METHODS FOR TREATING CANCER

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 63/089,965, filed on October 9, 2020; and U.S. Provisional Application Serial No. 63/151,468, filed on February 19, 2021; each of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

This disclosure provides chemical entities (e.g., a compound or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that inhibit epidermal growth factor receptor (EGFR, ERBB1) and/or Human epidermal growth factor receptor 2 (HER2, ERBB2). These chemical entities are useful, e.g., for treating a condition, disease or disorder in which increased (e.g., excessive) EGFR and/or HER2 activation contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). This disclosure also provides compositions containing the same as well as methods of using and making the same.

BACKGROUND

Epidermal growth factor receptor (EGFR, ERBB1) and Human epidermal growth factor receptor 2 (HER2, ERBB2) are members of a family of proteins which regulate cellular processes implicated in tumor growth, including proliferation and differentiation. Several investigators have demonstrated the role of EGFR and HER2 in development and cancer (Reviewed in Salomon, et al., Crit. Rev. Oncol. Hematol. (1995) 19:183-232, Klapper, et al., Adv. Cancer Res. (2000) 77, 25-79 and Hynes and Stern, Biochim. Biophys. Acta (1994) 1198:165-184). EGFR overexpression is present in at least 70% of human cancers, such as non-small cell lung carcinoma (NSCLC), breast cancer, glioma, and prostate cancer. HER2 overexpression occurs in approximately 30% of all breast cancer. It has also been implicated in other human cancers including colon, ovary, bladder, stomach,

esophagus, lung, uterus and prostate. HER2 overexpression has also been correlated with poor prognosis in human cancer, including metastasis, and early relapse.

EGFR and HER2 are, therefore, widely recognized as targets for the design and development of therapies that can specifically bind and inhibit tyrosine kinase activity and its signal transduction pathway in cancer cells, and thus can serve as diagnostic or therapeutic agents. For example, EGFR tyrosine kinase inhibitors (TKIs) are effective clinical therapies for EGFR mutant advanced non-small cell lung cancer (NSCLC) patients. However, the vast majority of patients develop disease progression following successful treatment with an EGFR TKI. Common mechanisms of resistance include acquired, secondary mutation T790M, C797S, and EGFR exon 20 insertion mutations. For example, NSCLC tumors can have EGFR exon 20 insertion mutations that are intrinsically resistant to current EGFR TKIs.

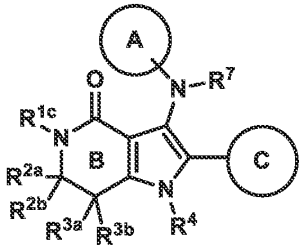
Overexpression of another protein, BUB1 (Budding uninhibited by benzimidazole, BUB1) kinase, is often associated with proliferating cells, including cancer cells, and tissues (Bolanos-Garcia VM and Blundell TL, Trends Biochem. Sci. 36, 141, 2010). This protein is an essential part of the complex network of proteins that form the mitotic checkpoint. The major function of an unsatisfied mitotic checkpoint is to keep the anaphase-promoting complex/cyclosome (APC/C) in an inactive state. As soon as the checkpoint gets satisfied the APC/C ubiquitin-ligase targets cyclin B and securin for proteolytic degradation leading to separation of the paired chromosomes and exit from mitosis.

Incomplete mitotic checkpoint function has been linked with aneuploidy and tumourigenesis (see Weaver BA and Cleveland DW, Cancer Res. 67, 10103, 2007; King RW, Biochim Biophys Acta 1786, 4, 2008). In contrast, complete inhibition of the mitotic checkpoint has been recognized to result in severe chromosome missegregation and induction of apoptosis in tumor cells (see Kops GJ et al., Nature Rev. Cancer 5, 773, 2005; Schmidt M and Medema RH, Cell Cycle 5, 159, 2006; Schmidt M and Bastians H, Drug Res. Updates 10, 162, 2007). Thus, mitotic checkpoint inhibition through inhibition of BUB1 kinase represents an approach for the treatment of proliferative disorders, including solid tumors such as carcinomas, sarcomas, leukemias and lymphoid malignancies or other disorders, associated with uncontrolled cellular proliferation.

SUMMARY

This disclosure provides chemical entities (e.g., a compound or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that inhibit epidermal growth factor receptor (EGFR, ERBB1) and/or Human epidermal growth factor receptor 2 (HER2, ERBB2). These chemical entities are useful, e.g., for treating a condition, disease or disorder in which increased (e.g., excessive) EGFR and/or HER2 activation contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). This disclosure also provides compositions containing the same as well as methods of using and making the same.

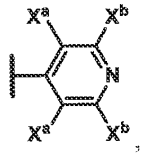
In one aspect, this disclosure features compounds of Formula **(I)**:



Formula **(I)**

or a pharmaceutically acceptable salt thereof, wherein:

Ring C is selected from the group consisting of:

- 

, wherein:
  - each $\mathbf{X^b}$ is independently $\mathbf{X^1}$, $\mathbf{R^c}$, or H; and
  - each $\mathbf{X^a}$ is independently selected from the group consisting of: H, halo; cyano; $C_{1\text{-}10}$ alkyl which is optionally substituted with from 1-6 independently selected $\mathbf{R^a}$; $C_{2\text{-}6}$ alkenyl; $-S(O)_{1\text{-}2}(C_{1\text{-}4}$ alkyl); $-S(O)(=NH)(C_{1\text{-}4}$ alkyl); $-N\mathbf{R^eR^f}$; –OH; $-S(O)_{1\text{-}2}N\mathbf{R'R''}$; $-C_{1\text{-}4}$ thioalkoxy; $-NO_2$; $-C(=O)(C_{1\text{-}10}$ alkyl); $-C(=O)O(C_{1\text{-}4}$ alkyl); $-C(=O)OH$; $-C(=O)N\mathbf{R'R''}$; and $-SF_5$;

- 2-pyridyl or 3-pyridyl, each optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;
- 2-pyridonyl or 4-pyridonyl, each optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$, wherein the ring nitrogen atom is optionally substituted with $\mathbf{R^d}$;
- heteroaryl including 6 ring atoms, wherein from 2-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N($\mathbf{R^d}$), and wherein the heteroaryl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;
- heteroaryl including 5 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;
- bicyclic heteroaryl including 7-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$; and
- C_{6-10} aryl optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;

$\mathbf{X^1}$ is $-(\mathbf{X^2})_{\mathbf{m}}\text{-}\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein: $\mathbf{m}$ is 0 or 1;

$\mathbf{X^2}$ is selected from the group consisting of:

- -O-, -N($\mathbf{R}^N$)-, or –S(O)$_{0-2}$;
-  ;
- C_{2-6} alkenylene optionally substituted with from 1-3 $\mathbf{R}^a$;
- -C(=O)O-*, -C(=O)N($\mathbf{R}^N$)-*, or –S(O)$_{1-2}$N($\mathbf{R}^N$)-*;
- -OC(=O)-*, -N($\mathbf{R}^N$)C(=O)-*, or –N($\mathbf{R}^N$)S(O)$_{1-2}$-*; and
- -OC(=O)N($\mathbf{R}^N$)-*, -N($\mathbf{R}^N$)C(=O)O-*, -N($\mathbf{R}^N$)C(=O)N($\mathbf{R}^N$)-*, or –N($\mathbf{R}^N$)S(O)$_{1-2}$N($\mathbf{R}^N$)-*,

wherein the asterisk represents point of attachment to $\mathbf{L}^1$;

$\mathbf{L}^1$ is selected from the group consisting of: a bond and C_{1-10} alkylene optionally substituted with from 1-6 $\mathbf{R}^a$;

$\mathbf{R}^5$ is selected from the group consisting of:

- H;
- halo;
- -OH;
- -N$\mathbf{R}^e\mathbf{R}^f$;
- -C_{1-6} alkoxy or -S(O)$_{0-2}$(C_{1-6} alkyl), each optionally substituted with from 1-6 $\mathbf{R}^a$;
- -$\mathbf{R}^g$;
- -$\mathbf{L}^5$-$\mathbf{R}^g$;
- -$\mathbf{R}^{g2}$-$\mathbf{R}^W$ or -$\mathbf{R}^{g2}$-$\mathbf{R}^Y$; and
- -$\mathbf{L}^5$-$\mathbf{R}^{g2}$-$\mathbf{R}^W$ or –$\mathbf{L}^5$-$\mathbf{R}^{g2}$-$\mathbf{R}^Y$;

provided that:

when $\mathbf{L}^1$ is a bond, then $\mathbf{R}^5$ is selected from the group consisting of: H, -$\mathbf{R}^g$, -$\mathbf{R}^{g2}$-$\mathbf{R}^W$, and -$\mathbf{R}^{g2}$-$\mathbf{R}^Y$; and

$\mathbf{X}^1$ is other than H, -OH, or NH_2;

$\mathbf{L}^5$ is selected from the group consisting of: –O-, -S(O)$_{0-2}$, -NH, and -N($\mathbf{R}^d$)-;

$\mathbf{R^W}$ is $-\mathbf{L^W}$-$\mathbf{W}$,

wherein $\mathbf{L^W}$ is C(=O), $S(O)_{1-2}$, OC(=O)*, NHC(=O)*, $NR^dC(=O)$*, $NHS(O)_{1-2}$*, or $NR^dS(O)_{1-2}$*, wherein the asterisk represents point of attachment to **W**, and

W is selected from the group consisting of:

- C_{2-6} alkenyl; C_{2-6} alkynyl; or C_{3-10} allenyl, each of which is optionally substituted with from 1-3 $\mathbf{R^a}$ and further optionally substituted with $\mathbf{R^g}$, wherein **W** is attached to $\mathbf{L^W}$ via an sp^2 or sp hybridized carbon atom, thereby providing an α, β-unsaturated system; and
- bicyclo[**x**.**y**.0]cycloalkyl optionally substituted with from 1-2 $\mathbf{R^c}$, wherein **x** is 1 or 2; and **y** is an integer from 1 to 6;

$\mathbf{R^Y}$ is selected from the group consisting of: $-\mathbf{R^g}$ and $-(\mathbf{L^a})_g$-$\mathbf{R^g}$;

each of $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$ is independently selected from the group consisting of: H; halo; -OH; -C(O)OH or $-C(O)NH_2$; -CN; $-\mathbf{R^b}$; $-\mathbf{L^b}$-$\mathbf{R^b}$; $-NR^eR^f$; $-\mathbf{R^g}$; $-(\mathbf{L^a})_g$-$\mathbf{R^g}$; and $-C_{1-6}$ alkoxy or $-C_{1-6}$ thioalkoxy, each optionally substituted with from 1-6 $\mathbf{R^a}$; provided that $\mathbf{R^{1c}}$ is other than halo, –CN, or –C(O)OH; or

or two of variables $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$, together with the **Ring B** ring atoms to which each is attached, form a fused saturated or unsaturated ring of 3-12 ring atoms;

- wherein from 0-2 of the ring atoms are each an independently selected heteroatom (in addition to $-N(\mathbf{R^{1c}})$- when $-N(\mathbf{R^{1c}})$- forms part of the fused saturated or unsaturated ring), wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, $N(\mathbf{R^d})$, O, and $S(O)_{0-2}$; and
- wherein the fused saturated or unsaturated ring of 3-12 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo, $\mathbf{R^c}$, and $\mathbf{R^W}$;

Ring A is $\mathbf{R^g}$;

$\mathbf{R^4}$ and $\mathbf{R^7}$ are independently H or $\mathbf{R^d}$;

each occurrence of $\mathbf{R^a}$ is independently selected from the group consisting of: –OH; -halo; –N$\mathbf{R^eR^f}$; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)O(C_{1-4} alkyl); -C(=O)(C_{1-4} alkyl); -C(=O)OH; -CON**R'R''**; -S(O)$_{1-2}$N**R'R''**; -S(O)$_{1-2}$(C_{1-4} alkyl); and cyano;

each occurrence of $\mathbf{R^b}$ is independently C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each of which is optionally substituted with from 1-6 $\mathbf{R^a}$;

each occurrence of $\mathbf{L^b}$ is independently C(=O); C(=O)O; S(O)$_{1-2}$; C(=O)NH*; C(=O)N$\mathbf{R^d}$*; S(O)$_{1-2}$NH*; or S(O)$_{1-2}$N($\mathbf{R^d}$)*, wherein the asterisk represents point of attachment to $\mathbf{R^b}$;

each occurrence of $\mathbf{R^c}$ is independently selected from the group consisting of: halo; cyano; C_{1-10} alkyl which is optionally substituted with from 1-6 independently selected $\mathbf{R^a}$; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy or C_{1-4} haloalkoxy; C_{1-4} haloalkoxy; -S(O)$_{1-2}$(C_{1-4} alkyl); -S(O)(=NH)(C_{1-4} alkyl); -N$\mathbf{R^eR^f}$; –OH; -S(O)$_{1-2}$N**R'R''**; -C_{1-4} thioalkoxy; -NO_2; -C(=O)(C_{1-10} alkyl); -C(=O)O(C_{1-4} alkyl); -C(=O)OH; -C(=O)N**R'R''**; and –SF_5;

each occurrence of $\mathbf{R^d}$ is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-3 independently selected $\mathbf{R^a}$; -C(O)(C_{1-4} alkyl); -C(O)O(C_{1-4} alkyl); -CON**R'R''**; -S(O)$_{1-2}$N**R'R''**; -S(O)$_{1-2}$(C_{1-4} alkyl); -OH; and C_{1-4} alkoxy;

each occurrence of $\mathbf{R^e}$ and $\mathbf{R^f}$ is independently selected from the group consisting of: H; C_{1-6} alkyl optionally substituted with from 1-3 substituents each independently selected from the group consisting of N**R'R''**, -OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and halo; -C(O)(C_{1-4} alkyl); -C(O)O(C_{1-4} alkyl); -CON**R'R''**; -S(O)$_{1-2}$N**R'R''**; -S(O)$_{1-2}$(C_{1-4} alkyl); -OH; and C_{1-4} alkoxy;

each occurrence of $\mathbf{R^g}$ is independently selected from the group consisting of:

- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R^c}$; and
- C_{6-10} aryl optionally substituted with from 1-4 $\mathbf{R^c}$;

each occurrence of $\mathbf{L^g}$ is independently selected from the group consisting of: -O-, -NH-, -N$\mathbf{R^d}$, -S(O)$_{0-2}$, C(O), and C_{1-3} alkylene optionally substituted with from 1-3 $\mathbf{R^a}$;

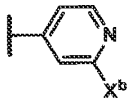
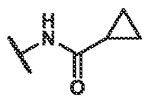
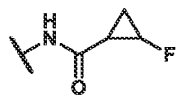
each **g** is independently 1, 2, or 3;

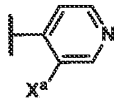
each $\mathbf{R^{g2}}$ is a divalent $\mathbf{R^g}$ group;

each occurrence of **R'** and **R''** is independently selected from the group consisting of: H; -OH; and C_{1-4} alkyl; and

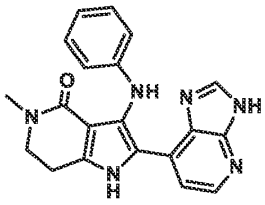
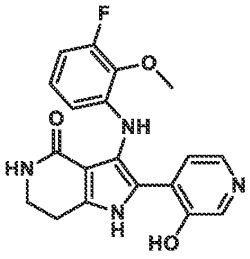
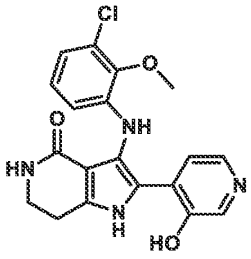
each occurrence of $\mathbf{R^N}$ is independently H, C_{1-3} alkyl, or C_{3-6} cycloalkyl.

In some embodiments, it is provided that one or more of the following applies:

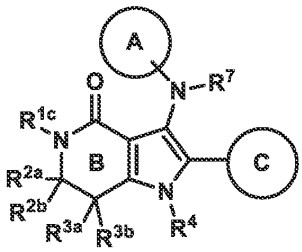
- when $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are H or methyl; $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ are H; **Ring C** is  ; and $\mathbf{X^b}$ is H, methyl, NH_2, NHC(=O)Me, NHC(=O)iPr, NHC(=O)NHEt,  ,  , then **Ring A** is other than unsubstituted phenyl;

- when R^{2a}, R^{2b}, R^{3a}, and R^{3b} are each H; **Ring C** is  ; and X^a is methyl or F, then **Ring A** is other than unsubstituted phenyl;

- when R^{1c}, R^{2a}, R^{2b}, R^{3a}, and R^{3b} are each H; **Ring C** is  , then **Ring A** is other than 4-fluorophenyl; and

- the compound is other than:  ,  , or  .

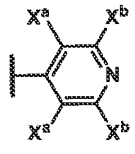
In one aspect, the disclosure features A compound of Formula (**I**):



Formula (**I**)

or a pharmaceutically acceptable salt thereof, wherein:

Ring C is selected from the group consisting of:

-  , wherein:
  - each X^b is independently X^1, R^c, or H; and
  - each X^a is independently selected from the group consisting of: H, halo; cyano; C_{1-10} alkyl which is optionally substituted with from 1-6 independently selected R^a; C_{2-6} alkenyl; $-S(O)_{1-2}(C_{1-4}$ alkyl); $-S(O)(=NH)(C_{1-4}$ alkyl); $-NR^eR^f$; –OH; $-S(O)_{1-2}NR'R''$; $-C_{1-4}$ thioalkoxy; $-NO_2$; $-C(=O)(C_{1-10}$ alkyl); $-C(=O)O(C_{1-4}$ alkyl); $-C(=O)OH$; $-C(=O)NR'R''$; and $–SF_5$;
- 2-pyridyl or 3-pyridyl, each optionally substituted with X^1 and further optionally substituted with from 1-4 R^c;
- 2-pyridonyl or 4-pyridonyl, each optionally substituted with X^1 and further optionally substituted with from 1-4 R^c, wherein the ring nitrogen atom is optionally substituted with R^d;
- heteroaryl including 6 ring atoms, wherein from 2-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N(R^d), and wherein the heteroaryl is optionally substituted with X^1 and further optionally substituted with from 1-4 R^c;
- heteroaryl including 5 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with X^1 and further optionally substituted with from 1-4 R^c;
- bicyclic heteroaryl including 7-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with X^1 and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c;

- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$; and
- C_{6-10} aryl optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;

$\mathbf{X^1}$ is $-(\mathbf{X^2})_{\mathbf{m}}\text{-}\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein: $\mathbf{m}$ is 0 or 1;

$\mathbf{X^2}$ is selected from the group consisting of:

- -O-, -N($\mathbf{R^N}$)-, or $-S(O)_{0-2}$;
-  ;
- $-C_{2-6}$ alkenylene optionally substituted with from 1-3 $\mathbf{R^a}$;
- -C(=O)O-*, -C(=O)N($\mathbf{R^N}$)-*, or $-S(O)_{1-2}N(\mathbf{R^N})$-*;
- -OC(=O)-*, -N($\mathbf{R^N}$)C(=O)-*, or $-N(\mathbf{R^N})S(O)_{1-2}$-*; and
- -OC(=O)N($\mathbf{R^N}$)-*, -N($\mathbf{R^N}$)C(=O)O-*, -N($\mathbf{R^N}$)C(=O)N($\mathbf{R^N}$)-*, or $-N(\mathbf{R^N})S(O)_{1-2}N(\mathbf{R^N})$-*,

wherein the asterisk represents point of attachment to $\mathbf{L^1}$;

$\mathbf{L^1}$ is selected from the group consisting of: a bond and C_{1-10} alkylene optionally substituted with from 1-6 $\mathbf{R^a}$;

$\mathbf{R^5}$ is selected from the group consisting of:

- H;
- halo;
- -OH;
- $-N\mathbf{R^e}\mathbf{R^f}$;

- -C_{1-6} alkoxy or -$S(O)_{0-2}(C_{1-6}$ alkyl), each optionally substituted with from 1-6 $\mathbf{R^a}$;
- -$\mathbf{R^g}$;
- -$\mathbf{L^5}$-$\mathbf{R^g}$;
- -$\mathbf{R^{g2}}$-$\mathbf{R^W}$ or -$\mathbf{R^{g2}}$-$\mathbf{R^Y}$; and
- -$\mathbf{L^5}$-$\mathbf{R^{g2}}$-$\mathbf{R^W}$ or –$\mathbf{L^5}$-$\mathbf{R^{g2}}$-$\mathbf{R^Y}$;

provided that:

when $\mathbf{L^1}$ is a bond, then $\mathbf{R^5}$ is selected from the group consisting of: H, -$\mathbf{R^g}$, -$\mathbf{R^{g2}}$-$\mathbf{R^W}$, and -$\mathbf{R^{g2}}$-$\mathbf{R^Y}$; and

$\mathbf{X^1}$ is other than H, -OH, or NH_2;

$\mathbf{L^5}$ is selected from the group consisting of: –O-, -$S(O)_{0-2}$, -NH-, and -N($\mathbf{R^d}$)-;

$\mathbf{R^W}$ is –$\mathbf{L^W}$-$\mathbf{W}$,

wherein $\mathbf{L^W}$ is C(=O), $S(O)_{1-2}$, OC(=O)*, NHC(=O)*, N$\mathbf{R^d}$C(=O)*, NHS$(O)_{1-2}$*, or N$\mathbf{R^d}$S$(O)_{1-2}$*, wherein the asterisk represents point of attachment to $\mathbf{W}$, and

$\mathbf{W}$ is selected from the group consisting of:

- C_{2-6} alkenyl; C_{2-6} alkynyl; or C_{3-10} allenyl, each of which is optionally substituted with from 1-3 $\mathbf{R^a}$ and further optionally substituted with $\mathbf{R^g}$, wherein $\mathbf{W}$ is attached to $\mathbf{L^W}$ via an sp^2 or sp hybridized carbon atom, thereby providing an α, β-unsaturated system; and
- bicyclo[**x**.**y**.0]cycloalkyl optionally substituted with from 1-2 $\mathbf{R^c}$, wherein **x** is 1 or 2; and **y** is an integer from 1 to 6;

$\mathbf{R^Y}$ is selected from the group consisting of: -$\mathbf{R^g}$ and -$(\mathbf{L^s})_g$-$\mathbf{R^g}$,

each of $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$ is independently selected from the group consisting of: H; halo; -OH; -C(O)OH or –$C(O)NH_2$; -CN; -$\mathbf{R^b}$; -$\mathbf{L^b}$-$\mathbf{R^b}$; -N$\mathbf{R^e}\mathbf{R^f}$; -$\mathbf{R^g}$; -$(\mathbf{L^s})_g$-$\mathbf{R^g}$; -$(\mathbf{L^s})_g$-$\mathbf{R^W}$; -$(\mathbf{L^s})_g$-$\mathbf{R^{g2}}$-$\mathbf{R^W}$; and -C_{1-6} alkoxy or -C_{1-6} thioalkoxy, each optionally substituted with from 1-6 $\mathbf{R^a}$; provided that $\mathbf{R^{1c}}$ is other than halo, –CN, or –C(O)OH; or

two of variables $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$, together with the **Ring B** ring atoms to which each is attached, form a fused saturated or unsaturated ring of 3-12 ring atoms;

- wherein from 0-2 of the ring atoms are each an independently selected heteroatom (in addition to –N($\mathbf{R^{1c}}$)- when –N($\mathbf{R^{1c}}$)- forms part of the fused saturated or unsaturated ring), wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^{d}}$), O, and S(O)$_{0-2}$; and
- wherein the fused saturated or unsaturated ring of 3-12 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo, $\mathbf{R^{c}}$, and $\mathbf{R^{W}}$; or

one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ combine to form a double bond between the **Ring B** atoms to which each is attached;

Ring A is $\mathbf{R^{g}}$;

$\mathbf{R^{4}}$ and $\mathbf{R^{7}}$ are independently H or $\mathbf{R^{d}}$;

each occurrence of $\mathbf{R^{a}}$ is independently selected from the group consisting of: –OH; -halo; –N$\mathbf{R^{e}R^{f}}$; C$_{1-4}$ alkoxy; C$_{1-4}$ haloalkoxy; -C(=O)O(C$_{1-4}$ alkyl); -C(=O)(C$_{1-4}$ alkyl); -C(=O)OH; -CON$\mathbf{R'R''}$; -S(O)$_{1-2}$N$\mathbf{R'R''}$; -S(O)$_{1-2}$(C$_{1-4}$ alkyl); and cyano;

each occurrence of $\mathbf{R^{b}}$ is independently C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, or C$_{2-6}$ alkynyl, each of which is optionally substituted with from 1-6 $\mathbf{R^{a}}$;

each occurrence of $\mathbf{L^{b}}$ is independently C(=O); C(=O)O; S(O)$_{1-2}$; C(=O)NH*; C(=O)N$\mathbf{R^{d}}$*; S(O)$_{1-2}$NH*; or S(O)$_{1-2}$N($\mathbf{R^{d}}$)*, wherein the asterisk represents point of attachment to $\mathbf{R^{b}}$;

each occurrence of $\mathbf{R^{c}}$ is independently selected from the group consisting of: halo; cyano; C$_{1-10}$ alkyl which is optionally substituted with from 1-6 independently selected $\mathbf{R^{a}}$; C$_{2-6}$ alkenyl; C$_{2-6}$ alkynyl; C$_{1-4}$ alkoxy optionally substituted with C$_{1-4}$ alkoxy or C$_{1-4}$ haloalkoxy; C$_{1-4}$ haloalkoxy; -S(O)$_{1-2}$(C$_{1-4}$ alkyl); -S(O)(=NH)(C$_{1-4}$ alkyl); -N$\mathbf{R^{e}R^{f}}$; –OH; -S(O)$_{1-2}$N$\mathbf{R'R''}$; -C$_{1-4}$ thioalkoxy; -NO$_2$; -C(=O)(C$_{1-10}$ alkyl); -C(=O)O(C$_{1-4}$ alkyl); -C(=O)OH; -C(=O)N$\mathbf{R'R''}$; and –SF$_5$;

each occurrence of $\mathbf{R^d}$ is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-3 independently selected $\mathbf{R^a}$; -C(O)(C_{1-4} alkyl); -C(O)O(C_{1-4} alkyl); -CON**R'R''**; -S(O)$_{1-2}$N**R'R''**; -S(O)$_{1-2}$(C_{1-4} alkyl); -OH; and C_{1-4} alkoxy;

each occurrence of $\mathbf{R^e}$ and $\mathbf{R^f}$ is independently selected from the group consisting of: H; C_{1-6} alkyl optionally substituted with from 1-3 substituents each independently selected from the group consisting of N**R'R''**, -OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and halo; -C(O)(C_{1-4} alkyl); -C(O)O(C_{1-4} alkyl); -CON**R'R''**; -S(O)$_{1-2}$N**R'R''**; -S(O)$_{1-2}$(C_{1-4} alkyl); -OH; and C_{1-4} alkoxy;

each occurrence of $\mathbf{R^g}$ is independently selected from the group consisting of:

- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R^c}$; and
- C_{6-10} aryl optionally substituted with from 1-4 $\mathbf{R^c}$;

each occurrence of $\mathbf{L^g}$ is independently selected from the group consisting of: -O-, -NH-, -N$\mathbf{R^d}$, -S(O)$_{0-2}$, C(O), and C_{1-3} alkylene optionally substituted with from 1-3 $\mathbf{R^a}$;

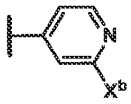
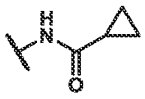
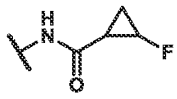
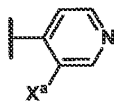
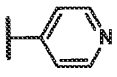
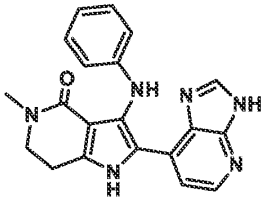
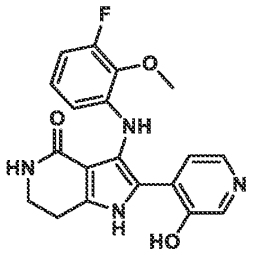
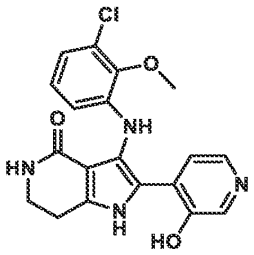
each **g** is independently 1, 2, or 3;

each $\mathbf{R^{g2}}$ is a divalent $\mathbf{R^g}$ group;

each occurrence of **R'** and **R''** is independently selected from the group consisting of: H; -OH; and C_{1-4} alkyl; and

each occurrence of $\mathbf{R^N}$ is independently H, C_{1-3} alkyl, or C_{3-6} cycloalkyl,

provided that one or more of the following applies:

- when $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are H or methyl; $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ are H; **Ring C** is  ; and $\mathbf{X^b}$ is H, methyl, NH_2, NHC(=O)Me, NHC(=O)iPr, NHC(=O)NHEt,  ,  , then **Ring A** is other than unsubstituted phenyl;
- when $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$ are each H; **Ring C** is  ; and $\mathbf{X^a}$ is methyl or F, then **Ring A** is other than unsubstituted phenyl;
- when $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$ are each H; **Ring C** is  , then **Ring A** is other than 4-fluorophenyl; and
- the compound is other than:  ,  , or  .

Also provided herein is a pharmaceutical composition comprising a compound of

Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Provided herein is a method for treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Also provided herein is a method for treating cancer in a subject in need thereof, the method comprising (a) determining that the cancer is associated with a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same; and (b) administering to the subject a therapeutically effective amount of a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Provided herein is a method of treating an EGFR-associated disease or disorder in a subject, the method comprising administering to a subject identified or diagnosed as having an EGFR-associated disease or disorder a therapeutically effective amount of a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

This disclosure also provides a method of treating an EGFR-associated disease or disorder in a subject, the method comprising: determining that the cancer in the subject is an EGFR-associated disease or disorder; and administering to the subject a therapeutically effective amount of a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein. Further provided herein is a method of treating an EGFR-associated cancer in a subject, the method comprising administering to a subject identified or diagnosed as having an EGFR-associated cancer a therapeutically effective amount of a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or

a pharmaceutical composition as provided herein.

This disclosure also provides a method of treating an EGFR-associated cancer in a subject, the method comprising: determining that the cancer in the subject is an EGFR-associated cancer; and administering to the subject a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Provided herein is a method of treating a subject, the method comprising administering a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein, to a subject having a clinical record that indicates that the subject has a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same.

Also provided herein is a method of treating a subject having a cancer, wherein the method comprises:

(a) administering one or more doses of a first EGFR inhibitor to the subject for a period of time;

(b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one EGFR inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor of step (a); and

(c) administering a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has been determined to have a cancer cell that has at least one EGFR inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor of step (a); or

(d) administering additional doses of the first EGFR inhibitor of step (a) to the subject if the subject has not been determined to have a cancer cell that has at least one

EGFR inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor of step (a).

Further provided herein is a method of treating a subject having a cancer, wherein the method comprises:

(a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first EGFR inhibitor has one or more EGFR inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor that was previously administered to the subject; and

(b) administering a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has been determined to have a cancer cell that has at least one EGFR inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor that was previously administered to the subject; or

(c) administering additional doses of the first EGFR inhibitor to the subject if the subject has not been determined to have a cancer cell that has at least one EGFR inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor previously administered to the subject.

Also provided herein is a method of treating a subject having a cancer, wherein the method comprises:

(a) determining that a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first EGFR inhibitor has one or more EGFR inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor that was previously administered to the subject; and

(b) administering a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, as a monotherapy or in conjunction with another anticancer agent to the subject.

Further provided herein is a method of treating a subject having a cancer, wherein the method comprises:

(a) determining that a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first EGFR inhibitor does not have one or more EGFR inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor that was previously administered to the subject; and

(b) administering additional doses of the first EGFR inhibitor to the subject.

This disclosure also provides a method for inhibiting EGFR in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof.

Also provided herein is a method for treating cancer in a subject in need thereof, the method comprising (a) determining that the cancer is associated with a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same; and (b) administering to the subject a therapeutically effective amount of a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Further provided herein is a method of treating a HER2-associated cancer in a subject, the method comprising administering to a subject identified or diagnosed as having a HER2-associated cancer a therapeutically effective amount of a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

This disclosure also provides a method of treating a HER2-associated cancer in a subject, the method comprising: determining that the cancer in the subject is a HER2-associated cancer; and administering to the subject a therapeutically effective amount of a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Provided herein is a method of treating a subject having a cancer, the method comprising administering a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein, to a subject having a clinical record that indicates that the subject has a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same.

Also provided herein is a method of treating a subject having a cancer, wherein the method comprises:

(a) administering one or more doses of a first HER2 inhibitor to the subject for a period of time;

(b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one HER2 inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first HER2 inhibitor of step (a), and

(c) administering a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has been determined to have a cancer cell that has at least one HER2 inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first HER2 inhibitor of step (a); or

(d) administering additional doses of the first HER2 inhibitor of step (a) to the subject if the subject has not been determined to have a cancer cell that has at least one HER2 inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first HER2 inhibitor of step (a).

Further provided herein is a method of treating a subject having a cancer, wherein the method comprises:

(a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first HER2 inhibitor has one or more HER2 inhibitor resistance mutations that confer increased resistance to a cancer

cell or tumor to treatment with the first HER2 inhibitor that was previously administered to the subject; and

(b) administering a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has been determined to have a cancer cell that has at least one HER2 inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first HER2 inhibitor that was previously administered to the subject; or

(c) administering additional doses of the first HER2 inhibitor to the subject if the subject has not been determined to have a cancer cell that has at least one HER2 inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first HER2 inhibitor previously administered to the subject.

Also provided herein is a method of treating a subject having a cancer, wherein the method comprises:

(a) determining that a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first HER2 inhibitor has one or more HER2 inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment with the first HER2 inhibitor that was previously administered to the subject; and

(b) administering a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, as a monotherapy or in conjunction with another anticancer agent to the subject.

Further provided herein is a method of treating a subject having a cancer, wherein the method comprises:

(a) determining that a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first HER2 inhibitor does not have one or more HER2 inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment with the first HER2 inhibitor that was previously administered to the subject; and

(b) administering additional doses of the first HER2 inhibitor to the subject.

This disclosure also provides a method for inhibiting HER2 in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof.

Also provided herein is a method for treating cancer in a subject in need thereof, the method comprising (a) determining that the cancer is associated with a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same and that the cancer is associated with a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same; and (b) administering to the subject a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Further provided herein is a method of treating an EGFR-associated and HER2-associated cancer in a subject, the method comprising administering to a subject identified or diagnosed as having an EGFR-associated and a HER2-associated cancer a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

This disclosure also provides a method of treating a an EGFR-associated and HER2-associated cancer in a subject, the method comprising: determining that the cancer in the subject is an EGFR-associated and a HER2-associated cancer; and administering to the subject a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Provided herein is a method of treating a subject, the method comprising administering a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein, to a subject having a clinical record that indicates that the subject has a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any

of the same and a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same.

This disclosure also provides a method for inhibiting EGFR and HER2 in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof.

In addition to the above, provided herein is a method for inhibiting a BUB (budding uninhibited by benzimidazole, BUB1-3) kinase. In some embodiments, the methods provided herein include methods for inhibiting BUB11. For example, a method for inhibiting BUB1 in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof.

Other embodiments include those described in the Detailed Description and/or in the claims.

Additional Definitions

To facilitate understanding of the disclosure set forth herein, a number of additional terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Each of the patents, applications, published applications, and other publications that are mentioned throughout the specification and the attached appendices are incorporated herein by reference in their entireties.

The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

"API" refers to an active pharmaceutical ingredient.

The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of a chemical entity being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case is determined using any suitable technique, such as a dose escalation study.

The term "excipient" or "pharmaceutically acceptable excipient" means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, carrier, solvent, or encapsulating material. In one embodiment, each component is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, e.g., Remington: The Science and Practice of Pharmacy, 21st ed.*; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients, 6th ed.*; Rowe *et al.*, Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives, 3rd ed.*; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation, 2nd ed.*; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In certain instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. In some instances, pharmaceutically acceptable salts are obtained by reacting a compound having acidic group described herein with a base to form

a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods previously determined. The pharmacologically acceptable salt s not specifically limited as far as it can be used in medicaments. Examples of a salt that the compounds described hereinform with a base include the following: salts thereof with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum; salts thereof with organic bases such as methylamine, ethylamine and ethanolamine; salts thereof with basic amino acids such as lysine and ornithine; and ammonium salt. The salts may be acid addition salts, which are specifically exemplified by acid addition salts with the following: mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid:organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, and ethanesulfonic acid; acidic amino acids such as aspartic acid and glutamic acid.

The term "pharmaceutical composition" refers to a mixture of a compound described herein with other chemical components (referred to collectively herein as "excipients"), such as carriers, stabilizers, diluents, dispersing agents, suspending agents, and/or thickening agents. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to: rectal, oral, intravenous, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

The term "subject" refers to an animal, including, but not limited to, a primate (*e.g.*, human), monkey, cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human.

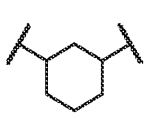
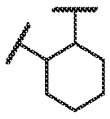
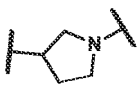
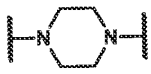
The term "halo" refers to fluoro (F), chloro (Cl), bromo (Br), or iodo (I).

The term "oxo" refers to a divalent doubly bonded oxygen atom (i.e., "=O"). As used herein, oxo groups are attached to carbon atoms to form carbonyls.

The term "alkyl" refers to a saturated acyclic hydrocarbon radical that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C_{1-10} indicates that the group may have from 1 to 10 (inclusive) carbon atoms in it. Alkyl groups can either be unsubstituted or substituted with one or more substituents. Non-limiting examples include methyl, ethyl, *iso*-propyl, *tert*-butyl, *n*-hexyl. The term "saturated" as used in this context means only single bonds present between constituent carbon atoms and other available valences occupied by hydrogen and/or other substituents as defined herein.

The term "haloalkyl" refers to an alkyl, in which one or more hydrogen atoms is/are replaced with an independently selected halo.

The term "alkoxy" refers to an -O-alkyl radical (e.g., $-OCH_3$).

The term "alkylene" refers to a divalent alkyl (e.g., $-CH_2-$). Similarly, terms such as "cycloalkylene" and "heterocyclylene" refer to divalent cycloalkyl and heterocyclyl respectively. For avoidance of doubt, in "cycloalkylene" and "heterocyclylene", the two radicals can be on the same ring carbon atom (e.g., a geminal diradical such as  or ) or on different ring atoms (e.g., ring carbon and/or nitrogen atoms (e.g., vicinal ring carbon and/or nitrogen atoms)) (e.g.,  ,  ,  , ).

The term "alkenyl" refers to an acyclic hydrocarbon chain that may be a straight chain or branched chain having one or more carbon-carbon double bonds. The alkenyl moiety contains the indicated number of carbon atoms. For example, C_{2-6} indicates that the group may have from 2 to 6 (inclusive) carbon atoms in it. Alkenyl groups can either be unsubstituted or substituted with one or more substituents.

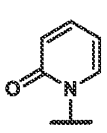
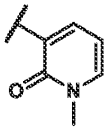
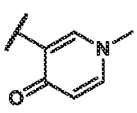
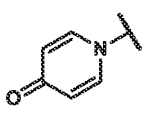
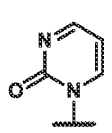
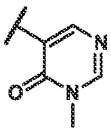
The term "alkynyl" refers to an acyclic hydrocarbon chain that may be a straight chain or branched chain having one or more carbon-carbon triple bonds. The alkynyl moiety contains the indicated number of carbon atoms. For example, C_{2-6} indicates that the group may have from 2 to 6 (inclusive) carbon atoms in it. Alkynyl groups can either be unsubstituted or substituted with one or more substituents.

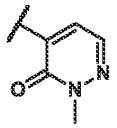
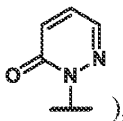
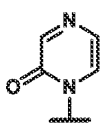
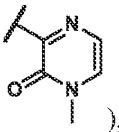
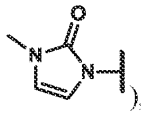
The term "aryl" refers to a 6-20 carbon mono-, bi-, tri- or polycyclic group wherein at least one ring in the system is aromatic (e.g., 6-carbon monocyclic, 10-carbon bicyclic, or 14-carbon tricyclic aromatic ring system); and wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent. Examples of aryl groups include phenyl, naphthyl, tetrahydronaphthyl, and the like.

The term "cycloalkyl" as used herein refers to cyclic saturated hydrocarbon groups having, e.g., 3 to 20 ring carbons, preferably 3 to 16 ring carbons, and more preferably 3 to 12 ring carbons or 3-10 ring carbons or 3-6 ring carbons, wherein the cycloalkyl group may be optionally substituted. Examples of cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Cycloalkyl may include multiple fused and/or bridged rings. Non-limiting examples of fused/bridged cycloalkyl includes: bicyclo[1.1.0]butane, bicyclo[2.1.0]pentane, bicyclo[1.1.1]pentane, bicyclo[3.1.0]hexane, bicyclo[2.1.1]hexane, bicyclo[3.2.0]heptane, bicyclo[4.1.0]heptane, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane, bicyclo[4.2.0]octane, bicyclo[3.2.1]octane, bicyclo[2.2.2]octane, and the like. Cycloalkyl also includes spirocyclic rings (e.g., spirocyclic bicycle wherein two rings are connected through just one atom). Non-limiting examples of spirocyclic cycloalkyls include spiro[2.2]pentane, spiro[2.5]octane, spiro[3.5]nonane, spiro[3.5]nonane, spiro[3.5]nonane, spiro[4.4]nonane, spiro[2.6]nonane, spiro[4.5]decane, spiro[3.6]decane, spiro[5.5]undecane, and the like. The term "saturated" as used in this context means only single bonds present between constituent carbon atoms.

The term "cycloalkenyl" as used herein means partially unsaturated cyclic hydrocarbon groups having 3 to 20 ring carbons, preferably 3 to 16 ring carbons, and more preferably 3 to 12 ring carbons or 3-10 ring carbons or 3-6 ring carbons, wherein the cycloalkenyl group may be optionally substituted. Examples of cycloalkenyl groups include, without limitation, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl.

As partially unsaturated cyclic hydrocarbon groups, cycloalkenyl groups may have any degree of unsaturation provided that one or more double bonds is present in the ring, none of the rings in the ring system are aromatic, and the cycloalkenyl group is not fully saturated overall. Cycloalkenyl may include multiple fused and/or bridged and/or spirocyclic rings.

The term "heteroaryl", as used herein, means a mono-, bi-, tri- or polycyclic group having 5 to 20 ring atoms, alternatively 5, 6, 9, 10, or 14 ring atoms; wherein at least one ring in the system contains one or more heteroatoms independently selected from the group consisting of N, O, and S and at least one ring in the system is aromatic (but does not have to be a ring which contains a heteroatom, e.g. tetrahydroisoquinolinyl, e.g., tetrahydroquinolinyl). Heteroaryl groups can either be unsubstituted or substituted with one or more substituents. Examples of heteroaryl include thienyl, pyridinyl, furyl, oxazolyl, oxadiazolyl, pyrrolyl, imidazolyl, triazolyl, thiodiazolyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiazolyl benzothienyl, benzoxadiazolyl, benzofuranyl, benzimidazolyl, benzotriazolyl, cinnolinyl, indazolyl, indolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, purinyl, thienopyridinyl, pyrido[2,3-*d*]pyrimidinyl, pyrrolo[2,3-*b*]pyridinyl, quinazolinyl, quinolinyl, thieno[2,3-*c*]pyridinyl, pyrazolo[3,4-*b*]pyridinyl, pyrazolo[3,4-*c*]pyridinyl, pyrazolo[4,3-*c*]pyridine, pyrazolo[4,3-*b*]pyridinyl, tetrazolyl, chromane, 2,3-dihydrobenzo[*b*][1,4]dioxine, benzo[*d*][1,3]dioxole, 2,3-dihydrobenzofuran, tetrahydroquinoline, 2,3-dihydrobenzo[*b*][1,4]oxathiine, isoindoline, and others. In some embodiments, the heteroaryl is selected from thienyl, pyridinyl, furyl, pyrazolyl, imidazolyl, isoindolinyl, pyranyl, pyrazinyl, and pyrimidinyl. For purposes of clarification, heteroaryl also includes aromatic lactams, aromatic cyclic ureas, or vinylogous analogs thereof, in which each ring nitrogen adjacent to a carbonyl is tertiary (i.e., all three valences are occupied by non-hydrogen substituents), such as one or more of pyridone (e.g.,  ,  ,  , or ), pyrimidone (e.g.,  or ), pyridazinone

(e.g.,  or ), pyrazinone (e.g.,  or ), and imidazolone (e.g., ), wherein each ring nitrogen adjacent to a carbonyl is tertiary (i.e., the oxo group (i.e., "=O") herein is a constituent part of the heteroaryl ring).

The term "heterocyclyl" refers to a mono-, bi-, tri-, or polycyclic saturated ring system with 3-16 ring atoms (e.g., 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system) having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic or polycyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent. Examples of heterocyclyl groups include piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, tetrahydrofuranyl, and the like. Heterocyclyl may include multiple fused and bridged rings. Non-limiting examples of fused/bridged heteorocyclyl includes: 2-azabicyclo[1.1.0]butane, 2-azabicyclo[2.1.0]pentane, 2-azabicyclo[1.1.1]pentane, 3-azabicyclo[3.1.0]hexane, 5-azabicyclo[2.1.1]hexane, 3-azabicyclo[3.2.0]heptane, octahydrocyclopenta[c]pyrrole, 3-azabicyclo[4.1.0]heptane, 7-azabicyclo[2.2.1]heptane, 6-azabicyclo[3.1.1]heptane, 7-azabicyclo[4.2.0]octane, 2-azabicyclo[2.2.2]octane, 3-azabicyclo[3.2.1]octane, 2-oxabicyclo[1.1.0]butane, 2-oxabicyclo[2.1.0]pentane, 2-oxabicyclo[1.1.1]pentane, 3-oxabicyclo[3.1.0]hexane, 5-oxabicyclo[2.1.1]hexane, 3-oxabicyclo[3.2.0]heptane, 3-oxabicyclo[4.1.0]heptane, 7-oxabicyclo[2.2.1]heptane, 6-oxabicyclo[3.1.1]heptane, 7-oxabicyclo[4.2.0]octane, 2-oxabicyclo[2.2.2]octane, 3-oxabicyclo[3.2.1]octane, and the like. Heterocyclyl also includes spirocyclic rings (e.g., spirocyclic bicycle wherein two rings are connected through just one atom). Non-limiting examples of spirocyclic heterocyclyls include 2-azaspiro[2.2]pentane, 4-azaspiro[2.5]octane, 1-azaspiro[3.5]nonane, 2-azaspiro[3.5]nonane, 7-azaspiro[3.5]nonane, 2-azaspiro[4.4]nonane, 6-azaspiro[2.6]nonane, 1,7-diazaspiro[4.5]decane, 7-azaspiro[4.5]decane 2,5-

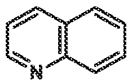
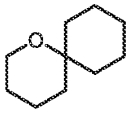
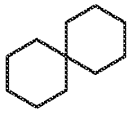
diazaspiro[3.6]decane, 3-azaspiro[5.5]undecane, 2-oxaspiro[2.2]pentane, 4-oxaspiro[2.5]octane, 1-oxaspiro[3.5]nonane, 2-oxaspiro[3.5]nonane, 7-oxaspiro[3.5]nonane, 2-oxaspiro[4.4]nonane, 6-oxaspiro[2.6]nonane, 1,7-dioxaspiro[4.5]decane, 2,5-dioxaspiro[3.6]decane, 1-oxaspiro[5.5]undecane, 3-oxaspiro[5.5]undecane, 3-oxa-9-azaspiro[5.5]undecane and the like. The term "saturated" as used in this context means only single bonds present between constituent ring atoms and other available valences occupied by hydrogen and/or other substituents as defined herein.

The term "heterocycloalkenyl" as used herein means partially unsaturated cyclic ring system with 3-16 ring atoms (e.g., 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system) having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic or polycyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent. Examples of heterocycloalkenyl groups include, without limitation, tetrahydropyridyl, dihydropyrazinyl, dihydropyridyl, dihydropyrrolyl, dihydrofuranyl, dihydrothiophenyl. As partially unsaturated cyclic groups, heterocycloalkenyl groups may have any degree of unsaturation provided that one or more double bonds is present in the ring, none of the rings in the ring system are aromatic, and the heterocycloalkenyl group is not fully saturated overall. Heterocycloalkenyl may include multiple fused and/or bridged and/or spirocyclic rings.

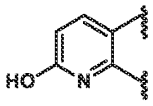
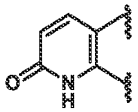
As used herein, examples of aromatic rings include: benzene, pyridine, pyrimidine, pyrazine, pyridazine, pyridone, pyrrole, pyrazole, oxazole, thioazole, isoxazole, isothiazole, and the like.

As used herein, when a ring is described as being "partially unsaturated", it means said ring has one or more additional degrees of unsaturation (in addition to the degree of unsaturation attributed to the ring itself; e.g., one or more double or tirple bonds between constituent ring atoms), provided that the ring is not aromatic. Examples of such rings include: cyclopentene, cyclohexene, cycloheptene, dihydropyridine, tetrahydropyridine, dihydropyrrole, dihydrofuran, dihydrothiophene, and the like.

For the avoidance of doubt, and unless otherwise specified, for rings and cyclic groups (e.g., aryl, heteroaryl, heterocyclyl, heterocycloalkenyl, cycloalkenyl, cycloalkyl,

and the like described herein) containing a sufficient number of ring atoms to form bicyclic or higher order ring systems (e.g., tricyclic, polycyclic ring systems), it is understood that such rings and cyclic groups encompass those having fused rings, including those in which the points of fusion are located (i) on adjacent ring atoms (e.g., [x.x.0] ring systems, in which 0 represents a zero atom bridge (e.g., )); (ii) a single ring atom (spiro-fused ring systems) (e.g.,  ,  , or ), or (iii) a contiguous array of ring atoms (bridged ring systems having all bridge lengths > 0) (e.g.,  ,  , or ).

In addition, atoms making up the compounds of the present embodiments are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C.

In addition, the compounds generically or specifically disclosed herein are intended to include all tautomeric forms. Thus, by way of example, a compound containing the moiety:  encompasses the tautomeric form containing the moiety:  . Similarly, a pyridinyl or pyrimidinyl moiety that is described to be optionally substituted with hydroxyl encompasses pyridone or pyrimidone tautomeric forms.

The compounds provided herein may encompass various stereochemical forms. The compounds also encompass diastereomers as well as optical isomers, e.g., mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and

diastereomers, which arise as a consequence of structural asymmetry in certain compounds. Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

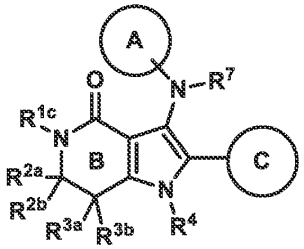
The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features and advantages of the invention will be apparent from the description and drawings, and from the claims.

DETAILED DESCRIPTION

This disclosure provides chemical entities (e.g., a compound or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that inhibit epidermal growth factor receptor (EGFR, ERBB1) and/or Human epidermal growth factor receptor 2 (HER2, ERBB2). These chemical entities are useful, e.g., for treating a condition, disease or disorder in which increased (e.g., excessive) EGFR and/or HER2 activation contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). In some embodiments, the chemical entities provided herein can inhibit an EGFR kinase and/or a HER2 kinase that has an exon 20 mutation (e.g., any of the exon 20 mutations described herein). Exon 20 mutations can confer intrinsic resistance to EGFR and/or HER2 inhibitors, and there are currently only limited targeted therapies that have been approved for subjects with these mutations. This disclosure also provides compositions containing the chemical entities provided herein as well as methods of using and making the same.

Formulae (I) Compounds

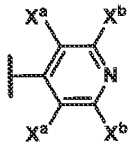
In one aspect, this disclosure features compounds of Formula **(I)**:



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

Ring C is selected from the group consisting of:

-  , wherein:
  - each X^b is independently X^1, R^c, or H; and
  - each X^a is independently selected from the group consisting of: H, halo; cyano; C_{1-10} alkyl which is optionally substituted with from 1-6 independently selected R^a; C_{2-6} alkenyl; $-S(O)_{1-2}(C_{1-4}$ alkyl); $-S(O)(=NH)(C_{1-4}$ alkyl); $-NR^eR^f$; –OH; $-S(O)_{1-2}NR'R''$; $-C_{1-4}$ thioalkoxy; $-NO_2$; $-C(=O)(C_{1-10}$ alkyl); $-C(=O)O(C_{1-4}$ alkyl); $-C(=O)OH$; $-C(=O)NR'R''$; and $-SF_5$;
- 2-pyridyl or 3-pyridyl, each optionally substituted with X^1 and further optionally substituted with from 1-4 R^c;
- 2-pyridonyl or 4-pyridonyl, each optionally substituted with X^1 and further optionally substituted with from 1-4 R^c, wherein the ring nitrogen atom is optionally substituted with R^d;
- heteroaryl including 6 ring atoms, wherein from 2-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N(R^d), and wherein the heteroaryl is optionally substituted with X^1 and further optionally substituted with from 1-4 R^c;
- heteroaryl including 5 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with X^1 and further optionally substituted with from 1-4 R^c;
- bicyclic heteroaryl including 7-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with X^1 and further

optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;

- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$; and
- C_{6-10} aryl optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;

$\mathbf{X^1}$ is $-(\mathbf{X^2})_{\mathbf{m}}\text{-}\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein: **m** is 0 or 1;

$\mathbf{X^2}$ is selected from the group consisting of:

- -O-, -N($\mathbf{R^N}$)-, or $-S(O)_{0-2}$;
-  ;
- C_{2-6} alkenylene optionally substituted with from 1-3 $\mathbf{R^a}$;
- -C(=O)O-*, -C(=O)N($\mathbf{R^N}$)-*, or $-S(O)_{1-2}N(\mathbf{R^N})$-*;
- -OC(=O)-*, -N($\mathbf{R^N}$)C(=O)-*, or $-N(\mathbf{R^N})S(O)_{1-2}$-*; and
- -OC(=O)N($\mathbf{R^N}$)-*, -N($\mathbf{R^N}$)C(=O)O-*, -N($\mathbf{R^N}$)C(=O)N($\mathbf{R^N}$)-*, or $-N(\mathbf{R^N})S(O)_{1-2}N(\mathbf{R^N})$-*,

wherein the asterisk represents point of attachment to $\mathbf{L^1}$;

$\mathbf{L^1}$ is selected from the group consisting of: a bond and C_{1-10} alkylene optionally substituted with from 1-6 $\mathbf{R^a}$;

$\mathbf{R^5}$ is selected from the group consisting of:

- H;
- halo;

- -OH;
- $-NR^eR^f$;
- $-C_{1-6}$ alkoxy or $-S(O)_{0-2}(C_{1-6}$ alkyl), each optionally substituted with from 1-6 R^a;
- $-R^g$;
- $-L^5-R^g$;
- $-R^{g2}-R^W$ or $-R^{g2}-R^Y$; and
- $-L^5-R^{g2}-R^W$ or $-L^5-R^{g2}-R^Y$;

provided that:

when L^1 is a bond, then R^5 is selected from the group consisting of: H, $-R^g$, $-R^{g2}-R^W$, and $-R^{g2}-R^Y$; and

X^1 is other than H, -OH, or NH_2;

L^5 is selected from the group consisting of: –O-, $-S(O)_{0-2}$, -NH, and $-N(R^d)-$;

R^W is $-L^W-W$,

wherein L^W is $C(=O)$, $S(O)_{1-2}$, $OC(=O)*$, $NHC(=O)*$, $NR^dC(=O)*$, $NHS(O)_{1-2}*$, or $NR^dS(O)_{1-2}*$, wherein the asterisk represents point of attachment to W, and

W is selected from the group consisting of:

- C_{2-6} alkenyl; C_{2-6} alkynyl; or C_{3-10} allenyl, each of which is optionally substituted with from 1-3 R^a and further optionally substituted with R^g, wherein W is attached to L^W via an sp^2 or sp hybridized carbon atom, thereby providing an α, β-unsaturated system; and
- bicyclo[x.y.0]cycloalkyl optionally substituted with from 1-2 R^c, wherein x is 1 or 2; and y is an integer from 1 to 6;

R^Y is selected from the group consisting of: $-R^g$ and $-(L^g)_g-R^g$;

each of R^{1c}, R^{2a}, R^{2b}, R^{3a}, and R^{3b} is independently selected from the group consisting of: H; halo; -OH; $-C(O)OH$ or $-C(O)NH_2$; -CN; $-R^b$; $-L^b-R^b$; $-NR^eR^f$; $-R^g$; -

$(L^a)_g$-R^g; and -C_{1-6} alkoxy or -C_{1-6} thioalkoxy, each optionally substituted with from 1-6 R^a; provided that R^{1c} is other than halo, –CN, or –C(O)OH; or

or two of variables R^{1c}, R^{2a}, R^{2b}, R^{3a}, and R^{3b}, together with the **Ring B** ring atoms to which each is attached, form a fused saturated or unsaturated ring of 3-12 ring atoms;

- wherein from 0-2 of the ring atoms are each an independently selected heteroatom (in addition to –N(R^{1c})- when –N(R^{1c})- forms part of the fused saturated or unsaturated ring), wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N(R^d), O, and S(O)$_{0-2}$; and
- wherein the fused saturated or unsaturated ring of 3-12 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo, R^c, and R^w;

Ring A is R^g;

R^4 and R^7 are independently H or R^d;

each occurrence of R^a is independently selected from the group consisting of: –OH; -halo; –NR^eR^f; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)O(C_{1-4} alkyl); -C(=O)(C_{1-4} alkyl); -C(=O)OH; -CON**R'R''**; -S(O)$_{1-2}$N**R'R''**; -S(O)$_{1-2}$(C_{1-4} alkyl); and cyano;

each occurrence of R^b is independently C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each of which is optionally substituted with from 1-6 R^a;

each occurrence of L^b is independently C(=O); C(=O)O; S(O)$_{1-2}$; C(=O)NH*; C(=O)NR^d*; S(O)$_{1-2}$NH*; or S(O)$_{1-2}$N(R^d)*, wherein the asterisk represents point of attachment to R^b;

each occurrence of R^c is independently selected from the group consisting of: halo; cyano; C_{1-10} alkyl which is optionally substituted with from 1-6 independently selected R^a; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy or C_{1-4} haloalkoxy; C_{1-4} haloalkoxy; -S(O)$_{1-2}$(C_{1-4} alkyl); -S(O)(=NH)(C_{1-4} alkyl); -NR^eR^f; –OH; -S(O)$_{1-2}$N**R'R''**; -C_{1-4} thioalkoxy; -NO_2; -C(=O)(C_{1-10} alkyl); -C(=O)O(C_{1-4} alkyl); -C(=O)OH; -C(=O)N**R'R''**; and –SF_5;

each occurrence of $\mathbf{R^d}$ is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-3 independently selected $\mathbf{R^a}$; -C(O)(C_{1-4} alkyl); -C(O)O(C_{1-4} alkyl); -CON**R'R''**; -S(O)$_{1-2}$N**R'R''**; -S(O)$_{1-2}$(C_{1-4} alkyl); -OH; and C_{1-4} alkoxy;

each occurrence of $\mathbf{R^e}$ and $\mathbf{R^f}$ is independently selected from the group consisting of: H; C_{1-6} alkyl optionally substituted with from 1-3 substituents each independently selected from the group consisting of N**R'R''**, -OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and halo; -C(O)(C_{1-4} alkyl); -C(O)O(C_{1-4} alkyl); -CON**R'R''**; -S(O)$_{1-2}$N**R'R''**; -S(O)$_{1-2}$(C_{1-4} alkyl); -OH; and C_{1-4} alkoxy;

each occurrence of $\mathbf{R^g}$ is independently selected from the group consisting of:

- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R^c}$; and
- C_{6-10} aryl optionally substituted with from 1-4 $\mathbf{R^c}$;

each occurrence of $\mathbf{L^g}$ is independently selected from the group consisting of: -O-, -NH-, -N$\mathbf{R^d}$, -S(O)$_{0-2}$, C(O), and C_{1-3} alkylene optionally substituted with from 1-3 $\mathbf{R^a}$;

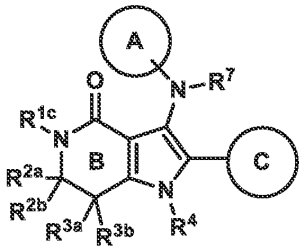
each **g** is independently 1, 2, or 3;

each $\mathbf{R^{g2}}$ is a divalent $\mathbf{R^g}$ group;

each occurrence of **R'** and **R''** is independently selected from the group consisting of: H; -OH; and C_{1-4} alkyl; and

each occurrence of $\mathbf{R^N}$ is independently H, C_{1-3} alkyl, or C_{3-6} cycloalkyl.

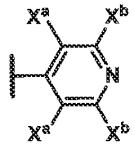
In one aspect, this disclosure features compounds of Formula (**I**):



Formula (**I**)

or a pharmaceutically acceptable salt thereof, wherein:

Ring C is selected from the group consisting of:

- 

, wherein:
  - each $\mathbf{X^b}$ is independently $\mathbf{X^1}$, $\mathbf{R^c}$, or H; and
  - each $\mathbf{X^a}$ is independently selected from the group consisting of: H, halo; cyano; C_{1-10} alkyl which is optionally substituted with from 1-6 independently selected $\mathbf{R^a}$; C_{2-6} alkenyl; $-S(O)_{1-2}(C_{1-4}$ alkyl); $-S(O)(=NH)(C_{1-4}$ alkyl); $-NR^eR^f$, –OH; $-S(O)_{1-2}NR'R''$; $-C_{1-4}$ thioalkoxy; $-NO_2$; $-C(=O)(C_{1-10}$ alkyl); $-C(=O)O(C_{1-4}$ alkyl); $-C(=O)OH$; $-C(=O)NR'R''$; and $–SF_5$;
- 2-pyridyl or 3-pyridyl, each optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;
- 2-pyridonyl or 4-pyridonyl, each optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$, wherein the ring nitrogen atom is optionally substituted with $\mathbf{R^d}$;

- heteroaryl including 6 ring atoms, wherein from 2-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N($\mathbf{R^d}$), and wherein the heteroaryl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;
- heteroaryl including 5 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;
- bicyclic heteroaryl including 7-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$; and
- C_{6-10} aryl optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;

$\mathbf{X^1}$ is $-(\mathbf{X^2})_{\mathbf{m}}\text{-}\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein: $\mathbf{m}$ is 0 or 1;

$\mathbf{X^2}$ is selected from the group consisting of:

- -O-, -N($\mathbf{R^N}$)-, or $-S(O)_{0-2}$;
-  ;
- C_{2-6} alkenylene optionally substituted with from 1-3 $\mathbf{R^a}$;
- -C(=O)O-*, -C(=O)N($\mathbf{R^N}$)-*, or $-S(O)_{1-2}N(\mathbf{R^N})$-*;

- -OC(=O)-*, -N($\mathbf{R}^N$)C(=O)-*, or –N($\mathbf{R}^N$)S(O)$_{1-2}$-*; and
- -OC(=O)N($\mathbf{R}^N$)-*, -N($\mathbf{R}^N$)C(=O)O-*, -N($\mathbf{R}^N$)C(=O)N($\mathbf{R}^N$)-*, or –N($\mathbf{R}^N$)S(O)$_{1-2}$N($\mathbf{R}^N$)-*,

wherein the asterisk represents point of attachment to $\mathbf{L}^1$;

$\mathbf{L}^1$ is selected from the group consisting of: a bond and C$_{1-10}$ alkylene optionally substituted with from 1-6 $\mathbf{R}^a$;

$\mathbf{R}^5$ is selected from the group consisting of:

- H;
- halo;
- -OH;
- -N$\mathbf{R}^e\mathbf{R}^f$;
- -C$_{1-6}$ alkoxy or -S(O)$_{0-2}$(C$_{1-6}$ alkyl), each optionally substituted with from 1-6 $\mathbf{R}^a$;
- -$\mathbf{R}^g$;
- -$\mathbf{L}^5$-$\mathbf{R}^g$;
- -$\mathbf{R}^{g2}$-$\mathbf{R}^W$ or -$\mathbf{R}^{g2}$-$\mathbf{R}^Y$; and
- -$\mathbf{L}^5$-$\mathbf{R}^{g2}$-$\mathbf{R}^W$ or –$\mathbf{L}^5$-$\mathbf{R}^{g2}$-$\mathbf{R}^Y$;

provided that:

when $\mathbf{L}^1$ is a bond, then $\mathbf{R}^5$ is selected from the group consisting of: H, -$\mathbf{R}^g$, -$\mathbf{R}^{g2}$-$\mathbf{R}^W$, and -$\mathbf{R}^{g2}$-$\mathbf{R}^Y$; and

$\mathbf{X}^1$ is other than H, -OH, or NH$_2$;

$\mathbf{L}^5$ is selected from the group consisting of: –O-, -S(O)$_{0-2}$, -NH, and -N($\mathbf{R}^d$)-;

$\mathbf{R}^W$ is –$\mathbf{L}^W$-$\mathbf{W}$,

wherein $\mathbf{L}^W$ is C(=O), S(O)$_{1-2}$, OC(=O)*, NHC(=O)*, N$\mathbf{R}^d$C(=O)*, NHS(O)$_{1-2}$*, or N$\mathbf{R}^d$S(O)$_{1-2}$*, wherein the asterisk represents point of attachment to $\mathbf{W}$, and

W is C_{2-6} alkenyl; C_{2-6} alkynyl; or C_{3-10} allenyl, each of which is optionally substituted with from 1-3 $\mathbf{R^a}$ and further optionally substituted with $\mathbf{R^g}$, wherein **W** is attached to $\mathbf{L^W}$ via an sp^2 or sp hybridized carbon atom, thereby providing an α, β-unsaturated system; and

$\mathbf{R^Y}$ is selected from the group consisting of: -$\mathbf{R^g}$ and -$(\mathbf{L^g})_g$-$\mathbf{R^g}$;

each of $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$ is independently selected from the group consisting of: H; halo; -OH; -C(O)OH or –C(O)NH_2; -CN; -$\mathbf{R^b}$; -$\mathbf{L^b}$-$\mathbf{R^b}$; -N$\mathbf{R^c}$$\mathbf{R^f}$; -$\mathbf{R^g}$; -$(\mathbf{L^g})_g$-$\mathbf{R^g}$; and -$C_{1-6}$ alkoxy or -C_{1-6} thioalkoxy, each optionally substituted with from 1-6 $\mathbf{R^a}$; provided that $\mathbf{R^{1c}}$ is other than halo, –CN, or –C(O)OH; or

or two of variables $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$, together with the **Ring B** ring atoms to which each is attached, form a fused saturated or unsaturated ring of 3-12 ring atoms;

- wherein from 0-2 of the ring atoms are each an independently selected heteroatom (in addition to –N($\mathbf{R^{1c}}$)- when –N($\mathbf{R^{1c}}$)- forms part of the fused saturated or unsaturated ring), wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and $S(O)_{0-2}$; and
- wherein the fused saturated or unsaturated ring of 3-12 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo, $\mathbf{R^c}$, and $\mathbf{R^W}$;

Ring A is $\mathbf{R^g}$;

$\mathbf{R^4}$ and $\mathbf{R^7}$ are independently H or $\mathbf{R^d}$;

each occurrence of $\mathbf{R^a}$ is independently selected from the group consisting of: –OH; -halo; –N$\mathbf{R^c}$$\mathbf{R^f}$; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)O(C_{1-4} alkyl); -C(=O)(C_{1-4} alkyl); -C(=O)OH; -CON**R'R''**; -$S(O)_{1-2}$N**R'R''**; -$S(O)_{1-2}$(C_{1-4} alkyl); and cyano;

each occurrence of $\mathbf{R^b}$ is independently C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each of which is optionally substituted with from 1-6 $\mathbf{R^a}$;

each occurrence of $\mathbf{L^b}$ is independently C(=O); C(=O)O; $S(O)_{1-2}$; C(=O)NH*; C(=O)N$\mathbf{R^d}$*; $S(O)_{1-2}NH$*; or $S(O)_{1-2}N(\mathbf{R^d})$*, wherein the asterisk represents point of attachment to $\mathbf{R^b}$;

each occurrence of $\mathbf{R^c}$ is independently selected from the group consisting of: halo; cyano; C_{1-10} alkyl which is optionally substituted with from 1-6 independently selected $\mathbf{R^a}$; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy or C_{1-4} haloalkoxy; C_{1-4} haloalkoxy; $-S(O)_{1-2}(C_{1-4}$ alkyl); $-S(O)(=NH)(C_{1-4}$ alkyl); $-N\mathbf{R^e}\mathbf{R^f}$; –OH; $-S(O)_{1-2}N\mathbf{R'R''}$; $-C_{1-4}$ thioalkoxy; $-NO_2$; $-C(=O)(C_{1-10}$ alkyl); $-C(=O)O(C_{1-4}$ alkyl); -C(=O)OH; -C(=O)N**R'R''**; and $-SF_5$;

each occurrence of $\mathbf{R^d}$ is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-3 independently selected $\mathbf{R^a}$; $-C(O)(C_{1-4}$ alkyl); $-C(O)O(C_{1-4}$ alkyl), -CON**R'R''**; $-S(O)_{1-2}N\mathbf{R'R''}$; $-S(O)_{1-2}(C_{1-4}$ alkyl); -OH; and C_{1-4} alkoxy;

each occurrence of $\mathbf{R^e}$ and $\mathbf{R^f}$ is independently selected from the group consisting of: H; C_{1-6} alkyl optionally substituted with from 1-3 substituents each independently selected from the group consisting of N**R'R''**, -OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and halo; $-C(O)(C_{1-4}$ alkyl); $-C(O)O(C_{1-4}$ alkyl); -CON**R'R''**; $-S(O)_{1-2}N\mathbf{R'R''}$; $-S(O)_{1-2}(C_{1-4}$ alkyl); -OH; and C_{1-4} alkoxy;

each occurrence of $\mathbf{R^g}$ is independently selected from the group consisting of:

- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;

- heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R^c}$; and
- C_{6-10} aryl optionally substituted with from 1-4 $\mathbf{R^c}$;

each occurrence of $\mathbf{L^g}$ is independently selected from the group consisting of: -O-, -NH-, -N$\mathbf{R^d}$, -S(O)$_{0-2}$, C(O), and C_{1-3} alkylene optionally substituted with from 1-3 $\mathbf{R^a}$;

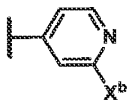
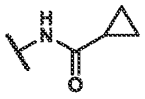
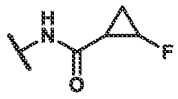
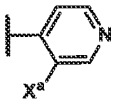
each **g** is independently 1, 2, or 3;

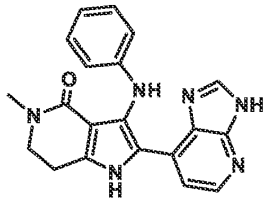
each $\mathbf{R^{g2}}$ is a divalent $\mathbf{R^g}$ group;

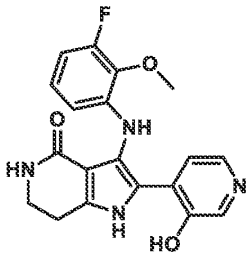
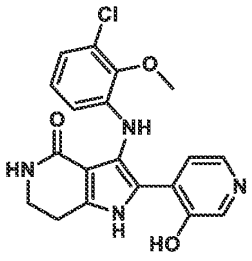
each occurrence of **R'** and **R''** is independently selected from the group consisting of: H; -OH; and C_{1-4} alkyl; and

each occurrence of $\mathbf{R^N}$ is independently H, C_{1-3} alkyl, or C_{3-6} cycloalkyl.

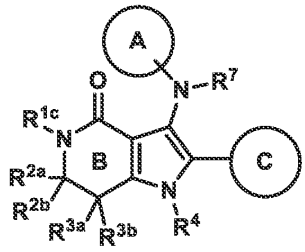
In some embodiments, it is provided that one or more of the following applies:

- when $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are H or methyl; $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ are H; **Ring C** is  ; and $\mathbf{X^b}$ is H, methyl, NH_2, NHC(=O)Me, NHC(=O)iPr, NHC(=O)NHEt,  ,  , then **Ring A** is other than unsubstituted phenyl;
- when $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$ are each H; **Ring C** is  ; and $\mathbf{X^a}$ is methyl or F, then **Ring A** is other than unsubstituted phenyl;
- when $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$ are each H; **Ring C** is  , then **Ring A** is other than 4-fluorophenyl; and

- the compound is other than:  ,

 , or  .

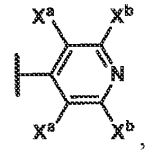
In one aspect, this disclosure features a compound of Formula **(I)**:



Formula **(I)**

or a pharmaceutically acceptable salt thereof, wherein:

Ring C is selected from the group consisting of:

-  , wherein:
  - each $\mathbf{X^b}$ is independently $\mathbf{X^1}$, $\mathbf{R^c}$, or H; and
  - each $\mathbf{X^a}$ is independently selected from the group consisting of: H, halo; cyano; C_{1-10} alkyl which is optionally substituted with from 1-6 independently selected $\mathbf{R^a}$; C_{2-6} alkenyl; $-S(O)_{1-2}(C_{1-4}$ alkyl); $-S(O)(=NH)(C_{1-4}$ alkyl); $-N\mathbf{R^e}\mathbf{R^f}$; –OH; $-S(O)_{1-2}N\mathbf{R'}\mathbf{R''}$; $-C_{1-4}$

thioalkoxy; $-NO_2$; $-C(=O)(C_{1-10}$ alkyl); $-C(=O)O(C_{1-4}$ alkyl); $-C(=O)OH$; $-C(=O)NR'R''$; and $-SF_5$;

- 2-pyridyl or 3-pyridyl, each optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;
- 2-pyridonyl or 4-pyridonyl, each optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$, wherein the ring nitrogen atom is optionally substituted with $\mathbf{R^d}$;
- heteroaryl including 6 ring atoms, wherein from 2-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N($\mathbf{R^d}$), and wherein the heteroaryl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;
- heteroaryl including 5 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;
- bicyclic heteroaryl including 7-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$; and
- C_{6-10} aryl optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;

X^1 is $-(X^2)_m-L^1-R^5$, wherein: m is 0 or 1;

X^2 is selected from the group consisting of:

- -O-, -N(R^N)-, or $-S(O)_{0-2}$;
-  ;
- -C_{2-6} alkenylene optionally substituted with from 1-3 R^a;
- -C(=O)O-*, -C(=O)N(R^N)-*, or $-S(O)_{1-2}N(R^N)$-*;
- -OC(=O)-*, -N(R^N)C(=O)-*, or $-N(R^N)S(O)_{1-2}$-*; and
- -OC(=O)N(R^N)-*, -N(R^N)C(=O)O-*, -N(R^N)C(=O)N(R^N)-*, or $-N(R^N)S(O)_{1-2}N(R^N)$-*,

wherein the asterisk represents point of attachment to L^1;

L^1 is selected from the group consisting of: a bond and C_{1-10} alkylene optionally substituted with from 1-6 R^a;

R^5 is selected from the group consisting of:

- H;
- halo;
- -OH;
- -NR^eR^f;
- -C_{1-6} alkoxy or -$S(O)_{0-2}(C_{1-6}$ alkyl), each optionally substituted with from 1-6 R^a;
- -R^g;
- -L^5-R^g;
- -R^{g2}-R^W or -R^{g2}-R^Y; and
- -L^5-R^{g2}-R^W or $-L^5$-R^{g2}-R^Y;

provided that:

when L^1 is a bond, then R^5 is selected from the group consisting of: H, -R^g, -R^{g2}-R^W, and -R^{g2}-R^Y; and

X^1 is other than H, -OH, or NH_2;

$\mathbf{L^5}$ is selected from the group consisting of: –O-, -S(O)$_{0-2}$, -NH-, and -N($\mathbf{R^d}$)-;

$\mathbf{R^W}$ is –$\mathbf{L^W}$-$\mathbf{W}$,

wherein $\mathbf{L^W}$ is C(=O), S(O)$_{1-2}$, OC(=O)*, NHC(=O)*, N$\mathbf{R^d}$C(=O)*, NHS(O)$_{1-2}$*, or N$\mathbf{R^d}$S(O)$_{1-2}$*, wherein the asterisk represents point of attachment to **W**, and

W is selected from the group consisting of:

- C_{2-6} alkenyl; C_{2-6} alkynyl; or C_{3-10} allenyl, each of which is optionally substituted with from 1-3 $\mathbf{R^a}$ and further optionally substituted with $\mathbf{R^g}$, wherein **W** is attached to $\mathbf{L^W}$ via an sp^2 or sp hybridized carbon atom, thereby providing an α, β-unsaturated system; and
- bicyclo[**x**.**y**.0]cycloalkyl optionally substituted with from 1-2 $\mathbf{R^c}$, wherein **x** is 1 or 2; and **y** is an integer from 1 to 6;

$\mathbf{R^Y}$ is selected from the group consisting of: -$\mathbf{R^g}$ and -($\mathbf{L^s}$)$_g$-$\mathbf{R^g}$;

each of $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$ is independently selected from the group consisting of: H; halo; -OH; -C(O)OH or –C(O)NH$_2$; -CN; -$\mathbf{R^b}$; -$\mathbf{L^b}$-$\mathbf{R^b}$; -N$\mathbf{R^e}$$\mathbf{R^f}$; -$\mathbf{R^g}$; -($\mathbf{L^s}$)$_g$-$\mathbf{R^g}$; -($\mathbf{L^s}$)$_g$-$\mathbf{R^W}$; -($\mathbf{L^s}$)$_g$-$\mathbf{R^{g2}}$-$\mathbf{R^W}$; and -C$_{1-6}$ alkoxy or -C$_{1-6}$ thioalkoxy, each optionally substituted with from 1-6 $\mathbf{R^a}$; provided that $\mathbf{R^{1c}}$ is other than halo, –CN, or –C(O)OH; or

two of variables $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$, together with the **Ring B** ring atoms to which each is attached, form a fused saturated or unsaturated ring of 3-12 ring atoms;

- wherein from 0-2 of the ring atoms are each an independently selected heteroatom (in addition to –N($\mathbf{R^{1c}}$)- when –N($\mathbf{R^{1c}}$)- forms part of the fused saturated or unsaturated ring), wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and S(O)$_{0-2}$; and
- wherein the fused saturated or unsaturated ring of 3-12 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo, $\mathbf{R^c}$, and $\mathbf{R^W}$; or

one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ combine to form a double bond between the **Ring B** atoms to which each is attached;

Ring A is $\mathbf{R^g}$;

$\mathbf{R^4}$ and $\mathbf{R^7}$ are independently H or $\mathbf{R^d}$;

each occurrence of $\mathbf{R^a}$ is independently selected from the group consisting of: –OH; -halo; $-N\mathbf{R^e}\mathbf{R^f}$; C_{1-4} alkoxy; C_{1-4} haloalkoxy; $-C(=O)O(C_{1-4}$ alkyl); $-C(=O)(C_{1-4}$ alkyl); -C(=O)OH; $-CON\mathbf{R'R''}$; $-S(O)_{1-2}N\mathbf{R'R''}$; $-S(O)_{1-2}(C_{1-4}$ alkyl); and cyano;

each occurrence of $\mathbf{R^b}$ is independently C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each of which is optionally substituted with from 1-6 $\mathbf{R^a}$;

each occurrence of $\mathbf{L^b}$ is independently C(=O); C(=O)O; $S(O)_{1-2}$; C(=O)NH*; $C(=O)N\mathbf{R^d}$*; $S(O)_{1-2}NH$*; or $S(O)_{1-2}N(\mathbf{R^d})$*, wherein the asterisk represents point of attachment to $\mathbf{R^b}$;

each occurrence of $\mathbf{R^c}$ is independently selected from the group consisting of: halo; cyano; C_{1-10} alkyl which is optionally substituted with from 1-6 independently selected $\mathbf{R^a}$; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy or C_{1-4} haloalkoxy; C_{1-4} haloalkoxy; $-S(O)_{1-2}(C_{1-4}$ alkyl); $-S(O)(=NH)(C_{1-4}$ alkyl); $-N\mathbf{R^e}\mathbf{R^f}$; –OH; $-S(O)_{1-2}N\mathbf{R'R''}$; $-C_{1-4}$ thioalkoxy; $-NO_2$; $-C(=O)(C_{1-10}$ alkyl); $-C(=O)O(C_{1-4}$ alkyl); -C(=O)OH; $-C(=O)N\mathbf{R'R''}$; and $-SF_5$;

each occurrence of $\mathbf{R^d}$ is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-3 independently selected $\mathbf{R^a}$; $-C(O)(C_{1-4}$ alkyl); $-C(O)O(C_{1-4}$ alkyl); $-CON\mathbf{R'R''}$; $-S(O)_{1-2}N\mathbf{R'R''}$; $-S(O)_{1-2}(C_{1-4}$ alkyl); -OH; and C_{1-4} alkoxy;

each occurrence of $\mathbf{R^e}$ and $\mathbf{R^f}$ is independently selected from the group consisting of: H; C_{1-6} alkyl optionally substituted with from 1-3 substituents each independently selected from the group consisting of $N\mathbf{R'R''}$, -OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and halo; $-C(O)(C_{1-4}$ alkyl); $-C(O)O(C_{1-4}$ alkyl); $-CON\mathbf{R'R''}$; $-S(O)_{1-2}N\mathbf{R'R''}$; $-S(O)_{1-2}(C_{1-4}$ alkyl); -OH; and C_{1-4} alkoxy;

each occurrence of $\mathbf{R^g}$ is independently selected from the group consisting of:

- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R^c}$; and
- C_{6-10} aryl optionally substituted with from 1-4 $\mathbf{R^c}$;

each occurrence of $\mathbf{L^g}$ is independently selected from the group consisting of: -O-, -NH-, -N$\mathbf{R^d}$-, $-S(O)_{0-2}$-, C(O), and C_{1-3} alkylene optionally substituted with from 1-3 $\mathbf{R^a}$;

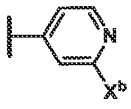
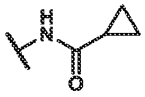
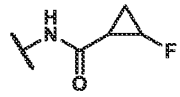
each **g** is independently 1, 2, or 3;

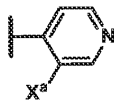
each $\mathbf{R^{g2}}$ is a divalent $\mathbf{R^g}$ group;

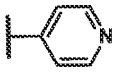
each occurrence of **R'** and **R''** is independently selected from the group consisting of: H; -OH; and C_{1-4} alkyl; and

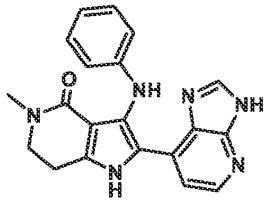
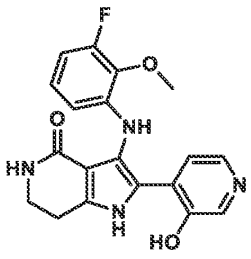
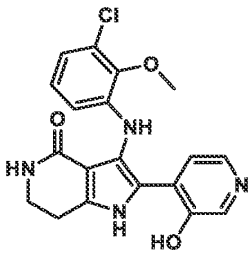
each occurrence of $\mathbf{R^N}$ is independently H, C_{1-3} alkyl, or C_{3-6} cycloalkyl,

provided that one or more of the following applies:

- when R^{2a} and R^{2b} are H or methyl; R^{3a} and R^{3b} are H; **Ring C** is  ; and X^b is H, methyl, NH_2, NHC(=O)Me, NHC(=O)iPr, NHC(=O)NHEt,  ,  , then **Ring A** is other than unsubstituted phenyl;

- when R^{2a}, R^{2b}, R^{3a}, and R^{3b} are each H; **Ring C** is  ; and X^a is methyl or F, then **Ring A** is other than unsubstituted phenyl;

- when R^{1c}, R^{2a}, R^{2b}, R^{3a}, and R^{3b} are each H; **Ring C** is  , then **Ring A** is other than 4-fluorophenyl; and

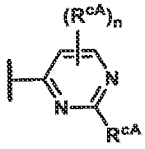
- the compound is other than:  ,  , or  .

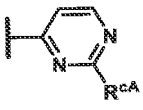
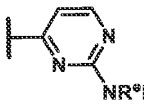
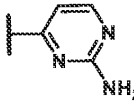
Variable Ring C

In some embodiments, **Ring C** is heteroaryl including 6 ring atoms, wherein from 2-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N(R^d), and wherein the heteroaryl is optionally substituted with X^1 and further optionally substituted with from 1-4 R^{cA}, wherein each R^{cA} is an independently selected R^c.

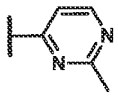
In certain of the foregoing embodiments, **Ring C** is heteroaryl including 6 ring atoms, wherein from 2-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N($\mathbf{R^d}$), and wherein the heteroaryl is optionally substituted with from 1-3 $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$.

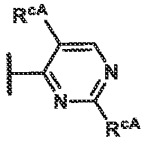
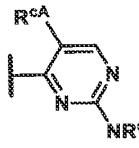
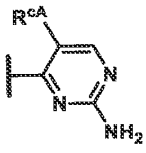
In certain of these embodiments, **Ring C** is pyrimidyl optionally substituted with from 1-3 $\mathbf{R^{cA}}$, such as pyrimidyl substituted with from 1-2 $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$.

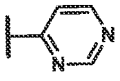
In certain embodiments, **Ring C** is  , wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$; and **n** is 0, 1, or 2.

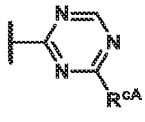
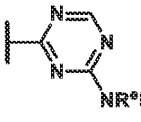
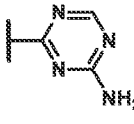
As a non-limiting example of the foregoing embodiments, **Ring C** can be  , such as  (e.g., ).

In certain foregoing embodiments, n is 0 and $\mathbf{R^{cA}}$ is $C_{1\text{-}10}$ alkyl optionally substituted with from 1-6 independently selected $\mathbf{R^a}$, e.g., $C_{1\text{-}3}$ alkyl optionally substituted with from 1-3 independently selected halo.

As a non-limiting example, **Ring C** can be  .

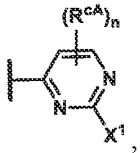
As another non-limiting example, **Ring C** can be  , such as   (e.g.,).

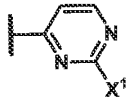
As another non-limiting example, **Ring C** can be  .

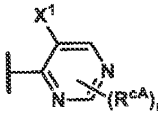
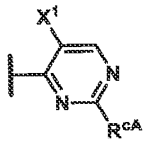
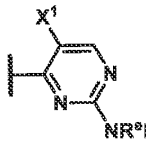
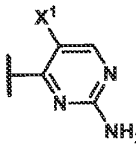
In certain embodiments, **Ring C** is triazinyl optionally substituted with from 1-2 $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$. For example, **Ring C** can be  , such as  (e.g., ).

