenyl)-2-(5-(dimethoxymethyl)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl) acetate (150 mg, 62% yield) as a white solid. LC-MS: *m/z* 479, 481 [M+H]⁺.

[00862] Step B: methyl 2-(4-bromophenyl)-2-(5-formyl-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)acetate



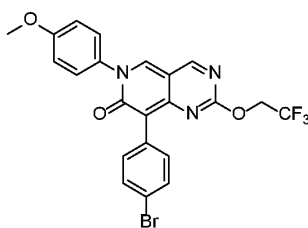
[00863] To a solution of methyl 2-(4-bromophenyl)-2-(5-(dimethoxymethyl)-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)acetate (120 mg, 0.25 mmol, 1.0 equiv) in acetone (1.5 mL) and H₂O (1.5 mL) was added *p*-TSA (10 mg, 0.075 mmol, 0.3 equiv). The resulting mixture was stirred at 70 °C for 1h. Then the reaction mixture was extracted with EtOAc (5 mL x 3), dried over anhydrous Na₂SO₄ and concentrated to afford 2-(4-bromophenyl)-2-(5-formyl-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)acetate (86 mg, crude) as a white solid. LC-MS: *m/z* 433, 435 [M+H]⁺.

[00864] Step C: 8-(4-bromophenyl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00865] To a solution of 2-(4-bromophenyl)-2-(5-formyl-2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl)acetate (86 mg, 0.20 mmol, 1.0 equiv) in AcOH (1 mL) and toluene (1 mL) was added NH₄OAc (512 mg, 6.4 mmol, 320 equiv). The resulting mixture was stirred at 100 °C for 1.5h, then the reaction was quenched by adding NaHCO₃ (aq.). The reaction mixture was extracted with EtOAc (5 mL x 3), dried over anhydrous Na₂SO₄ and concentrated. The resulting crude product was purified by silica gel chromatography to give 8-(4-bromophenyl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (60 mg, 75% yield) as a brown solid. LC-MS: *m/z* 400, 402 [M+H]⁺.

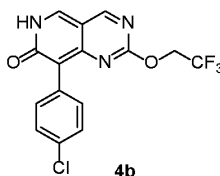
[00866] Step D: 8-(4-bromophenyl)-6-(4-methoxyphenyl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00867] To a solution of 8-(4-bromophenyl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (60 mg, 0.15 mmol, 1.0 equiv) in DCM (3 mL) was added (4-methoxyphenyl)boronic acid (32 mg, 0.3 mmol, 2.0 equiv), Cu(OAc)₂ (54 mg, 0.3 mmol, 2.0 equiv) and pyridine (48 mg, 0.6 mmol, 4.0 equiv). Then the mixture was stirred at 40 °C under O₂ (1 atm) atmosphere overnight. The crude mixture was concentrated under reduced pressure to give a brown oil, then the resulting residue was purified by RP-prep-HPLC to give the 8-(4-bromophenyl)-6-(4-methoxyphenyl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 261**).

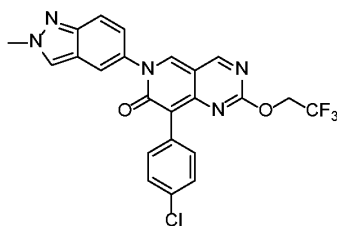
[00868] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.22 (s, 1H), 9.19 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 4.95 (q, *J* = 8.8 Hz, 2H), 3.84 (s, 3H). LC-MS: *m/z* 506, 508 [M+H]⁺.

[00869] Preparation of 8-(4-chlorophenyl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **4b**



[00870] 8-(4-chlorophenyl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **4b** was synthesized from methyl 2-(4-chlorophenyl)-2-(5-(dimethoxymethyl)-2-(methylsulfonyl)pyrimidin-4-yl)acetate *via* general procedure VI (Step A-C) LC-MS: *m/z* 356 [M+H]⁺.

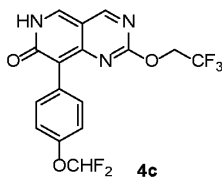
[00871] **Example 262:** Preparation of 8-(4-chlorophenyl)-6-(2-methyl-2*H*-indazol-5-yl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00872] The title compound was synthesized from intermediate **4b** with 2-methyl-2*H*-indazol-5-ylboronic acid *via* general procedure VI (Step D) (Cu(OAc)₂, pyridine, O₂ atmosphere, DCM, 40 °C).

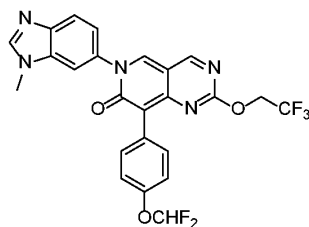
[00873] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.28 (s, 1H), 9.23 (s, 1H), 8.54 (s, 1H), 7.96 (d, *J* = 2.0 Hz, 1H), 7.74 (d, *J* = 9.2 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.38 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 4.95 (q, *J* = 9.2 Hz, 2H), 4.23 (s, 3H). LC-MS: *m/z* 486 [M+H]⁺.

[00874] Preparation of 8-(4-(difluoromethoxy)phenyl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **4c**



[00875] 8-(4-(difluoromethoxy)phenyl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **4c** was synthesized from methyl 2-(4-(difluoromethoxy)phenyl)-2-(5-(dimethoxymethyl)-2-(methylsulfonyl)pyrimidin-4-yl)acetate *via* general procedure VI (Step A-C). LC-MS: *m/z* 388 [M+H]⁺

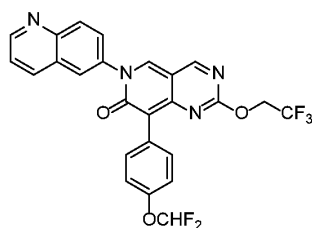
[00876] **Example 263:** Preparation of 8-(4-(difluoromethoxy)phenyl)-6-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00877] The title compound was synthesized from intermediate **4c** with 1-methyl-1*H*-benzo[*d*]imidazol-6-ylboronic acid *via* general procedure VI (Step D) (Cu(OAc)₂, pyridine, O₂ atmosphere, DCM, 40 °C).

[00878] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.26 (s, 1H), 9.24 (s, 1H), 8.37 (s, 1H), 7.91 (d, *J* = 2.0 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.40 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.29 (t, *J*_{HF} = 74.2 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 4.96 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H). LC-MS: *m/z* 518 [M+H]⁺.

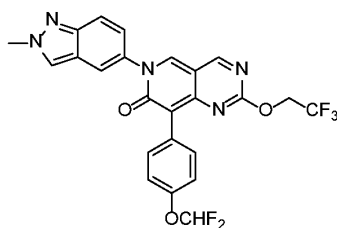
[00879] **Example 264:** 8-(4-(difluoromethoxy)phenyl)-6-(quinolin-6-yl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00880] The title compound was synthesized from intermediate **4c** with quinolin-6-ylboronic acid *via* general procedure VI (Step D) (Cu(OAc)₂, pyridine, O₂ atmosphere, DCM, 40 °C).

[00881] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.40 (s, 1H), 9.29 (s, 1H), 9.09 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.55 (d, *J* = 8.3 Hz, 1H), 8.34 (d, *J* = 2.4 Hz, 1H), 8.24 (d, *J* = 9.0 Hz, 1H), 8.02 (dd, *J* = 9.0 Hz, 2.4 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.72 (dd, *J* = 8.3 Hz, 4.2 Hz, 1H), 7.34 (t, *J*_{HF} = 74.2 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 5.01 (q, *J* = 8.9 Hz, 2H). LC-MS: *m/z* 515 [M+H]⁺.

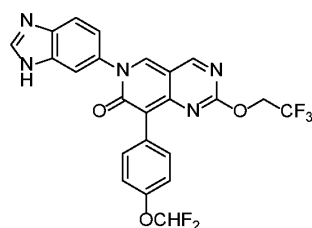
[00882] **Example 265:** 8-(4-(difluoromethoxy)phenyl)-6-(2-methyl-2*H*-indazol-5-yl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00883] The title compound was synthesized from intermediate **4c** with 2-methyl-2*H*-indazol-5-ylboronic acid *via* general procedure VI (Step D) (Cu(OAc)₂, pyridine, O₂ atmosphere, DCM, 40 °C).

[00884] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.26 (s, 1H), 9.23 (s, 1H), 8.54 (s, 1H), 7.96 (d, *J* = 2.0 Hz, 1H), 7.75-7.70 (m, 3H), 7.38 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 7.29 (t, *J*_{HF} = 74.4 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 4.96 (q, *J* = 9.0 Hz, 2H), 4.23 (s, 3H). LC-MS: *m/z* 518 [M+H]⁺.

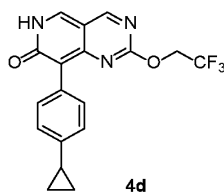
[00885] **Example 266:** 6-(*1H*-benzo[*d*]imidazol-6-yl)-8-(4-(difluoromethoxy)phenyl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00886] The title compound was synthesized from intermediate **4c** with 1-((2-(trimethylsilyl)ethoxy)methyl)-*1H*-benzo[*d*]imidazol-6-ylboronic acid *via* general procedure VI (Step D) (Cu(OAc)₂, pyridine, O₂ atmosphere, DCM, 40 °C), and then de-protection with TFA *via* general procedure I (Step F).

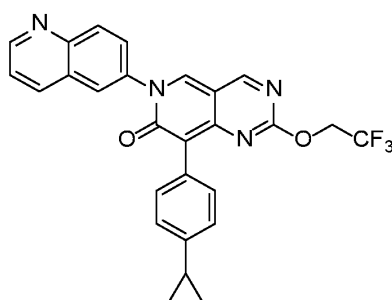
[00887] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.26 (s, 1H), 9.23 (s, 1H), 8.45 (br s, 1H), 8.38 (s, 1H), 7.85 (br s, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.37 (br s, 1H), 7.29 (t, *J*_{HF} = 74.0 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 4.96 (q, *J* = 9.2 Hz, 2H). LC-MS: *m/z* 504 [M+H]⁺.