In certain embodiments, **Ring C** is heteroaryl including 6 ring atoms, wherein from 2-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N($\mathbf{R}^{d}$), and wherein the heteroaryl is substituted with $\mathbf{X}^{1}$ and further optionally substituted with from 1-2 $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

In certain of the foregoing embodiments, **Ring C** is pyrimidyl substituted with $\mathbf{X}^{1}$ and further optionally substituted with from 1-2 $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

In certain of these embodiments, **Ring C** is  , wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$; and **n** is 0, 1, or 2.

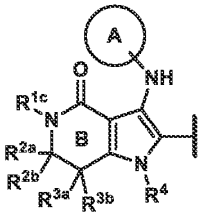
As a non-limiting example of the foregoing embodiments, **Ring C** can be  .

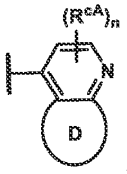
In certain embodiments, **Ring C** is  , wherein **n** is 0, 1, or 2; and each R^{cA} is an independently selected R^c. As a non-limiting example of the foregoing embodiments, **Ring C** can be  (e.g.,  (e.g., )).

In some embodiments, **Ring C** is bicyclic heteroaryl including 7-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with X^1 and further optionally substituted with from 1-4 R^{cA}, wherein each R^{cA} is an independently selected R^c.

In certain of the foregoing embodiments, **Ring C** is bicyclic heteroaryl including 9-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with X^1 and further optionally substituted with from 1-4 R^{cA}, wherein each R^{cA} is an independently selected R^c.

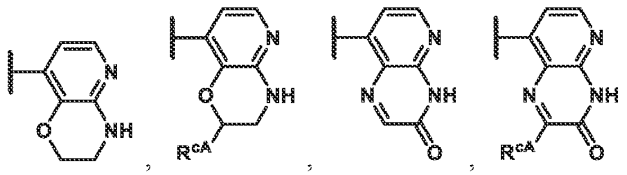
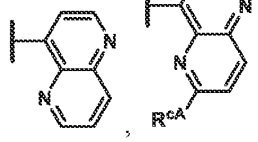
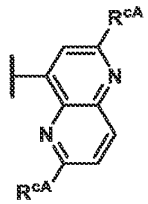
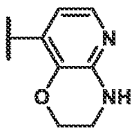
In certain of the foregoing embodiments, **Ring C** is bicyclic heteroaryl including 9-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 R^{cA}, wherein each R^{cA} is an independently selected R^c.

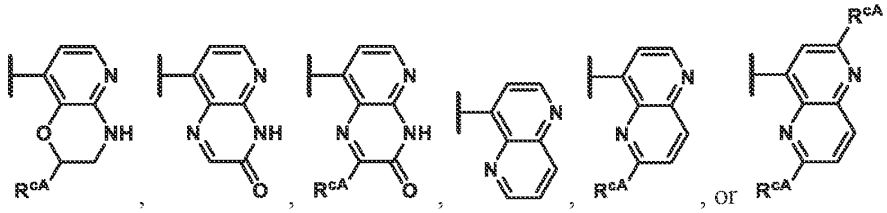
In certain of these embodiments, **Ring C** is connected to  via a 6-membered ring.



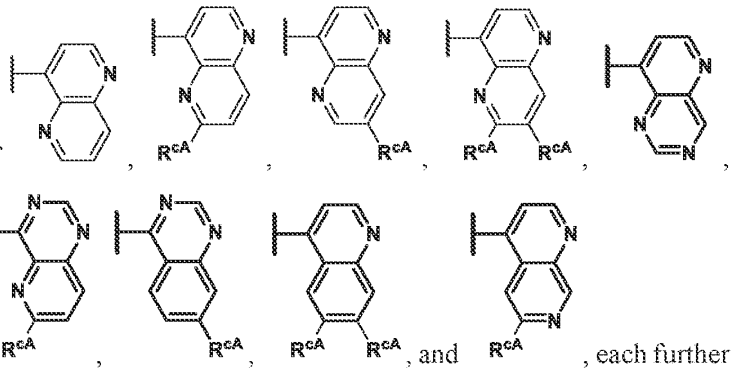
In certain embodiments, **Ring C** is ; **Ring D** is a partially unsaturated or aromatic ring including from 5-6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R}^{cA}$; **n** is 0, 1, or 2; and each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

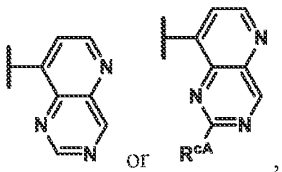
In certain of these embodiments, **Ring D** is a partially unsaturated or aromatic ring including 6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R}^{cA}$.

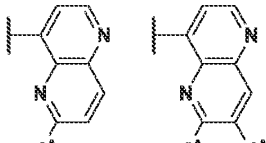
As non-limiting examples of the foregoing embodiments, **Ring C** can be selected from the group consisting of:  ,  , and  , each further optionally substituted with $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$. For example, **Ring C** can be 

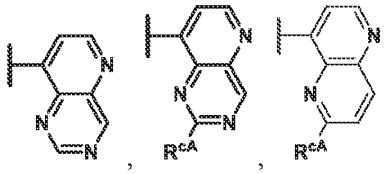
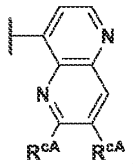


.

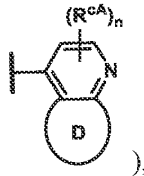
As non-limiting examples of the foregoing embodiments, **Ring C** is selected from the group consisting of  , each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^{c}.

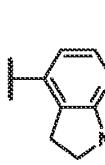
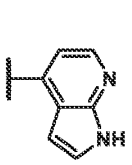
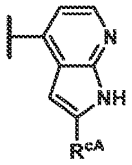
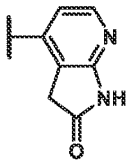
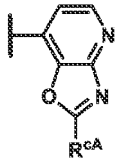
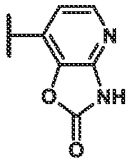
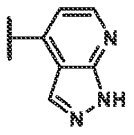
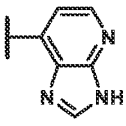
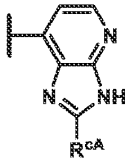
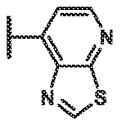
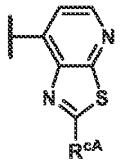
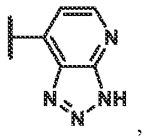
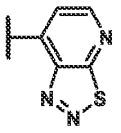
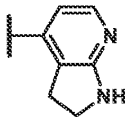
In certain of these embodiments, **Ring C** is  , wherein R^{cA} is an independently selected R^{c}.

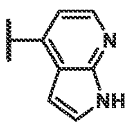
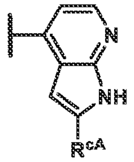
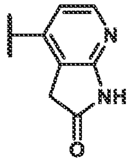
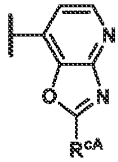
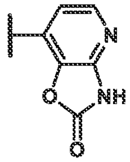
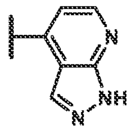
In certain of these embodiments, **Ring C** is  , wherein each R^{cA} is an independently selected R^{c}.

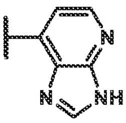
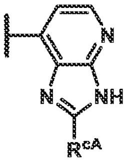
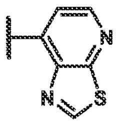
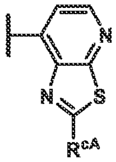
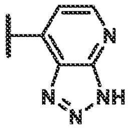
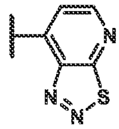
In certain of these embodiments, **Ring C** is  , and  , wherein each occurrence of R^{cA} is independently selected from the group consisting of: halo, $NR^{e}R^{f}$, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-3} alkyl, C_{1-3} alkyl substituted with from 1-3 independently selected halo, C_{1-3} alkyl substituted with C_{1-4} alkoxy, and C_{1-}

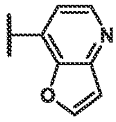
4 alkoxy substituted with C_{1-4} alkoxy, and wherein each occurrence of $\mathbf{R}^{cA}$ is independently selected from the group consisting of: C_{1-4} alkoxy; C_{1-4} haloalkoxy; C_{1-3} alkyl; and C_{1-3} alkyl substituted with from 1-3 independently selected halo.

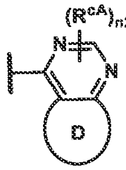
In certain embodiments (when **Ring C** is ), **Ring D** is a partially unsaturated or aromatic ring including 5 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and $S(O)_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R}^{cA}$.

As non-limiting examples of the foregoing embodiments, **Ring C** can be selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , each further optionally substituted with $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$. For example, **Ring C** can be 

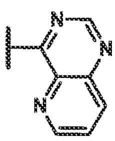
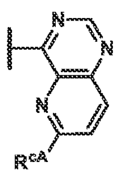
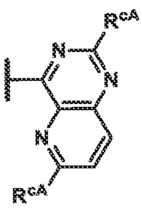
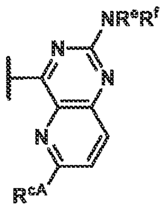
,  ,  (e.g., ),  (e.g., ),  ,

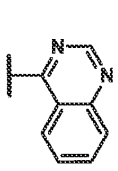
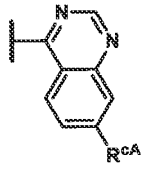
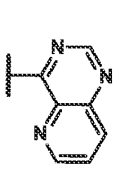
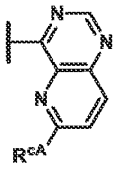
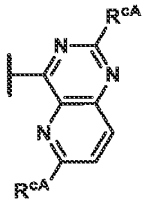
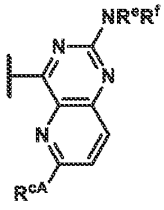
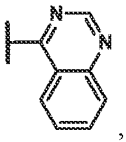
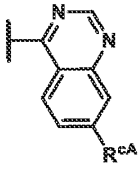
 ,  ,  ,  ,  , or  .

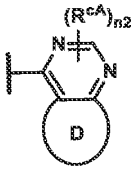
As another non-limiting example, **Ring C** can be  .

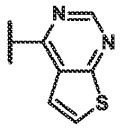
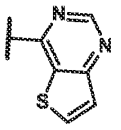
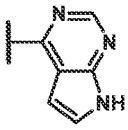
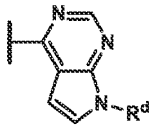
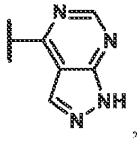
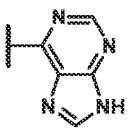
In certain embodiments, **Ring C** is  ; **Ring D** is a partially unsaturated or aromatic ring including from 5-6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$; **n2** is 0 or 1; and each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$.

In certain of these embodiments, **Ring D** is a partially unsaturated or aromatic ring including 6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

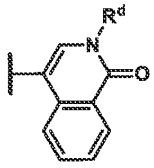
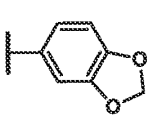
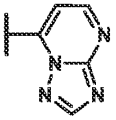
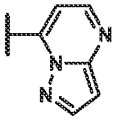
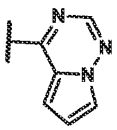
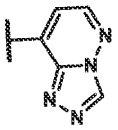
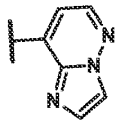
As non-limiting examples of the foregoing embodiments, **Ring C** can be selected from the group consisting of:  ,  ,  (e.g., ),

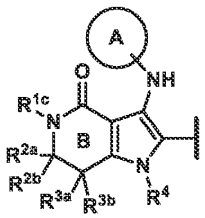
 , and  , each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^{c}. For example, **Ring C** can be  ,  ,  (e.g., ),  , or  .

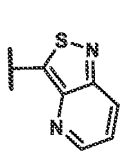
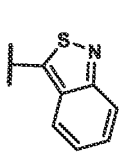
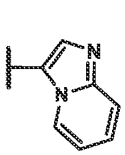
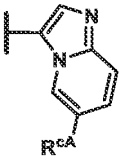
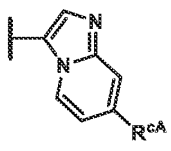
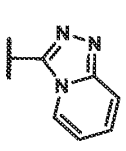
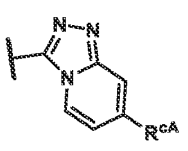
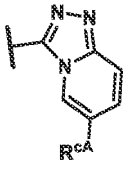
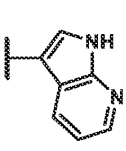
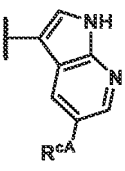
In certain embodiments (when **Ring C** is ), **Ring D** is a partially unsaturated or aromatic ring including 5 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N(R^{d}), O, and $S(O)_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 R^{cA}.

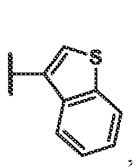
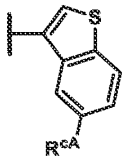
As non-limiting examples of the foregoing embodiments, **Ring C** can be selected from the group consisting of:  ,  ,  ,  ,  , and  , each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^{c}.

In certain embodiments, **Ring C** is selected from the group consisting of:

 ,  ,  ,  ,  ,  , and  , each further optionally substituted with $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

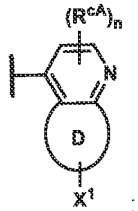
In certain embodiments (when **Ring C** is bicyclic heteroaryl including 9-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$), **Ring C** is connected to  via a 5-membered ring.

As non-limiting examples of the foregoing embodiments, **Ring C** can be selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,

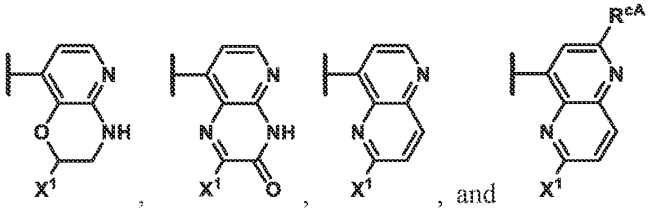



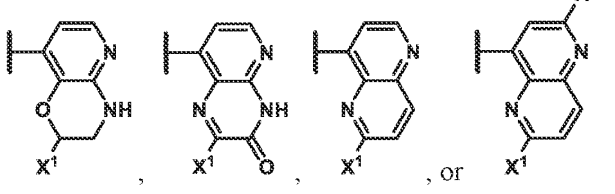
, and , each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^{c}.

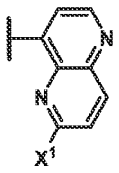
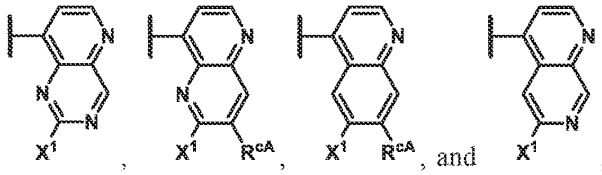
In certain embodiments, **Ring C** is bicyclic heteroaryl including 9-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^{d}), O, and S(O)$_{0-2}$, and wherein the heteroaryl is substituted with X^{1} and further optionally substituted with from 1-4 R^{cA}, wherein each R^{cA} is an independently selected R^{c}.

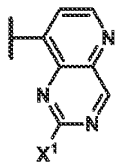
In certain of these embodiments, **Ring C** is  ; **Ring D** is a partially unsaturated or aromatic ring including from 5-6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N(R^{d}), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 R^{cA}; **n** is 0, 1, or 2; and each R^{cA} is an independently selected R^{c}.

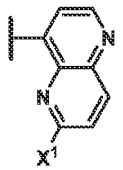
In certain of the foregoing embodiments, **Ring D** is a partially unsaturated or aromatic ring including 6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N(R^{d}), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 R^{cA}.

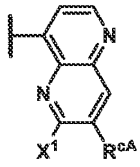
As non-limiting examples of the foregoing embodiments, **Ring C** can be selected from the group consisting of:  , and , .

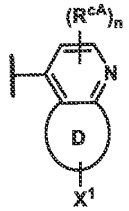
each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^c. For example, **Ring C** can be  .

As non-limiting examples of the foregoing embodiments, **Ring C** is  ,  , each of which is further optionally substituted with from 1-2 R^{cA}, wherein each R^{cA} is an independently selected R^c.

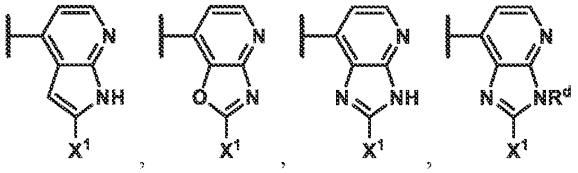
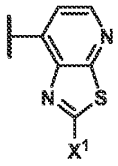
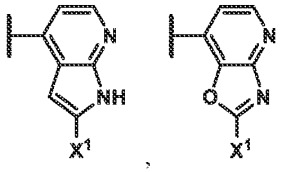
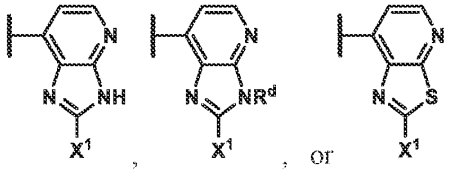
In certain of these embodiments, **Ring C** is  .

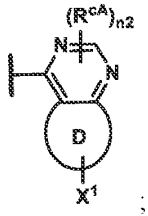
In certain of these embodiments, **Ring C** is  .

In certain of these embodiments, **Ring C** is  , wherein R^{cA} is an independently selected R^c.



In certain embodiments (when **Ring C** is), **Ring D** is a partially unsaturated or aromatic ring including 5 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and $S(O)_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R}^{cA}$.

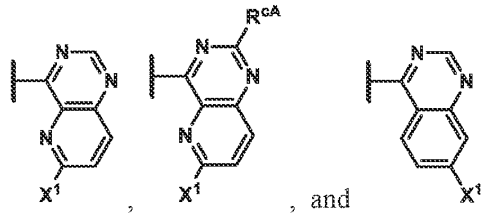
As non-limiting examples of the foregoing embodiments, **Ring C** can be selected from the group consisting of:  and  , each further optionally substituted with $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$. For example, **Ring C** can be  ,  , or .

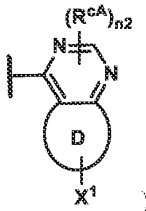


In certain embodiments, **Ring C** is ; **Ring D** is a partially unsaturated or aromatic ring including from 5-6 ring atoms, wherein from 0-2 of the ring atoms are

heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R}^{cA}$; **n2** is 0 or 1; and each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

In certain of these embodiments, **Ring D** is a partially unsaturated or aromatic ring including 6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R}^{cA}$.

As non-limiting examples of the foregoing embodiments, **Ring C** can be selected from the group consisting of:  , each further optionally substituted with $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

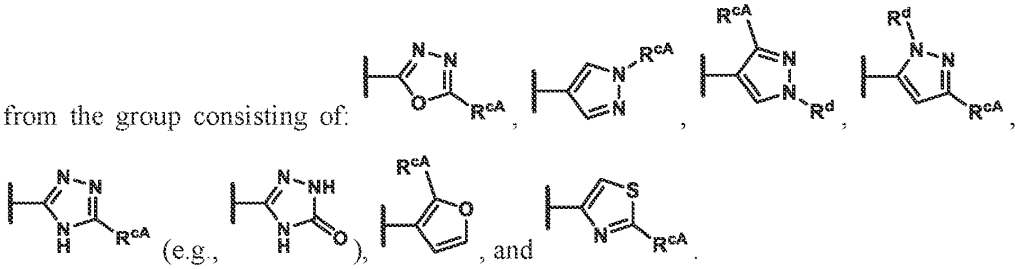
In certain embodiments (when **Ring C** is ), **Ring D** is a partially unsaturated or aromatic ring including 5 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R}^{cA}$.

In some embodiments, **Ring C** is heteroaryl including 5 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with $\mathbf{X}^{1}$ and further optionally substituted with from 1-4 $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

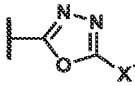
In certain of these embodiments, **Ring C** is heteroaryl including 5 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group

consisting of N, N(H), N($\mathbf{R}^d$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^c$.

In certain of the foregoing embodiments, **Ring C** is selected from the group consisting of: pyrazolyl, imidazolyl, thiazolyl, oxazolyl, triazolyl, furanyl, thiophenyl, oxadiazolyl, and thiadiazolyl, each optionally substituted with from 1-2 $\mathbf{R}^{cA}$, wherein a ring nitrogen atom is optionally substituted with $\mathbf{R}^d$, and each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^c$.

As non-limiting examples of the foregoing embodiments, **Ring C** can be selected from the group consisting of: 

In certain embodiments, **Ring C** is heteroaryl including 5 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^d$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is substituted with $\mathbf{X}^1$ and further optionally substituted with from 1-2 $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^c$.

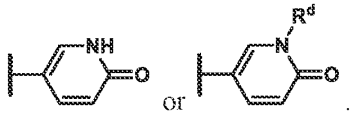
In certain embodiments, **Ring C** is selected from the group consisting of: pyrazolyl, imidazolyl, thiazolyl, oxazolyl, triazolyl, furanyl, thiophenyl, oxadiazolyl, and thiadiazolyl, each substituted with $\mathbf{X}^1$ and further optionally substituted with from 1-2 $\mathbf{R}^{cA}$, wherein a ring nitrogen atom is optionally substituted with $\mathbf{R}^d$, and each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^c$. For example, **Ring C** can be  .

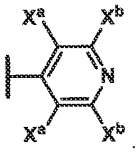
In some embodiments, **Ring C** is 2-pyridonyl or 4-pyridonyl, each optionally substituted with $\mathbf{X}^1$ and further optionally substituted with from 1-4 $\mathbf{R}^{cA}$, wherein the ring

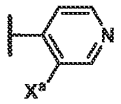
nitrogen atom is optionally substituted with $\mathbf{R}^{d}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

In certain of these embodiments, **Ring C** is 2-pyridonyl which is optionally substituted with $\mathbf{X}^{1}$ and further optionally substituted with from 1-4 $\mathbf{R}^{cA}$, wherein the ring nitrogen atom is optionally substituted with $\mathbf{R}^{d}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

In certain of the foregoing embodiments, **Ring C** is 2-pyridonyl which is optionally substituted with from 1-4 $\mathbf{R}^{cA}$, wherein the ring nitrogen atom is optionally substituted with $\mathbf{R}^{d}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$. For example, **Ring C** can be



In some embodiments, **Ring C** is  .

In certain of the foregoing embodiments, **Ring C** is  .

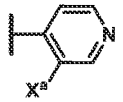
In certain of these embodiments, each $\mathbf{X}^{a}$ is selected from the group consisting of: H; halo; and C_{1-6} alkyl optionally substituted with from 1-6 $\mathbf{R}^{a}$.

In certain of these embodiments, from 1-2, such as 1, occurrence of $\mathbf{X}^{a}$ is an independently substituent other than H.

In certain of these embodiments, one occurrence of $\mathbf{X}^{a}$ is halo, such as –F or –Cl. For example, one occurrence of $\mathbf{X}^{a}$ is –F.

In certain of these embodiments, one occurrence of $\mathbf{X}^{a}$ is C_{1-3} alkyl optionally substituted with from 1-6 $\mathbf{R}^{a}$. For example, one occurrence of $\mathbf{X}^{a}$ is C_{1-3} alkyl substituted with from 1-3 independently selected halo, such as $-CF_3$ or $-CHF_2$.

In certain of these embodiments, each $\mathbf{X}^{a}$ is –H.

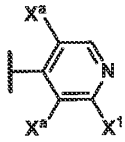
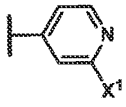
In certain of the foregoing embodiments, wherein **Ring C** is  , wherein X^a is selected from the group consisting of: -F, -Cl, -H, and C_{1-6} alkyl optionally substituted with from 1-6 R^a.

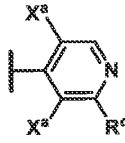
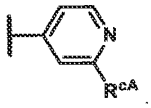
In certain of the forgoing embodiments, X^a is –F.

In certain of the forgoing embodiments, X^a is –Cl.

In certain of the forgoing embodiments, X^a is –H.

In certain of the forgoing embodiments, X^a is C_{1-3} alkyl substituted with from 1-3 independently selected halo, such as $-CF_3$ or $-CHF_2$.

In certain of the foregoing embodiments, **Ring C** is  . For example, **Ring C** can be  .

In certain embodiments, **Ring C** is  , wherein R^{cA} is an independently selected R^c. For example, **Ring C** can be  .

In certain of the foregoing embodiments, each X^a is selected from the group consisting of: H; halo; and C_{1-6} alkyl optionally substituted with from 1-6 R^a.

In certain of the foregoing embodiments, 1-2, such as 1, occurrence of X^a is an independently substituent other than H.

In certain of the foregoing embodiments, one occurrence of X^a is halo, such as –F or –Cl.

In certain of the foregoing embodiments, one occurrence of X^a is –F

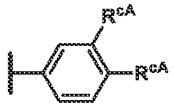
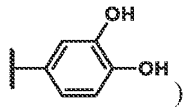
In certain of the foregoing embodiments, one occurrence of X^a is C_{1-3} alkyl optionally substituted with from 1-6 R^a.

In certain of the foregoing embodiments, one occurrence of $\mathbf{X^a}$ is C_{1-3} alkyl substituted with from 1-3 independently selected halo, such as but not limited to

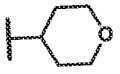
$-CF_3$ or $-CHF_2$.

In certain of the foregoing embodiments, each $\mathbf{X^a}$ is –H.

In some embodiments, **Ring C** is C_{6-10} aryl optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$.

In certain of the foregoing embodiments, **Ring C** is phenyl optionally substituted with from 1-4 $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$. For example, **Ring C** can be  (e.g., ).

In some embodiments, **Ring C** is heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$.

In certain of these embodiments, **Ring C** is heterocyclyl including from 4-8, such as 5-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$. For example, **Ring C** can be  .

Variables m, X^2, L^1, and R^5

In certain embodiments, **m** is 1. In some embodiments, **m** is 0.

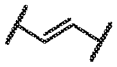
In certain embodiments, $\mathbf{X^2}$ is selected from the group consisting of: -O-, -N($\mathbf{R^N}$)-, and –S(O)$_{0-2}$. In certain of these embodiments, $\mathbf{X^2}$ is –N($\mathbf{R^N}$)-. For example, $\mathbf{X^2}$ can be –N(H)-. As another non-limiting example, $\mathbf{X^2}$ can be –O-.

In certain embodiments, $\mathbf{X^2}$ is selected from the group consisting of: -OC(=O)-*, -N($\mathbf{R^N}$)C(=O)-*, and –N($\mathbf{R^N}$)S(O)$_{1-2}$-*. In certain of these embodiments, $\mathbf{X^2}$ is -N($\mathbf{R^N}$)C(=O)-*. For example, $\mathbf{X^2}$ can be –N(H)C(=O)-*. In certain embodiments, $\mathbf{X^2}$ is –N($\mathbf{R^N}$)S(O)$_2$-*. For example, $\mathbf{X^2}$ can be –NHS(O)$_2$-.

In certain embodiments, $\mathbf{X^2}$ is selected from the group consisting of: -OC(=O)N($\mathbf{R^N}$)-*, -N($\mathbf{R^N}$)C(=O)O-*, -N($\mathbf{R^N}$)C(=O)N($\mathbf{R^N}$)-*, and –N($\mathbf{R^N}$)S(O)$_{1-2}$N($\mathbf{R^N}$)-*. In certain of these embodiments, $\mathbf{X^2}$ is -N($\mathbf{R^N}$)C(=O)O-*. For example, $\mathbf{X^2}$ can be –N(H)C(=O)O-*. $\mathbf{X^2}$ is -N($\mathbf{R^N}$)C(=O)N($\mathbf{R^N}$)-*, such as –N(H)C(=O)N(H)-*.

In certain embodiments, X^2 is -C(=O)O-*, -C(=O)N($\mathbf{R^N}$)-*, or –S(O)$_{1-2}$N($\mathbf{R^N}$)-*. In certain of these embodiments, $\mathbf{X^2}$ is –C(=O)N($\mathbf{R^N}$)-*. For example, $\mathbf{X^2}$ can be –C(=O)N(H)-*.

In certain embodiments, $\mathbf{X^2}$ is  .

In certain embodiments, $\mathbf{X^2}$ is C_{2-6} alkenylene optionally substituted with from 1-3 $\mathbf{R^a}$. For example, $\mathbf{X^2}$ can be  .

In certain embodiments, $\mathbf{L^1}$ is a bond.

In certain embodiments, $\mathbf{L^1}$ is C_{1-10} alkylene optionally substituted with from 1-6 $\mathbf{R^a}$.

In certain of these embodiments, $\mathbf{L^1}$ is C_{1-3} alkylene optionally substituted with from 1-6 $\mathbf{R^a}$. In certain of the foregoing embodiments, $\mathbf{L^1}$ is unsubstituted C_{1-3} alkylene. As non-limiting examples of the foregoing embodiments, $\mathbf{L^1}$ can be –CH_2-, -CH_2CH_2-, -CH_2CF_2-, or –CH(Me)-. For example, $\mathbf{L^1}$ can be –CH_2-, -CH_2CH_2-, or –CH(Me)-.

In certain embodiments, $\mathbf{L^1}$ is branched C_{3-6} alkylene optionally substituted with from 1-6 $\mathbf{R^a}$. For example, $\mathbf{L^1}$ can be  or  , wherein ***aa*** is the point of attachment to $\mathbf{R^5}$.

In certain embodiments, $\mathbf{R^5}$ is -C_{1-6} alkoxy or -$S(O)_{0-2}(C_{1-6}$ alkyl), each optionally substituted with from 1-6 $\mathbf{R^a}$. In certain of these embodiments, $\mathbf{R^5}$ is –C_{1-6} alkoxy optionally substituted with from 1-6 $\mathbf{R^a}$. As a non-limiting example of the foregoing embodiments, $\mathbf{R^5}$ can be –C_{1-3} alkoxy. For example, $\mathbf{R^5}$ can be methoxy.

In certain embodiments, $\mathbf{R^5}$ is H or halo. As non-limiting examples of the foregoing embodiments, $\mathbf{R^5}$ can be H or -F. For example, $\mathbf{R^5}$ can be H.

In certain embodiments, $\mathbf{R^5}$ is –OH or -$\mathbf{NR^eR^f}$. For example, $\mathbf{R^5}$ can be –OH.

In certain embodiments, $\mathbf{R^5}$ is -$\mathbf{R^g}$.

In certain of these embodiments, $\mathbf{R^5}$ is selected from the group consisting of:

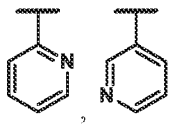
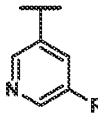
- heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R^e}$; and
- C_{6-10} aryl optionally substituted with from 1-4 $\mathbf{R^e}$.

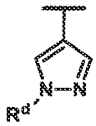
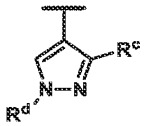
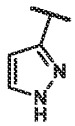
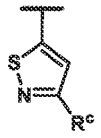
In certain of the foregoing embodiments, $\mathbf{R^5}$ is C_{6-10} aryl optionally substituted with from 1-4 $\mathbf{R^e}$. In certain of these embodiments, $\mathbf{R^5}$ is phenyl optionally substituted with from 1-4 $\mathbf{R^e}$. As non-limiting examples of the foregoing embodiments, $\mathbf{R^5}$ can be phenyl optionally substituted with from 1-2 independently selected halo, such as –F.

In certain embodiments, $\mathbf{R^5}$ is heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R^e}$.

In certain of the foregoing embodiments, $\mathbf{R^5}$ is heteroaryl including from 5-6 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the

group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 R^c.

In certain of these embodiments, R^5 is heteroaryl including 6 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N(R^d), and wherein the heteroaryl is optionally substituted with from 1-4 R^c. For example, R^5 can be  , , or  .

In certain embodiments, R^5 is heteroaryl including 5 ring atoms, wherein from 1-4, such as 2-4, ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 R^c. For example, R^5 can be  ,  ,  , or  .

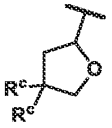
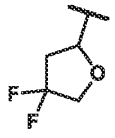
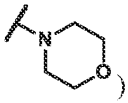
In certain embodiments, R^5 is selected from the group consisting of:

- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c; and
- heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c.

In certain of these embodiments, $\mathbf{R}^5$ is C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R}^c$.

In certain of the foregoing embodiments, $\mathbf{R}^5$ is C_{3-10} cycloalkyl (e.g., C_{3-6} cycloalkyl) optionally substituted with from 1-4 $\mathbf{R}^c$, such as wherein $\mathbf{R}^5$ is cyclopropyl.

In certain embodiments, $\mathbf{R}^5$ is heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^d$), O, and S(O)$_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R}^c$.

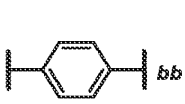
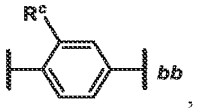
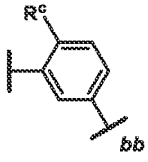
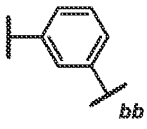
In certain of these embodiments, $\mathbf{R}^5$ is heterocyclyl including from 4-8, such as 4-6, ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^d$), O, and S(O)$_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R}^c$. For example, $\mathbf{R}^5$ can be  ,  ,  (e.g.,  , or ).

In certain embodiments, $\mathbf{R}^5$ is selected from the group consisting of: -$\mathbf{R}^{g2}$-$\mathbf{R}^W$ and –$\mathbf{R}^{g2}$-$\mathbf{R}^Y$. In certain of these embodiments, $\mathbf{R}^5$ is –$\mathbf{R}^{g2}$-$\mathbf{R}^Y$.

In certain embodiments, the –$\mathbf{R}^{g2}$ group present in $\mathbf{R}^5$ is C_{6-10} arylene optionally substituted with from 1-4 $\mathbf{R}^c$.

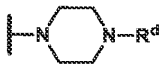
In certain of these embodiments, the –$\mathbf{R}^{g2}$ group present in $\mathbf{R}^5$ is phenylene optionally substituted with from 1-4 $\mathbf{R}^c$.

In certain of the foregoing embodiments, the –$\mathbf{R}^{g2}$ group present in $\mathbf{R}^5$ is 1,3-phenylene or 1,4-phenylene, each optionally substituted with from 1-4 $\mathbf{R}^c$. As non-limiting

examples of the foregoing embodiments, $-R^{g2}$ can be  ,  ,  , or  , wherein *bb* is the point of attachment to R^Y.

In certain embodiments, the R^Y group present in R^5 is $-R^g$.

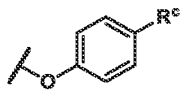
In certain of these embodiments, the R^Y group present in R^5 is heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^e.

In certain of the foregoing embodiments, the R^Y group present in R^5 is heterocyclyl including from 4-8, such as 4-6, ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^e, such as wherein R^Y is  .

In certain embodiments, R^5 is $-L^5$-R^g.

In certain of these embodiments, R^5 is $-O$-R^g.

In certain embodiments, R^5 is –O-(C$_{6-10}$ aryl) wherein the C$_{6-10}$ aryl is optionally substituted with from 1-4 R^e.

As a non-limiting example of the foregoing embodiments, R^5 can be –O-phenyl wherein the phenyl is optionally substituted with from 1-2 R^e. For example, R^5 can be  .

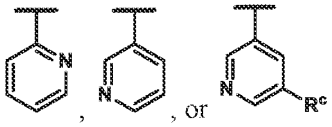
Non-Limiting Combinations of m, X^2, L^1, and R^5

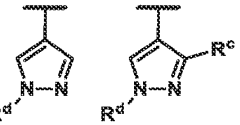
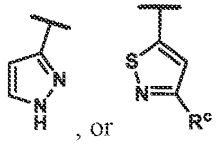
[AA]:

In certain embodiments, $\mathbf{X^1}$ is $-(\mathbf{X^2})_m\text{-}\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein:

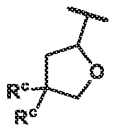
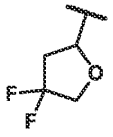
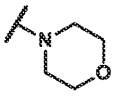
- **m** is 0 or 1;
- $\mathbf{X^2}$ is $-N(\mathbf{R^N})-$ or -O-;
- $\mathbf{L^1}$ is a bond or C_{1-6} alkylene optionally substituted with from 1-3 $\mathbf{R^a}$; and
- $\mathbf{R^5}$ is $-\mathbf{R^g}$.

In certain embodiments of **[AA]**, $\mathbf{R^5}$ is phenyl optionally substituted with from 1-4 $\mathbf{R^c}$, such as wherein $\mathbf{R^5}$ is phenyl optionally substituted with from 1-2 independently selected halo, such as –F.

In certain embodiments of **[AA]**, $\mathbf{R^5}$ is heteroaryl including 6 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and $N(\mathbf{R^d})$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R^c}$, such as wherein $\mathbf{R^5}$ is  .

In certain embodiments of **[AA]**, $\mathbf{R^5}$ is heteroaryl including 5 ring atoms, wherein from 1-4, such as 2-4, ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), $N(\mathbf{R^d})$, O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R^c}$, such as wherein $\mathbf{R^5}$ is  ,  , or .

In certain embodiments of **[AA]**, $\mathbf{R^5}$ is C_{3-10} cycloalkyl, such as C_{3-6} cycloalkyl, optionally substituted with from 1-4 $\mathbf{R^c}$, such as wherein $\mathbf{R^5}$ is cyclopropyl.

In certain embodiments of **[AA]**, $\mathbf{R^5}$ is heterocyclyl including from 4-8, such as 4-6, ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$. For example, $\mathbf{R^5}$ can be  ,  ,  such as  , or  .

In certain embodiments of **[AA]**, **m** is 0.

In certain embodiments of **[AA]**, **m** is 1.

In certain embodiments of **[AA]**, $\mathbf{X^2}$ is –N($\mathbf{R^N}$)- (e.g., N(H)).

In certain embodiments of **[AA]**, $\mathbf{X^2}$ is –O-.

In certain embodiments of **[AA]**, $\mathbf{L^1}$ is a bond.

In certain embodiments of **[AA]**, $\mathbf{L^1}$ is C$_{1-3}$ alkylene (e.g., –CH$_2$-, -CH$_2$CH$_2$-, or –CH(Me)-).

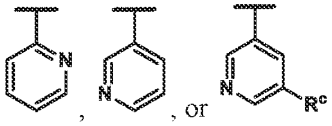
In certain embodiments of **[AA]**, $\mathbf{L^1}$ is branched C$_{3-6}$ alkylene. For example, $\mathbf{L^1}$ can be  or  , wherein ***aa*** is the point of attachment to $\mathbf{R^5}$.

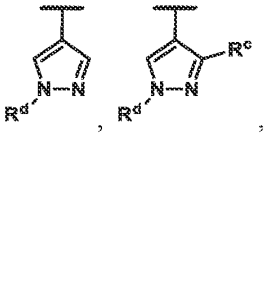
[BB]:

In certain embodiments, $\mathbf{X^1}$ is –$\mathbf{X^2}$-$\mathbf{L^1}$-$\mathbf{R^5}$, wherein:

- $\mathbf{X^2}$ is -N($\mathbf{R^N}$)C(=O)-*, -N($\mathbf{R^N}$)S(O)$_2$-*, -N($\mathbf{R^N}$)C(=O)O-*, or N($\mathbf{R^N}$)C(=O)N($\mathbf{R^N}$)*;
- $\mathbf{L^1}$ is a bond or C$_{1-6}$ alkylene optionally substituted with from 1-3 $\mathbf{R^a}$; and
- $\mathbf{R^5}$ is –$\mathbf{R^a}$.

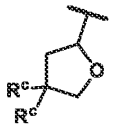
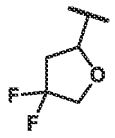
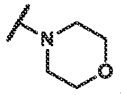
In certain embodiments of **[BB]**, R^5 is phenyl optionally substituted with from 1-4 R^c, such as wherein R^5 is phenyl optionally substituted with from 1-2 independently selected halo, such as –F.

In certain embodiments of **[BB]**, R^5 is heteroaryl including 6 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N(R^d), and wherein the heteroaryl is optionally substituted with from 1-4 R^c, such as wherein R^5 is  .

In certain embodiments of **[BB]**, R^5 is heteroaryl including 5 ring atoms, wherein from 1-4, such as 2-4, ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 R^c, such as wherein R^5 is  .

In certain embodiments of **[BB]**, R^5 is C_{3-10} cycloalkyl, such as C_{3-6} cycloalkyl, optionally substituted with from 1-4 R^c, such as wherein R^5 is cyclopropyl.

In certain embodiments of **[BB]**, R^5 is heterocyclyl including from 4-8, such as 4-6, ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group

consisting of oxo and R^c. For example, R^5 can be  ,  ,  such as  , or  .

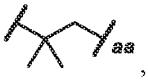
In certain embodiments of **[BB]**, X^2 is -N(R^N)C(=O)-* (e.g., –N(H)C(=O)-*).

In certain embodiments of **[BB]**, X^2 is -N(R^N)S(O)$_2$-, such as –N(H)S(O)$_2$-*.

In certain embodiments of **[BB]**, X^2 is -N(R^N)C(=O)O-*, or -N(R^N)C(=O)N(R^N)-* (e.g., –N(H)C(=O)O-*; e.g., –N(H)C(=O)N(H)-*).

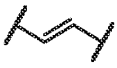
In certain embodiments of **[BB]**, L^1 is a bond.

In certain embodiments of **[BB]**, L^1 is C_{1-3} alkylene (e.g., –CH_2-, -CH_2CH_2-, or –CH(Me)-).

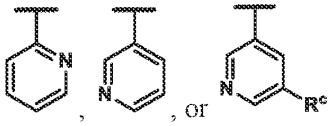
In certain embodiments of **[BB]**, L^1 is branched C_{3-6} alkylene. For example, L^1 can be  or  , wherein ***aa*** is the point of attachment to R^5.

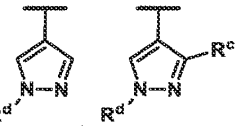
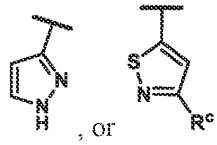
[CC]:

In certain embodiments, X^1 is –X^2-L^1-R^5, wherein:

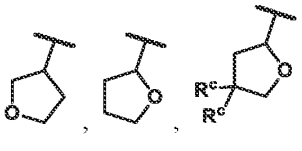
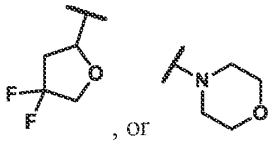
- X^2 is  or  ;
- L^1 is a bond or C_{1-6} alkylene optionally substituted with from 1-3 R^a; and
- R^5 is –R^g.

In certain embodiments of **[CC]**, R^5 is phenyl optionally substituted with from 1-4 R^c, such as wherein R^5 is phenyl optionally substituted with from 1-2 independently selected halo, such as –F.

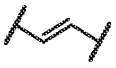
In certain embodiments of **[CC]**, R^5 is heteroaryl including 6 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N(R^d), and wherein the heteroaryl is optionally substituted with from 1-4 R^c, such as wherein R^5 is  .

In certain embodiments of **[CC]**, R^5 is heteroaryl including 5 ring atoms, wherein from 1-4, such as 2-4, ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 R^c, such as wherein R^5 is  ,  , or .

In certain embodiments of **[CC]**, R^5 is C_{3-10} cycloalkyl, such as C_{3-6} cycloalkyl, optionally substituted with from 1-4 R^c, such as wherein R^5 is cyclopropyl.

In certain embodiments of **[CC]**, R^5 is heterocyclyl including from 4-8, such as 4-6, ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c. For example, R^5 can be  , such as  , or .

In some embodiments of **[CC]**, X^2 is  .

In some embodiments of **[CC]**, $\mathbf{X^2}$ is  .

In certain embodiments of **[CC]**, $\mathbf{L^1}$ is a bond.

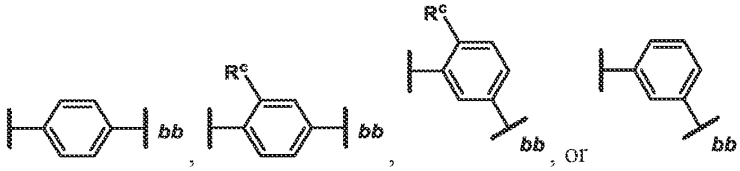
In certain embodiments of **[CC]**, $\mathbf{L^1}$ is C_{1-3} alkylene (e.g., $-CH_2-$, $-CH_2CH_2-$, or $-CH(Me)-$).

In certain embodiments of **[CC]**, $\mathbf{L^1}$ is branched C_{3-6} alkylene. For example, $\mathbf{L^1}$ can be  or  , wherein ***aa*** is the point of attachment to $\mathbf{R^5}$.

[DD]:

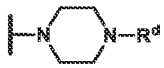
In certain embodiments, $\mathbf{X^1}$ is $-(\mathbf{X^2})_m\text{-}\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein:

- **m** is 0 or 1;
- $\mathbf{X^2}$ is $-N(\mathbf{R^N})-$ or $-O-$;
- $\mathbf{L^1}$ is a bond or C_{1-6} alkylene optionally substituted with from 1-3 $\mathbf{R^a}$; and
- $\mathbf{R^5}$ is $-\mathbf{R^{g2}}\text{-}\mathbf{R^Y}$.

In certain embodiments of **[DD]**, the $-\mathbf{R^{g2}}$ group present in $\mathbf{R^5}$ is 1,3-phenylene or 1,4-phenylene, each optionally substituted with from 1-4 $\mathbf{R^c}$, such as wherein $-\mathbf{R^{g2}}$ is  , wherein ***bb*** is the point of attachment to $\mathbf{R^Y}$.

In certain embodiments of **[DD]**, the $\mathbf{R^Y}$ group present in $\mathbf{R^5}$ is $-\mathbf{R^g}$.

In certain embodiments of **[DD]**, the $\mathbf{R^Y}$ group present in $\mathbf{R^5}$ is heterocyclyl including from 4-8, such as 4-6, ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), $N(\mathbf{R^d})$, O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents

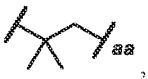
independently selected from the group consisting of oxo and R^c. For example, R^Y can be  .

In certain embodiments of **[DD]**, X^2 is $-N(R^N)-$ (e.g., N(H)).

In certain embodiments of **[DD]**, X^2 is –O-.

In certain embodiments of **[DD]**, L^1 is a bond.

In certain embodiments of **[DD]**, L^1 is C_{1-3} alkylene (e.g., $-CH_2-$, $-CH_2CH_2-$, or –CH(Me)-).

In certain embodiments of **[DD]**, L^1 is branched C_{3-6} alkylene. For example, L^1 can be  or  , wherein *aa* is the point of attachment to R^5.

[EE]:

In certain embodiments, X^1 is $-X^2\text{-}L^1\text{-}R^5$, wherein:

- X^2 is $-N(R^N)-$, –O-, $-N(R^N)C(=O)-*$, $-N(R^N)S(O)_2-$, $-N(R^N)C(=O)O-*$, or $-N(R^N)C(=O)N(R^N)-*$;
- L^1 is C_{1-6} alkylene optionally substituted with from 1-3 R^a; and
- R^5 is H, halo, C_{1-6} alkoxy optionally substituted with from 1-3 R^a, or –OH.

In certain embodiments of **[EE]**, R^5 is H.

In certain embodiments of **[EE]**, R^5 is halo (e.g., –F).

In certain embodiments of **[EE]**, R^5 is C_{1-6} alkoxy optionally substituted with from 1-3 R^a, such as wherein R^5 is C_{1-3} alkoxy such as methoxy.

In certain embodiments of **[EE]**, R^5 is –OH.

In certain embodiments of **[EE]**, X^2 is $-N(R^N)-$ (e.g., N(H)).

In certain embodiments of **[EE]**, X^2 is –O-.

In certain embodiments of **[EE]**, X^2 is $-N(R^N)C(=O)-*$ (e.g., $-N(H)C(=O)-*$).

In certain embodiments of **[EE]**, X^2 is $-N(R^N)S(O)_2-$, such as $-N(H)S(O)_2-*$.

In certain embodiments of **[EE]**, $\mathbf{X^2}$ is -N($\mathbf{R^N}$)C(=O)O-*, or -N($\mathbf{R^N}$)C(=O)N($\mathbf{R^N}$)-* (e.g., –N(H)C(=O)O-*; e.g., –N(H)C(=O)N(H)-*).

In certain embodiments of **[EE]**, $\mathbf{L^1}$ is C_{1-3} alkylene (e.g., –CH_2-, -CH_2CH_2-, or –CH(Me)-).

In certain embodiments of **[EE]**, $\mathbf{L^1}$ is branched C_{3-6} alkylene. For example, $\mathbf{L^1}$ can be  or  , wherein ***aa*** is the point of attachment to $\mathbf{R^5}$.

[FF]:

In certain embodiments, $\mathbf{X^1}$ is –$\mathbf{L^1}$-$\mathbf{R^5}$, wherein $\mathbf{L^1}$ is C_{1-6} alkylene optionally substituted with from 1-3 $\mathbf{R^a}$; and $\mathbf{R^5}$ is –$\mathbf{L^5}$-$\mathbf{R^g}$.

In certain embodiments of **[FF]**, $\mathbf{R^5}$ is –O-$\mathbf{R^g}$.

In certain embodiments of **[FF]**, $\mathbf{R^5}$ is –O-(phenyl), wherein the phenyl is optionally substituted with from 1-2 $\mathbf{R^c}$.

In certain embodiments of **[FF]**, $\mathbf{L^1}$ is C_{1-3} alkylene (e.g., –CH_2-, -CH_2CH_2-, or –CH(Me)-).

Variable R^{cA}

In certain embodiments, each occurrence of $\mathbf{R^{cA}}$ is independently selected from the group consisting of: halo; cyano; C_{1-10} alkyl which is optionally substituted with from 1-6 independently selected $\mathbf{R^a}$; C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy or C_{1-4} haloalkoxy; C_{1-4} haloalkoxy; -S(O)$_{1-2}$(C_{1-4} alkyl); -N$\mathbf{R^e}\mathbf{R^f}$; –OH; -S(O)$_{1-2}$N$\mathbf{R'R''}$; -C_{1-4} thioalkoxy; -C(=O)(C_{1-10} alkyl); -C(=O)O(C_{1-4} alkyl); -C(=O)OH; and -C(=O)N$\mathbf{R'R''}$.

In certain embodiments, one occurrence of $\mathbf{R^{cA}}$ is –N$\mathbf{R^e}\mathbf{R^f}$.

In certain of these embodiments, one occurrence of $\mathbf{R^{cA}}$ is –NH_2.

In certain of the foregoing embodiments, one occurrence of $\mathbf{R^{cA}}$ is –NH(C_{1-6} alkyl), wherein the C_{1-6} alkyl is optionally substituted with from 1-3 substituents each

independently selected from the group consisting of N**R'R''**, -OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and halo. For example, one occurrence of $\mathbf{R^{cA}}$ can be –NHMe, -$NHCH_2CF_3$, -$NHCH_2CH_2OH$, or –NHiPr.

In certain embodiments, one occurrence of $\mathbf{R^{cA}}$ is –NHC(=O)C_{1-4} alkyl, such as NHC(=O)CH_3.

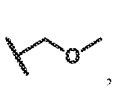
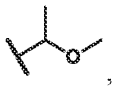
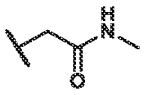
In certain embodiments, one occurrence of $\mathbf{R^{cA}}$ is N(C_{1-3} alkyl)$_2$ such as NMe_2.

In certain embodiments, one occurrence of $\mathbf{R^{cA}}$ is C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy or C_{1-4} haloalkoxy. For example, $\mathbf{R^{cA}}$ can be OMe or OCH_2CH_2OMe.

In certain embodiments, one occurrence of $\mathbf{R^{cA}}$ is C_{1-4} haloalkoxy (e.g., –OCH_2CF_3).

In certain embodiments, one occurrence of $\mathbf{R^{cA}}$ is C_{1-4} thioalkoxy (e.g., –SCH_3).

In certain embodiments, one occurrence of $\mathbf{R^{cA}}$ is C_{1-6} alkyl, such as methyl; or wherein one occurrence of $\mathbf{R^{cA}}$ is C_{1-6} alkyl substituted with from 1-6 independently selected halo. For example, one occurrence of $\mathbf{R^{cA}}$ can be –CF_3.

In certain embodiments, one occurrence of $\mathbf{R^{cA}}$ is C_{1-6} alkyl substituted with $\mathbf{R^a}$, such as C_{1-6} alkyl substituted with C_{1-3} alkoxy or C(=O)N**R'R''**. For example, one occurrence of $\mathbf{R^{cA}}$ can be  ,  , or  .

In certain embodiments, one occurrence of $\mathbf{R^{cA}}$ is halo (e.g., –F).

In certain embodiments, one occurrence of $\mathbf{R^{cA}}$ is –OH.

In certain embodiments, one occurrence of $\mathbf{R^{cA}}$ is C(=O)N**R'R''** (e.g., C(=O)NHMe).

Variables R^{1c}, R^{2a}, R^{2b}, R^{3a}, and R^{3b}

In some embodiments, $\mathbf{R^{1c}}$ is H.

In some embodiments, $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are both H.

In some embodiments, from 1-2 (e.g., 1 or 2) of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ is an independently selected substituent that is other than H.

In certain of these embodiments, one of R^{2a} and R^{2b} (e.g., R^{2a}), is a substituent that is other than H.

In certain of the foregoing embodiments, one of R^{2a} and R^{2b} (e.g., R^{2a}), is R^b. In certain of these embodiments, one of R^{2a} and R^{2b} (e.g., R^{2a}) is C_{1-6} alkyl which is optionally substituted with from 1-6 R^a. In certain of these embodiments, one of R^{2a} and R^{2b} (e.g., R^{2a}) is C_{1-3} alkyl, such as methyl or ethyl. In certain embodiments (when one of R^{2a} and R^{2b} is as defined *supra*), the other of R^{2a} and R^{2b} (e.g., R^{2b}) is H.

In some embodiments, R^{3a} and R^{3b} are both H.

In some embodiments, from 1-2 (e.g., 1 or 2) of R^{3a} and R^{3b} is an independently selected substituent that is other than H.

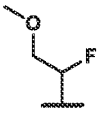
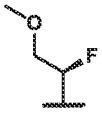
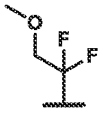
In certain of the foregoing embodiments, one of R^{3a} and R^{3b} (e.g., R^{3a}) is a substituent that is other than H. In certain of these embodiments, one of R^{3a} and R^{3b} (e.g., R^{3a}) is R^b. In certain of these embodiments, one of R^{3a} and R^{3b} (e.g., R^{3a}) is C_{1-6} alkyl which is optionally substituted with from 1-6 R^a. For example, one of R^{3a} and R^{3b} (e.g., R^{3a}) can be C_{1-3} alkyl, such as methyl or ethyl. In certain embodiments (when one of R^{3a} and R^{3b} is as defined *supra*), the other of R^{3a} and R^{3b} (e.g., R^{3b}) is H.

In some embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is C_{1-3} alkyl optionally substituted with from 1-3 independently selected halo. As non-limiting examples of the foregoing embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is $–CH_3$, $-CH_2CH_3$, $–CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CHF_2$, or $-CH_2CH_2F$.

In some embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is C_{1-3} alkyl substituted with C_{1-4} alkoxy, C_{1-4} haloalkoxy, or NR^eR^f. As non-limiting examples of the foregoing embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is $–CH_2OMe$, $-CH_2CH_2OMe$, $-CH(Me)CH_2OMe$, $-CH_2CH(Me)OMe$, $-CH_2OEt$, $-CH_2CH_2OCHF_2$, $-CH_2NR^eR^f$ (e.g., $-CH_2N(CF_3)Me$), or $–CH_2CH_2NR^eR^f$ (e.g., $-CH_2CH_2NMe_2$).

In some embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is C_{1-3} alkyl substituted with C_{1-4} alkoxy. As non-limiting examples of the foregoing embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is $–CH_2OMe$, $-CH_2CH_2OMe$, $-CH(Me)CH_2OMe$, $-CH_2CH(Me)OMe$, or $-CH_2OEt$, such as $–CH_2OMe$.

In some embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is C_{1-3} alkyl substituted with C_{1-4} alkoxy. As non-limiting examples of the foregoing embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is –CH_2OMe, -CH_2CH_2OMe, -$CH(Me)CH_2OMe$, -$CH_2CH(Me)OMe$, or -CH_2OEt, such as –CH_2OMe; such as -CH_2CH_2OMe; optionally the other one of R^{3a} and R^{3b}, such as R^{3b} is H.

In some embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is C_{1-3} alkyl substituted with C_{1-4} alkoxy, C_{1-4} haloalkoxy, or NR^eR^f and further substituted with from 1-3 independently selected halo. In certain embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is C_{1-3} alkyl substituted with C_{1-4} alkoxy and further substituted with from 1-3 independently selected halo. For example, one of R^{3a} and R^{3b}, such as R^{3a}, can be  (e.g.,  or ) or  .

In some embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is C_{3-6} alkyl substituted with C_{1-4} alkoxy, C_{1-4} haloalkoxy, or NR^eR^f. In certain of these embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is branched C_{3-6} alkyl substituted with C_{1-4} alkoxy, C_{1-4} haloalkoxy, or NR^eR^f. In certain of the foregoing embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is branched C_{3-6} alkyl substituted with C_{1-4} alkoxy. For example, one of R^{3a} and R^{3b}, such as R^{3a}, can be  .

In some embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is R^g or $–(L^g)_g$-R^g.

In certain of the foregoing embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is selected from the group consisting of:

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^e; and

C_{3-6} cycloalkyl optionally substituted with from 1-4 R^e.

As non-limiting examples of the foregoing embodiments, one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is selected from the group consisting of: cyclopropyl, cyclobutyl, oxetanyl, and azetidinyl, each of which is optionally substituted with from 1-2 substituents independently selected from the group consisting of: C_{1-3} alkyl and halo, wherein the ring nitrogen of the azetidinyl is optionally substituted with $\mathbf{R^{d}}$.

In certain of the foregoing embodiments, one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is –(C_{1-3} alkylene)-$\mathbf{R^{g}}$ or -(C_{1-3} alkylene)-O-$\mathbf{R^{g}}$, and optionally the $\mathbf{R^{g}}$ group of $\mathbf{R^{3a}}$ or $\mathbf{R^{3b}}$ is:

C_{3-6} cycloalkyl optionally substituted with from 1-4 $\mathbf{R^{c}}$, or

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^{d}}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^{c}}$.

In certain of the foregoing embodiments, one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is –CH_2-$\mathbf{R^{g}}$, –$CH_2CH_2\mathbf{R^{g}}$, or –CH_2-O-$\mathbf{R^{g}}$, wherein the $\mathbf{R^{g}}$ group of $\mathbf{R^{3a}}$ or $\mathbf{R^{3b}}$ is selected from the group:

C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl) optionally substituted with from 1-4 $\mathbf{R^{c}}$, or

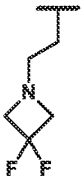
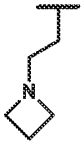
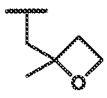
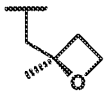
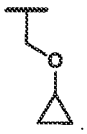
heterocyclyl including from 4-6 ring atoms (e.g., oxetanyl, azetidinyl), wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^{d}}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^{c}}$ (e.g., C_{1-3} alkyl, halo).

In certain of the foregoing embodiments, one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is –CH_2-$\mathbf{R^{g}}$, –$CH_2CH_2\mathbf{R^{g}}$, or –CH_2-O-$\mathbf{R^{g}}$, wherein the $\mathbf{R^{g}}$ group of $\mathbf{R^{3a}}$ or $\mathbf{R^{3b}}$ is selected from the group consisting of:

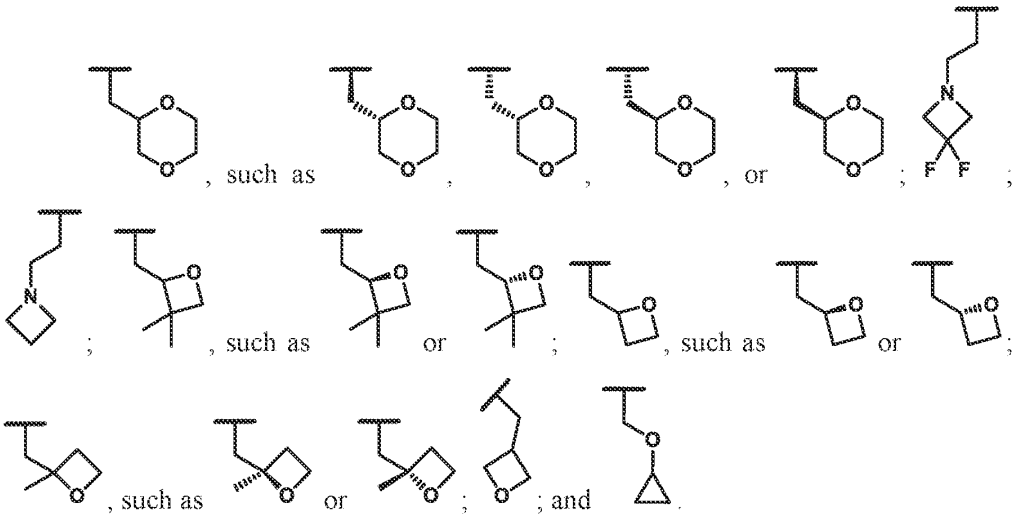
cyclopropyl, cyclobutyl, oxetanyl, and azetidinyl, each of which is optionally substituted with from 1-2 substituents independently selected from the group consisting of: C_{1-3} alkyl and halo, wherein the ring nitrogen of the azetidinyl is optionally substituted with $\mathbf{R^{d}}$.

In certain of the foregoing embodiments, one of $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$, such as $\mathbf{R}^{3a}$, is $-CH_2$-$\mathbf{R}^{g}$, $-CH_2CH_2\mathbf{R}^{g}$, or $-CH_2$-O-$\mathbf{R}^{g}$, wherein the $\mathbf{R}^{g}$ group of $\mathbf{R}^{3a}$ or $\mathbf{R}^{3b}$ is selected from the group consisting of:

cyclopropyl, cyclobutyl, oxetanyl, 1,4-dioxanyl, and azetidinyl, each of which is optionally substituted with from 1-2 substituents independently selected from the group consisting of: C_{1-3} alkyl and halo, wherein the ring nitrogen of the azetidinyl is optionally substituted with $\mathbf{R}^{d}$.

As non-limiting examples of the foregoing embodiments, one of $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$, such as $\mathbf{R}^{3a}$, can be selected from the group consisting of:  ;  ;  , such as  or  ;  , such as  or  ;  , such as  or  ;  ; and  .

As further non-limiting examples of the forgoing embodiments, one of $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$, such as $\mathbf{R}^{3a}$, can be selected from the group consisting of:

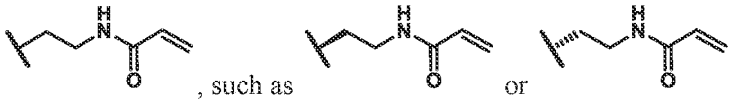


In some embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is-$(L^g)_g$-R^W.

In certain embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is –(C_{1-3} alkylene)-R^W; optionally one of R^{3a} and R^{3b}, such as R^{3a}, is –CH_2–R^W, or –CH_2CH_2–R^W.

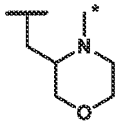
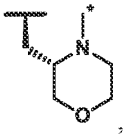
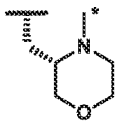
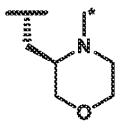
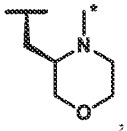
In certain embodiments, the R^W group of R^{3a} or R^{3b} is: C(=O)-CH=CH_2, or -NHC(=O)-CH=CH_2.

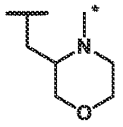
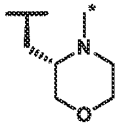
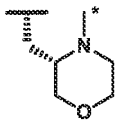
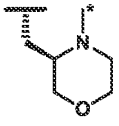
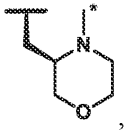
As a non-limiting example, one of R^{3a} and R^{3b}, such as R^{3a}, can be

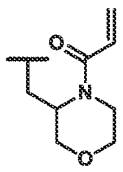
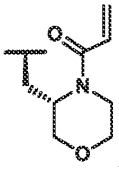
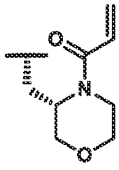
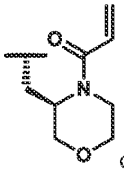
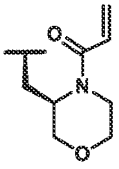


In some embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is -$(L^g)_g$-R^{g2}-R^W.

In some embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is -(C_{1-3} alkylene)-R^{g2}-R^W, and optionally one of R^{3a} and R^{3b}, such as R^{3a}, is -CH_2-R^{g2}-R^W, or -CH_2CH_2-R^{g2}-R^W.

In certain of these embodiments, the R^{g2} group of R^{3a} or R^{3b} is  , such as  ,   or  , wherein the waveline represents the point of attachment to L^g (e.g., -CH_2- or -CH_2CH_2-) and the asterisk represents the point of attachment to R^W; and wherein the R^W group of R^{3a} or R^{3b} is C(=O)-CH=CH_2, or -NHC(=O)-CH=CH_2.

In certain of these embodiments, one of R^{3a} and R^{3b}, such as R^{3a}, is -CH_2-R^{g2}-R^W, and wherein the R^{g2} group of R^{3a} or R^{3b} is  , such as    or  , wherein the waveline represents the point of attachment to L^g (e.g., -CH_2- or -CH_2CH_2-) and the asterisk represents the point of attachment to R^W; and wherein the R^W group of R^{3a} or R^{3b} is C(=O)-CH=CH_2, or -NHC(=O)-CH=CH_2.

As a non-limiting example, one of R^{3a} and R^{3b}, such as R^{3a}, is  , such as  ,   or  .

In some embodiments, the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is –H.

In some embodiments, the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is C_{1-3} alkyl, such as methyl.

In some embodiments, the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is halo, such as -F.

In certain embodiments (when one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is as defined anywhere *supra*), the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is selected from the group consisting of: -H; C_{1-3} alkyl (e.g., methyl); and –F.

In some embodiments, $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, together with the **Ring B** ring atom to which each is attached, form a fused saturated or unsaturated ring of 3-12 ring atoms;

- wherein from 0-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and $S(O)_{0-2}$; and
- wherein the fused saturated or unsaturated ring of 3-12 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo, $\mathbf{R^c}$, and $\mathbf{R^W}$.

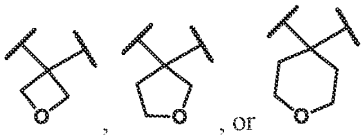
In certain of these embodiments, $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, together with the **Ring B** ring atom to which each is attached, form a fused saturated ring of 4-8 ring atoms;

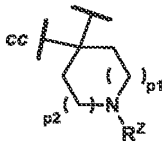
- wherein from 0-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and $S(O)_{0-2}$; and
- wherein the fused saturated ring of 4-8 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo, $\mathbf{R^c}$, and $\mathbf{R^W}$.

In certain of these embodiments, $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, together with the **Ring B** ring atom to which each is attached, form a fused saturated ring of 4-6 ring atoms;

- wherein from 1-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and $S(O)_{0-2}$; and

- wherein the fused saturated ring of 4-6 ring atoms is optionally substituted with from 1-2 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$.

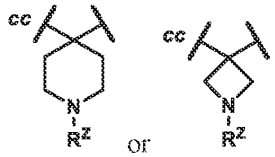
As non-limiting examples of the foregoing embodiments, $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, together with the **Ring B** ring atom to which each is attached, form  .

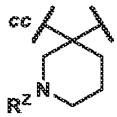
In certain embodiments, $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, together with the **Ring B** ring atom to which each is attached, form:  , which is optionally substituted with from 1-2 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$, wherein:

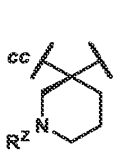
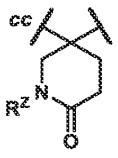
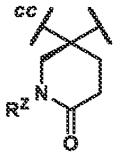
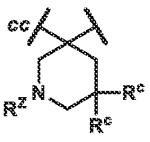
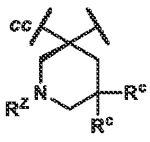
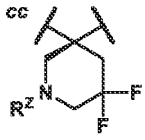
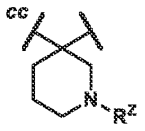
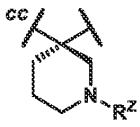
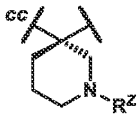
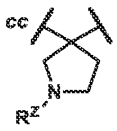
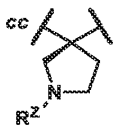
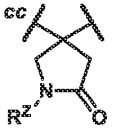
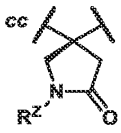
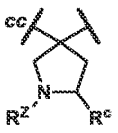
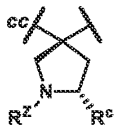
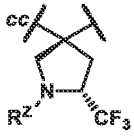
p1 and **p2** are independently 0, 1, or 2;

$\mathbf{R^Z}$ is H, $\mathbf{R^d}$, C(=O)-**W**, or $S(O)_2$**W**; and

cc represents the point of attachment to $C(\mathbf{R^{2a}R^{2b}})$.

In certain of these embodiments, $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, together with the **Ring B** ring atom to which each is attached, form  or , wherein $\mathbf{R^Z}$ is H, $\mathbf{R^d}$, C(=O)-**W**, or $S(O)_2$**W**; and *cc* represents the point of attachment to $C(\mathbf{R^{2a}R^{2b}})$.

In certain embodiments, $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, together with the **Ring B** ring atom to which each is attached, form a fused ring selected from the group consisting of:  (e.g.,


); 
(e.g., 
); 
such as 
(e.g., 
); 
(e.g., 
or 
); 
(e.g., 
); 
(e.g., 
); and 
such as 
(e.g., 
), wherein $\mathbf{R}^{Z}$ is H, $\mathbf{R}^{d}$, C(=O)-**W**, or $S(O)_2\mathbf{W}$; and *cc* represents the point of attachment to $C(\mathbf{R}^{2a}\mathbf{R}^{2b})$.

In certain embodiments, $\mathbf{R}^{Z}$ is H.

In certain embodiments, $\mathbf{R}^{Z}$ is $\mathbf{R}^{d}$. In certain of these embodiments, $\mathbf{R}^{Z}$ is C_{1-6} alkyl optionally substituted with from 1-3 independently selected $\mathbf{R}^{a}$.

In certain embodiments, $\mathbf{R}^{Z}$ is C(=O)-**W** or $S(O)_2\mathbf{W}$. In certain embodiments, **W** is C_{2-4} alkenyl. As a non-limiting example of the foregoing embodiments, $\mathbf{R}^{Z}$ can be $C(=O)\text{-}CH_2{=}CH_2$.

In certain embodiments, $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$, together with the **Ring B** ring atom to which each is attached, form a fused C_{3-6} cycloalkyl, wherein the fused C_{3-6} cycloalkyl is optionally substituted with from 1-2 $\mathbf{R}^{c}$.

As non-limiting examples of the foregoing embodiments, $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$, together with the **Ring B** ring atom to which each is attached, form 
, 
, or 
.

In certain of these foregoing embodiments, $\mathbf{R}^{1c}$, $\mathbf{R}^{2a}$, and $\mathbf{R}^{2b}$ are each H; and $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$ taken together with the **Ring B** ring carbon atom to which each is attached form a

fused C_{3-6} (such as C_3 or C_4) cycloalkyl, wherein the fused cycloalkyl ring is optionally substituted with from 1-2 $\mathbf{R^c}$.

In certain embodiments, one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$, such as $\mathbf{R^{2a}}$, and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, taken together with the **Ring B** ring atoms to which each is attached, form a fused saturated or unsaturated ring of 3-12 ring atoms;

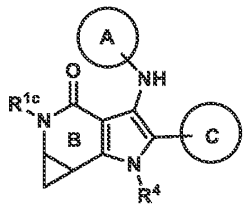
- wherein from 0-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and S(O)$_{0-2}$; and
- wherein the fused saturated or unsaturated ring of 3-12 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$.

In certain the the foregoing embodiments, one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ (such as $\mathbf{R^{2a}}$) and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ (such as $\mathbf{R^{3a}}$) taken together with the **Ring B** ring atoms to which each is attached, form a fused saturated ring of 3-8 ring atoms;

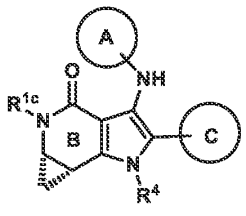
- wherein from 0-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and S(O)$_{0-2}$; and
- wherein the fused saturated ring of 3-8 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$.

In certain of these foregoing embodiments, one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$, such as $\mathbf{R^{2a}}$, and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, taken together with the **Ring B** ring atoms to which each is attached, form a fused C_{3-6} cycloalkyl which is optionally substituted with from 1-2 $\mathbf{R^c}$.

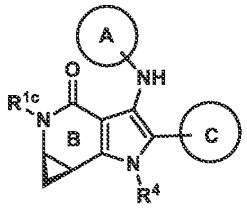
As non-limiting examples of the foregoing embodiments, one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ (such as $\mathbf{R^{2a}}$) and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ (such as $\mathbf{R^{3a}}$) taken together with the **Ring B** ring atoms to which each is attached, form a fused cyclobutyl or cyclopropyl ring, e.g.,



, such as



or



In some embodiments, one of R^{2a} and R^{2b} (such as R^{2a}) and one of R^{3a} and R^{3b} (such as R^{3a}) combine to form a double bond between the **Ring B** atoms to which each is attached.

In certain embodiments, the other one of R^{3a} and R^{3b} is R^g or $-(L^g)_g$-R^g.

In certain embodiments, the other one of R^{3a} and R^{3b} is $-(L^g)_g$-R^g.

In certain embodiment, the other one of R^{3a} and R^{3b} is $-(C_{1-3}$ alkylene)-R^g or -(C_{1-3} alkylene)-O-R^g, and optionally the R^g group of R^{3a} or R^{3b} is:

C_{3-6} cycloalkyl optionally substituted with from 1-4 R^c, or

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c.

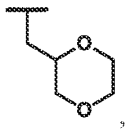
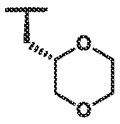
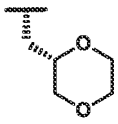
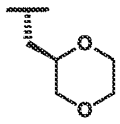
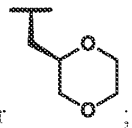
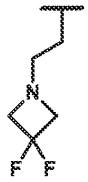
In certain embodiments, the other one of R^{3a} and R^{3b}, such as R^{3a}, is $-CH_2$-R^g, $-CH_2CH_2R^g$, or $-CH_2$-O-R^g, wherein the R^g group of R^{3a} or R^{3b} is:

C_{3-6} cycloalkyl optionally substituted with from 1-4 R^c, or

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c.

In certain enbodiments, the other one of R^{3a} and R^{3b}, such as R^{3a}, is $-CH_2$-R^g, $-CH_2CH_2R^g$, or $-CH_2$-O-R^g, wherein the R^g group of R^{3a} or R^{3b} is selected from the group consisting of:

cyclopropyl, cyclobutyl, oxetanyl, 1,4-dioxanyl, and azetidinyl, each of which is optionally substituted with from 1-2 substituents independently selected from the group consisting of: C_{1-3} alkyl and halo, wherein the ring nitrogen of the azetidinyl is optionally substituted with $\mathbf{R^d}$.

In certain embodiments, the other one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is selected from the group consisting of:  , such as  ,  ,  , or  ;  ;  ;  , such as  or  ;  , such as  or  ;  , such as  or  ;  ; and  .

In certain embodiments, $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H, and $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ are independently selected C_{1-3} alkyl.

In certain embodiments, $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is C_{1-3} alkyl optionally substituted with from 1-3 $\mathbf{R^a}$; and the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is H, optionally each $\mathbf{R^a}$ substituent present in $\mathbf{R^{3a}}$ or $\mathbf{R^{3b}}$ is independently selected from the group consisting of: halo, C_{1-4} alkoxy, and C_{1-4} haloalkoxy.

In certain embodiments, $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is C_{1-3} alkyl optionally substituted with from C_{1-4} alkoxy; optionally one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is -CH_2CH_2-OMe; and the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is H.

In certain embodiments, $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is C_{1-3} alkyl optionally substituted with from 1-3 $\mathbf{R^a}$; and the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is -F, optionally each $\mathbf{R^a}$ substituent present in $\mathbf{R^{3a}}$ or $\mathbf{R^{3b}}$ is independently selected from the group consisting of: halo, C_{1-4} alkoxy, and C_{1-4} haloalkoxy.

In certain embodiments, $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is C_{1-3} alkyl optionally substituted with from 1-3 $\mathbf{R^a}$; and the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is C_{1-3} alkyl (e.g., methyl), optionally each $\mathbf{R^a}$ substituent present in $\mathbf{R^{3a}}$ or $\mathbf{R^{3b}}$ is independently selected from the group consisting of: halo, C_{1-4} alkoxy, and C_{1-4} haloalkoxy.

In certain embodiments, $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is C_{3-6} (e.g., C_4) alkyl optionally substituted with from 1-3 $\mathbf{R^a}$; and the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is H, -F, or C_{1-3} alkyl (e.g., methyl), optionally each $\mathbf{R^a}$ substituent present in $\mathbf{R^{3a}}$ or $\mathbf{R^{3b}}$ is independently selected from the group consisting of: halo, C_{1-4} alkoxy, and C_{1-4} haloalkoxy.

In certain embodiments, $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H, and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is $-\mathbf{R^g}$, $-(C_{1-3}$ alkylene)-$\mathbf{R^g}$, or $-(C_{1-3}$ alkylene)-O-$\mathbf{R^g}$, optionally wherein the $\mathbf{R^g}$ group of $\mathbf{R^{3a}}$ or $\mathbf{R^{3b}}$ is:

C_{3-6} cycloalkyl optionally substituted with from 1-4 $\mathbf{R^c}$, or

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$; and

the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is H.

In some embodiments, $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; and $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ together with the **Ring B** ring atom to which each is attached, form a fused saturated ring of 4-6 ring atoms;

- wherein from 1-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and $S(O)_{0-2}$; and

- wherein the fused saturated ring of 4-6 ring atoms is optionally substituted with from 1-2 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$.

In certain embodoments, $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; and $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ taken together with the **Ring B** ring carbon atom to which each is attached form a fused C_{3-6} (such as C_3 or C_4) cycloalkyl, wherein the fused cycloalkyl ring is optionally substituted with from 1-2 $\mathbf{R^c}$.

In certain embodiments, $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; and $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ are independently selected C_{1-3} alkyl.

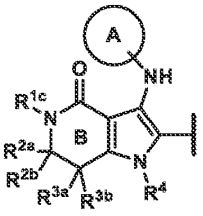
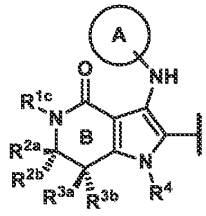
In some embodiments, $\mathbf{R^{1c}}$ is H, and one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ (such as $\mathbf{R^{2a}}$) and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ (such as $\mathbf{R^{3a}}$) taken together with the **Ring B** ring atoms to which each is attached, form a fused C_{3-6} (such as C_3 or C_4) cycloalkyl which is optionally substituted with from 1-2 $\mathbf{R^c}$; and the other of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ and the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ are each H.

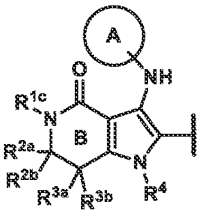
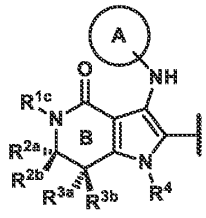
In some embodiments, the other of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ and the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ are each H.

In the some embodiments, the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is C_{1-3} alkyl. As non-limiting examples of the foregoing embodiments, the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is $-CH_3$, $-CH_2CH_3$.

In some embodiments, $\mathbf{R^{1c}}$ is H; one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ (such as $\mathbf{R^{2a}}$) and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ (such as $\mathbf{R^{3a}}$) taken together with the **Ring B** ring atoms to which each is attached, form a fused C_{3-6} (such as C_3 or C_4) cycloalkyl which is optionally substituted with from 1-2 $\mathbf{R^c}$; and the other of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ and the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ are each H.

In some embodiments, $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$ are each H.

In certain embodiments, the  moiety is  .

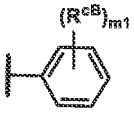
In certain embodiments, the  moiety is  .

Variable R^4, R^7, and Ring A

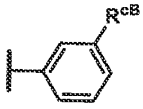
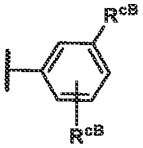
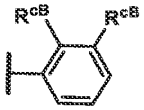
In some embodiments, $\mathbf{R^4}$ is hydrogen.

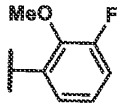
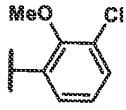
In some embodiments, $\mathbf{R^7}$ is hydrogen.

In certain embodiments, $\mathbf{R^4}$ is hydrogen; and $\mathbf{R^4}$ is hydrogen.

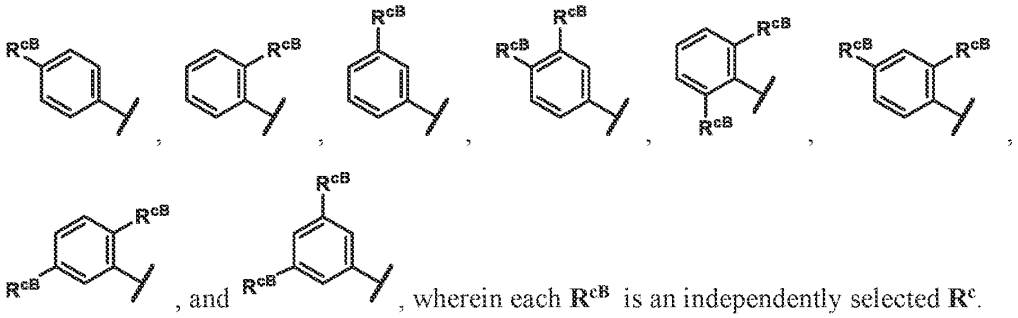
In some embodiments, **Ring A** is  , wherein each $\mathbf{R^{cB}}$ is an independently selected $\mathbf{R^c}$; and **m1** is 0, 1, 2, 3, or 4.

In certain of these embodiments, **m1** is 1, 2, or 3. For example, **m1** can be 1 or 2 (e.g., 2).

In certain embodiments, **Ring A** is  or  (e.g., ), wherein each $\mathbf{R^{cB}}$ is an independently selected $\mathbf{R^c}$.

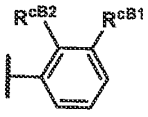
As non-limiting examples, **Ring A** can be  or  .

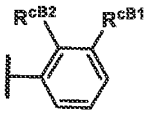
In certain embodiments, **Ring A** is selected from the group consisting of:



, wherein each $\mathbf{R^{cB}}$ is an independently selected $\mathbf{R^{c}}$.

In certain embodiments, each $\mathbf{R^{cB}}$ is independently selected from the group consisting of: -halo, such as -Cl and -F; -CN; C_{1-4} alkoxy; C_{1-4} haloalkoxy; C_{1-3} alkyl; and C_{1-3} alkyl substituted with from 1-6 independently selected halo.

In certain embodiments, **Ring A** is  , wherein $\mathbf{R^{cB1}}$ is $\mathbf{R^{c}}$; and $\mathbf{R^{cB2}}$ is H or $\mathbf{R^{c}}$, optionally wherein $\mathbf{R^{cB1}}$ and $\mathbf{R^{cB2}}$ are each independently selected from the group consisting of: -halo, such as -Cl and -F; -CN; C_{1-4} alkoxy; C_{1-4} haloalkoxy; C_{1-3} alkyl; and C_{1-3} alkyl substituted with from 1-6 independently selected halo.

In certain embodiments (when **Ring A** is ), $\mathbf{R^{cB1}}$ is halo, such as –F or –Cl, such as –F.

In certain embodiments, $\mathbf{R^{cB1}}$ is C_{1-3} alkyl or C_{1-3} alkyl substituted with from 1-6 independently selected halo. For example, $\mathbf{R^{cB1}}$ can be methyl, $–CHF_2$, or $–CF_3$.

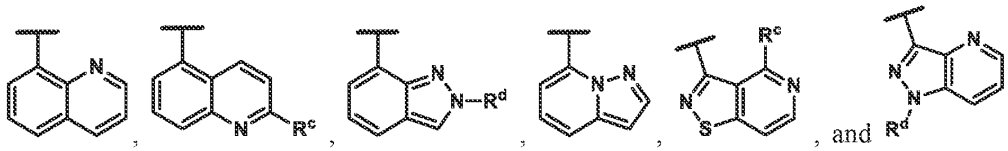
In certain embodiments, $\mathbf{R^{cB2}}$ is selected from the group consisting of: halo; -CN; C_{1-4} alkoxy; C_{1-4} haloalkoxy; C_{1-3} alkyl; and C_{1-3} alkyl substituted with from 1-6 independently selected halo. In certain of these embodiments, $\mathbf{R^{cB2}}$ is C_{1-4} alkoxy or C_{1-4} haloalkoxy.

In certain embodiments, $\mathbf{R^{cB2}}$ is selected from the group consisting of cyano; C_{1-3} alkyl; and C_{1-3} alkyl substituted with from 1-6 independently selected halo. For example, $\mathbf{R^{cB2}}$ can be cyano, methyl, ethyl, $-CHF_2$, $-CF_3$, or $-CH_2CHF_2$.

In some embodiments, **Ring A** is heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 substituents independently selected from the group consisting of $\mathbf{R^c}$ and oxo.

In certain of these embodiments, **Ring A** is bicyclic heteroaryl including from 9-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 substituents independently selected from the group consisting of $\mathbf{R^c}$ and oxo.

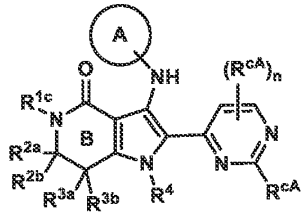
In certain embodiments, **Ring A** is selected from the group consisting of:



each of which is further optionally substituted with $\mathbf{R^c}$.

Non-Limiting Combinations

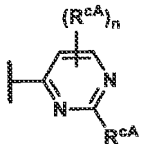
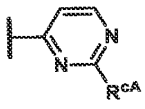
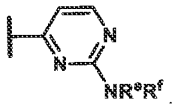
In certain embodiments, the compound is a compound of Formula (**I-a**):



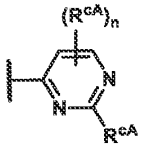
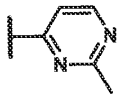
Formula (**I-a**)

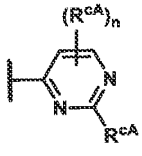
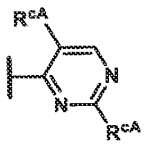
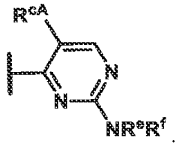
or a pharmaceutically acceptable salt thereof,

wherein: each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$; and **n** is 0, 1, or 2.

In certain embodiments of Formula **(I-a)**,  is  , such as  .

In certain of these foregoing embodiments, **n** is 0; and $\mathbf{R}^{cA}$ is C_{1-3} alkyl optionally substituted with from 1-3 independently selected halo.

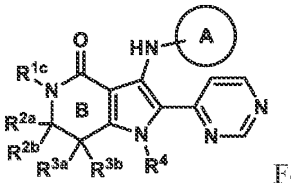
As a non-limiting example,  can be  .

In certain embodiments of Formula **(I-a)**,  is  , such as  .

In certain embodiments of Formula **(I-a)**, one of $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$, such as $\mathbf{R}^{3a}$, is C_{1-3} alkyl substituted with C_{1-4} alkoxy; optionally wherein the other one of of $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$, such as $\mathbf{R}^{3b}$ is H.

In certain embodiments of Formula **(I-a)**, one of $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$, such as $\mathbf{R}^{3a}$, is $-CH_2OMe$, $-CH_2CH_2OMe$, $-CH(Me)CH_2OMe$, $-CH_2CH(Me)OMe$, or $-CH_2OEt$; optionally wherein one of $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$, such as $\mathbf{R}^{3a}$ is $-CH_2CH_2OMe$.

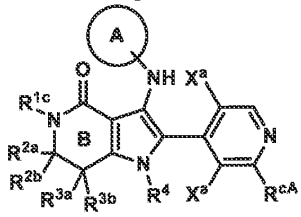
In certain embodiments, the compound is a compound of Formula **(I-b)**:



Formula (**I-b**)

or a pharmaceutically acceptable salt thereof.

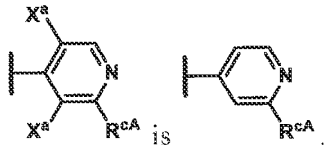
In certain embodiments, the compound is a compound of Formula (**I-c**):



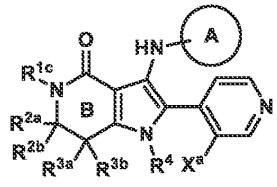
Formula (**I-c**)

or a pharmaceutically acceptable salt thereof,

wherein: $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

In certain embodiments of Formula (**I-c**),  is .

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



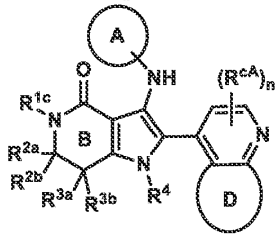
Formula (**I-d**)

or a pharmaceutically acceptable salt thereof.

In certain embodiments of Formula (**I-d**), $\mathbf{X}^{a}$ is selected from H, -F, -Cl, C_{1-6} alkyl, and C_{1-3} alkyl substituted with from 1-3 independently selected halo. For example, $\mathbf{X}^{a}$ is -F. In certain embodiments of Formula (**I-d**), $\mathbf{X}^{a}$ is C_{1-3} substituted with from 1-3

independently selected halo. As non-limiting examples of these foregoing embodiments of Formula **(I-d)**, $\mathbf{X^a}$ is $-CF_2H$ or $-CF_3$.

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



Formula **(I-e)**

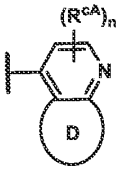
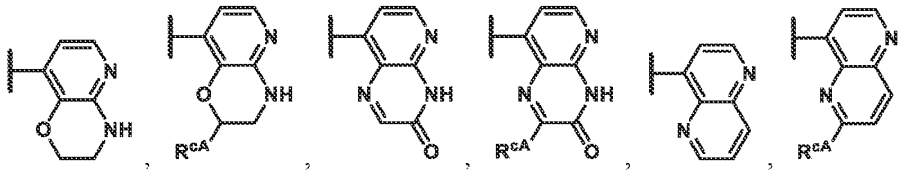
or a pharmaceutically acceptable salt thereof,

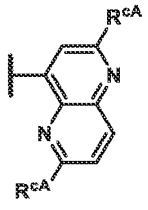
wherein: each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$;

n is 0, 1, or 2; and

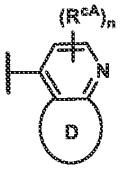
Ring D is a partially unsaturated or aromatic ring including from 5-6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

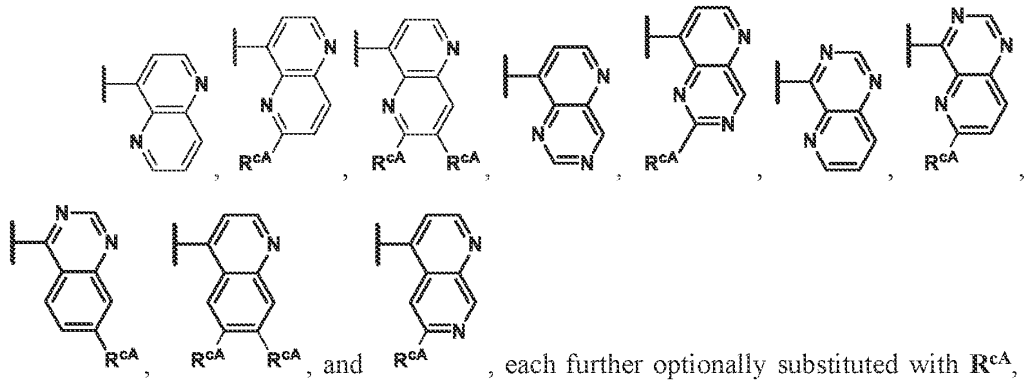
In certain embodiments of Formula **(I-e)**, **Ring D** is a partially unsaturated or aromatic ring including 6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

In certain of these embodiments,  is selected from the group consisting of:  , and

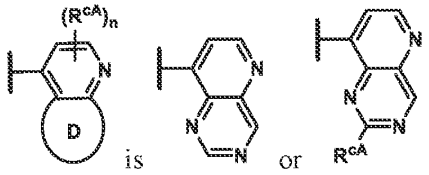


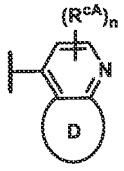
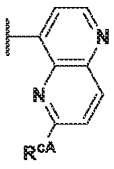
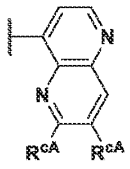
, each further optionally substituted with $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

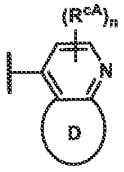
In certain of these embodiments,  is selected from the group consisting of:

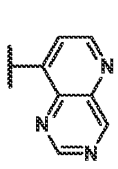
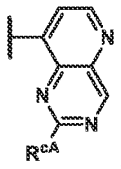
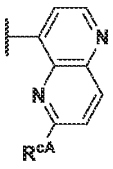
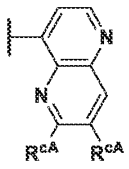


, each further optionally substituted with $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

In certain of the foregoing embodiments,  is , wherein $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

In certain of the foregoing embodiments,  is  or  , wherein each R^{cA} is an independently selected R^{c}.

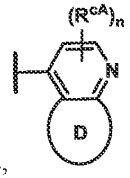
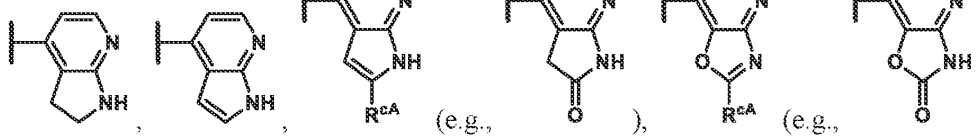
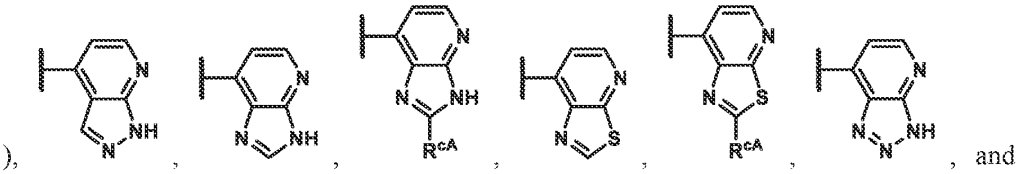
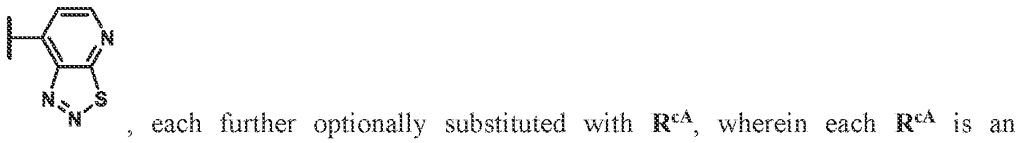
In certain of the foregoing embodiments,  is selected from the group consisting of:

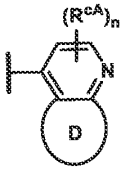
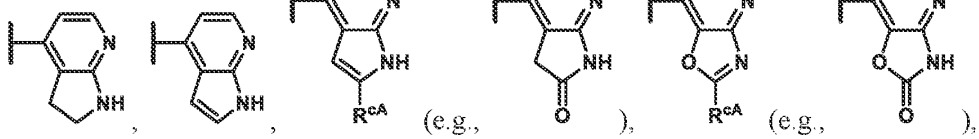
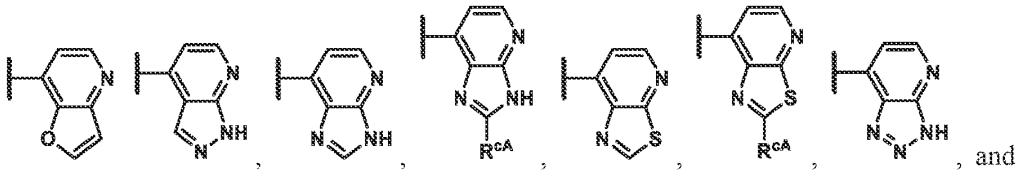
 ,  ,  , and  , wherein:

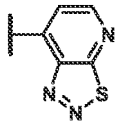
each occurrence of R^{cA} is independently selected from the group consisting of: halo; $NR^{e}R^{f}$; C_{1-4} alkoxy; C_{1-4} haloalkoxy; C_{1-3} alkyl; C_{1-3} alkyl substituted with from 1-3 independently selected halo; C_{1-3} alkyl substituted with C_{1-4} alkoxy; and C_{1-4} alkoxy substituted with C_{1-4} alkoxy;

such as wherein each occurrence of R^{cA} is independently selected from the group consisting of: C_{1-4} alkoxy; C_{1-4} haloalkoxy; C_{1-3} alkyl; and C_{1-3} alkyl substituted with from 1-3 independently selected halo.

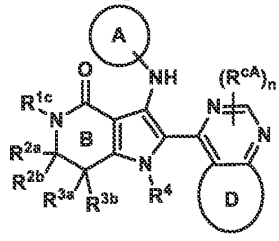
In certain embodiments of Formula **(I-e)**, **Ring D** is a partially unsaturated or aromatic ring including 5 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), $N(R^{d})$, O, and $S(O)_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 R^{cA}.

In certain of these embodiments,  is selected from the group consisting of:  , ),  , and , each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^c.

In certain of these embodiments,  is selected from the group consisting of:  , ), , and


, each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^{c}.

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


Formula **(I-f)**

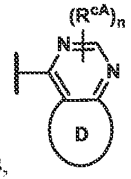
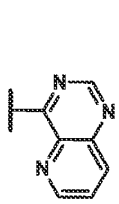
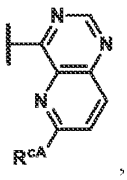
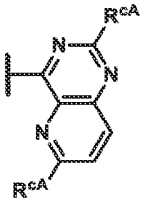
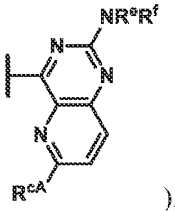
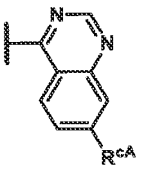
or a pharmaceutically acceptable salt thereof,

wherein: each R^{cA} is an independently selected R^{c};

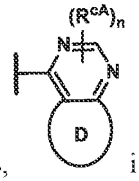
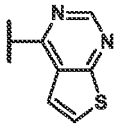
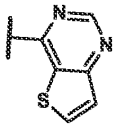
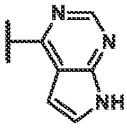
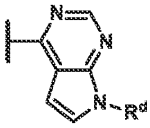
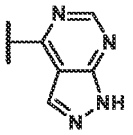
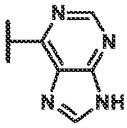
n is 0 or 1; and

Ring D is a partially unsaturated or aromatic ring including from 5-6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N(R^{d}), O, and $S(O)_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 R^{cA}.

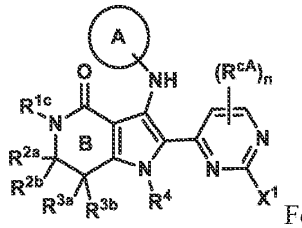
In certain embodiments of Formula **(I-f)**, **Ring D** is a partially unsaturated or aromatic ring including 6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N(R^{d}), O, and $S(O)_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 R^{cA}.

In certain of these embodiments,  is selected from the group consisting of:  ,  ,  ,  (e.g.,),  , and  , each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^c.

In certain embodiments of Formula **(I-f)**, **Ring D** is a partially unsaturated or aromatic ring including 5 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 R^{cA}.

In certain of these embodiments,  is selected from the group consisting of:  ,  ,  ,  ,  , and  , each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^c.

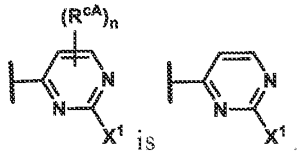
In certain embodiments, the compound is a compound of Formula **(I-g)**:



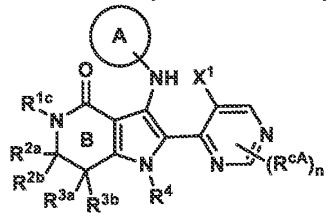
Formula (I-g)

or a pharmaceutically acceptable salt thereof,

wherein: each R^{cA} is an independently selected R^c; and **n** is 0, 1, or 2.

In certain embodiments of Formula (I-g),  is .

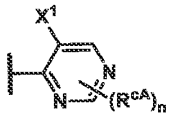
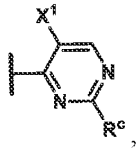
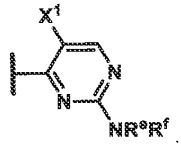
In certain embodiments, the compound is a compound of Formula (I-h):



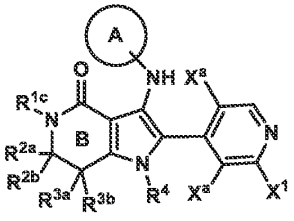
Formula (I-h)

or a pharmaceutically acceptable salt thereof,

wherein: each R^{cA} is an independently selected R^c; and **n** is 0, 1, or 2.

In certain embodiments of Formula (I-h),  is  , such as  .

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

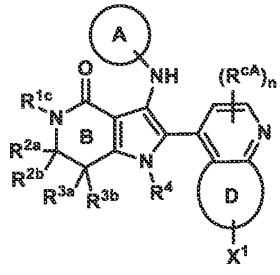


Formula (**I-i**)

or a pharmaceutically acceptable salt thereof.

In certain embodiments of Formula (**I-i**), each X^a is H.

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



Formula (**I-j**)

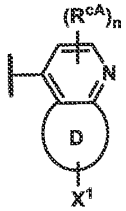
or a pharmaceutically acceptable salt thereof;

wherein **n** is 0, 1, or 2;

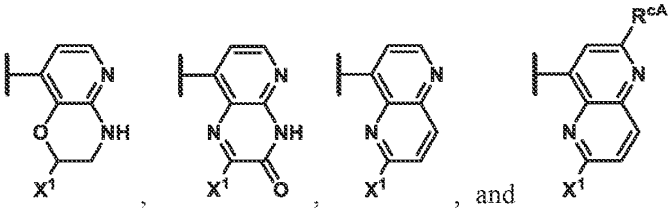
each R^{cA} is an independently selected R^c; and

Ring D is a partially unsaturated or aromatic ring including from 5-6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 R^{cA}.

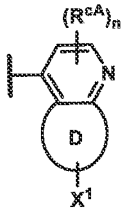
In certain embodiments of Formula (**I-j**), **Ring D** is a partially unsaturated or aromatic ring including 6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 R^{cA}.



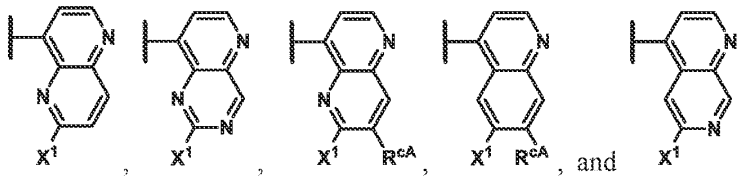
In certain of these embodiments, is selected from the group consisting



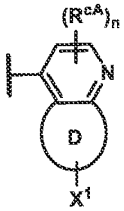
of: , , , and , each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^c.



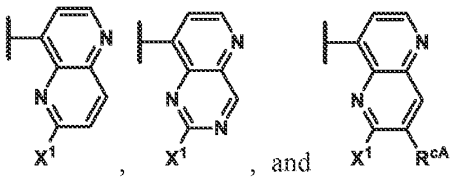
In certain of the foregoing embodiments, is selected from the group



consisting of: , , , , and , each of which is further optionally substituted with from 1-2 R^{cA}, wherein each R^{cA} is an independently selected R^c.

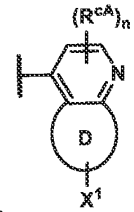
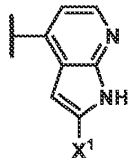
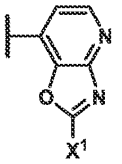
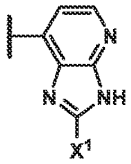
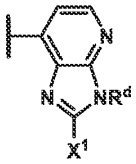
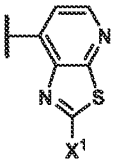


In certain of the foregoing embodiments, is selected from the group

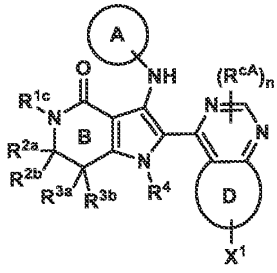


consisting of: , , and .

In certain embodiments of Formula **(I-j)**, **Ring D** is a partially unsaturated or aromatic ring including 5 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

In certain of these embodiments,  is selected from the group consisting of:  ,  ,  ,  , and  , each further optionally substituted with $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$.

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



Formula **(I-k)**

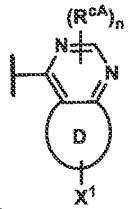
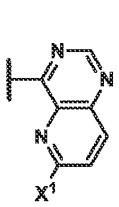
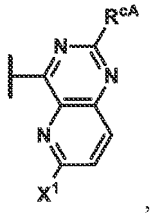
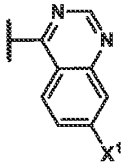
or a pharmaceutically acceptable salt thereof;

wherein **n** is 0 or 1;

each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$; and

Ring D is a partially unsaturated or aromatic ring including from 5-6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

In certain of these embodiments, **Ring D** is a partially unsaturated or aromatic ring including 6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

In certain embodiments of Formula **(I-k)**,  is selected from the group consisting of:  ,  , and  , each further optionally substituted with $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$.

In certain embodiments of Formula **(I-k)**, **Ring D** is a partially unsaturated or aromatic ring including 5 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, each occurrence of $\mathbf{R^{cA}}$ is independently selected from the group consisting of: halo; cyano; C$_{1-10}$ alkyl which is optionally substituted with from 1-6 independently selected $\mathbf{R^a}$; C$_{1-4}$ alkoxy optionally substituted with C$_{1-4}$ alkoxy or C$_{1-4}$ haloalkoxy; C$_{1-4}$ haloalkoxy; -S(O)$_{1-2}$(C$_{1-4}$ alkyl); -N$\mathbf{R^eR^f}$; –OH; -S(O)$_{1-2}$N$\mathbf{R'R''}$; -C$_{1-4}$ thioalkoxy; -C(=O)(C$_{1-10}$ alkyl); -C(=O)O(C$_{1-4}$ alkyl); -C(=O)OH; and -C(=O)N$\mathbf{R'R''}$.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, one occurrence of $\mathbf{R^{cA}}$ is –N$\mathbf{R^eR^f}$.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, one occurrence of $\mathbf{R^{cA}}$ is –NH$_2$.

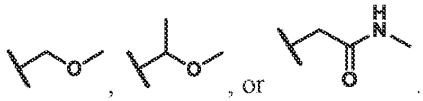
In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, one occurrence of $\mathbf{R}^{cA}$ is –NH(C_{1-6} alkyl), wherein the C_{1-6} alkyl is optionally substituted with from 1-3 substituents each independently selected from the group consisting of N**R'R''**, -OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and halo. For example, one occurrence of $\mathbf{R}^{cA}$ can be –NHMe, -NHCH$_2$CF$_3$, -NHCH$_2$CH$_2$OH, or –NHiPr.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, one occurrence of $\mathbf{R}^{cA}$ is –NHC(=O)C_{1-4} alkyl, such as NHC(=O)CH$_3$; or wherein one occurrence of $\mathbf{R}^{cA}$ is N(C_{1-3} alkyl)$_2$ such as NMe$_2$.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, one occurrence of $\mathbf{R}^{cA}$ is C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy or C_{1-4} haloalkoxy. For example, one occurrence of $\mathbf{R}^{cA}$ can be OMe or OCH$_2$CH$_2$OMe. As another non-limiting example, $\mathbf{R}^{cA}$ can be C_{1-4} haloalkoxy, such as –OCH$_2$CF$_3$.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, one occurrence of $\mathbf{R}^{cA}$ is C_{1-4} thioalkoxy (e.g., SCH$_3$).

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, one occurrence of $\mathbf{R}^{cA}$ is C_{1-6} alkyl, such as methyl; or wherein one occurrence of $\mathbf{R}^{cA}$ is C_{1-6} alkyl substituted with from 1-6 independently selected halo (e.g., $\mathbf{R}^{cA}$ can be –CF$_3$).

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, one occurrence of $\mathbf{R}^{cA}$ is C_{1-6} alkyl substituted with $\mathbf{R}^{a}$, such as C_{1-6} alkyl substituted with C_{1-3} alkoxy or C(=O)N**R'R"**. For example, one occurrence of $\mathbf{R}^{cA}$ can be  .

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, one occurrence of $\mathbf{R}^{cA}$ is halo (e.g., –F).

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, one occurrence of $\mathbf{R}^{cA}$ is –OH.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, one occurrence of $\mathbf{R}^{cA}$ is C(=O)N**R'R"**, such as C(=O)NHMe.

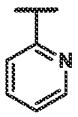
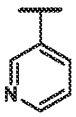
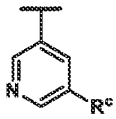
In Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{X^1}$ can be as defined anywhere herein. In certain embodiments, $\mathbf{X^1}$ can be as defined in **[AA1]**, **[BB1]**, **[CC1]**, **[DD1]**, **[EE1]**, or **[FF1]**, *infra*:

[AA1]:

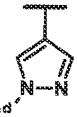
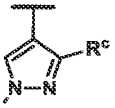
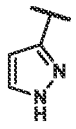
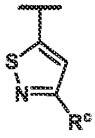
In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{X^1}$ is $-(\mathbf{X^2})_m\text{-}\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein:

- **m** is 0 or 1;
- $\mathbf{X^2}$ is $-N(\mathbf{R^N})-$ or -O-;
- $\mathbf{L^1}$ is a bond or C_{1-6} alkylene optionally substituted with from 1-3 $\mathbf{R^a}$; and
- $\mathbf{R^5}$ is $-\mathbf{R^g}$.

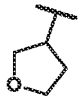
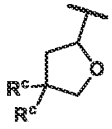
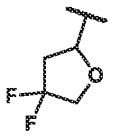
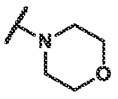
In certain embodiments of **[AA1]**, $\mathbf{R^5}$ is phenyl optionally substituted with from 1-4 $\mathbf{R^c}$, such as wherein $\mathbf{R^5}$ is phenyl optionally substituted with from 1-2 independently selected halo, such as –F.

In certain embodiments of **[AA1]**, $\mathbf{R^5}$ is heteroaryl including 6 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and $N(\mathbf{R^d})$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R^c}$, such as wherein $\mathbf{R^5}$ is  ,  , or  .

In certain embodiments of **[AA1]**, $\mathbf{R^5}$ is heteroaryl including 5 ring atoms, wherein from 1-4, such as 2-4, ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), $N(\mathbf{R^d})$, O, and $S(O)_{0-2}$, and wherein the heteroaryl is

optionally substituted with from 1-4 R^c, such as wherein R^5 is  ,  ,  , or  .

In certain embodiments of **[AA1]**, R^5 is C_{3-10} cycloalkyl, such as C_{3-6} cycloalkyl, optionally substituted with from 1-4 R^c, such as wherein R^5 is cyclopropyl.

In certain embodiments of **[AA1]**, R^5 is heterocyclyl including from 4-8, such as 4-6, ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c. For example, R^5 can be  ,  ,  such as  , or  .

In certain embodiments of **[AA1]**, **m** is 0.

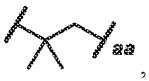
In certain embodiments of **[AA1]**, **m** is 1.

In certain embodiments of **[AA1]**, X^2 is –N(R^N)- (e.g., N(H)).

In certain embodiments of **[AA1]**, X^2 is –O-.

In certain embodiments of **[AA1]**, L^1 is a bond.

In certain embodiments of **[AA1]**, L^1 is C_{1-3} alkylene (e.g., –CH_2-, -CH_2CH_2-, or –CH(Me)-).

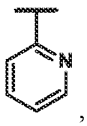
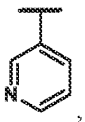
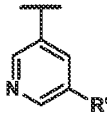
In certain embodiments of **[AA1]**, L^1 is branched C_{3-6} alkylene. For example, L^1 can be  or  , wherein *aa* is the point of attachment to R^5.

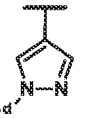
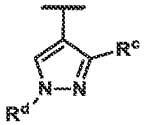
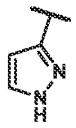
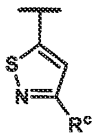
[BB1]:

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, X^1 is $–X^2\text{-}L^1\text{-}R^5$, wherein:

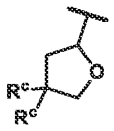
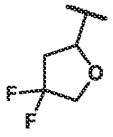
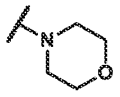
- X^2 is -N(R^N)C(=O)-*, -N(R^N)S(O)$_2$-*, -N(R^N)C(=O)O-*, or N(R^N)C(=O)N(R^N)*;
- L^1 is a bond or C_{1-6} alkylene optionally substituted with from 1-3 R^a; and
- R^5 is $–R^g$.

In certain embodiments of **[BB1]**, R^5 is phenyl optionally substituted with from 1-4 R^c, such as wherein R^5 is phenyl optionally substituted with from 1-2 independently selected halo, such as –F.

In certain embodiments of **[BB1]**, R^5 is heteroaryl including 6 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N(R^d), and wherein the heteroaryl is optionally substituted with from 1-4 R^c, such as wherein R^5 is  ,  , or  .

In certain embodiments of **[BB1]**, R^5 is heteroaryl including 5 ring atoms, wherein from 1-4, such as 2-4, ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 R^c, such as wherein R^5 is  ,  ,  , or  .

In certain embodiments of **[BB1]**, R^5 is C_{3-10} cycloalkyl, such as C_{3-6} cycloalkyl, optionally substituted with from 1-4 R^c, such as wherein R^5 is cyclopropyl.

In certain embodiments of **[BB1]**, $\mathbf{R^5}$ is heterocyclyl including from 4-8, such as 4-6, ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$. For example, $\mathbf{R^5}$ can be  ,  ,  such as  , or  .

In certain embodiments of **[BB1]**, $\mathbf{X^2}$ is -N($\mathbf{R^N}$)C(=O)-* (e.g., –N(H)C(=O)-*).

In certain embodiments of **[BB1]**, $\mathbf{X^2}$ is -N($\mathbf{R^N}$)S(O)$_2$-, such as –N(H)S(O)$_2$-*.

In certain embodiments of **[BB1]**, $\mathbf{X^2}$ is -N($\mathbf{R^N}$)C(=O)O-*, or -N($\mathbf{R^N}$)C(=O)N($\mathbf{R^N}$)-* (e.g., –N(H)C(=O)O-*; e.g., –N(H)C(=O)N(H)-*).

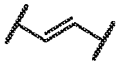
In certain embodiments of **[BB1]**, $\mathbf{L^1}$ is a bond.

In certain embodiments of **[BB1]**, $\mathbf{L^1}$ is C$_{1-3}$ alkylene (e.g., –CH$_2$-, -CH$_2$CH$_2$-, or –CH(Me)-).

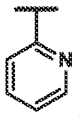
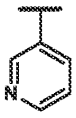
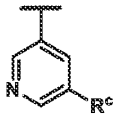
In certain embodiments of **[BB1]**, $\mathbf{L^1}$ is branched C$_{3-6}$ alkylene. For example, $\mathbf{L^1}$ can be  or  , wherein *aa* is the point of attachment to $\mathbf{R^5}$.

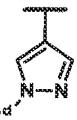
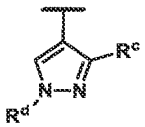
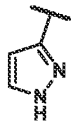
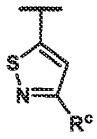
[CC1]:

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{X^1}$ is –$\mathbf{X^2}$-$\mathbf{L^1}$-$\mathbf{R^5}$, wherein:

- $\mathbf{X^2}$ is  or  ;
- $\mathbf{L^1}$ is a bond or C$_{1-6}$ alkylene optionally substituted with from 1-3 $\mathbf{R^a}$; and
- $\mathbf{R^5}$ is –$\mathbf{R^g}$.

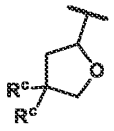
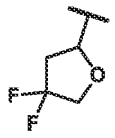
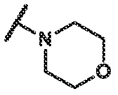
In certain embodiments of **[CC1]**, R^5 is phenyl optionally substituted with from 1-4 R^c, such as wherein R^5 is phenyl optionally substituted with from 1-2 independently selected halo, such as –F.

In certain embodiments of **[CC1]**, R^5 is heteroaryl including 6 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N(R^d), and wherein the heteroaryl is optionally substituted with from 1-4 R^c, such as wherein R^5 is  ,  , or  .

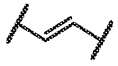
In certain embodiments of **[CC1]**, R^5 is heteroaryl including 5 ring atoms, wherein from 1-4, such as 2-4, ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 R^c, such as wherein R^5 is  ,  ,  , or  .

In certain embodiments of **[CC1]**, R^5 is C_{3-10} cycloalkyl, such as C_{3-6} cycloalkyl, optionally substituted with from 1-4 R^c, such as wherein R^5 is cyclopropyl.

In certain embodiments of **[CC1]**, R^5 is heterocyclyl including from 4-8, such as 4-6, ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group

consisting of oxo and R^c. For example, R^5 can be  ,  ,  such as  , or  .

In some embodiments of **[CC1]**, X^2 is  .

In some embodiments of **[CC1]**, X^2 is  .

In certain embodiments of **[CC1]**, L^1 is a bond.

In certain embodiments of **[CC1]**, L^1 is C_{1-3} alkylene (e.g., $-CH_2-$, $-CH_2CH_2-$, or $-CH(Me)-$).

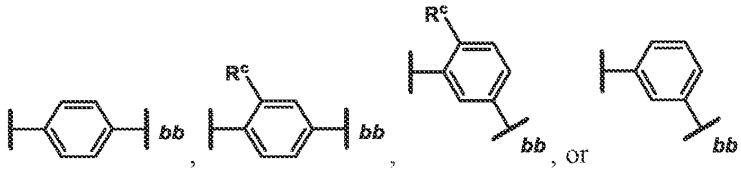
In certain embodiments of **[CC1]**, L^1 is branched C_{3-6} alkylene. For example, L^1 can be  or  , wherein *aa* is the point of attachment to R^5.

[DD1]:

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, X^1 is $-(X^2)_m-L^1-R^5$, wherein:

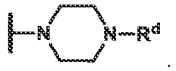
- **m** is 0 or 1;
- X^2 is $-N(R^N)-$ or $-O-$;
- L^1 is a bond or C_{1-6} alkylene optionally substituted with from 1-3 R^a; and
- R^5 is $-R^{g2}-R^Y$.

In certain embodiments of **[DD1]**, the $-R^{g2}$ group present in R^5 is 1,3-phenylene or 1,4-phenylene, each optionally substituted with from 1-4 R^c, such as wherein $-R^{g2}$ is



, wherein ***bb*** is the point of attachment to $\mathbf{R^Y}$.

In certain embodiments of **[DD1]**, the $\mathbf{R^Y}$ group present in $\mathbf{R^5}$ is $-\mathbf{R^g}$.

In certain embodiments of **[DD1]**, the $\mathbf{R^Y}$ group present in $\mathbf{R^5}$ is heterocyclyl including from 4-8, such as 4-6, ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$. For example, $\mathbf{R^Y}$ can be 

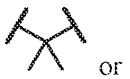
.

In certain embodiments of **[DD1]**, $\mathbf{X^2}$ is $-N(\mathbf{R^N})-$ (e.g., N(H)).

In certain embodiments of **[DD1]**, $\mathbf{X^2}$ is –O-.

In certain embodiments of **[DD1]**, $\mathbf{L^1}$ is a bond.

In certain embodiments of **[DD1]**, $\mathbf{L^1}$ is C_{1-3} alkylene (e.g., $-CH_2-$, $-CH_2CH_2-$, or –CH(Me)-).

In certain embodiments of **[DD1]**, $\mathbf{L^1}$ is branched C_{3-6} alkylene. For example, $\mathbf{L^1}$ can be  or 

, wherein ***aa*** is the point of attachment to $\mathbf{R^5}$.

[EE1]:

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{X^1}$ is $-\mathbf{X^2}\text{-}\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein:

- $\mathbf{X^2}$ is -N($\mathbf{R^N}$)-, –O-, -N($\mathbf{R^N}$)C(=O)-*, -N($\mathbf{R^N}$)S(O)$_2$-, -N($\mathbf{R^N}$)C(=O)O-*, or -N($\mathbf{R^N}$)C(=O)N($\mathbf{R^N}$)-*;
- $\mathbf{L^1}$ is C_{1-6} alkylene optionally substituted with from 1-3 $\mathbf{R^a}$; and
- $\mathbf{R^5}$ is H, halo, C_{1-6} alkoxy optionally substituted with from 1-3 $\mathbf{R^a}$, or –OH.

In certain embodiments of **[EE1]**, R^5 is H.

In certain embodiments of **[EE1]**, R^5 is halo (e.g., –F).

In certain embodiments of **[EE1]**, R^5 is C_{1-6} alkoxy optionally substituted with from 1-3 R^a, such as wherein R^5 is C_{1-3} alkoxy such as methoxy.

In certain embodiments of **[EE1]**, R^5 is –OH.

In certain embodiments of **[EE1]**, X^2 is $–N(R^N)-$ (e.g., N(H)).

In certain embodiments of **[EE1]**, X^2 is –O-.

In certain embodiments of **[EE1]**, X^2 is $-N(R^N)C(=O)-*$ (e.g., $–N(H)C(=O)-*$).

In certain embodiments of **[EE1]**, X^2 is $-N(R^N)S(O)_2-$, such as $–N(H)S(O)_2-*$.

In certain embodiments of **[EE1]**, X^2 is $-N(R^N)C(=O)O-*$, or $-N(R^N)C(=O)N(R^N)-*$ (e.g., $–N(H)C(=O)O-*$; e.g., $–N(H)C(=O)N(H)-*$).

In certain embodiments of **[EE1]**, L^1 is C_{1-3} alkylene (e.g., $–CH_2-$, $-CH_2CH_2-$, or –CH(Me)-).

In certain embodiments of **[EE1]**, L^1 is branched C_{3-6} alkylene. For example, L^1 can be  or  , wherein *aa* is the point of attachment to R^5.

[FF1]:

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, X^1 is $–L^1-R^5$, wherein L^1 is C_{1-6} alkylene optionally substituted with from 1-3 R^a; and R^5 is $–L^5-R^g$.

In certain embodiments of **[FF1]**, R^5 is $–O-R^g$.

In certain embodiments of **[FF1]**, R^5 is –O-(phenyl), wherein the phenyl is optionally substituted with from 1-2 R^c.

In certain embodiments of **[FF1]**, L^1 is C_{1-3} alkylene (e.g., $–CH_2-$, $-CH_2CH_2-$, or –CH(Me)-).

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{R^{1c}}$ is H.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are both H.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{R^{2a}}$ is a substituent that is other than H. In certain of these embodiments, $\mathbf{R^{2a}}$ is C_{1-6} alkyl which is optionally substituted with from 1-6 $\mathbf{R^a}$, such as wherein $\mathbf{R^{2a}}$ is C_{1-3} alkyl, such as methyl or ethyl.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{R^{2b}}$ is H.

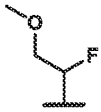
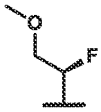
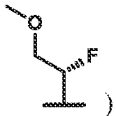
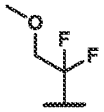
In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ are both H.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{R^{3a}}$ is a substituent that is other than H. In certain of these embodiments, $\mathbf{R^{3a}}$ is C_{1-6} alkyl which is optionally substituted with from 1-6 $\mathbf{R^a}$, such as wherein $\mathbf{R^{3a}}$ is C_{1-3} alkyl, such as methyl or ethyl.

In certain of foregoing embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{R^{3a}}$ is C_{1-3} alkyl substituted with from 1-3 independently selected halo. As non-limiting examples of the foregoing embodiments, $\mathbf{R^{3a}}$ is $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CHF_2$, or $-CH_2CH_2F$.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{R^{3a}}$ is C_{1-3} alkyl substituted with C_{1-4} alkoxy, C_{1-4} haloalkoxy, or $\mathbf{NR^eR^f}$. Non-limiting examples of $\mathbf{R^{3a}}$ in these embodiments include $-CH_2OMe$, $-CH_2CH_2OMe$, $-CH(Me)CH_2OMe$, $-CH_2CH(Me)OMe$, $-CH_2OEt$, $-CH_2CH_2OCHF_2$, $-CH_2N\mathbf{R^eR^f}$ (e.g., $-CH_2N(CF_3)Me$), or $-CH_2CH_2N\mathbf{R^eR^f}$ (e.g., $-CH_2CH_2NMe_2$).

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{R^{3a}}$ is C_{1-3} alkyl substituted with C_{1-4} alkoxy, C_{1-4} haloalkoxy, or $\mathbf{NR^eR^f}$ and further substituted with from 1-3 independently selected halo. In certain of these

embodiments, R^{3a} is C_{1-3} alkyl substituted with C_{1-4} alkoxy and further substituted with from 1-3 independently selected halo. Non-limiting examples of R^{3a} in these embodiments include:  (e.g.,  or ) or  .

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3a} is C_{3-6} alkyl substituted with C_{1-4} alkoxy, C_{1-4} haloalkoxy, or NR^eR^f. In certain of these embodiments, R^{3a} is branched C_{3-6} alkyl substituted with C_{1-4} alkoxy, C_{1-4} haloalkoxy, or NR^eR^f. In certain of the foregoing embodiments, R^{3a} is branched C_{3-6} alkyl substituted with C_{1-4} alkoxy. For example, R^{3a} can be  .

In certain of the foregoing embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3a} is selected from the group consisting of:

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c; and

C_{3-6} cycloalkyl optionally substituted with from 1-4 R^c.

In certain of the foregoing embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3a} is –(C_{1-3} alkylene)-R^g or -(C_{1-3} alkylene)-O-R^g, and optionally the R^g group of R^{3a} is:

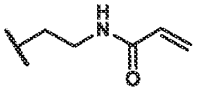
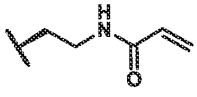
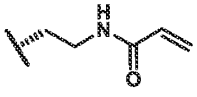
C_{3-6} cycloalkyl optionally substituted with from 1-4 R^c, or

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c.

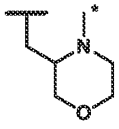
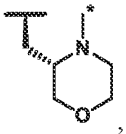
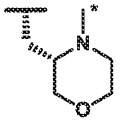
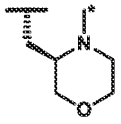
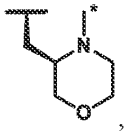
In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3a} is $–CH_2$-R^g, or $–CH_2CH_2R^g$, wherein R^g is 1,4-dioxanyl.

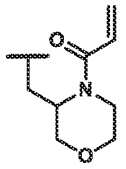
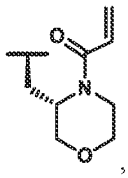
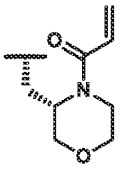
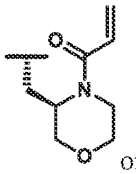
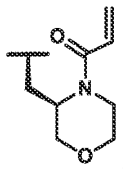
In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3a} is-$(L^g)_g$-R^W.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3a} is-CH_2CH_2-R^W, wherein the R^W group is C(=O)-CH=CH_2, or -NHC(=O)-CH=CH_2.

As a non-limiting example of certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3a} is  , such as  or  .

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3a} is -$(L^g)_g$-R^{g2}-R^W.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3a} is -CH_2-R^{g2}-R^W, wherein the R^{g2} group is  , such as  ,   or  , wherein the waveline represents the point of attachment to -CH_2- and the asterisk represents the point of attachment to R^W; and optionally the R^W group is C(=O)-CH=CH_2.

As a non-limitng example of certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3a} can be  , such as  ,   or  .

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3b} is H.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3b} is C_{1-3} alkyl. As non-limiting examples of the foregoing embodiments, R^{3b} is methyl, ethyl, or propyl. For example, R^{3b} is methyl.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3b} is H.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3b} is halo. For example, R^{3b} can be –F.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3a} and R^{3b}, together with the **Ring B** ring atom to which each is attached, form a fused saturated ring of 4-8 ring atoms;

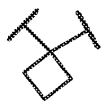
- wherein from 0-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N(R^{d}), O, and $S(O)_{0-2}$; and

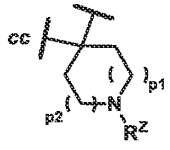
- wherein the fused saturated ring of 4-8 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo, $\mathbf{R^c}$, and $\mathbf{R^W}$.

In certain of the foregoing embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ together with the **Ring B** ring atom to which each is attached, form a fused saturated ring of 4-6 ring atoms;

- wherein from 1-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and $S(O)_{0-2}$; and
- wherein the fused saturated ring of 4-6 ring atoms is optionally substituted with from 1-2 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$.

In certain embodiments, $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, together with the **Ring B** ring atom to which each is attached, form a fused C_{3-6} cycloalkyl, wherein the fused C_{3-6} cycloalkyl is optionally substituted with from 1-2 $\mathbf{R^c}$.

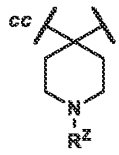
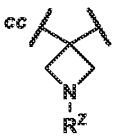
As non-limiting examples of the foregoing embodiments, $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, together with the **Ring B** ring atom to which each is attached, form  ,  , or  .

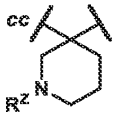
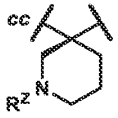
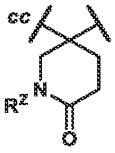
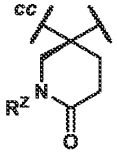
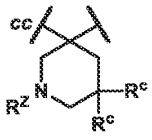
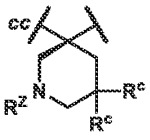
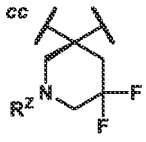
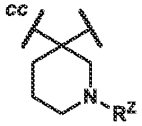
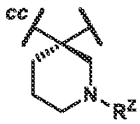
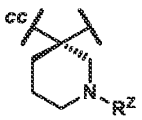
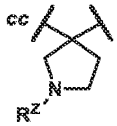
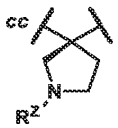
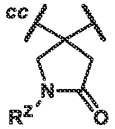
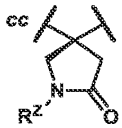
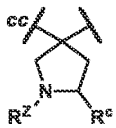
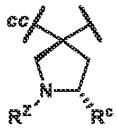
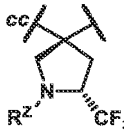
In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, together with the **Ring B** ring atom to which each is attached, form:  , which is optionally substituted with from 1-2 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$, wherein:

p1 and **p2** are independently 0, 1, or 2;

$\mathbf{R^Z}$ is H, $\mathbf{R^d}$, C(=O)-**W**, or $S(O)_2\mathbf{W}$; and

cc represents the point of attachment to $C(\mathbf{R^{2a}R^{2b}})$.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3a} and R^{3b}, together with the **Ring B** ring atom to which each is attached, form  or  , wherein R^Z is H, R^d, C(=O)-**W**, or $S(O)_2$**W**; and *cc* represents the point of attachment to C($R^{2a}R^{2b}$).

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{3a} and R^{3b}, together with the **Ring B** ring atom to which each is attached, form a fused ring selected from the group consisting of:  such as  ;  such as  ;  such as  (e.g., );  such as  or  ;  such as  ;  such as  ; and  such as  (e.g., ),wherein R^Z is H, R^d, C(=O)-**W**, or $S(O)_2$**W**; and *cc* represents the point of attachment to C($R^{2a}R^{2b}$).

In certain embodiments, R^Z is H. In certain embodiments, R^Z is C_{1-6} alkyl optionally substituted with from 1-3 independently selected R^a. In certain embodiments, R^Z is C(=O)-W or $S(O)_2W$, optionally wherein W is C_{2-4} alkenyl.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{1c}, R^{2a}, and R^{2b} are each H; and R^{3a} and R^{3b} taken together with the **Ring B** ring carbon atom to which each is attached form a fused C_{3-6} (such as C_3 or C_4) cycloalkyl, wherein the fused cycloalkyl ring is optionally substituted with from 1-2 R^c.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{1c}, R^{2a}, and R^{2b} are each H; and R^{3a} and R^{3b} together with the **Ring B** ring atom to which each is attached, form a fused saturated ring of 4-6 ring atoms;

- wherein from 1-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, $N(R^d)$, O, and $S(O)_{0-2}$; and
- wherein the fused saturated ring of 4-6 ring atoms is optionally substituted with from 1-2 substituents independently selected from the group consisting of oxo and R^c.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, one of R^{2a} and R^{2b} (such as R^{2a}) and one of R^{3a} and R^{3b} (such as R^{3a}) taken together with the **Ring B** ring atoms to which each is attached, form a fused saturated or unsaturated ring of 3-12 ring atoms;

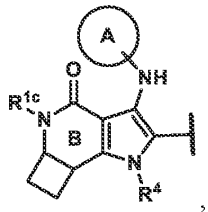
- wherein from 0-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, $N(R^d)$, O, and $S(O)_{0-2}$; and
- wherein the fused saturated or unsaturated ring of 3-12 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c.

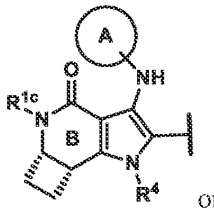
In certain of the foregoing embodiments, one of R^{2a} and R^{2b} (such as R^{2a}) and one of R^{3a} and R^{3b} (such as R^{3a}) taken together with the **Ring B** ring atoms to which each is attached, form a fused saturated ring of 3-8 ring atoms;

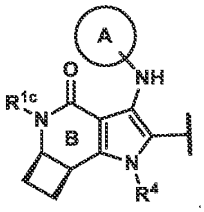
- wherein from 0-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and S(O)$_{0-2}$; and
- wherein the fused saturated ring of 3-8 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$.

In certain of these foregoing embodiments, one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ (such as $\mathbf{R^{2a}}$) and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ (such as $\mathbf{R^{3a}}$) taken together with the **Ring B** ring atoms to which each is attached, form a fused C_{3-6} cycloalkyl which is optionally substituted with from 1-2 $\mathbf{R^c}$.

As non-limiting examples of the foregoing embodiments, one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ (such as $\mathbf{R^{2a}}$) and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ (such as $\mathbf{R^{3a}}$) taken together with the **Ring B** ring atoms to which each is attached, form a fused cyclopropyl or cyclobutyl ring, e.g.,

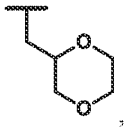
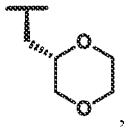
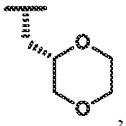
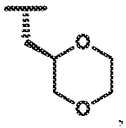
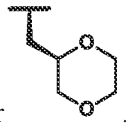


, such as


or


.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{R^{1c}}$ is H; $\mathbf{R^{2a}}$ and $\mathbf{R^{3a}}$ combine to form a double bond between the **Ring B** atoms to which each is attached; and $\mathbf{R^{2b}}$ is H; and $\mathbf{R^{3b}}$ is $\mathbf{-(L^g)_g\text{-}R^g}$.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, $\mathbf{R^{1c}}$ is H; $\mathbf{R^{2a}}$ and $\mathbf{R^{3a}}$ combine to form a double bond between the **Ring B** atoms to which each is attached; and $\mathbf{R^{2b}}$ is H; and $\mathbf{R^{3b}}$ is

, such as

,

,

, or

.

In certain of these foregoing embodiments , R^{1c} is H, and R^{2b} and R^{3b} are each H.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{2b} and R^{3b} are each H.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{1c}, R^{2a}, and R^{2b} are each H, and R^{3a} is C_{1-3} alkyl optionally substituted with from 1-3 R^a.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{1c}, R^{2a}, and R^{2b} are each H; R^{3a}, is C_{1-3} alkyl optionally substituted with from 1-3 R^a; and R^{3b} is H, optionally each R^a substituent present in R^{3a} is independently selected from the group consisting of: halo, C_{1-4} alkoxy, and C_{1-4} haloalkoxy.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{1c}, R^{2a}, and R^{2b} are each H; and R^{3a} and R^{3b} are independently selected C_{1-3} alkyl.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{1c} is H; R^{2a} and R^{3a} taken together with the **Ring B** ring atoms to which each is attached, form a fused C_{3-6} (e.g., C_3 or C_4) cycloalkyl which is optionally substituted with from 1-2 R^c; and R^{2b} and R^{3b} are each H.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{1c}, R^{2a}, R^{2b}, R^{3a}, and R^{3b} are each H.

In certain of these foregoing emodiments, R^{3b} is H, and each optionally present R^a substituent in R^{3a} is independently selected from the group consisting of: halo, C_{1-4} alkoxy, and C_{1-4} haloalkoxy.

In certain of emodiments, R^{3b} is -F, and each optionally present R^a substituent in R^{3a} is independently selected from the group consisting of: halo, C_{1-4} alkoxy, and C_{1-4} haloalkoxy.

In certain of emodiments, R^{3b} is C_{1-3} alkyl (e.g., methyl), and each optionally present R^a substituent in R^{3a} is independently selected from the group consisting of: halo, C_{1-4} alkoxy, and C_{1-4} haloalkoxy.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{1c}, R^{2a}, and R^{2b} are each H; R^{3a}, is $-R^g$, $-(C_{1-3}$ alkylene$)-R^g$, or $-(C_{1-3}$ alkylene$)$-O-R^g,

optionally wherein the R^g group of R^{3a} is:

C_{3-6} cycloalkyl optionally substituted with from 1-4 R^c, or

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c; and

R^{3b} is H.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{1c}, R^{2a}, and R^{2b} are each H; and R^{3a} is C_{1-3} alkyl optionally substituted with from 1-3 R^a; and R^{3b} is H, optionally each R^a substituent present in R^{3a} is independently selected from the group consisting of: halo, C_{1-4} alkoxy, and C_{1-4} haloalkoxy.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{1c}, R^{2a}, and R^{2b} are each H and R^{3a}, is $-R^g$, $-(C_{1-3}$ alkylene$)-R^g$, or $-(C_{1-3}$ alkylene$)$-O-R^g,

optionally wherein the R^g group of R^{3a} is:

C_{3-6} cycloalkyl optionally substituted with from 1-4 R^c, or

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c; and

R^{3b} is H.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{1c}, R^{2a}, and R^{2b} are each H, and R^{3a} and R^{3b} taken together with the **Ring B** ring carbon atom to which each is attached form a fused C_{3-6} (such as C_3 or C_4) cycloalkyl, wherein the fused cycloalkyl ring is optionally substituted with from 1-2 R^c.

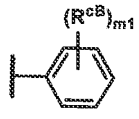
In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{1c}, R^{2a}, and R^{2b} are each H, and R^{3a} and R^{3b} together with the **Ring B** ring atom to which each is attached, form a fused saturated ring of 4-6 ring atoms;

- wherein from 1-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N(R^d), O, and S(O)$_{0-2}$; and
- wherein the fused saturated ring of 4-6 ring atoms is optionally substituted with from 1-2 substituents independently selected from the group consisting of oxo and R^c.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{1c} is H, and R^{2a} and R^{3a} taken together with the **Ring B** ring atoms to which each is attached, form a fused C_{3-6} (e.g., C_3 or C_4) cycloalkyl which is optionally substituted with from 1-2 R^c, and R^{2b} and R^{3b} are each H.

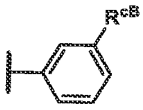
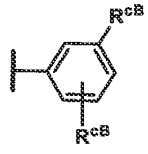
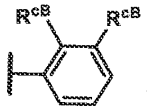
In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^{1c}, R^{2a}, R^{2b}, R^{3a}, and R^{3b} are each H.

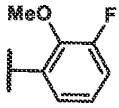
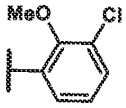
In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, R^4 is H.

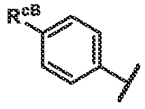
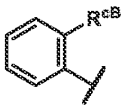
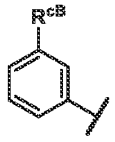
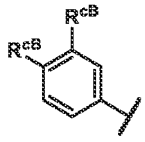
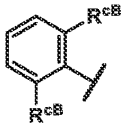
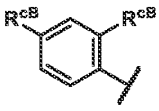
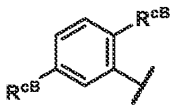
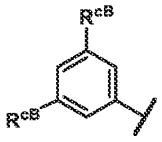
In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, **Ring A** is 

, wherein each R^{cB} is an independently selected

R^c; and **m1** is 0, 1, 2, 3, or 4. In certain of these embodiments, **m1** is 1, 2, or 3, such as 1 or 2.

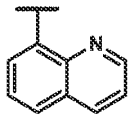
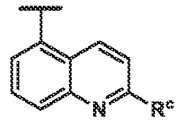
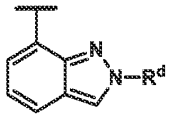
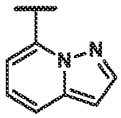
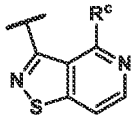
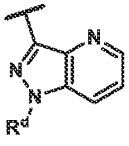
In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, **Ring A** is  or  (e.g., ), wherein each R^{cB} is an independently selected R^c.

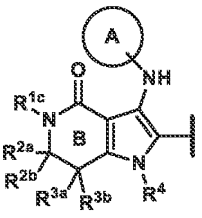
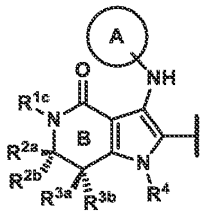
As non-limiting example of certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, **Ring A** can be  or  .

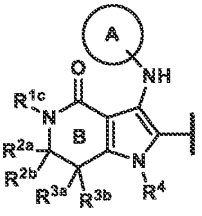
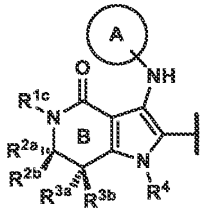
In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, **Ring A** is selected from the group consisting of:  ,  ,  ,  ,  ,  ,  , and  , wherein each R^{cB} is an independently selected R^c.

In certain embodiments, each R^{cB} is independently selected from the group consisting of: -halo, such as -Cl and -F; -CN; C_{1-4} alkoxy; C_{1-4} haloalkoxy; C_{1-3} alkyl; and C_{1-3} alkyl substituted with from 1-6 independently selected halo.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, **Ring A** is bicyclic heteroaryl including from 9-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally

substituted with from 1-4 substituents independently selected from the group consisting of R^c and oxo, such as wherein: **Ring A** is selected from the group consisting of:  ,  ,  ,  ,  , and  , each of which is further optionally substituted with R^c.

In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, the  moiety is  .

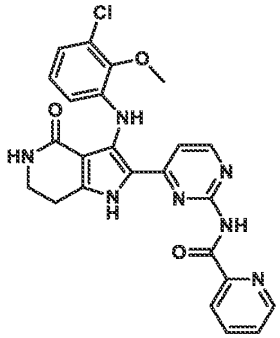
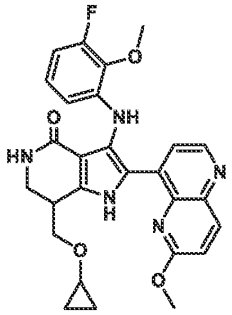
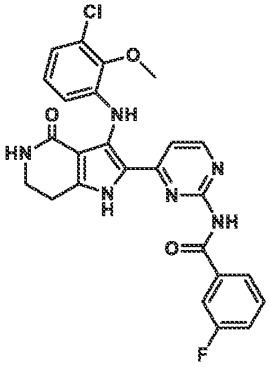
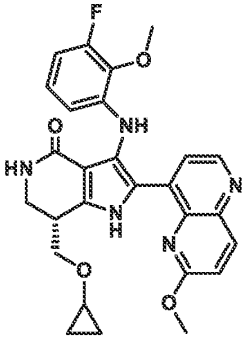
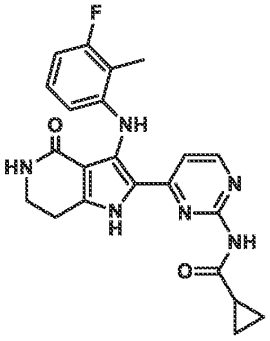
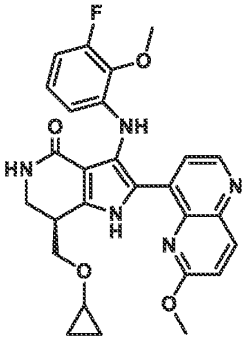
In certain embodiments of Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**, the  moiety is  .

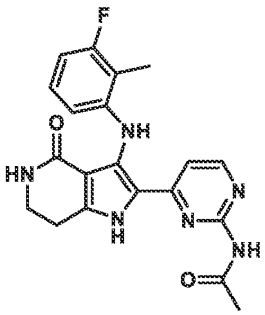
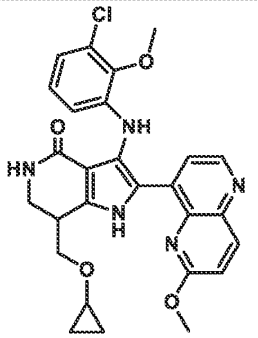
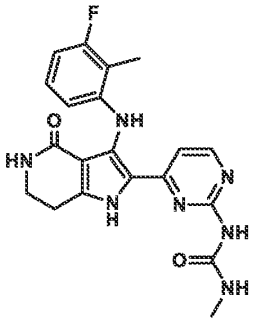
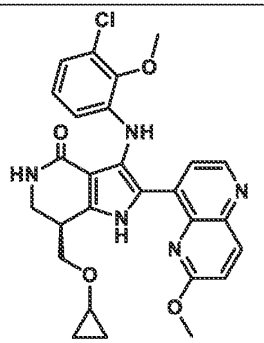
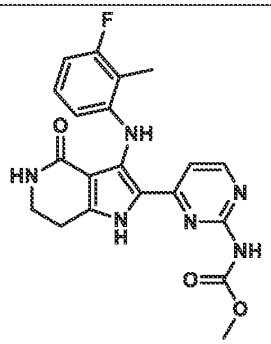
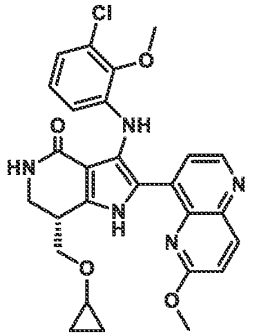
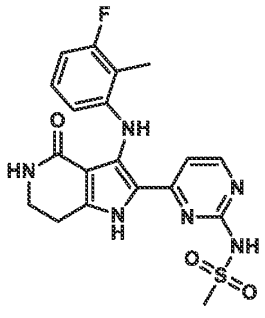
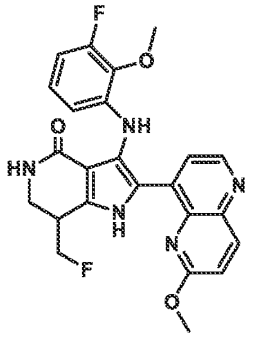
Non-Limiting Exemplary Compounds

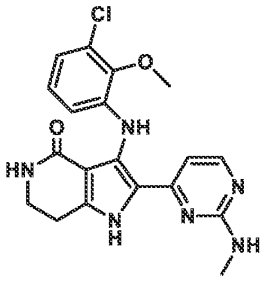
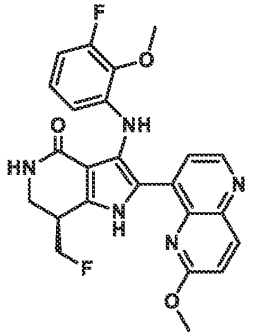
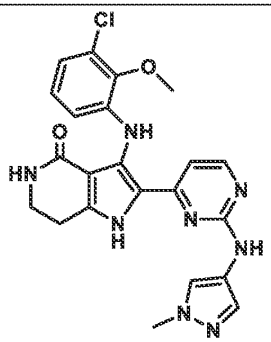
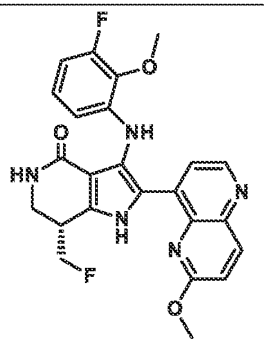
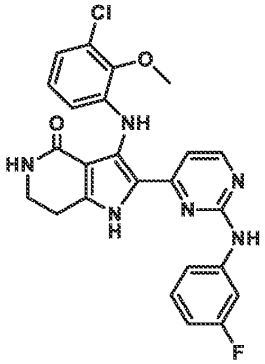
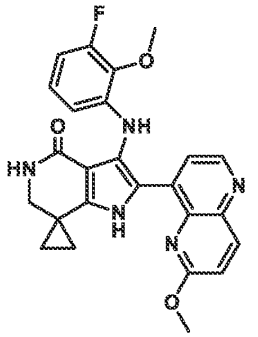
In certain embodiments, the compound is selected from the group consisting of the compounds delineated in **Table C1**, or a pharmaceutically acceptable salt thereof.

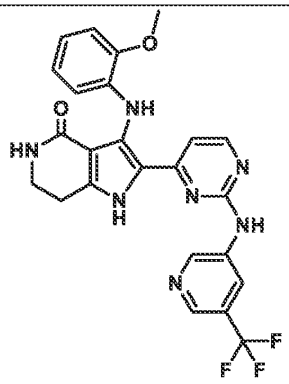
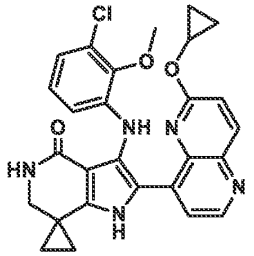
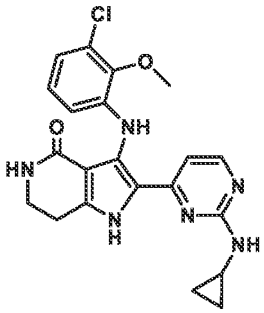
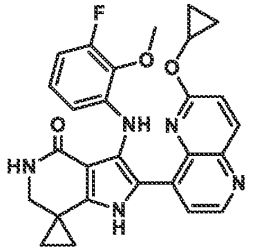
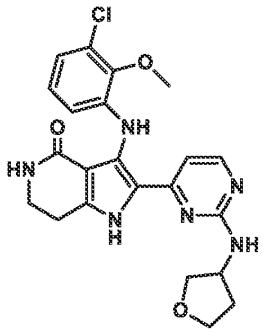
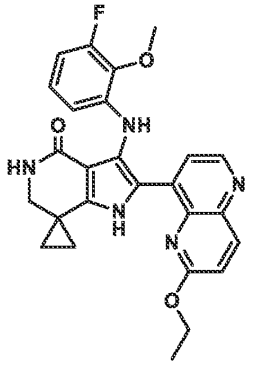
Table C1

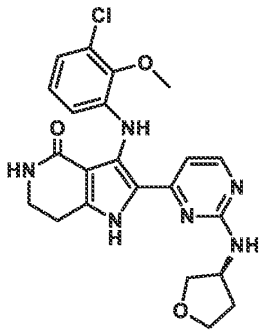
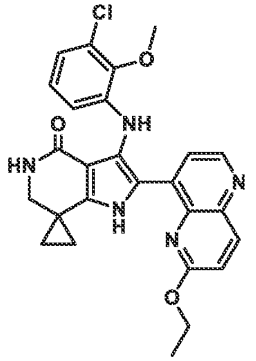
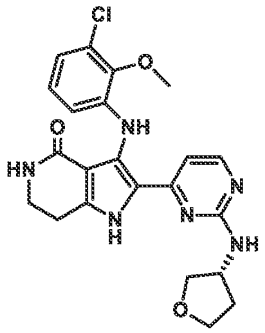
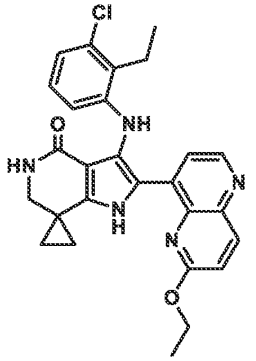
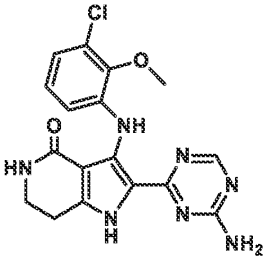
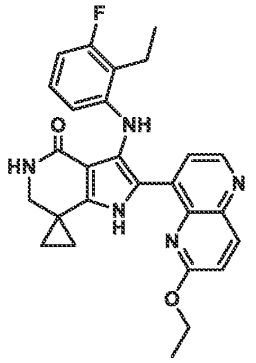
For certain compounds, the symbol * at a chiral center denotes that this chiral center has been resolved (i.e., is a single epimer) and the absolute stereochemistry at that center has not been determined.

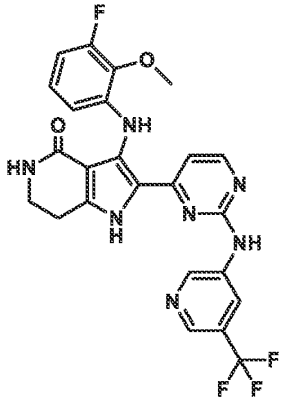
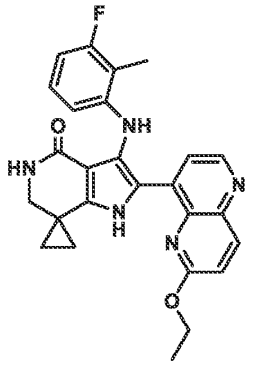
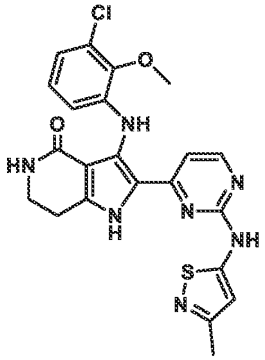
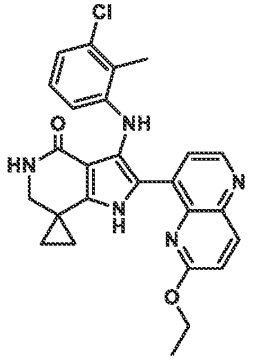
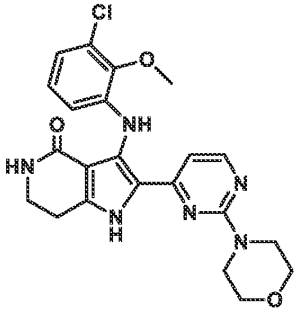
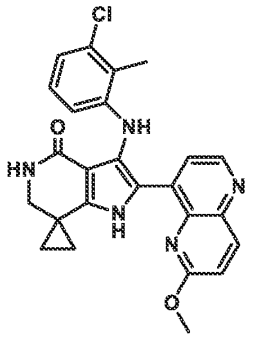
No.	Structure	No.	Structure
101		319	
102		319a	
103		319b	

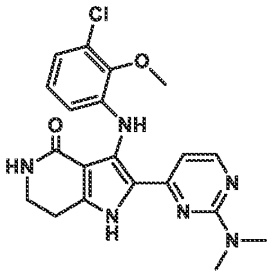
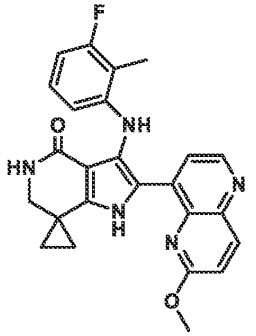
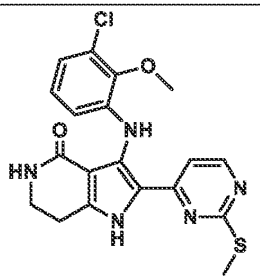
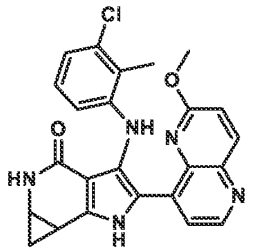
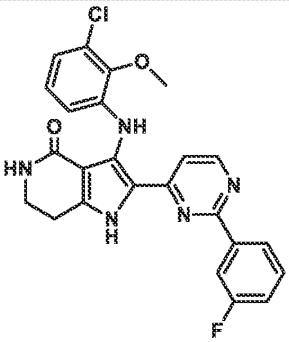
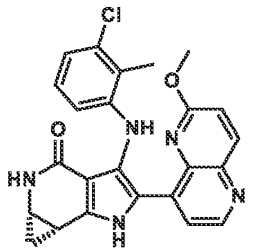
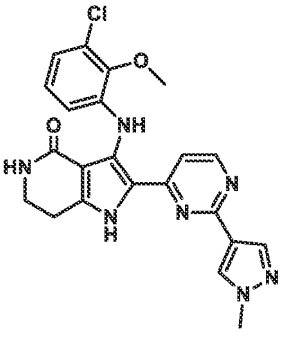
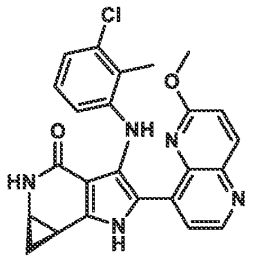
No.	Structure	No.	Structure
104		320	
105		320a	
106		320b	
107		321	

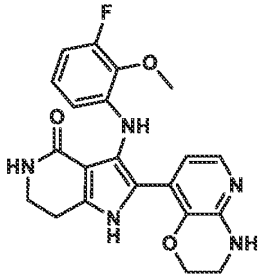
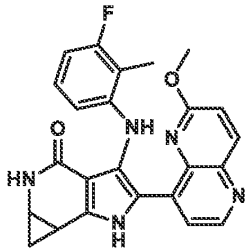
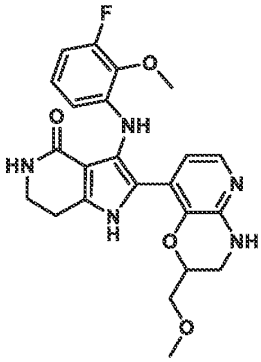
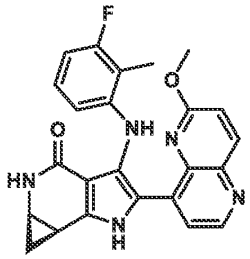
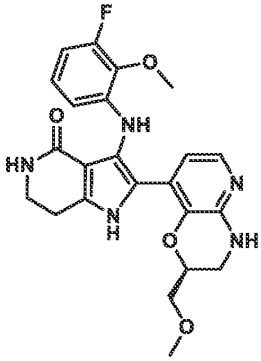
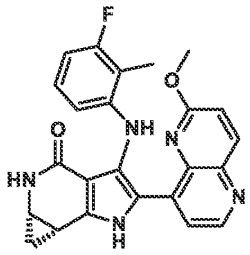
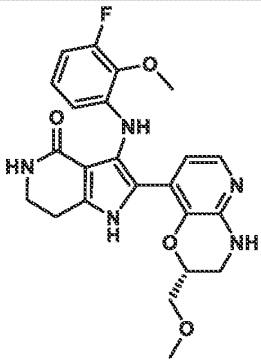
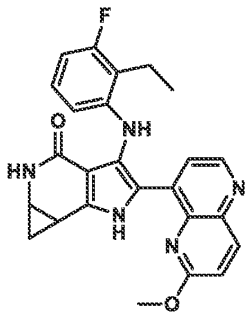
No.	Structure	No.	Structure
108		321a	
109		321b	
110		322	

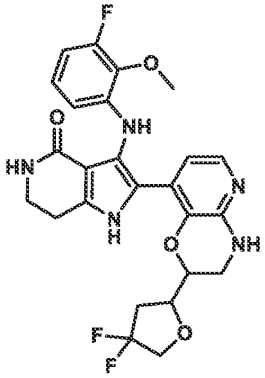
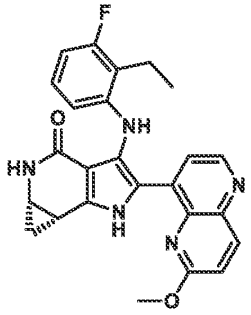
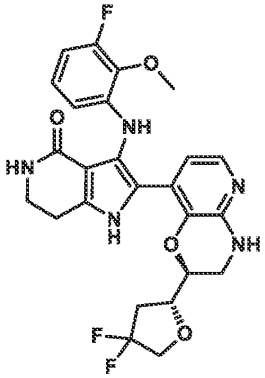
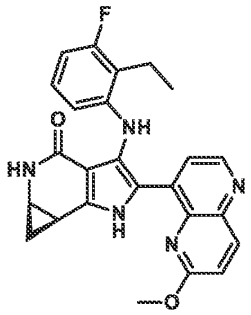
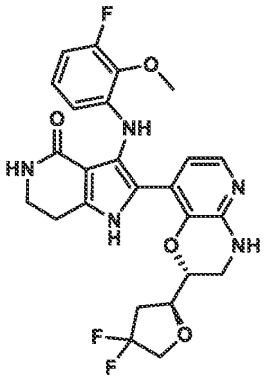
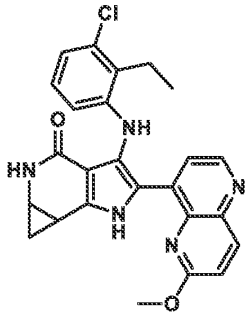
No.	Structure	No.	Structure
111		323	
112		324	
113		325	

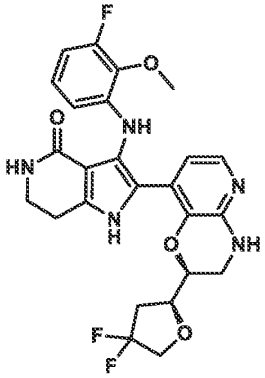
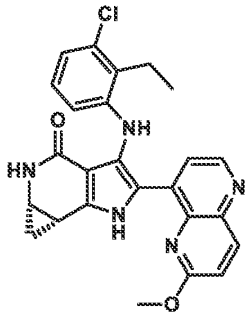
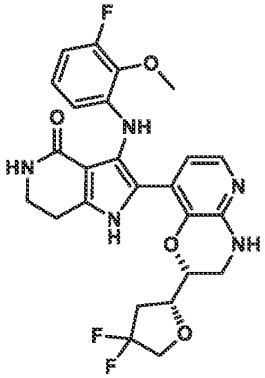
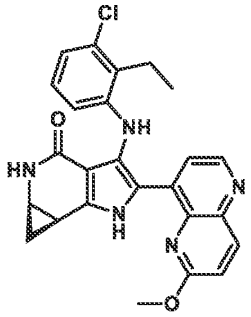
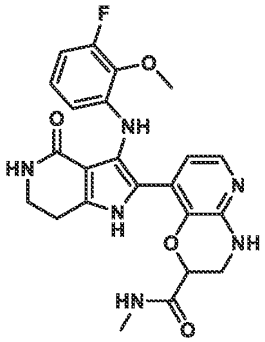
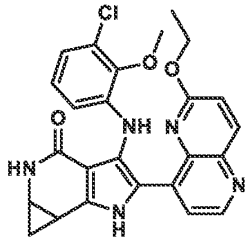
No.	Structure	No.	Structure
113a		326	
113b		327	
114		328	

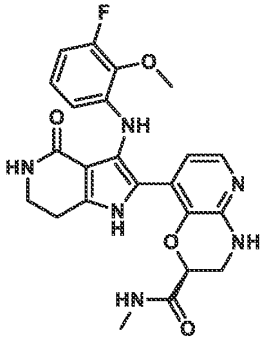
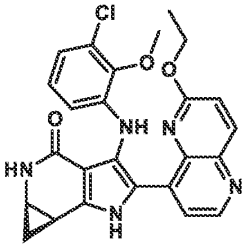
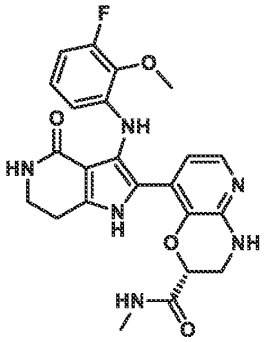
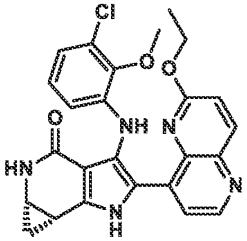
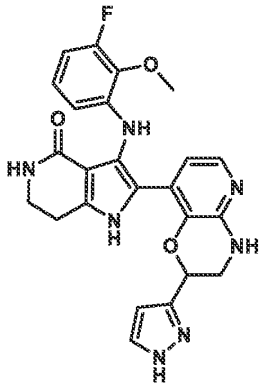
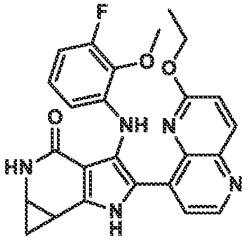
No.	Structure	No.	Structure
115		329	
116		330	
117		331	

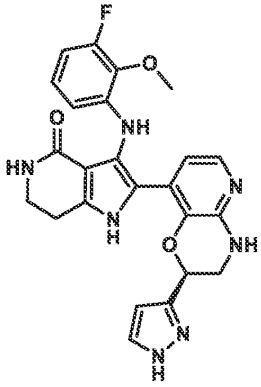
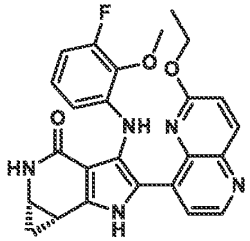
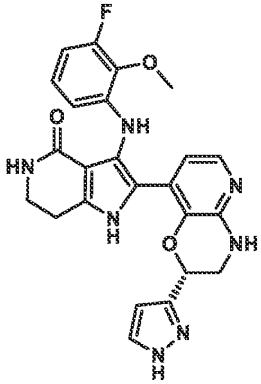
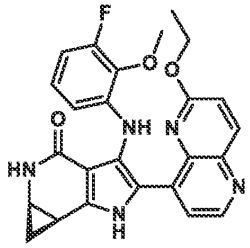
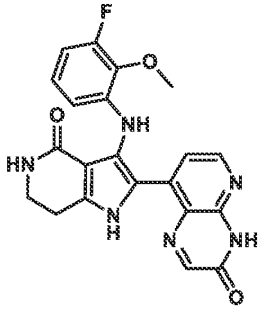
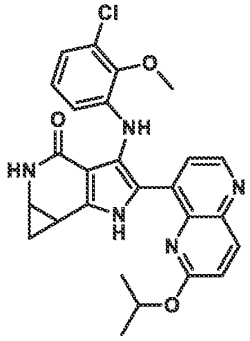
No.	Structure	No.	Structure
118		332	
119		333	
120		333a	
121		333b	

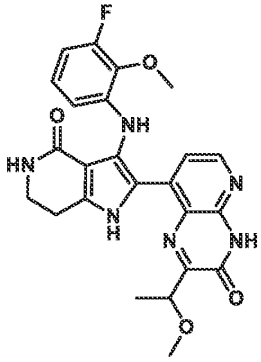
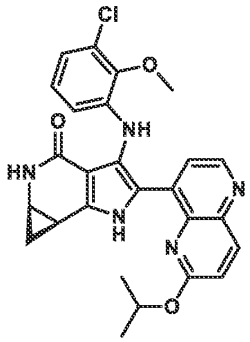
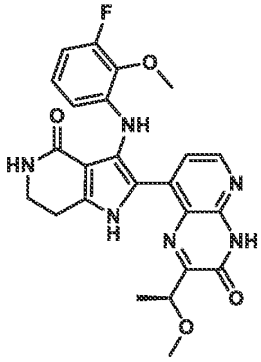
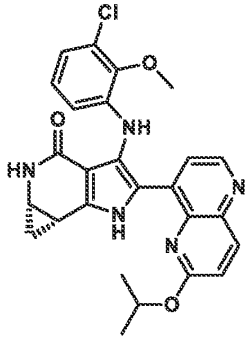
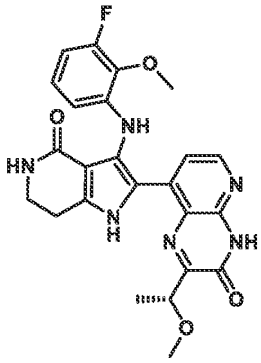
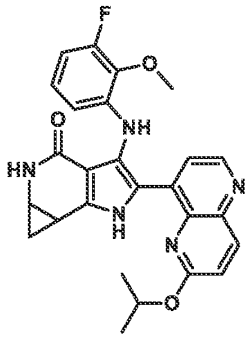
No.	Structure	No.	Structure
122		334	
123		334a	
123a		334b	
123b		335	

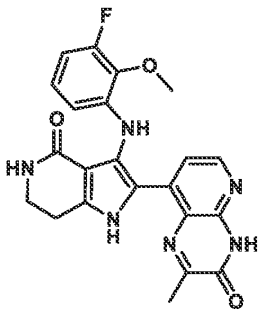
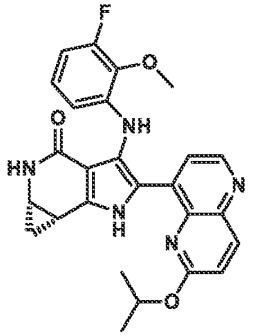
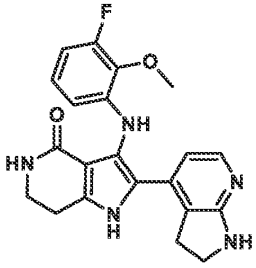
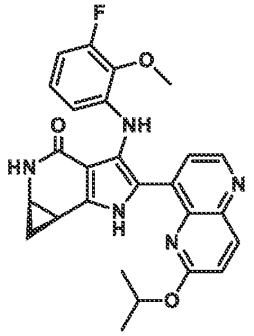
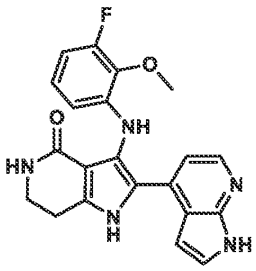
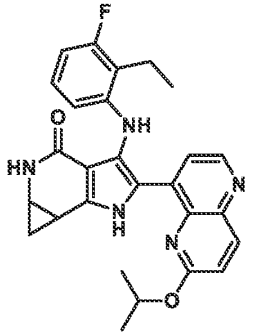
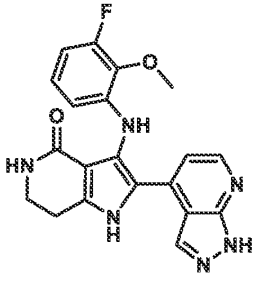
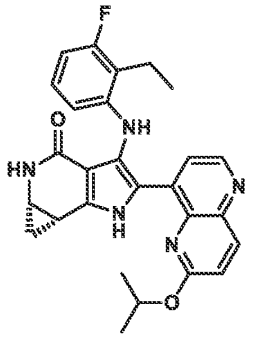
No.	Structure	No.	Structure
124		335a	
124a		335b	
124b		336	

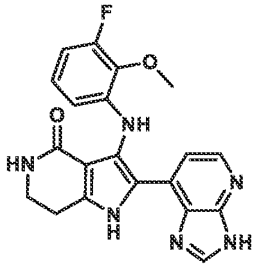
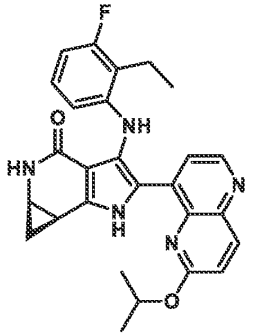
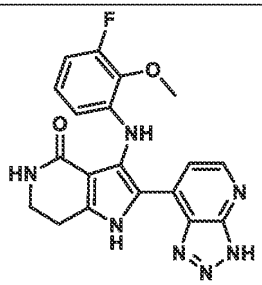
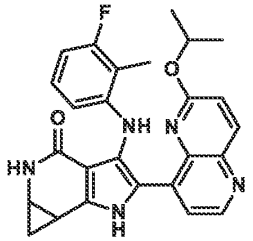
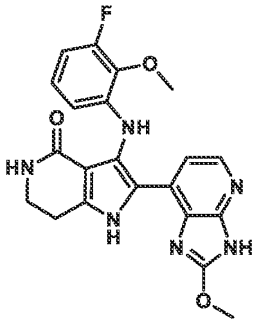
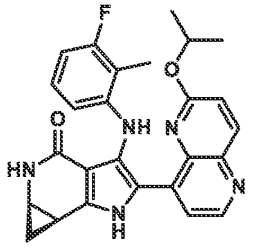
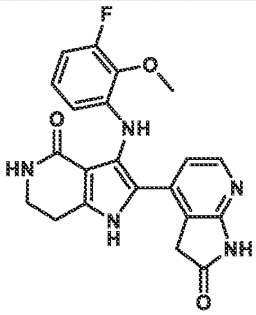
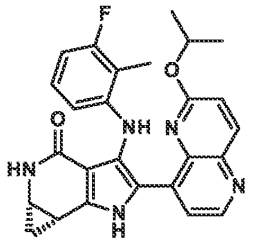
No.	Structure	No.	Structure
124c		336a	
124d		336b	
125		337	