[00888] Preparation of 8-(4-cyclopropylphenyl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **4d**



[00889] 8-(4-cyclopropylphenyl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **4d** was synthesized from methyl 2-(4-cyclopropylphenyl)-2-(5-(dimethoxymethyl)-2-(methylsulfonyl)pyrimidin-4-yl)acetate *via* general procedure VI (Step A-C). LC-MS: *m/z* 362 [M+H]⁺

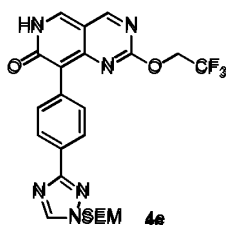
[00890] **Example 267:** Preparation of 8-(4-cyclopropylphenyl)-6-(quinolin-6-yl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00891] The title compound was synthesized from intermediate **4d** with quinolin-6-ylboronic acid *via* general procedure VI (Step D) ($\text{Cu}(\text{OAc})_2$, pyridine, O_2 atmosphere, DCM, 40°C).

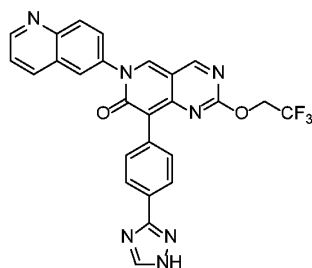
[00892] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 9.31 (s, 1H), 9.23 (s, 1H), 9.04 (dd, $J = 4.4$ Hz, 1.6 Hz, 1H), 8.49 (d, $J = 7.2$ Hz, 1H), 8.28 (d, $J = 2.4$ Hz, 1H), 8.19 (d, $J = 9.0$ Hz, 1H), 7.97 (d, $J = 9.0$ Hz, 2.4 Hz, 1H), 7.66 (dd, $J = 8.4$ Hz, 4.4 Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.09 (d, $J = 8.4$ Hz, 2H), 4.97 (q, $J = 9.2$ Hz, 2H), 1.99-1.90 (m, 1H), 1.01-0.93 (m, 2H), 0.73-0.67 (m, 2H). LC-MS: m/z 489 $[\text{M}+\text{H}]^+$.

[00893] Preparation of 2-(2,2,2-trifluoroethoxy)-8-(4-(1-((2-(trimethylsilyl)ethoxy)methyl)-*1H*-1,2,4-triazol-3-yl)phenyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **4e**



[00894] 2-(2,2,2-trifluoroethoxy)-8-(4-(1-((2-(trimethylsilyl)ethoxy)methyl)-*1H*-1,2,4-triazol-3-yl)phenyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **4e** was synthesized from methyl 2-(5-(dimethoxymethyl)-2-(methylsulfonyl)pyrimidin-4-yl)-2-(4-(1-((2-(trimethylsilyl)ethoxy)methyl)-*1H*-1,2,4-triazol-3-yl)phenyl)acetate *via* general procedure VI (Step A-C). LC-MS: m/z 519 $[\text{M}+\text{H}]^+$

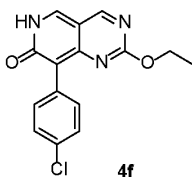
[00895] **Example 268:** Preparation of 8-(4-(*1H*-1,2,4-triazol-3-yl)phenyl)-6-(quinolin-6-yl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00896] The title compound was synthesized from intermediate **4e** with quinolin-6-ylboronic acid *via* general procedure VI (Step D) ($\text{Cu}(\text{OAc})_2$, pyridine, O_2 atmosphere, DCM, 40°C), and then de-protection with TFA *via* general procedure I (Step F).

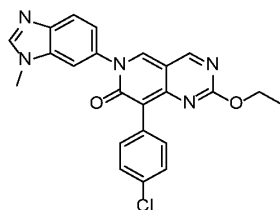
[00897] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 14.20 (br s, 1H), 9.38 (s, 1H), 9.27 (s, 1H), 9.05 (dd, $J = 8.0$ Hz, 1.6 Hz, 1H), 8.51 (d, $J = 8.0$ Hz, 1H), 7.91 (s, 1H), 8.31 (d, $J = 2.0$ Hz, 1H), 8.21 (d, $J = 8.8$ Hz, 1H), 8.05 (d, $J = 8.4$ Hz, 2H), 8.00 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 7.83 (d, $J = 8.4$ Hz, 1H), 7.68 (dd, $J = 8.4$ Hz, 4.0 Hz, 1H), 4.99 (q, $J = 8.8$ Hz, 2H). LC-MS: m/z 516 $[\text{M}+\text{H}]^+$.

[00898] Preparation of 8-(4-chlorophenyl)-2-ethoxypyrido[4,3-*d*]pyrimidin-7(6*H*)-one **4f**



[00899] 8-(4-chlorophenyl)-2-ethoxypyrido[4,3-*d*]pyrimidin-7(6*H*)-one **4f** was synthesized from methyl 2-(4-chlorophenyl)-2-(5-(dimethoxymethyl)-2-(methylsulfonyl)pyrimidin-4-yl)acetate with EtOH *via* general procedure VI (Step A-C). LC-MS: m/z 302 $[\text{M}+\text{H}]^+$

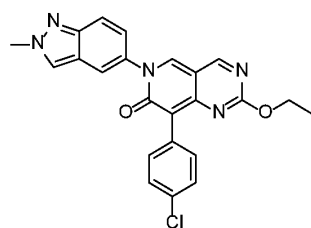
[00900] Preparation of 8-(4-chlorophenyl)-2-ethoxy-6-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one (**Example 269**)



The title compound was synthesized from intermediate **4f** with 1-methyl-1*H*-benzo[*d*]imidazol-6-ylboronic acid *via* general procedure VI (Step D) (Cu(OAc)₂, pyridine, O₂ atmosphere, DCM, 40 °C).

¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.17 (s, 2H), 8.36 (s, 1H), 7.89 (d, *J* = 2.0 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.38 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H). LC-MS: *m/z* 432 [M+H]⁺.

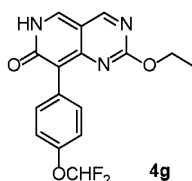
[00901] Example 270: 8-(4-chlorophenyl)-2-ethoxy-6-(2-methyl-2*H*-indazol-5-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00902] The title compound was synthesized from intermediate **4f** with 2-methyl-2*H*-indazol-5-ylboronic acid *via* general procedure VI (Step D) (Cu(OAc)₂, pyridine, O₂ atmosphere, DCM, 40 °C).

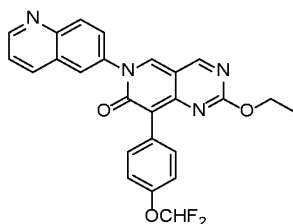
[00903] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.17 (s, 1H), 9.15 (s, 1H), 8.53 (s, 1H), 7.94 (d, *J* = 2.0 Hz, 1H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.36 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 4.23 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H). LC-MS: *m/z* 432 [M+H]⁺.

[00904] Preparation of 8-(4-(difluoromethoxy)phenyl)-2-ethoxypyrido[4,3-*d*]pyrimidin-7(6*H*)-one **4g**



[00905] 8-(4-(difluoromethoxy)phenyl)-2-ethoxypyrido[4,3-*d*]pyrimidin-7(6*H*)-one **4g** was synthesized from methyl 2-(4-(difluoromethoxy)phenyl)-2-(5-(dimethoxymethyl)-2-(methylsulfonyl)pyrimidin-4-yl)acetate with EtOH *via* general procedure VI (Step A-C). LC-MS: *m/z* 334 [M+H]⁺

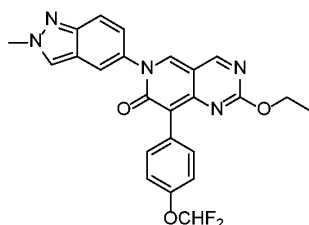
[00906] Example 271: Preparation of 8-(4-(difluoromethoxy)phenyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-2-ethoxy-6-(quinolin-6-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00907] The title compound was synthesized from intermediate **4g** with quinolin-6-ylboronic acid *via* general procedure VI (Step D) (Cu(OAc)₂, pyridine, O₂ atmosphere, DCM, 40 °C).

[00908] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.30 (s, 1H), 9.22 (s, 1H), 9.08 (dd, *J* = 4.3 Hz, 1.6 Hz, 1H), 8.54 (d, *J* = 8.4 Hz, 1H), 8.32 (d, *J* = 2.4 Hz, 1H), 8.23 (d, *J* = 9.0 Hz, 1H), 8.01 (dd, *J* = 9.0 Hz, 2.4 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.71 (dd, *J* = 8.8 Hz, 4.3 Hz, 1H), 7.34 (t, *J*_{HF} = 74.4 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H). LC-MS: *m/z* 461 [M+H]⁺.

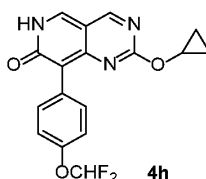
[00909] Example 272: 8-(4-(difluoromethoxy)phenyl)-2-ethoxy-6-(2-methyl-2*H*-indazol-5-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00910] The title compound was synthesized from intermediate **4g** with 2-methyl-2*H*-indazol-5-ylboronic acid *via* general procedure VI (Step D) (Cu(OAc)₂, pyridine, O₂ atmosphere, DCM, 40 °C).