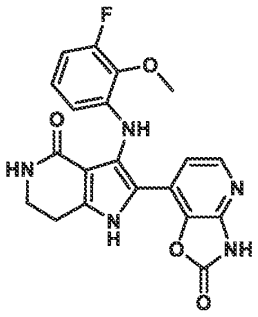
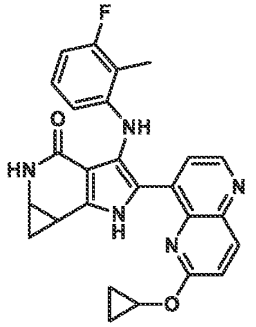
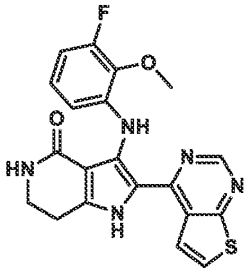
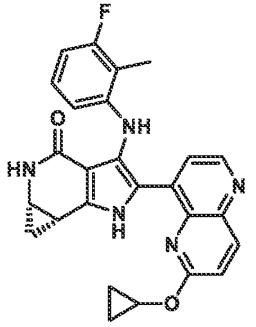
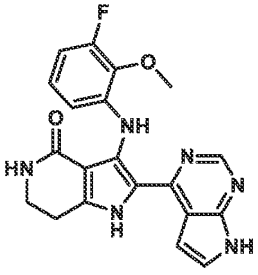
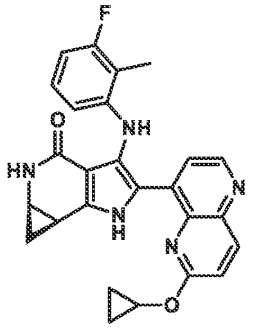
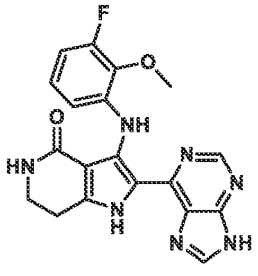
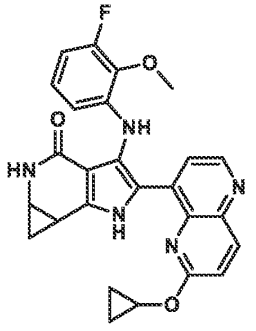
No.	Structure	No.	Structure
125a		337a	
125b		337b	
126		338	

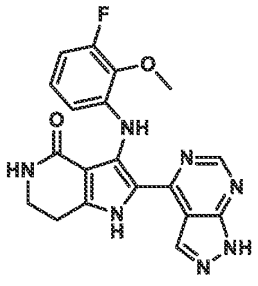
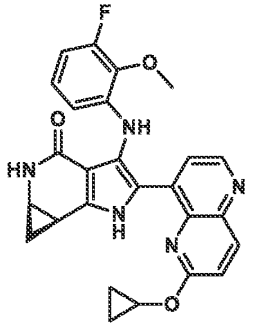
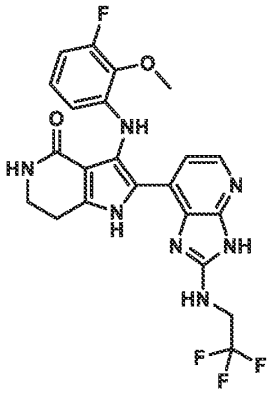
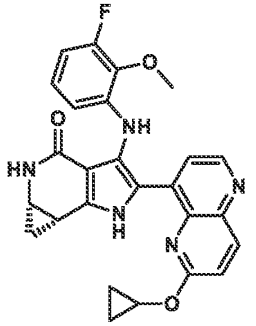
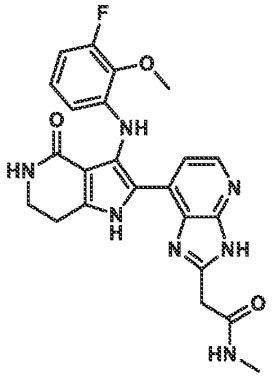
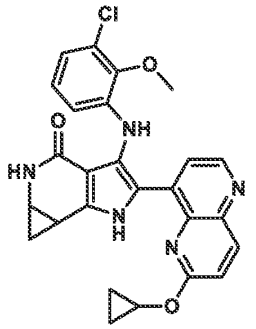
No.	Structure	No.	Structure
126a		338a	
126b		338b	
127		339	

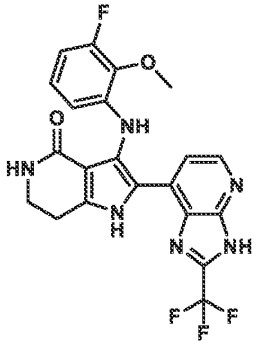
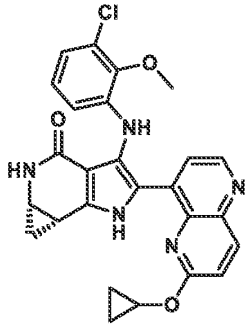
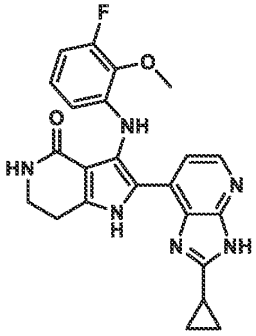
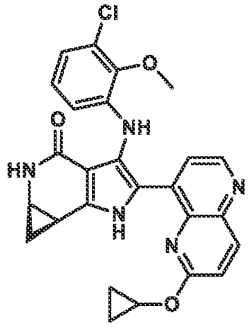
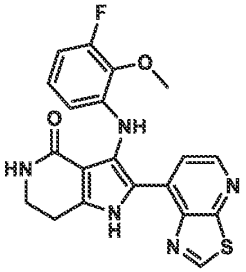
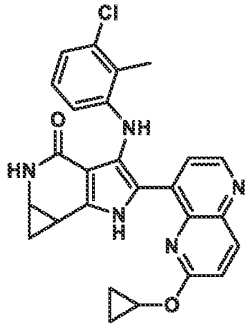
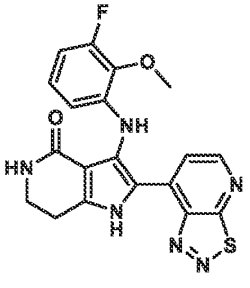
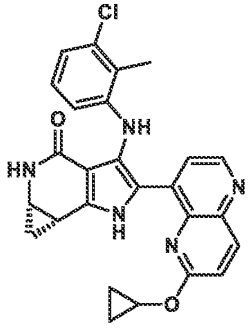
No.	Structure	No.	Structure
128		339a	
128a		339b	
128b		340	

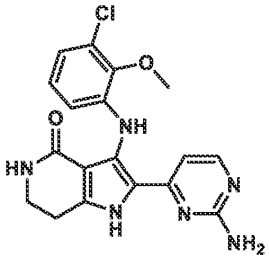
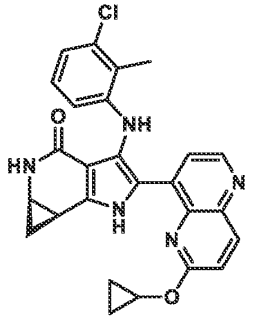
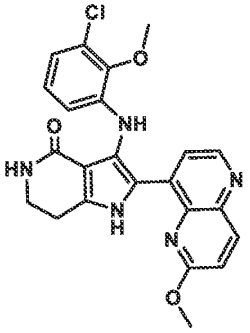
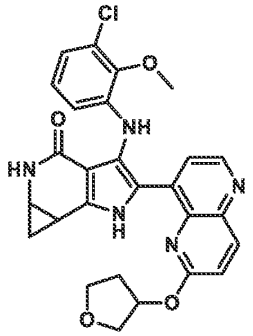
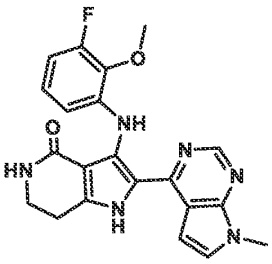
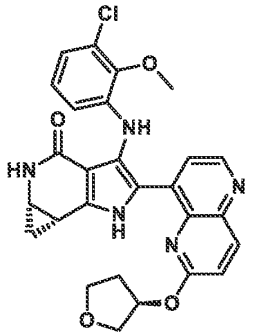
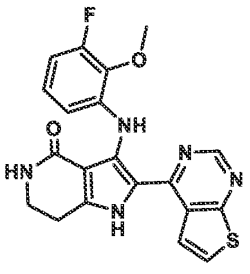
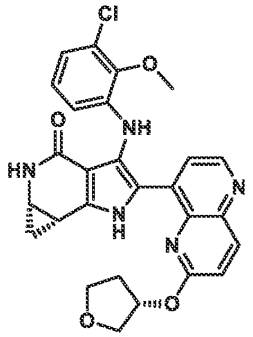
No.	Structure	No.	Structure
129		340a	
130		340b	
131		341	
132		341a	

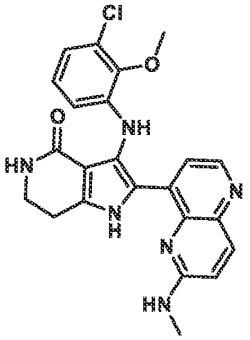
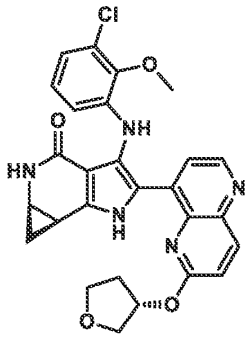
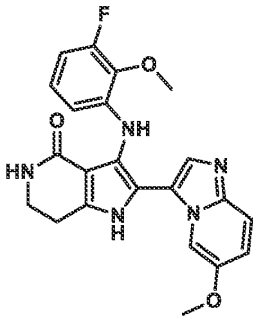
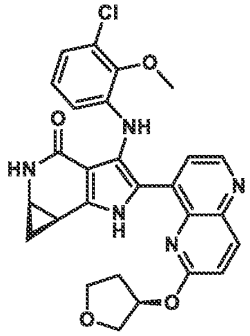
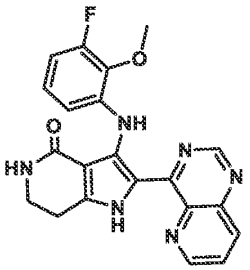
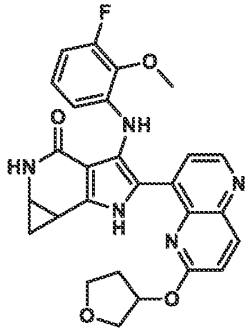
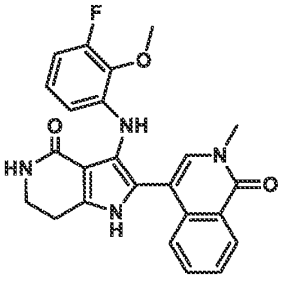
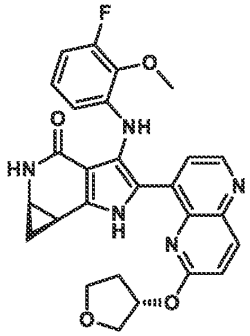
No.	Structure	No.	Structure
133		341b	
134		342	
135		342a	
136		342b	

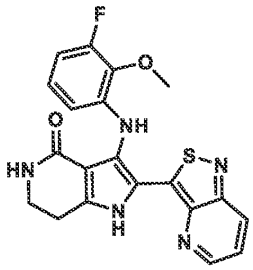
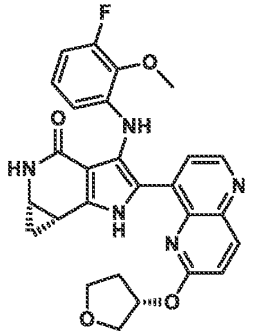
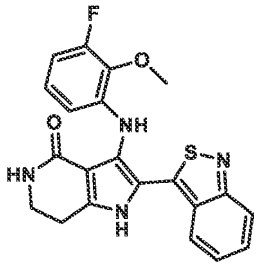
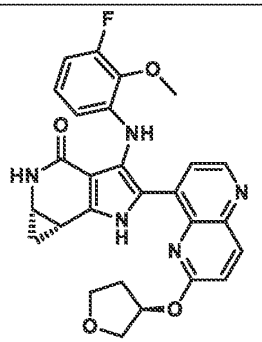
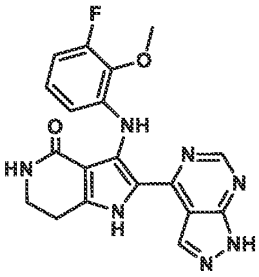
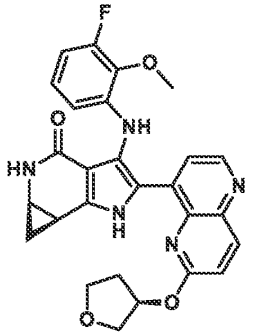
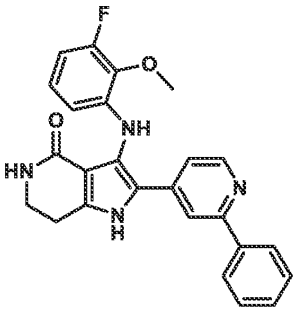
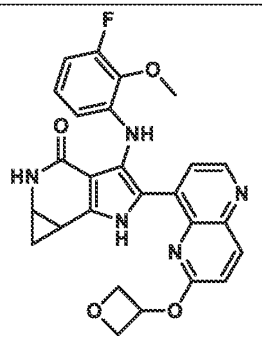
No.	Structure	No.	Structure
137		343	
138		343a	
139		343b	
140		344	

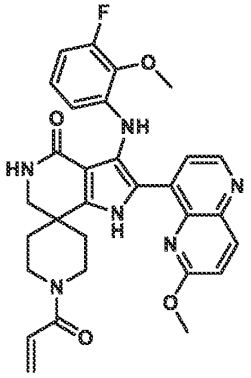
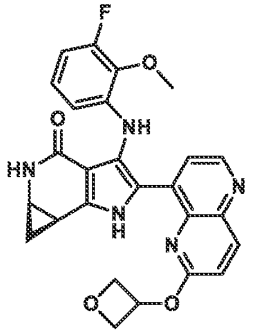
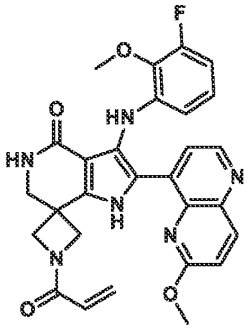
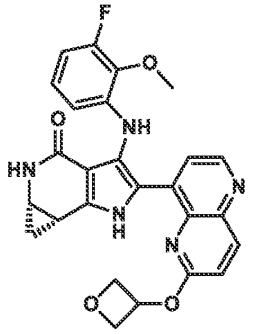
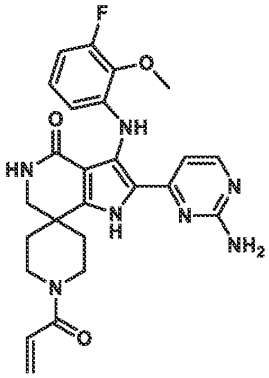
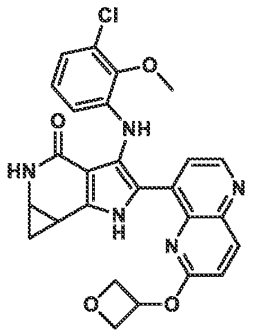
No.	Structure	No.	Structure
141		344a	
142		344b	
143		345	

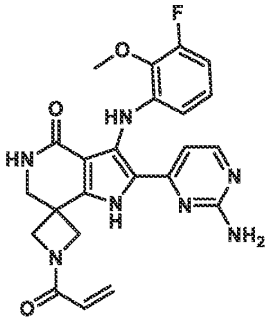
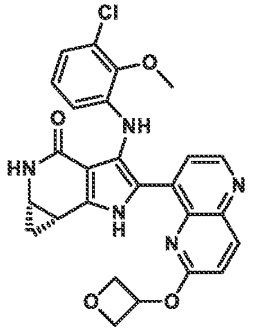
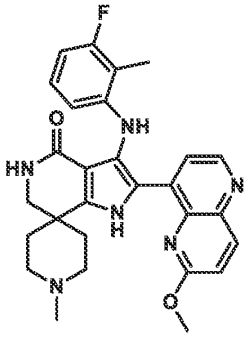
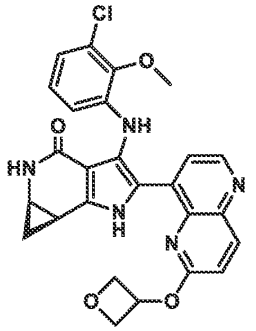
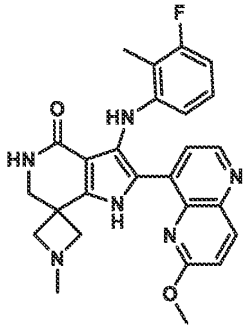
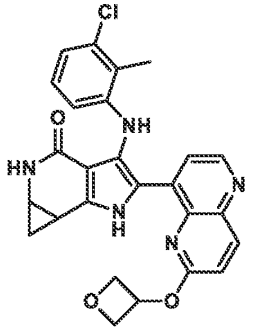
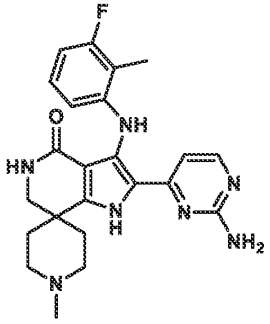
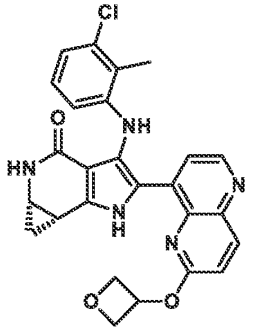
No.	Structure	No.	Structure
144		345a	
145		345b	
146		346	
147		346a	

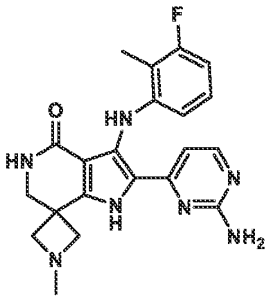
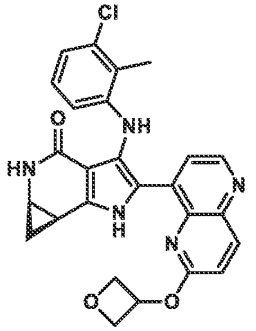
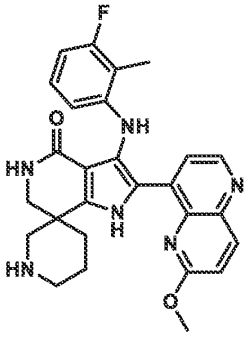
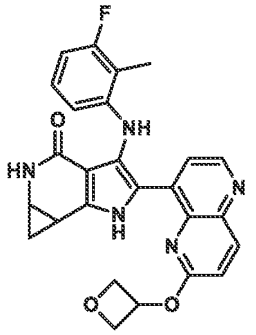
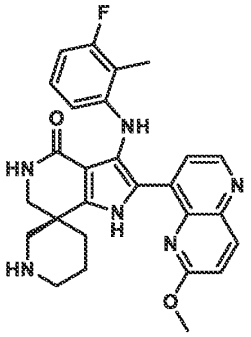
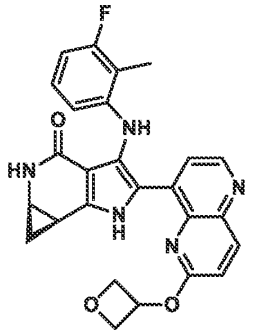
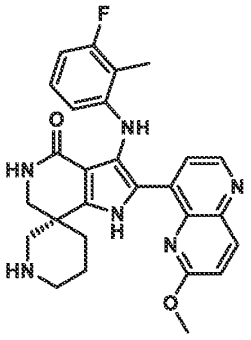
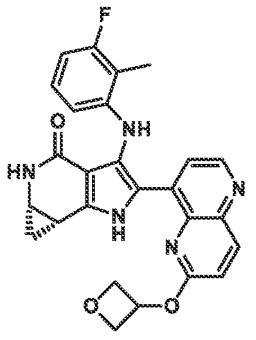
No.	Structure	No.	Structure
148		346b	
149		347	
150		347a	
151		347b	

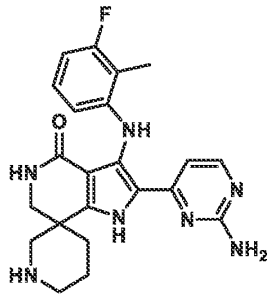
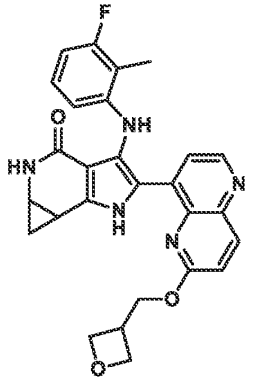
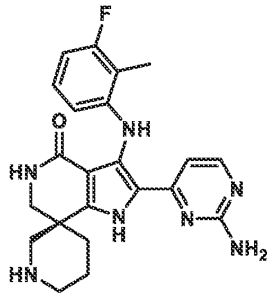
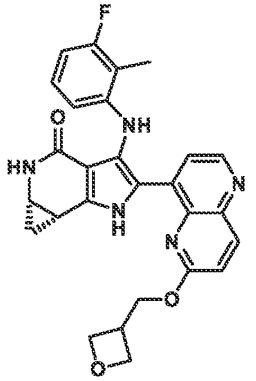
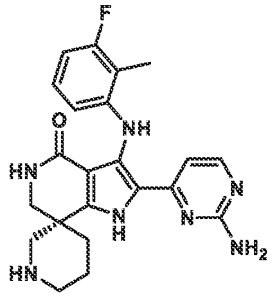
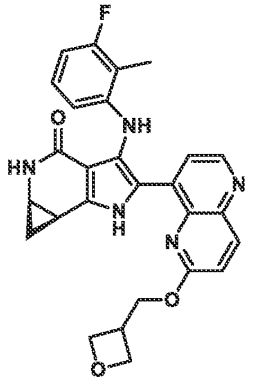
No.	Structure	No.	Structure
152		347c	
153		347d	
154		348	
155		348a	

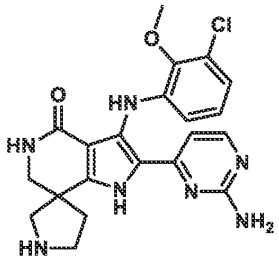
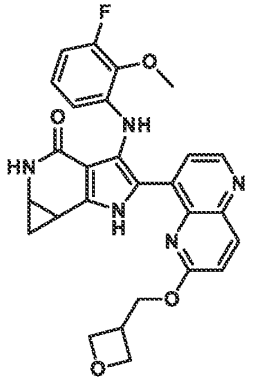
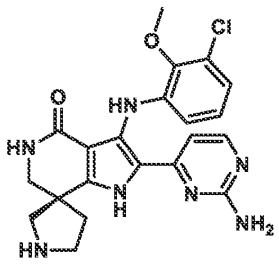
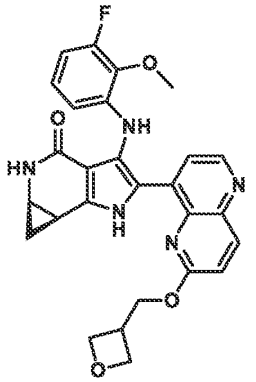
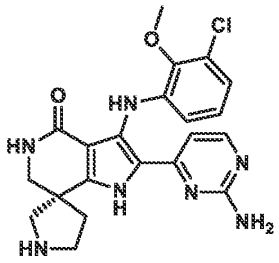
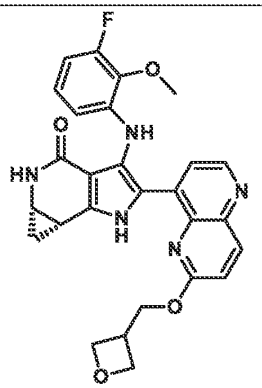
No.	Structure	No.	Structure
156		348b	
157		348c	
158		348d	
159		349	

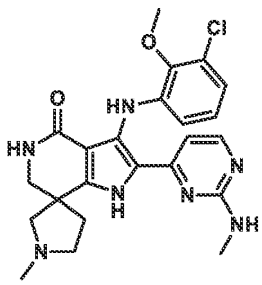
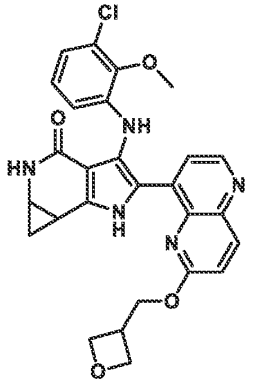
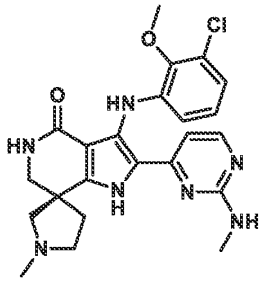
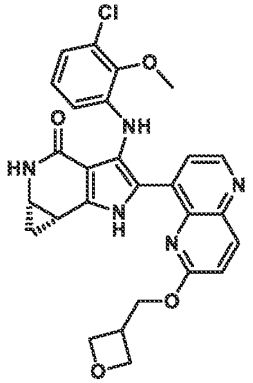
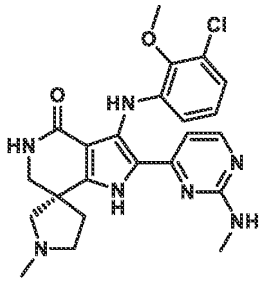
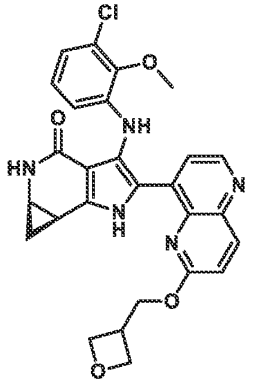
No.	Structure	No.	Structure
160		349a	
161		349b	
162		350	

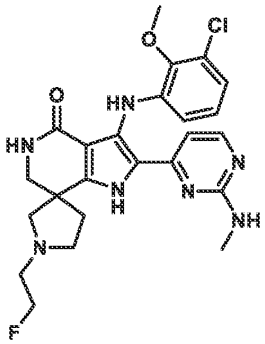
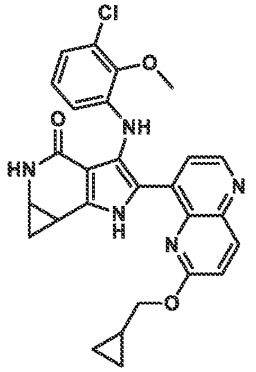
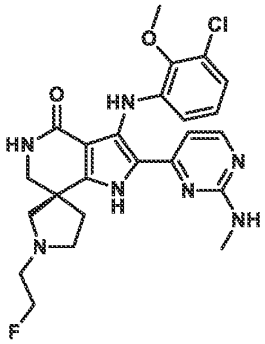
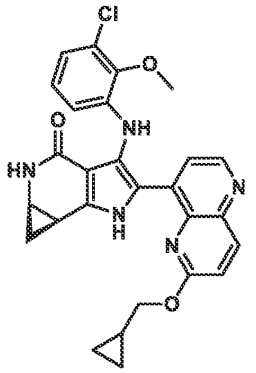
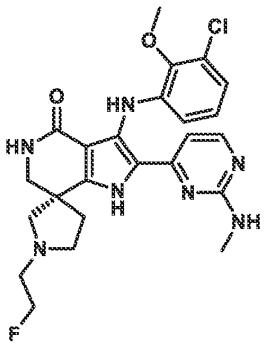
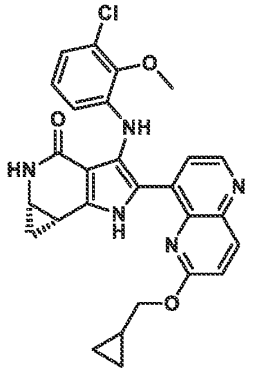
No.	Structure	No.	Structure
163		350a	
164		350b	
165		351	
166		351a	

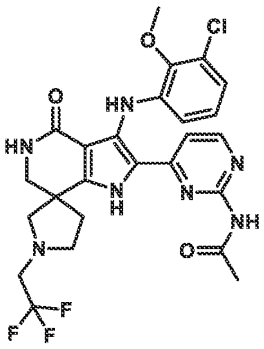
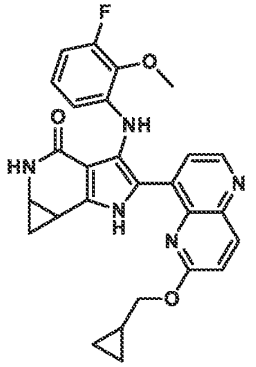
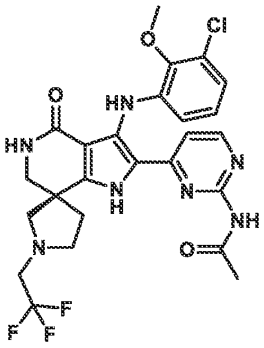
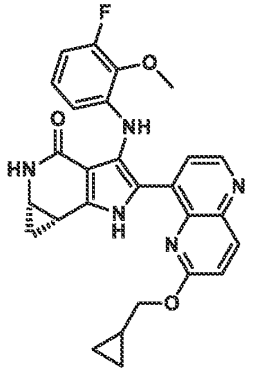
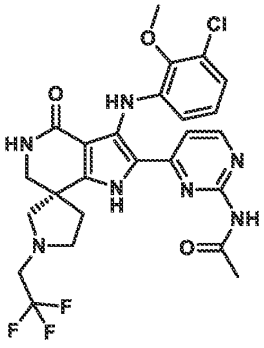
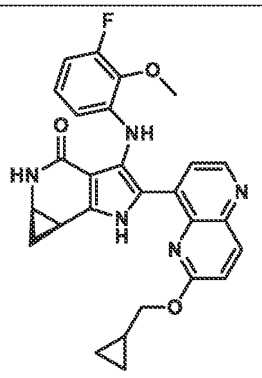
No.	Structure	No.	Structure
167		351b	
168		352	
168a		352a	
168b		352b	

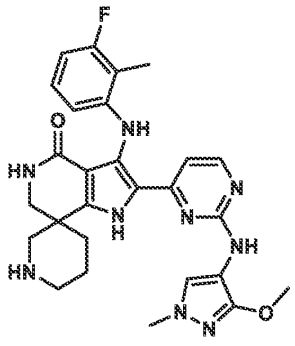
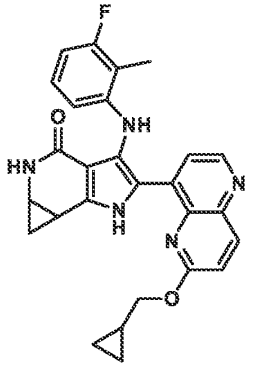
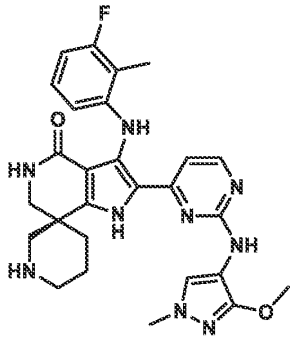
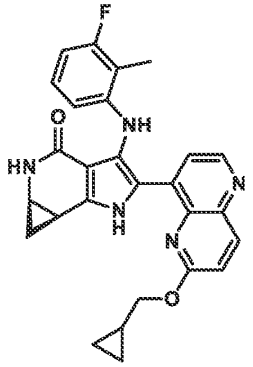
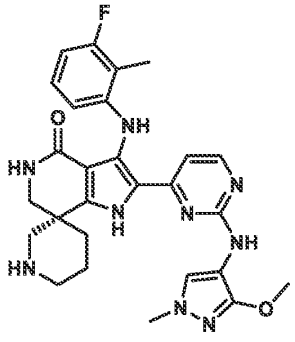
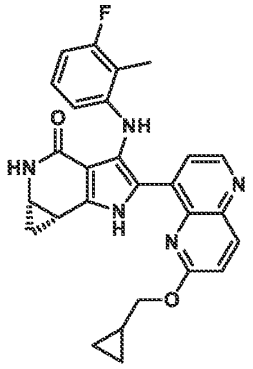
No.	Structure	No.	Structure
169		353	
169a		353a	
169b		353b	

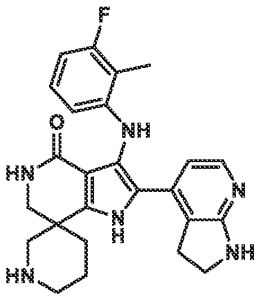
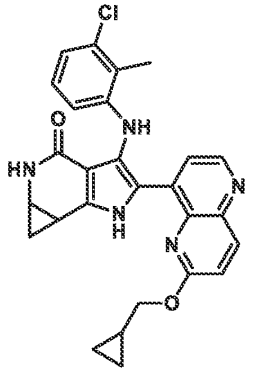
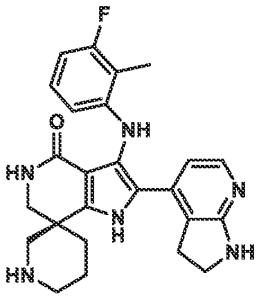
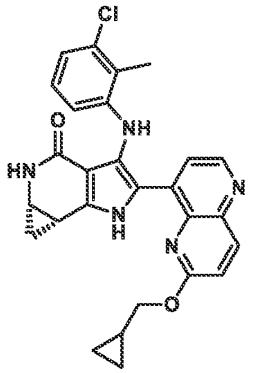
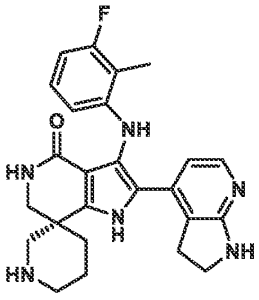
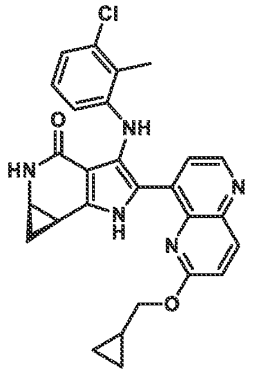
No.	Structure	No.	Structure
170		354	
170a		354a	
170b		354b	

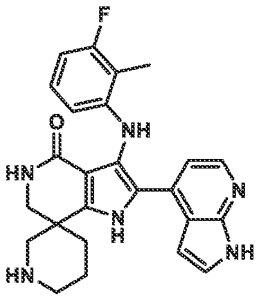
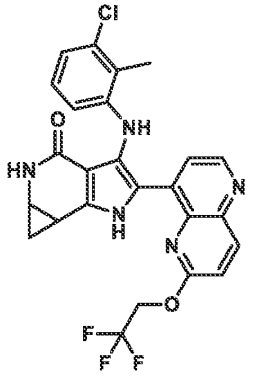
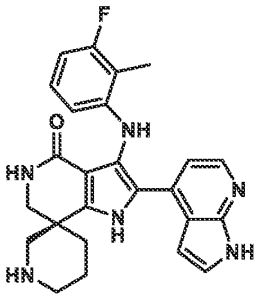
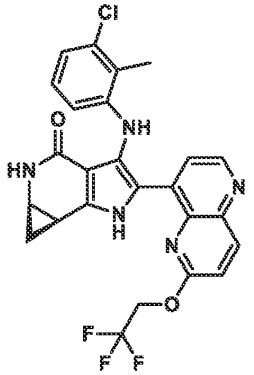
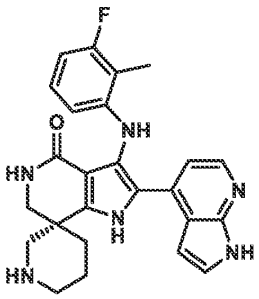
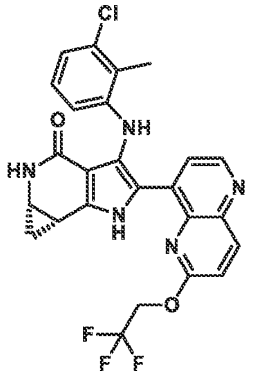
No.	Structure	No.	Structure
171		355	
171a		355a	
171b		355b	

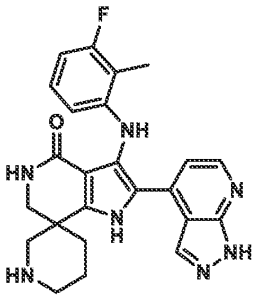
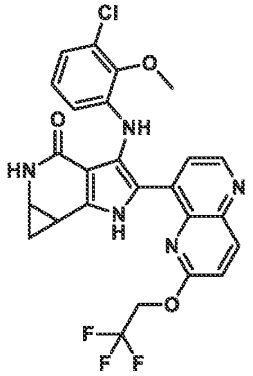
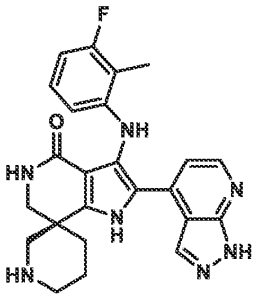
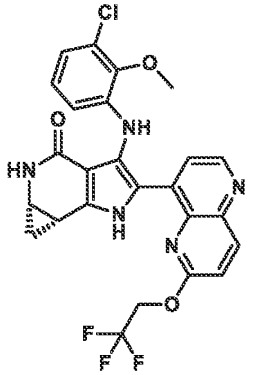
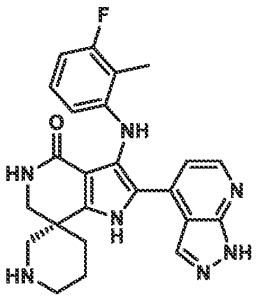
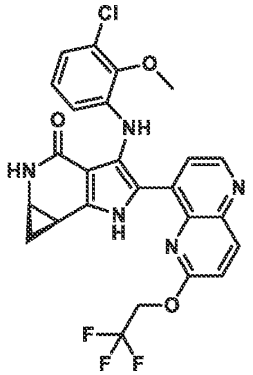
No.	Structure	No.	Structure
172		356	
172a		356a	
172b		356b	

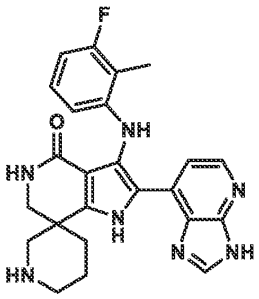
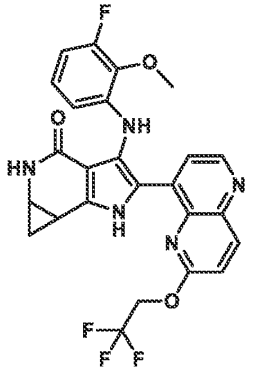
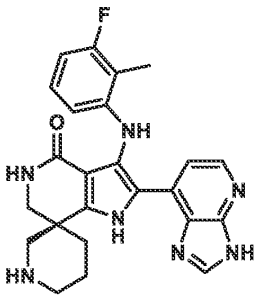
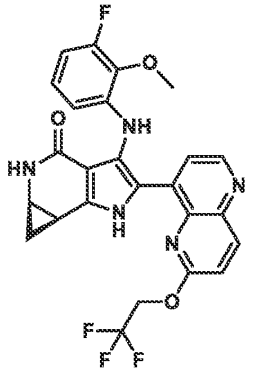
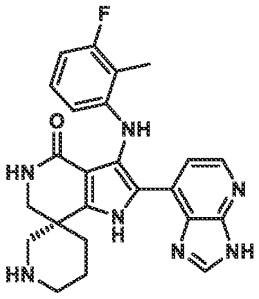
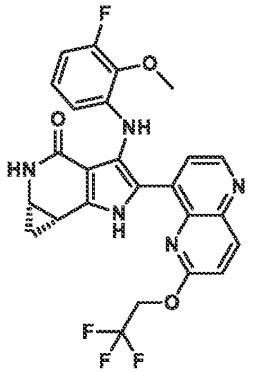
No.	Structure	No.	Structure
173		357	
173a		357a	
173b		357b	

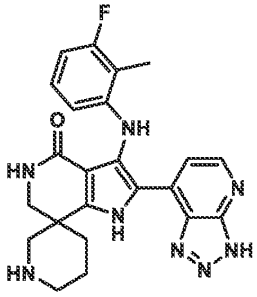
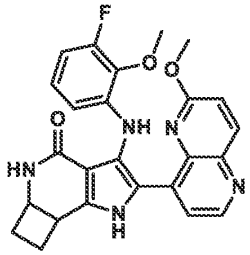
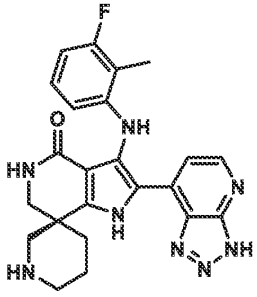
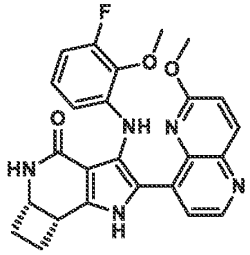
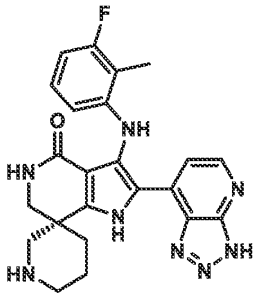
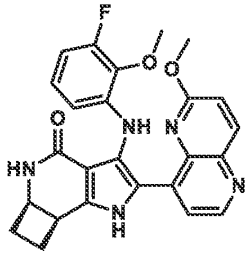
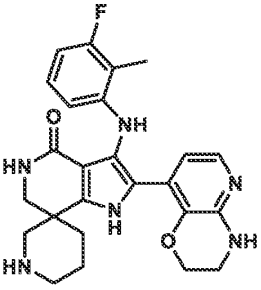
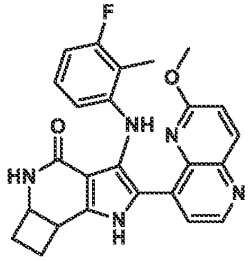
No.	Structure	No.	Structure
174		358	
174a		358a	
174b		358b	

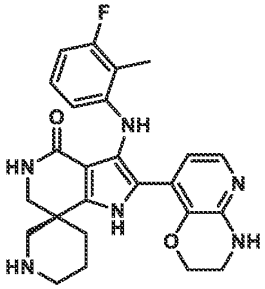
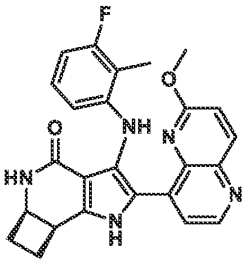
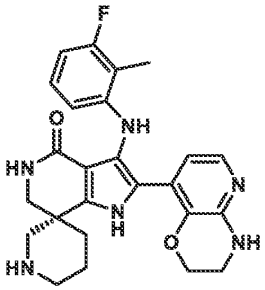
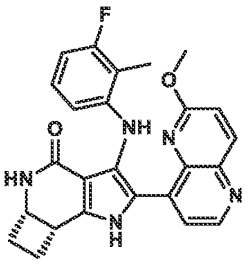
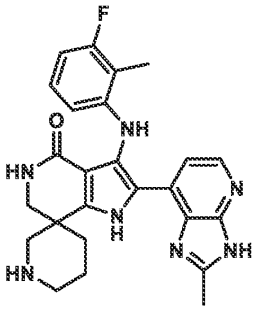
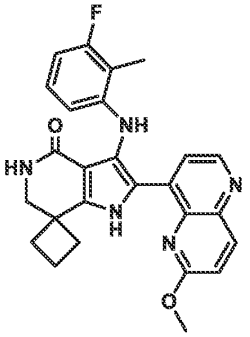
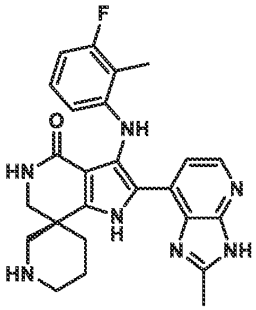
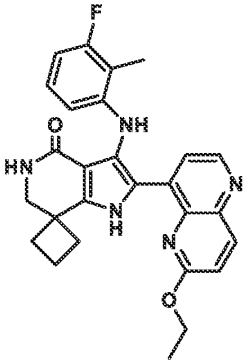
No.	Structure	No.	Structure
175		359	
175a		359a	
175b		359b	

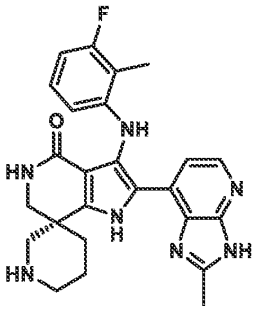
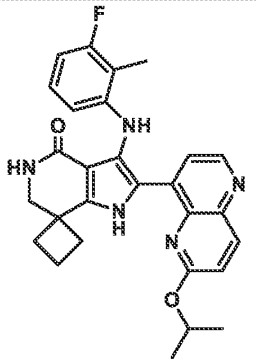
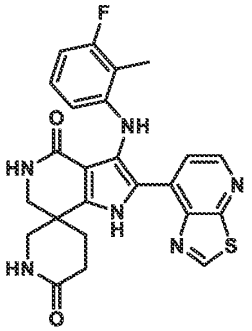
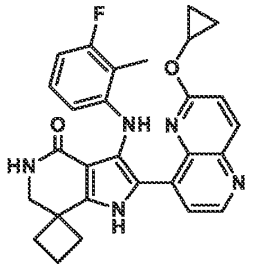
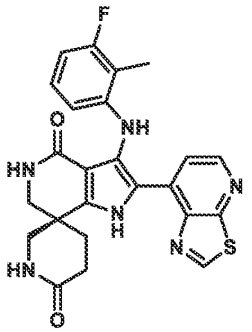
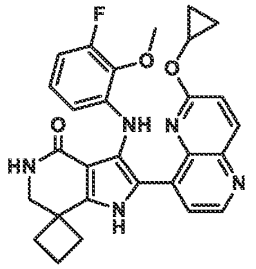
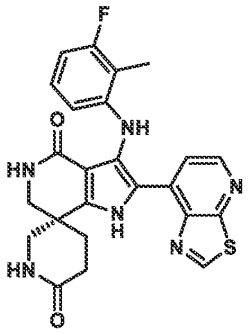
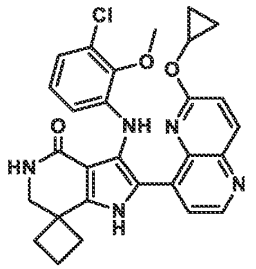
No.	Structure	No.	Structure
176		360	
176a		360a	
176b		360b	

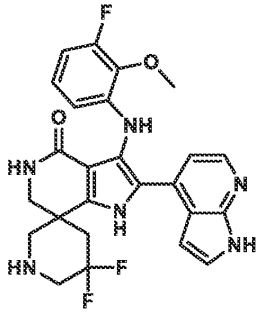
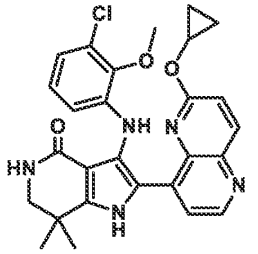
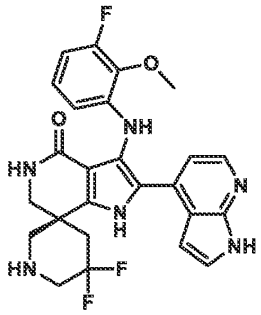
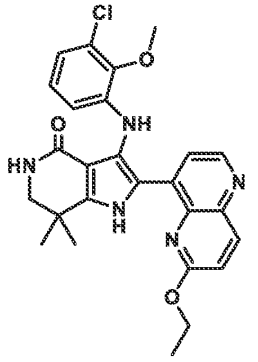
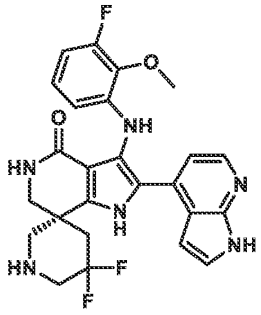
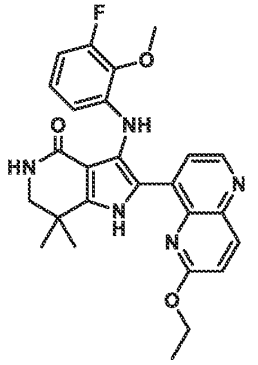
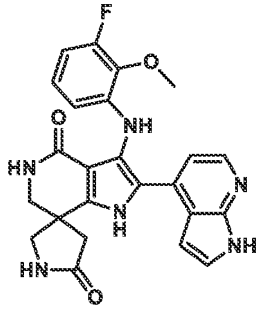
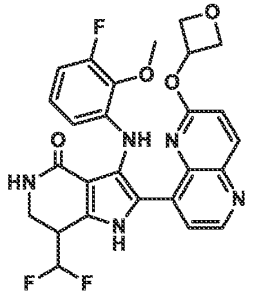
No.	Structure	No.	Structure
177		361	
177a		361a	
177b		361b	

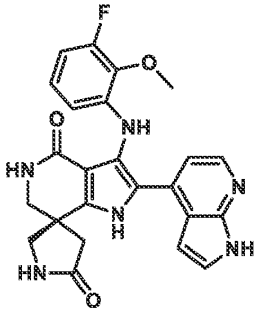
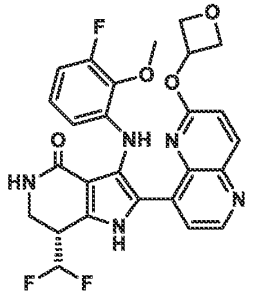
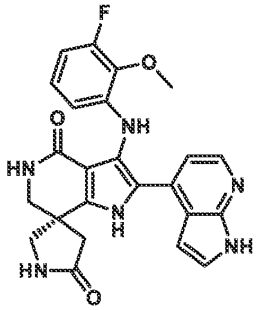
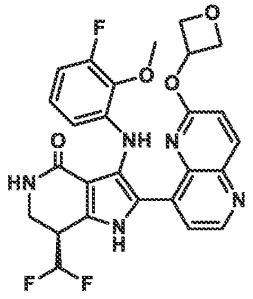
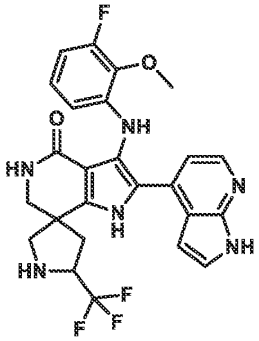
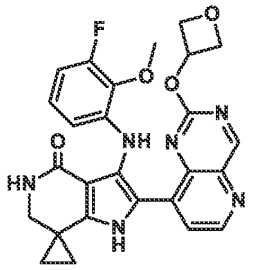
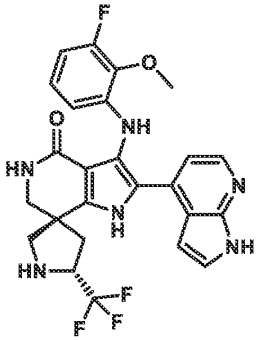
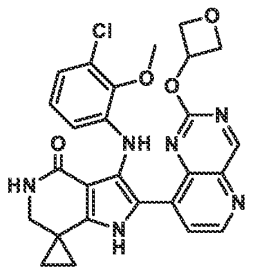
No.	Structure	No.	Structure
178		362	
178a		362a	
178b		362b	

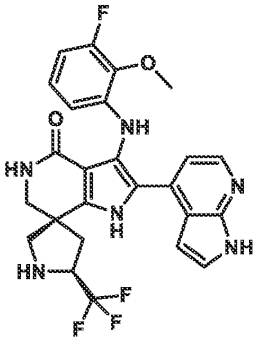
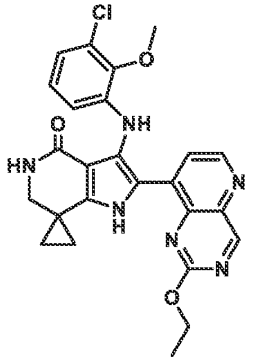
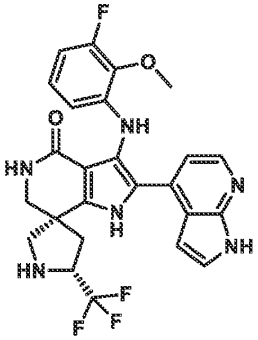
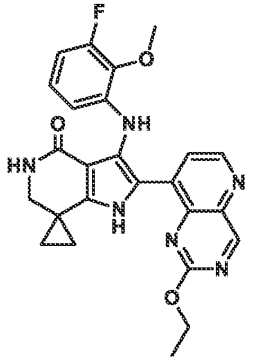
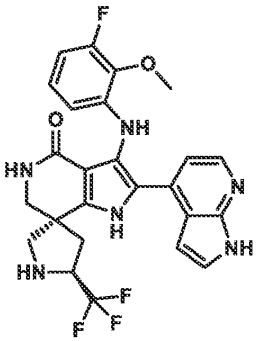
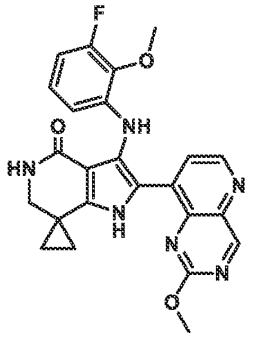
No.	Structure	No.	Structure
179		363	
179a		363a	
179b		363b	
180		364	

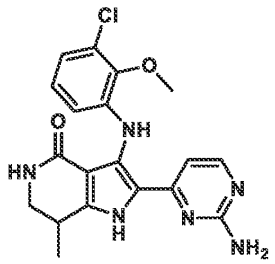
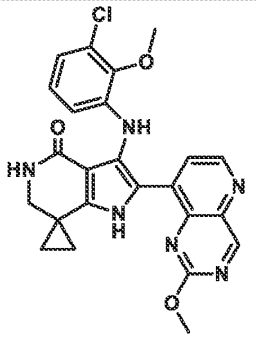
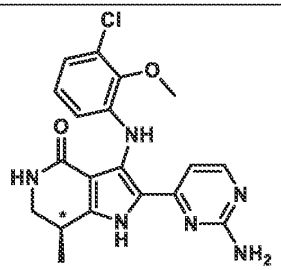
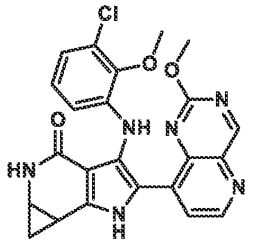
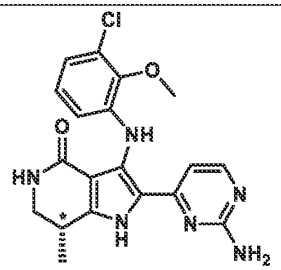
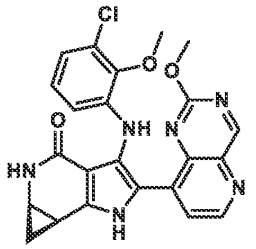
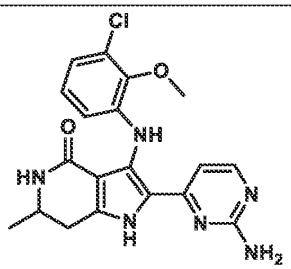
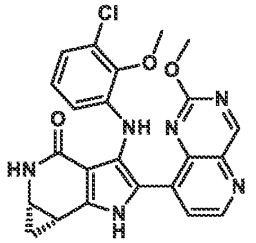
No.	Structure	No.	Structure
180a		364a	
180b		364b	
181		365	
181a		366	

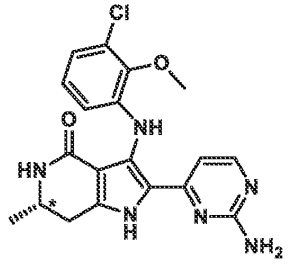
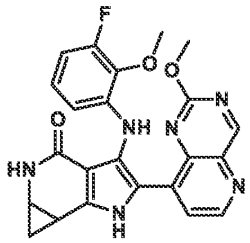
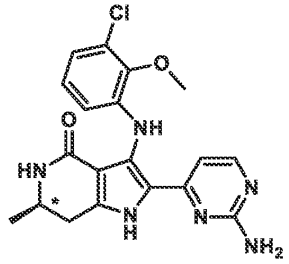
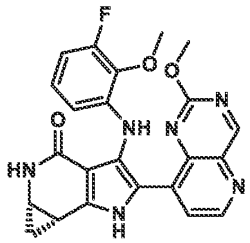
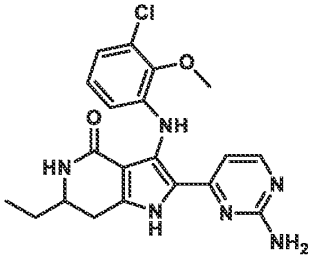
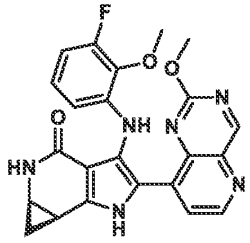
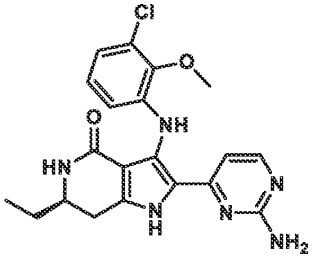
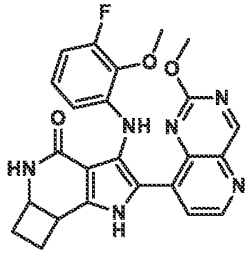
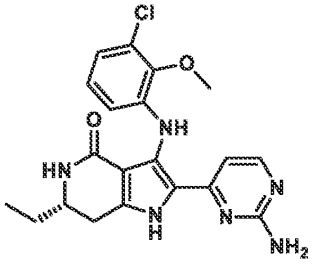
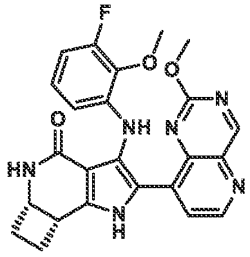
No.	Structure	No.	Structure
181b		367	
182		368	
182a		369	
182b		370	

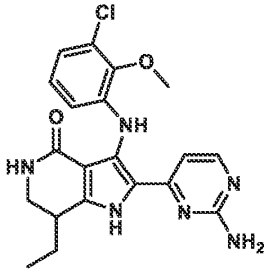
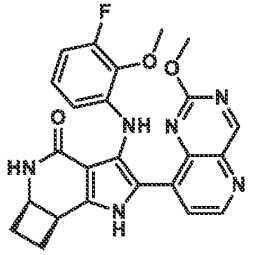
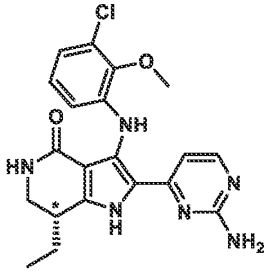
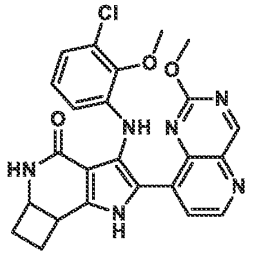
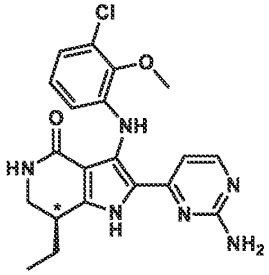
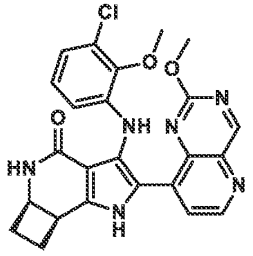
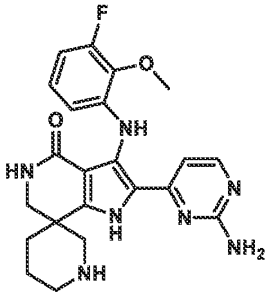
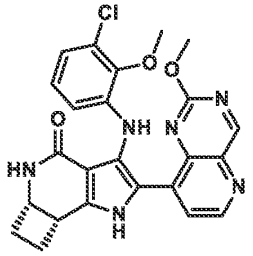
No.	Structure	No.	Structure
183		371	
183a		372	
183b		373	
184		374	

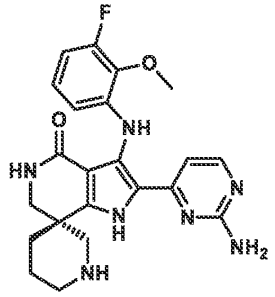
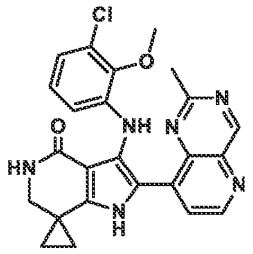
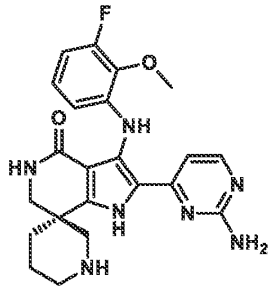
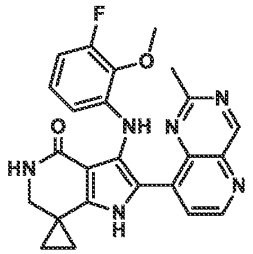
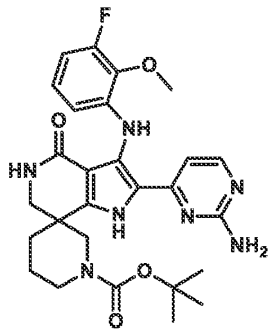
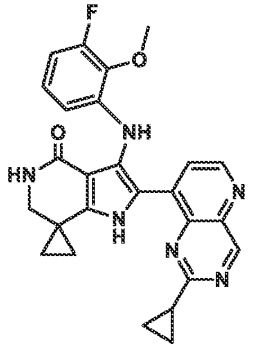
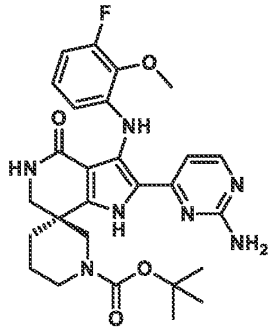
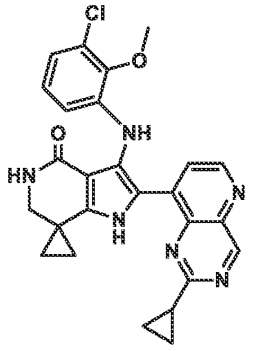
No.	Structure	No.	Structure
184a		374a	
184b		374b	
185		375	
185a		376	

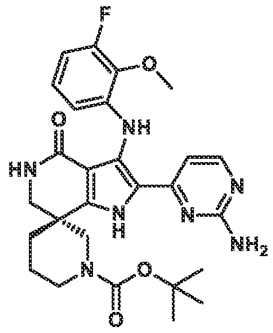
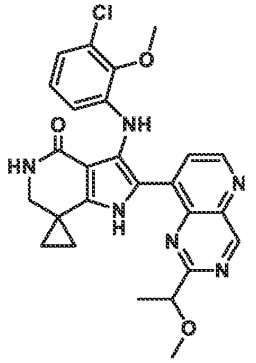
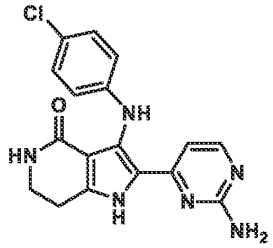
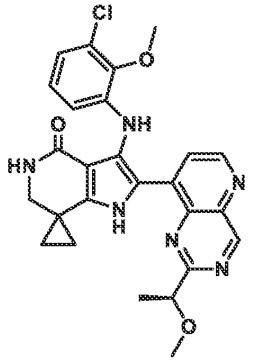
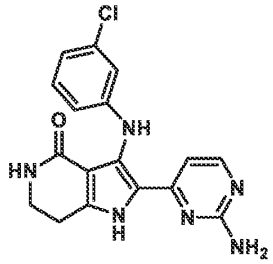
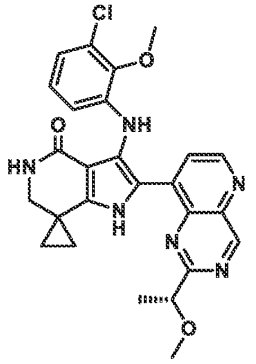
No.	Structure	No.	Structure
185b		377	
185c		378	
185d		379	

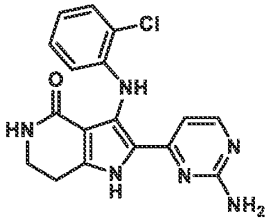
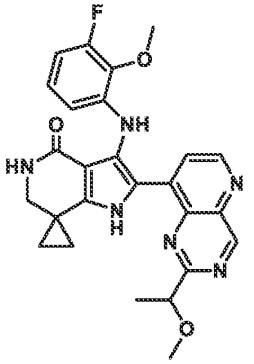
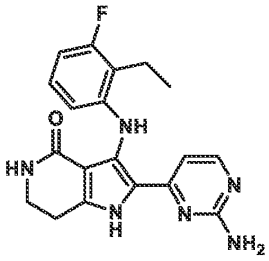
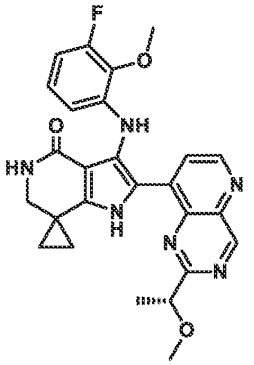
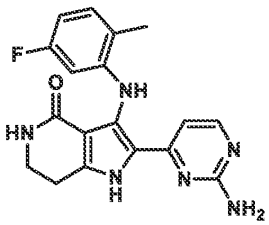
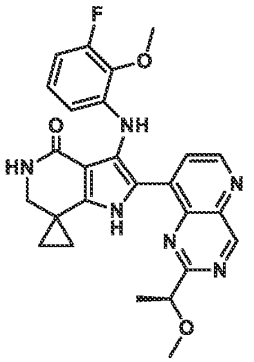
No.	Structure	No.	Structure
186		380	
186a		381	
186b		381a	
187		381b	

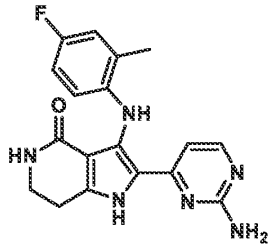
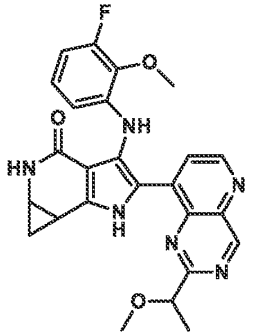
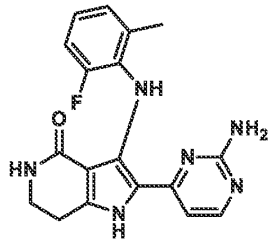
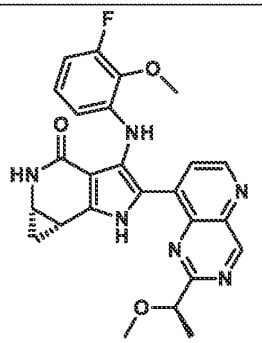
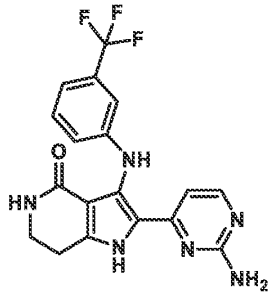
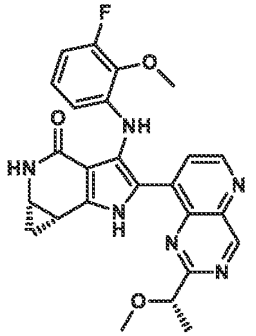
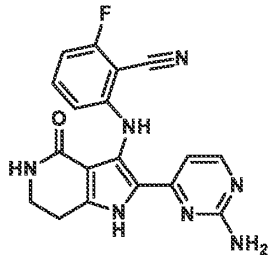
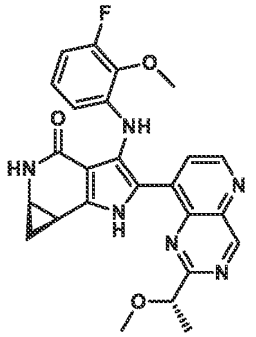
No.	Structure	No.	Structure
187a		382	
187b		382a	
188		382b	
188a		383	
188b		383a	

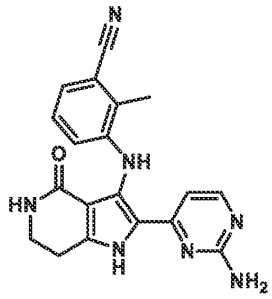
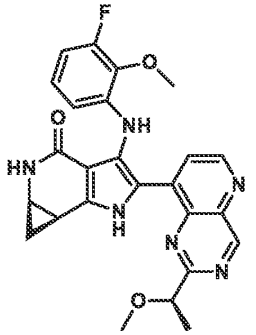
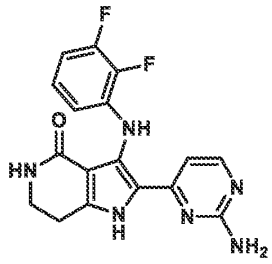
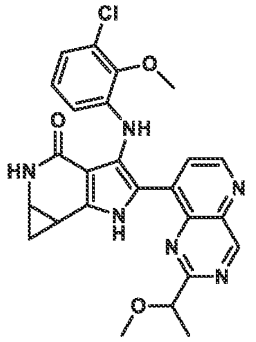
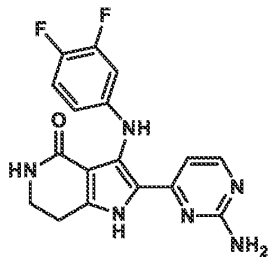
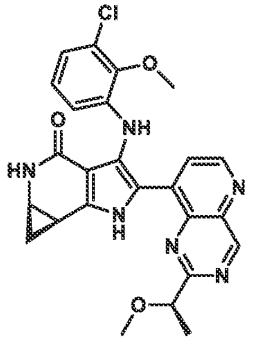
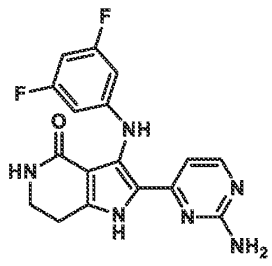
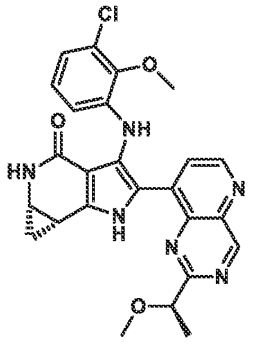
No.	Structure	No.	Structure
189		383b	
189a		384	
189b		384a	
190		384b	

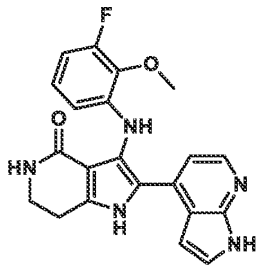
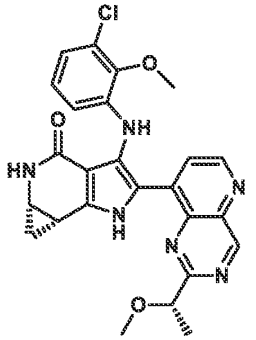
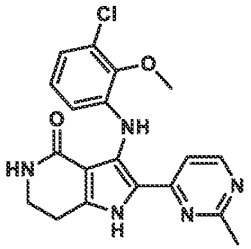
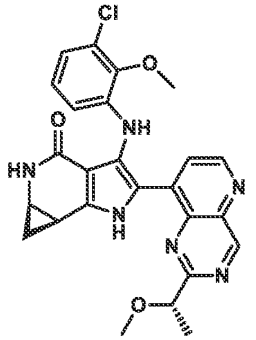
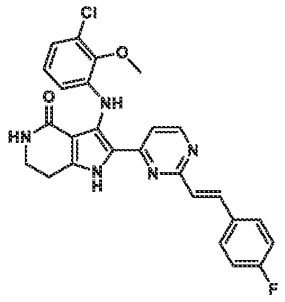
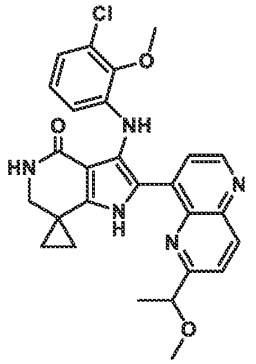
No.	Structure	No.	Structure
190a		385	
190b		386	
191		387	
191a		388	

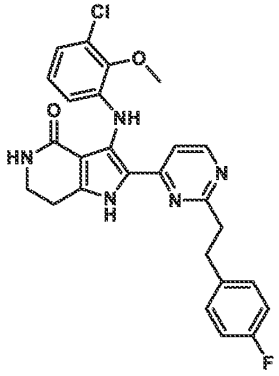
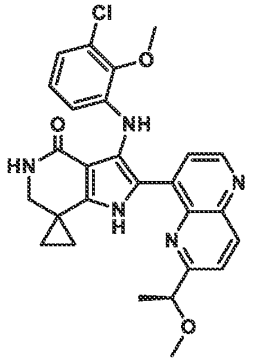
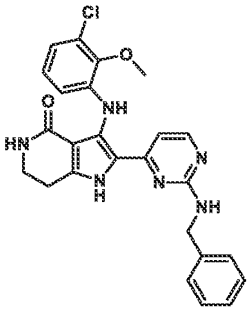
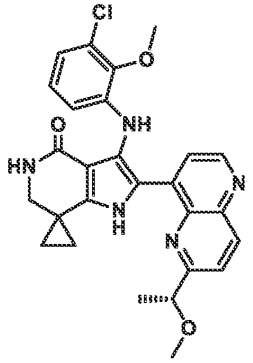
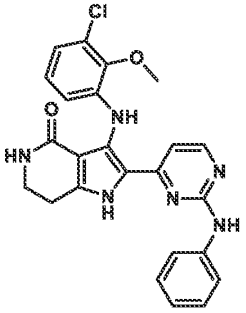
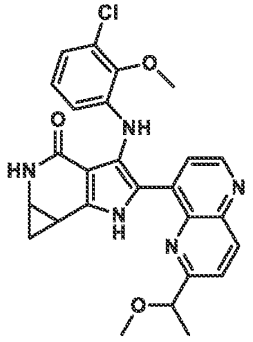
No.	Structure	No.	Structure
191b		389	
192		389a	
193		389b	

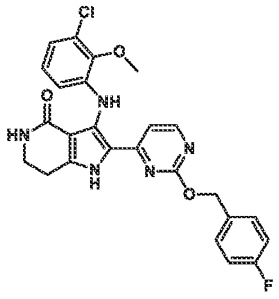
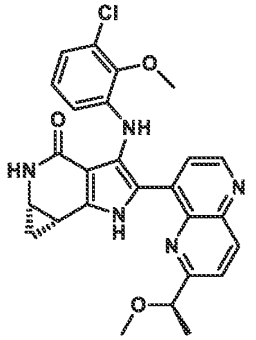
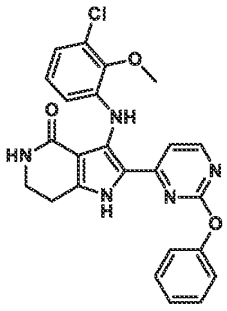
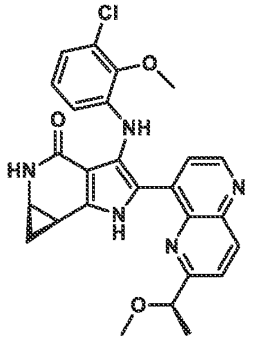
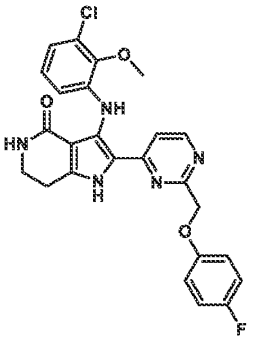
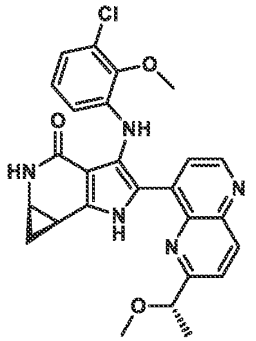
No.	Structure	No.	Structure
194		390	
195		390a	
196		390b	

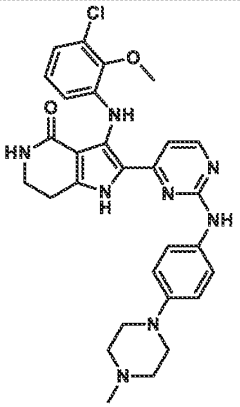
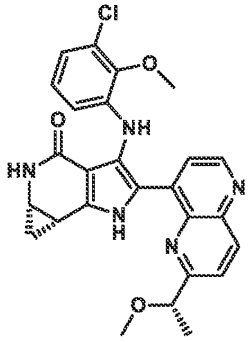
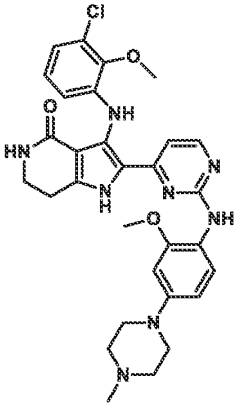
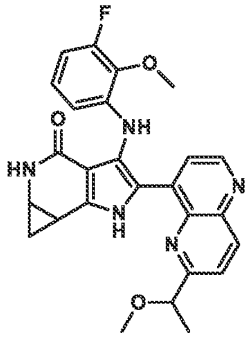
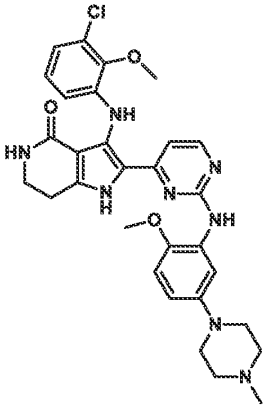
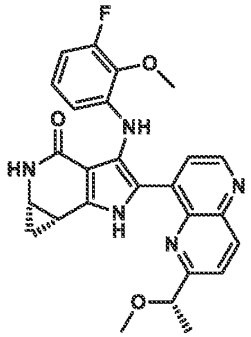
No.	Structure	No.	Structure
197		391	
198		391a	
199		391b	
200		391c	

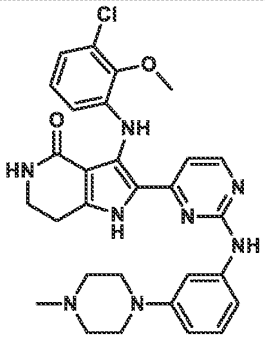
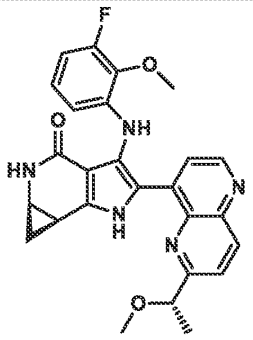
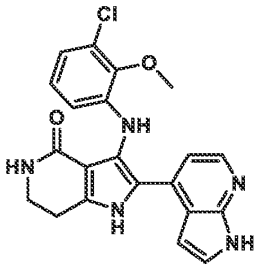
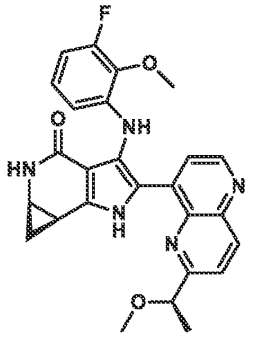
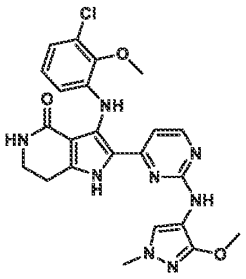
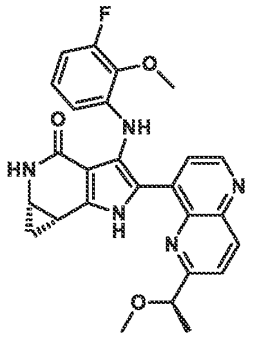
No.	Structure	No.	Structure
201		391d	
202		392	
203		392a	
204		392b	

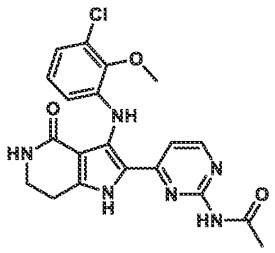
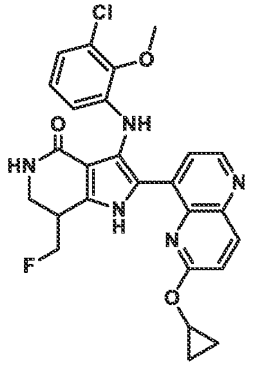
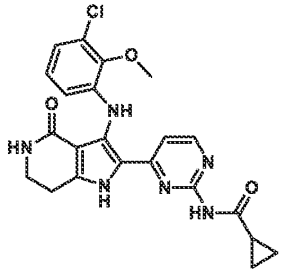
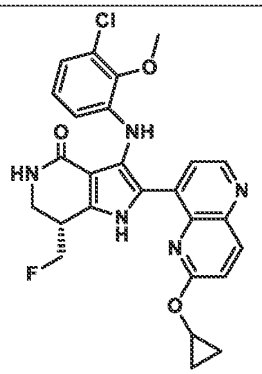
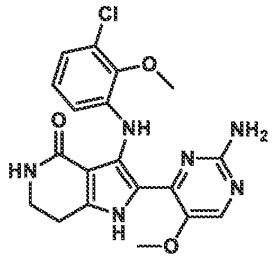
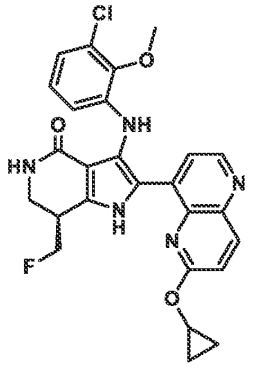
No.	Structure	No.	Structure
205		392c	
206		392d	
207		393	

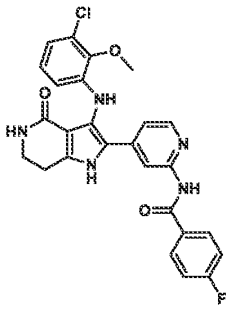
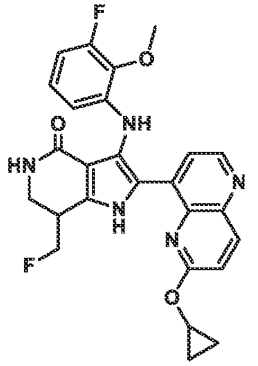
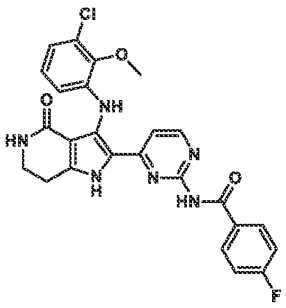
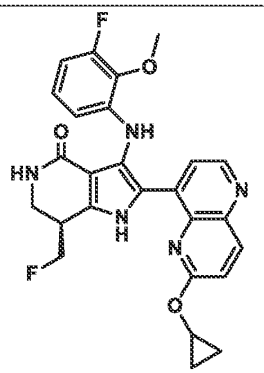
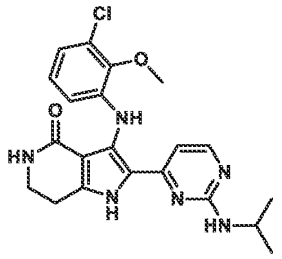
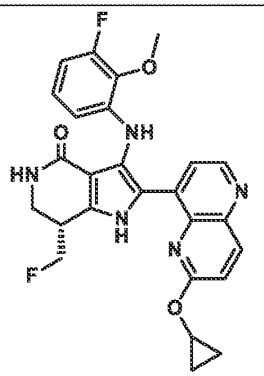
No.	Structure	No.	Structure
208		393a	
209		393b	
210		394	

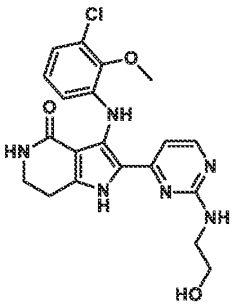
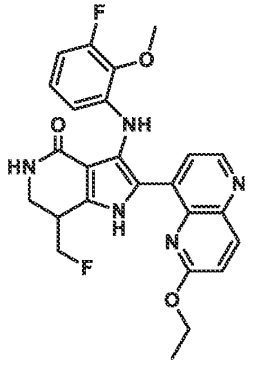
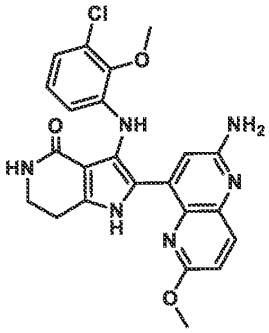
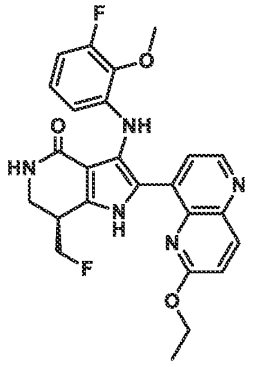
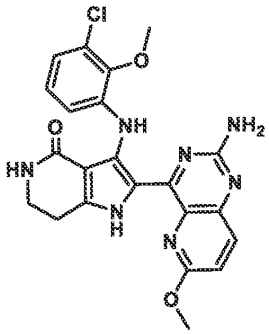
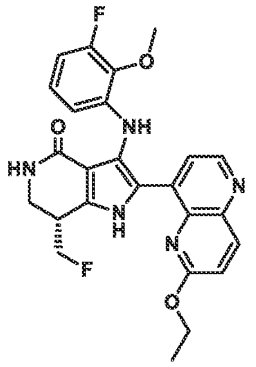
No.	Structure	No.	Structure
211		394a	
212		394b	
213		394c	

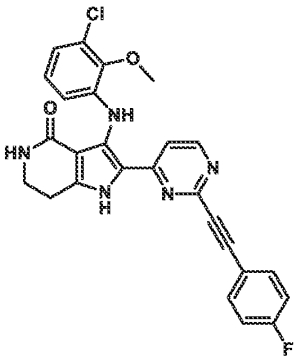
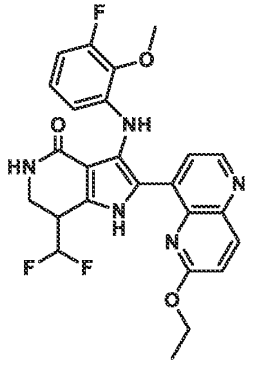
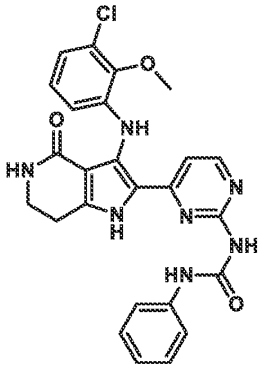
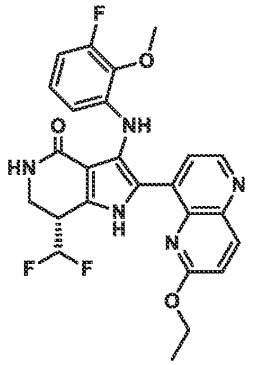
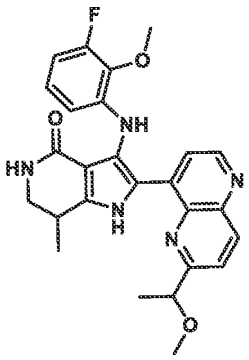
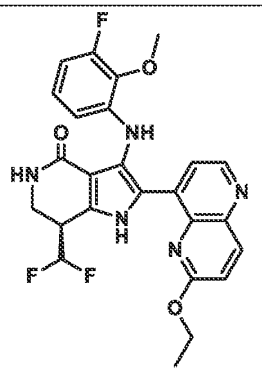
No.	Structure	No.	Structure
214		394d	
215		395	
216		395a	