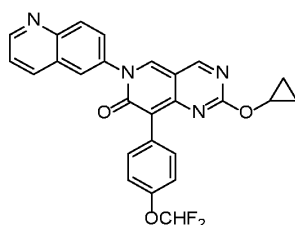
[00911] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.16 (s, 1H), 9.15 (s, 1H), 8.53 (s, 1H), 7.95 (d, *J* = 2.0 Hz, 1H), 7.75-7.70 (m, 3H), 7.36 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 7.29 (t, *J*_{HF} = 74.4 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.23 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H). LC-MS: *m/z* 464 [M+H]⁺.

[00912] Preparation of 2-cyclopropoxy-8-(4-(difluoromethoxy)phenyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **4h**



[00913] 2-cyclopropoxy-8-(4-(difluoromethoxy)phenyl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **4h** was synthesis from methyl 2-(4-(difluoromethoxy)phenyl)-2-(5-(dimethoxymethyl)-2-(methylsulfonyl)pyrimidin-4-yl)acetate with cyclopropanol *via* general procedure VI (Step A-C). LC-MS: *m/z* 346 [M+H]⁺

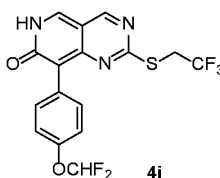
[00914] **Example 273:** Preparation of 2-cyclopropoxy-8-(4-(difluoromethoxy)phenyl)-6-(quinolin-6-yl)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one



[00915] The title compound was synthesized from intermediate **4h** with quinolin-6-ylboronic acid *via* general procedure VI (Step D) (Cu(OAc)₂, pyridine, O₂ atmosphere, DCM, 40 °C).

[00916] ¹H NMR (400 MHz, DMSO-*d*₆) δ: 9.28 (s, 1H), 9.17 (s, 1H), 9.04 (dd, *J* = 4.4 Hz, 1.6 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.28 (d, *J* = 2.4 Hz, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 7.97 (dd, *J* = 9.0 Hz, 2.4 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.67 (dd, *J* = 8.4 Hz, 4.4 Hz, 1H), 7.28 (t, *J*_{HF} = 74.4 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 4.28-4.19 (m, 1H), 0.80-0.73 (m, 4H). LC-MS: *m/z* 473 [M+H]⁺.

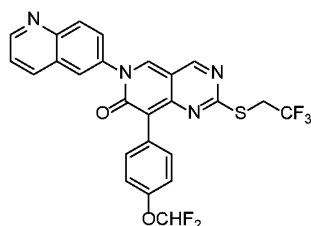
[00917] Preparation of 8-(4-(difluoromethoxy)phenyl)-2-(2,2,2-trifluoroethylthio)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **4i**



[00918] 8-(4-(difluoromethoxy)phenyl)-2-(2,2,2-trifluoroethylthio)pyrido[4,3-*d*]pyrimidin-7(6*H*)-one **4i** was synthesized from

methyl 2-(4-(difluoromethoxy)phenyl)-2-(5-(dimethoxymethyl)-2-(methylsulfonyl)pyrimidin-4-yl)acetate with 2,2,2-trifluoroethanethiol *via* general procedure VI (Step A-C). LC-MS: m/z 404 $[M+H]^+$

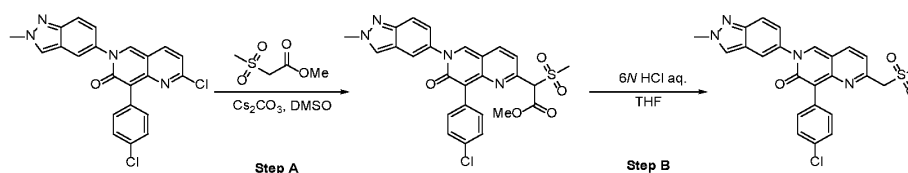
[00919] Example 274: Preparation of 8-(4-(difluoromethoxy)phenyl)-6-(quinolin-6-yl)-2-(2,2,2-trifluoroethylthio)pyrido[4,3-*d*]pyrimidin-7(6H)-one



[00920] The title compound was synthesized from intermediate **4i** with quinolin-6-ylboronic acid *via* general procedure VI (Step D) ($\text{Cu}(\text{OAc})_2$, pyridine, O_2 atmosphere, DCM, 40°C).

[00921] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 9.36 (s, 1H), 9.12 (s, 1H), 9.08 (dd, $J = 4.3$ Hz, 1.6 Hz, 1H), 8.55 (d, $J = 8.4$ Hz, 1H), 8.32 (d, $J = 2.4$ Hz, 1H), 8.22 (d, $J = 9.0$ Hz, 1H), 8.01 (dd, $J = 9.0$ Hz, 2.4 Hz, 1H), 7.71 (dd, $J = 8.4$ Hz, 4.3 Hz, 1H), 7.68 (d, $J = 8.8$ Hz, 2H), 7.29 (t, $J_{\text{HF}} = 74.0$ Hz, 1H), 7.19 (d, $J = 8.8$ Hz, 2H), 4.11 (q, $J = 10.4$ Hz, 2H). LC-MS: m/z 531 $[M+H]^+$.

[00922] Example 135-A: 8-(4-chlorophenyl)-6-(2-methyl-2H-indazol-5-yl)-2-((methylsulfonyl)methyl)-1,6-naphthyridin-7(6H)-one



[00923] Step A. methyl 2-(8-(4-chlorophenyl)-6-(2-methyl-2H-indazol-5-yl)-7-oxo-6,7-dihydro-1,6-naphthyridin-2-yl)-2-(methylsulfonyl)acetate

[00924] To a solution of 2-chloro-8-(4-chlorophenyl)-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one (200 mg, 0.47 mmol, 1.0 eq., as synthesized in Example 209) in DMSO (3.0 mL) was added Cs_2CO_3 (308 mg, 0.95 mmol, 2.0 eq.) and methyl 2-(methylsulfonyl)acetate (144 mg, 0.95 mmol, 2.0 eq.) at room temperature. The reaction mixture was stirred at 100°C for 14

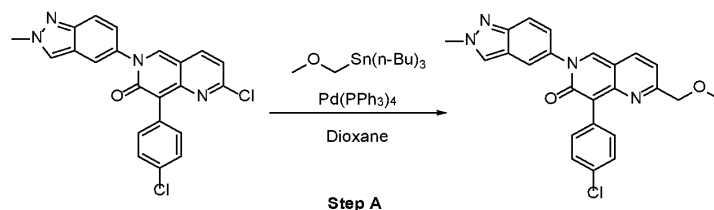
hrs. The resulting mixture was poured into ice water, the reaction mixture was extracted with EtOAc (20 mL x 3), the combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give methyl 2-(8-(4-chlorophenyl)-6-(2-methyl-2H-indazol-5-yl)-7-oxo-6,7-dihydro-1,6-naphthyridin-2-yl)-2-(methylsulfonyl)acetate (70 mg, yield 23%) as a yellow solid. LC-MS (ESI): *m/z* 537 [M+H]⁺.

[00925] Step B. 8-(4-chlorophenyl)-6-(2-methyl-2H-indazol-5-yl)-2-((methylsulfonyl)methyl)-1,6-naphthyridin-7(6H)-one (**135-A**)

[00926] To a solution of methyl 2-(8-(4-chlorophenyl)-6-(2-methyl-2H-indazol-5-yl)-7-oxo-6,7-dihydro-1,6-naphthyridin-2-yl)-2-(methylsulfonyl)acetate (30 mg, 0.05 mmol, 1.0 eq.) in THF (3 mL) was added 6*N* HCl aq. (1 mL) at room temperature. The reaction mixture was stirred at 100 °C for 14 hrs. The reaction mixture was extracted with EtOAc (20 mL x 3), the combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure, the residue was purified by RP-prep-HPLC to give 8-(4-chlorophenyl)-6-(2-methyl-2H-indazol-5-yl)-2-((methylsulfonyl)methyl)-1,6-naphthyridin-7(6H)-one.

[00927] ¹H NMR (400 MHz, DMSO-*d*₆) (ratio of tautomers 5:2) δ (ppm): 9.04 (s, 1H), 8.56 (d, *J* = 8.1 Hz, 0.4H), 8.52 (s, 1H), 8.42 (s, 0.4H), 8.15 (d, *J* = 8.6 Hz, 1H), 7.94 (d, *J* = 2.0 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 0.4H), 7.72 (d, *J* = 9.1 Hz, 1H), 7.66 (d, *J* = 8.9 Hz, 0.4H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 0.8H), 7.40 (m, 3H), 7.08 (d, *J* = 8.7 Hz, 1H), 4.77 (s, 0.8H), 4.66 (s, 2H), 4.23 (s, 3H), 4.20 (s, 1.2H), 3.01 (s, 3H), 2.84 (s, 1.2H). LC-MS (ESI): *m/z* 479 [M+H]⁺.

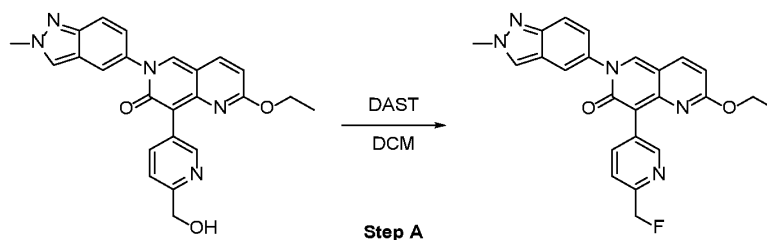
[00928] Example 136-A: Preparation of: 8-(4-chlorophenyl)-2-(methoxymethyl)-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one



[00929] Step A: 8-(4-chlorophenyl)-2-(methoxymethyl)-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one

[00930] A solution of 2-chloro-8-(4-chlorophenyl)-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one (100 mg, 0.24 mmol, 1.0 eq., as synthesized in Example 209), tributyl(methoxymethyl)stannane (159 mg, 0.48 mmol, 2.0 eq.) and Pd(PPh₃)₄ (24 mg, 0.024 mmol, 0.1 eq.) in dioxane (5mL) was stirred at 50 °C for 14 hrs under N₂ atmosphere. The reaction mixture was dilute with H₂O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by RP-prep-HPLC to give 8-(4-chlorophenyl)-2-(methoxymethyl)-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one (**136-A**). LC-MS (ESI): *m/z* 431 [M+H]⁺.