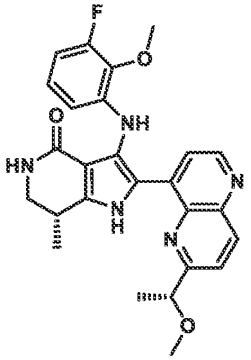
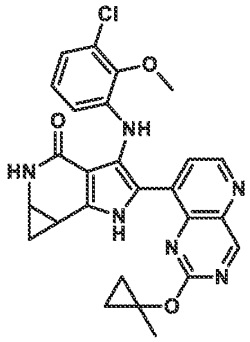
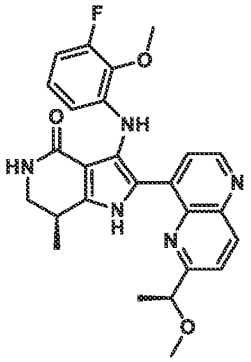
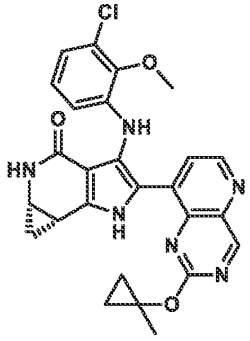
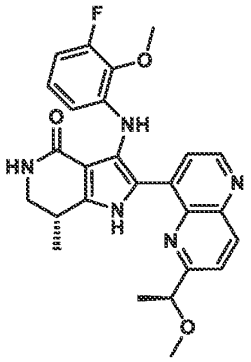
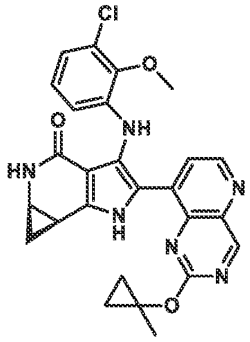
No.	Structure	No.	Structure
217		395b	
218		395c	
219		395d	

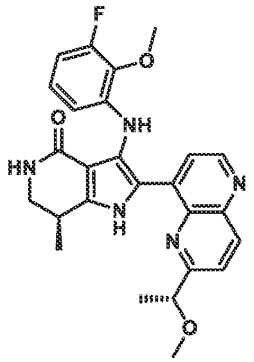
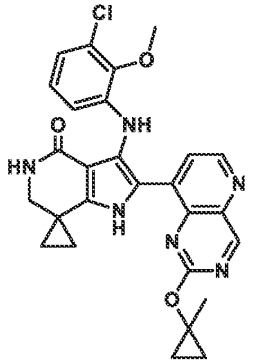
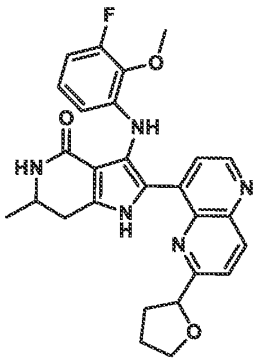
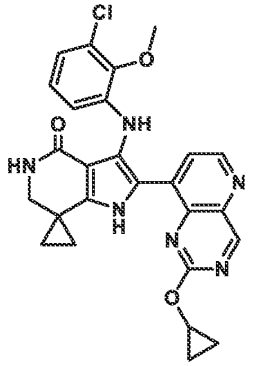
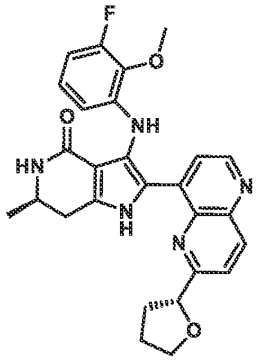
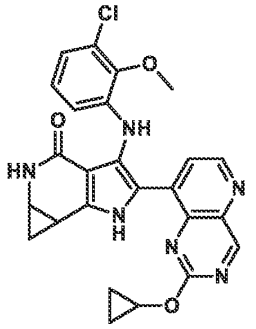
No.	Structure	No.	Structure
220		396	
221		396a	
222		396b	

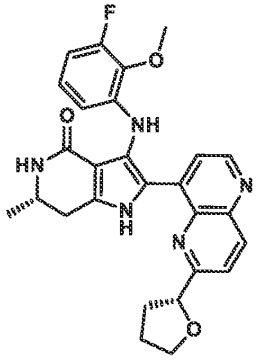
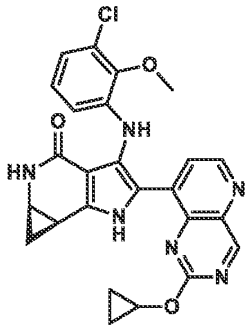
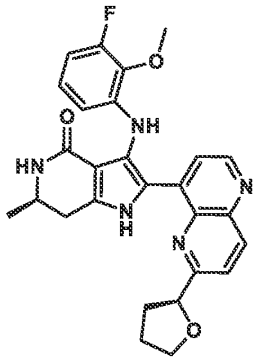
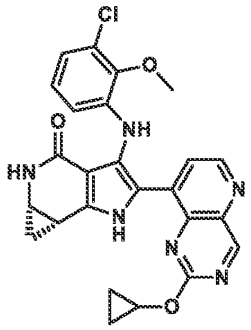
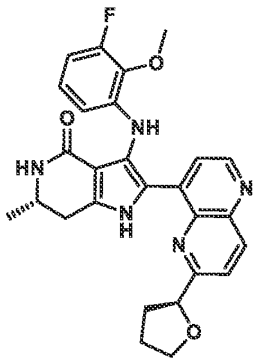
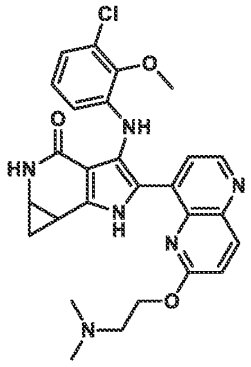
No.	Structure	No.	Structure
223		397	
224		397a	
225		397b	

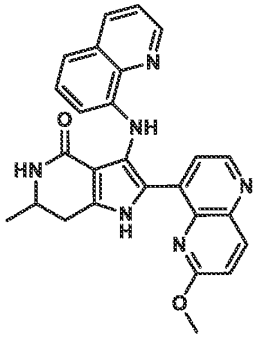
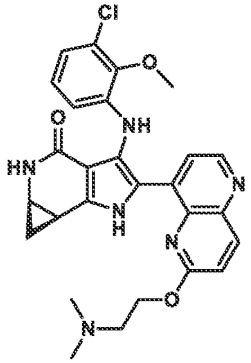
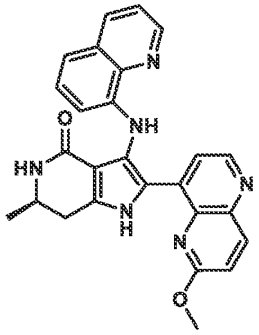
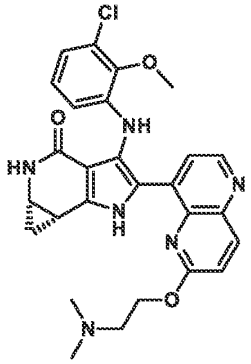
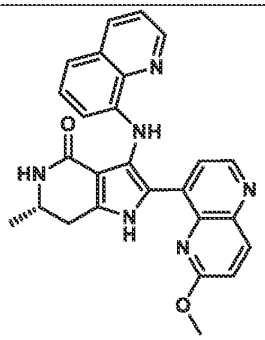
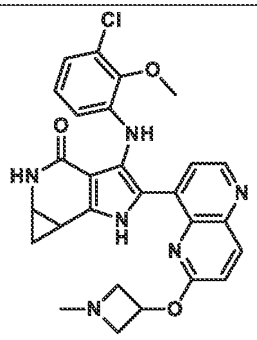
No.	Structure	No.	Structure
226		398	
227		398a	
228		398b	

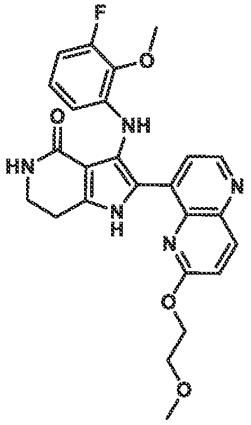
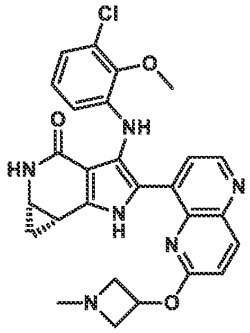
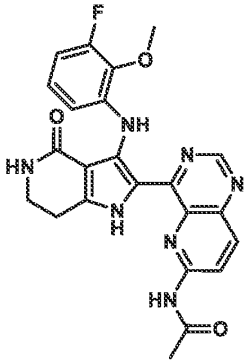
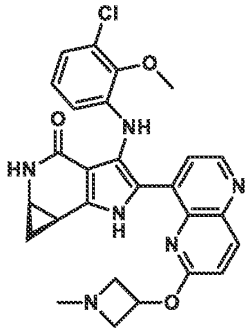
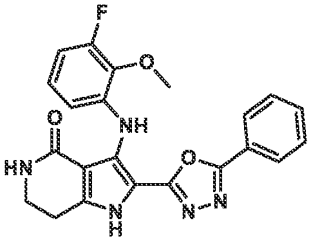
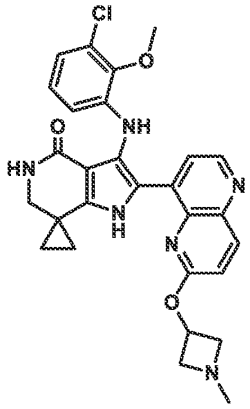
No.	Structure	No.	Structure
229		399	
230		399a	
231		399b	

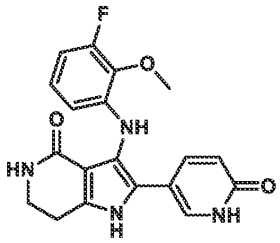
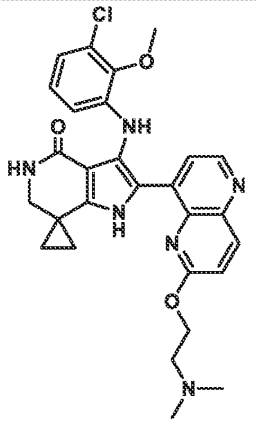
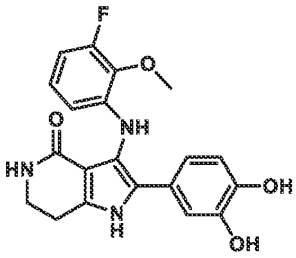
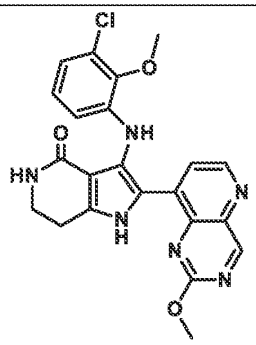
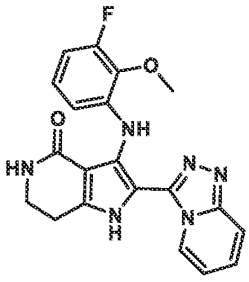
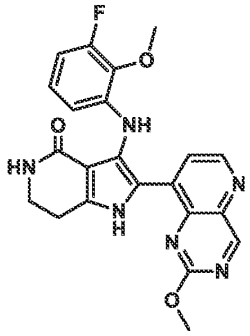
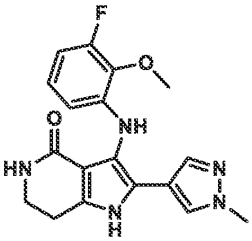
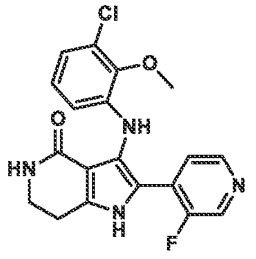
No.	Structure	No.	Structure
231a		400	
231b		400a	
231c		400b	

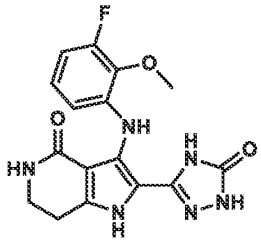
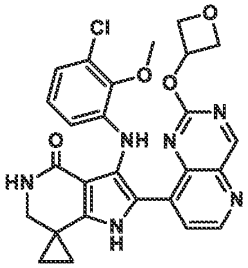
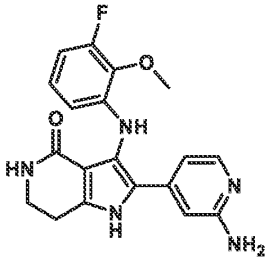
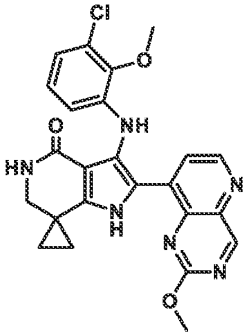
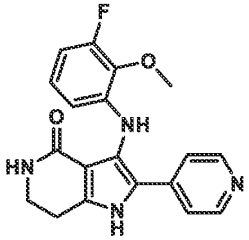
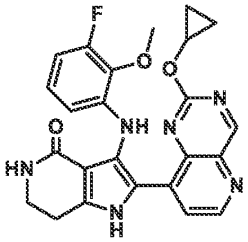
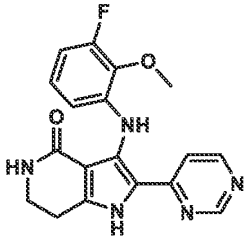
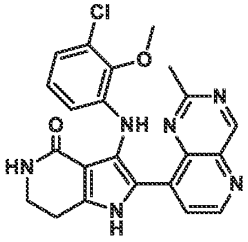
No.	Structure	No.	Structure
231d		401	
232		402	
232a		403	

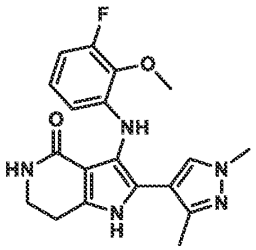
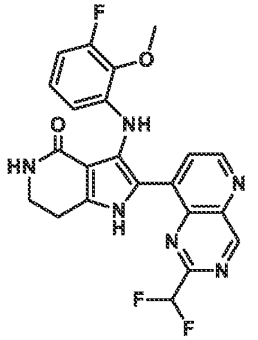
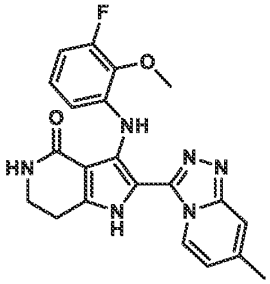
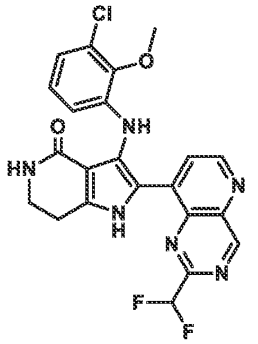
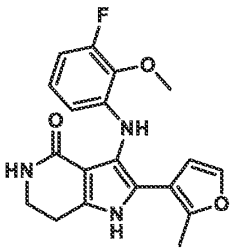
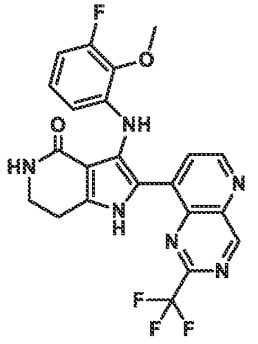
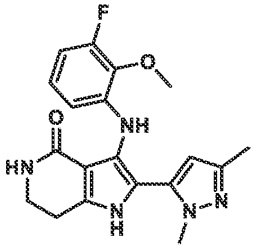
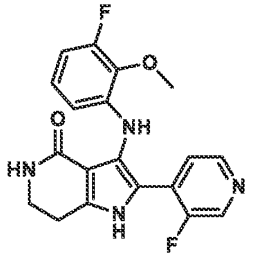
No.	Structure	No.	Structure
232b		403a	
232c		403b	
232d		404	

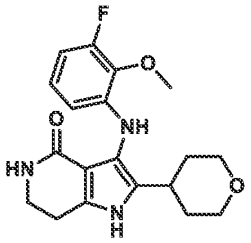
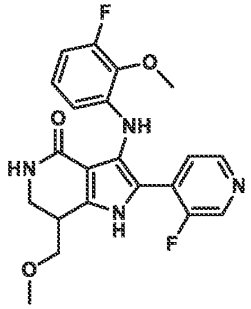
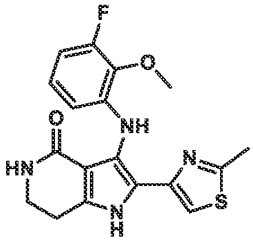
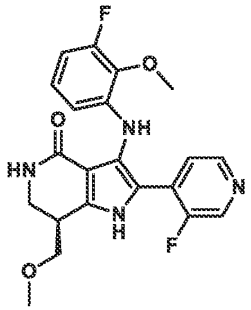
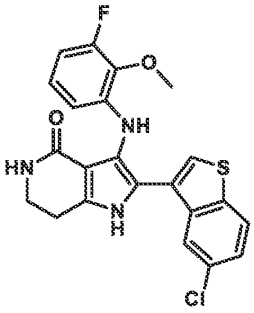
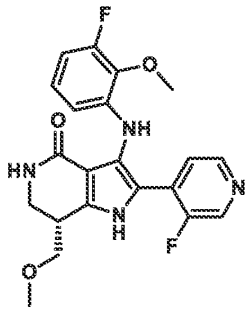
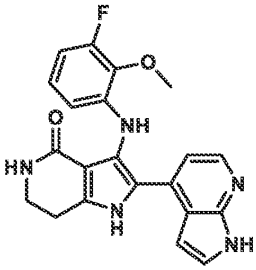
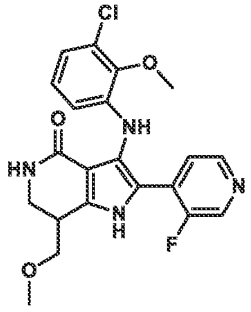
No.	Structure	No.	Structure
233		404a	
233a		404b	
233b		405	

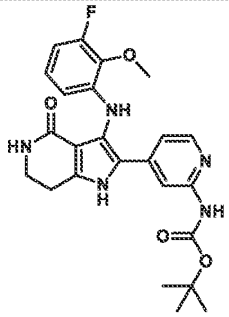
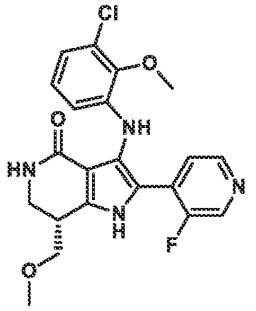
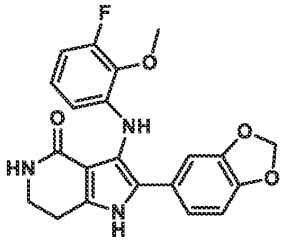
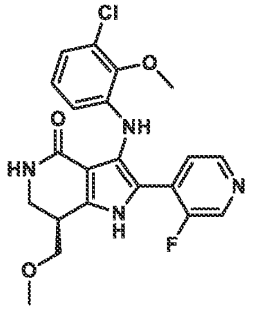
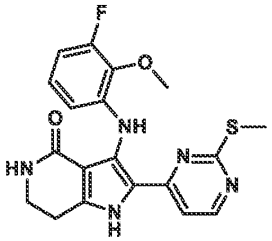
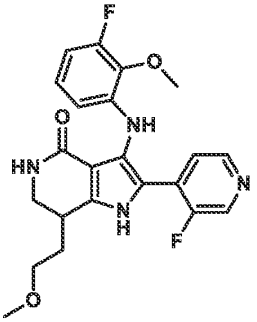
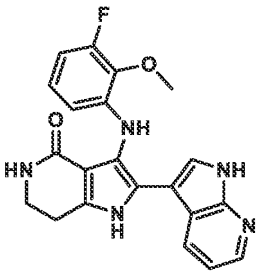
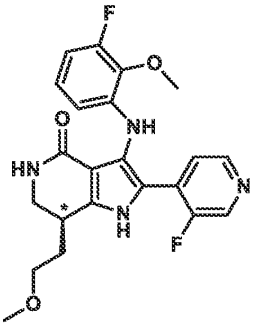
No.	Structure	No.	Structure
234		405a	
235		405b	
236		406	

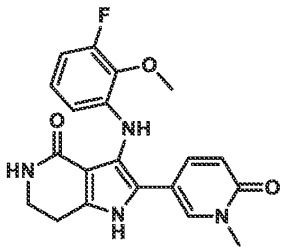
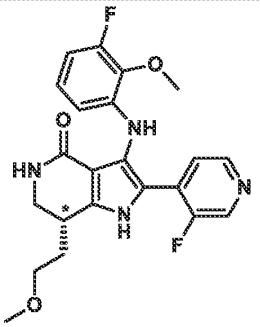
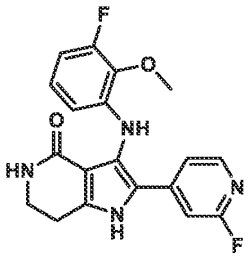
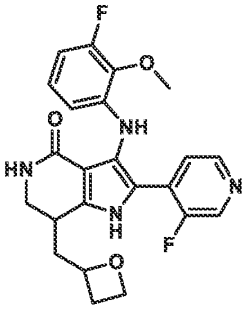
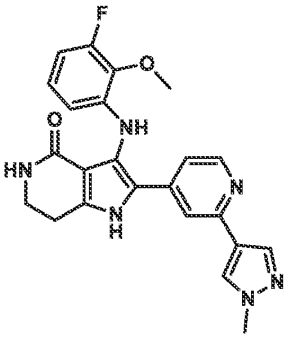
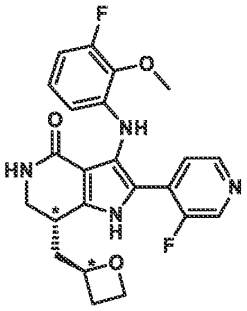
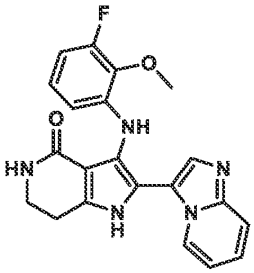
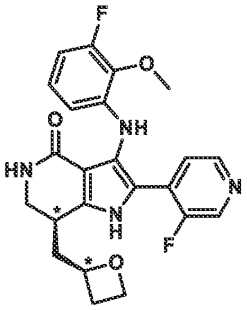
No.	Structure	No.	Structure
237		407	
238		408	
239		409	
240		410	

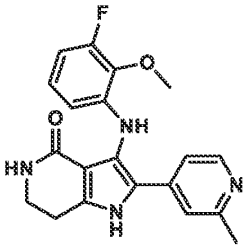
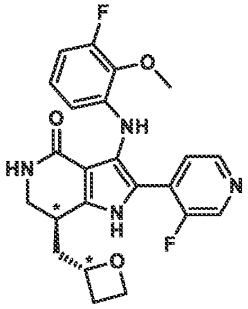
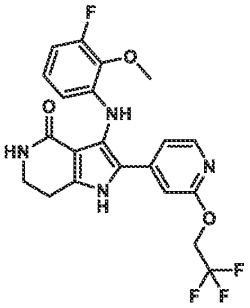
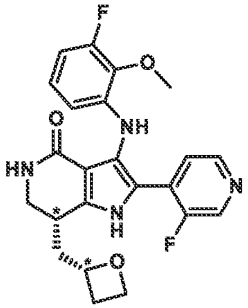
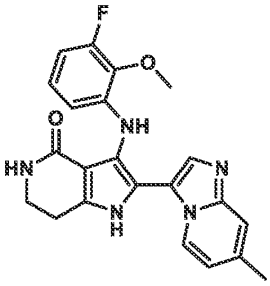
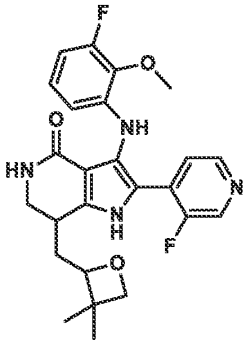
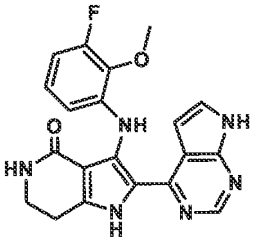
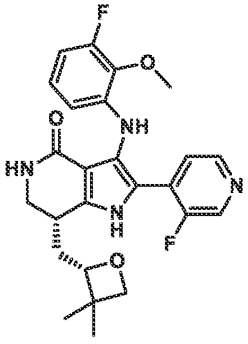
No.	Structure	No.	Structure
241		411	
242		412	
243		413	
244		414	

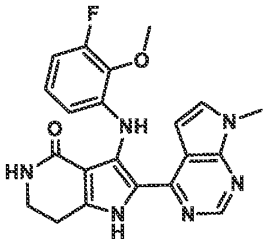
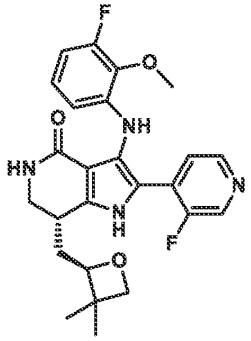
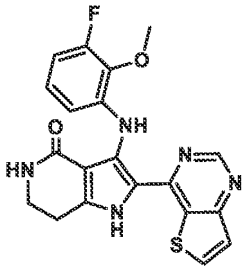
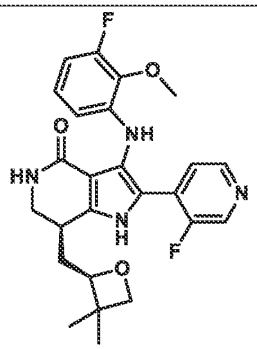
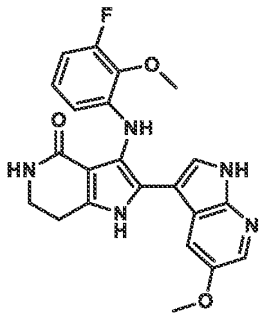
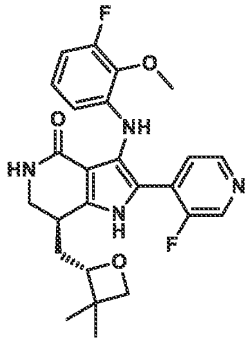
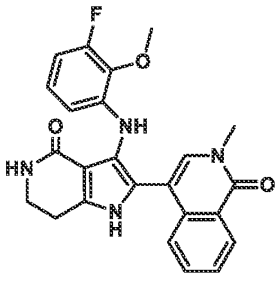
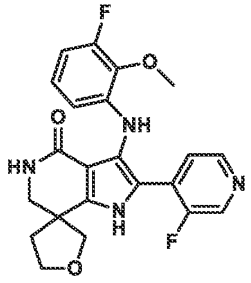
No.	Structure	No.	Structure
245		415	
246		416	
247		417	
248		418	

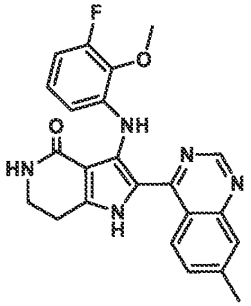
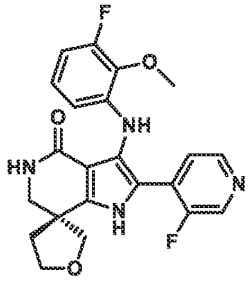
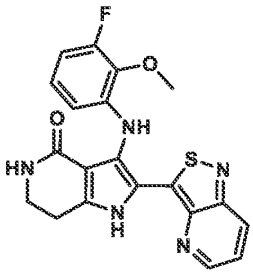
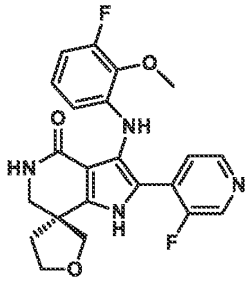
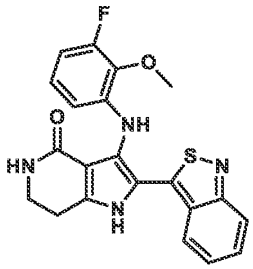
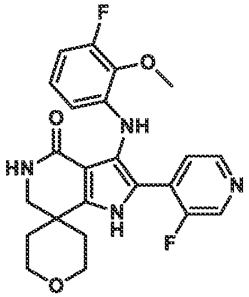
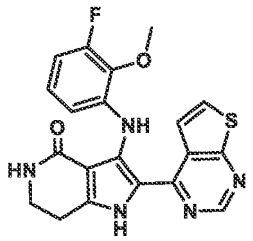
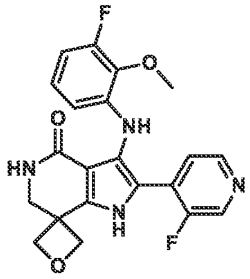
No.	Structure	No.	Structure
249		419	
250		419a	
251		419b	
252		420	

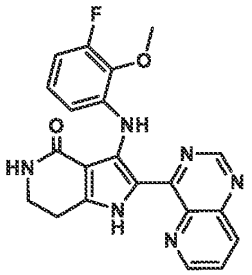
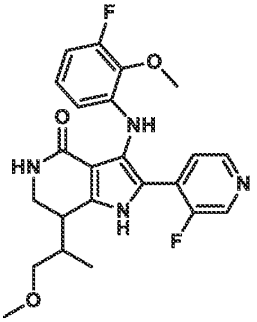
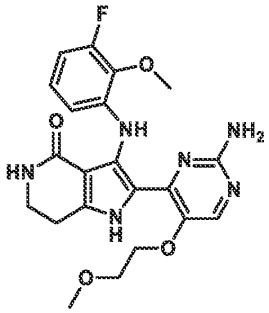
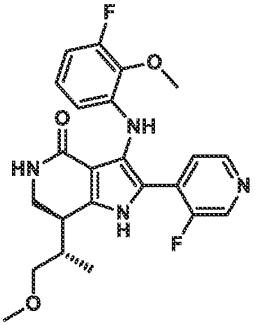
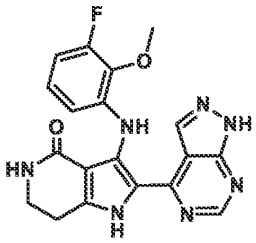
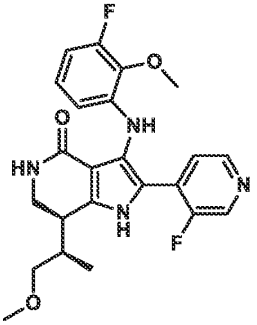
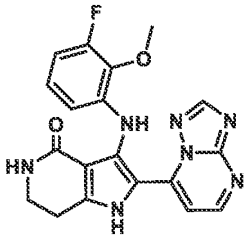
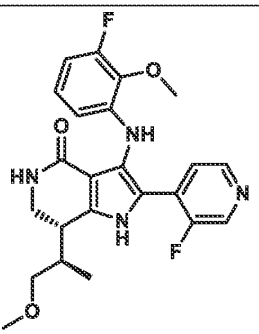
No.	Structure	No.	Structure
253		420a	
254		420b	
255		421	
256		421a	

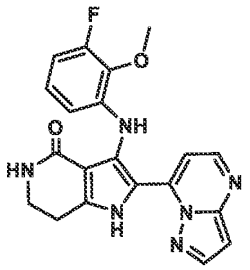
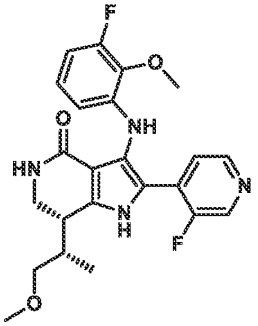
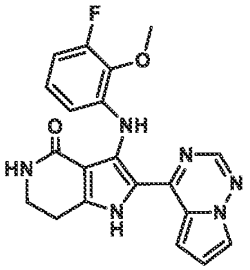
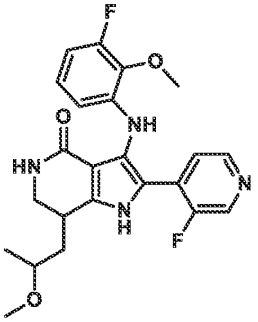
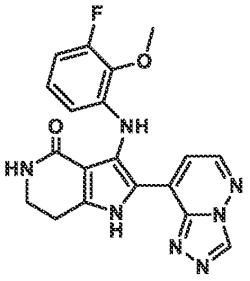
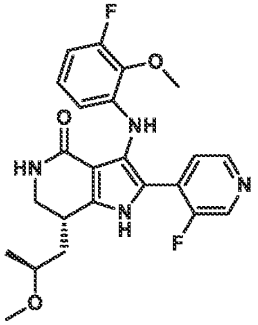
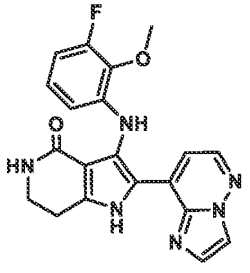
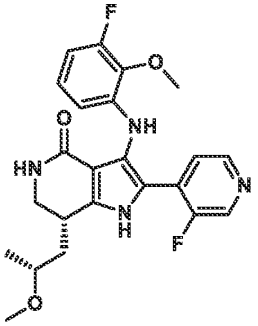
No.	Structure	No.	Structure
257		421b	
258		422	
259		422a	
260		422b	

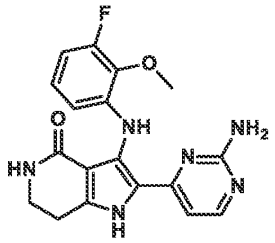
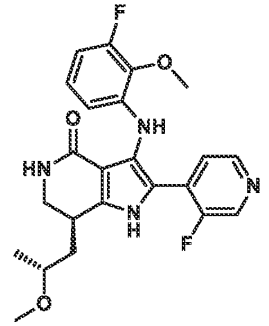
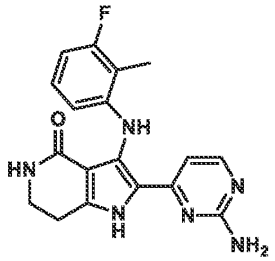
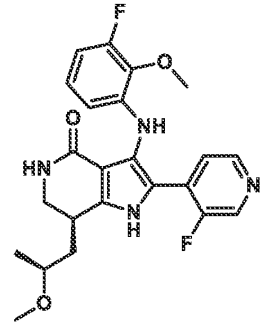
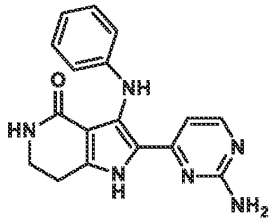
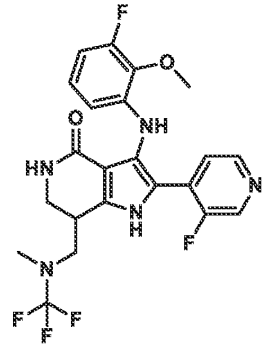
No.	Structure	No.	Structure
261		422c	
262		422d	
263		423	
264		423a	

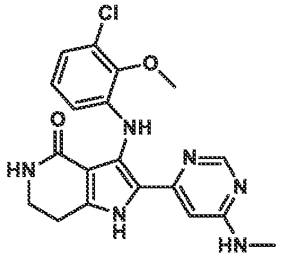
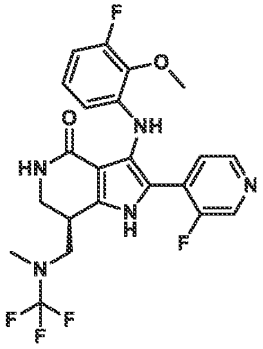
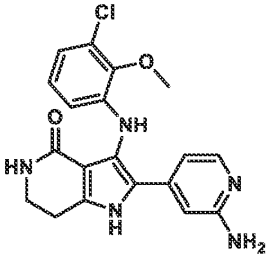
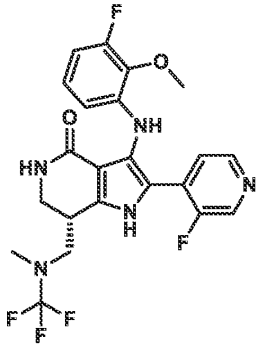
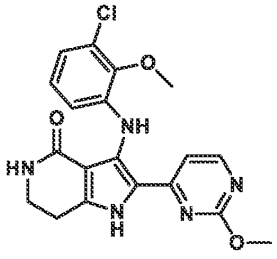
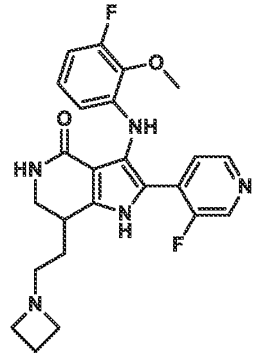
No.	Structure	No.	Structure
265		423b	
266		423c	
267		423d	
268		424	

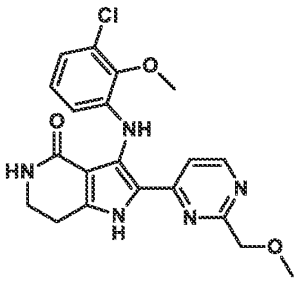
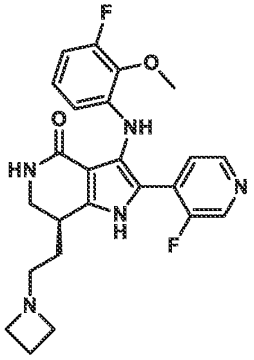
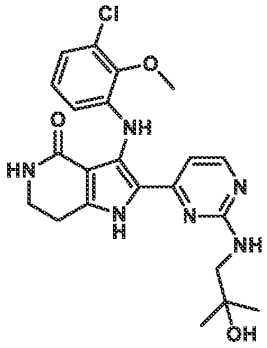
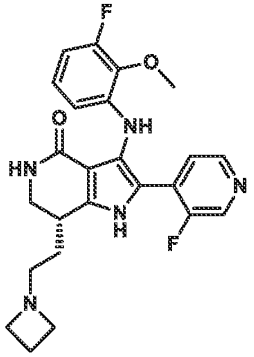
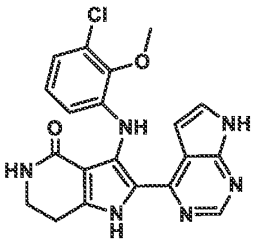
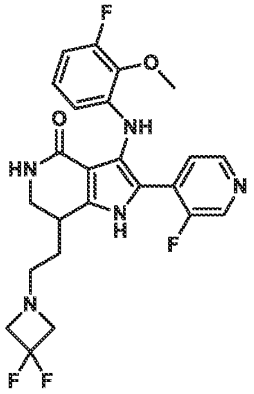
No.	Structure	No.	Structure
269		424a	
270		424b	
271		425	
272		426	

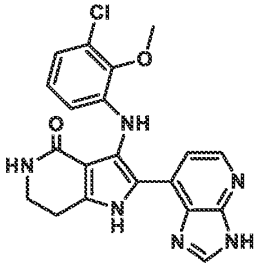
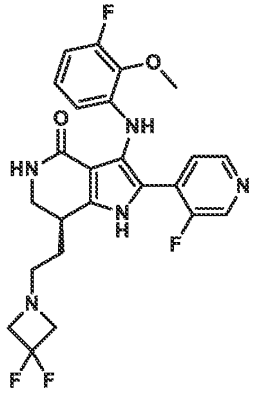
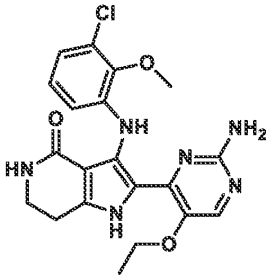
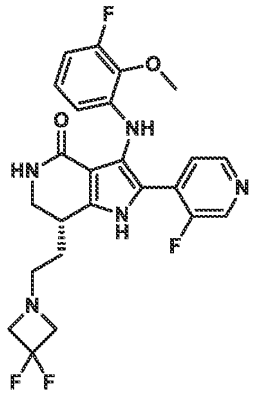
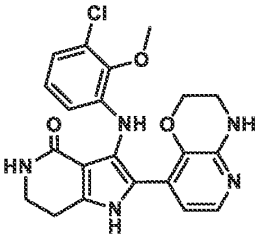
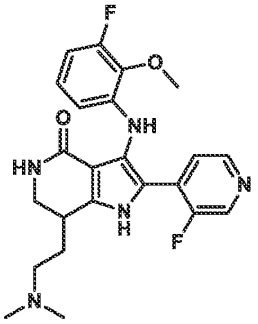
No.	Structure	No.	Structure
273		427	
274		427a	
275		427b	
276		427c	

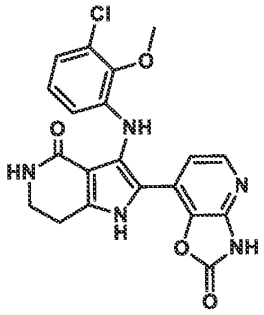
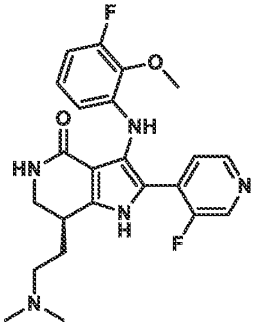
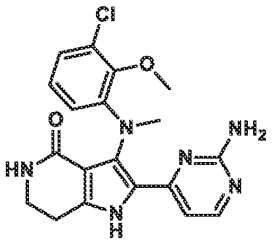
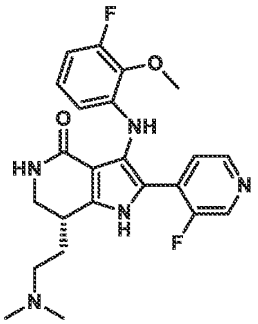
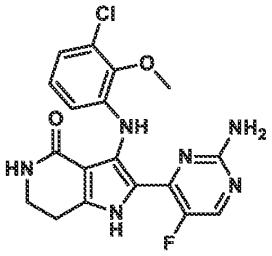
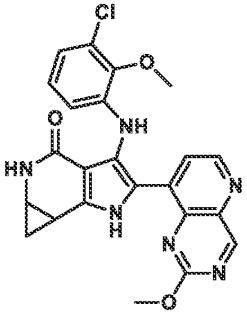
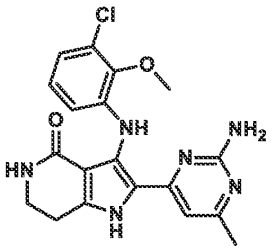
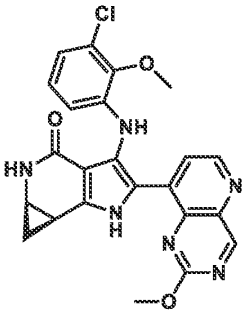
No.	Structure	No.	Structure
277		427d	
278		428	
279		428a	
280		428b	

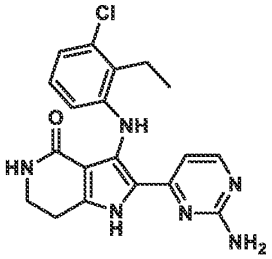
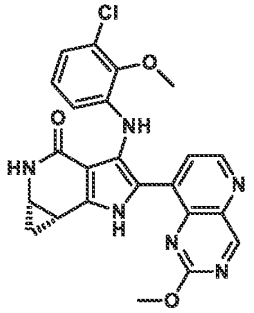
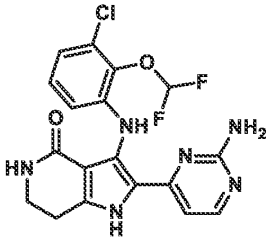
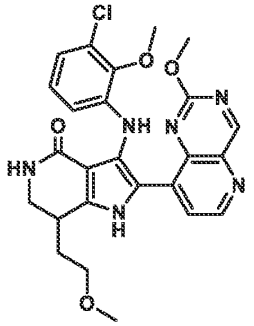
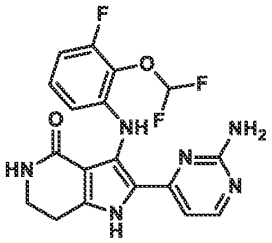
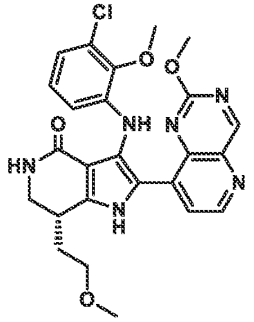
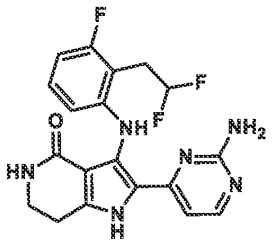
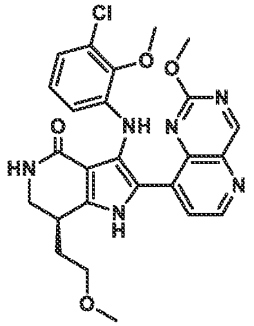
No.	Structure	No.	Structure
281		428c	
282		428d	
283			

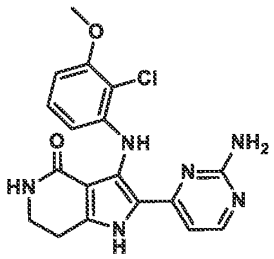
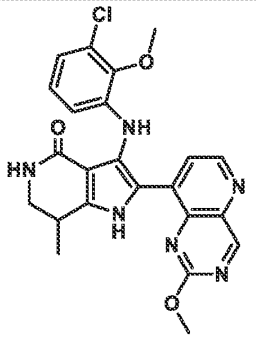
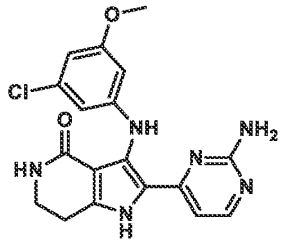
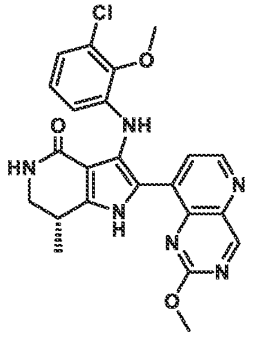
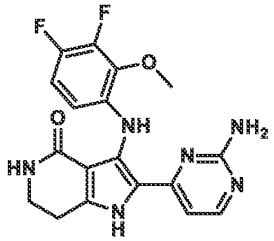
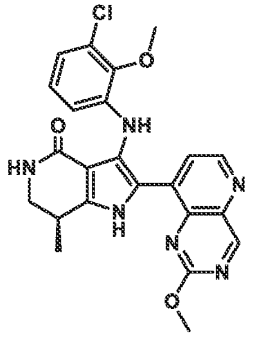
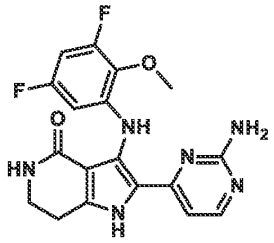
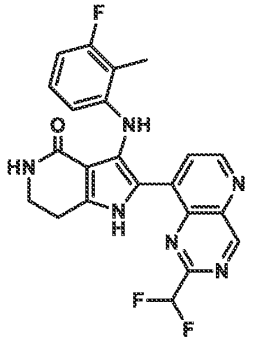
No.	Structure	No.	Structure
284		429a	
285		429b	
286		430	

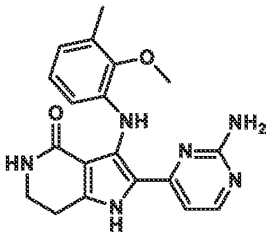
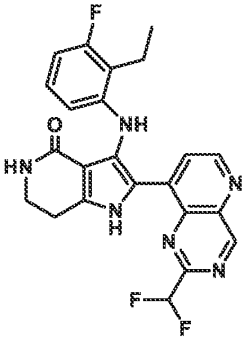
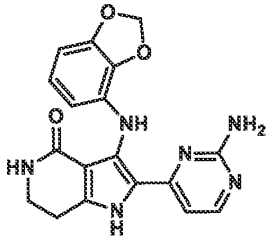
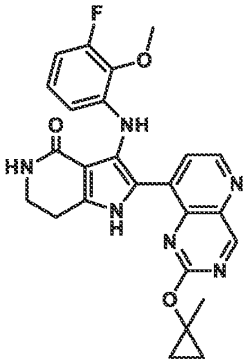
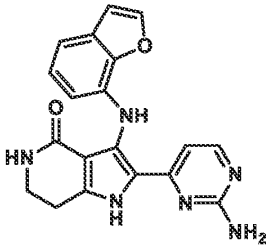
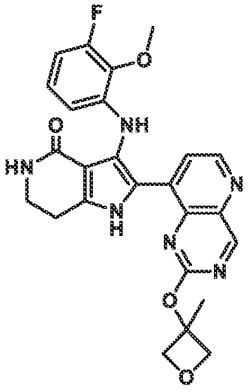
No.	Structure	No.	Structure
287		430a	
288		430b	
289		431	

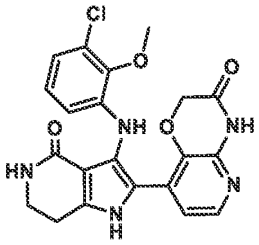
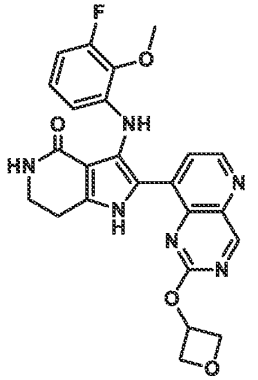
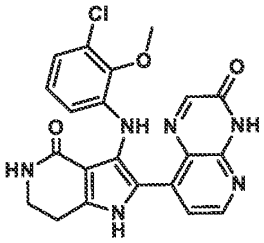
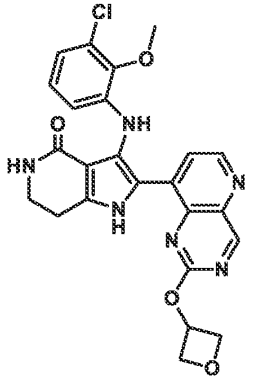
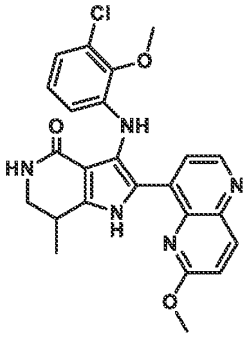
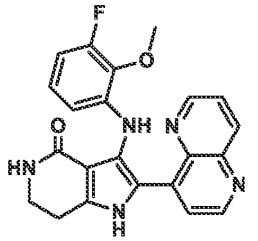
No.	Structure	No.	Structure
290		431a	
291		431b	
292		432	

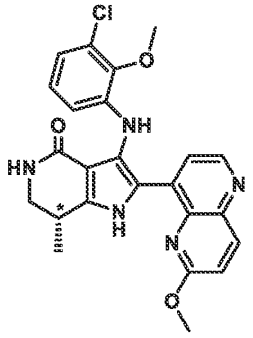
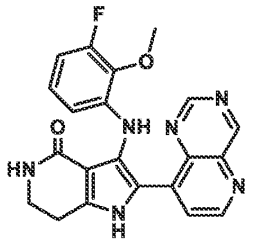
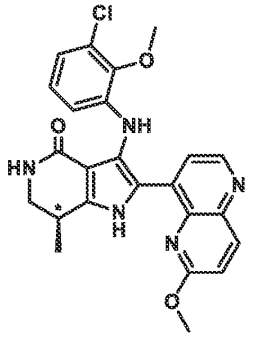
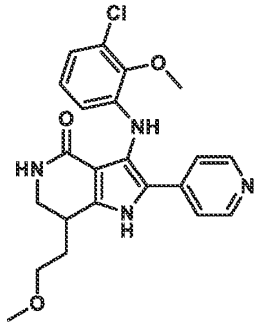
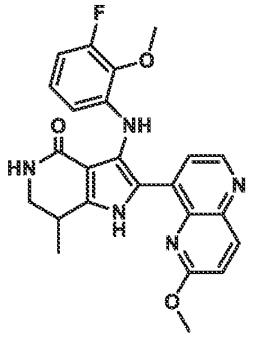
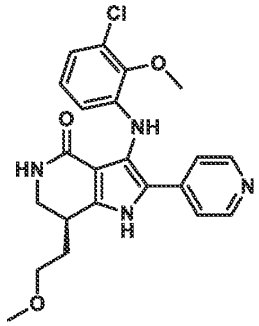
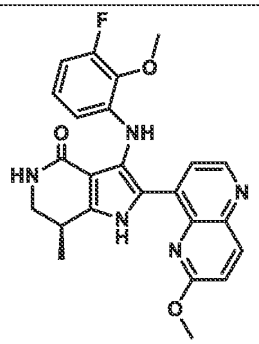
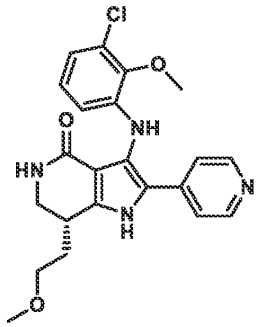
No.	Structure	No.	Structure
293		432a	
294		432b	
295		433	
296		433a	

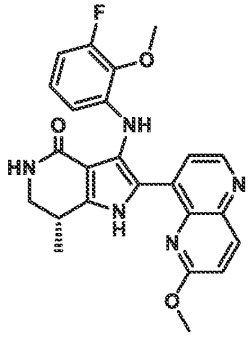
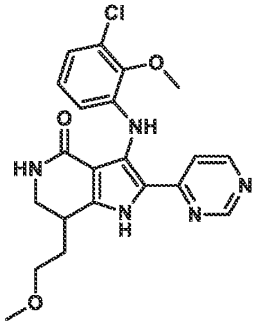
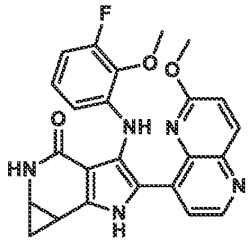
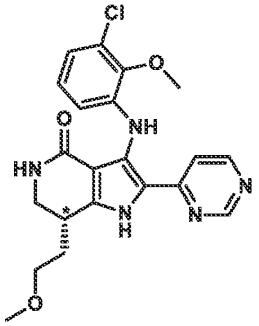
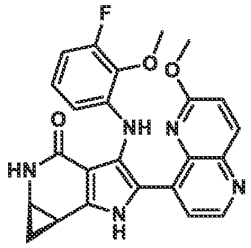
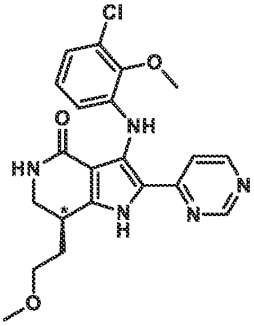
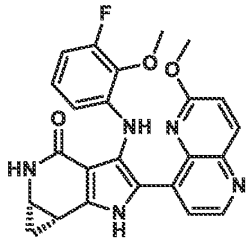
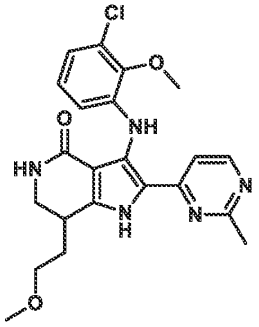
No.	Structure	No.	Structure
297		433b	
298		434	
299		434a	
300		434b	

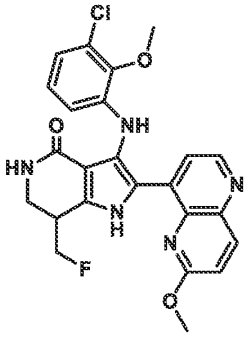
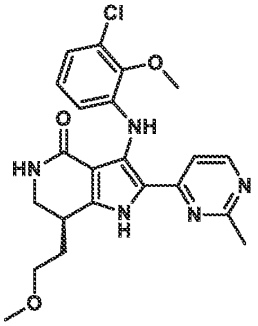
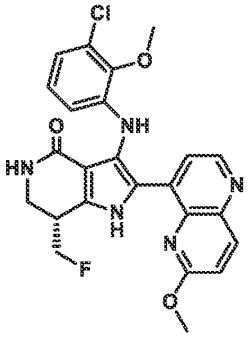
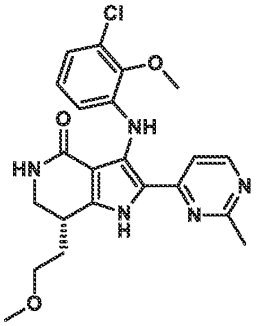
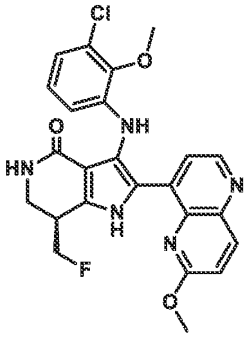
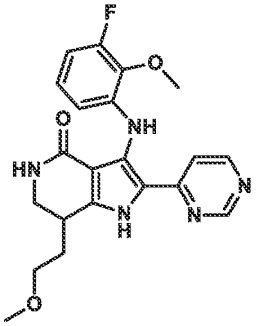
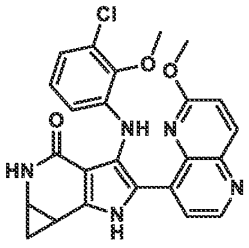
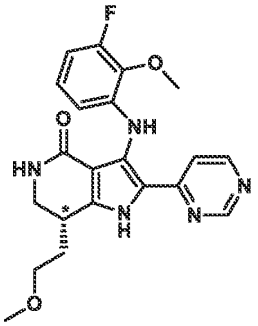
No.	Structure	No.	Structure
301		435	
302		435a	
303		435b	
304		436	

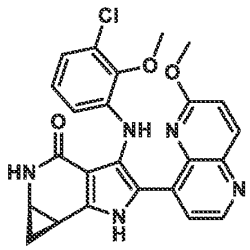
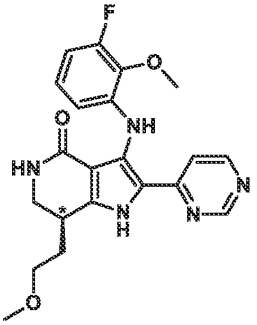
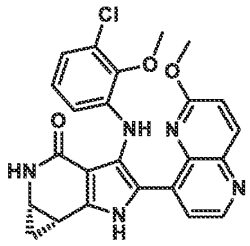
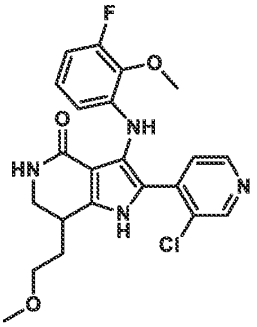
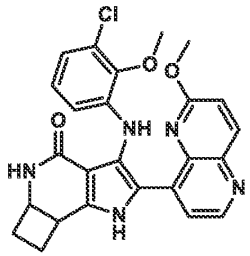
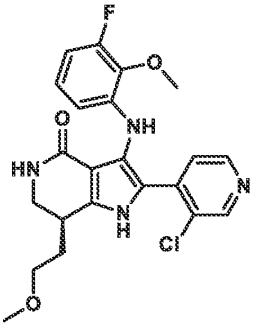
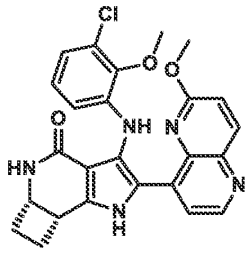
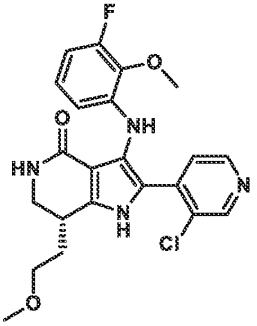
No.	Structure	No.	Structure
305		437	
306		438	
307		439	

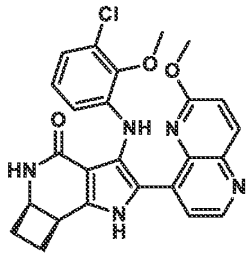
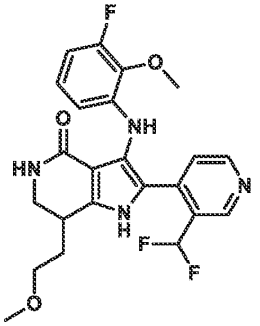
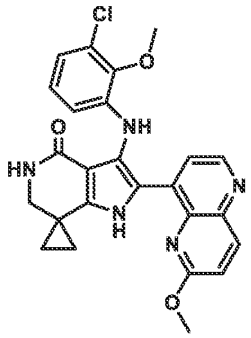
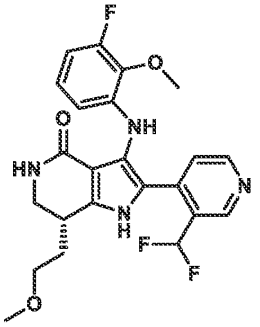
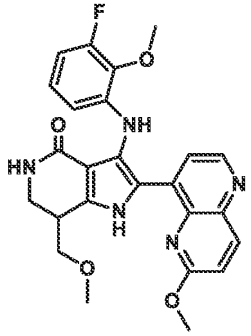
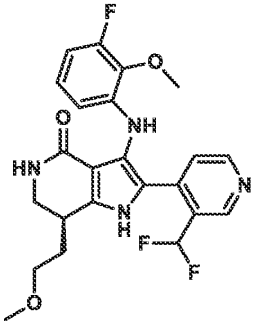
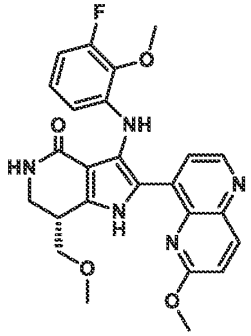
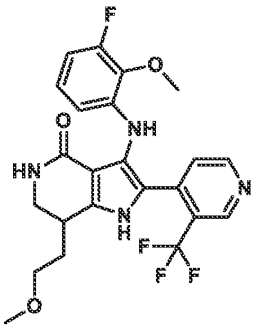
No.	Structure	No.	Structure
308		440	
309		441	
310		442	

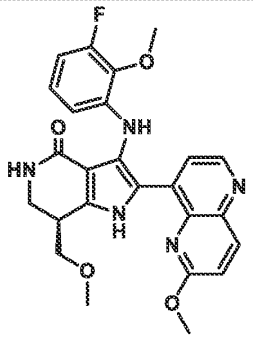
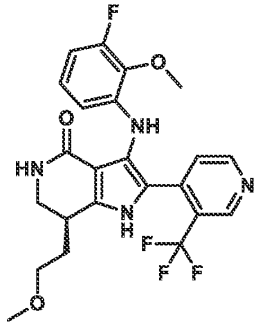
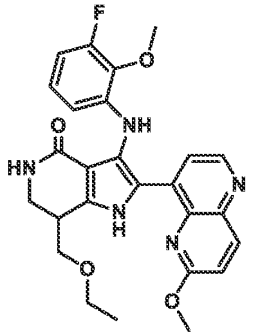
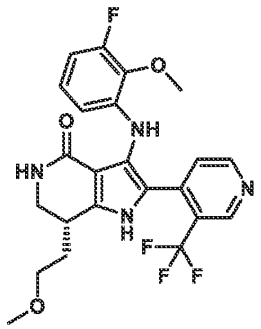
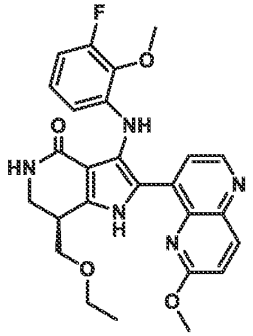
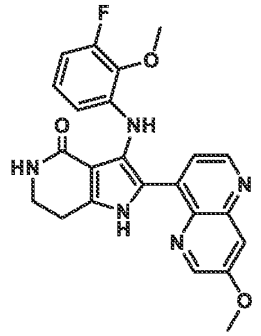
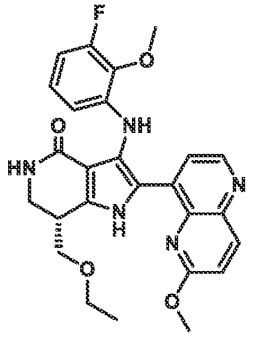
No.	Structure	No.	Structure
310a		443	
310b		444	
311		444a	
311a		444b	

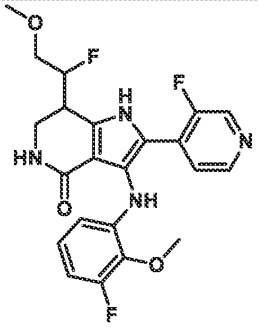
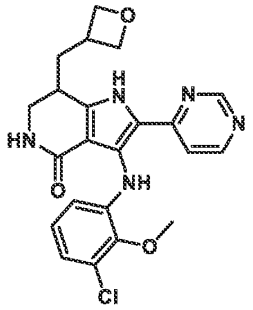
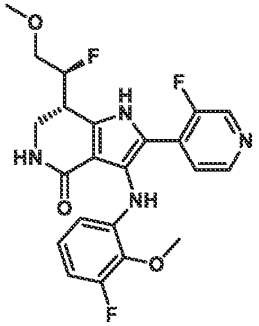
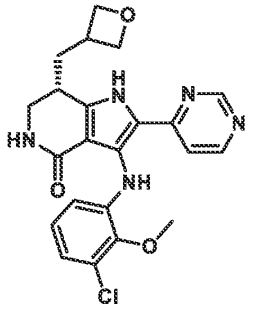
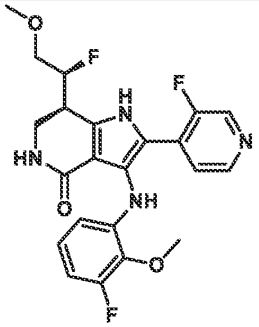
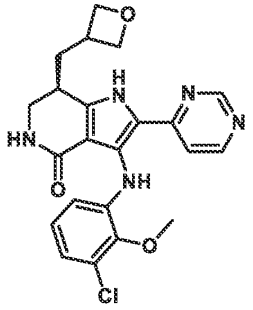
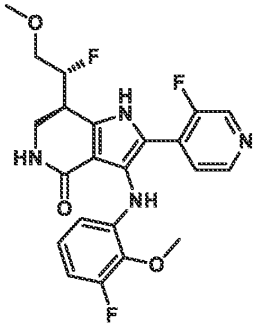
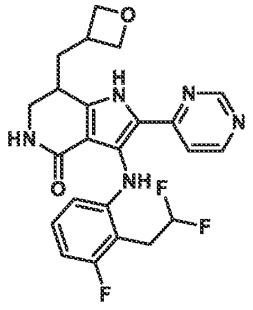
No.	Structure	No.	Structure
311b		445	
312		445a	
312a		445b	
312b		446	

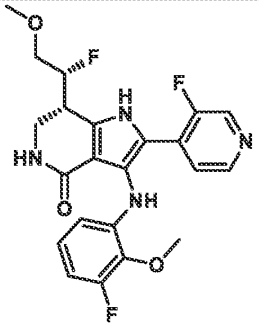
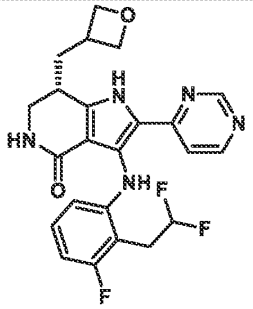
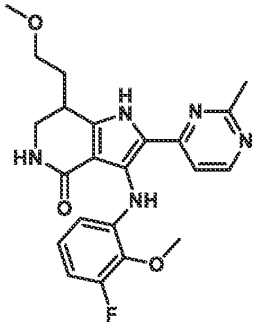
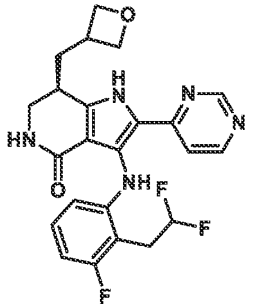
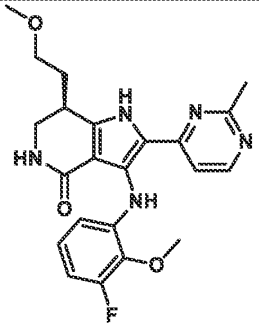
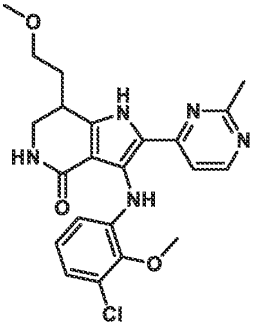
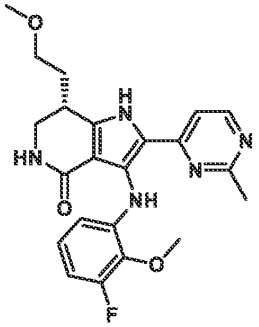
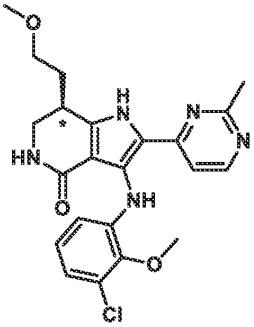
No.	Structure	No.	Structure
313		446a	
313a		446b	
313b		447	
314		447a	

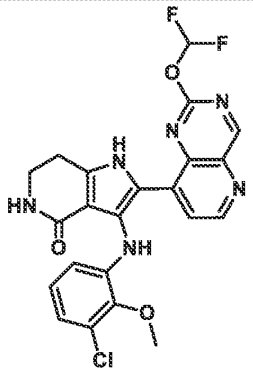
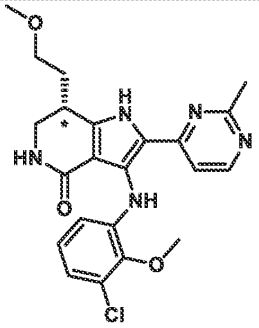
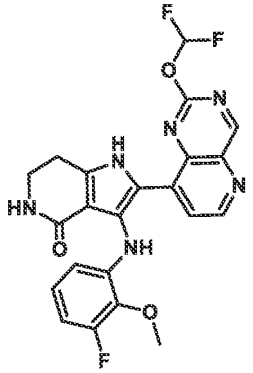
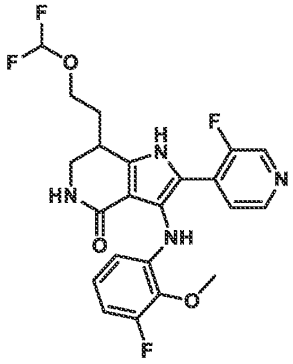
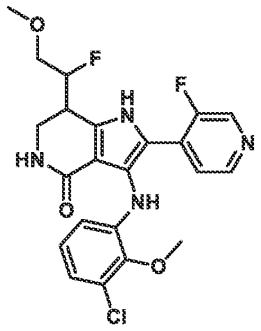
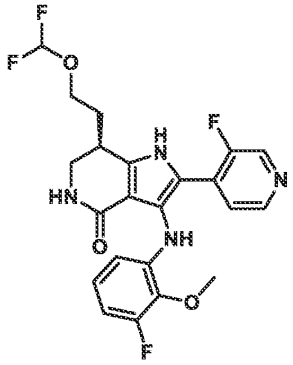
No.	Structure	No.	Structure
314a		447b	
314b		448	
315		448a	
315a		448b	

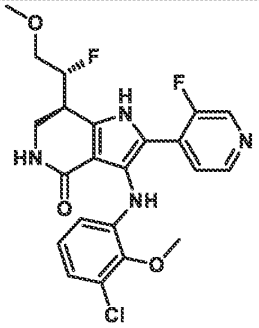
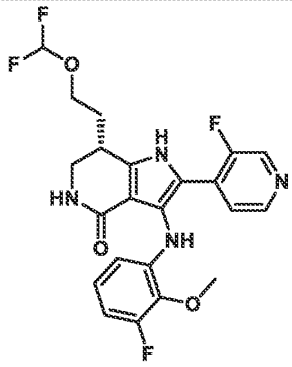
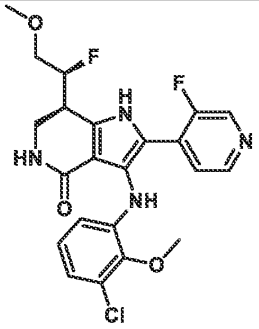
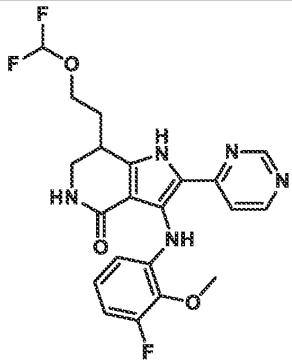
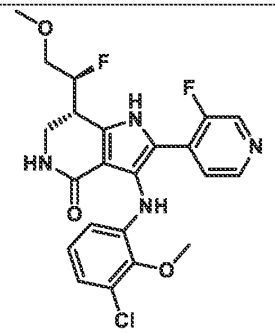
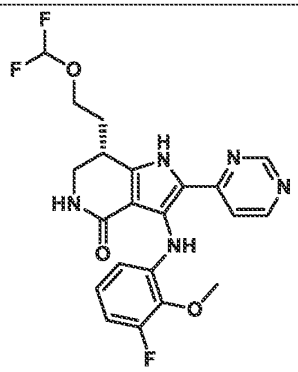
No.	Structure	No.	Structure
315b		449	
316		449a	
317		449b	
317a		450	

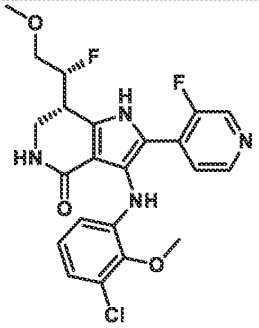
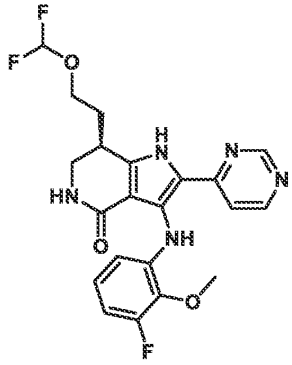
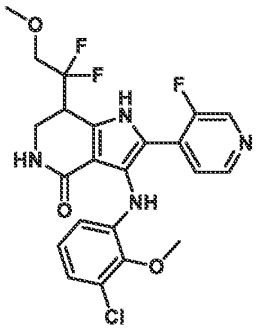
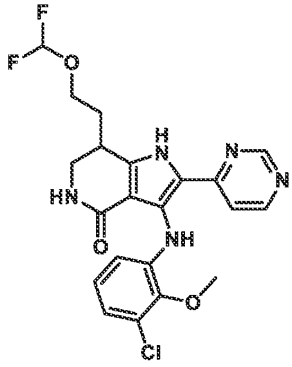
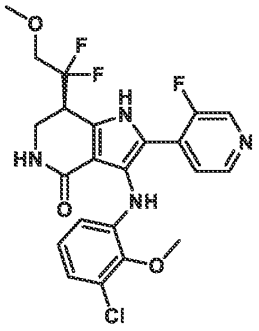
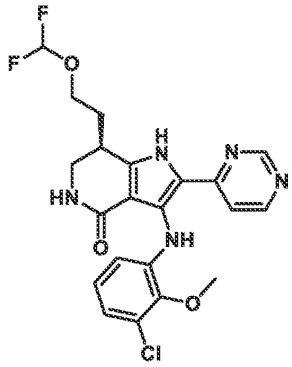
No.	Structure	No.	Structure
317b		450a	
318		450b	
318a		451	
318b			

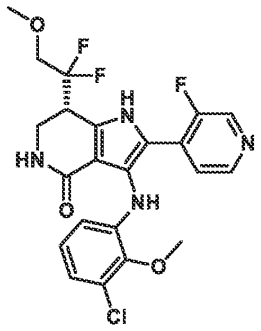
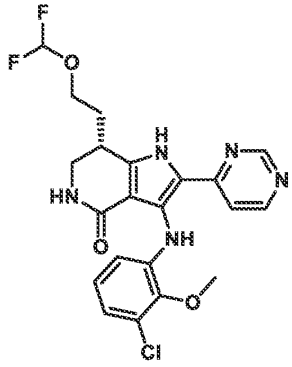
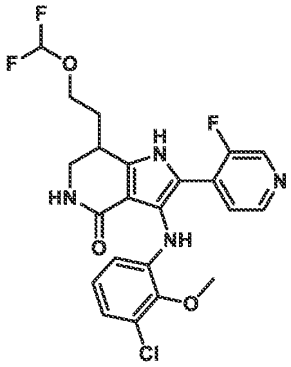
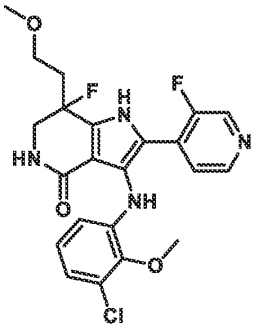
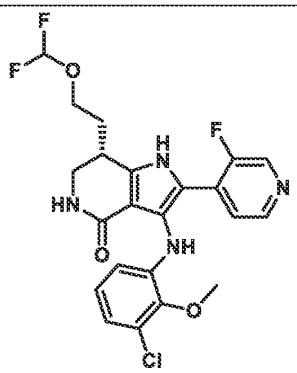
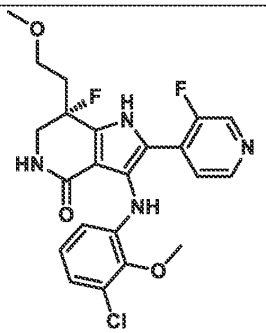
No.	Structure	No.	Structure
452		461	
452a		461a	
452b		461b	
452c		462	

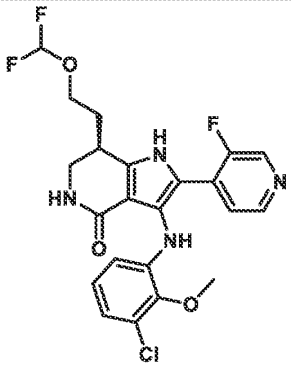
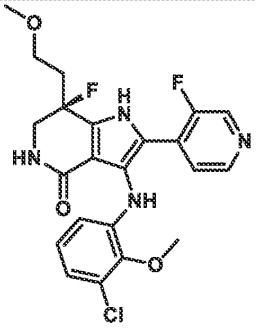
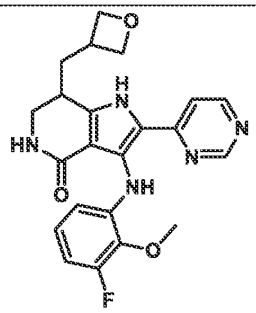
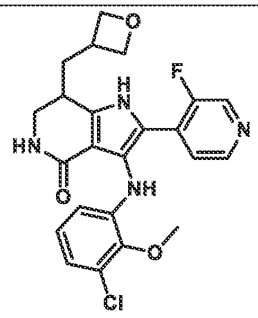
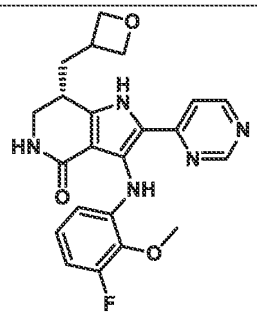
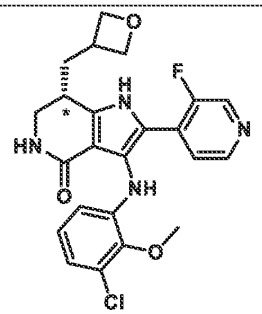
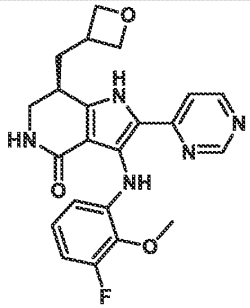
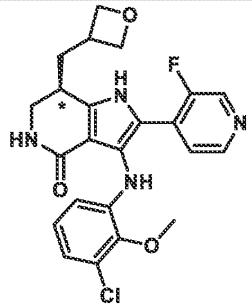
No.	Structure	No.	Structure
452d		462a	
453		462b	
453a		463	
453b		463a	

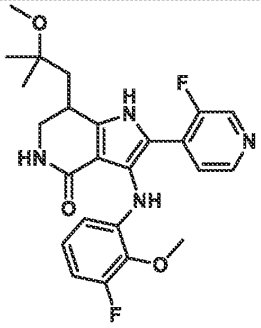
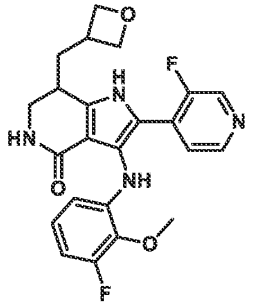
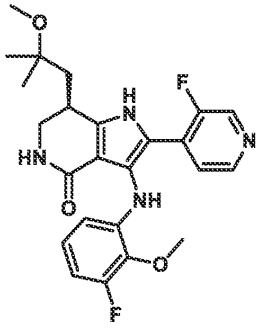
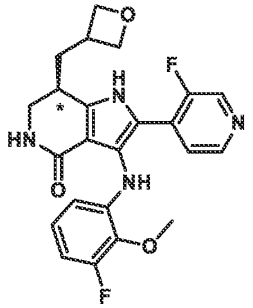
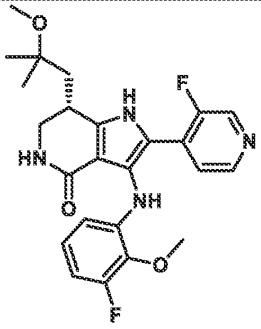
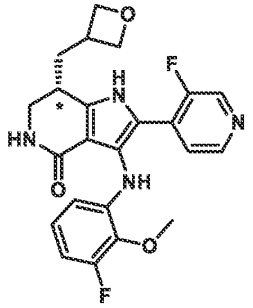
No.	Structure	No.	Structure
454		463b	
455		464	
456		464a	

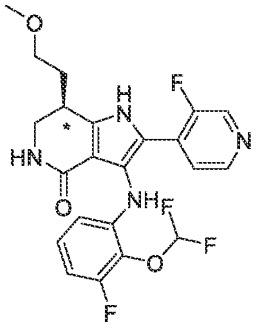
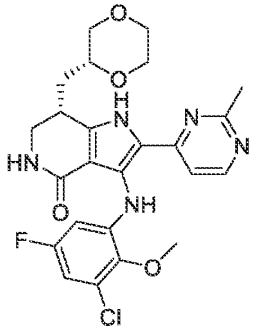
No.	Structure	No.	Structure
456a		464b	
456b		465	
456c		465a	

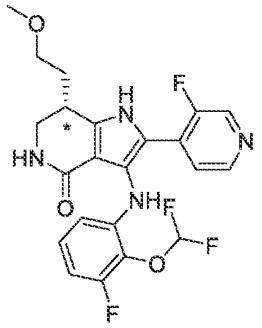
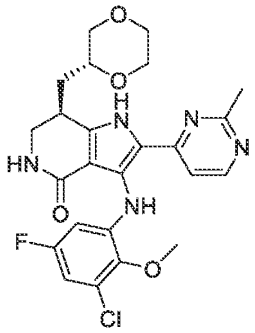
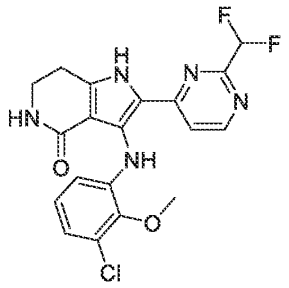
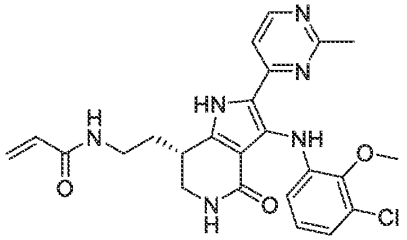
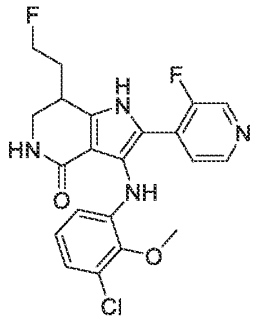
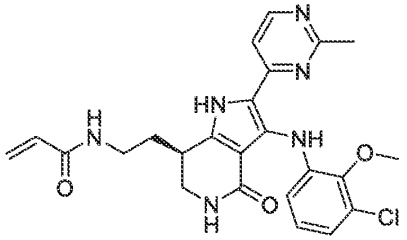
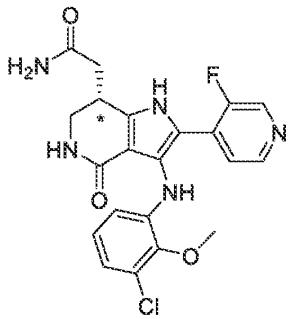
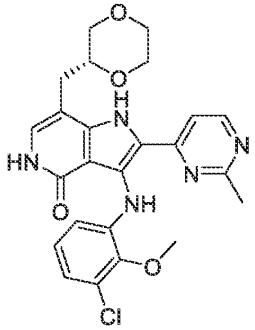
No.	Structure	No.	Structure
456d		465b	
457		466	
457a		466a	

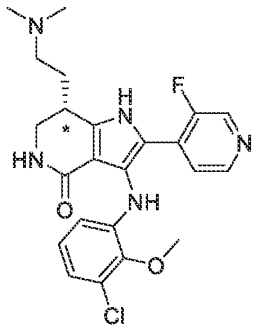
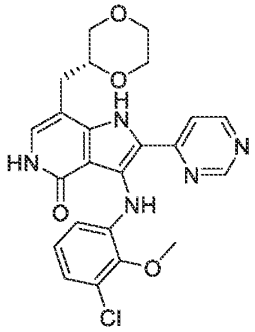
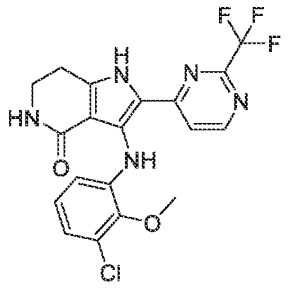
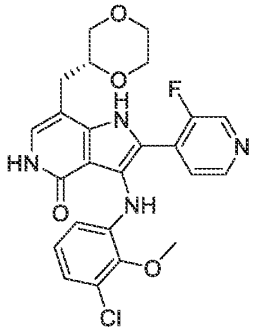
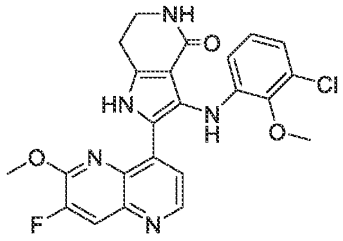
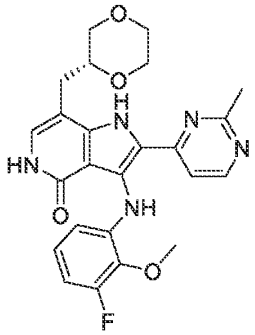
No.	Structure	No.	Structure
457b		466b	
458		467	
458a		467a	