[00931] Example 137-A: Preparation of: 2-ethoxy-8-(6-(fluoromethyl)pyridin-3-yl)-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one



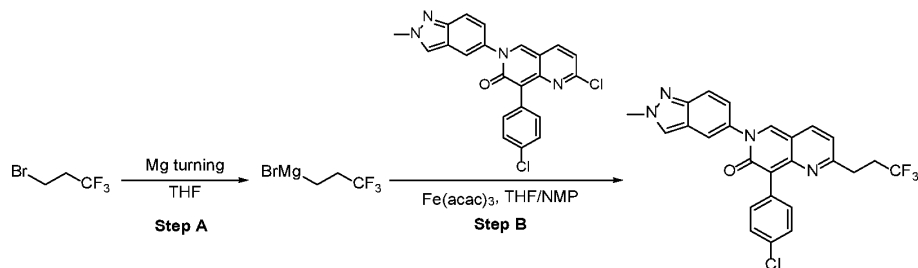
[00932] Step A: 2-ethoxy-8-(6-(fluoromethyl)pyridin-3-yl)-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one

[00933] To a solution of 2-ethoxy-8-(6-(hydroxymethyl)pyridin-3-yl)-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one (synthesized from 8-bromo-2-ethoxy-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one (as synthesized in Example 215) and (6-(hydroxymethyl)pyridin-3-yl)boronic acid *via General Procedure V (Step M)*) (150 mg, 0.35 mmol, 1.0 eq.) in DCM (4mL) was added DAST (161 mg, 0.70 mmol, 2.0 eq.) at 0 °C under N₂. The resulting mixture was stirred at 0 °C for an additional 1hr before the reaction was quenched by adding ice water (3 mL). The resulting mixture was extracted with EtOAc (10 mL x 3), the combined organic layers were washed with brine (10

mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by RP-prep-HPLC to give 2-ethoxy-8-(6-(fluoromethyl)pyridin-3-yl)-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one (**137-A**).

[00934] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.86 (d, $J = 2.1$ Hz, 1H), 8.81 (s, 1H), 8.51 (s, 1H), 8.15 (dd, $J = 8.0, 2.1$ Hz, 1H), 8.01 (d, $J = 9.1$ Hz, 1H), 7.92 (dd, $J = 2.1, 0.8$ Hz, 1H), 7.72 (dt, $J = 9.1, 0.9$ Hz, 1H), 7.52 (d, $J = 8.1$ Hz, 1H), 7.36 (dd, $J = 9.1, 2.1$ Hz, 1H), 6.58 (d, $J = 9.0$ Hz, 1H), 5.50 (d, $J_{\text{HF}} = 47.2$ Hz, 2H), 4.27 (q, $J = 7.2$ Hz, 2H), 4.23 (s, 3H), 1.28 (t, $J = 7.1$ Hz, 3H). LC-MS (ESI): m/z 431 $[\text{M}+\text{H}]^+$.

[00935] **Example 138-A:** Preparation of: 8-(4-chlorophenyl)-6-(2-methyl-2H-indazol-5-yl)-2-(3,3,3-trifluoropropyl)-1,6-naphthyridin-7(6H)-one



[00936] **Step A:** (3,3,3-trifluoropropyl)magnesium bromide

[00937] Magnesium turnings (136 mg, 5.65 mmol, 1.0 eq.) were suspended in dry THF (4mL), then 3-bromo-1,1,1-trifluoropropane (1.0 g, 5.65 mmol, 1.0 eq.) was added at room temperature drop-wise. The flask was gently warmed using a heat gun, until bubbling was observed on the surface of the magnesium turnings. The resulting mixture was stirred at 70 °C for an additional 1h, then the flask was allowed to cool to room temperature resulting in a pale gray solution. The crude Grignard reagent was used in the next step without any further purification or isolation.

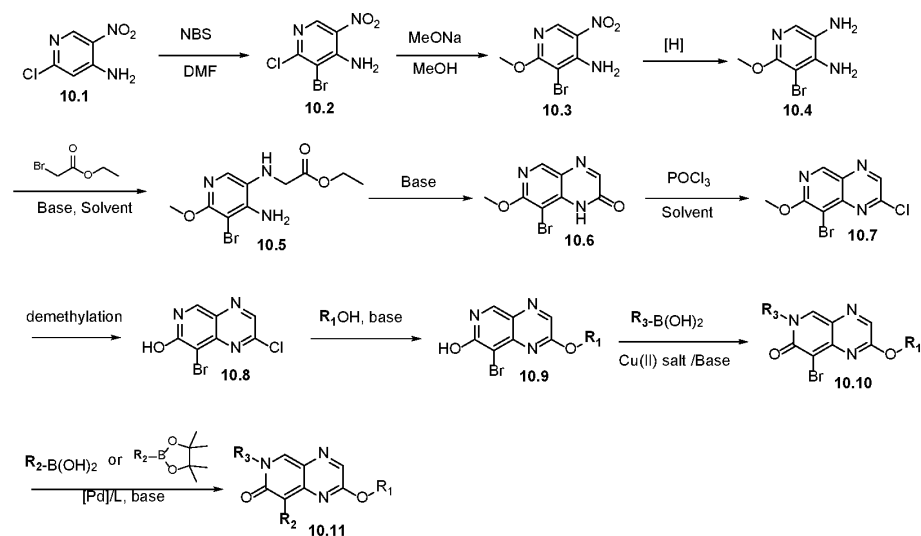
[00938] **Step B:** 8-(4-chlorophenyl)-6-(2-methyl-2H-indazol-5-yl)-2-(3,3,3-trifluoropropyl)-1,6-naphthyridin-7(6H)-one

[00939] To a solution of 2-chloro-8-(4-chlorophenyl)-6-(2-methyl-2H-indazol-5-yl)-1,6-naphthyridin-7(6H)-one (100 mg, 0.24 mmol, 1.0 eq., as synthesized in Example 209) and $\text{Fe}(\text{acac})_3$ (85 mg, 0.24 mmol, 1.0 eq.) in

THF/NMP mixture (4.4 mL, 10/1, v/v) was added the crude (3,3,3-trifluoropropyl)magnesium bromide (2 mL, 2.4 mmol, 10 eq.) solution drop-wise at room temperature. The resulting mixture was stirred at room temperature for 14 hrs, then the reaction was quenched by adding NH_4Cl (Sat. aq.) (5 mL) at 0 °C. The mixture was extracted with EtOAc (10 mL x 3), the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by RP-prep-HPLC to give 8-(4-chlorophenyl)-6-(2-methyl-2H-indazol-5-yl)-2-(3,3,3-trifluoropropyl)-1,6-naphthyridin-7(6H)-one (**138-A**).

[00940] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.94 (s, 1H), 8.51 (s, 1H), 8.04 (d, $J = 8.7$ Hz, 1H), 7.93 (dd, $J = 2.1, 0.8$ Hz, 1H), 7.72 (dt, $J = 9.0, 0.9$ Hz, 1H), 7.67 – 7.60 (m, 2H), 7.41 (d, $J = 8.6$ Hz, 2H), 7.37 (dd, $J = 9.1, 2.0$ Hz, 1H), 7.00 (d, $J = 8.7$ Hz, 1H), 4.23 (s, 3H), 3.03 (t, $J = 7.6$ Hz, 2H), 2.77 – 2.60 (m, 2H). LC-MS (ESI): m/z 483 $[\text{M}+\text{H}]^+$.

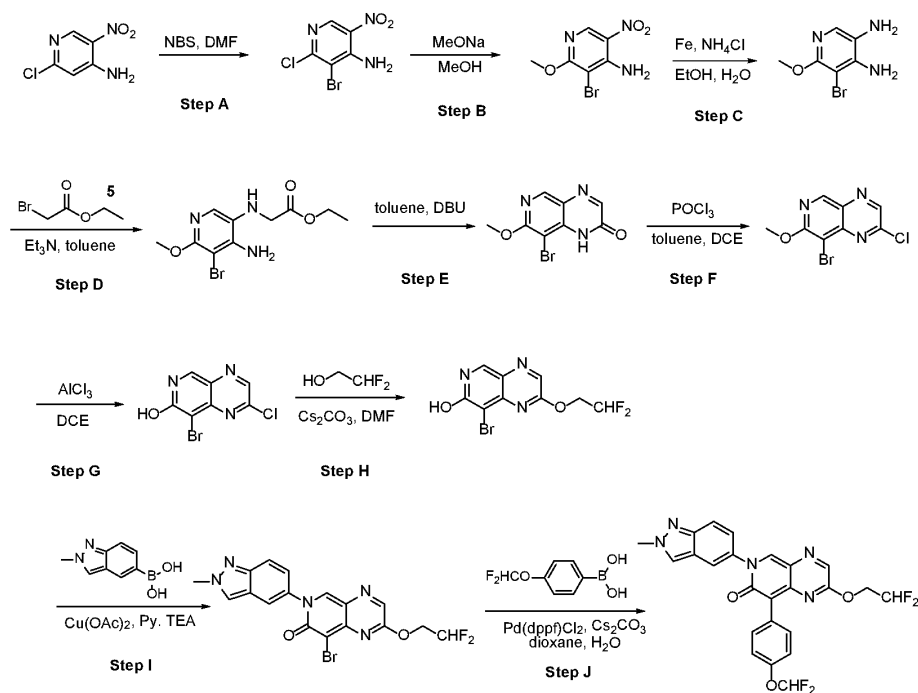
[00941] General Procedure VII



[00942] Compounds of structure **10.11** were obtained by General Procedure VII. Substituted pyridine **10.1** was treated with NBS to generate bromo-pyridine **10.2**, reacted with NaOMe to generate methoxy-pyridine **10.3**, and then reduced to give diamino-pyridine **10.4**. Compound **10.4** was reacted with ethyl bromoacetate to give compound **10.5** and then treated with base to

generate bicyclic structure **10.6**. Following treatment with POCl_3 to generate compound **10.7** and demethylation to generate compound **10.8**, the desired R groups could be installed sequentially. The desired R_1 group was introduced through a nucleophilic aromatic substitution reaction to afford compounds of structure **10.9**. The desired R_3 group was introduced through a copper mediated Chan-Lam coupling to afford compounds of structure **10.10**. The desired R_2 group was introduced through a palladium mediated Suzuki coupling to afford final compounds of structure **10.11**.

[00943] Example 139-A: Preparation of 139-A via General Procedure VII



Step A: 3-bromo-2-chloro-5-nitropyridin-4-amine

[00944] To a solution of 2-chloro-5-nitropyridin-4-amine (5.0 g, 28.8 mmol, 1.0 eq.) in DMF (20 mL) was added NBS (6.16 g, 34.6 mmol, 1.2 eq.) in several portions. After stirring at room temperature for 4 hrs, most of the solvent was removed under reduced pressure, the residue was suspended in cool water (30 mL), and the solid was filtered and dried under reduced pressure to give 3-bromo-2-chloro-5-nitropyridin-4-amine (6.2 g, 85% yield) as an off-white solid. LC-MS (ESI): m/z 252, 254 $[\text{M}+\text{H}]^+$.

[00945] Step B: 3-bromo-2-methoxy-5-nitropyridin-4-amine

[00946] To a suspension of 3-bromo-2-chloro-5-nitropyridin-4-amine (6.0 g, 23.8 mmol, 1.0 eq.) in methanol (50 mL) was added a solution of NaOMe (freshly prepared from Na (658 mg, 28.6 mmol, 1.2 eq.) in 5mL anhydrous MeOH). The reaction mixture was refluxed for 12 hrs. The methanol was removed under reduced pressure, the residue was suspended in cool water (50 mL), and the resulting precipitate was filtered, washed with ice water and dried under vacuum to give 3-bromo-2-methoxy-5-nitropyridin-4-amine (5.8 g, 98% yield) as an off-white solid. LC-MS (ESI): m/z 248, 250 $[M+H]^+$

[00947] Step C: 5-bromo-6-methoxypyridine-3,4-diamine

[00948] To a solution of 3-bromo-2-methoxy-5-nitropyridin-4-amine (5.8 g, 23.3 mmol, 1.0 eq.) and NH_4Cl (6.35 g, 116.5 mmol, 5.0 eq.) in EtOH/ H_2O (40 mL, 3/1, v/v) was added iron powder (5.22 g, 93.2 mmol, 4.0 eq.), and the resulting mixture was heated to 80 °C for 4 hrs. The mixture was allowed to cool to room temperature, filtered through a short pad of Celite®, and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4 , concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel to give 5-bromo-6-methoxypyridine-3,4-diamine (4.0 g, 79% yield) as a brown solid, which should be used as soon as possible in next step. LC-MS (ESI): m/z 218, 220 $[M+H]^+$

[00949] Step D: ethyl (4-amino-5-bromo-6-methoxypyridin-3-yl)glycinate

[00950] To a mixture of 5-bromo-6-methoxypyridine-3,4-diamine (3.6 g, 16.4 mmol, 1.0 eq.) and TEA (2.5 mL, 18.0 mmol, 1.1 eq.) in dry toluene (30 mL) was added ethyl 2-bromoacetate (3.0 g, 18.0 mmol, 1.1 eq.) drop-wise at 0 °C. After addition, the reaction mixture was allowed to warm to room temperature and stirred for another 4 hrs. The reaction was then quenched by adding NH_4Cl (Sat. aq.) (20 mL), the resulting mixture was extracted with EtOAc (30 mL x 3), the combined organic layers were dried over Na_2SO_4 and then concentrated under reduced pressure to give a crude mixture (5.2 g, crude oil), which was used in next step without further purification.

[00951] Step E: 8-bromo-7-methoxypyrido[3,4-b]pyrazin-2(1H)-one

[00952] A mixture containing crude ethyl (4-amino-5-bromo-6-methoxypyridin-3-yl)glycinate (5.2 g) and DBU (2.74 g, 18.0 mmol, 1.1 eq) in toluene (20 mL) was refluxed for 14 hrs. The resulting mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel to give 8-bromo-7-methoxypyrido[3,4-b]pyrazin-2(1H)-one (2.1 g, two step overall 50% yield) as an off-white solid. LC-MS (ESI): m/z 256, 258 $[M+H]^+$.

[00953] Step F: 8-bromo-2-chloro-7-methoxypyrido[3,4-b]pyrazine

[00954] To a solution of 8-bromo-7-methoxy-1H,2H-pyrido[3,4-b]pyrazin-2-one (1.5g, 5.85 mmol, 1.0 eq.) in toluene/DCE (40mL, 1/1, v/v) was added $POCl_3$ (2.70 g, 17.6 mmol, 3.0 eq.) and the reaction mixture was stirred at 90 °C for 15 hrs. The reaction mixture was then concentrated under reduced pressure, the residue was diluted with ice water (50 mL), basified to pH = 7-8 with Na_2CO_3 (sat. aq.), and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , concentrated under reduced pressure, and purified by flash column chromatography on silica gel to afford 8-bromo-2-chloro-7-methoxypyrido[3,4-b]pyrazine (1g, 3.64mmol, 62 %) as a pale yellow oil. LC-MS (ESI): m/z 274, 276 $[M+H]^+$.

[00955] Step G: 8-bromo-2-chloropyrido[3,4-b]pyrazin-7-ol

[00956] To a solution of 8-bromo-2-chloro-7-methoxypyrido[3,4-b]pyrazine (1g, 3.64 mmol, 1.0 eq.) in DCE (15mL) was added anhydrous $AlCl_3$ (0.73 g, 5.46 mmol, 1.5 eq.) and the reaction mixture was stirred at 70 °C for 2 hrs. The reaction mixture was cooled to 0 °C, quenched with ice water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel to afford 8-bromo-2-chloropyrido[3,4-b]pyrazin-7-ol (700 mg, 74% yield) as a pale yellow solid. LC-MS (ESI): m/z 260, 262 $[M+H]^+$.

[00957] Step H: 8-bromo-2-(2,2-difluoroethoxy)pyrido[3,4-b]pyrazin-7-ol

[00958] To a solution of 8-bromo-2-chloropyrido[3,4-b]pyrazin-7-ol (390 mg, 1.5 mmol, 1.0 eq.) in 2,2-difluoroethan-1-ol (5 mL) was added Cs_2CO_3 (978

mg, 3.0 mmol, 2.0 eq.) and the reaction mixture was stirred at 90 °C for 3 hrs. The reaction mixture was cooled to 0 °C, quenched with ice water (30 mL), adjusted to pH = 6 with dilute HCl (1N, aq.), and extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel to afford 8-bromo-2-(2,2-difluoroethoxy)pyrido[3,4-b]pyrazin-7-ol (30 mg, 7%) as a pale yellow solid. LC-MS (ESI): *m/z* 306, 308 [M+H]⁺.

[00959] Step I: 8-bromo-2-(2,2-difluoroethoxy)-6-(2-methyl-2H-indazol-5-yl)pyrido[3,4-b]pyrazin-7(6H)-one

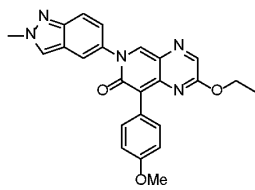
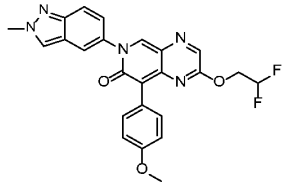
[00960] A mixture of 8-bromo-2-(2,2-difluoroethoxy)pyrido[3,4-b]pyrazin-7-ol (30 mg, 0.1 mmol), (2-methyl-2H-indazol-5-yl)boronic acid (35 mg, 0.2 mmol), Cu(OAc)₂ (29 mg, 0.15 mmol, 1.5 eq.), pyridine (24 µL, 0.3 mmol, 0.3 eq.) and TEA (42 µL, 0.3 mmol, 0.3 eq.) in DCM (0.5 mL) was stirred under O₂ atmosphere at 40 °C for 15 hrs. The reaction mixture was diluted with H₂O (5 mL) and extracted with DCM (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, and the residue was purified by flash column chromatography on silica gel to afford 8-bromo-2-(2,2-difluoroethoxy)-6-(2-methyl-2H-indazol-5-yl)pyrido[3,4-b]pyrazin-7(6H)-one (20 mg, 46%) as a yellow solid. LC-MS (ESI): *m/z* 436, 438 [M+H]⁺.