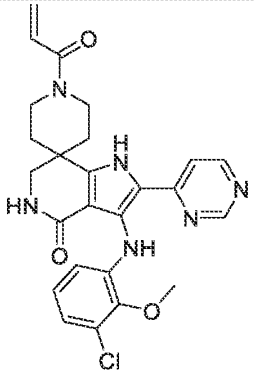
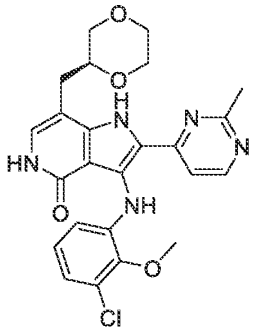
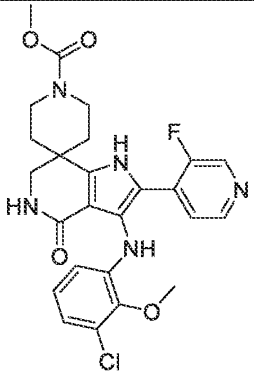
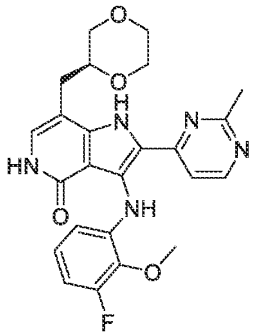
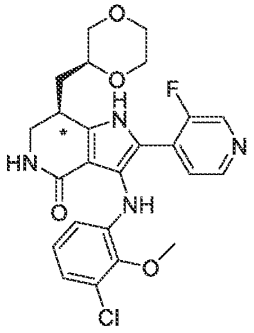
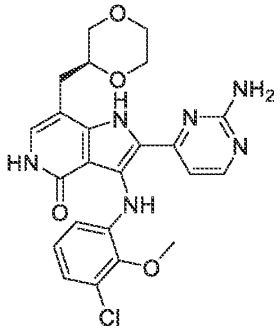
No.	Structure	No.	Structure
458b		467b	
459		468	
459a		468a	
459b		468b	

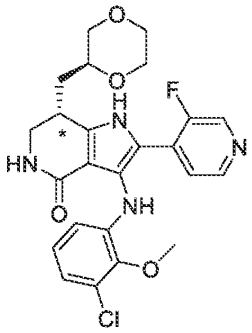
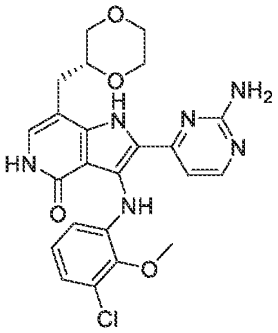
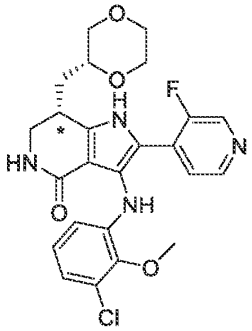
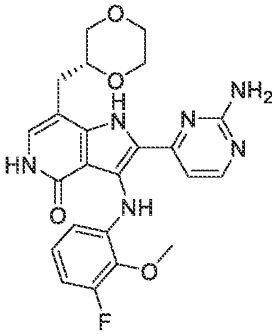
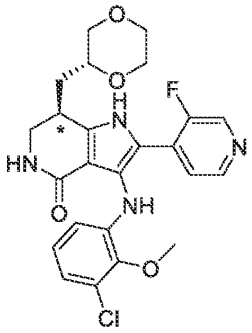
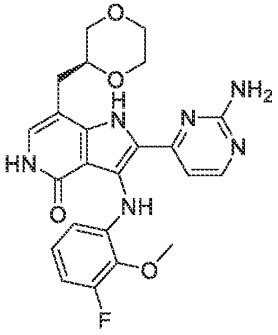
No.	Structure	No.	Structure
460		469	
460a		469a	
460b		469b	

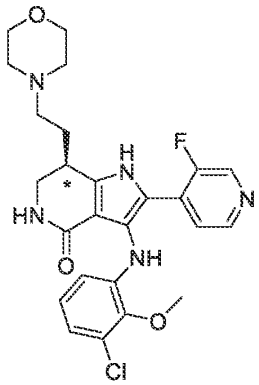
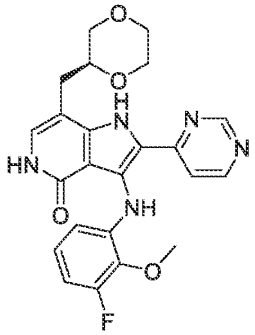
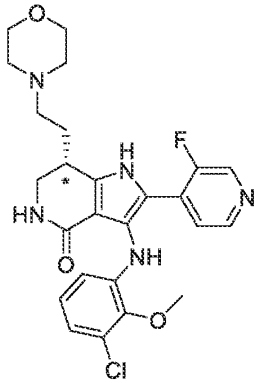
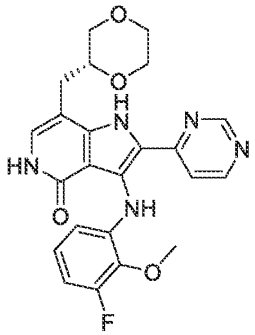
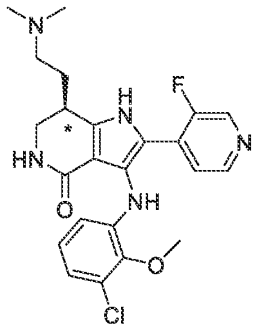
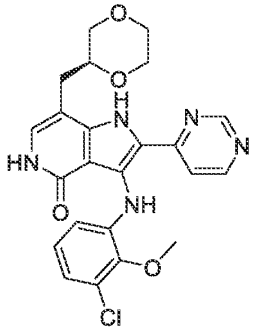
470		651	

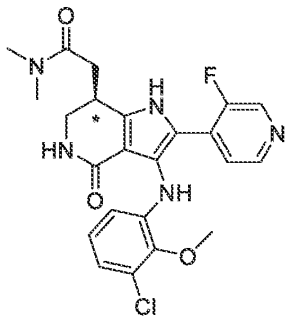
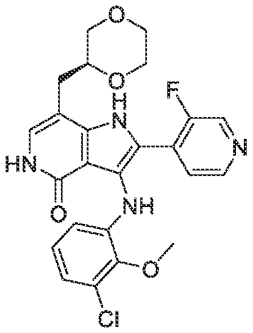
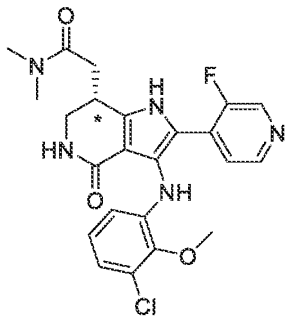
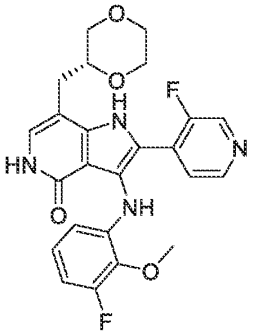
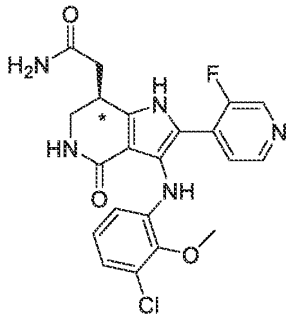
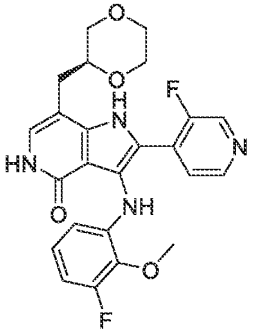
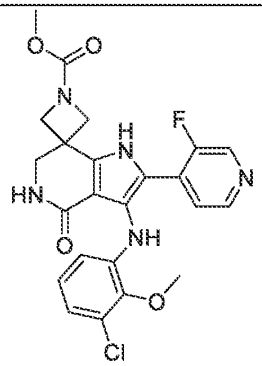
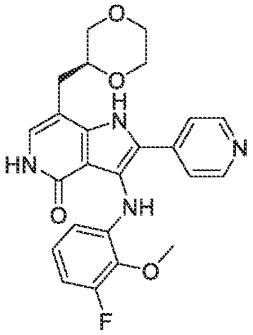
471		652	
472		653	
473		654	
474		655	

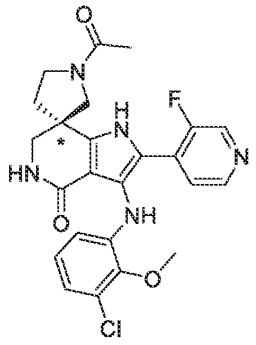
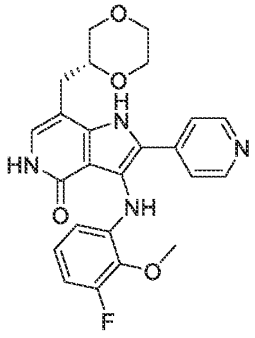
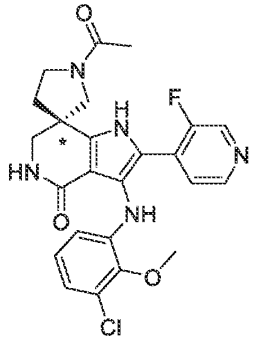
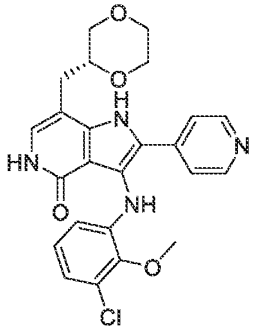
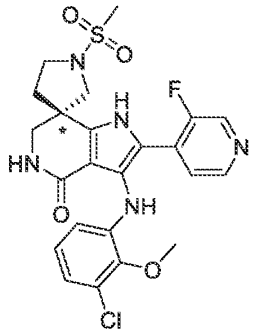
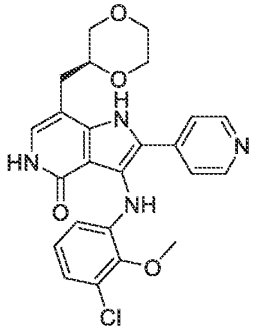
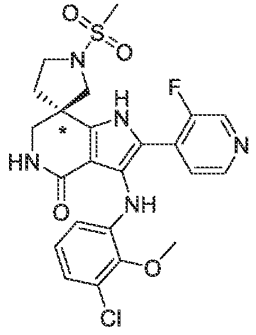
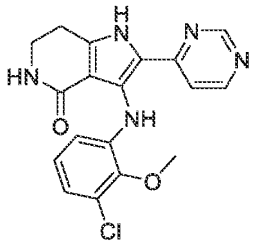
475		656	
476		657	
477		658	

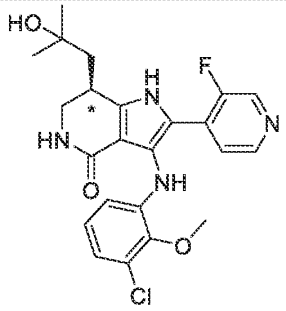
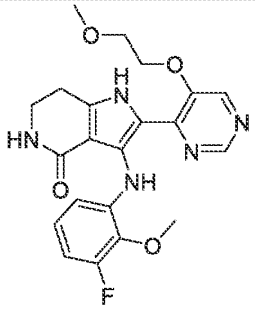
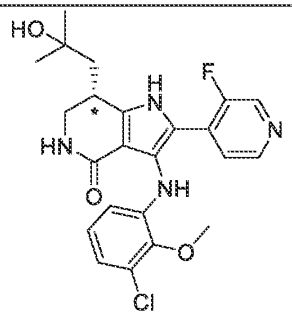
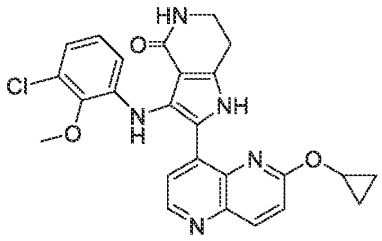
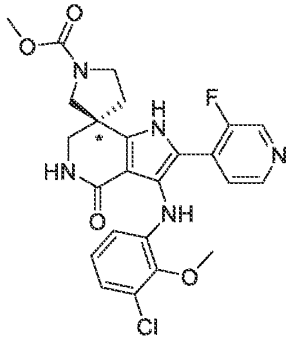
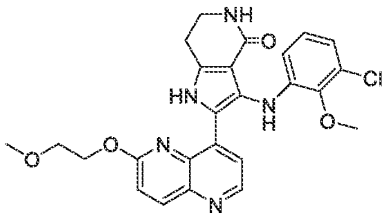
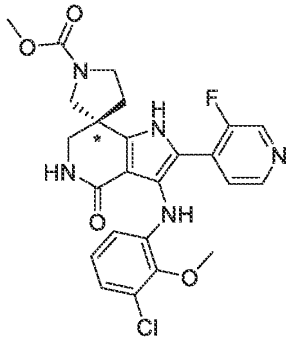
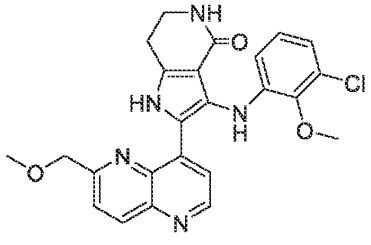
478		659	
479		660	
480		661	

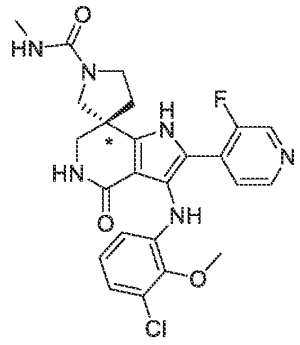
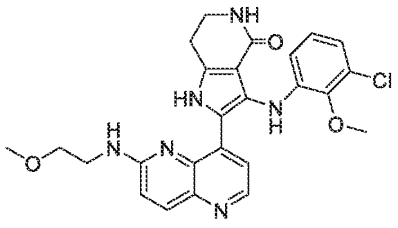
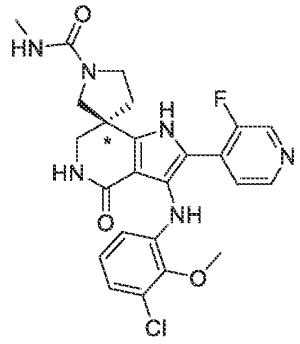
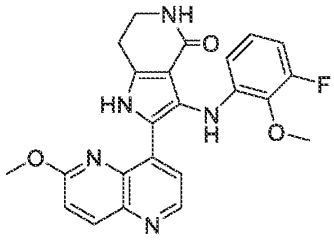
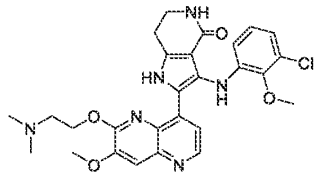
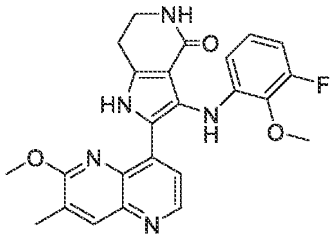
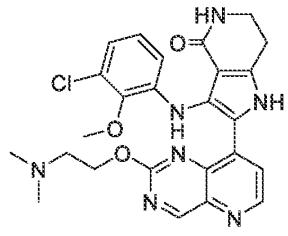
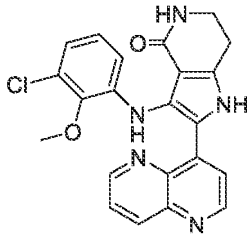
481		662	
482		663	
483		664	

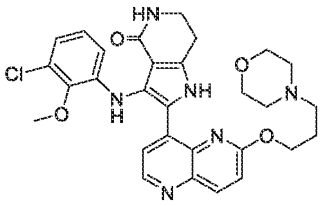
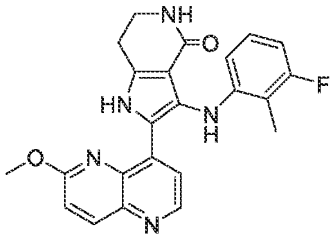
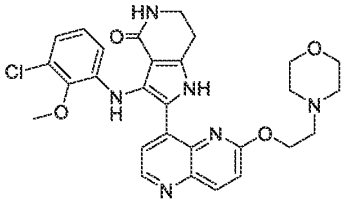
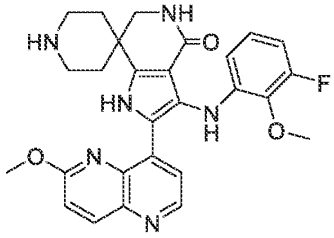
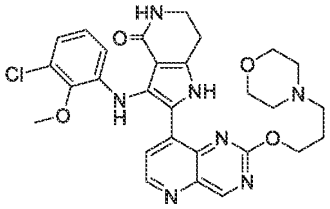
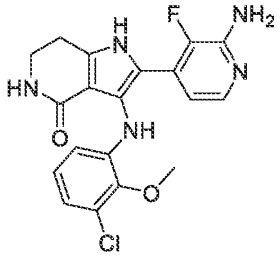
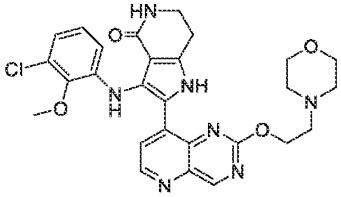
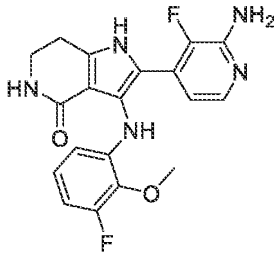
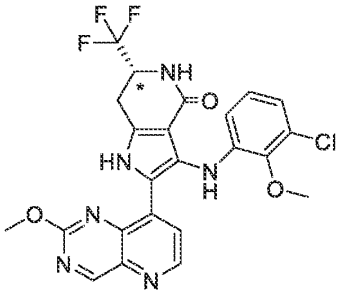
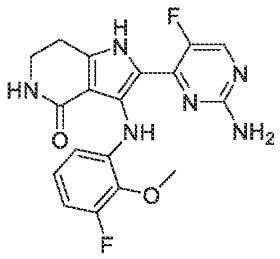
484		665	
485		666	
486		667	

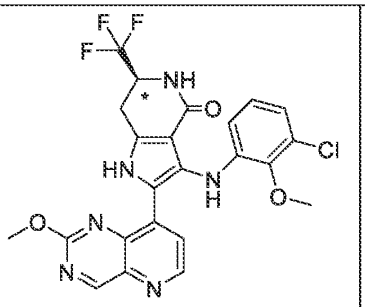
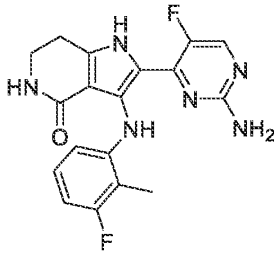
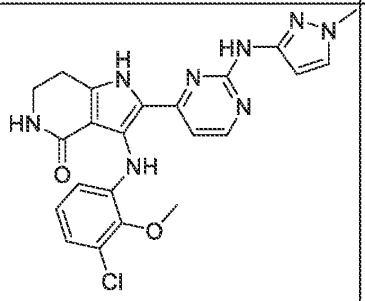
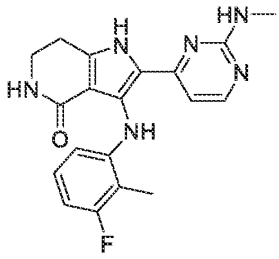
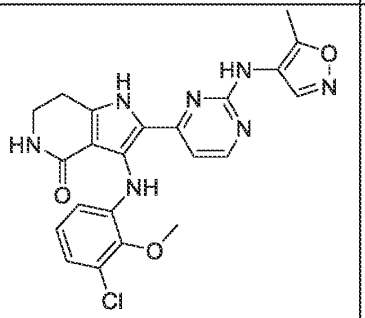
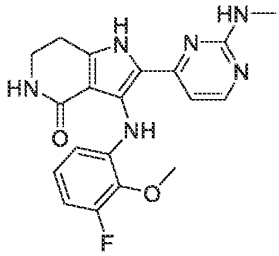
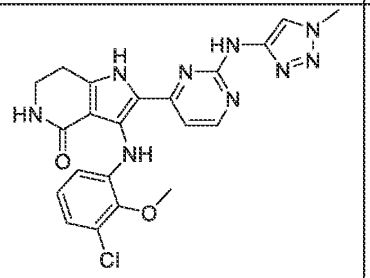
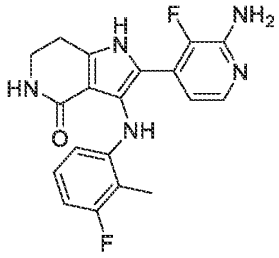
487		668	
488		669	
489		670	
490		671	

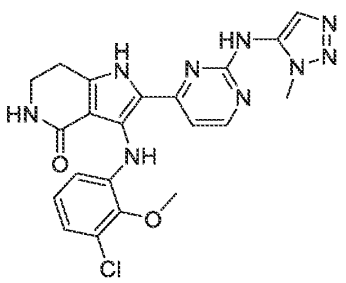
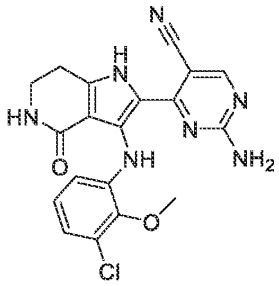
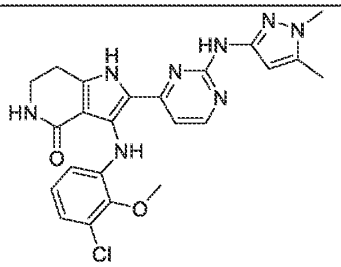
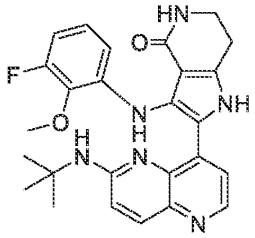
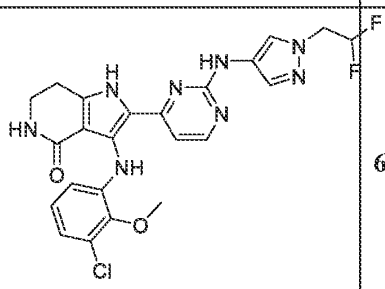
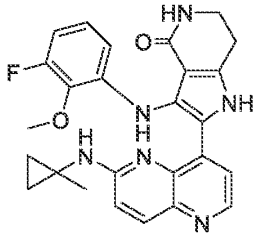
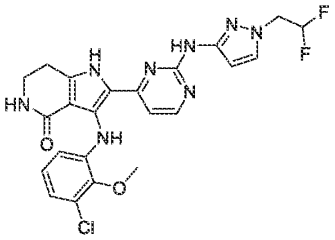
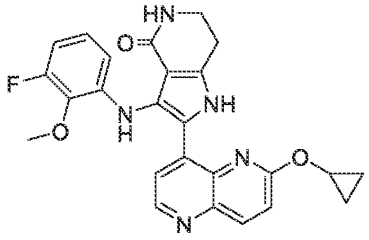
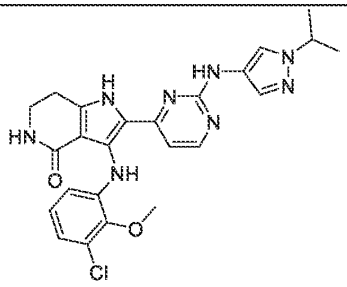
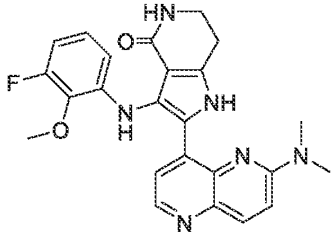
491		672	
492		673	
493		674	
494		675	

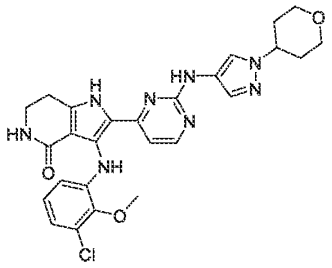
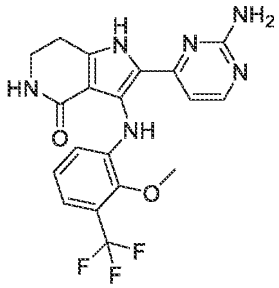
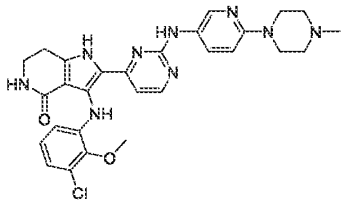
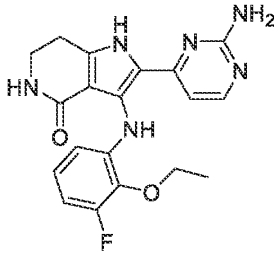
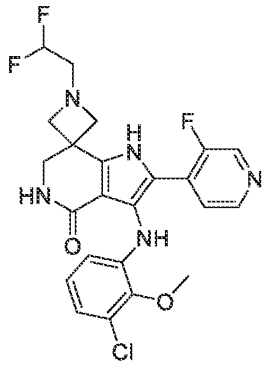
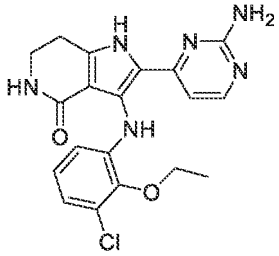
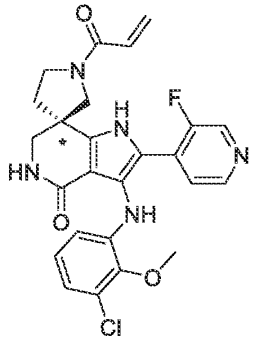
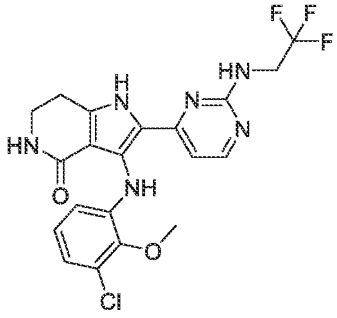
495		676	
496		677	
497		678	
498		679	

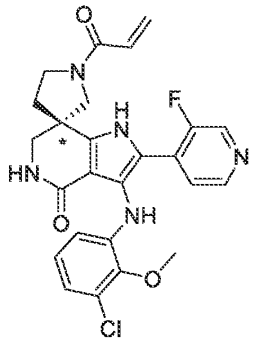
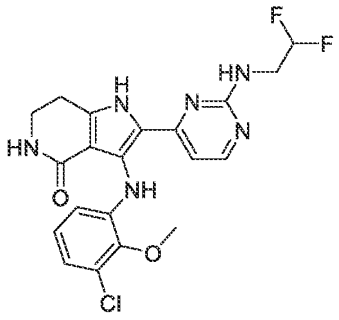
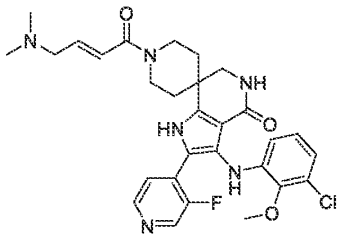
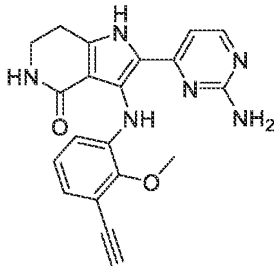
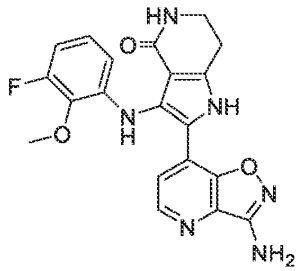
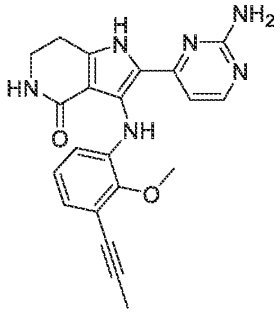
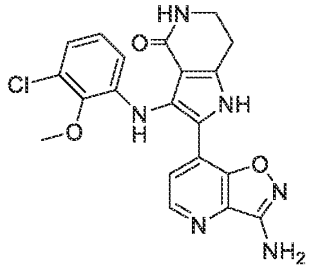
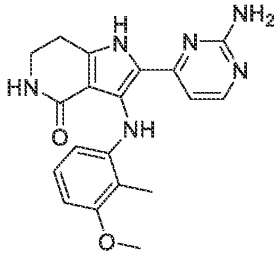
499		680	
500		681	
501		682	
502		683	

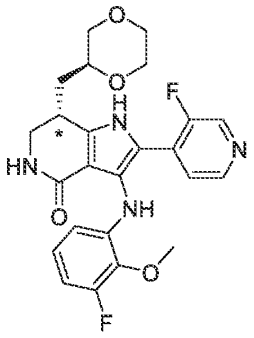
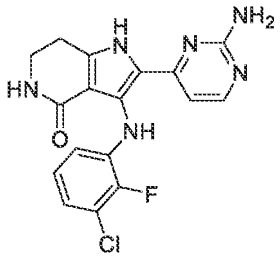
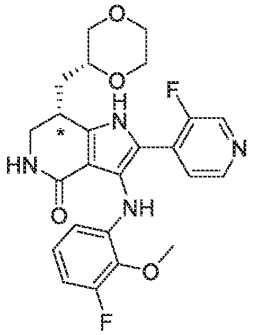
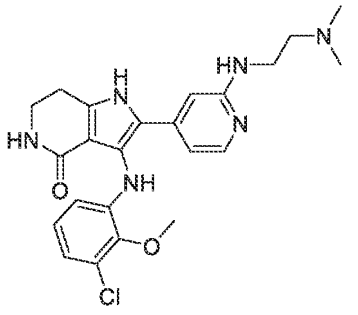
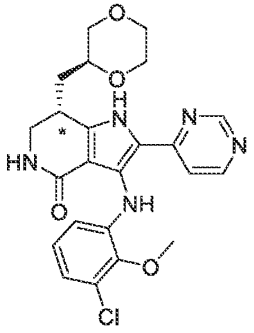
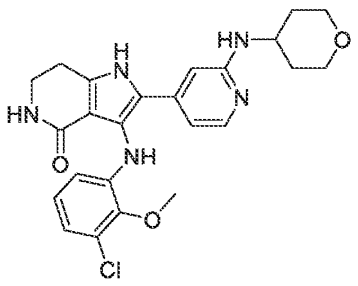
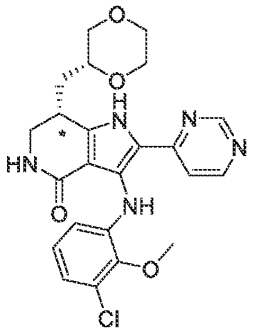
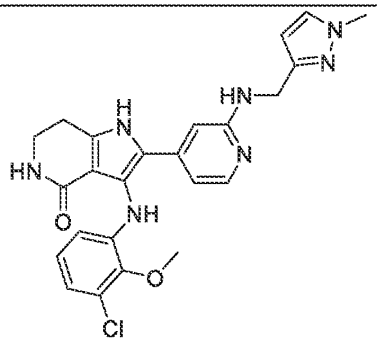
503		684	
504		685	
505		686	
506		687	
507		688	

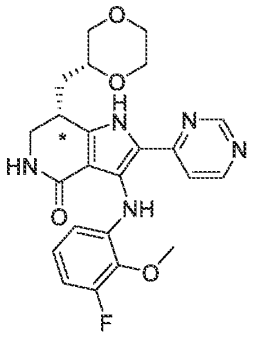
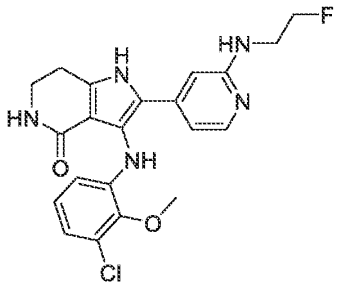
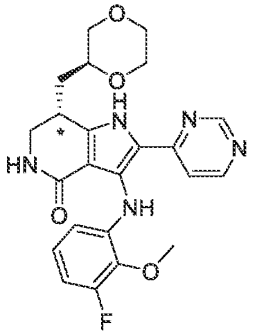
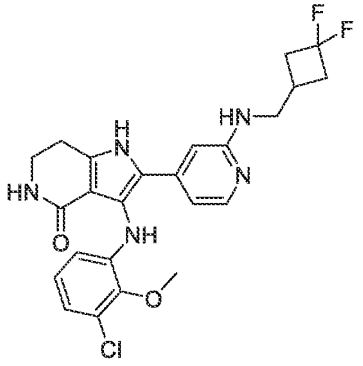
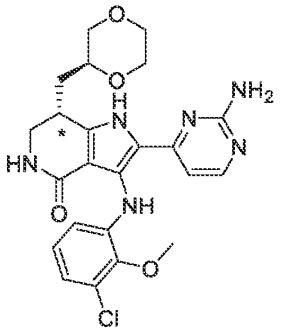
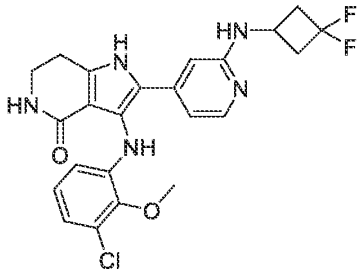
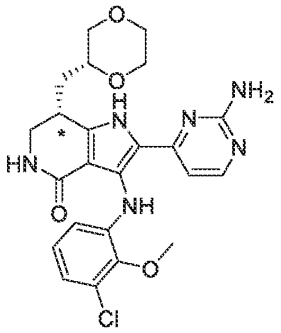
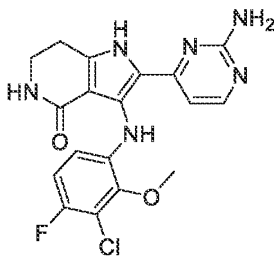
508		689	
509		690	
510		691	
511		692	

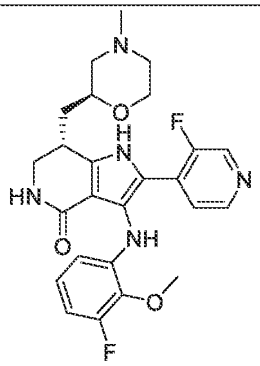
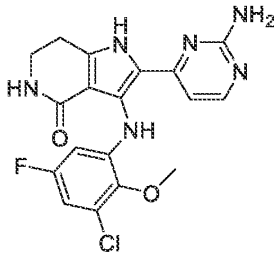
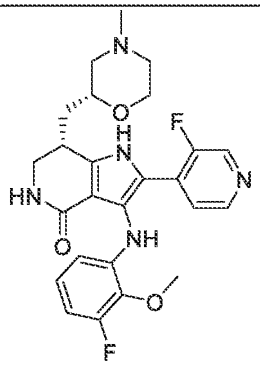
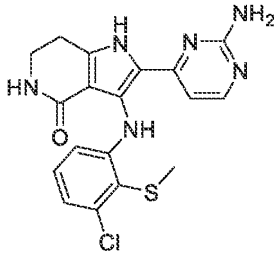
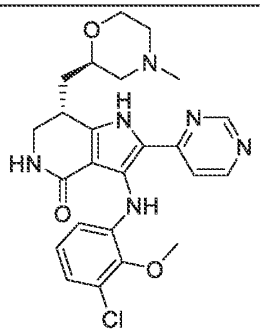
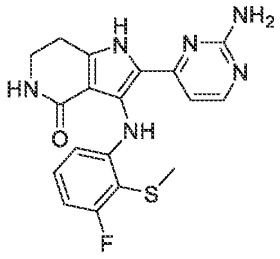
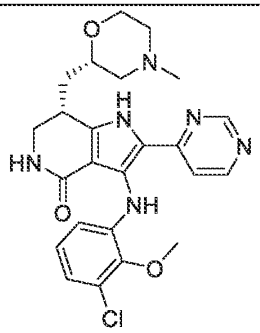
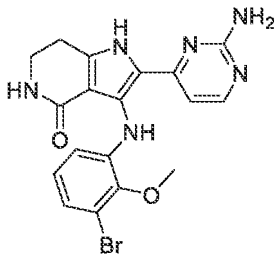
512		693	
513		694	
514		695	
515		696	
516		697	

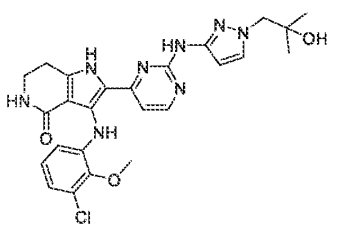
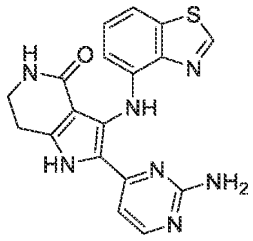
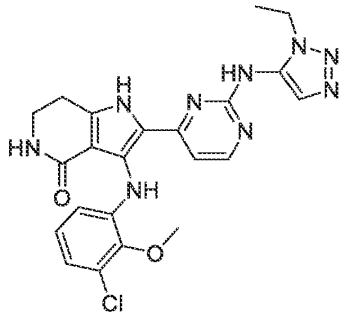
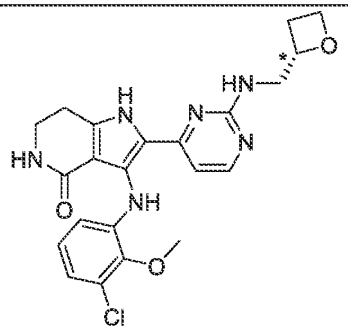
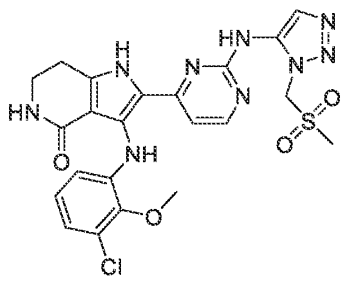
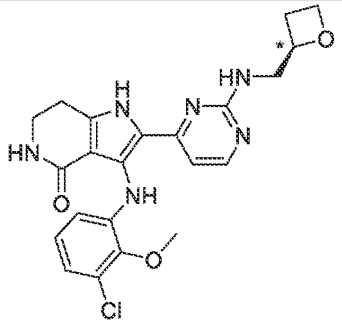
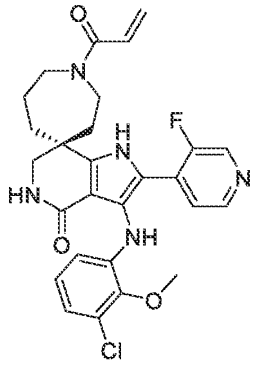
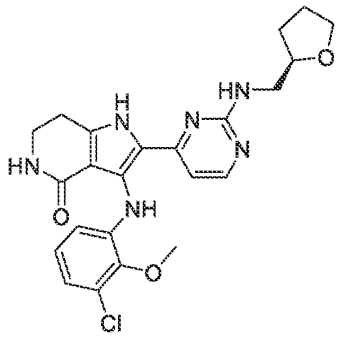
517		698	
518		699	
519		700	
520		701	

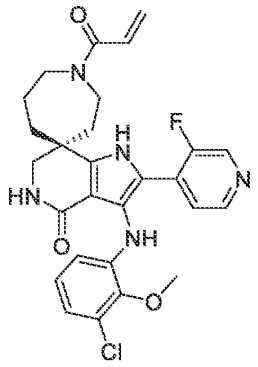
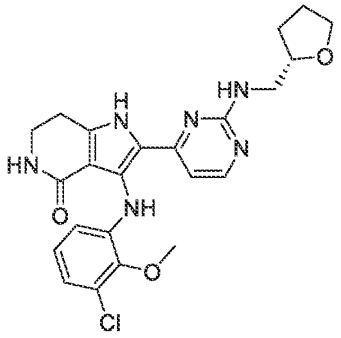
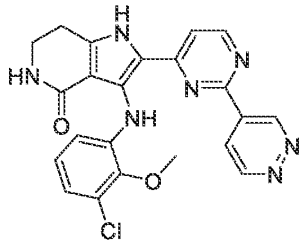
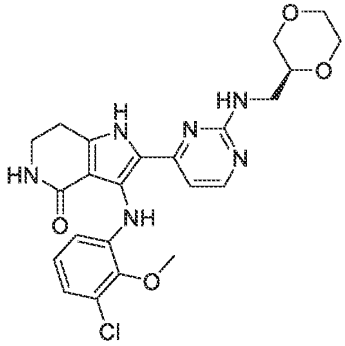
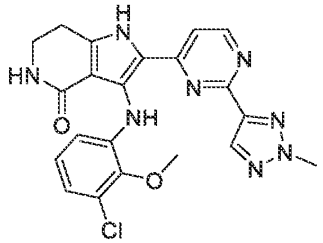
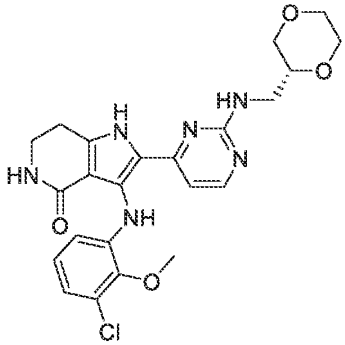
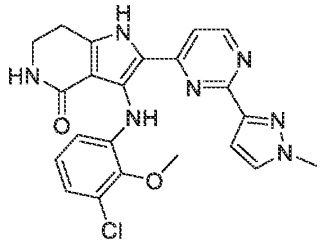
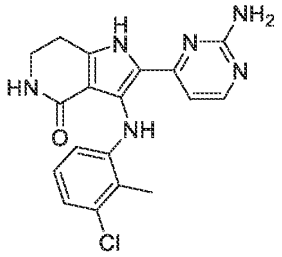
521		702	
522		703	
523		704	
524		705	

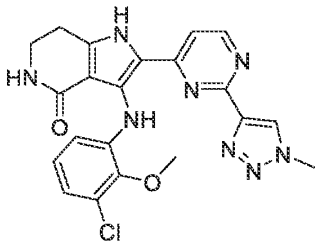
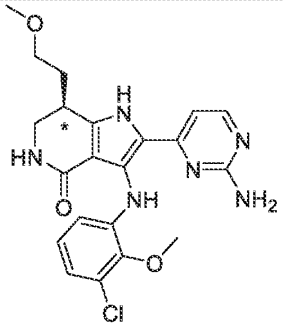
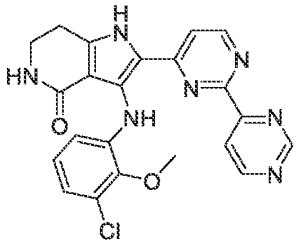
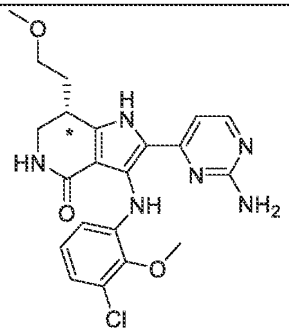
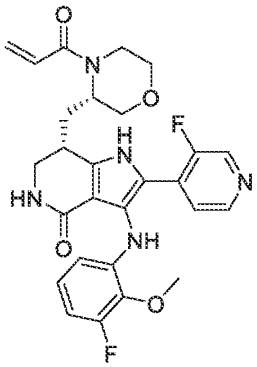
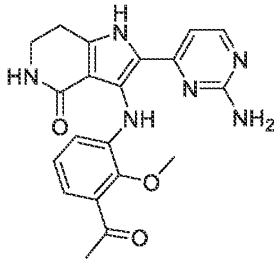
525		706	
526		707	
527		708	
528		709	

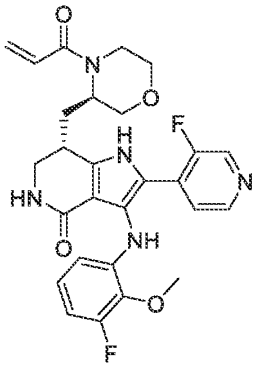
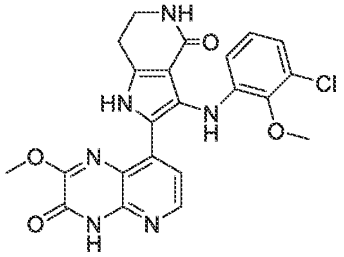
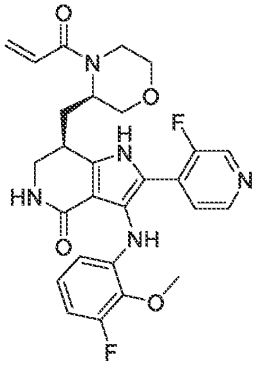
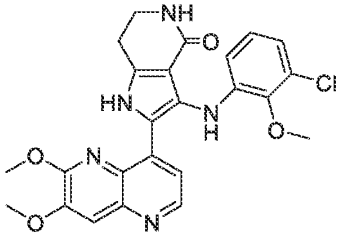
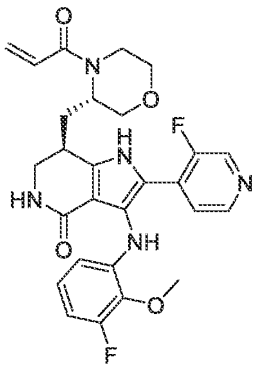
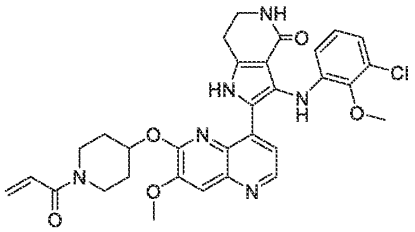
529		710	
530		711	
531		712	
532		713	

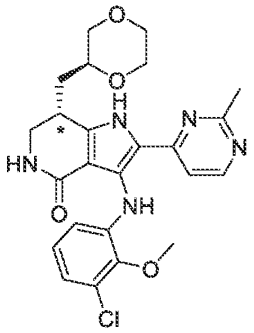
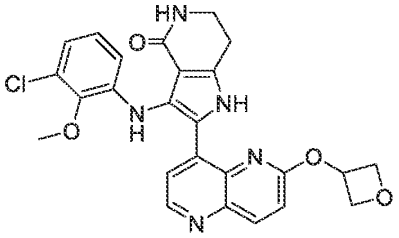
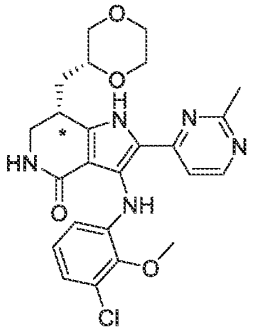
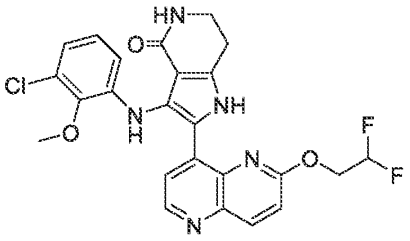
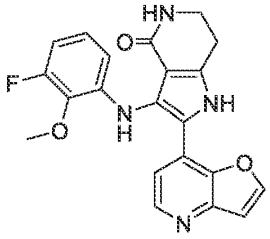
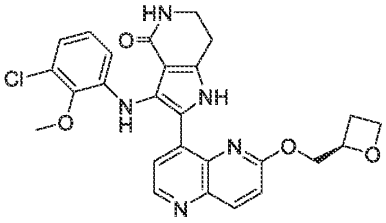
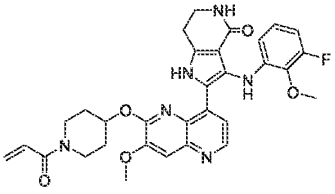
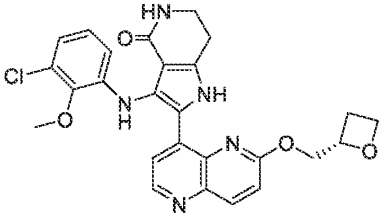
533		714	
534		715	
535		716	
536		717	

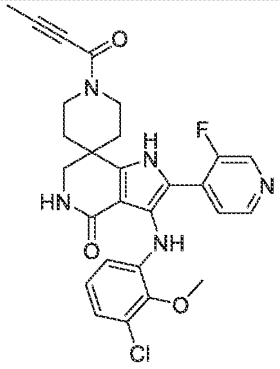
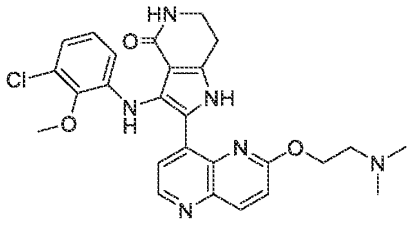
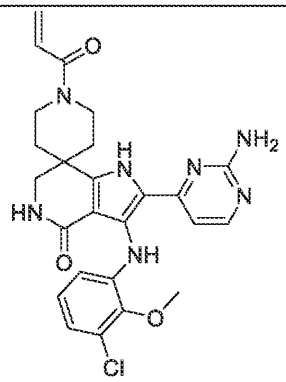
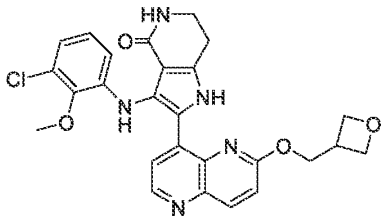
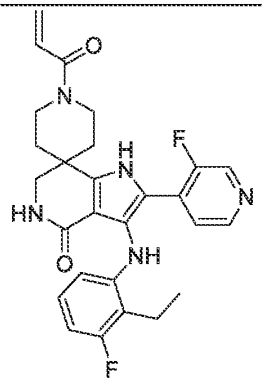
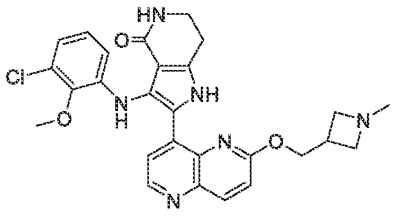
537		718	
538		719	
539		720	
540		721	

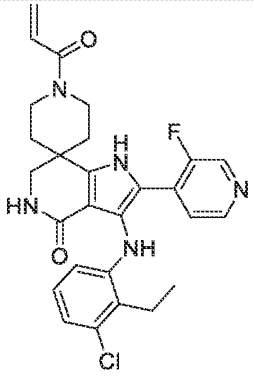
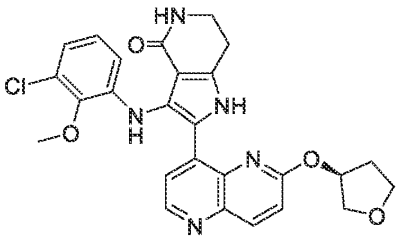
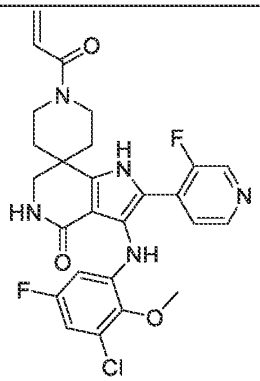
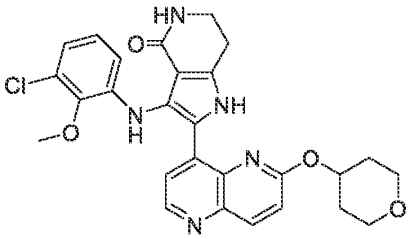
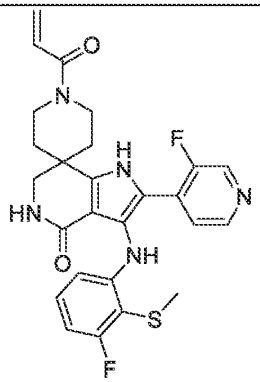
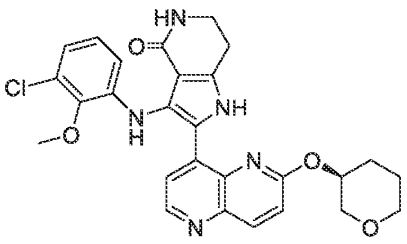
541		722	
542		723	
543		724	
544		725	

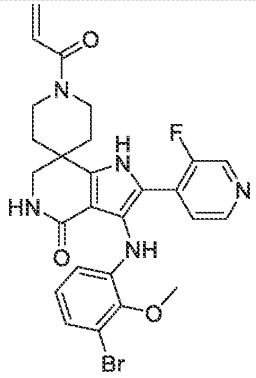
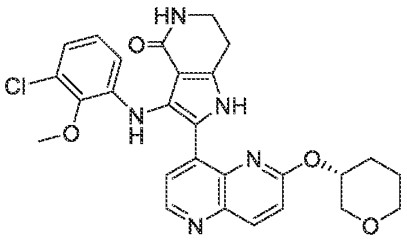
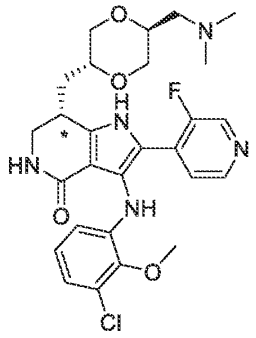
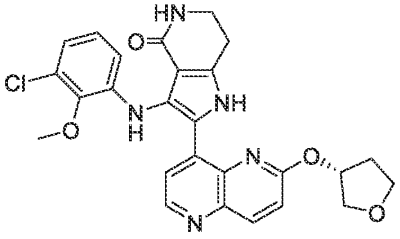
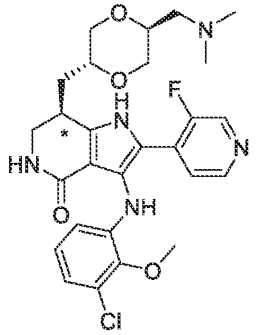
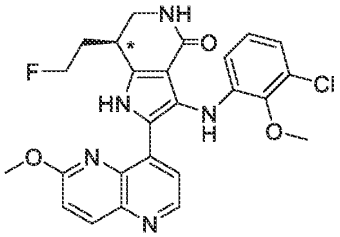
545		726	
546		727	
547		728	

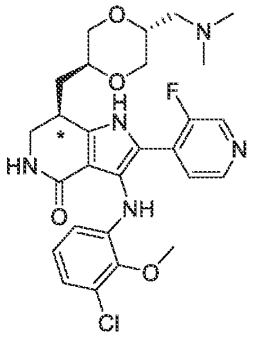
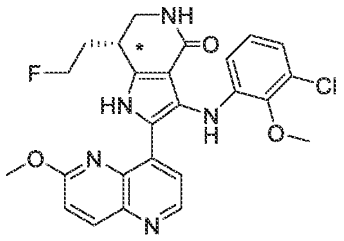
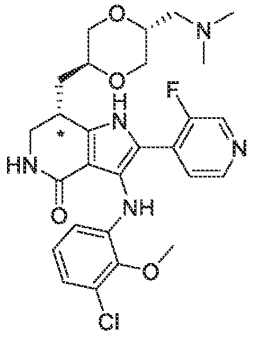
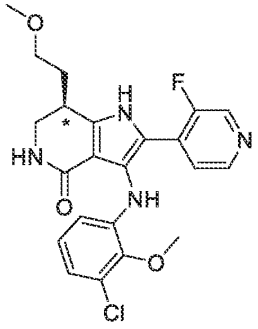
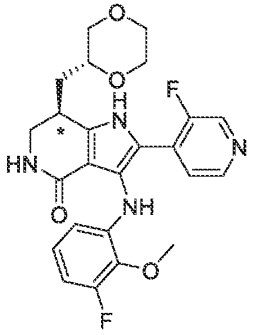
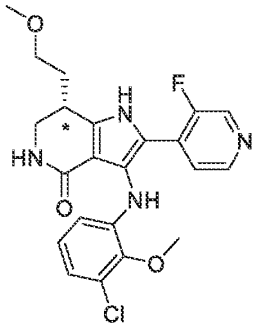
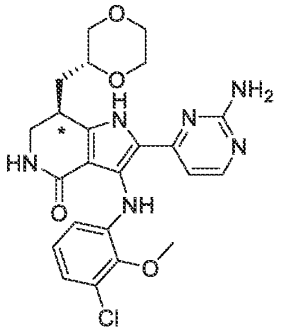
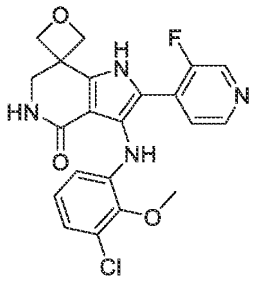
548		729	
549		730	
550		731	

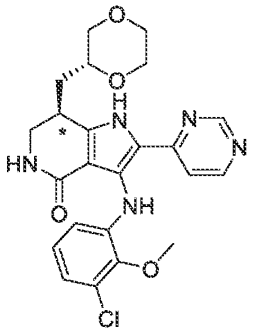
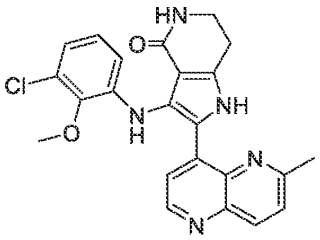
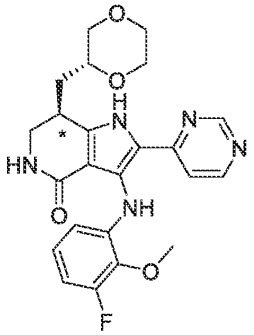
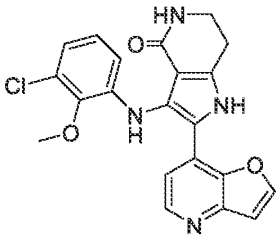
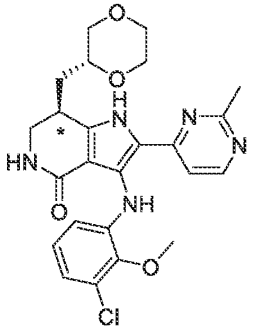
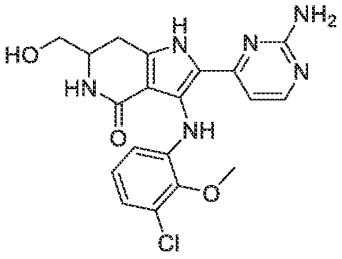
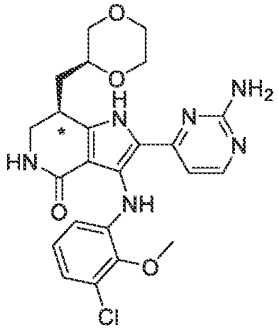
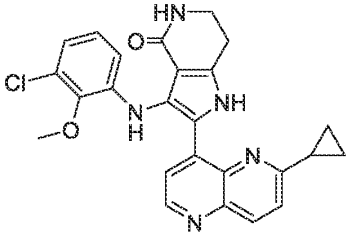
551		732	
552		733	
553		734	
554		735	

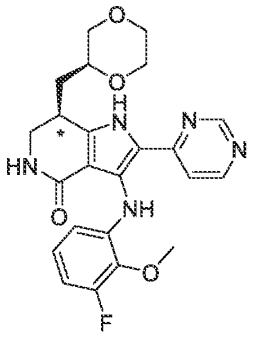
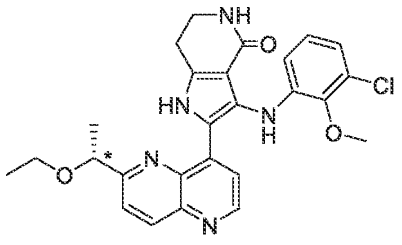
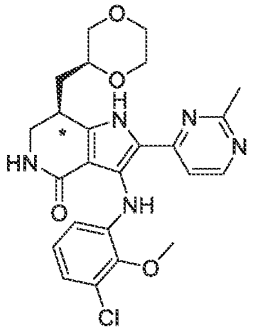
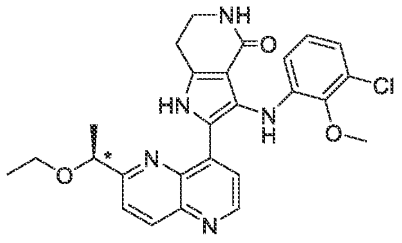
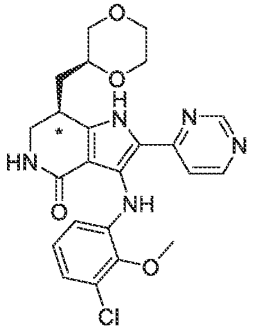
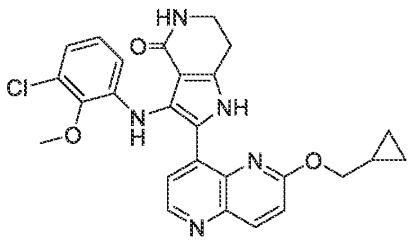
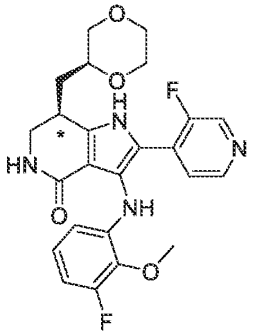
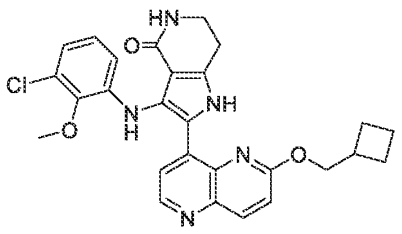
555		736	
556		737	
557		738	

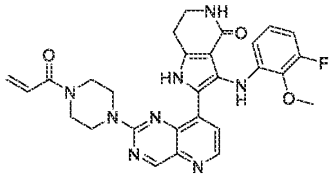
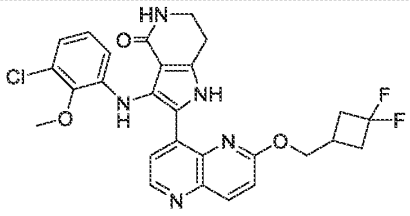
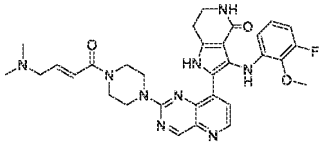
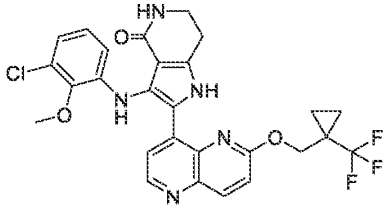
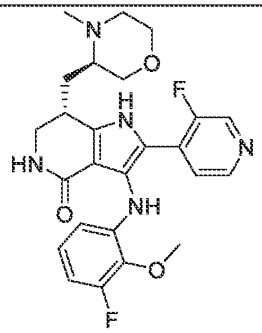
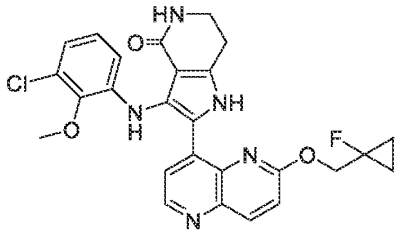
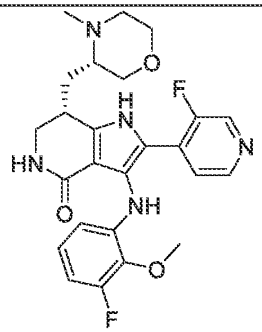
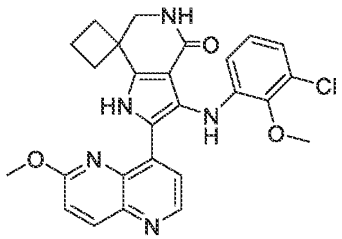
558		739	
559		740	
560		741	

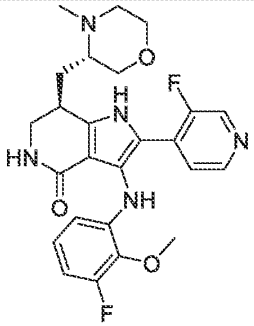
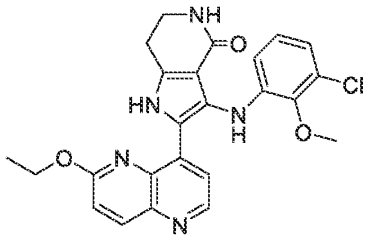
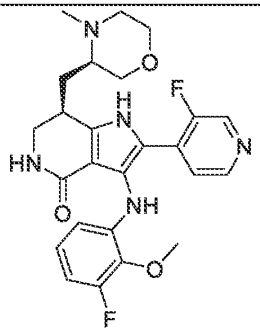
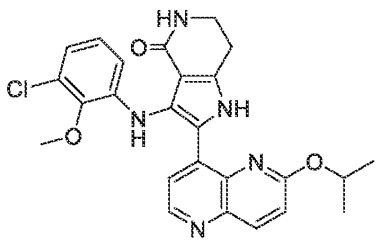
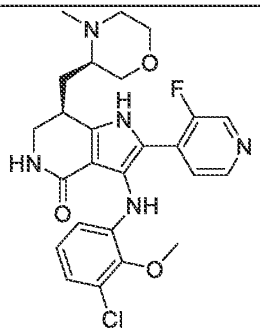
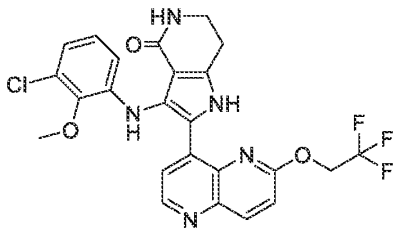
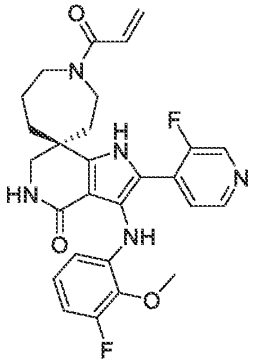
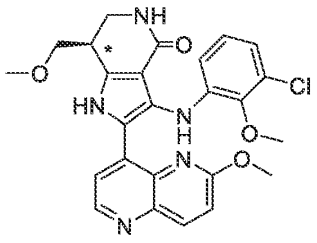
561		742	
562		743	
563		744	

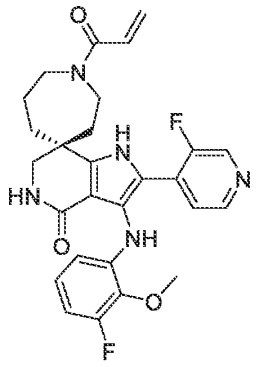
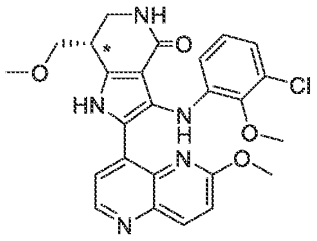
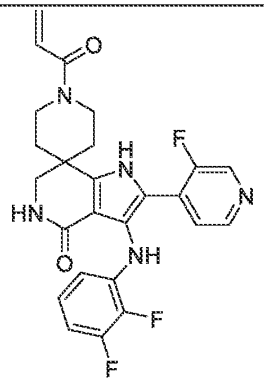
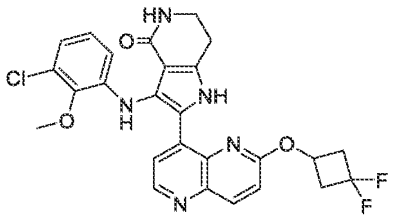
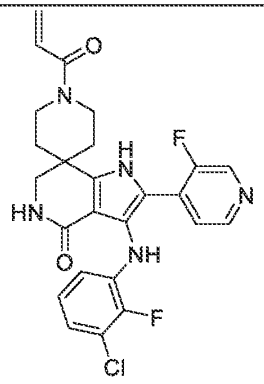
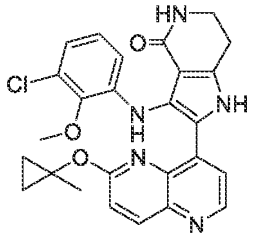
564		745	
565		746	
566		747	
567		748	

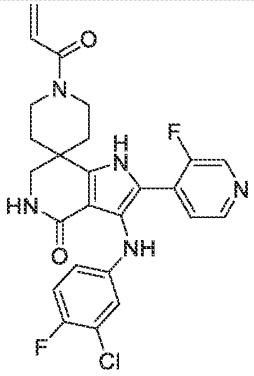
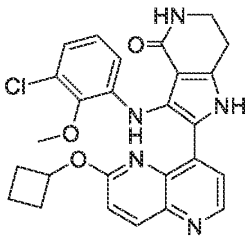
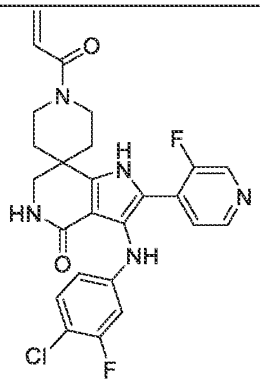
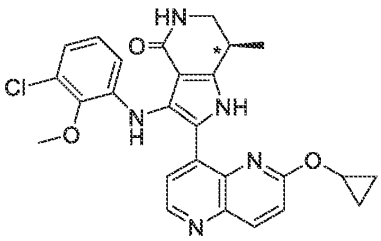
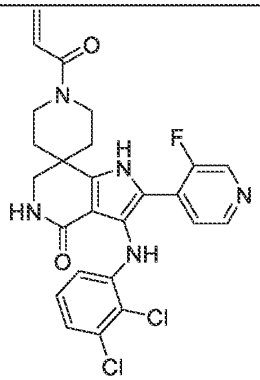
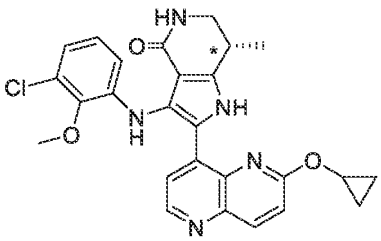
568		749	
569		750	
570		751	
571		752	

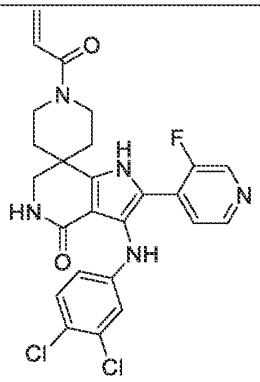
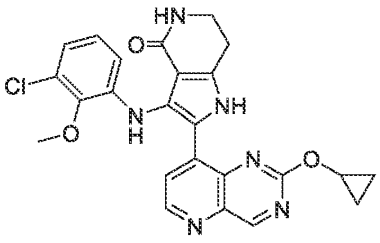
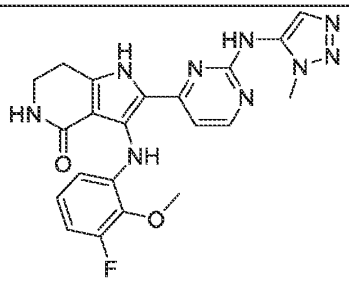
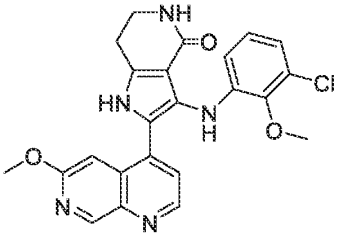
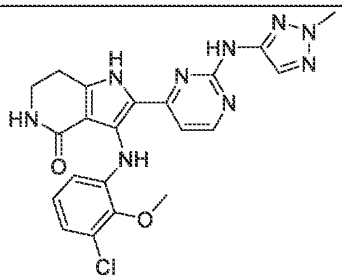
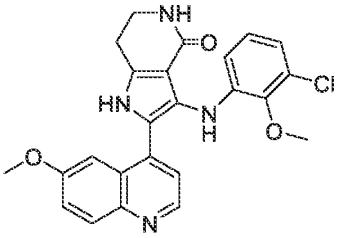
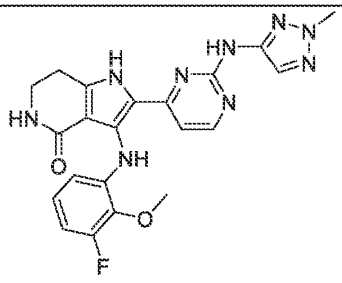
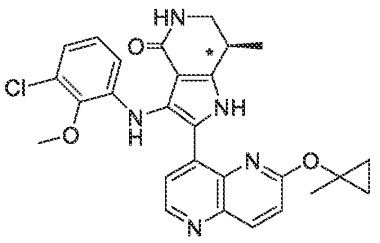
572		753	
573		754	
574		755	
575		756	

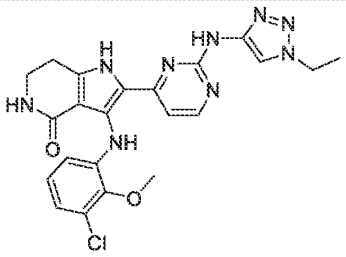
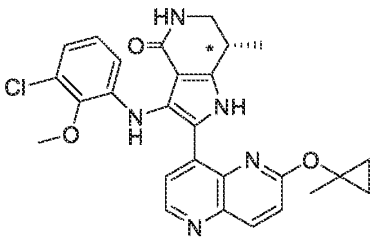
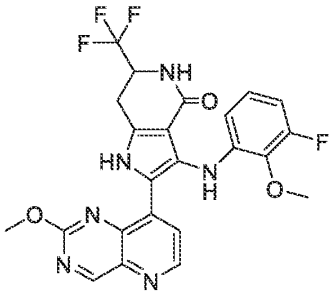
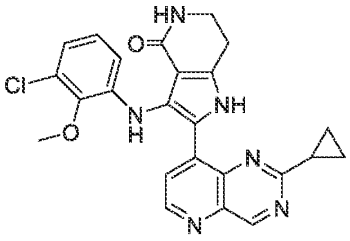
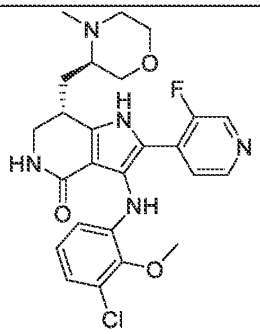
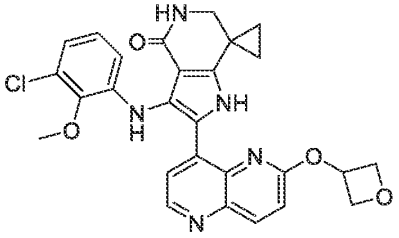
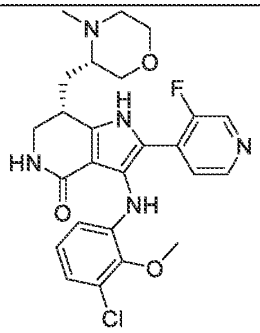
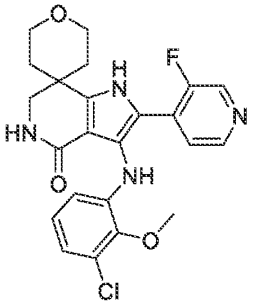
576		757	
577		758	
578		759	
579		760	

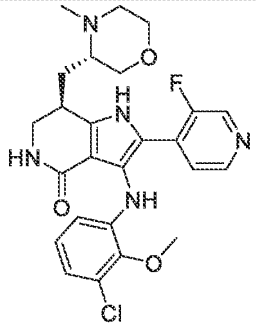
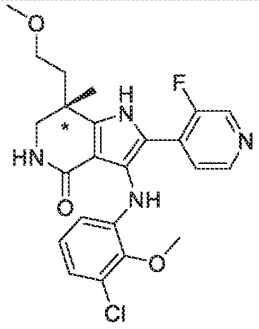
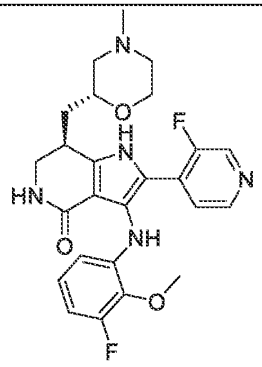
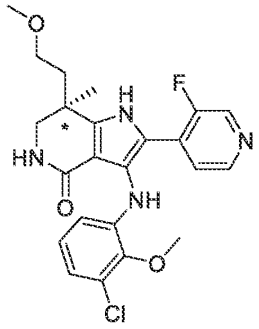
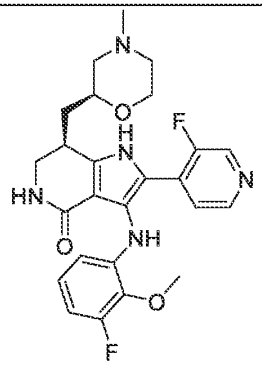
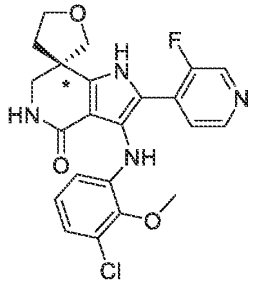
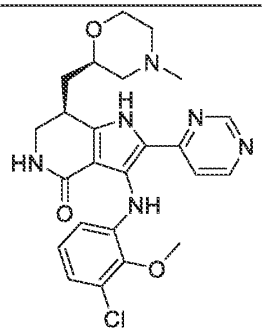
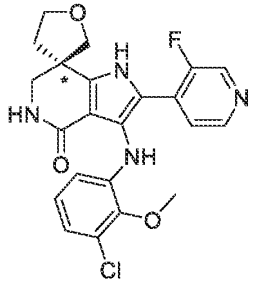
580		761	
581		762	
582		763	
583		764	

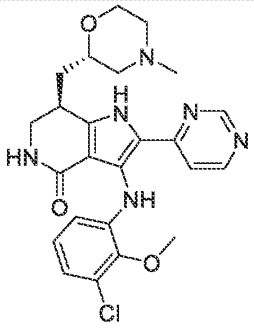
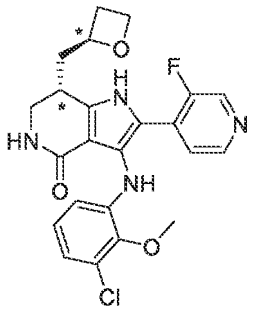
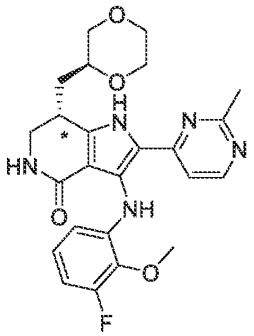
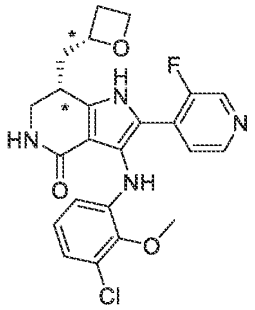
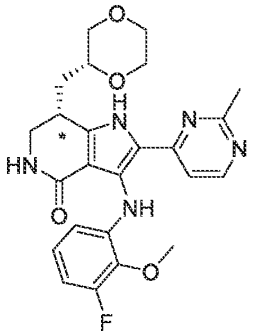
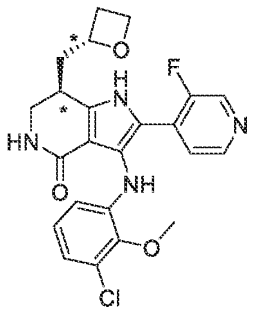
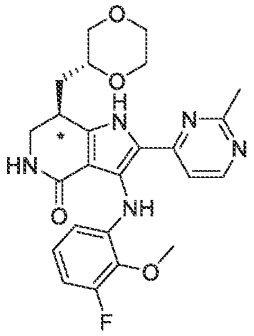
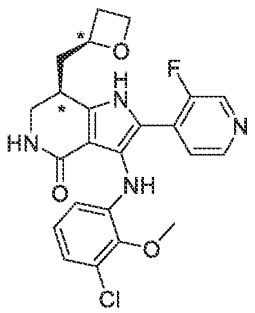
584		765	
585		766	
586		767	

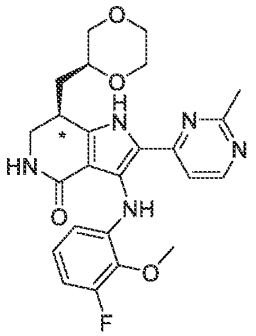
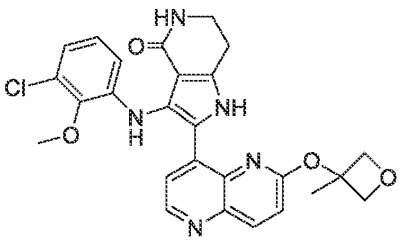
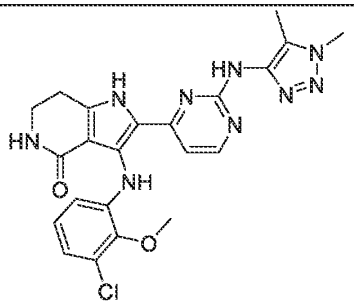
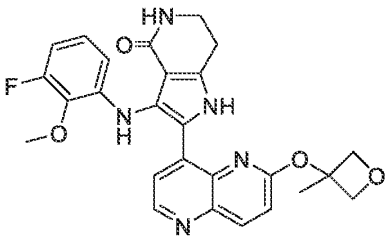
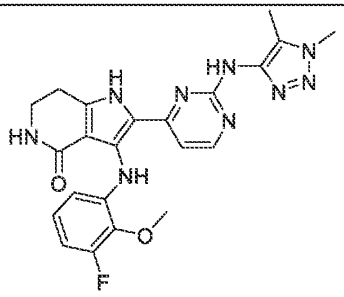
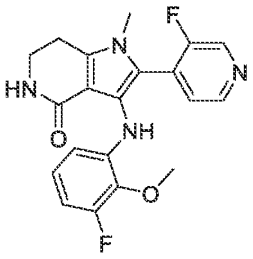
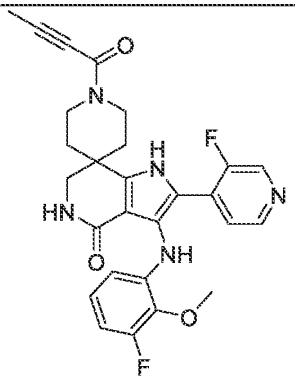
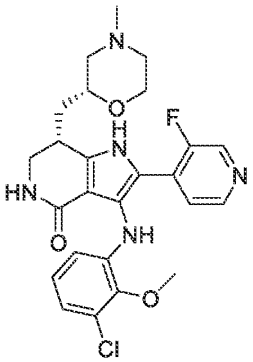
587		768	
588		769	
589		770	

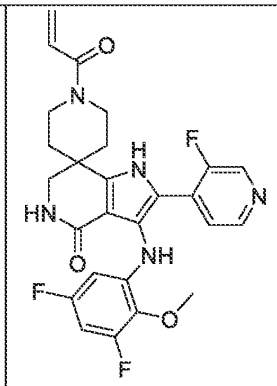
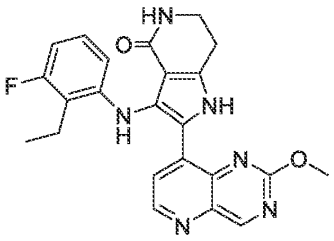
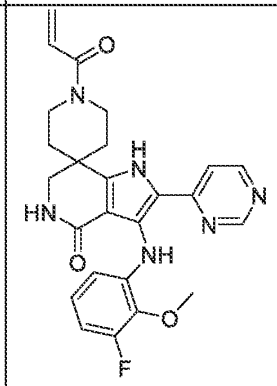
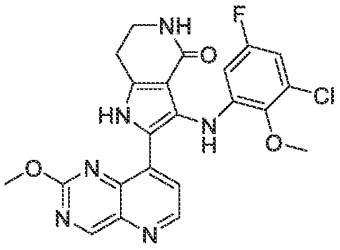
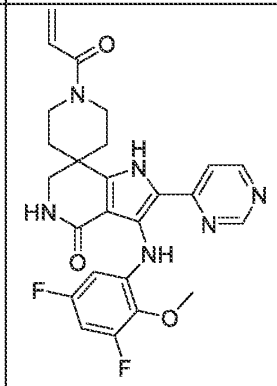
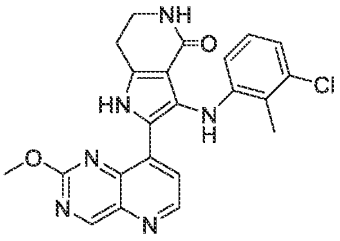
590		771	
591		772	
592		773	
593		774	

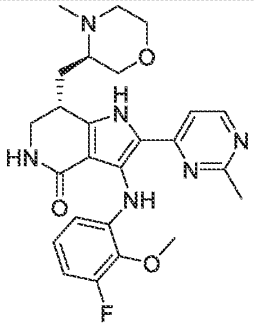
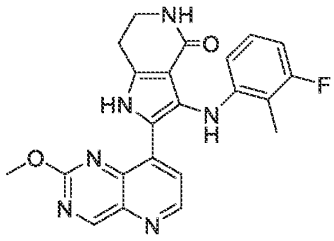
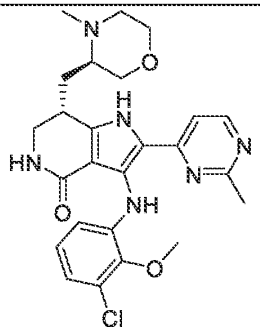
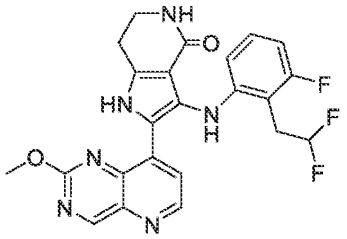
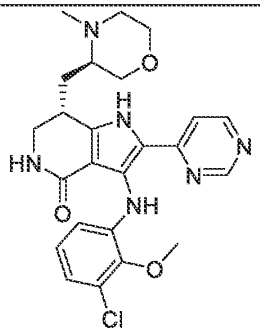
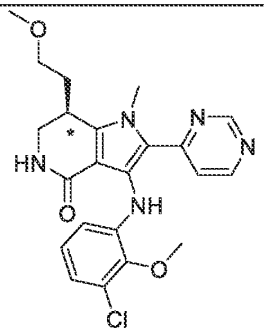
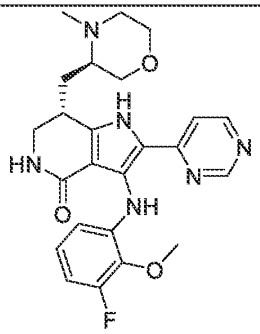
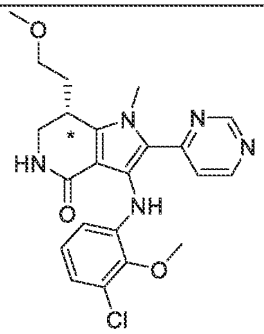
594		775	
595		776	
596		777	
597		778	

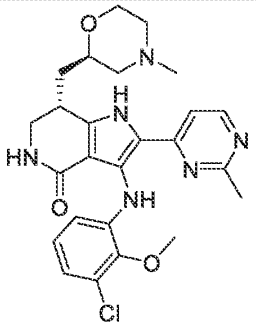
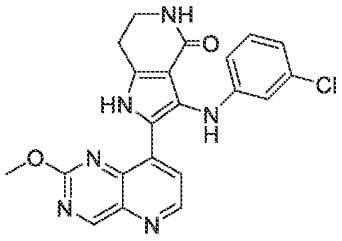
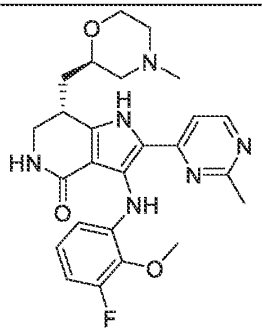
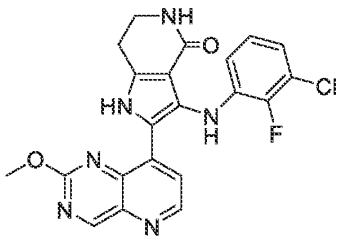
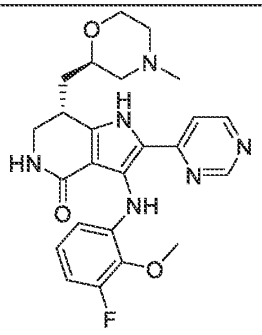
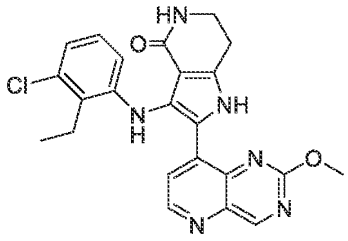
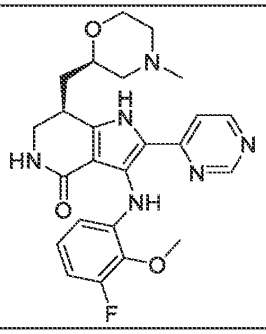
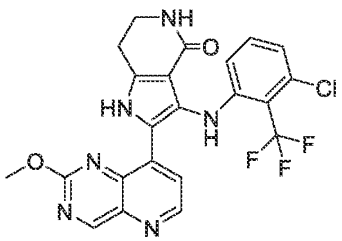
598		779	
599		780	
600		781	
601		782	