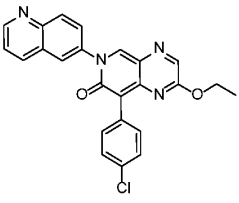
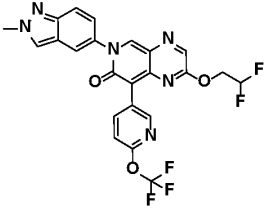
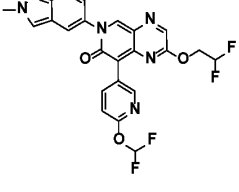
[00961] Step J: 2-(2,2-difluoroethoxy)-8-(4-(difluoromethoxy)phenyl)-6-(2-methyl-2H-indazol-5-yl)pyrido[3,4-b]pyrazin-7(6H)-one

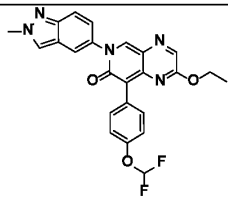
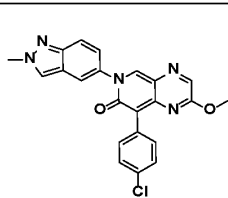
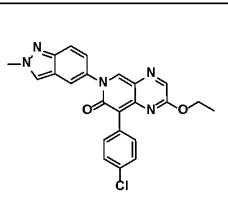
[00962] A mixture of 8-bromo-2-(2,2-difluoroethoxy)-6-(2-methyl-2H-indazol-5-yl)pyrido[3,4-b]pyrazin-7(6H)-one (20 mg, 0.046 mmol, 1.0 eq.), (4-(difluoromethoxy)phenyl)boronic acid (17 mg, 0.092 mmol, 2.0 eq.), Pd(dppf)Cl₂ (6.8 mg, 0.009 mmol, 0.2 eq.) and Cs₂CO₃ (50 mg, 0.138 mmol, 3.0 eq.) in a dioxane/H₂O mixture (0.5 mL, 9/1, v/v) was stirred at 100 °C under N₂ atmosphere for 15 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by RP-prep-HPLC to afford 2-(2,2-difluoroethoxy)-8-(4-(difluoromethoxy)phenyl)-6-(2-methyl-2H-indazol-5-yl)pyrido[3,4-b]pyrazin-7(6H)-one (**139-A**).

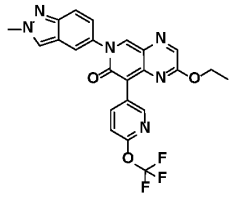
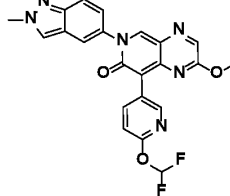
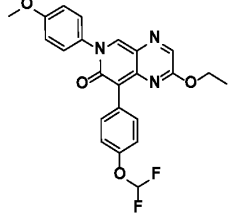
[00963] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.85 (s, 1H), 8.51 (s, 1H), 8.26 (s, 1H), 7.93 (d, $J = 1.2$ Hz, 1H), 7.73-7.67 (m, 3H), 7.35 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 7.29 (t, $J_{\text{HF}} = 74.2$ Hz, 1H), 7.18 (d, $J = 8.8$ Hz, 2H), 6.41 (tt, $J_{\text{HF}} = 54.2$ Hz, $J = 3.2$ Hz, 1H), 4.57 (td, $J_{\text{HF}} = 14.8$ Hz, $J = 3.2$ Hz, 2H), 4.23 (s, 3H). LC-MS (ESI): m/z 500 $[\text{M}+\text{H}]^+$.

[00964] The procedure set forth above for **General Procedure VII** was used to synthesize the following compounds by using appropriate starting materials:

Example	Structure	Characterization
140-A	 2-ethoxy-8-(4-methoxyphenyl)-6-(2-methyl-2H-indazol-5-yl)pyrido[3,4-b]pyrazin-7(6H)-one	LC-MS (ESI): m/z 428 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.50 (s, 1H), 8.11 (s, 1H), 7.91 (d, $J = 2.0$ Hz, 1H), 7.70 (d, $J = 9.1$ Hz, 1H), 7.60 – 7.54 (m, 2H), 7.34 (dd, $J = 9.1$, 2.1 Hz, 1H), 6.94 (d, $J = 8.8$ Hz, 2H), 4.32 (q, $J = 7.1$ Hz, 2H), 4.23 (s, 3H), 3.79 (s, 3H), 1.33 (t, $J = 7.0$ Hz, 3H).
141-A	 2-(2,2-difluoroethoxy)-8-(4-methoxyphenyl)-6-(2-methyl-2H-indazol-5-yl)pyrido[3,4-b]pyrazin-7(6H)-one	LC-MS (ESI): m/z 464 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.50 (s, 1H), 8.23 (s, 1H), 7.92 (d, $J = 2.1$ Hz, 1H), 7.70 (d, $J = 9.0$ Hz, 1H), 7.58 (d, $J = 8.8$ Hz, 2H), 7.34 (dd, $J = 9.1$, 2.0 Hz, 1H), 6.94 (d, $J = 8.9$ Hz, 2H), 6.41 (tt, $J_{\text{HF}} = 54.3$, $J = 3.3$ Hz, 1H), 4.57 (td, $J_{\text{HF}} = 15.1$, $J = 3.3$ Hz, 2H), 4.23 (s, 3H), 3.79 (s, 3H).

142-A	 8-(4-chlorophenyl)-2-ethoxy-6-(quinolin-6-yl)pyrido[3,4-b]pyrazin-7(6H)-one	LC-MS (ESI): m/z 429 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.03 (dd, <i>J</i> = 4.2, 1.7 Hz, 1H), 8.94 (s, 1H), 8.49 (d, <i>J</i> = 8.2 Hz, 1H), 8.27 (d, <i>J</i> = 2.4 Hz, 1H), 8.20 – 8.14 (m, 2H), 7.96 (dd, <i>J</i> = 9.0, 2.4 Hz, 1H), 7.72 – 7.62 (m, 3H), 7.49 – 7.40 (m, 2H), 4.33 (q, <i>J</i> = 7.0 Hz, 2H), 1.34 (t, <i>J</i> = 7.1 Hz, 3H).
143-A	 2-(2,2-difluoroethoxy)-6-(2-methyl-2H-indazol-5-yl)-8-(6-(trifluoromethoxy)pyridin-3-yl)pyrido[3,4-b]pyrazin-7(6H)-one	LC-MS (ESI): m/z 519 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.97 (s, 1H), 8.64 (d, <i>J</i> = 2.3 Hz, 1H), 8.52 (s, 1H), 8.31 (s, 1H), 8.30 (dd, <i>J</i> = 8.6, 2.5 Hz, 1H), 7.96 (dd, <i>J</i> = 2.1, 0.8 Hz, 1H), 7.73 (dd, <i>J</i> = 9.1, 0.9 Hz, 1H), 7.38 (dd, <i>J</i> = 9.1, 2.1 Hz, 1H), 7.34 (d, <i>J</i> = 8.5 Hz, 1H), 6.42 (tt, <i>J</i>_{HF} = 54.2, <i>J</i> = 3.3 Hz, 1H), 4.60 (td, <i>J</i>_{HF} = 15.1, <i>J</i> = 3.3 Hz, 2H), 4.24 (s, 3H).
144-A	 2-(2,2-difluoroethoxy)-8-(6-(difluoromethoxy)pyridin-3-yl)-6-(2-methyl-2H-indazol-5-yl)pyrido[3,4-b]pyrazin-7(6H)-one	LC-MS (ESI): m/z 501 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.92 (s, 1H), 8.56 – 8.49 (m, 2H), 8.29 (s, 1H), 8.19 (dd, <i>J</i> = 8.6, 2.3 Hz, 1H), 7.94 (s, 1H), 7.72 (d, <i>J</i> = 9.1 Hz, 1H), 7.67 (t, <i>J</i>_{HF} = 73.1 Hz, 1H), 7.37 (dd, <i>J</i> = 9.2, 2.0 Hz, 1H), 7.13 (d, <i>J</i> = 8.5 Hz, 1H), 6.42 (t, <i>J</i>_{HF} = 54.2 Hz, 1H), 4.59 (td, <i>J</i>_{HF} = 15.2, <i>J</i> = 3.2 Hz, 2H), 4.23 (s, 3H).

145-A	 8-(4-(difluoromethoxy)phenyl)-2-ethoxy-6-(2-methyl-2H-indazol-5-yl)pyrido[3,4-b]pyrazin-7(6H)-one	LC-MS (ESI): m/z 464 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.50 (s, 1H), 8.14 (s, 1H), 7.92 (dd, $J = 2.0, 0.8$ Hz, 1H), 7.74 – 7.66 (m, 3H), 7.35 (dd, $J = 9.1, 2.1$ Hz, 1H), 7.30 (t, $J_{HF} = 74.3$ Hz, 1H), 7.18 (d, $J = 8.7$ Hz, 2H), 4.32 (q, $J = 7.0$ Hz, 2H), 4.23 (s, 3H), 1.33 (t, $J = 7.0$ Hz, 3H).
146-A	 8-(4-chlorophenyl)-2-(2,2-difluoroethoxy)-6-(2-methyl-2H-indazol-5-yl)pyrido[3,4-b]pyrazin-7(6H)-one	LC-MS (ESI): m/z 468 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.89 (s, 1H), 8.51 (s, 1H), 8.27 (s, 1H), 7.94 (d, $J = 2.0$ Hz, 1H), 7.71 (d, $J = 9.1$ Hz, 1H), 7.68 (d, $J = 8.6$ Hz, 2H), 7.44 (d, $J = 8.6$ Hz, 2H), 7.36 (dd, $J = 9.1, 2.1$ Hz, 1H), 6.42 (tt, $J_{HF} = 54.2, J = 3.2$ Hz, 1H), 4.58 (td, $J_{HF} = 15.2, J = 3.2$ Hz, 2H), 4.23 (s, 3H).
147-A	 8-(4-chlorophenyl)-2-ethoxy-6-(2-methyl-2H-indazol-5-yl)pyrido[3,4-b]pyrazin-7(6H)-one	LC-MS (ESI): m/z 432 $[M+H]^+$. 1H NMR (400 MHz, Chloroform-d) δ 8.38 (s, 1H), 7.99 (d, $J = 11.4$ Hz, 2H), 7.81 (d, $J = 9.1$ Hz, 1H), 7.75 (d, $J = 1.9$ Hz, 1H), 7.66 (d, $J = 8.5$ Hz, 2H), 7.37 (dd, $J = 8.7, 1.9$ Hz, 3H), 4.37 (q, $J = 7.1$ Hz, 2H), 4.27 (s, 3H), 1.39 (t, $J = 7.1$ Hz, 3H).

148-A	 2-ethoxy-6-(2-methyl-2H-indazol-5-yl)-8-(6-(trifluoromethoxy)pyridin-3-yl)pyrido[3,4-b]pyrazin-7(6H)-one	LC-MS (ESI): m/z 483 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.89 (d, <i>J</i> = 0.5 Hz, 1H), 8.63 (d, <i>J</i> = 2.3 Hz, 1H), 8.52 (s, 1H), 8.29 (dd, <i>J</i> = 8.5, 2.4 Hz, 1H), 8.19 (s, 1H), 7.94 (dd, <i>J</i> = 2.1, 0.8 Hz, 1H), 7.72 (dt, <i>J</i> = 9.1, 0.9 Hz, 1H), 7.40 – 7.30 (m, 2H), 4.35 (q, <i>J</i> = 7.0 Hz, 2H), 4.23 (s, 3H), 1.33 (t, <i>J</i> = 7.1 Hz, 3H).
149-A	 8-(6-(difluoromethoxy)pyridin-3-yl)-2-ethoxy-6-(2-methyl-2H-indazol-5-yl)pyrido[3,4-b]pyrazin-7(6H)-one	LC-MS (ESI): m/z 465 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.84 (d, <i>J</i> = 0.6 Hz, 1H), 8.54 – 8.48 (m, 2H), 8.22 – 8.14 (m, 2H), 7.93 (dd, <i>J</i> = 2.0, 0.8 Hz, 1H), 7.77 (t, <i>J</i>_{HF} = 73.0 Hz, 1H), 7.71 (dt, <i>J</i> = 9.2, 0.9 Hz, 1H), 7.36 (dd, <i>J</i> = 9.1, 2.0 Hz, 1H), 7.12 (dd, <i>J</i> = 8.6, 0.7 Hz, 1H), 4.33 (q, <i>J</i> = 7.1 Hz, 2H), 4.23 (s, 3H), 1.33 (t, <i>J</i> = 7.1 Hz, 3H).
150-A	 8-(4-(difluoromethoxy)phenyl)-2-ethoxy-6-(4-methoxyphenyl)pyrido[3,4-b]pyrazin-7(6H)-one	LC-MS (ESI): m/z 440 [M+H]⁺. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.69 (s, 1H), 8.13 (s, 1H), 7.67 (d, <i>J</i> = 8.6 Hz, 2H), 7.53 – 7.45 (m, 2H), 7.39 (t, <i>J</i>_{HF} = 73.5 Hz, 1H), 7.18 (d, <i>J</i> = 8.5 Hz, 2H), 7.10 (d, <i>J</i> = 8.9 Hz, 2H), 4.30 (q, <i>J</i> = 7.0 Hz, 2H), 3.84 (s, 3H), 1.32 (t, <i>J</i> = 7.1 Hz, 3H).

[00965] **Example 275: Biochemical Assay**

[00966] Mat2A protein was expressed by recombinant baculovirus in SF9 infected cells using the Bac to Bac system cloned into the pFASTBAC1 vector (Invitrogen, Carlsbad, CA). Recombinant MAT2A was isolated from the cell lysate of 150 g of infected cells using HP Ni sepharose column chromatography. Recombinant MAT2A homodimer was eluted with 250 and 500 mM imidazole, and fractions containing MAT2A were identified by sodium dodecyl sulfate polyacrylamide gel electrophoresis and pooled.

[00967] For determination of the inhibitory potency of compounds against the MAT2A homodimer, protein was diluted to 4 µg/mL in assay buffer (50 mM Tris, pH 8.0, 50 mM KCl, 15 mM MgCl₂, 0.3 mM EDTA, 0.005% [w/v] bovine serum albumin [BSA]). Test compound was prepared in 100% dimethyl sulfoxide (DMSO) at 50× the desired final concentration. A 1 µL volume of compound dilution was added to 40 µL of enzyme dilution and the mixture was allowed to equilibrate for 60 minutes at 25 °C. The enzymatic assay was initiated by the addition of 10 µL of substrate mix (500 µM ATP, pH 7.0, 400 µM L-methionine in 1× assay buffer), and the mixture was incubated for a further 60 minutes at 25 °C. The reaction was halted and the liberated phosphate released by the enzyme in stoichiometric amounts by the production of S-adenosyl methionine (SAM) was measured using the PiColorLock Gold kit (Innova Biosciences, UK). Absolute product amounts were determined by comparison to a standard curve of potassium phosphate buffer, pH 8.0.

[00968] Specific compounds disclosed herein were tested in the foregoing assay and they were determined to inhibit MAT2A with an IC₅₀ according to the following scores: (A) less than 100 nM, (B) between 100 nM and 1 µM, and (C) between 1 µM and 10 µM, as shown in Table 4 below.

[00969] **Example 276 Cellular Assay of target engagement (SAM)**

[00970] Measurement of MAT2A activity in cells was made by direct quantitation of the abundance of the product of its enzymatic activity, SAM. Cancer cells were treated with candidate MAT2A inhibitors for a suitable incubation period, and the cells were then lysed using a reagent which quenched any further enzyme activity. Soluble metabolites including SAM were collected and SAM itself was directly measured from the lysate using quantitative LC-MS/MS.

[00971] A typical assay was performed using an HCT116 human colon carcinoma cell line which was genetically engineered to delete the MTAP gene (commercially available from Horizon Discovery). This cell line was utilized because it was determined that loss of the MTAP gene predicts sensitivity to MAT2A inhibitors. Cells were plated in 96-well dishes at appropriate cell density. Following 24 hours, cells were then treated with the candidate MAT2A inhibitor. Prior to addition to cells, the compound was first serially diluted in 100% DMSO, typically as a 3-fold serial dilution starting at 500× top dose with 10 dose points including DMSO only control. Compound was then transferred to a working stock plate in cell culture media by adding 5 µl of compound in DMSO to 495 µl of cell culture media. This working stock was then added to cells via a further 5-fold dilution, by adding 25 µl of working stock to 100 µl of cells in culture media. Following compound addition, cells were incubated at 37 °C / 5% CO₂ for 72 hrs.

[00972] To quantitate SAM levels following compound treatment, cells were gently washed once in Ammonium Carbonate buffer (75mM at pH 7.4), placed on dry ice, and lysed with metabolite extraction buffer (80% cold methanol and 20% water (v/v) with acetic acid at 1M final concentration with 200 ng/mL deuterated d3-SAM as internal control). Following centrifugation at 4 °C at 3,200 rpm for 30 minutes, the supernatant was collected and stored at -80 °C until analysis by Liquid Chromatography with tandem Mass Spectrometry (LC-MS/MS). LC-MS/MS analysis was performed using an API6500 Mass Spectrometer (Sciex, Framingham, MA, USA) operating in positive ion spray mode and equipped with a Waters UPLC Acquity (Waters, Milford, MA, USA) BEH Amide column. Multiple Reaction Monitoring data was acquired for SAM and the d3-SAM standard, using a mass transition pair at m/z 399.2→250.1 and 402.2→250.1, respectively. In a typical LC-MS/MS analysis, the initial flow rate was 0.5 ml/min of 25% mobile phase A (acetonitrile and water at 5:95 (v/v) with 1% formic acid and 10 mM ammonium acetate) and 75% mobile phase B (acetonitrile and water at 95:5 (v/v) with 1% formic acid and 10 mM ammonium acetate), 0.2–0.5 minutes with 75% - 35% mobile phase B, 25%-65% mobile phase A, at 0.5 min 65% mobile phase A and 35% mobile phase B, 1.0–1.1 minutes with 35% –75% mobile phase B, 65%-25% mobile phase A, at 1.1min

25% mobile phase A and 75% mobile phase B with a total run time of 1.5 minutes.

[00973] Specific compounds disclosed herein were tested in the foregoing assay and they were determined to inhibit SAM with an IC_{50} according to the following scores: (A) less than 100 nM (> 60% maximum inhibition), (B) between 100 nM and 1 μ M (> 60% maximum inhibition), and (NT) not tested, as shown in Table 4 below.

[00974] Example 277: Assay for Inhibition of Cellular Proliferation

[00975] Test compound impact on cancer cell growth was assessed by treating cancer cells with compound for 4 days and then measuring proliferation using an ATP-based cell proliferation readout (Cell Titer Glo, Promega Corporation).

[00976] In a typical assay an isogenic pair of HCT116 human colon carcinoma cell lines which vary only in MTAP deletion status (HCT116 MTAP^{+/+} and HCT116 MTAP^{-/-}) were plated in 96-well dishes at appropriate cell density. Following 24 hours, cells were then treated with the candidate MAT2A inhibitor. Prior to addition to cells, the compound was first serially diluted in 100% DMSO, typically as a 3-fold serial dilution starting at 500 $\times$ top dose with 10 dose points including DMSO only control. Compound was then transferred to a working stock plate in cell culture media by adding 5 μ l of compound in DMSO to 495 μ l of cell culture media. This working stock was then added to cells via a further 5-fold dilution, by adding 25 μ l of working stock to 100 μ l of cells in culture media. Following compound addition, cells were incubated at 37 °C / 5% CO₂ for 4 days.