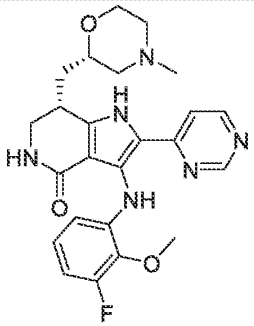
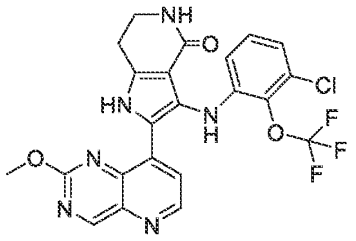
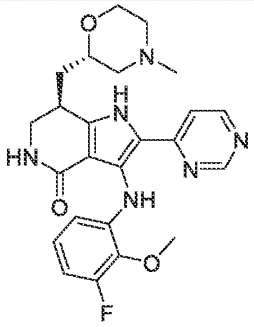
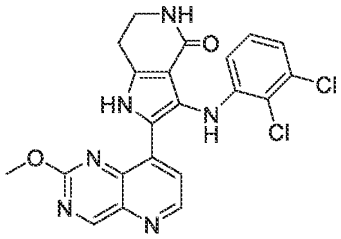
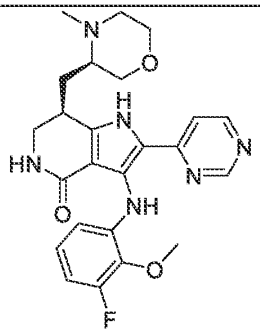
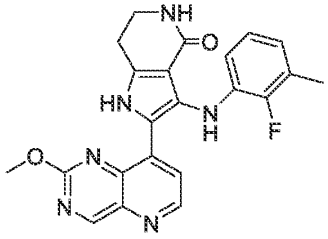
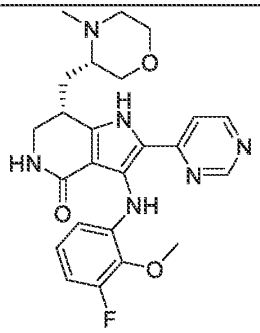
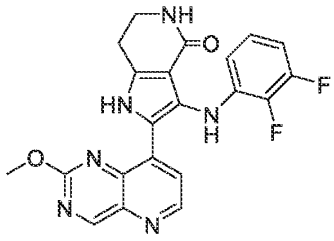
602		783	
603		784	
604		785	
605		786	

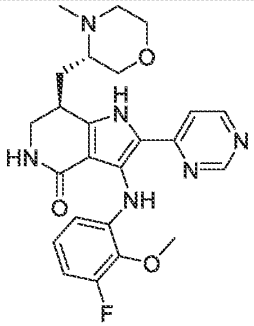
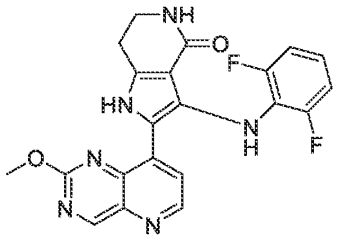
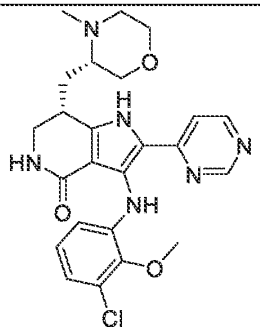
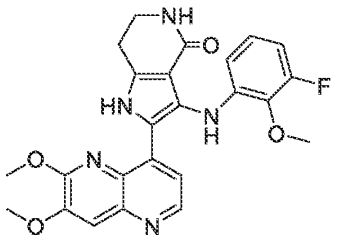
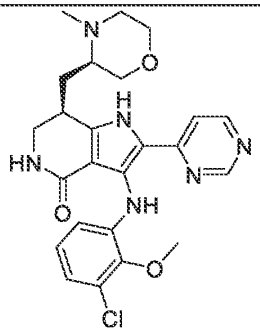
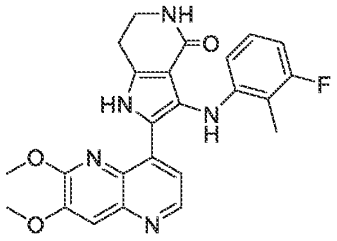
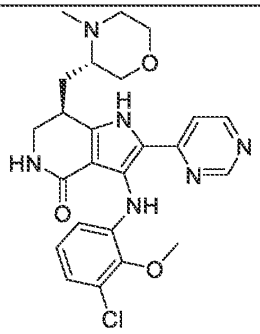
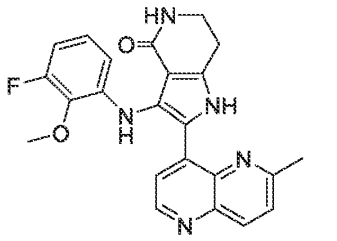
606		787	
607		788	
608		789	
609		790	

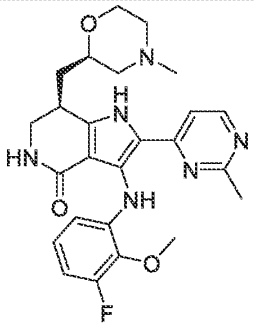
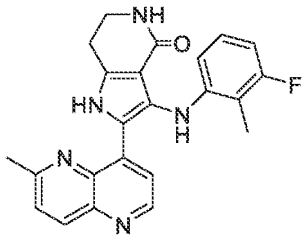
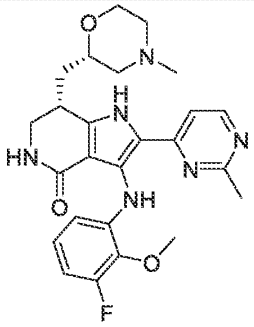
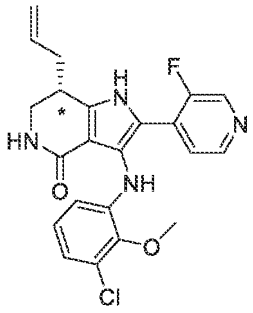
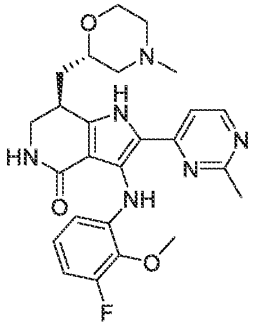
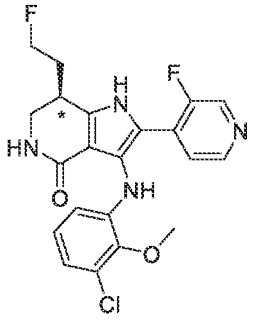
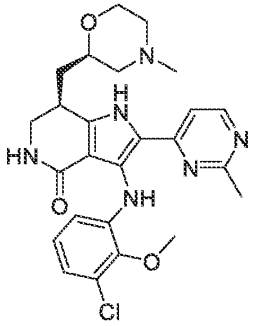
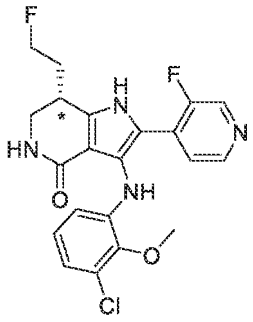
610		791	
611		792	
612		793	

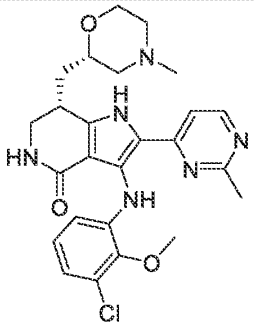
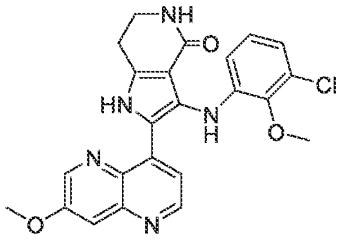
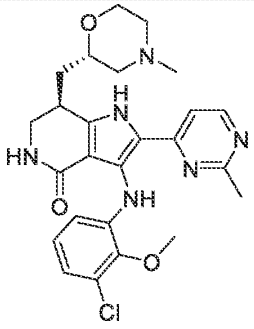
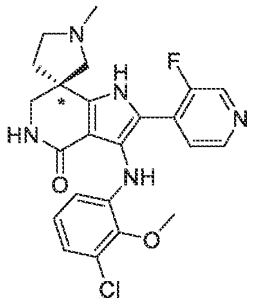
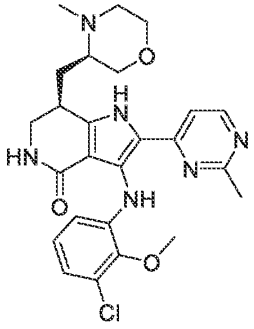
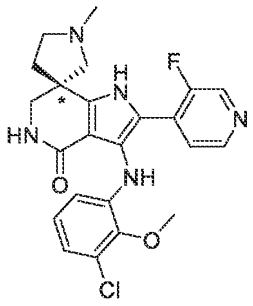
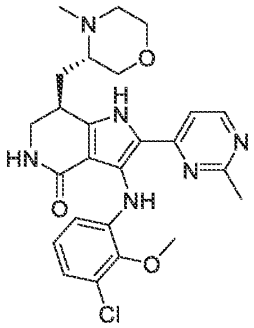
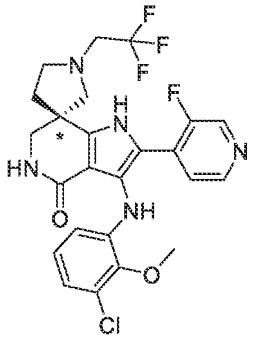
613		794	
614		795	
615		796	
616		797	

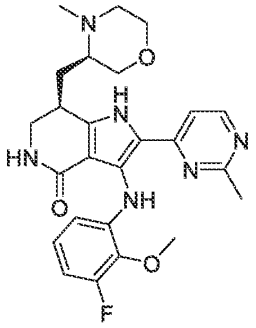
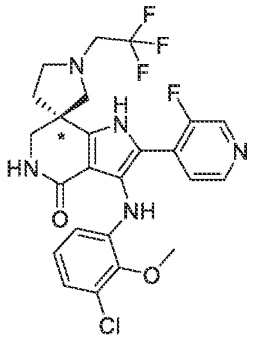
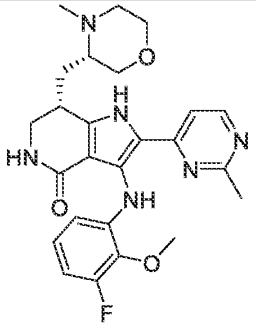
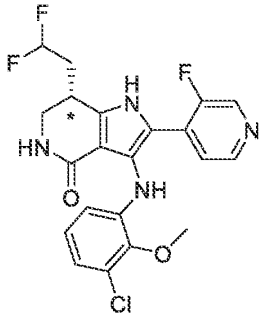
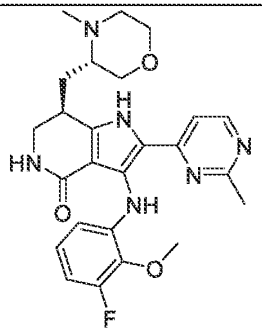
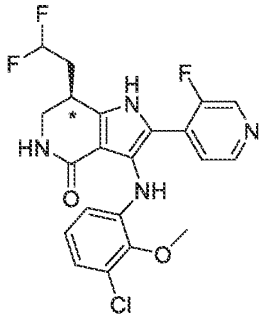
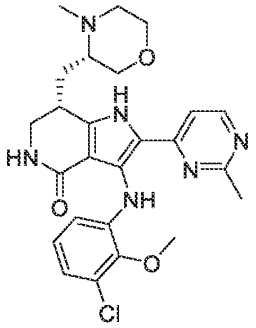
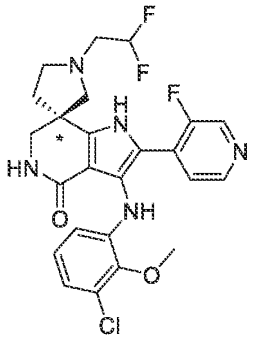
617		798	
618		799	
619		800	
620		801	

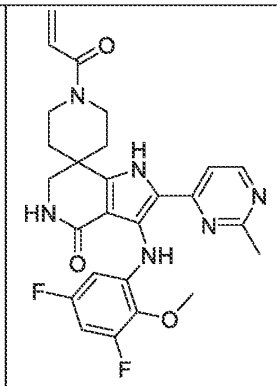
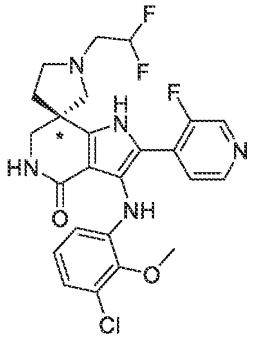
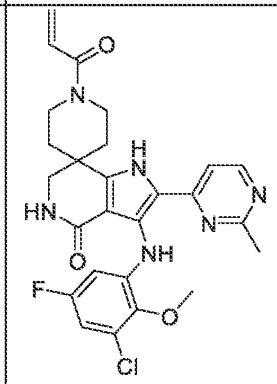
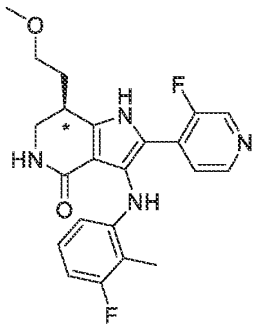
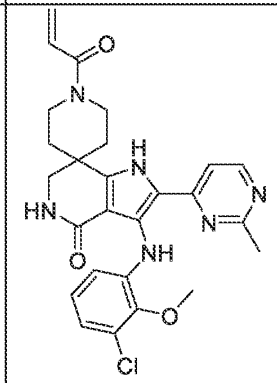
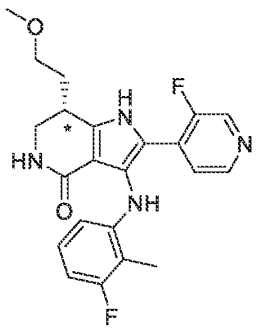
621		802	
622		803	
623		804	
624		805	

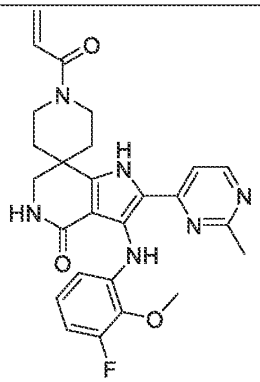
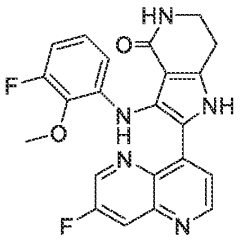
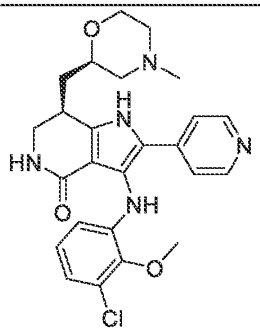
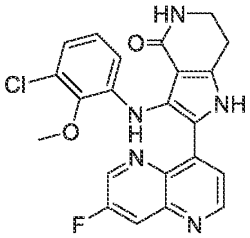
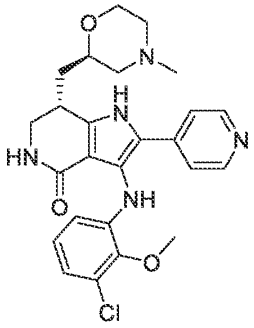
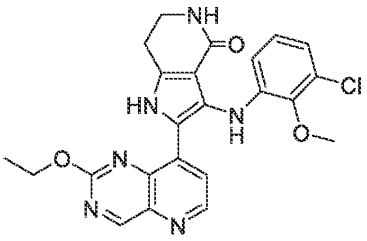
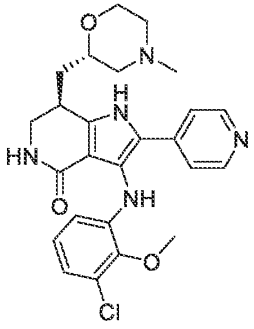
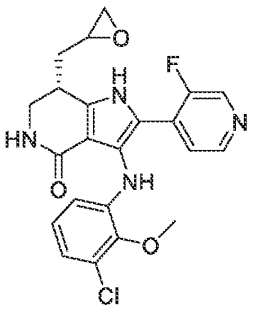
625		806	
626		807	
627		808	
628		809	

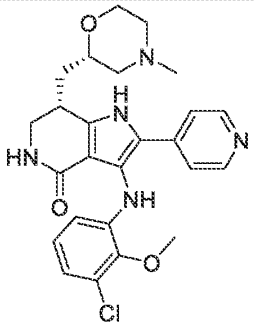
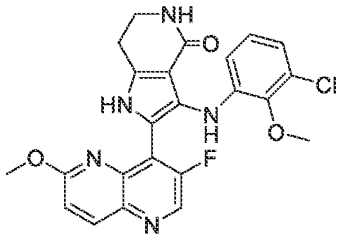
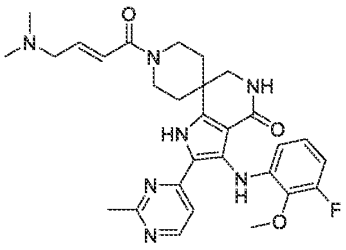
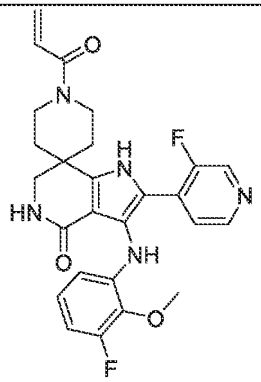
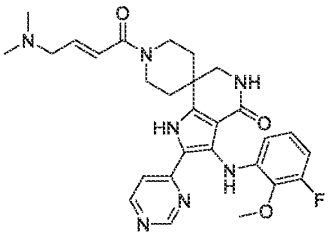
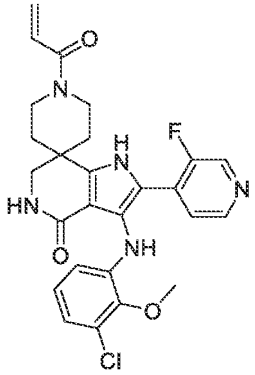
629		810	
630		811	
631		812	
632		813	

633		814	
634		815	
635		816	
636		817	

637		818	
638		819	
639		820	
640		821	

641		822	
642		823	
643		824	

644		825	
645		826	
646		827	
647		828	

648		829	
649		830	
650		831	

Pharmaceutical Compositions and Administration

General

In some embodiments, a chemical entity (e.g., a compound that inhibits EGFR and/or HER2, or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination thereof) is administered as a pharmaceutical composition that includes the chemical entity and one or more pharmaceutically acceptable excipients, and optionally one or more additional therapeutic agents as described herein.

In some embodiments, the chemical entities can be administered in combination with one or more conventional pharmaceutical excipients. Pharmaceutically acceptable excipients include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens, poloxamers or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, tris, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium-chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethyl cellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, and wool fat. Cyclodextrins such as α-, β, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-β-cyclodextrins, or other solubilized derivatives can also be used to enhance delivery of compounds described herein. Dosage forms or compositions containing a chemical entity as described herein in the range of 0.005% to 100% with the balance made up from non-toxic excipient may be prepared. The contemplated compositions may contain 0.001%-100% of a chemical entity provided herein, in one embodiment 0.1-95%, in another embodiment 75-85%, in a further embodiment 20-80%. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy*, 22nd Edition (Pharmaceutical Press, London, UK. 2012).

Routes of Administration and Composition Components

In some embodiments, the chemical entities described herein or a pharmaceutical composition thereof can be administered to subject in need thereof by any accepted route of administration. Acceptable routes of administration include, but are not limited to, buccal, cutaneous, endocervical, endosinusial, endotracheal, enteral, epidural, interstitial, intra-abdominal, intra-arterial, intrabronchial, intrabursal, intracerebral, intracisternal, intracoronary, intradermal, intraductal, intraduodenal, intradural, intraepidermal, intraesophageal, intragastric, intragingival, intraileal, intralymphatic, intramedullary, intrameningeal, intramuscular, intraovarian, intraperitoneal, intraprostatic, intrapulmonary, intrasinal, intraspinal, intrasynovial, intratesticular, intrathecal, intratubular, intratumoral, intrauterine, intravascular, intravenous, nasal, nasogastric, oral, parenteral, percutaneous, peridural, rectal, respiratory (inhalation), subcutaneous, sublingual, submucosal, topical, transdermal, transmucosal, transtracheal, ureteral, urethral and vaginal. In certain embodiments, a preferred route of administration is parenteral (e.g., intratumoral).

Compositions can be formulated for parenteral administration, e.g., formulated for injection via the intravenous, intramuscular, sub-cutaneous, or even intraperitoneal routes. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for use to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified. The preparation of such formulations will be known to those of skill in the art in light of the present disclosure.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil, or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that it may be easily injected. It also should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

The carrier also can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can

be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion, and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques, which yield a powder of the active ingredient, plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Intratumoral injections are discussed, e.g., in Lammers, et al., *"Effect of Intratumoral Injection on the Biodistribution and the Therapeutic Potential of HPMA Copolymer-Based Drug Delivery Systems" Neoplasia.* **2006**, *10*, 788–795.

Pharmacologically acceptable excipients usable in the rectal composition as a gel, cream, enema, or rectal suppository, include, without limitation, any one or more of cocoa butter glycerides, synthetic polymers such as polyvinylpyrrolidone, PEG (like PEG ointments), glycerine, glycerinated gelatin, hydrogenated vegetable oils, poloxamers, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol Vaseline, anhydrous lanolin, shark liver oil, sodium saccharinate, menthol, sweet almond oil, sorbitol, sodium benzoate, anoxid SBN, vanilla essential oil, aerosol, parabens in phenoxyethanol, sodium methyl p-oxybenzoate, sodium propyl p-oxybenzoate, diethylamine, carbomers, carbopol, methyloxybenzoate, macrogol cetostearyl ether, cocoyl caprylocaprate, isopropyl alcohol, propylene glycol, liquid paraffin, xanthan gum, carboxy-metabisulfite, sodium edetate, sodium benzoate, potassium

metabisulfite, grapefruit seed extract, methyl sulfonyl methane (MSM) , lactic acid, glycine, vitamins, such as vitamin A and E and potassium acetate.

In certain embodiments, suppositories can be prepared by mixing the chemical entities described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum and release the active compound. In other embodiments, compositions for rectal administration are in the form of an enema.

In other embodiments, the compounds described herein or a pharmaceutical composition thereof are suitable for local delivery to the digestive or GI tract by way of oral administration (e.g., solid or liquid dosage forms.).

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the chemical entity is mixed with one or more pharmaceutically acceptable excipients, such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

In one embodiment, the compositions will take the form of a unit dosage form such as a pill or tablet and thus the composition may contain, along with a chemical entity provided herein, a diluent such as lactose, sucrose, dicalcium phosphate, or the like; a lubricant such as magnesium stearate or the like; and a binder such as starch, gum acacia,

polyvinylpyrrolidine, gelatin, cellulose, cellulose derivatives or the like. In another solid dosage form, a powder, marume, solution or suspension (*e.g.*, in propylene carbonate, vegetable oils, PEG's, poloxamer 124 or triglycerides) is encapsulated in a capsule (gelatin or cellulose base capsule). Unit dosage forms in which one or more chemical entities provided herein or additional active agents are physically separated are also contemplated; *e.g.*, capsules with granules (or tablets in a capsule) of each drug; two-layer tablets; two-compartment gel caps, etc. Enteric coated or delayed release oral dosage forms are also contemplated.

Other physiologically acceptable compounds include wetting agents, emulsifying agents, dispersing agents or preservatives that are particularly useful for preventing the growth or action of microorganisms. Various preservatives are well known and include, for example, phenol and ascorbic acid.

In certain embodiments the excipients are sterile and generally free of undesirable matter. These compositions can be sterilized by conventional, well-known sterilization techniques. For various oral dosage form excipients such as tablets and capsules sterility is not required. The USP/NF standard is usually sufficient.

In certain embodiments, solid oral dosage forms can further include one or more components that chemically and/or structurally predispose the composition for delivery of the chemical entity to the stomach or the lower GI; e.g., the ascending colon and/or transverse colon and/or distal colon and/or small bowel. Exemplary formulation techniques are described in, e.g., Filipski, K.J., et al., *Current Topics in Medicinal Chemistry*, **2013**, *13*, 776-802, which is incorporated herein by reference in its entirety.

Examples include upper-GI targeting techniques, e.g., Accordion Pill (Intec Pharma), floating capsules, and materials capable of adhering to mucosal walls.

Other examples include lower-GI targeting techniques. For targeting various regions in the intestinal tract, several enteric/pH-responsive coatings and excipients are available. These materials are typically polymers that are designed to dissolve or erode at specific pH ranges, selected based upon the GI region of desired drug release. These materials also function to protect acid labile drugs from gastric fluid or limit exposure in cases where the active ingredient may be irritating to the upper GI (e.g., hydroxypropyl methylcellulose phthalate series, Coateric (polyvinyl acetate phthalate), cellulose acetate

phthalate, hydroxypropyl methylcellulose acetate succinate, Eudragit series (methacrylic acid–methyl methacrylate copolymers), and Marcoat). Other techniques include dosage forms that respond to local flora in the GI tract, Pressure-controlled colon delivery capsule, and Pulsincap.

Ocular compositions can include, without limitation, one or more of any of the following: viscogens (e.g., Carboxymethylcellulose, Glycerin, Polyvinylpyrrolidone, Polyethylene glycol); Stabilizers (e.g., Pluronic (triblock copolymers), Cyclodextrins); Preservatives (e.g., Benzalkonium chloride, ETDA, SofZia (boric acid, propylene glycol, sorbitol, and zinc chloride; Alcon Laboratories, Inc.), Purite (stabilized oxychloro complex; Allergan, Inc.)).

Topical compositions can include ointments and creams. Ointments are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. Creams containing the selected active agent are typically viscous liquid or semisolid emulsions, often either oil-in-water or water-in-oil. Cream bases are typically water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also sometimes called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and non-sensitizing.

In any of the foregoing embodiments, pharmaceutical compositions described herein can include one or more one or more of the following: lipids, interbilayer crosslinked multilamellar vesicles, biodegradeable poly(D,L-lactic-co-glycolic acid) [PLGA]-based or poly anhydride-based nanoparticles or microparticles, and nanoporous particle-supported lipid bilayers.

Dosages

The dosages may be varied depending on the requirement of the patient, the severity of the condition being treating and the particular compound being employed. Determination of the proper dosage for a particular situation can be determined by one

skilled in the medical arts. The total daily dosage may be divided and administered in portions throughout the day or by means providing continuous delivery.

In some embodiments, the compounds described herein are administered at a dosage of from about 0.001 mg/Kg to about 500 mg/Kg (e.g., from about 0.001 mg/Kg to about 200 mg/Kg; from about 0.01 mg/Kg to about 200 mg/Kg; from about 0.01 mg/Kg to about 150 mg/Kg; from about 0.01 mg/Kg to about 100 mg/Kg; from about 0.01 mg/Kg to about 50 mg/Kg; from about 0.01 mg/Kg to about 10 mg/Kg; from about 0.01 mg/Kg to about 5 mg/Kg; from about 0.01 mg/Kg to about 1 mg/Kg; from about 0.01 mg/Kg to about 0.5 mg/Kg; from about 0.01 mg/Kg to about 0.1 mg/Kg; from about 0. 1 mg/Kg to about 200 mg/Kg; from about 0. 1 mg/Kg to about 150 mg/Kg; from about 0. 1 mg/Kg to about 100 mg/Kg; from about 0.1 mg/Kg to about 50 mg/Kg; from about 0. 1 mg/Kg to about 10 mg/Kg; from about 0. 1 mg/Kg to about 5 mg/Kg; from about 0. 1 mg/Kg to about 1 mg/Kg; from about 0. 1 mg/Kg to about 0.5 mg/Kg).

Regimens

The foregoing dosages can be administered on a daily basis (e.g., as a single dose or as two or more divided doses) or non-daily basis (e.g., every other day, every two days, every three days, once weekly, twice weeks, once every two weeks, once a month).

In some embodiments, the period of administration of a compound described herein is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 1 1 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 1 1 months, 12 months, or more. In a further embodiment, a period of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 1 1 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 1 1 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 1 1 months, 12 months, or more. In an embodiment, a therapeutic compound is administered to an individual for a period of time followed by a separate period of time. In another embodiment, a therapeutic compound is administered for a first period and a second period following the first period, with administration stopped during the second period, followed by a third period where

administration of the therapeutic compound is started and then a fourth period following the third period where administration is stopped. In an aspect of this embodiment, the period of administration of a therapeutic compound followed by a period where administration is stopped is repeated for a determined or undetermined period of time. In a further embodiment, a period of administration is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In a further embodiment, a period of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more.

Methods of Treatment

Indications

Provided herein are methods for inhibiting epidermal growth factor receptor tyrosine kinase (EGFR) and/or human epidermal growth factor receptor 2 (HER2). For example, provided herein are inhibitors of EGFR useful for treating or preventing diseases or disorders associated with dysregulation of an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same (i.e., an EGFR-associated disease or disorder), such as a central nervous system diseases, a pulmonary disorder, cardiovascular disease, ischemia, liver disease, a gastrointestinal disorder, a viral or bacterial infection, an inflammatory and/or autoimmune disease, or cancer (e.g., EGFR-associated cancer). In some embodiments, provided herein are inhibitors of HER2 useful for treating or preventing diseases or disorders associated with dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, such as cancer (e.g., HER2-associated cancer). In some embodiments, provided herein are inhibitors of EGFR and HER2.

An "EGFR inhibitor" as used herein includes any compound exhibiting EGFR

inactivation activity (e.g., inhibiting or decreasing). In some embodiments, an EGFR inhibitor can be selective for an EGFR kinase having one or more mutations. For example, an EGFR inhibitor can bind to the adenosine triphosphate (ATP)-binding site in the tyrosine kinase domain. In some embodiments, an EGFR inhibitor is an allosteric inhibitor.

The compounds provided herein can inhibit EGFR. In some embodiments, the compounds can bind to the EGFR adenosine triphosphate (ATP)-binding site in the tyrosine kinase domain.

The ability of test compounds to act as inhibitors of EGFR may be demonstrated by assays known in the art. The activity of the compounds and compositions provided herein as EGFR inhibitors can be assayed in vitro, in vivo, or in a cell line. In vitro assays include assays that determine inhibition of the kinase and/or ATPase activity. Alternate in vitro assays quantitate the ability of the inhibitor to bind to the protein kinase and can be measured either by radio labelling the compound prior to binding, isolating the compound/kinase complex and determining the amount of radio label bound, or by running a competition experiment where new compounds are incubated with the kinase bound to known radioligands. In some cases, an EGFR inhibitor can be evaluated by its effect on the initial velocity of EGFR tyrosine kinase catalyzed peptide phosphorylation (e.g., Yun et al. *Cancer Cell.* 2007;11(3):217–227). In some embodiments, the binding constant of an EGFR inhibitor can be determined using fluorescence kinetics (e.g., Yun et al. *Cancer Cell.* 2007;11(3):217–227). Examples of surface plasmon resonance (SPR) binding assays include those disclosed in Li, Shiqing, et al. Cancer cell 7.4 (2005): 301-311. Additional EGFR inhibitor assays can be found, for example, in WO 2019/246541 and WO 2019/165358 both of which are incorporated by reference in their entireties).

Assays can include, for example, proliferation inhibition assays such as those that measure cell growth inhibition, such as an MTS assay or by Cell Titer Glo Luminescent Cell viability assay (Promega®). To perform such an assay, cells are seeded and grown in cell culture plates before being exposed to a test compound for varying durations. Assessment of the viability of the cells following this exposure is then performed. Data are normalized with respect to untreated cells and can be displayed graphically. Growth curves can be fitted using a nonlinear regression model with sigmoidal dose response. As another example, a Western Blot analysis can be used. In such assays cells are seeded and grown

in culture plates and then treated with a test compound the following day for varying durations. Cells are washed with PBS and lysed. SDS-PAGE gels are used to separate the lysates which are transferred to nitrocellulose membranes, and probed with appropriate antibodies (e.g., phospho-EGFR(Tyrl 068)(3777), total EGFR (2232), p-Akt(Ser473) (4060), total Akt (9272), p-ERK(Thr202/Tyr204)(4370), total ERK (9102), and HSP90 (SC-7947)).

Additional assays can include, for example, assays based on ALPHALISA TECHNOLOGY® (e.g., see the ALPHALISA® EGF/EGFR binding kit from Promega). Such assays use a luminescent oxygen-channeling chemistry to detect molecules of interest in, for example, buffer, cell culture media, serum, and plasma. For example, a biotinylated EGF is bound to streptavidin-coated Alpha donor beads, and EGFR-Fc is captured by anti-human IgG Fc-specific AlphaLISA acceptor beads. When EGF is bound to EGFR, donor beads and acceptor beads come into close proximity, and the excitation of the donor beads provokes the release of singlet oxygen molecules that triggers a cascade of energy transfers in the acceptor beads. This results in a sharp peak of light emission at 615 nm. Such assays can be used, for example, in competitive binding experiments.

Further examples of assays can include assays based on Sox technology (e.g., see the PHOSPHOSENS® Sox-based Homogeneous, Kinetic or Endpoint/Red Fluorescence-based Assays from ASSAYQUANT®). Such assays utilize chelation-enhanced fluorescence (CHEF) using a sulfonamido-oxine (Sox) chromophore in peptide or protein substrates to create real-time sensors of phosphorylation. See, e.g., U.S. Patent Nos. 8,586,570 and 6,906,194.

Potency of an EGFR inhibitor as provided herein can be determined by EC_{50} value. A compound with a lower EC_{50} value, as determined under substantially similar conditions, is a more potent inhibitor relative to a compound with a higher EC_{50} value. In some embodiments, the substantially similar conditions comprise determining an EGFR-dependent phosphorylation level, in vitro or in vivo (e.g., in tumor cells, A431 cells, Ba/F3 cells, or 3T3 cells cells expressing a wild type EGFR, a mutant EGFR, or a fragment of any thereof).

Potency of an EGFR inhibitor as provided herein can also be determined by IC_{50} value. A compound with a lower IC_{50} value, as determined under substantially similar

conditions, is a more potent inhibitor relative to a compound with a higher IC_{50} value. In some embodiments, the substantially similar conditions comprise determining an EGFR-dependent phosphorylation level, in vitro or in vivo (e.g., in tumor cells, A431 cells, Ba/F3 cells, or 3T3 cells expressing a wild type EGFR, a mutant EGFR, or a fragment of any thereof).

The selectivity between wild type EGFR and EGFR containing one or more mutations as described herein can also be measured using cellular proliferation assays where cell proliferation is dependent on kinase activity. For example, murine Ba/F3 cells transfected with a suitable version of wild type EGFR (such as VIII; containing a wild type EGFR kinase domain), or Ba/F3 cells transfected with L858R/T790M, Del/T790M/L718Q, L858R/T790M/L718Q, L858R/T790M/C797S, Del/T790M/C797S, L858R/T790M/I941R, exon 19 deletion/T790M, or an exon 20 insertion such as V769_D770insX, D770_N771insX, N771_P772insX, P772_H773insX, or H773_V774insX (e.g., A767_V769dupASV, V769_D770insASV, D770_N771insNPG, D770_N771insNPY, D770_N771insSVD, D770_N771insGL, N771_H773dupNPH, N771_P772insN, N771_P772insH, N771_P772insV, P772_H773insDNP, P772_H773insPNP, H773_V774insNPH, H773_V774insH, H773_V774insPH, H773_V774insAH, or P772_H773insPNP) can be used. Proliferation assays are performed at a range of inhibitor concentrations (e.g., 10 μM, 3 μM, 1.1 μM, 330 nM, 110 nM, 33 nM, 11 nM, 3 nM, 1 nM) and an EC_{50} is calculated.

An alternative method to measure effects on EGFR activity is to assay EGFR phosphorylation. Wildtype or mutant (L858R/T790M, Del/T790M, Del/T790M/L718Q, L858R/T790M/C797S, Del/T790M/C797S, L858R/T790M/I941R, or L858R/T790M/L718Q) EGFR can be transfected into cells which do not normally express endogenous EGFR and the ability of the inhibitor (e.g., using concentrations as above) to inhibit EGFR phosphorylation can be assayed. Cells are exposed to increasing concentrations of inhibitor and stimulated with EGF. The effects on EGFR phosphorylation are assayed by Western Blotting using phospho-specific EGFR antibodies.

In some embodiments, the compounds provided herein can exhibit potent and selective inhibition of EGFR. For example, the compounds provided herein can bind to the EGFR adenosine triphosphate (ATP)-binding site in the tyrosine kinase domain. In some

embodiments, the compounds provided herein can exhibit nanomolar potency against an EGFR kinase including an activating mutation or an EGFR inhibitor resistance mutation, including, for example, the resistance mutations in **Table 2a** and **2b** (e.g., L747S, D761Y, T790M, and T854A), with minimal activity against related kinases (e.g., wild type EGFR). Inhibition of wild type EGFR can cause undesireable side effects (e.g., diarrhea and skin rashes) that can impact quality of life and compliance. In some cases, the inhibititon of wild type EGFR can lead to dose limiting toxicities. See, e.g., Morphy. J. Med. Chem. 2010, 53, 4, 1413–1437 and Peters. J. Med. Chem. 2013, 56, 22, 8955–8971.

In some embodiments, the compounds of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, can selectively target an EGFR kinase. For example, a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, can selectively target an EGFR kinase over another kinase or non-kinase target.

In some embodiments, a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, can exhibit greater inhibition of EGFR containing one or more mutations as described herein (e.g., one or more mutations as described in **Table 1a** and **1b**) relative to inhibition of wild type EGFR. In some embodiments, a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof can exhibit at least 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold or 100-fold greater inhibition of EGFR containing one or more mutations as described herein relative to inhibition of wild type EGFR. In some embodiments, a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, can exhibit up to 1000-fold greater inhibition of EGFR containing one or more mutations as described herein relative to inhibition of wild type EGFR. In some embodiments, a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, can exhibit up to 10000-fold greater inhibition of EGFR having a combination of mutations described herein relative to inhibition of wild type EGFR.

In some embodiments, a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, can exhibit from about 2-fold to about 10-fold greater inhibition of EGFR

containing one or more mutations as described herein relative to inhibition of wild type EGFR. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, can exhibit from about 10-fold to about 100-fold greater inhibition of EGFR containing one or more mutations as described herein relative to inhibition of wild type EGFR. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, can exhibit from about 100-fold to about 1000-fold greater inhibition of EGFR containing one or more mutations as described herein relative to inhibition of wild type EGFR. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, can exhibit from about 1000-fold to about 10000-fold greater inhibition of EGFR containing one or more mutations as described herein relative to inhibition of wild type EGFR.

In other embodiments, a compound of Formula **(I)** (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, in combination with a second EGFR inhibitor can exhibit greater inhibition of EGFR containing one or more mutations as described herein (e.g., one or more mutations as described in **Table 1a** and **1b**) relative to inhibition of wild type EGFR. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in combination with a second EGFR inhibitor can exhibit at least 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold or 100-fold greater inhibition of EGFR containing one or more mutations as described herein relative to inhibition of wild type EGFR. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in combination with a second EGFR inhibitor can exhibit up to 1000-fold greater inhibition of EGFR containing one or more mutations as described herein relative to inhibition of wild type EGFR. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in combination with a second EGFR inhibitor can exhibit up to 10000-fold greater inhibition of EGFR having a combination of mutations described herein relative to inhibition of wild type EGFR.

In other embodiments, a compound of Formula **(I)** (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, in combination with a second EGFR inhibitor can exhibit from about 2-fold to about 10-fold greater inhibition of EGFR containing one or more mutations as described

herein relative to inhibition of wild type EGFR. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in combination with a second EGFR inhibitor can exhibit from about 10-fold to about 100-fold greater inhibition of EGFR containing one or more mutations as described herein relative to inhibition of wild type EGFR. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in combination with a second EGFR inhibitor can exhibit from about 100-fold to about 1000-fold greater inhibition of EGFR containing one or more mutations as described herein relative to inhibition of wild type EGFR. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in combination with a second EGFR inhibitor can exhibit from about 1000-fold to about 10000-fold greater inhibition of EGFR containing one or more mutations as described herein relative to inhibition of wild type EGFR.

Compounds of Formula **(I)** (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or pharmaceutically acceptable salts or solvates thereof, are useful for treating diseases and disorders which can be treated with an EGFR inhibitor, such as EGFR-associated diseases and disorders, e.g., central nervous system diseases (e.g., neurodegenerative diseases), pulmonary disorders, cardiovascular disease, ischemia, liver disease, gastrointestinal disorders, viral or bacterial infections, inflammatory and/or autoimmune diseases (e.g., psoriasis and atopic dermatitis), and proliferative disorders such as cancers, including hematological cancers and solid tumors (e.g., advanced solid tumors).

A "HER2 inhibitor" as used herein includes any compound exhibiting HER2 inactivation activity (e.g., inhibiting or decreasing). In some embodiments, a HER2 inhibitor can be selective for a HER2 kinase having one or more mutations. In some embodiments, a HER2 inhibitor can bind to the HER2 adenosine triphosphate (ATP)-binding site in the tyrosine kinase domain.

The compounds provided herein can inhibit HER2. For example, the compounds can bind to the HER2 adenosine triphosphate (ATP)-binding site in the tyrosine kinase domain. In some embodiments, the compounds provided herein can inhibit wild type HER2. In some embodiments, the compounds provided herein can inhibit HER2 having one or more mutations as described herein.

The ability of test compounds to act as inhibitors of HER2 may be demonstrated by assays known in the art. The activity of the compounds or compositions provided herein as HER2 inhibitors can be assayed in vitro, in vivo, or in a cell line. In vitro assays include assays that determine inhibition of the kinase and/or ATPase activity. Alternate in vitro assays quantitate the ability of the inhibitor to bind to the protein kinase and can be measured either by radio labelling the compound prior to binding, isolating the compound/kinase complex and determining the amount of radio label bound, or by running a competition experiment where new compounds are incubated with the kinase bound to known radioligands. In some cases, a HER2 inhibitor can be evaluated by its effect on the initial velocity of HER2 tyrosine kinase catalyzed peptide phosphorylation (e.g., Yun et al. Cancer Cell. 2007;11(3):217–227). For example, an assay that indirectly measures ADP formed from the HER2 kinase reaction can be used (see, e.g., ATP/NADH coupled assay systems and luminescent kinase assays such as ADP-GLO™ Kinase Assay from Promega). See, e.g., Hanker et al. Cancer Discov. 2017 Jun;7(6):575-585; Robichaux et al. Nat Med. 2018 May; 24(5): 638–646; and Yun et al. Proc Natl Acad Sci U S A. 2008 Feb 12;105(6):2070-5. In some embodiments, an assay that detects substrate phosphorylation using a labeled anti-phospho-tyrosine antibody can be used (see, e.g., Rabindran et al. Cancer Res. 2004 Jun 1;64(11):3958-65). In some embodiments, the binding constant of a HER2 inhibitor can be determined using fluorescence kinetics (e.g., Yun et al. Cancer Cell. 2007;11(3):217–227). Examples of SPR binding assays include those disclosed in Li, Shiqing, et al. Cancer cell 7.4 (2005): 301-311. In some embodiments, covalent binding of a HER2 inhibitor to HER2 can be detected using mass spectrometry, see, e.g., Irie et al. Mol Cancer Ther. 2019 Apr;18(4):733-742. Additional HER2 inhibitor assays can be found, for example, in U.S. Patent No. 9,920,060, WO 2019/241715, and U.S. Publication No. 2017/0166598, each of which are incorporated by reference in their entireties.

Potency of a HER2 inhibitor as provided herein can be determined by EC_{50} value. A compound with a lower EC_{50} value, as determined under substantially similar conditions, is a more potent inhibitor relative to a compound with a higher EC_{50} value. In some embodiments, the substantially similar conditions comprise determining an HER2-dependent phosphorylation level, in vitro or in vivo (e.g., in tumor cells or Ba/F3 cells expressing a wild type HER2, a mutant HER2, or a fragment of any thereof).

Potency of an HER2 inhibitor as provided herein can also be determined by IC_{50} value. A compound with a lower IC_{50} value, as determined under substantially similar conditions, is a more potent inhibitor relative to a compound with a higher IC_{50} value. In some embodiments, the substantially similar conditions comprise determining an HER2-dependent phosphorylation level, in vitro or in vivo (e.g., in tumor cells or Ba/F3 cells expressing a wild type HER2, a mutant HER2, or a fragment of any thereof).

Assays can include, for example, proliferation inhibition assays such as those that measure cell growth inhibition, such as an MTS assay or by Cell Titer Glo Luminescent Cell viability assay (Promega®). To perform such an assay, cells are seeded and grown in cell culture plates before being exposed to a test compound for varying durations. Assessment of the viability of the cells following this exposure is then performed. Data are normalized with respect to untreated cells and can be displayed graphically. Growth curves can be fitted using a nonlinear regression model with sigmoidal dose response. As another example, a Western Blot analysis can be used. In such assays cells are seeded and grown in culture plates and then treated with a test compound the following day for varying durations. Cells are washed with PBS and lysed. SDS-PAGE gels are used to separate the lysates which are transferred to nitrocellulose membranes, and probed with appropriate antibodies (e.g., phospho-HER2(Tyr1248)(2247), phospho-EGFR-Tyr1173 phospho-HER2-Tyr877, phospho-HER2-Tyr1221, total HER2, phospho-AKT-Thr308, phospho-AKT-Ser374, total AKT, phospho-p44/42 MAPK-Thr202/Tyr204, and p44/42 MAPK).

The selectivity between wild type HER2 and HER2 containing one or more mutations as described herein can also be measured using cellular proliferation assays where cell proliferation is dependent on kinase activity. For example, murine Ba/F3 cells transfected with a suitable version of wild type HER2, or Ba/F3 cells transfected with HER2 having one or more mutations such as S310F, S310Y, R678Q, R678W, R678P, I767M, V773M, V777L, V842I, M774AYVM, M774del insWLV, A775_G776insYVMA, A775_G776insAVMA, A775_G776insSVMA, A775_G776insVAG, A775insV G776C, A775_G776insI, G776del insVC2, G776del insVV, G776del insLC, G776C V777insC, G776C V777insV, V777_G778insCG, G778_S779insCPG, or P780_Y781insGSP can be used. Proliferation assays are performed at a range of inhibitor concentrations (e.g., 10 μM, 3 μM, 1.1 μM, 330 nM, 110 nM, 33 nM, 11 nM, 3 nM, 1 nM) and an EC_{50} is calculated.

An alternative method to measure effects on HER2 activity is to assay HER2 phosphorylation. Wildtype or mutant (S310F, S310Y, R678Q, R678W, R678P, I767M, V773M, V777L, V842I, M774AYVM, M774del insWLV, A775_G776insYVMA, A775_G776insAVMA, A775_G776insSVMA, A775_G776insVAG, A775insV G776C, A775_G776insI, G776del insVC2, G776del insVV, G776del insLC, G776C V777insC, G776C V777insV, V777_G778insCG, G778_S779insCPG, or P780_Y781insGSP) HER2 can be transfected into cells which do not normally express endogenous HER2 and the ability of the inhibitor (e.g., using concentrations as above) to inhibit HER2 phosphorylation can be assayed. Cells are exposed to increasing concentrations of inhibitor and stimulated with EGF. The effects on HER2 phosphorylation are assayed by Western Blotting using phospho-specific HER2 antibodies.

In some embodiments, the compounds provided herein can exhibit potent and selective inhibition of HER2. For example, the compounds provided herein can bind to the HER2 adenosine triphosphate (ATP)-binding site in the tyrosine kinase domain. In some embodiments, the compounds provided herein can exhibit nanomolar potency against a HER2 kinase including an activating mutation or a HER2 inhibitor resistance mutation, including, for example, exon 20 insertions and/or the resistance mutations in **Table 5** (e.g., L755S, L755P, T798I, and T798M), with minimal activity against related kinases (e.g., wild type EGFR).

In some embodiments, the compounds of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, can selectively target a HER2 kinase. For example, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, can selectively target a HER2 kinase over another kinase (e.g., wild type EGFR) or non-kinase target. It can be desireable to selectively target a HER2 kinase over a wild type EGFR kinase due to undesireable side effects (e.g., diarrhea and skin rashes) that can impact quality of life and compliance. See, e.g., Morphy. J. Med. Chem. 2010, 53, 4, 1413–1437 and Peters. J. Med. Chem. 2013, 56, 22, 8955–8971.

In some embodiments, a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, can exhibit greater inhibition of wild type HER2 or HER2 containing one or more

mutations as described herein (e.g., one or more mutations as described in **Table 3**) relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof can exhibit at least 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold or 100-fold greater inhibition of wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, can exhibit up to 1000-fold greater inhibition of wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, can exhibit up to 10000-fold greater inhibition of wild type HER2 or HER2 having a combination of mutations described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target.

In some embodiments, a compound of Formula **(I)** (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, can exhibit from about 2-fold to about 10-fold greater inhibition of wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, can exhibit from about 10-fold to about 100-fold greater inhibition of wild type HER2 or containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, can exhibit from about 100-fold to about 1000-fold greater inhibition of wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, can exhibit from about 1000-fold to about 10000-fold greater inhibition of wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target.

In other embodiments, a compound of Formula **(I)** (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**,

(I-d), **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, in combination with a second EGFR inhibitor can exhibit greater inhibition of wild type HER2 or HER2 containing one or more mutations as described herein (e.g., one or more mutations as described in **Table 3**) relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in combination with a second HER2 inhibitor can exhibit at least 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold or 100-fold greater inhibition of wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in combination with a second HER2 inhibitor can exhibit up to 1000-fold greater inhibition of wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in combination with a second HER2 inhibitor can exhibit up to 10000-fold greater inhibition of wild type HER2 or HER2 having a combination of mutations described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target.

In other embodiments, a compound of Formula **(I)** (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, in combination with a second HER2 inhibitor can exhibit from about 2-fold to about 10-fold greater inhibition of wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in combination with a second HER2 inhibitor can exhibit from about 10-fold to about 100-fold greater inhibition of wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in combination with a second HER2 inhibitor can exhibit from about 100-fold to about 1000-fold greater inhibition of wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some

embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in combination with a second HER2 inhibitor can exhibit from about 1000-fold to about 10000-fold greater inhibition of wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target.

Compounds of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or pharmaceutically acceptable salts or solvates thereof, are useful for treating diseases and disorders which can be treated with a HER2 inhibitor, such as HER2-associated diseases and disorders, e.g., proliferative disorders such as cancers (e.g., a HER2-associated cancer), including hematological cancers and solid tumors (e.g., advanced solid tumors).

In some embodiments, the compounds provided herein can also inhibit EGFR and HER2 as described herein.

In some embodiments, the compounds provided herein can exhibit potent and selective inhibition of EGFR and HER2. In some embodiments, the compounds provided herein can exhibit nanomolar potency against an EGFR kinase having one or more mutations, including, for example, one or more of the mutations in **Tables 1a, 1b** and **2a, 2b**, and a HER2 kinase having one or more mutations, including, for example, the mutations in **Table 3**, with minimal activity against related kinases (e.g., wild type EGFR).

In some embodiments, the compounds of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, can selectively target an EGFR and a HER2 kinase. For example, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, can selectively target an EGFR kinase and a HER2 kinase over another kinase or non-kinase target.

In some embodiments, a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, can exhibit greater inhibition of EGFR containing one or more mutations as described herein and wild type HER2 or HER2 containing one or more mutations as described herein (e.g., one or more mutations as described in **Tables 3-5**) relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof

can exhibit at least 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold or 100-fold greater inhibition of EGFR containing one or more mutations as described herein and wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, can exhibit up to 1000-fold greater inhibition of EGFR containing one or more mutations as described herein and wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, can exhibit up to 10000-fold greater inhibition of EGFR containing one or more mutations as described herein and wild type HER2 or HER2 having one or more mutations described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target.

In some embodiments, a compound of Formula **(I)** (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, can exhibit from about 2-fold to about 10-fold greater inhibition of EGFR containing one or more mutations as described herein and wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, can exhibit from about 10-fold to about 100-fold greater inhibition of EGFR containing one or more mutations as described herein and wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, can exhibit from about 100-fold to about 1000-fold greater inhibition of EGFR containing one or more mutations as described herein and wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, can exhibit from about 1000-fold to about 10000-fold greater inhibition of EGFR containing one or more mutations as described herein and wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type

EGFR) or non-kinase target.

In other embodiments, a compound of Formula (**I**) (e.g., Formula (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-i**), (**I-j**), **or** (**I-k**)), or a pharmaceutically acceptable salt thereof, in combination with a second EGFR and/or second HER2 inhibitor can exhibit greater inhibition of EGFR containing one or more mutations as described herein and wild type HER2 or HER2 containing one or more mutations as described herein (e.g., one or more mutations as described in **Table 3**) relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, in combination with a second EGFR and/or second HER2 inhibitor can exhibit at least 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold or 100-fold greater inhibition of EGFR containing one or more mutations as described herein and wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, in combination with a second EGFR and/or second HER2 inhibitor can exhibit up to 1000-fold greater inhibition of EGFR containing one or more mutations as described herein and wild type HER2 or HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, in combination with a second EGFR and/or HER2 inhibitor can exhibit up to 10000-fold greater inhibition of EGFR containing one or more mutations as described herein and wild type HER2 or HER2 having a combination of mutations described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target.

In other embodiments, a compound of Formula (**I**) (e.g., Formula (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-i**), (**I-j**), **or** (**I-k**)), or a pharmaceutically acceptable salt thereof, in combination with a second EGFR and/or second HER2 inhibitor can exhibit from about 2-fold to about 10-fold greater inhibition of EGFR containing one or more mutations as described herein and HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, in combination with a second EGFR and/or second HER2 inhibitor can exhibit

from about 10-fold to about 100-fold greater inhibition of EGFR containing one or more mutations as described herein and HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in combination with a second EGFR and/or second HER2 inhibitor can exhibit from about 100-fold to about 1000-fold greater inhibition of EGFR containing one or more mutations as described herein and second HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target. In some embodiments, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in combination with a second EGFR and/or second HER2 inhibitor can exhibit from about 1000-fold to about 10000-fold greater inhibition of EGFR containing one or more mutations as described herein and HER2 containing one or more mutations as described herein relative to inhibition of another kinase (e.g., wild type EGFR) or non-kinase target.

Also provided herein are methods for inhibiting a BUB (budding uninhibited by benzimidazole, BUB1-3) kinase. For example, provided herein are inhibitors of BUB1 kinase useful for treating or preventing diseases or disorders associated with enhanced uncontrolled proliferative cellular processes such as, for example, cancer, inflammation, arthritis, viral diseases, cardiovascular diseases, or fungal diseases. See, for example, WO 2013/050438, WO 2013/092512, WO 2013/167698, WO 2014/147203, WO 2014/147204, WO 2014/202590, WO 2014/202588, WO 2014/202584, WO 2014/202583, WO 2015/063003, WO2015/193339, WO 2016/202755, and WO 2017/021348. In some embodiments, the disease or disorder is cancer.

A "BUB1 inhibitor" as used herein includes any compound exhibiting BUB1 inactivation activity (e.g., inhibiting or decreasing). In some embodiments, a BUB1 inhibitor can be selective for BUB1 over other kinases (e.g., wildtype EGFR).

The compounds provided herein can inhibit a Bub kinase. In some embodiments, the compounds provided herein can inhibit BUB1 kinase.

The ability of test compounds to act as inhibitors of BUB1 may be demonstrated by assays known in the art. The activity of the compounds and compositions provided herein as BUB1 inhibitors can be assayed in vitro, in vivo, or in a cell line. In vitro assays

include assays that determine inhibition of the kinase. For example, BUB1 inhibition of a compound provided herein can be determined using a time-resolved fluorescence energy transfer (TR-FRET) assay which measures phosphorylation of a synthetic peptide (e.g., Biotin-AHX-VLLPKKSFAEPG (C-terminus in amide form) by the (recombinant) catalytic domain of human BUB1 (amino acids 704-1085), expressed in Hi5 insect cells with an N-terminal His6-tag and purified by affinity- (Ni-NTA) and size exclusion chromatography. See, for example, WO 2017/021348. In addition, BUB1 activity can be determined at a high ATP concentration using a BUB1 TR-FRET high ATP kinase assay using similar methods as those described above. See, e.g. WO 2019/081486.

In some embodiments, the compounds provided herein exhibit central nervous system (CNS) penetrance. For example, such compounds can be capable of crossing the blood brain barrier (BBB) and inhibiting an EGFR and/or HER2 kinase in the brain and/or other CNS structures. In some embodiments, the compounds provided herein are capable of crossing the blood brain barrier in a therapeutically effective amount. For example, treatment of a patient with cancer (e.g., an EGFR-associated cancer or a HER2-associated cancer such as an EGFR- or HER2-associated brain or CNS cancer or an EGFR-associated or a HER2-associated cancer that has metastasized to the brain or CNS) can include administration (e.g., oral administration) of the compound to the patient.

The ability of the compounds described herein, to cross the BBB can be demonstrated by assays known in the art. Such assays include BBB models such as the transwell system, the hollow fiber (dynamic in vitro BBB) model, other microfluidic BBB systems, the BBB spheroid platform, and other cell aggregate-based BBB models. See, e.g., Cho et al. Nat Commun. 2017; 8: 15623; Bagchi et al. Drug Des Devel Ther. 2019; 13: 3591–3605; Gastfriend et al. Curr Opin Biomed Eng. 2018 Mar; 5: 6–12; and Wang et al. Biotechnol Bioeng. 2017 Jan; 114(1): 184–194. In some embodiments, the compounds described herein, are fluorescently labeled, and the fluorescent label can be detected using microscopy (e.g., confocal microscopy). In some such embodiments, the ability of the compound to penetrate the surface barrier of the model can be represented by the fluorescence intensity at a given depth below the surface. In some assays, such as a calcein-AM-based assay, the fluorescent label is non-fluorescent until it permeates live cells and is hydrolyzed by intracellular esterases to produce a fluorescent compound that is retained in

the cell and can be quantified with a spectrophotometer. Non-limiting examples of fluorescent labels that can be used in the assays described herein include Cy5, rhodamine, infrared IRDye® CW-800 (LICOR #929-71012), far-red IRDye® 650 (LICOR #929-70020), sodium fluorescein (Na-F), lucifer yellow (LY), 5'carboxyfluorescein, and calcein-acetoxymethylester (calcein-AM). In some embodiments, the BBB model (e.g., the tissue or cell aggregate) can be sectioned, and a compound described herein can be detected in one or more sections using mass spectrometry (e.g., MALDI-MSI analyses). In some embodiments, the ability of a compound described herein to cross the BBB through a transcellular transport system, such as receptor-mediated transport (RMT), carrier-mediated transport (CMT), or active efflux transport (AET), can be demonstrated by assays known in the art. See, e.g., Wang et al. Drug Deliv. 2019; 26(1): 551–565. In some embodiments, assays to determine if compounds can be effluxed by the P-glycoprotein (Pgp) include monolayer efflux assays in which movement of compounds through Pgp is quantified by measuring movement of digoxin, a model Pgp substrate (see, e.g., Doan et al. 2002. J Pharmacol Exp Ther. 303(3):1029-1037). Alternative in vivo assays to identify compounds that pass through the blood-brain barriers include phage-based systems (see, e.g., Peng et al. 2019. ChemRxiv. Preprint doi.org/10.26434/chemrxiv.8242871.v1). In some embodiments, binding of the compounds described herein to brain tissue is quantified. For example, a brain tissue binding assay can be performed using equilibrium dialysis, and the fraction of a compound described herein unbound to brain tissue can be detected using LC-MS/MS (Cyprotex: Brain Tissue Binding Assay www.cyprotex.com/admepk/protein_binding/brain-tissue-binding/).

Compounds of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or pharmaceutically acceptable salts or solvates thereof, are useful for treating diseases and disorders which can be treated with an EGFR inhibitor, a HER2 inhibitor, a dual EGFR and HER2 inhibitor, and/or a BUB1 inhibitor, such as those described herein, e.g., cancer. Accordingly, provided herein is a method for treating a disease or disorder as provided herein in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the disease or disorder is cancer.

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

As used herein, the terms "subject," "individual," or "patient," are used interchangeably, refers to any animal, including mammals such as mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some embodiments, the subject is a human. In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented.

In some embodiments, the subject has been identified or diagnosed as having a cancer with a dysregulation of an *EGFR* gene, an EGFR protein, or expression or activity, or level of any of the same (an EGFR-associated cancer) (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the subject has a tumor that is positive for a dysregulation of an *EGFR* gene, an EGFR protein, or expression or activity, or level of any of the same (e.g., as determined using a regulatory agency-approved assay or kit). For example, the subject has a tumor that is positive for a mutation as described in **Table 1a** and **1b**. The subject can be a subject with a tumor(s) that is positive for a dysregulation of an *EGFR* gene, an EGFR protein, or expression or activity, or level of any of the same (e.g., identified as positive using a regulatory agency-approved, e.g., FDA-approved, assay or kit). The subject can be a subject whose tumors have a dysregulation of an *EGFR* gene, an EGFR protein, or expression or activity, or a level of the same (e.g., where the tumor is identified as such using a regulatory agency-approved, e.g., FDA-approved, kit or assay). In some embodiments, the subject is suspected of having an EGFR-associated cancer. In some embodiments, the subject has a clinical record indicating that the subject has a tumor that has a dysregulation of an *EGFR* gene, an EGFR protein, or expression or activity, or level of any of the same (and optionally the clinical

record indicates that the subject should be treated with any of the compositions provided herein).

In some embodiments, the subject has been identified or diagnosed as having a cancer with a dysregulation of a *HER2* gene, a HER2 protein, or expression or activity, or level of any of the same (a HER2-associated cancer) (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the subject has a tumor that is positive for a dysregulation of a *HER2* gene, a HER2 protein, or expression or activity, or level of any of the same (e.g., as determined using a regulatory agency-approved assay or kit). For example, the subject has a tumor that is positive for a mutation as described in **Table 3**. The subject can be a subject with a tumor(s) that is positive for a dysregulation of a *HER2* gene, a HER2 protein, or expression or activity, or level of any of the same (e.g., identified as positive using a regulatory agency-approved, e.g., FDA-approved, assay or kit). The subject can be a subject whose tumors have a dysregulation of a *HER2* gene, a HER2 protein, or expression or activity, or a level of the same (e.g., where the tumor is identified as such using a regulatory agency-approved, e.g., FDA-approved, kit or assay). In some embodiments, the subject is suspected of having a HER2-associated cancer. In some embodiments, the subject has a clinical record indicating that the subject has a tumor that has a dysregulation of a *HER2* gene, a HER2 protein, or expression or activity, or level of any of the same (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein).

In some embodiments, the subject is a pediatric subject.

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

days of age to less than two years of age, from two years of age to less than 12 years of age, or 12 years of age through 21 years of age (up to, but not including, the twenty-second birthday). In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than 1 year of age, from one month of age to less than four months of age, from three months of age to less than seven months of age, from six months of age to less than 1 year of age, from 1 year of age to less than 2 years of age, from 2 years of age to less than 3 years of age, from 2 years of age to less than seven years of age, from 3 years of age to less than 5 years of age, from 5 years of age to less than 10 years of age, from 6 years of age to less than 13 years of age, from 10 years of age to less than 15 years of age, or from 15 years of age to less than 22 years of age.

In certain embodiments, compounds of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or pharmaceutically acceptable salts or solvates thereof, are useful for preventing diseases and disorders as defined herein (for example, autoimmune diseases, inflammatory diseases, pulmonary disorders, cardiovascular disease, ischemia, liver disease, gastrointestinal disorders, viral or bacterial infections, central nervous system diseases (e.g., neurodegenerative diseases), and cancer). The term "preventing" as used herein means to delay the onset, recurrence or spread, in whole or in part, of the disease or condition as described herein, or a symptom thereof.

The term "EGFR-associated disease or disorder" as used herein refers to diseases or disorders associated with or having a dysregulation of an *EGFR* gene, an EGFR kinase (also called herein an EGFR kinase protein), or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of an *EGFR* gene, an EGFR kinase, an EGFR kinase domain, or the expression or activity or level of any of the same described herein). Non-limiting examples of an EGFR-associated disease or disorder include, for example, cancer, a central nervous system disease, a pulmonary disorder, cardiovascular disease, ischemia, liver disease, a gastrointestinal disorder, a viral or bacterial infection, and an inflammatory and/or autoimmune disease (e.g., psoriasis, eczema, atopic dermatitis, and atherosclerosis).

In some embodiments of any of the methods or uses described herein, the inflammatory and/or autoimmune disease is selected from arthritis, systemic lupus erythematosus, atherosclerosis, and skin related disorders such as psoriasis, eczema, and

atopic dermatitis. See, e.g., Wang et al. Am J Transl Res. 2019; 11(2): 520–528; Starosyla et al. World J Pharmacol. Dec 9, 2014; 3(4): 162-173; Choi et al. Biomed Res Int. 2018 May 15;2018:9439182; and Wang et al. Sci Rep. 2017; 7: 45917.

In some embodiments of any of the methods or uses described herein, the central nervous system disease is a neurodegenerative disease. In some embodiments, the central nervous system disease is selected from Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, peripheral neuropathy, brain ischemia, and a psychiatric disorder such as schizophrenia. See, e.g., Iwakura and Nawa. Front Cell Neurosci. . 2013 Feb 13;7:4; and Chen et al. Sci Rep. 2019 Feb 21;9(1):2516.

The term "EGFR-associated cancer" as used herein refers to cancers associated with or having a dysregulation of an *EGFR* gene, an EGFR kinase (also called herein an EGFR kinase protein), or expression or activity, or level of any of the same. Non-limiting examples of an EGFR-associated cancer are described herein.

The phrase "dysregulation of an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same" refers to a genetic mutation (e.g., a mutation in an *EGFR* gene that results in the expression of an EGFR protein that includes a deletion of at least one amino acid as compared to a wild type EGFR protein, a mutation in an *EGFR* gene that results in the expression of an EGFR protein with one or more point mutations as compared to a wild type EGFR protein, a mutation in an *EGFR* gene that results in the expression of an EGFR protein with at least one inserted amino acid as compared to a wild type EGFR protein, a gene duplication that results in an increased level of EGFR protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of EGFR protein in a cell), an alternative spliced version of an EGFR mRNA that results in an EGFR protein having a deletion of at least one amino acid in the EGFR protein as compared to the wild type EGFR protein), or increased expression (e.g., increased levels) of a wild type EGFR kinase in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of an *EGFR* gene, an EGFR protein, or expression or activity, or level of any of the same, can be a mutation in an *EGFR* gene that encodes an EGFR protein that is constitutively active or has increased

activity as compared to a protein encoded by an *EGFR* gene that does not include the mutation. Non-limiting examples of EGFR kinase protein point mutations/insertions/deletions are described in **Table 1a** and **1b**. Additional examples of EGFR kinase protein mutations (e.g., point mutations) are EGFR inhibitor resistance mutations (e.g., EGFR inhibitor mutations). Non-limiting examples of EGFR inhibitor resistance mutations are described in **Table 2a** and **2b**. For example, the one or more EGFR inhibitor resistance mutations can include a substitution at amino acid position 718, 747, 761, 790, 797, or 854 (e.g., L718Q, L747S, D761Y, T790M, C797S, or T854A). Such mutation and overexpression is associated with the development of a variety of cancers (Shan et al., *Cell* 2012, 149(4) 860-870).

In some embodiments, dysregulation of an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same can be caused by an activating mutation in an *EGFR* gene. In some embodiments, dysregulation of an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same can be caused by a genetic mutation that results in the expression of an EGFR kinase that has increased resistance to an EGFR inhibitor, a tyrosine kinase inhibitor (TKI), and/or a multi-kinase inhibitor (MKI), e.g., as compared to a wild type EGFR kinase (see, e.g., the amino acid substitutions in **Table 2a** and **2b**). In some embodiments, dysregulation of an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same can be caused by a mutation in a nucleic acid encoding an altered EGFR protein (e.g., an EGFR protein having a mutation (e.g., a primary mutation)) that results in the expression of an altered EGFR protein that has increased resistance to inhibition by an EGFR inhibitor, a tyrosine kinase inhibitor (TKI), and/or a multi-kinase inhibitor (MKI), e.g., as compared to a wild type EGFR kinase (see, e.g., the amino acid substitutions in **Table 2a** and **2b**). The exemplary EGFR kinase point mutations, insertions, and deletions shown in **Tables 1a, 1b** and **2a, 2b** can be caused by an activating mutation and/or can result in the expression of an EGFR kinase that has increased resistance to an EGFR inhibitor), tyrosine kinase inhibitor (TKI), and/or a multi-kinase inhibitor (MKI).

In some embodiments, the individual has two or more EGFR inhibitor resistance mutations that increase resistance of the cancer to a first EGFR inhibitor. For example, the individual can have two EGFR inhibitor resistance mutations. In some embodiments, the

two mutations occur in the same EGFR protein. In some embodiments, the two mutations occur in separate EGFR proteins. In some embodiments, the individual can have three EGFR inhibitor resistance mutations. In some embodiments, the three mutations occur in the same EGFR protein. In some embodiments, the three mutations occur in separate EGFR proteins. For example, the individual has two or more EGFR inhibitor resistance mutations selected from Del 19/L718Q, Del 19/T790M, Del 19/L844V, Del 19/T790M/L718Q, Del/T790M/C797S, Del 19/T790M/L844V, L858R/L718Q, L858R/L844V, L858R/T790M, L858R/T790M/L718Q, L858R/T790M/C797S, and L858R/T790M/I941R, or any combination thereof; e.g., any two of the aforementioned EGFR inhibitor resistance mutations.

The term "activating mutation" in reference to EGFR describes a mutation in an *EGFR* gene that results in the expression of an EGFR kinase that has an increased kinase activity, e.g., as compared to a wild type EGFR kinase, e.g., when assayed under identical conditions. For example, an activating mutation can be a mutation in an *EGFR* gene that results in the expression of an EGFR kinase that has one or more (e.g., two, three, four, five, six, seven, eight, nine, or ten) amino acid substitutions (e.g., any combination of any of the amino acid substitutions described herein) that has increased kinase activity, e.g., as compared to a wild type EGFR kinase, e.g., when assayed under identical conditions. In another example, an activating mutation can be a mutation in an *EGFR* gene that results in the expression of an EGFR kinase that has one or more (e.g., two, three, four, five, six, seven, eight, nine, or ten) amino acids deleted, e.g., as compared to a wild type EGFR kinase, e.g., when assayed under identical conditions. In another example, an activating mutation can be a mutation in an *EGFR* gene that results in the expression of an EGFR kinase that has at least one (e.g., at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 12, at least 14, at least 16, at least 18, or at least 20) amino acid inserted as compared to a wild type EGFR kinase, e.g., the exemplary wild type EGFR kinase described herein, e.g., when assayed under identical conditions. Additional examples of activating mutations are known in the art.

The term "wild type" or "wild-type" describes a nucleic acid (e.g., an *EGFR* gene or an EGFR mRNA) or protein (e.g., an EGFR protein) sequence that is typically found in a subject that does not have a disease or disorder related to the reference nucleic acid or

protein.

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

Provided herein is a method of treating cancer (e.g., an EGFR-associated cancer) in a subject in need of such treatment, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. For example, provided herein are methods for treating an EGFR-associated cancer in a subject in need of such treatment, the method comprising a) detecting a dysregulation of an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same in a sample from the subject; and b) administering a therapeutically effective amount of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof. In some embodiments, the dysregulation of an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same includes one or more EGFR kinase protein point mutations/insertions. Non-limiting examples of EGFR kinase protein point mutations/insertions/deletions are described in **Table 1a** and **1b**. In some embodiments, the EGFR kinase protein point mutations/insertions/deletions are selected from the group consisting of G719S, G719C, G719A, L747S, D761Y, T790M, T854A, L858R, L861Q, a deletion in exon 19 (e.g., L747_A750del), and an insertion in exon 20 (e.g., V769_D770insX, D770_N771insX, N771_P772insX, P772_H773insX, or H773_V774insX). In some embodiments, the EGFR kinase protein point mutations/insertions/deletions are selected from the group consisting of L858R, deletions in exon 19 (e.g., L747_A750del), L747S, D761Y, T790M, and T854A. In some embodiments, the EGFR kinase protein insertion is an exon 20 insertion. In some

embodiments, the EGFR kinase protein insertion is an exon 20 insertion selected from the group consisting of: V769_D770insX, D770_N771insX, N771_P772insX, P772_H773insX, and H773_V774insX. For example, the EGFR kinase protein insertion is an exon 20 insertion selected from the group consisting of: A767_V769dupASV, V769_D770insASV, D770_N771insNPG, D770_N771insNPY, D770_N771insSVD, D770_N771insGL, N771_H773dupNPH, N771_P772insN, N771_P772insH, N771_P772insV, P772_H773insDNP, P772_H773insPNP, H773_V774insNPH, H773_V774insH, H773_V774insPH, H773_V774insAH, and P772_H773insPNP; or any combination thereof; e.g., any two or more independently selected exon 20 insertions; e.g., any two independently selected exon 20 insertions (e.g., V769_D770insASV and D770_N771insSVD).

In some embodiments of any of the methods or uses described herein, the cancer (e.g., EGFR-associated cancer) is selected from a hematological cancer (e.g., acute lymphocytic cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, and leukemia such as acute-myelogenous leukemia (AML), chronic-myelogenous leukemia (CML), acute-promyelocytic leukemia, and acute lymphocytic leukemia (ALL)), central or peripheral nervous system tissue cancer, an endocrine or neuroendocrine cancer including multiple neuroendocrine type I and type II tumors, Li-Fraumeni tumors, alveolar rhabdomyosarcoma, bone cancer, brain cancer, breast cancer, cancer of the anus, anal canal, or anorectum, cancer of the eye, cancer of the intrahepatic bile duct, cancer of the joints, cancer of the neck, gallbladder, or pleura, cancer of the nose, nasal cavity, or middle ear, oral cancer, oropharyngeal cancer, nasopharyngeal cancer, respiratory cancer, urogenital cancer, cancer of the vulva, colon cancer, esophageal cancer, tracheal cancer, cervical cancer, gastrointestinal carcinoid tumor, hypopharynx cancer, kidney cancer, larynx cancer, liver cancer, lung cancer, malignant mesothelioma, melanoma, multiple myeloma, nasopharynx cancer, ovarian cancer, pancreatic cancer including pancreatic islet cell cancer, peritoneum, omentum, and mesentery cancer, pharynx cancer, prostate cancer, rectal cancer, renal cancer (e.g., renal cell carcinoma (RCC)), small intestine cancer, soft tissue cancer, stomach cancer, testicular cancer, thyroid cancer, parathyroid cancer, pituitary tumors, adrenal gland tumors, ureter cancer, biliary cancer, and urinary bladder cancer. In some embodiments, the cancer is selected from the group consisting of: head

and neck, ovarian, cervical, bladder and oesophageal cancers, pancreatic, gastrointestinal cancer, gastric, breast, endometrial and colorectal cancers, hepatocellular carcinoma, glioblastoma, bladder, lung cancer, e.g., non-small cell lung cancer (NSCLC), bronchioloalveolar carcinoma. In some embodiments, the cancer is pancreatic cancer, head and neck cancer, melanoma, colon cancer, renal cancer, leukemia, lung cancer, or breast cancer. In some cases, the cancer is melanoma, colon cancer, renal cancer, leukemia, or breast cancer.

In some such embodiments, the compounds provided herein are useful for treating a primary brain tumor or metastatic brain tumor. For example, the compounds can be used in the treatment of one or more of gliomas such as glioblastoma (also known as glioblastoma multiforme), astrocytomas, oligodendrogliomas, ependymomas, and mixed gliomas, meningiomas, medulloblastomas, gangliogliomas, schwannomas (neurilemmomas), and craniopharyngiomas (see, for example, Liu et al. J Exp Clin Cancer Res. 2019 May 23;38(1):219); and Ding et al. Cancer Res. 2003 Mar 1;63(5):1106-13). In some embodiments, the brain tumor is a primary brain tumor. In some embodiments, the brain tumor is a metastatic brain tumor, e.g., a metastatic brain tumor from lung cancer, melanoma, breast cancer, ovarian cancer, colorectal cancer, kidney cancer, bladder cancer, or undifferentiated carcinoma. In some embodiments, the brain tumor is a metastatic brain tumor from lung cancer (e.g., non-small cell lung cancer). In some embodiments, the compounds provided herein exhibit brain and/or central nervous system (CNS) penetrance. In some embodiments, the patient has previously been treated with another anticancer agent, e.g., another EGFR and/or HER2 inhibitor (e.g., a compound that is not a compound of Formula I) or a multi-kinase inhibitor.

In some embodiments, the cancer is a cancer of B cell origin. In some embodiments, the cancer is a lineage dependent cancer. In some embodiments, the cancer is a lineage dependent cancer where EGFR or the dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, plays a role in the initiation and/or development of the cancer.

In some embodiments, the cancer is an EGFR-associated cancer. Accordingly, also provided herein is a method for treating a subject diagnosed with or identified as having an EGFR-associated cancer, e.g., any of the exemplary EGFR-associated cancers disclosed

herein, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, as defined herein.

In some embodiments, the dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, includes one or more deletions (e.g., deletion of an amino acid at position 4), insertions, or point mutation(s) in an EGFR kinase. In some embodiments, dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, includes at least one deletion, insertion, or point mutation in an *EGFR* gene that results in the production of an EGFR kinase that has one or more of the amino acid substitutions, insertions, or deletions in **Table 1a** and **1b**. In some embodiments, the dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, includes a deletion of one or more residues from the EGFR kinase, resulting in constitutive activity of the EGFR kinase domain.

In some embodiments, the dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, includes at least one point mutation in an *EGFR* gene that results in the production of an EGFR kinase that has one or more amino acid substitutions, insertions, or deletions as compared to the wild type EGFR kinase (see, for example, the point mutations listed in **Table 1a** and **1b**).In some embodiments, dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, includes at least one point mutation in an *EGFR* gene that results in the production of an EGFR kinase that has one or more of the amino acid substitutions, insertions, or deletions in **Table 1a** and **1b**.

In some embodiments, the dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, includes an insertion of one or more residues in exon 20 of the *EGFR* gene (e.g., any of the exon 20 insertions described in **Table 1a** and **1b**). Exon 20 of EGFR has two major regions, the c -helix (residues 762-766) and the loop following the c-helix (residues 767-774). Studies suggest that for some exon 20 insertions (e.g., insertions after residue 764), a stabilized and ridged active conformation induces resistance to first generation EGFR inhibitors. In some embodiments, the dysregulation of an *EGFR* gene, an EGFR kinase, or expression or

activity or level of any of the same, includes an insertion of one or more residues in exon 20 selected from the group consisting of: V769_D770insX, D770_N771insX, N771_P772insX, P772_H773insX, and H773_V774insX. For example, the EGFR kinase protein insertion is an exon 20 insertion selected from the group consisting of: A767_V769dupASV, V769_D770insASV, D770_N771insNPG, D770_N771insNPY, D770_N771insSVD, D770_N771insGL, N771_H773dupNPH, N771_P772insN, N771_P772insH, N771_P772insV, P772_H773insDNP, P772_H773insPNP, H773_V774insNPH, H773_V774insH, H773_V774insPH, H773_V774insAH, and P772_H773insPNP H773insPNP; or any combination thereof; e.g., any two 10 or more independently selected exon 20 insertions; e.g., any two independently selected exon 20 insertions (e.g., V769_D770insASV and D770_N771insSVD).

Table 1a. EGFR Protein Amino Acid Substitutions/Insertions/Deletions[A]

Amino Acid Position(s)	Non-Limiting Exemplary Mutations	Non-limiting Exemplary EGFR-associated Cancer(s)
62	L62R[11,B]	
108	R108K[11,B]	
216	A216T[11,B]	
222	R222C[11,B]	
252	R252C[11,B]	
289	A289D, A289T, A289V[11,B]	
292	V292L[11,B]	
304	H304Y[11,B]	
306	S306L[11,B]	
492	S492R[11,B]	
596	P596L[11,B]	
598	G598V[11,B]	
688	L688F[6]	Lung adenocarcinoma[6]
689	V689L[6]	Lung adenocarcinoma[6]
703	L703I, L703P[11,B]	
706	I706T[6]	Lung adenocarcinoma[6]
709	E709A, E709G, E709K, E709H, E709V[2,6,9]	Lung adenocarcinoma[2,6], NSCLC[9]

709-710 (sometimes also called exon 18 deletion or del_18)	E709_T710delinsD[9]	NSCLC[9]
714	K714R[11,B]	
718	L718Q[1,11,B]	
719	G719S, G719C, G719A, G719D[1,4]	NSCLC[3]
719 and 706	G719A/I706T[6]	Lung adenocarcinoma[6]
719 and 709	G719S/E709K[6], G719S/E709A[11,B], G719C/E709A[11,B]	Lung adenocarcinoma[6]
719 and exon 18 deletion	G719X/del_18[9]	NSCLC[9]
720	S720F[11,B]	
735	G735S[11,B]	
741	P741L[11,B]	
744	I744M[11,B]	
747	L747S[11,B]	
749	E749Q[6]	Lung adenocarcinoma[6]
750	A750P[5,10]	NSCLC[5], lung adenocarcinoma[10]
750 and 749	A750P/E749Q[6]	
751	T751I[11,B]	
752	S752F[10]	Lung adenocarcinoma[10]
753	P753S[11,B]	
765	V765A[3], V765M[11,B]	NSCLC[3]
767	A767V[11,B]	
768	S768I[2,9]	Lung adenocarcinoma[2], NSCLC[9]
768 and 719	S768I/G719A[11,B], S768I/G719C[11,B], S768I/G719S[11,B],	
769	V769M[3], V769L[11,B]	
771	N771F[6]	Lung adenocarcinoma[6]
773	H773Y[6], H773L[11,B], H773Y[11,B]	Lung adenocarcinoma[6]

774	V774M, V774A[2,3]	Lung adenocarcinoma[2], NSCLC[3]
774 and 773	V774M/H773L[10]	NSCLC[10]
776	R776H, R776C[6], R776G[11,B]	Lung adenocarcinoma[6]
776 and 719	R776H/G719S[6]	Lung adenocarcinoma[6]
779	G779S[11,B]	
783	T783A[3]	NSCLC[3]
784	S784P[3]	
785	T785I[6]	Lung adenocarcinoma[6]
786	V786M[11,B]	
790	T790M[3]	NSCLC[3]
790 and 719	T790M/G719A[11,B]	
790 and 948	T790M/V948R[1]	
797 and 790	C797S/T790M[11,B]	
798	P798H[11,B]	
802	V802I[11,B]	
813	Y813H[6]	Lung adenocarcinoma[6]
824	G824S[6]	Lung adenocarcinoma[6]
824 and 688	G824S/L688F[6]	Lung adenocarcinoma[6]
831	R831H, R831L[11,B]	
833	L833V[2,8], L833F[11,B]	Lung adenocarcinoma[2], NSCLC[8]
834	V834L, V834M[11,B]	
835	H835L[11,B]	
835, 833, and 670	H835L/L833V/R670W[8]	NSCLC[8]
838	L838V[11,B]	
843	V843I[3]	NSCLC[3]
844	L844V[1]	
845	V845M[6]	Lung adenocarcinoma[6]
848	P848L[11,B]	
851	V851I[6]	Lung adenocarcinoma[6]
854	T854A[11,B]	
857	G857R[6]	Lung adenocarcinoma[6]
857, 851, 845, 813, and 785	G857R/V851I/V845M/Y813H/T785I[6]	Lung adenocarcinoma[6]
858	L858R[1]	

858 and 108	L858R/R108K[11,B]	
858 and 289	L858R/A289T[11,B]	
858 and 292	L858R/V292L[11,B]	
858 and 306	L858R/S306L[11,B]	
858 and 703	L858R/L703I[11,B]	
858 and 709	L858R/E709A[11,B], L858R/E709G[11,B], L858R/E709K[11,B], L858R/E709V[11,B],	
858 and 714	L858R/K714R[11,B]	
858 and 718	L858R/L718Q[1]	
858 and 720	L858R/S720F[11,B]	
858 and 744	L858R/I744M[11,B]	
858 and 768	L858R/S768I[11,B]	
858 and 769	L858R/V769L[6]	Lung adenocarcinoma[6]
858 and 776	L858R/R776H[6], L858R/R776C[11,B], L858R/R776G[11,B]	Lung adenocarcinoma[6]
858 and 790	L858R/T790M[11,B]	
858 and 833	L858R/L833V[6]	Lung adenocarcinoma[6]
858 and 838	L858R/L838V[11,B]	
858 and 843	L858R/V843I[11,B]	
858 and 844	L858R/L844V[1]	
858 and exon 18 deletion	L858R/del_18[9]	NSCLC[9]
859	A859T[11,B]	
860	K860R[11,B]	
861	L861Q, L861R, L681G[1,5,6,7,9]	Lung adenocarcinoma[6], NSCLC[5,9]
861 and 719	L861Q/G719X[10], L861Q/G719A[11,B], L861R/G719A[11,B]	Lung adenocarcinoma[10]
861 and 858	L861Q/L858R[11,B]	
861, 768, and 719	L861Q/S768I/G719X[10]	Lung adenocarcinoma[10]
864	A864T[11,B]	
865	E865K[11,B]	
870	H870R[6]	Lung adenocarcinoma[6]
870 and 858	H870R/L858R	
871	A871E, A871G[3,6], A871T[11,B]	Lung adenocarcinoma[6]
871 and 858	A871G/L858R[6]	Lung adenocarcinoma[6]
873	G873E[11,B]	

874	G874S[11,B]	
941	I941R[1]	
948	V948R[1]	
1118	A1118T[11,B]	
1153	S1153I[11,B]	
Exon 19 insertion (sometimes also called ins_19)		
	V738_K739insKIPVAI[6]	Lung adenocarcinoma[6]
	I744_K745insKIPVAI[9,10]	NSCLC[9,10]
	K745_E746insTPVAIK[9,10]	NSCLC[9,10]
	K745_E746insVPVAIK[10]	NSCLC[10]
	K745_E746insIPVAIK[9,10]	NSCLC[9,10]
Exon 19 deletion (sometimes also called del_19)[1,2]		
	E746_A750del[1]	
	E746_A750delinsP[1]	
	E746_A750delinsIP[11,B]	
	E746_A750del/T790M[11,B]	
	E746_A750del/A1118T[11,B]	
	E746_T751delinsV[11,B]	
	E746_S752delinsV[2]	Lung adenocarcinoma[2]
	E746_S752delinsV/A216T[11,B]	
	L747_E749del[5]	NSCLC[5]
	L747_A750del[3]	NSCLC[3]
	L747_A750delinsP[2]	Lung adenocarcinoma[2]
	L747_T751del[2]	Lung adenocarcinoma[2]
	L747_T751delinsA[10]	NSCLC[10]
	L747_T751delinsP[10]	NSCLC[10]
	L747_T751delinsS[11,B]	
	L747_T751delinsQ[2]	Lung adenocarcinoma[2]
	L747_S752del[2]	Lung adenocarcinoma[2]
	L747_P753del[10]	NSCLC[10]
	L747_P753delinsS[2]	Lung adenocarcinoma[2]
	L747_P753delinsQ[11,B]	
	L747_P753delinsVS[10]	NSCLC[10]
	T751_I759delinsN[11,B]	
	S752_I759del[2,10]	Lung adenocarcinoma[2], NSCLC[10]

Exon 19 deletion and 706	Del_19 and I706T[6]	Lung adenocarcinoma[6]
Exon 19 deletion and 718	Del_19 and L718Q[1]	
Exon 19 deletion and 844	Del_19 and L844V[1]	
Exon 19 deletion and 858	Del_19 and L858R[6]	Lung adenocarcinoma[6]
Exon 19 deletion and Exon 18 deletion	Del_19 and del_18[9]	NSCLC[9]
Exon 20 insertion (sometimes also called ins_20)[1]		
	D761_E762insX[5], e.g., D761_E762insEAFQ[10]	NSCLC[5]
	A763_Y764insX[5], e.g., A763_Y764insFQEA[5,9,10]	NSCLC[5,9,10]
	Y764_V765insX[5], e.g., V764_V765insHH[13]	NSCLC[5]
	V765_M766insX[5]	NSCLC[5]
	M766_A767insASV[6]	Lung adenocarcinoma[6]
	A767_S768insX[5]; A767insASV[14]	NSCLC[5]
	A767_V769dupASV[5]	NSCLC[5]
	S768_V769insX[12]; S768dupSVD[14]	NSCLC
	V769_D770insX[5], e.g., V769_D770insASV[8,9,10]	NSCLC[5,8,10]
	D770delinsGY[5,10]	NSCLC[5,10]
	D770_N771insX[5], e.g., D770_N771insNPG[2,5,9], D770_N771insG+N771T[6], D770_N771insNPY[6], D770_N771insSVD[9,10], D770_N771insGL[13]	NSCLC[3,5,10]
	D770_N771insX and amino acid position 773, e.g., D770_N771insNPY/H773Y[6]	Lung adenocarcinoma[6]

	N771_P772insX[5], e.g., N771_P772insN[10], N771_P772insH[13], N771_P772insV[13]	NSCLC[5,10]
	N771_H773dupNPH[5]	NSCLC[5]
	N771delinsGY[13]; N771del insFH[14]	
	P772_H773insX[5], e.g., P772_H773insDNP[9], P772_H773insPNP[9]	NSCLC[5,9]
	H773_V774insX[5], e.g., H773_V774insNPH[9], H773_V774insH[10], H773_V774insPH[10], H773_V774insAH[10], P772_H773insPNP[13]	NSCLC[5,9,10]
	H773_dupH[13]	
	V774_C775insX[5], e.g., V774_C775insHV[10]	NSCLC[5]
	A775_G776insX, e.g., A775_G776insYVMA[13]	
Kinase domain duplication (KDD)	Duplication of exons 18-25, 18-26, 14-26, or 17-25[9]	NSCLC[9]

[A] The EGFR mutations shown may be activating mutations and/or confer increased resistance of EGFR to an EGFR inhibitor and/or a multi-kinase inhibitor (MKI), e.g., as compared to a wild type EGFR

[B] Potentially oncogenic variant. See, e.g., Kohsaka, Shinji, et al. Science translational medicine 9.416 (2017): eaan6566.