[00977] To measure inhibition of cellular proliferation, cells were allowed to equilibrate to room temperature for 30 minutes, and were then treated with 125 μ l of Cell Titer Glo reagent. The plate was then covered with aluminum foil and shaken for 15 minutes to ensure complete mixing and full cell lysis. Luminescent signal was then measured using a plate-based luminometer Veritas version 1.9.2 using ATP standard curve to confirm assay reproducibility from run to run. This luminescence measure was converted to a proliferation index by subtracting from each data point the ATP luminescence signal measured from a

bank (no cells) well and dividing by the ATP luminescence signal measured in 0.2% DMSO control well adjusted for signal in blank well. Compound activity was then represented as a percentage change in proliferation relative to a within-plate DMSO control against log₁₀ of compound concentration in molar (M) units.

[00978] Specific compounds disclosed herein were tested in the foregoing assay and they were determined to inhibit cellular proliferation with an IC₅₀ according to the following scores: **(A)** less than 100 nM (> 30% maximum inhibition for MTAP -/-; > 10% maximum inhibition for MTAP +/+), **(B)** between 100 nM and 10 μM (> 30% maximum inhibition for MTAP -/-; > 10% maximum inhibition for MTAP +/+), **(C)** greater than 10 μM, and **(NT)** not tested, as shown in Table 4 below.

[00979] Table 4

Compound No.	Enzyme Inhibition (Example 275)	Cell 72 h SAM Inhibition (MTAP -/-; Example 276)	4 Day Relative Growth Inhibition (MTAP -/-; Example 277)	4 Day Relative Growth Inhibition (MTAP +/+; Example 277)
101	B	NT	NT	NT
102	C	NT	NT	NT
103	B	NT	NT	NT
104	C	NT	NT	NT
105	C	NT	NT	NT
106	C	NT	NT	NT
107	C	NT	NT	NT
108	C	NT	NT	NT
109	B	NT	NT	NT
110	B	NT	NT	NT
111	C	NT	NT	NT
112	B	NT	NT	NT
113	B	NT	NT	NT
114	B	NT	NT	NT
115	B	NT	NT	NT
116	C	NT	NT	NT
117	C	NT	NT	NT
118	C	NT	NT	NT
119	C	NT	NT	NT
120	C	NT	NT	NT

Compound No.	Enzyme Inhibition (Example 275)	Cell 72 h SAM Inhibition (MTAP -/-; Example 276)	4 Day Relative Growth Inhibition (MTAP -/-; Example 277)	4 Day Relative Growth Inhibition (MTAP +/-; Example 277)
121	B	NT	NT	NT
122	B	NT	NT	NT
123	A	A	A	B
124	A	A	A	C
125	A	NT	NT	NT
126	C	NT	NT	NT
127	A	A	A	C
128	A	NT	NT	NT
129	A	B	B	C
130	A	NT	NT	NT
131	A	NT	NT	NT
132	A	A	A	C
133	A	A	A	C
134	A	NT	NT	NT
135	A	A	A	B
136	B	NT	NT	NT
137	A	B	B	C
138	B	NT	NT	NT
139	A	A	B	C
140	B	NT	NT	NT
141	A	A	A	C
142	B	NT	NT	NT
143	A	B	B	C
144	A	B	B	C
145	A	A	A	C
146	B	NT	NT	NT
147	A	B	B	C
148	A	A	A	B
149	A	NT	NT	NT
150	A	A	B	B
151	A	A	A	B
152	A	A	A	C
153	A	A	A	C
154	A	NT	NT	NT
155	A	B	B	B
156	A	A	A	C
157	A	A	B	C

Compound No.	Enzyme Inhibition (Example 275)	Cell 72 h SAM Inhibition (MTAP -/-; Example 276)	4 Day Relative Growth Inhibition (MTAP -/-; Example 277)	4 Day Relative Growth Inhibition (MTAP +/-; Example 277)
158	A	A	A	C
159	A	A	A	B
160	A	A	A	C
161	A	A	A	C
162	A	NT	NT	NT
163	C	NT	NT	NT
164	A	NT	NT	NT
165	A	NT	NT	NT
166	A	A	A	C
167	A	B	B	C
168	A	A	A	C
169	A	A	A	C
170	A	NT	NT	NT
171	A	A	A	C
172	A	A	A	C
173	A	NT	NT	NT
174	A	NT	NT	NT
175	A	NT	NT	NT
176	B	NT	NT	NT
177	A	A	B	C
178	A	A	B	B
179	A	B	B	C
180	A	A	A	C
181	A	A	B	C
182	A	A	B	C
183	A	B	B	C
184	A	NT	NT	NT
185	C	NT	NT	NT
186	B	NT	NT	NT
187	C	NT	NT	NT
188	A	A	B	C
189	A	A	B	B
190	A	NT	NT	NT
191	A	NT	NT	NT
192	A	A	B	C
193	A	B	B	C
194	B	NT	NT	NT

Compound No.	Enzyme Inhibition (Example 275)	Cell 72 h SAM Inhibition (MTAP -/-; Example 276)	4 Day Relative Growth Inhibition (MTAP -/-; Example 277)	4 Day Relative Growth Inhibition (MTAP +/-; Example 277)
195	A	A	A	C
196	A	NT	NT	NT
197	B	NT	NT	NT
198	A	B	B	C
199	C	NT	NT	NT
200	A	B	B	B
201	B	NT	NT	NT
202	A	B	B	C
203	A	B	C	C
204	B	NT	NT	NT
205	A	A	B	C
206	A	B	B	B
207	B	NT	NT	NT
208	A	NT	NT	NT
209	A	A	A	C
210	A	A	A	C
211	A	A	A	C
212	A	A	A	C
213	A	A	A	C
214	A	NT	NT	NT
215	A	A	A	B
216	A	A	A	B
217	A	A	B	C
218	A	A	A	B
219	A	A	A	B
220	A	A	A	B
221	A	A	B	C
222	A	A	B	C
223	A	B	B	C
224	A	B	C	C
225	B	A	B	B
226	A	A	A	B
227	A	A	A	B
228	A	A	A	B
229	A	A	A	B
230	A	A	A	B
231	A	A	B	C

Compound No.	Enzyme Inhibition (Example 275)	Cell 72 h SAM Inhibition (MTAP -/-; Example 276)	4 Day Relative Growth Inhibition (MTAP -/-; Example 277)	4 Day Relative Growth Inhibition (MTAP +/-; Example 277)
232	A	A	A	C
233	A	A	A	C
234	A	A	A	C
235	A	A	A	C
236	A	A	A	C
237	A	A	A	C
238	A	NT	NT	NT
239	A	A	A	B
240	A	A	A	C
241	A	A	A	B
242	A	A	A	C
243	A	A	A	C
244	A	A	A	B
245	A	A	B	C
246	A	B	B	B
247	A	A	A	B
248	A	A	A	B
249	A	A	B	B
250	A	A	A	B
251	A	A	A	B
252	A	A	B	B
253	A	A	A	B
254	A	A	A	C
255	A	A	A	C
256	A	A	B	B
257	A	A	A	B
258	A	A	B	B
259	A	A	A	C
260	A	A	A	C
261	A	NT	NT	NT
262	A	A	B	C
263	A	NT	NT	NT
264	A	A	B	B
265	A	A	A	C
266	B	NT	NT	NT
267	A	NT	NT	NT
268	A	B	B	C

Compound No.	Enzyme Inhibition (Example 275)	Cell 72 h SAM Inhibition (MTAP -/-; Example 276)	4 Day Relative Growth Inhibition (MTAP -/-; Example 277)	4 Day Relative Growth Inhibition (MTAP +/-; Example 277)
269	A	A	B	C
270	A	A	A	C
271	A	NT	NT	NT
272	A	A	B	C
273	A	NT	NT	NT
274	A	NT	NT	NT
101-A	A	A	A	C
102-A	A	A	A	B
103-A	A	A	A	C
104-A	A	A	B	B
105-A	A	A	A	B
106-A	A	A	B	C
107-A	A	A	A	B
108-A	A	A	A	B
109-A	A	A	A	B
110-A	A	A	A	B
111-A	A	A	A	B
112-A	A	A	A	B
113-A	A	A	A	B
114-A	A	A	A	B
115-A	A	A	A	B
116-A	A	A	A	C
117-A	A	A	A	B
118-A	A	A	A	B
119-A	A	A	A	B
120-A	A	A	A	B
121-A	A	A	B	B
122-A	A	A	A	B
123-A	A	A	A	B
124-A	A	A	B	B
125-A	A	A	A	B
126-A	A	A	A	B
127-A	A	B	A	B
128-A	A	A	A	B
129-A	A	A	B	B
130-A	A	A	A	B
131-A	A	A	B	B

Compound No.	Enzyme Inhibition (Example 275)	Cell 72 h SAM Inhibition (MTAP -/-; Example 276)	4 Day Relative Growth Inhibition (MTAP -/-; Example 277)	4 Day Relative Growth Inhibition (MTAP +/-; Example 277)
132-A	A	A	A	B
133-A	A	A	A	B
134-A	A	A	A	C
135-A	B	NT	NT	NT
136-A	A	NT	NT	NT
137-A	A	A	A	B
138-A	A	B	B	B
139-A	A	A	A	B
140-A	A	A	A	C
141-A	A	A	A	B
142-A	A	B	B	C
143-A	A	A	A	B
144-A	A	A	B	B
145-A	A	A	A	B
146-A	A	A	A	B
147-A	A	A	A	C
148-A	A	A	B	B
149-A	A	A	B	B
150-A	A	A	B	B

[00980] Additional compounds as set forth in Table 5 below exhibit enzyme inhibition greater than 10 μ m (Example 275) or less than 50% inhibition at maximum concentration.

[00981] Table 5