[1] PCT Patent Application Publication No. WO2019/246541.

[2] Grosse A, Grosse C, Rechsteiner M, Soltermann A. Diagn Pathol. 2019;14(1):18. Published 2019 Feb 11. doi:10.1186/s13000-019-0789-1.

[3] Stewart EL, Tan SZ, Liu G, Tsao MS. Transl Lung Cancer Res. 2015;4(1):67–81. doi:10.3978/j.issn.2218-6751.2014.11.06.

[4] Pines, Gur, Wolfgang J. Köstler, and Yosef Yarden. FEBS letters 584.12 (2010): 2699-2706.

[5] Yasuda, Hiroyuki, Susumu Kobayashi, and Daniel B. Costa. The Lancet Oncology 13.1 (2012): e23-e31.

[6] Kim EY, Cho EN, Park HS, et al. Cancer Biol Ther. 2016;17(3):237–245. doi:10.1080/15384047.2016.1139235.

[7] Shah, Riyaz, and Jason F. Lester. Clinical Lung Cancer (2019).

[8] Aran, Veronica, and Jasminka Omerovic. International journal of molecular sciences 20.22 (2019): 5701. doi: 10.3390/ijms20225701.

[9] Beau-Faller, Michele, et al. (2012): 10507-10507. doi: 10.1016/j.semcancer.2019.09.015.

[10] Masood, Ashiq, Rama Krishna Kancha, and Janakiraman Subramanian. Seminars in oncology. WB Saunders, 2019. doi: 10.1053/j.seminoncol.2019.08.004.

[11] Kohsaka, Shinji, et al. Science translational medicine 9.416 (2017): eaan6566.

[12] Vyse and Huang et al. Signal Transduct Target Ther. 2019 Mar 8;4:5. doi: 10.1038/s41392-019-0038-9.

[13] PCT Patent Application Publication No. WO2019/046775.

[14] PCT Patent Application Publication No. WO 2018/094225.

Table 1b. EGFR Protein Amino Acid Substitutions/Insertions/Deletions[A]

Amino Acid Position(s)	Non-Limiting Exemplary Mutations	Non-limiting Exemplary EGFR-associated Cancer(s)
62	L62R[11,B]	
108	R108K[11,B]	
216	A216T[11,B]	
222	R222C[11,B]	
252	R252C[11,B]	
289	A289D, A289T, A289V[11,B]	
292	V292L[11,B]	
304	H304Y[11,B]	
306	S306L[11,B]	
492	S492R[11,B]	
596	P596L[11,B]	
598	G598V[11,B]	
688	L688F[6]	Lung adenocarcinoma[6]
689	V689L[6]	Lung adenocarcinoma[6]
703	L703I, L703P[11,B]	
706	I706T[6]	Lung adenocarcinoma[6]
709	E709A, E709G, E709K, E709H, E709V[2,6,9]	Lung adenocarcinoma[2,6], NSCLC[9]
709-710 (sometimes also called exon 18 deletion or del_18)	E709_T710delinsD[9]	NSCLC[9]
714	K714R[11,B]	
718	L718Q[1,11,B]	
719	G719S, G719C, G719A, G719D[1,4]	NSCLC[3]
719 and 706	G719A/I706T[6]	Lung adenocarcinoma[6]
719 and 709	G719S/E709K[6], G719S/E709A[11,B], G719C/E709A[11,B]	Lung adenocarcinoma[6]

719 and exon 18 deletion	G719X/del_18[9]	NSCLC[9]
720	S720F[11,B]	
735	G735S[11,B]	
741	P741L[11,B]	
744	I744M[11,B]	
747	L747S[11,B]	
749	E749Q[6]	Lung adenocarcinoma[6]
750	A750P[5,10]	NSCLC[5], lung adenocarcinoma[10]
750 and 749	A750P/E749Q[6]	
751	T751I[11,B]	
752	S752F[10]	Lung adenocarcinoma[10]
753	P753S[11,B]	
765	V765A[3], V765M[11,B]	NSCLC[3]
767	A767V[11,B]	
768	S768I[2,9]	Lung adenocarcinoma[2], NSCLC[9]
768 and 719	S768I/G719A[11,B], S768I/G719C[11,B], S768I/G719S[11,B],	
769	V769M[3], V769L[11,B]	
771	N771F[6]	Lung adenocarcinoma[6]
773	H773Y[6], H773L[11,B], H773Y[11,B]	Lung adenocarcinoma[6]
774	V774M, V774A[2,3]	Lung adenocarcinoma[2], NSCLC[3]
774 and 773	V774M/H773L[10]	NSCLC[10]
776	R776H, R776C[6], R776G[11,B]	Lung adenocarcinoma[6]
776 and 719	R776H/G719S[6]	Lung adenocarcinoma[6]
779	G779S[11,B]	
783	T783A[3]	NSCLC[3]
784	S784P[3]	
785	T785I[6]	Lung adenocarcinoma[6]
786	V786M[11,B]	
790	T790M[3]	NSCLC[3]
790 and 719	T790M/G719A[11,B]	
790 and 948	T790M/V948R[1]	
797 and 790	C797S/T790M[11,B]	
798	P798H[11,B]	
802	V802I[11,B]	

813	Y813H[6]	Lung adenocarcinoma[6]
824	G824S[6]	Lung adenocarcinoma[6]
824 and 688	G824S/L688F[6]	Lung adenocarcinoma[6]
831	R831H, R831L[11,B]	
833	L833V[2,8], L833F[11,B]	Lung adenocarcinoma[2], NSCLC[8]
834	V834L, V834M[11,B]	
835	H835L[11,B]	
835, 833, and 670	H835L/L833V/R670W[8]	NSCLC[8]
838	L838V[11,B]	
843	V843I[3]	NSCLC[3]
844	L844V[1]	
845	V845M[6]	Lung adenocarcinoma[6]
848	P848L[11,B]	
851	V851I[6]	Lung adenocarcinoma[6]
854	T854A[11,B]	
857	G857R[6]	Lung adenocarcinoma[6]
857, 851, 845, 813, and 785	G857R/V851I/V845M/Y813H/T785I[6]	Lung adenocarcinoma[6]
858	L858R[1]	
858 and 108	L858R/R108K[11,B]	
858 and 289	L858R/A289T[11,B]	
858 and 292	L858R/V292L[11,B]	
858 and 306	L858R/S306L[11,B]	
858 and 703	L858R/L703I[11,B]	
858 and 709	L858R/E709A[11,B], L858R/E709G[11,B], L858R/E709K[11,B], L858R/E709V[11,B],	
858 and 714	L858R/K714R[11,B]	
858 and 718	L858R/L718Q[1]	
858 and 720	L858R/S720F[11,B]	
858 and 744	L858R/I744M[11,B]	
858 and 768	L858R/S768I[11,B]	
858 and 769	L858R/V769L[6]	Lung adenocarcinoma[6]
858 and 776	L858R/R776H[6], L858R/R776C[11,B], L858R/R776G[11,B]	Lung adenocarcinoma[6]
858 and 790	L858R/T790M[11,B]	
858 and 833	L858R/L833V[6]	Lung adenocarcinoma[6]

858 and 838	L858R/L838V[11,B]	
858 and 843	L858R/V843I[11,B]	
858 and 844	L858R/L844V[1]	
858 and exon 18 deletion	L858R/del_18[9]	NSCLC[9]
859	A859T[11,B]	
860	K860R[11,B]	
861	L861Q, L861R, L681G[1,5,6,7,9]	Lung adenocarcinoma[6], NSCLC[5,9]
861 and 719	L861Q/G719X[10], L861Q/G719A[11,B], L861R/G719A[11,B]	Lung adenocarcinoma[10]
861 and 858	L861Q/L858R[11,B]	
861, 768, and 719	L861Q/S768I/G719X[10]	Lung adenocarcinoma[10]
864	A864T[11,B]	
865	E865K[11,B]	
870	H870R[6]	Lung adenocarcinoma[6]
870 and 858	H870R/L858R	
871	A871E, A871G[3,6], A871T[11,B]	Lung adenocarcinoma[6]
871 and 858	A871G/L858R[6]	Lung adenocarcinoma[6]
873	G873E[11,B]	
874	G874S[11,B]	
941	I941R[1]	
948	V948R[1]	
1118	A1118T[11,B]	
1153	S1153I[11,B]	
Exon 19 insertion (sometimes also called ins_19)		
	V738_K739insKIPVAI[6]	Lung adenocarcinoma[6]
	I744_K745insKIPVAI[9,10]	NSCLC[9,10]
	K745_E746insTPVAIK[9,10]	NSCLC[9,10]
	K745_E746insVPVAIK[10]	NSCLC[10]
	K745_E746insIPVAIK[9,10]	NSCLC[9,10]
Exon 19 deletion (sometimes also called del_19)[1,2]		
	E746_A750del[1]	
	E746_A750delinsP[1]	
	E746_A750delinsIP[11,B]	
	E746_A750del/T790M[11,B]	
	E746_A750del/A1118T[11,B]	
	E746_T751delinsV[11,B]	

	E746_S752delinsV[2]	Lung adenocarcinoma[2]
	E746_S752delinsV/A216T[11,B]	
	L747_E749del[5]	NSCLC[5]
	L747_A750del[3]	NSCLC[3]
	L747_A750delinsP[2]	Lung adenocarcinoma[2]
	L747_T751del[2]	Lung adenocarcinoma[2]
	L747_T751delinsA[10]	NSCLC[10]
	L747_T751delinsP[10]	NSCLC[10]
	L747_T751delinsS[11,B]	
	L747_T751delinsQ[2]	Lung adenocarcinoma[2]
	L747_S752del[2]	Lung adenocarcinoma[2]
	L747_P753del[10]	NSCLC[10]
	L747_P753delinsS[2]	Lung adenocarcinoma[2]
	L747_P753delinsQ[11,B]	
	L747_P753delinsVS[10]	NSCLC[10]
	T751_I759delinsN[11,B]	
	S752_I759del[2,10]	Lung adenocarcinoma[2], NSCLC[10]
Exon 19 deletion and 706	Del_19 and I706T[6]	Lung adenocarcinoma[6]
Exon 19 deletion and 718	Del_19 and L718Q[1]	
Exon 19 deletion and 844	Del_19 and L844V[1]	
Exon 19 deletion and 858	Del_19 and L858R[6]	Lung adenocarcinoma[6]
Exon 19 deletion and Exon 18 deletion	Del_19 and del_18[9]	NSCLC[9]
Exon 20 insertion (sometimes also called ins_20)[1]		
	D761_E762insX[5], e.g., D761_E762insEAFQ[10]	NSCLC[5]
	A763_Y764insX[5], e.g., A763_Y764insFQEA[5,9,10]	NSCLC[5,9,10]

	Y764_V765insX[5], e.g., V764_V765insHH[13]	NSCLC[5]
	V765_M766insX[5]	NSCLC[5]
	M766_A767insASV[6]	Lung adenocarcinoma[6]
	M766delinsMASVx2[15]	Pediatric bithalamic glioma[15]
	A767_S768insX[5]; A767insASV[14]	NSCLC[5]
	A767_V769dupASV[5]	NSCLC[5]
	A767delinsASVDx3; A767delinsASVG[15]	Pediatric bithalamic glioma[15]
	S768_V769insX[12]; S768dupSVD[14, 16]	NSCLC[12, 14]; Sinonasal squamous cell carcinoma[16]
	V769_D770insX[5], e.g., V769_D770insASV[8,9,10]	NSCLC[5,8,10]
	D770delinsGY[5,10]; D770delinsDN; D770delinsDNPH[15]	NSCLC[5,10]; Pediatric bithalamic glioma[15]
	D770_N771insX[5, 16], e.g., D770_N771insNPG[2,5,9], D770_N771insG+N771T[6], D770_N771insNPY[6], D770_N771insSVD[9,10], D770_N771insGL[13]	NSCLC[3,5,10]; Sinonasal squamous cell carcinoma[16]
	D770_N771insX and amino acid position 773, e.g., D770_N771insNPY/H773Y[6]	Lung adenocarcinoma[6]
	N771_P772insX[5, 16], e.g., N771_P772insN[10], N771_P772insH[13], N771_P772insV[13]	NSCLC[5,10]; Sinonasal squamous cell carcinoma[16]
	N771_H773dupNPH[5]	NSCLC[5]
	N771delinsGY[13]; N771del insFH[14]; N771delinsNPH[15]	NSCLC[13,14]; Pediatric bithalamic glioma[15]
	N771_H773dup[16]	Sinonasal squamous cell carcinoma[16]
	P772_H773insX[5], e.g., P772_H773insDNP[9], P772_H773insPNP[9]	NSCLC[5,9]
	H773_V774insX[5], e.g., H773_V774insNPH[9], H773_V774insH[10],	NSCLC[5,9,10]

	H773_V774insPH[10], H773_V774insAH[10], P772_H773insPNP[13]	
	H773_dupH[13]	
	V774_C775insX[5], e.g., V774_C775insHV[10]	NSCLC[5]
	A775_G776insX, e.g., A775_G776insYVMA[13]	
Kinase domain duplication (KDD)	Duplication of exons 18-25, 18-26, 14-26, or 17-25[9]	NSCLC[9]

[A] The EGFR mutations shown may be activating mutations and/or confer increased resistance of EGFR to an EGFR inhibitor and/or a multi-kinase inhibitor (MKI), e.g., as compared to a wild type EGFR

[B] Potentially oncogenic variant. See, e.g., Kohsaka, Shinji, et al. Science translational medicine 9.416 (2017): eaan6566.

[1] PCT Patent Application Publication No. WO2019/246541.

[2] Grosse A, Grosse C, Rechsteiner M, Soltermann A. Diagn Pathol. 2019;14(1):18. Published 2019 Feb 11. doi:10.1186/s13000-019-0789-1.

[3] Stewart EL, Tan SZ, Liu G, Tsao MS. Transl Lung Cancer Res. 2015;4(1):67–81. doi:10.3978/j.issn.2218-6751.2014.11.06.

[4] Pines, Gur, Wolfgang J. Köstler, and Yosef Yarden. FEBS letters 584.12 (2010): 2699-2706.

[5] Yasuda, Hiroyuki, Susumu Kobayashi, and Daniel B. Costa. The Lancet Oncology 13.1 (2012): e23-e31.

[6] Kim EY, Cho EN, Park HS, et al. Cancer Biol Ther. 2016;17(3):237--245. doi:10.1080/15384047.2016.1139235.

[7] Shah, Riyaz, and Jason F. Lester. Clinical Lung Cancer (2019).

[8] Aran, Veronica, and Jasminka Omerovic. International journal of molecular sciences 20.22 (2019): 5701. doi: 10.3390/ijms20225701.

[9] Beau-Faller, Michele, et al. (2012): 10507-10507. doi: 10.1016/j.semcancer.2019.09.015.

[10] Masood, Ashiq, Rama Krishna Kancha, and Janakiraman Subramanian. Seminars in oncology. WB Saunders, 2019. doi: 10.1053/j.seminoncol.2019.08.004.

[11] Kohsaka, Shinji, et al. Science translational medicine 9.416 (2017): eaan6566.

[12] Vyse and Huang et al. Signal Transduct Target Ther. 2019 Mar 8;4:5. doi: 10.1038/s41392-019-0038-9.

[13] PCT Patent Application Publication No. WO2019/046775.

[14] PCT Patent Application Publication No. WO 2018/094225.

[15] Mondal, Gourish, et al. Acta Neuropathol. 2020; 139(6): 1071-1088

[16] Udager, Aaron M., et al. Cancer Res, 2015; 75(13): 2600-2606

In some embodiments, the dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, includes a splice variation in an EGFR mRNA which results in an expressed protein that is an alternatively spliced variant of EGFR having at least one residue deleted (as compared to the wild type EGFR kinase) resulting in a constitutive activity of an EGFR kinase domain.

In some embodiments, the dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, includes at least one point mutation in an *EGFR* gene that results in the production of an EGFR kinase that has one or more amino acid substitutions or insertions or deletions in an *EGFR* gene that results in the production of an EGFR kinase that has one or more amino acids inserted or removed, as compared to the wild type EGFR kinase. In some cases, the resulting EGFR kinase is more resistant to inhibition (e.g., inhibition of its signaling activity) by one or more first EGFR inhibitors, as compared to a wild type EGFR kinase or an EGFR kinase not including the same mutation. Such mutations, optionally, do not decrease the sensitivity of the cancer cell or tumor having the EGFR kinase to treatment with a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, (e.g., as compared to a cancer cell or a tumor that does not include the particular EGFR inhibitor resistance mutation).

In other embodiments, the dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, includes at least one point mutation in an *EGFR* gene that results in the production of an EGFR kinase that has one or more amino acid substitutions as compared to the wild type EGFR kinase, and which has increased resistance to a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, as compared to a wild type EGFR kinase or an EGFR kinase not including the same mutation. In such embodiments, an EGFR inhibitor resistance mutation can result in an EGFR kinase that has one or more of an increased V_{max}, a decreased K_m, and a decreased K_D in the presence of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, as compared to a wild type EGFR kinase or an EGFR kinase not having the same mutation in the presence of the same compound of Formula (**I**), or a pharmaceutically acceptable salt thereof.

Exemplary Sequence of Mature Human EGFR Protein (UniProtKB entry P00533) (SEQ ID NO: 1)

MRPSGTAGAA LLALLAALCP ASRALEEKKV CQGTSNKLTQ LGTFEDHFLS
LQRMFNNCEV VLGNLEITYV QRNYDLSFLK TIQEVAGYVL IALNTVERIP
LENLQIIRGN MYYENSYALA VLSNYDANKT GLKELPMRNL QEILHGAVRF
SNNPALCNVE SIQWRDIVSS DFLSNMSMDF QNHLGSCQKC DPSCPNGSCW
GAGEENCQKL TKIICAQQCS GRCRGKSPSD CCHNQCAAGC TGPRESDCLV
CRKFRDEATC KDTCPPLMLY NPTTYQMDVN PEGKYSFGAT CVKKCPRNYV
VTDHGSCVRA CGADSYEMEE DGVRKCKKCE GPCRKVCNGI GIGEFKDSLS
INATNIKHFK NCTSISGDLH ILPVAFRGDS FTHTPPLDPQ ELDILKTVKE
ITGFLLIQAW PENRTDLHAF ENLEIIRGRT KQHGQFSLAV VSLNITSLGL
RSLKEISDGD VIISGNKNLC YANTINWKKL FGTSGQKTKI ISNRGENSCK
ATGQVCHALC SPEGCWGPEP RDCVSCRNVS RGRECVDKCN LLEGEPREFV
ENSECIQCHP ECLPQAMNIT CTGRGPDNCI QCAHYIDGPH CVKTCPAGVM
GENNTLVWKY ADAGHVCHLC HPNCTYGCTG PGLEGCPTNG PKIPSIATGM
VGALLLLLVV ALGIGLFMRR RHIVRKRTLR RLLQERELVE PLTPSGEAPN
QALLRILKET EFKKIKVLGS GAFGTVYKGL WIPEGEKVKI PVAIKELREA
TSPKANKEIL DEAYVMASVD NPHVCRLLGI CLTSTVQLIT QLMPFGCLLD
YVREHKDNIG SQYLLNWCVQ IAKGMNYLED RRLVHRDLAA RNVLVKTPQH
VKITDFGLAK LLGAEEKEYH AEGGKVPIKW MALESILHRI YTHQSDVWSY
GVTVWELMTF GSKPYDGIPA SEISSILEKG ERLPQPPICT IDVYMIMVKC
WMIDADSRPK FRELIIEFSK MARDPQRYLV IQGDERMHLP SPTDSNFYRA
LMDEEDMDDV VDADEYLIPQ QGFFSSPSTS RTPLLSSLSA TSNNSTVACI
DRNGLQSCPI KEDSFLQRYS SDPTGALTED SIDDTFLPVP EYINQSVPKR
PAGSVQNPVY HNQPLNPAPS RDPHYQDPHS TAVGNPEYLN TVQPTCVNST
FDSPAHWAQK GSHQISLDNP DYQQDFFPKE AKPNGIFKGS TAENAEYLRV
APQSSEFIGA

In some embodiments, dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, includes at least one EGFR inhibitor resistance mutation in an *EGFR* gene that results in the production of an EGFR kinase that has one or more of the amino acid substitutions, insertions, or deletions as described in **Table 2a** and **2b.** In some embodiments, compounds of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**) and pharmaceutically acceptable salts and solvates thereof, are useful in treating subjects that develop cancers with EGFR inhibitor resistance mutations (e.g., that result in an increased resistance to a first EGFR inhibitor, e.g., a substitution at amino acid position 718, 747, 761, 790, 797, or

854 (e.g., L718Q, L747S, D761Y, T790M, C797S, T854A), and/or one or more EGFR inhibitor resistance mutations listed in **Table 2a** and **2b**) by either dosing in combination or as a subsequent or additional (e.g., follow-up) therapy to existing drug treatments (e.g., other inhibitors of EGFR; e.g., first and/or second EGFR inhibitors).

5

Table 2a. EGFR Protein Amino Acid Resistance Mutations

Amino Acid Position(s)	Non-Limiting Exemplary Mutations	Non-limiting Exemplary EGFR-associated Cancer(s)
747	L747S[2,4,6], L747P[6]	NSCLC[2]
761	D761Y[2,4]	NSCLC[2]
769	V769M[2]	NSCLC[2]
790	T790M[1,4]	NSCLC[2]
792	L792H[6]	NSCLC[6]
796	G796R[6]	NSCLC[6]
797	C797S[5]	NSCLC[5]
797 and 790	C797S/T790M[5]	NSCLC[5]
843	V843I[2,5]	NSCLC[2]
854	T854A[2,4]	NSCLC[2]
858 and 747	L858R/L747S[6]	NSCLC[6]
858 and 790	L858R/T790M[1]	
858, 797, and 790	L858R/C797S/T790M[1]	
871	A871E[2]	NSCLC[2]
941, 858, and 790	I941R/L858R/T790M[1]	
Exon 19 deletion and 790	Del_19 and T790M[1]	
Exon 19 deletion, 844, and 790	Del_19 and T790M/L844V[1]	
Exon 19 deletion, 797, and 790	Del_19 and C797S/T790M[1]	
Exon 20 insertion (also called ins_20)[2,3]		
	A767_V769dupASV[5]	NSCLC[5]
	D770_N771insX[3], e.g., D770_N771insNPG[2,3,7]	NSCLC[2,3]
	N771_H771dupNPH[3]	NSCLC[3]
	P772_H773insX[3] e.g., P772_H773insDNP[7]	NSCLC[3,7]
	H773_V774insNPH[7]	NSCLC[7]

[1] PCT Patent Application Publication No. WO2019/246541

[2] Stewart EL, Tan SZ, Liu G, Tsao MS. Transl Lung Cancer Res. 2015;4(1):67–81. doi:10.3978/j.issn.2218-6751.2014.11.06

[3] Yasuda, Hiroyuki, Susumu Kobayashi, and Daniel B. Costa. The Lancet Oncology 13.1 (2012): e23-e31.

[4] Kim EY, Cho EN, Park HS, et al. Cancer Biol Ther. 2016;17(3):237–245. doi:10.1080/15384047.2016.1139235

[5]Shah, Riyaz, and Jason F. Lester. Clinical Lung Cancer (2019).

[6] Aran, Veronica, and Jasminka Omerovic. International journal of molecular sciences 20.22 (2019): 5701. doi: 10.3390/ijms20225701.

[7] Beau-Faller, Michele, et al. (2012): 10507-10507. doi: 10.1016/j.semcancer.2019.09.015

[8] Masood, Ashiq, Rama Krishna Kancha, and Janakiraman Subramanian. Seminars in oncology. WB Saunders, 2019. doi: 10.1053/j.seminoncol.2019.08.004

Table 2b. EGFR Protein Amino Acid Resistance Mutations

Amino Acid Position(s)	Non-Limiting Exemplary Mutations	Non-limiting Exemplary EGFR-associated Cancer(s)
747	L747S[2,4,6], L747P[6]	NSCLC[2]
761	D761Y[2,4]	NSCLC[2]
769	V769M[2]	NSCLC[2]
790	T790M[1,4]	NSCLC[2]
792	L792H[6]	NSCLC[6]
796	G796R[6]	NSCLC[6]
797	C797S[5]	NSCLC[5]
797 and 790	C797S/T790M[5]	NSCLC[5]
843	V843I[2,5]	NSCLC[2]
854	T854A[2,4]	NSCLC[2]
858 and 747	L858R/L747S[6]	NSCLC[6]
858 and 790	L858R/T790M[1]	
858 and 797	L858R/C797S (or C797G)[9]	NSCLC[9]
858, 797, and 790	L858R/C797S/T790M[1]	
871	A871E[2]	NSCLC[2]
941, 858, and 790	I941R/L858R/T790M[1]	
Exon 19 deletion and 790	Del_19 and T790M[1]	

Exon 19 deletion and 797	Del_19 and C797S (or C797G)[9]	NSCLC[9]
Exon 19 deletion, 844, and 790	Del_19 and T790M/L844V[1]	
Exon 19 deletion, 797, and 790	Del_19 and C797S/T790M[1]	
Exon 20 insertion (also called ins_20)[2,3]		
	A767_V769dupASV[5]	NSCLC[5]
	D770_N771insX[3], e.g., D770_N771insNPG[2,3,7]	NSCLC[2,3]
	N771_H771dupNPH[3]	NSCLC[3]
	P772_H773insX[3] e.g., P772_H773insDNP[7]	NSCLC[3,7]
	H773_V774insNPH[7]	NSCLC[7]

[1] PCT Patent Application Publication No. WO2019/246541

[2] Stewart EL, Tan SZ, Liu G, Tsao MS. Transl Lung Cancer Res. 2015;4(1):67–81. doi:10.3978/j.issn.2218-6751.2014.11.06

[3] Yasuda, Hiroyuki, Susumu Kobayashi, and Daniel B. Costa. The Lancet Oncology 13.1 (2012): e23-e31.

[4] Kim EY, Cho EN, Park HS, et al. Cancer Biol Ther. 2016;17(3):237–245. doi:10.1080/15384047.2016.1139235

[5] Shah, Riyaz, and Jason F. Lester. Clinical Lung Cancer (2019).

[6] Aran, Veronica, and Jasminka Omerovic. International journal of molecular sciences 20.22 (2019): 5701. doi: 10.3390/ijms20225701.

[7] Beau-Faller, Michele, et al. (2012): 10507-10507. doi: 10.1016/j.semcancer.2019.09.015

[8] Masood, Ashiq, Rama Krishna Kancha, and Janakiraman Subramanian. Seminars in oncology. WB Saunders, 2019. doi: 10.1053/j.seminoncol.2019.08.004

[9] Papadimitrakopoulou, V.A., et al. Annals of Oncology 2018; 29 Supplement 8 VIII741

In some embodiments, the EGFR Protein Amino Acid Substitutions/Insertions/Deletions include any one or more, or any two or more (e.g., any two), of the EGFR Protein Amino Acid Substitutions/Insertions/Deletions delineated in Table 1a, 1b and/or Table 2a, 2b; e.g., any one or more, or any two or more (e.g., any two), of the following and independently selected EGFR Protein Amino Acid

Substitutions/Insertions/Deletions: V769L; V769M; M766delinsMASVx2; A767_V769dupASV; A767delinsASVDx3; A767delinsASVG; S768_V769insX; V769_D770insX; V769_D770insASV; D770delinsDN; D770delinsDNPH; D770_N771insSV; N771delinsNPH; N771_H773dup; L858R/C797S (or C797G); or Del_19 and C797S (or C797G), or any combination thereof.

As used herein, a "first inhibitor of EGFR" or "first EGFR inhibitor" is an EGFR inhibitor as defined herein, but which does not include a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, as defined herein. As used herein, a "second inhibitor of EGFR" or a "second EGFR inhibitor" is an EGFR inhibitor as defined herein, but which does not include a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as defined herein. When both a first and a second inhibitor of EGFR are present in a method provided herein, the first and second inhibitors of EGFR are different. In some embodiments, the first and/or second inhibitor of EGFR bind in a different location than a compound of Formula **(I)**. For example, in some embodiments, a first and/or second inhibitor of EGFR can inhibit dimerization of EGFR, while a compound of Formula **(I)** can inhibit the active site. In some embodiments, a first and/or second EGFR inhibitor can be an allosteric inhibitor of EGFR, while a compound of Formula **(I)** can inhibit the EGFR active site.

Exemplary first and second inhibitors of EGFR are described herein. In some embodiments, a first or second inhibitor of EGFR can be selected from the group consisting of osimertinib, gefitinib, erlotinib, afatinib, lapatinib, neratinib, AZD-9291, CL-387785, CO-1686, or WZ4002.

In some embodiments, compounds of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or pharmaceutically acceptable salts and solvates thereof, are useful for treating a cancer that has been identified as having one or more EGFR inhibitor resistance mutations (that result in an increased resistance to a first or second inhibitor of EGFR, e.g., a substitution described in **Table 2a** and **2b** including substitutions at amino acid position 747, 761, 790, 797, or 854 (e.g., L718Q, L747S, D761Y, T790M, C797S, T854A)). In some embodiments, the one or more EGFR inhibitor

resistance mutations occurs in a nucleic acid sequence encoding a mutant EGFR protein (e.g., a mutant EGFR protein having any of the mutations described in **Table 2a** and **2b**) resulting in a mutant EGFR protein that exhibits EGFR inhibitor resistance.

The epidermal growth factor receptor (EGFR) belongs to the ErbB family of receptor tyrosine kinases (RTKs) and provides critical functions in epithelial cell physiology (Schlessinger J (2014) *Cold Spring Harb Perspect Biol* 6, a008912). It is frequently mutated and/or overexpressed in different types of human cancers and is the target of multiple cancer therapies currently adopted in the clinical practice (Yarden Y and Pines G (2012) *Nat Rev Cancer* 12, 553–563).

Accordingly, provided herein are methods for treating a subject diagnosed with (or identified as having) a cancer that include administering to the subject a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof.

Also provided herein are methods for treating a subject identified or diagnosed as having an EGFR-associated cancer that include administering to the subject a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In some embodiments, the subject that has been identified or diagnosed as having an EGFR-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved test or assay for identifying dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, in a subject or a biopsy sample from the subject or by performing any of the non-limiting examples of assays described herein. In some embodiments, the test or assay is provided as a kit. In some embodiments, the cancer is an EGFR-associated cancer. For example, the EGFR-associated cancer can be a cancer that includes one or more EGFR inhibitor resistance mutations.

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

Also provided are methods for treating cancer in a subject in need thereof, the method comprising: (a) detecting an EGFR-associated cancer in the subject; and (b)

administering to the subject a therapeutically effective amount of a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. Some embodiments of these methods further include administering to the subject another anticancer agent (e.g., a second EGFR inhibitor, a second compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, or an immunotherapy). In some embodiments, the subject was previously treated with a first EGFR inhibitor or previously treated with another anticancer treatment, e.g., at least partial resection of the tumor or radiation therapy. In some embodiments, the subject is determined to have an EGFR-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved test or assay for identifying dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, in a subject or a biopsy sample from the subject or by performing any of the non-limiting examples of assays described herein. In some embodiments, the test or assay is provided as a kit. In some embodiments, the cancer is an EGFR-associated cancer. For example, the EGFR-associated cancer can be a cancer that includes one or more EGFR inhibitor resistance mutations.

Also provided are methods of treating a subject that include performing an assay on a sample obtained from the subject to determine whether the subject has a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, and administering (e.g., specifically or selectively administering) a therapeutically effective amount of a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, to the subject determined to have a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same. Some embodiments of these methods further include administering to the subject another anticancer agent (e.g., a second EGFR inhibitor, a second compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, or immunotherapy). In some embodiments of these methods, the subject was previously treated with a first EGFR inhibitor or previously treated with another anticancer treatment, e.g., at least partial resection of a tumor or radiation therapy. In some embodiments, the subject is a subject suspected of having an EGFR-associated cancer, a subject presenting with one or more symptoms of an EGFR-

associated cancer, or a subject having an elevated risk of developing an EGFR-associated cancer. In some embodiments, the assay utilizes next generation sequencing, pyrosequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved assay, e.g., FDA-approved kit. In some embodiments, the assay is a liquid biopsy. Additional, non-limiting assays that may be used in these methods are described herein. Additional assays are also known in the art. In some embodiments, the dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same includes one or more EGFR inhibitor resistance mutations.

Also provided is a compound of Formula **(I)** (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use in treating an EGFR-associated cancer in a subject identified or diagnosed as having an EGFR-associated cancer through a step of performing an assay (e.g., an in vitro assay) on a sample obtained from the subject to determine whether the subject has a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, where the presence of a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, identifies that the subject has an EGFR-associated cancer. Also provided is the use of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating an EGFR-associated cancer in a subject identified or diagnosed as having an EGFR-associated cancer through a step of performing an assay on a sample obtained from the subject to determine whether the subject has a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same where the presence of dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, identifies that the subject has an EGFR-associated cancer. Some embodiments of any of the methods or uses described herein further include recording in the subject's clinical record (e.g., a computer readable medium) that the subject is determined to have a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, through the performance of the assay, should be administered a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In some embodiments,

the assay utilizes next generation sequencing, pyrosequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved assay, e.g., FDA-approved kit. In some embodiments, the assay is a liquid biopsy. In some embodiments, the dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same includes one or more EGFR inhibitor resistance mutations.

Also provided is a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, for use in the treatment of a cancer in a subject in need thereof, or a subject identified or diagnosed as having an EGFR-associated cancer. Also provided is the use of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a cancer in a subject identified or diagnosed as having an EGFR-associated cancer. In some embodiments, the cancer is an EGFR-associated cancer, for example, an EGFR-associated cancer having one or more EGFR inhibitor resistance mutations. In some embodiments, a subject is identified or diagnosed as having an EGFR-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved, kit for identifying dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same, in a subject or a biopsy sample from the subject. As provided herein, an EGFR-associated cancer includes those described herein and known in the art.

In some embodiments of any of the methods or uses described herein, the subject has been identified or diagnosed as having a cancer with a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the subject has a tumor that is positive for a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the subject can be a subject with a tumor(s) that is positive for a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the subject can be a subject whose tumors have a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses

described herein, the subject is suspected of having an EGFR-associated cancer (e.g., a cancer having one or more EGFR inhibitor resistance mutations). In some embodiments, provided herein are methods for treating an EGFR-associated cancer in a subject in need of such treatment, the method comprising a) detecting a dysregulation of an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same in a sample from the subject; and b) administering a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof. In some embodiments, the dysregulation of an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same includes one or more EGFR kinase protein point mutations/insertions/deletions. Non-limiting examples of EGFR kinase protein point mutations/insertions/deletions are described in **Table 1a** and **1b**. In some embodiments, the EGFR kinase protein point mutations/insertions/deletions are selected from the group consisting of G719S, G719C, G719A, L747S, D761Y, T790M, T854A, L858R, L861Q, a deletion in exon 19 (e.g., L747_A750del), and an insertion in exon 20. In some embodiments, the EGFR kinase protein point mutations/insertions/deletions are selected from the group consisting of L858R, deletions in exon 19 (e.g., L747_A750del), L747S, D761Y, T790M, and T854A. In some embodiments, the dysregulation of an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same includes one or more EGFR inhibitor resistance mutations. Non-limiting examples of EGFR inhibitor resistance mutations are described in **Table 2a** and **2b**. In some embodiments, the EGFR inhibitor resistance mutation is a substitution at amino acid position 718, 747, 761, 790, 797, or 854 (e.g., L718Q, L747S, D761Y, T790M, C797S, and T854A). In some embodiments, the dysregulation of an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same includes one or more point mutations/insertions/deletions in exon 20. Non-limiting examples of EGFR exon 20 mutations are described in **Tables 1a, 1b** and **2a, 2b**. In some embodiments, the EGFR exon 20 mutation is an exon 20 insertion such as V769_D770insX, D770_N771insX, N771_P772insX, P772_H773insX, and H773_V774insX. For example, the EGFR kinase protein insertion is an exon 20 insertion selected from the group consisting of: A767_V769dupASV, V769_D770insASV, D770_N771insNPG, D770_N771insNPY,

D770_N771insSVD, D770_N771insGL, N771_H773dupNPH, N771_P772insN, N771_P772insH, N771_P772insV, P772_H773insDNP, P772_H773insPNP, H773_V774insNPH, H773_V774insH, H773_V774insPH, H773_V774insAH, and P772_H773insPNP. In some embodiments, the cancer with a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit. In some embodiments, the tumor that is positive for a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same is a tumor positive for one or more EGFR inhibitor resistance mutations. In some embodiments, the tumor with a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit.

In some embodiments of any of the methods or uses described herein, the subject has a clinical record indicating that the subject has a tumor that has a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same (e.g., a tumor having one or more EGFR inhibitor resistance mutations). Also provided are methods of treating a subject that include administering a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, to a subject having a clinical record that indicates that the subject has a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same.

In some embodiments, the methods provided herein include performing an assay on a sample obtained from the subject to determine whether the subject has a dysregulation of an *EGFR* gene, an EGFR protein, or expression or level of any of the same. In some such embodiments, the method also includes administering to a subject determined to have a dysregulation of an *EGFR* gene, an EGFR protein, or expression or activity, or level of any of the same a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof. In some embodiments, the method includes determining that a subject has a dysregulation of an *EGFR* gene, an EGFR protein, or expression or level of any of the same via an assay performed on a sample obtained from

the subject. In such embodiments, the method also includes administering to a subject a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the dysregulation in an *EGFR* gene, an EGFR kinase protein, or expression or activity or level of any of the same is one or more point mutation in the *EGFR* gene (e.g., any of the one or more of the EGFR point mutations described herein). The one or more point mutations in an *EGFR* gene can result, e.g., in the translation of an EGFR protein having one or more of the following amino acid substitutions, deletions, and insertions: G719S, G719C, G719A, L747S, D761Y, T790M, T854A, L858R, L861Q, a deletion in exon 19 (e.g., L747_A750del), and an insertion in exon 20 (e.g., V769_D770insX, D770_N771insX, N771_P772insX, P772_H773insX, and H773_V774insX). The one or more mutations in an *EGFR* gene can result, e.g., in the translation of an EGFR protein having one or more of the following amino acid substitutions or deletions: L858R, deletions in exon 19 (e.g., L747_A750del), L747S, D761Y, T790M, and T854A. In some embodiments, the dysregulation in an *EGFR* gene, an EGFR kinase protein, or expression or activity or level of any of the same is one or more EGFR inhibitor resistance mutations (e.g., any combination of the one or more EGFR inhibitor resistance mutations described herein). In some embodiments, the dysregulation in an *EGFR* gene, an EGFR kinase protein, or expression or activity or level of any of the same is one or more EGFR exon 20 insertions (e.g., any of the exon 20 insertions described herein). In some embodiments, the EGFR kinase protein insertion is an exon 20 insertion selected from the group consisting of: V769_D770insX, D770_N771insX, N771_P772insX, P772_H773insX, and H773_V774insX. In some embodiments, the EGFR kinase protein insertion is an exon 20 insertion selected from the group consisting of: V769_D770insX, D770_N771insX, N771_P772insX, P772_H773insX, and H773_V774insX. In some embodiments, the EGFR kinase protein insertion is an exon 20 insertion selected from the group consisting of: A767_V769dupASV, V769_D770insASV, D770_N771insNPG, D770_N771insNPY, D770_N771insSVD, D770_N771insGL, N771_H773dupNPH, N771_P772insN, N771_P772insH, N771_P772insV, P772_H773insDNP, P772_H773insPNP, H773_V774insNPH, H773_V774insH, H773_V774insPH, H773_V774insAH, and P772_H773insPNP. Some embodiments of these methods further include administering to the subject another anticancer agent (e.g., a

second EGFR inhibitor, a second compound of Formula (I), or a pharmaceutically acceptable salt thereof, or immunotherapy).

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

In some embodiments, dysregulation of an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same can be identified using a liquid biopsy (variously referred to as a fluid biopsy or fluid phase biopsy). See, e.g., Karachialiou et al., "Real-time liquid biopsies become a reality in cancer treatment", *Ann. Transl. Med.*, 3(3):36, 2016. Liquid biopsy methods can be used to detect total tumor burden and/or the dysregulation of an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same. Liquid biopsies can be performed on biological samples obtained relatively easily from a subject (e.g., via a simple blood draw) and are generally less invasive than traditional methods used to detect tumor burden and/or dysregulation of an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same. In some embodiments, liquid biopsies can be used to detect the presence of dysregulation of

an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same at an earlier stage than traditional methods. In some embodiments, the biological sample to be used in a liquid biopsy can include, blood, plasma, urine, cerebrospinal fluid, saliva, sputum, broncho-alveolar lavage, bile, lymphatic fluid, cyst fluid, stool, ascites, and combinations thereof. In some embodiments, a liquid biopsy can be used to detect circulating tumor cells (CTCs). In some embodiments, a liquid biopsy can be used to detect cell-free DNA. In some embodiments, cell-free DNA detected using a liquid biopsy is circulating tumor DNA (ctDNA) that is derived from tumor cells. Analysis of ctDNA (e.g., using sensitive detection techniques such as, without limitation, next-generation sequencing (NGS), traditional PCR, digital PCR, or microarray analysis) can be used to identify dysregulation of an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same.

The term "HER2-associated disease or disorder" as used herein refers to diseases or disorders associated with or having a dysregulation of a *HER2* gene, a HER2 kinase, or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a *HER2* gene, a HER2 kinase, a HER2 kinase domain, or the expression or activity or level of any of the same described herein). Non-limiting examples of a HER2-associated disease or disorder include, for example, cancer.

The term "HER2-associated cancer" as used herein refers to cancers associated with or having a dysregulation of a *HER2* gene, a HER2 kinase (also called herein a HER2 protein), or expression or activity, or level of any of the same. Non-limiting examples of a HER2-associated cancer are described herein.

In some embodiments, the EGFR-associated cancer is also a HER2-associated cancer. For example, an EGFR-associated cancer can also have a dysregulation of a *HER2* gene, a HER2 kinase, or the expression or activity or level of any of the same.

The phrase "dysregulation of a *HER2* gene, a HER2 kinase, or the expression or activity or level of any of the same" refers to a genetic mutation (e.g., a mutation in a *HER2* gene that results in the expression of a HER2 protein that includes a deletion of at least one amino acid as compared to a wild type HER2 protein, a mutation in a *HER2* gene that results in the expression of a HER2 protein with one or more point mutations as compared to a wild type HER2 protein, a mutation in a *HER2* gene that results in the expression of a

HER2 protein with at least one inserted amino acid as compared to a wild type HER2 protein, a gene duplication that results in an increased level of HER2 protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of HER2 protein in a cell), an alternative spliced version of a HER2 mRNA that results in a HER2 protein having a deletion of at least one amino acid in the HER2 protein as compared to the wild-type HER2 protein), or increased expression (e.g., increased levels) of a wild type HER2 kinase in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-cancerous cell). As another example, a dysregulation of a *HER2* gene, a HER2 protein, or expression or activity, or level of any of the same, can be a mutation in a *HER2* gene that encodes a HER2 protein that is constitutively active or has increased activity as compared to a protein encoded by a *HER2* gene that does not include the mutation. Non-limiting examples of HER2 kinase protein fusions and point mutations/insertions/deletions are described in **Tables 3-5**. Such mutation and overexpression is associated with the development of a variety of cancers (Moasser. Oncogene. 2007 Oct 4; 26(45): 6469–6487).

Compounds of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or pharmaceutically acceptable salts or solvates thereof, are useful for treating diseases and disorders such as HER2-associated diseases and disorders, e.g., proliferative disorders such as cancers, including hematological cancers and solid tumors (e.g., advanced solid tumors).

In some embodiments, dysregulation of a *HER2* gene, a HER2 kinase, or the expression or activity or level of any of the same can be caused by an activating mutation in a *HER2* gene. The exemplary HER2 kinase fusions or point mutations, insertions, and deletions shown in **Tables 3-5** can be caused by an activating mutation.

The term "activating mutation" in reference to HER2 describes a mutation in a *HER2* gene that results in the expression of a HER2 kinase that has an increased kinase activity, e.g., as compared to a wild type HER2 kinase, e.g., when assayed under identical conditions. For example, an activating mutation can be a mutation in a *HER2* gene (that results in the expression of a HER2 kinase that has one or more (e.g., two, three, four, five, six, seven, eight, nine, or ten) amino acid substitutions (e.g., any combination of any of the amino acid substitutions described herein) that has increased kinase activity, e.g., as

compared to a wild type HER2 kinase, e.g., when assayed under identical conditions. In another example, an activating mutation can be a mutation in a *HER2* gene that results in the expression of a HER2 kinase that has one or more (e.g., two, three, four, five, six, seven, eight, nine, or ten) amino acids deleted, e.g., as compared to a wild type HER2 kinase, e.g., when assayed under identical conditions. In another example, an activating mutation can be a mutation in a *HER2* gene that results in the expression of a HER2 kinase that has at least one (e.g., at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 12, at least 14, at least 16, at least 18, or at least 20) amino acid inserted as compared to a wild type HER2 kinase, e.g., the exemplary wild type HER2 kinase described herein, e.g., when assayed under identical conditions. Additional examples of activating mutations are known in the art.

The term "wild type HER2" or "wild-type HER2 kinase" describes a HER2nucleic acid (e.g., a *HER2* gene or a HER2 mRNA) or protein (e.g., a HER2 protein) that is found in a subject that does not have a HER2-associated disease, e.g., a HER2-associated cancer (and optionally also does not have an increased risk of developing a HER2-associated disease and/or is not suspected of having a HER2-associated disease), or is found in a cell or tissue from a subject that does not have a HER2-associated disease, e.g., a HER2-associated cancer (and optionally also does not have an increased risk of developing a HER2-associated disease and/or is not suspected of having a HER2-associated disease).

Provided herein is a method of treating a HER2-associated cancer (in a subject in need of such treatment, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. For example, provided herein are methods for treating a HER2-associated cancer in a subject in need of such treatment, the method comprising a) detecting a dysregulation of a *HER2* gene, a HER2 kinase, or the expression or activity or level of any of the same in a sample from the subject; and b) administering a therapeutically effective amount of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof. In some embodiments, the dysregulation of a *HER2* gene, a HER2 kinase, or the expression or activity or level of any of the same includes one or more HER2 kinase protein point mutations/insertions. Non-limiting

examples of HER2 kinase protein fusions and point mutations/insertions/deletions are described in **Tables 3-5**. In some embodiments, the HER2 kinase protein point mutations/insertions/deletions are selected from the group consisting of S310F, S310Y, R678Q, R678W, R678P, I767M, V773M, V777L, V842I, Y772_A775dup, A775_G776insYVMA, G776delinsVC, G776delinsVV, V777_G778insGSP, and P780_Y781insGSP. In some embodiments, the HER2 kinase protein point mutations/insertions/deletions are exon 20 point mutations/insertions/deletions selected from the group consisting of V773M, G776C, G776V, G776S, V777L, V777M, S779T, P780L, S783P, M774AYVM, M774del insWLV, A775_G776insYVMA, A775_G776insAVMA, A775_G776insSVMA, A775_G776insVAG, A775insV G776C, A775_G776insI, G776del insVC2, G776del insVV, G776del insLC, G776C V777insC, G776C V777insV, V777_G778insCG, G778_S779insCPG, and P780_Y781insGSP. In some embodiments, the HER2 kinase protein point mutations/insertions/deletions are exon 20 point mutations/insertions/deletions selected from the group consisting of Y772_A775dup, A775_G776insYVMA, G776delinsVC, G776delinsVV, V777_G778insGSP, and P780_Y781insGSP.

In some embodiments of any of the methods or uses described herein, the cancer (e.g., HER2-associated cancer) is selected from a hematological cancer (e.g., Hodgkin lymphoma, non-Hodgkin lymphoma, and leukemia such as acute-myelogenous leukemia (AML), chronic-myelogenous leukemia (CML), acute-promyelocytic leukemia, and acute lymphocytic leukemia (ALL)), alveolar rhabdomyosarcoma, central or peripheral nervous system tissue cancer, an endocrine or neuroendocrine cancer including multiple neuroendocrine type I and type II tumors, Li-Fraumeni tumors, alveolar rhabdomyosarcoma, bone cancer, brain cancer, breast cancer, cancer of the anus, anal canal, or anorectum, cancer of the eye, cancer of the intrahepatic bile duct, cancer of the joints, cancer of the neck, gallbladder, or pleura, cancer of the nose, nasal cavity, or middle ear, tracheal cancer, oral cancer, oropharyngeal cancer, nasopharyngeal cancer, respiratory cancer, urogenital cancer, cancer of the vulva, colon cancer, esophageal cancer, cervical cancer, gastrointestinal carcinoid tumor, hypopharynx cancer, kidney cancer, larynx cancer, liver cancer, lung cancer, malignant mesothelioma, melanoma, multiple myeloma, nasopharynx cancer, non-Hodgkin lymphoma, ovarian cancer, pancreatic cancer including

pancreatic islet cell cancer, peritoneum, omentum, and mesentery cancer, pharynx cancer, prostate cancer, rectal cancer, renal cancer (e.g., renal cell carcinoma (RCC)), small intestine cancer, soft tissue cancer, stomach cancer, testicular cancer, thyroid cancer, parathyroid cancer, pituitary tumors, adrenal gland tumors, ureter cancer, biliary cancer, and urinary bladder cancer. In some embodiments, the cancer is selected from the group consisting of: head and neck, ovarian, cervical, bladder and oesophageal cancers, pancreatic, gastrointestinal cancer, gastric, breast, endometrial and colorectal cancers, hepatocellular carcinoma, glioblastoma, bladder, lung cancer, e.g., non-small cell lung cancer (NSCLC), bronchioloalveolar carcinoma. In some embodiments, the cancer is pancreatic cancer, head and neck cancer, melanoma, colon cancer, renal cancer, leukemia, lung cancer, or breast cancer. In some cases, the cancer is melanoma, colon cancer, renal cancer, leukemia, or breast cancer.

In some such embodiments, the compounds provided herein are useful for treating a primary brain tumor or metastatic brain tumor. For example, the compounds can be used in the treatment of one or more of gliomas such as glioblastoma (also known as glioblastoma multiforme), astrocytomas, oligodendrogliomas, ependymomas, and mixed gliomas, meningiomas, medulloblastomas, gangliogliomas, schwannomas (neurilemmomas), and craniopharyngiomas (see, for example, Liu et al. J Exp Clin Cancer Res. 2019 May 23;38(1):219); and Ding et al. Cancer Res. 2003 Mar 1;63(5):1106-13). In some embodiments, the brain tumor is a primary brain tumor. In some embodiments, the brain tumor is a metastatic brain tumor, e.g., a metastatic brain tumor from lung cancer, melanoma, breast cancer, ovarian cancer, colorectal cancer, kidney cancer, bladder cancer, or undifferentiated carcinoma. In some embodiments, the brain tumor is a metastatic brain tumor from lung cancer (e.g., non-small cell lung cancer). In some embodiments, the compounds provided herein exhibit brain and/or central nervous system (CNS) penetrance. In some embodiments, the patient has previously been treated with another anticancer agent, e.g., another EGFR and/or HER2 inhibitor (e.g., a compound that is not a compound of Formula I) or a multi-kinase inhibitor.

In some embodiments, the cancer is a cancer of B cell origin. In some embodiments, the cancer is a lineage dependent cancer. In some embodiments, the cancer is a lineage dependent cancer where HER2 or the dysregulation of an *HER2* gene, an HER2 kinase, or

expression or activity or level of any of the same, plays a role in the initiation and/or development of the cancer.

Also provided herein is a method for treating a subject diagnosed with or identified as having a HER2-associated cancer, e.g., any of the exemplary HER2-associated cancers disclosed herein, comprising administering to the subject a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, as defined herein.

In some embodiments, the dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, includes one or more deletions (e.g., deletion of an amino acid at position 12), insertions, or point mutation(s) in a HER2 kinase. In some embodiments, the dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, includes a deletion of one or more residues from the HER2 kinase, resulting in increased signaling activity of HER2.

In some embodiments, the dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, includes at least one point mutation in a *HER2* gene that results in the production of a HER2 kinase that has one or more amino acid substitutions, insertions, or deletions as compared to the wild-type HER2 kinase (see, for example, the point mutations listed in **Table 3**). In some embodiments, dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, includes at least one point mutation in a *HER2* gene that results in the production of a HER2 kinase that has one or more of the amino acid substitutions, insertions, or deletions in **Table 3**.

In some embodiments, the dysregulation of an *HER2* gene, an HER2 kinase, or expression or activity or level of any of the same, includes an insertion of one or more residues in exon 20 of the *HER2* gene (e.g., any of the exon 20 insertions described in **Table 1a** and **1b**). Exon 20 of HER2 has two major regions, the c-helix (residues 770-774) and the loop following the c-helix (residues 775-783). In some embodiments, the dysregulation of an *HER2* gene, an HER2 kinase, or expression or activity or level of any of the same, includes an insertion of one or more residues in exon 20 selected from the

group consisting of: Y772_A775dup, A775_G776insYVMA, G776delinsVC, G776delinsVV, V777_G778insGSP, and P780_Y781insGSP.

Table 3. HER2 Protein Amino Acid Substitutions/Insertions/Deletions[A]

Amino Acid Position(s)	Non-Limiting Exemplary Mutations	Non-limiting Exemplary HER2-associated Cancer(s)
122	P122L[11]	Metastatic Colorectal Cancer
263	I263T[7]	Colorectal Cancer[7]
265	E265K[11]	Metastatic Colorectal Cancer
270	A270S[6]	Breast Cancer
292	G292R[11]	Metastatic Colorectal Cancer
309	G309A[3], G309E[15]	Breast Cancer
310	S310F[7], S310Y[8]	Colorectal Cancer[7]
311	C311R[8]	
313	L313V[11]	Metastatic Colorectal Cancer
429	S429R[15], S429H[15]	
466	A466T[7]	Colorectal Cancer[7]
648	A648V[10]	Urinary Cancer
650	P650L[10], P650S[10]	Melanoma, Uterine Cancer
651	L651V[10]	Breast Cancer, Cervical Cancer
652	T652M[10], T652R[10]	Lung Cancer, Colorectal Cancer, Liver Cancer, Head And Neck Cancer, Endometrial Cancer, Ovarian Cancer
653	S653C[10], S653P[10]	Breast Cancer[10], Urinary Cancer, Breast Cancer, Colorectal Cancer, Liver Cancer, Metastatic Colorectal Cancer[11]
654	I654T[10], I654M[10], I654L[10]	Lower Gastrointestinal Cancer, Neuroendocrine Cancer, Breast Cancer, Esophageal Cancer, Soft Tissue Cancer
655	I655M[10], I655V[14]	Lung Cancer, Colorectal Cancer, Ovarian Cancer, Urinary Cancer
656	S656C[10]	Esophageal Cancer
657	A657V[10]	Prostate Cancer, Colorectal Cancer

659	V659E[10], V659D[10], V659L[10], V659F[10],	Lung cancer[10], Biliary Cancer, Colorectal Cancer, Breast Cancer, Metastatic Colorectal Cancer[11]
659-661	V659_I661>VVEGI[10]	Lung Cancer
659-660	V659_G660>ER[10]	Lung Cancer
660	G660D[10]	Biliary Cancer[10], Lung Cancer, Urinary Cancer, Colorectal Cancer, Glioma, Lower Gastrointestinal Cancer, Gastric Cancer, Liver Cancer, Metastatic Colorectal Cancer[11]
661	I661V[10]	Colorectal Cancer
662	L662V[10]	Cervical Cancer, Lung Cancer, Breast Cancer
663	L663P[10]	Soft Tissue Cancer
664	V664F[10], V664I[10]	Lung Cancer, Breast Cancer, Gastric Cancer
665	V665M[10]	Prostate Cancer, Colorectal Cancer
665-666	V665_V666del[10]	Breast Cancer
666	V666I[10]	Colorectal Cancer
667	L667*[10], L667S[10]	Breast Cancer, Soft Tissue Cancer
668	G668E[10], G668R[10]	Glioma, Lung Cancer
669	V669A[10], V669L[10]	Biliary Cancer, Breast Cancer, Glioma
672	G672R[10]	SSC other, Lung Cancer
673	I673F[10], I673M[10], I673V[10]	Colorectal Cancer, Lung Cancer
674	L674V[10], L674I[10]	Colorectal Cancer, Lung Cancer
675	I675M[10], I675T[10], I675L[10]	Lung Cancer, Urinary Cancer, Thyroid Cancer,
676	K676M[10]	Lung Cancer
677	R677*[10], R677L[10], R677Q[10]	Lung Cancer, Endometrial Cancer, Pancreatic Cancer, Neuroendocrine Cancer, Colorectal Cancer, Glioma, Myeloma
678	R678Q[7], R678W[10], R678P[10]	Colorectal Cancer[7], Gastric Cancer[10], Biliary Cancer[10], Urinary Cancer[10], Ovarian Cancer[10], Endometrial Cancer[10], Carcinoma of Unknown Primary[10], Lung Cancer[10], Appendicidal Cancer[10],

		Pancreatic Cancer[10], Breast Cancer [10], Neuroendocrine Cancer[10], Cervical Cancer[10], Lower Gastrointestinal Cancer[10], Prostate Cancer[10], Liver Cancer[10], Central Nervous System Cancer (Non-Glioma)[10], Melanoma[10], Salivary Gland Cancer[10], Metastatic Colorectal Cancer[11]
679	Q679E[10], Q679H[10]	Pancreatic Cancer, Colorectal Cancer
680	Q680del[10]	Cervical Cancer
681	K681N[10]	Lung Cancer
682	I682T[10], I682M[10]	Endometrial Cancer, Colorectal Cancer
683	R683W[10], R683Q[10]	Breast Cancer, Pancreatic Cancer, Endometrial Cancer, Bone Cancer, Colorectal Cancer,
684	K684N[10]	Colorectal Cancer
685	Y685H[10]	Colorectal Cancer, Carcinoma of Unknown Primary
686	T686M[10], T686A[10], T686R[10]	Colorectal Cancer, Urinary Cancer, Ovarian Cancer, Endometrial Cancer
688	R688L[10], R688W[10], R688Q[10]	Skin Cancer, Colorectal Cancer, Melanoma
689	R689K[10], R689I[10]	Lung Cancer, Endometrial Cancer
691	L691R[10]	Endometrial Cancer
693	E693K[10], E693G[10]	Ovarian Cancer, Melanoma, Colorectal Cancer, Breast Cancer, Carcinoma of Unknown Primary
694	T694M[10], T694S[10]	Carcinoma of Unknown Primary, Colorectal Cancer, Pancreatic Cancer
695	E695K[10]	Melanoma, Urinary Cancer
697	V697L[10], V697M[10], V697del[10]	Breast Cancer, Lung Cancer, Ovarian Cancer, Lower Gastrointestinal Cancer, Colorectal Cancer, Skin Cancer, Pancreatic Cancer, Salivary Gland Cancer,

		Carcinoma of Unknown Primary, Cervical Cancer, Endometrial Cancer, Gastric Cancer,
699	P699del[10], P699S	Endometrial Cancer
701	T701I[10]	Ovarian Cancer
702	P702S[10], P702L[10]	Gastric Cancer, Lower Gastrointestinal Cancer, Carcinoma of Unknown Primary, Endometrial Cancer, Breast Cancer, Ovarian Cancer, Liver Cancer
704	G704E[10], G704R[10]	Glioma, Colorectal Cancer
705	A705V[10]	Colorectal Cancer, Soft Tissue Cancer
706	M706V[10]	Breast Cancer
707	P707L[10]	Soft Tissue Cancer
709	Q709L[10], Q709K[10]	Glioma, Lung Cancer, Lower Gastrointestinal Cancer
710	A710V[10]	Lung Cancer
711	Q711H[10]	Breast Cancer, Lung Cancer
712	M712L[10]	Neuroendocrine Cancer, Esophageal Cancer
713	R713Q[10], R713W[10], R713L[10]	Prostate Cancer, Lung Cancer, Endometrial Cancer
726	L726I[15], L726F[15]	
733	733I[11]	Metastatic Colorectal Cancer[11]
755	L755S[2,7], L755W[3], L755P[8], L755F[14]	Lung Adenocarcinoma[2], Breast Cancer[3], Bone Metastases From Breast Cancer[5], Colorectal Cancer[7], Metastatic Colorectal Cancer[11]
755-759	del. 755--759[3]	Breast Cancer[3]
760	S760A[15]	
767	I767M[11]	Metastatic Colorectal Cancer[11]
769	D769H[2], D769Y[3], D769N[11]	Lung Adenocarcinoma[2], Breast Cancer[3], Metastatic Colorectal Cancer[11]
773	V773M[11]	Metastatic Colorectal Cancer[11]

776	G776C[2], G776V[8], G776S[11]	Lung Adenocarcinoma, Metastatic Colorectal Cancer[11]
777	V777L[2,7], V777M[2]	Lung Adenocarcinoma[2], Breast Cancer[3], Bone Metastases From Breast Cancer[5], Colorectal Cancer[7], Metastatic Colorectal Cancer[11]
779	S779T[8]	Breast Cancer
780	P780ins[3], P780L[15]	Breast Cancer[3]
783	S783P2	Breast Cancer
784	R784G[12]	Metastatic Colorectal Cancer[12]
785	L785F[15]	Breast Cancer
798	T798I[4], T798M[15]	Breast Cancer
835	Y835F[15]	
838	R838Q[15]	
842	V842I[3,7]	Breast Cancer[3], Colorectal Cancer[7], Metastatic Colorectal Cancer[11]
862	T862A[11]	Metastatic Colorectal Cancer[11]
866	866M[7]	Colorectal Cancer[7]
868	R868W[7]	Colorectal Cancer[7]
869	L869R[4]	Breast Cancer
869 + 798	L869R + T798I[4]	Breast Cancer
878	H878Y[11]	Metastatic Colorectal Cancer[11]
887	M887I[15]	
896	R896C[3], R896H[11]	Breast Cancer[3], Metastatic Colorectal Cancer[11]
896 + 755	R896C + L755W[3]	Breast Cancer[3]
1136	Q1136fs*5[11]	Metastatic Colorectal Cancer[11]
1170	P1170fs*88+[11]	Metastatic Colorectal Cancer[11]
1189	G1189fs*9[11]	Metastatic Colorectal Cancer[11]
1201	G1201V[15]	
1219	N1219S[7]	Colorectal Cancer[7]
1232	A1232fs*25+[11]	Metastatic Colorectal Cancer[11]
Exon 16	Deletion[11]	Metastatic Colorectal Cancer[11]
Exon 20 deletions and insertions		
	M774AYVM[13]	Non-Small Cell Lung Cancer[13]
	M774delinsWLV[9]	Non-Small Cell Lung Cancer[9]

	A775_G776insYVMA (c. 2324_2325ins12)[1]	Lung Adenocarcinoma
	A775_G776insAVMA (c. 2324_2325ins12)[14]	Lung Adenocarcinoma
	A775_G776insSVMA[9]	Non-Small Cell Lung Cancer[9]
	A775_G776insVAG[14]	Lung Adenocarcinoma
	A775insV G776C[8]	
	A775_G776insI[9]	Non-Small Cell Lung Cancer[9]
	G776delinsVC[2,8]; G776del insVV[8]; G776delinsLC[9]	Lung Adenocarcinoma
	G776C V777insC[8]; G776C V777insV[8]	
	V777_G778insCG[2], V777_G778insGSP[16]	Lung Adenocarcinoma[2], Non-Small Cell Lung Cancer[16]
	G778_S779insCPG[9]	Non-Small Cell Lung Cancer[9]
	P780_Y781insGSP[2,8]	Lung Adenocarcinoma

[A] The HER2 mutations shown may be activating mutations and/or confer increased resistance of HER2 to a HER2 inhibitor and/or a multi-kinase inhibitor (MKI), e.g., as compared to a wildtype HER2.

[1] Li et al. J Thorac Oncol. 2016 Mar;11(3):414-9.

[2] Arcila et al. Clin Cancer Res. 2012 Sep 15; 18(18): 10.1158/1078-0432.CCR-12-0912.

[3] Bose et al. Cancer Discov. 2013 Feb;3(2):224-37.

[4] Hanker et al. Cancer Discov. 2017 Jun;7(6):575-585.

[5] Christgen et al. Virchows Arch. 2018 Nov;473(5):577-582.

[6] Si et al. Cancer Biomark. 2018;23(2):165-171.

[7] Kavuri et al. Cancer Discov. 2015 Aug; 5(8): 832–841.

[8] Robichaux et al. Nat Med. 2018 May; 24(5): 638–646.

[9] Kosaka et al. Cancer Res. 2017 May 15; 77(10): 2712–2721.

[10] Pahuja et al. Cancer Cell. 2018 Nov 12; 34(5): 792–806.e5.

[11] Ross et al. Cancer. 2018 Apr 1;124(7):1358-1373.

[12] Gharib et al. J Cell Physiol. 2019 Aug;234(8):13137-13144.

[13] Krawczyk et al. Oncol Lett. 2013 Oct; 6(4): 1063–1067.

[14] Lai et al. Eur J Cancer. 2019 Mar; 109: 28–35.

[15] Sun et al. J Cell Mol Med. 2015 Dec; 19(12): 2691–2701.

[16] Xu et al. Thorac Cancer. 2020 Mar;11(3):679-685.

In some embodiments, the dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, includes a splice variation in a HER2

mRNA which results in an expressed protein that is an alternatively spliced variant of HER2 having at least one residue deleted (as compared to the wild-type HER2 kinase) resulting in a constitutive activity of a HER2 kinase domain. In some embodiments, the splice variant of HER2 is Δ16HER-3 or p95HER - 2. See, e.g., Sun et al. J Cell Mol Med. 2015 Dec; 19(12): 2691 - 2701.

In some embodiments, dysregulation of an *HER2* gene, an HER2 kinase, or the expression or activity or level of any of the same can be caused by a splice variation in a HER2 mRNA that results in the expression of an altered HER2 protein that has increased resistance to inhibition by an HER2 inhibitor, a tyrosine kinase inhibitor (TKI), and/or a multi-kinase inhibitor (MKI), e.g., as compared to a wild type HER2 kinase (e.g., the HER2 variants described herein). See, e.g., Rexer and Arteaga. Crit Rev Oncog. 2012; 17(1): 1–16.

In some embodiments, the dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, includes one or more chromosome translocations or inversions resulting in *HER2* gene fusions, respectively. In some embodiments, the dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, is a result of genetic translocations in which the expressed protein is a fusion protein containing residues from a non-HER2 partner protein and HER2, and include a minimum of a functional HER2 kinase domain, respectively.

Table 4. Exemplary HER2 Fusion Proteins and Cancers

Non-limiting Exemplary HER2 Fusions	Non-limiting Exemplary HER2-associated Cancer(s)
ZNF207_ex2/HER2_ex18[1]	Gastric Cancer
MDK_ex4/HER2_ex11[1]	Gastric Cancer
NOS2_ex2/HER2_ex2[1]	Gastric Cancer

[1] Yu et al. J Transl Med. 2015; 13: 116.

In some embodiments, the dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, includes at least one point mutation in a *HER2* gene that results in the production of a HER2 kinase that has one or more amino acid substitutions or insertions or deletions in a *HER2* gene that results in the production

of a HER2 kinase that has one or more amino acids inserted or removed, as compared to the wild-type HER2 kinase.

In other embodiments, the dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, includes at least one point mutation in a *HER2* gene that results in the production of a HER2 kinase that has one or more amino acid substitutions as compared to the wild-type HER2 kinase, and which has increased resistance to a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, as compared to a wild type HER2 kinase or a HER2 kinase not including the same mutation.

Exemplary Sequence of Mature Human HER2 Protein (UniProtKB entry P04626) (SEQ ID NO: 2)

MELAALCRWG LLLALLPPGA ASTQVCTGTD MKLRLPASPE THLDMLRHLY
QGCQVVQGNL ELTYLPTNAS LSFLQDIQEV QGYVLIAHNQ VRQVPLQRLR
IVRGTQLFED NYALAVLDNG DPLNNTTPVT GASPGGLREL QLRSLTEILK
GGVLIQRNPQ LCYQDTILWK DIFHKNNQLA LTLIDTNRSR ACHPCSPMCK
GSRCWGESSE DCQSLTRTVC AGGCARCKGP LPTDCCHEQC AAGCTGPKHS
DCLACLHFNH SGICELHCPA LVTYNTDTFE SMPNPEGRYT FGASCVTACP
YNYLSTDVGS CTLVCPLHNQ EVTAEDGTQR CEKCSKPCAR VCYGLGMEHL
REVRAVTSAN IQEFAGCKKI FGSLAFLPES FDGDPASNTA PLQPEQLQVF
ETLEEITGYL YISAWPDSLP DLSVFQNLQV IRGRILHNGA YSLTLQGLGI
SWLGLRSLRE LGSGLALIHH NTHLCFVHTV PWDQLFRNPH QALLHTANRP
EDECVGEGLA CHQLCARGHC WGPGPTQCVN CSQFLRGQEC VEECRVLQGL
PREYVNARHC LPCHPECQPQ NGSVTCFGPE ADQCVACAHY KDPPFCVARC
PSGVKPDLSY MPIWKFPDEE GACQPCPINC THSCVDLDDK GCPAEQRASP
LTSIISAVVG ILLVVVLGVV FGILIKRRQQ KIRKYTMRRL LQETELVEPL
TPSGAMPNQA QMRILKETEL RKVKVLGSGA FGTVYKGIWI PDGENVKIPV
AIKVLRENTS PKANKEILDE AYVMAGVGSP YVSRLLGICL TSTVQLVTQL
MPYGCLLDHV RENRGRLGSQ DLLNWCMQIA KGMSYLEDVR LVHRDLAARN
VLVKSPNHVK ITDFGLARLL DIDETEYHAD GGKVPIKWMA LESILRRRFT
HQSDVWSYGV TVWELMTFGA KPYDGIPARE IPDLLEKGER LPQPPICTID
VYMIMVKCWM IDSECRPRFR ELVSEFSRMA RDPQRFVVIQ NEDLGPASPL

DSTFYRSLLE DDDMGDLVDA EEYLVPQQGF FCPDPAPGAG GMVHHRHRSS
STRSGGGDLT LGLEPSEEEA PRSPLAPSEG AGSDVFDGDL GMGAAKGLQS
LPTHDPSPLQ RYSEDPTVPL PSETDGYVAP LTCSPQPEYV NQPDVRPQPP
SPREGPLPAA RPAGATLERP KTLSPGKNGV VKDVFAFGGA VENPEYLTPQ
GGAAPQPHPP PAFSPAFDNL YYWDQDPPER GAPPSTFKGT PTAENPEYLG
LDVPV

In some embodiments, dysregulation of an *HER2* gene, an HER2 kinase, or expression or activity or level of any of the same, includes at least one HER2 inhibitor resistance mutation in an *HER2* gene that results in the production of an HER2 kinase that has one or more of the amino acid substitutions, insertions, or deletions as described in **Table 5.** In some embodiments, compounds of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**) and pharmaceutically acceptable salts and solvates thereof, are useful in treating subjects that develop cancers with HER2 inhibitor resistance mutations (e.g., that result in an increased resistance to a first HER2 inhibitor, e.g., a substitution at amino acid position 755 or 798 (e.g., L755S, L755P, T798I, and T798M), and/or one or more HER2 inhibitor resistance mutations listed in **Table 5**) by either dosing in combination or as a subsequent or additional (e.g., follow-up) therapy to existing drug treatments (e.g., other inhibitors of HER2; e.g., first and/or second HER2 inhibitors).

Table 5. HER2 Protein Amino Acid Resistance Mutations

Amino Acid Position(s)	**Non-Limiting Exemplary Mutations**	**Non-limiting Exemplary HER2-associated Cancer(s)**
726	L726I, L726F[2]	Breast Cancer
755	L755S[2], L755P[2]	Breast Cancer
780	P780L[2]	Breast Cancer
783	S783P[2]	Breast Cancer
785	L785F[2]	Breast Cancer
798	T798I[1], T798M[2]	Breast Cancer

[1]Hanker et al. Cancer Discov. 2017 Jun;7(6):575-585.

[2] Sun et al. J Cell Mol Med. 2015 Dec; 19(12): 2691–2701.

As used herein, a "first inhibitor of HER2" or "first HER2 inhibitor" is a HER2 inhibitor as defined herein, but which does not include a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, as defined herein. As used herein, a "second inhibitor of HER2" or a "second HER2 inhibitor" is a HER2 inhibitor as defined herein, but which does not include a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as defined herein. When both a first and a second inhibitor of HER2 are present in a method provided herein, the first and second inhibitors of HER2 are different. In some embodiments, the first and/or second inhibitor of HER2 bind in a different location than a compound of Formula **(I)**. For example, in some embodiments, a first and/or second inhibitor of HER2 can inhibit dimerization of HER2, while a compound of Formula **(I)** can inhibit the active site. In some embodiments, a first and/or second inhibitor of HER2 can be an allosteric inhibitor of HER2, while a compound of Formula **(I)** can inhibit the HER2 active site.

Exemplary first and second inhibitors of HER2 are described herein. In some embodiments, a first or second inhibitor of HER2 can be selected from the group consisting of: trastuzumab (e.g., TRAZIMERA™, HERCEPTIN®), pertuzumab (e.g., PERJETA®), trastuzumab emtansine (T-DM1 or ado-trastuzumab emtansine, e.g., KADCYLA®), lapatinib, KU004, neratinib (e.g., NERLYNX®), dacomitinib (e.g., VIZIMPRO®), afatinib (GILOTRIF®), tucatinib (e.g., TUKYSA™), erlotinib (e.g., TARCEVA®), pyrotinib, poziotinib, CP-724714, CUDC-101, sapitinib (AZD8931), tanespimycin (17-AAG), IPI-504, PF299, pelitinib, S- 22261 1, and AEE-788.

In some embodiments, compounds of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or pharmaceutically acceptable salts and solvates thereof, are useful for treating a cancer that has been identified as having one or more HER2 inhibitor resistance mutations (that result in an increased resistance to a first or second inhibitor of HER2, e.g., a substitution described in **Table 5** including substitutions at amino acid position 755 or 798 (e.g., L755S, L755P, T798I, and T798M)). In some embodiments, the one or more HER2 inhibitor resistance mutations occurs in a

nucleic acid sequence encoding a mutant HER2 protein (e.g., a mutant HER2 protein having any of the mutations described in **Table 3**) resulting in a mutant HER2 protein that exhibits HER2 inhibitor resistance.

Like EGFR, the epidermal growth factor receptor 2 (HER2) belongs to the ErbB family of receptor tyrosine kinases (RTKs) and provides critical functions in epithelial cell physiology (Schlessinger J (2014) *Cold Spring Harb Perspect Biol* 6, a008912; and Moasser. *Oncogene*. 2007 Oct 4; 26(45): 6469–6487). It is frequently mutated and/or overexpressed in different types of human cancers and is the target of multiple cancer therapies currently adopted in the clinical practice (Moasser. *Oncogene*. 2007 Oct 4; 26(45): 6469–6487).

Accordingly, provided herein are methods for treating a subject identified or diagnosed as having a HER2-associated cancer that include administering to the subject a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In some embodiments, the subject that has been identified or diagnosed as having a HER2-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved test or assay for identifying dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, in a subject or a biopsy sample from the subject or by performing any of the non-limiting examples of assays described herein. In some embodiments, the test or assay is provided as a kit. In some embodiments, the cancer is a HER2-associated cancer. Also provided are methods for treating cancer in a subject in need thereof, the method comprising: (a) detecting a HER2-associated cancer in the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. Some embodiments of these methods further include administering to the subject another anticancer agent (e.g., a second HER2 inhibitor, a second compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, or an immunotherapy). In some embodiments, the subject was previously treated with a first HER2 inhibitor or previously treated with another anticancer treatment, e.g., at least partial resection of the tumor or radiation therapy. In some embodiments, the subject is determined to have a HER2-associated cancer

through the use of a regulatory agency-approved, e.g., FDA-approved test or assay for identifying dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, in a subject or a biopsy sample from the subject or by performing any of the non-limiting examples of assays described herein. In some embodiments, the test or assay is provided as a kit. In some embodiments, the cancer is a HER2-associated cancer.

Also provided are methods of treating a subject that include performing an assay on a sample obtained from the subject to determine whether the subject has a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, and administering (e.g., specifically or selectively administering) a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, to the subject determined to have a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same. Some embodiments of these methods further include administering to the subject another anticancer agent (e.g., a second HER2 inhibitor, a second compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, or immunotherapy). In some embodiments of these methods, the subject was previously treated with a first HER2 inhibitor or previously treated with another anticancer treatment, e.g., at least partial resection of a tumor or radiation therapy. In some embodiments, the subject is a subject suspected of having a HER2-associated cancer, a subject presenting with one or more symptoms of a HER2-associated cancer, or a subject having an elevated risk of developing a HER2-associated cancer. In some embodiments, the assay utilizes next generation sequencing, pyrosequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved assay, e.g., FDA-approved kit. In some embodiments, the assay is a liquid biopsy. Additional, non-limiting assays that may be used in these methods are described herein. Additional assays are also known in the art.

As used herein, a "first inhibitor of HER2" or "first HER2 inhibitor" is a HER2 inhibitor as defined herein, which does not include a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, as defined herein. As used herein, a "second inhibitor of HER2" or a "second HER2 inhibitor" is an inhibitor of HER2 as defined herein,

which does not include a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as defined herein. When both a first and a second HER2 inhibitor are present in a method provided herein, the first and second HER2 inhibitors are different.

Also provided is a compound of Formula **(I)** (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, for use in treating a HER2-associated cancer in a subject identified or diagnosed as having a HER2-associated cancer through a step of performing an assay (e.g., an in vitro assay) on a sample obtained from the subject to determine whether the subject has a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, where the presence of a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, identifies that the subject has a HER2-associated cancer. Also provided is the use of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a HER2-associated cancer in a subject identified or diagnosed as having a HER2-associated cancer through a step of performing an assay on a sample obtained from the subject to determine whether the subject has a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same where the presence of dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, identifies that the subject has a HER2-associated cancer. Some embodiments of any of the methods or uses described herein further include recording in the subject's clinical record (e.g., a computer readable medium) that the subject is determined to have a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, through the performance of the assay, should be administered a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In some embodiments, the assay utilizes next generation sequencing, pyrosequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved assay, e.g., FDA-approved kit. In some embodiments, the assay is a liquid biopsy.

Also provided is a compound of Formula **(I)** (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, for use in the treatment of a cancer in a subject in need thereof, or a subject identified or

diagnosed as having a HER2-associated cancer. Also provided is the use of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a cancer in a subject identified or diagnosed as having a HER2-associated cancer (. In some embodiments, a subject is identified or diagnosed as having a HER2-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved, kit for identifying dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, in a subject or a biopsy sample from the subject. As provided herein, a HER2-associated cancer includes those described herein and known in the art.

In some embodiments of any of the methods or uses described herein, the subject has been identified or diagnosed as having a cancer with a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the subject has a tumor that is positive for a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the subject can be a subject with a tumor(s) that is positive for a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the subject can be a subject whose tumors have a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the subject is suspected of having a HER2-associated cancer. In some embodiments, provided herein are methods for treating a HER2-associated cancer in a subject in need of such treatment, the method comprising a) detecting a dysregulation of a *HER2* gene, a HER2 kinase, or the expression or activity or level of any of the same in a sample from the subject; and b) administering a therapeutically effective amount of a compound of Formula **(I)** (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof. In some embodiments, the dysregulation of a *HER2* gene, a HER2 kinase, or the expression or activity or level of any of the same includes one or more HER2 kinase protein point mutations/insertions/deletions. Non-limiting examples of HER2 kinase protein fusions and point mutations/insertions/deletions are described in **Tables 3-5**. In some embodiments, the HER2 kinase protein point

mutations/insertions/deletions are selected from the group consisting of a point mutation at amino acid position 310, 678, 755, 767, 773, 777, or 842 (e.g., S310F, S310Y, R678Q, R678W, R678P, I767M, V773M, V777L, and V842I) and/or an insertion or deletion at amino acid positions 772, 775, 776, 777, and 780 (e.g., Y772_A775dup, A775_G776insYVMA, G776delinsVC, G776delinsVV, V777_G778insGSP, and P780_Y781insGSP). In some embodiments, the HER2 kinase protein point mutation/insertion/deletion is an exon 20 point mutation/insertion/deletion. In some embodiments, the HER2 exon 20 point mutation/insertion/deletion is a point mutation at amino acid position 773, 776, 777, 779, 780, and 783 (e.g., V773M, G776C, G776V, G776S, V777L, V777M, S779T, P780L, and S783P) and/or an exon 20 insertion/deletion such as an insertion/deletion at amino acid positions 774, 775, 776, 777, 778, and 780. In some embodiments, the HER2 kinase protein insertion is an exon 20 insertion selected from the group consisting of: A775_G776insYVMA, A775_G776insAVMA, A775_G776insSVMA, A775_G776insVAG, A775insV G776C, A775_G776insI, G776del insVC2, G776del insVV, G776del insLC, G776C V777insC, G776C V777insV, V777_G778insCG, G778_S779insCPG, and P780_Y781insGSP. In some embodiments, the HER2 kinase protein mutation/insertion/deletion is an exon 20 insertion/deletion selected from the group consisting of: is Y772_A775dup, A775_G776insYVMA, G776delinsVC, G776delinsVV, V777_G778insGSP, or P780_Y781insGSP. In some embodiments, the cancer with a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit. In some embodiments, the tumor that is positive for a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same is a tumor positive for one or more HER2 inhibitor resistance mutations. In some embodiments, the tumor with a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit.

In some embodiments of any of the methods or uses described herein, the subject has a clinical record indicating that the subject has a tumor that has a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same. Also provided are methods of treating a subject that include administering a therapeutically

effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, to a subject having a clinical record that indicates that the subject has a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same.

In some embodiments, the methods provided herein include performing an assay on a sample obtained from the subject to determine whether the subject has a dysregulation of a *HER2* gene, a HER2 kinase, or expression or level of any of the same. In some such embodiments, the method also includes administering to a subject determined to have a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity, or level of any of the same a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof. In some embodiments, the method includes determining that a subject has a dysregulation of a *HER2* gene, a HER2 kinase, or expression or level of any of the same via an assay performed on a sample obtained from the subject. In such embodiments, the method also includes administering to a subject a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the dysregulation in a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same is one or more point mutation in the *HER2* gene (e.g., any of the one or more of the HER2 point mutations described herein). The one or more point mutations in a *HER2* gene can result, e.g., in the translation of a HER2 protein having one or more of the following amino acid substitutions: S310F, S310Y, R678Q, R678W, R678P, I767M, V773M, V777L, and V842I. The one or more point mutations in a *HER2* gene can result, e.g., in the translation of a HER2 protein having one or more of the following exon 20 amino acid substitutions: V773M, G776C, G776V, G776S, V777L, V777M, S779T, P780L, and S783P. In some embodiments, the dysregulation in a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same is one or more insertions in the *HER2* gene (e.g., any of the one or more of the HER2 insertions described herein). The one or more insertions in a *HER2* gene can result, e.g., in the translation of a HER2 protein having one or more of the following exon 20 insertions: M774AYVM, M774del insWLV, A775_G776insYVMA, A775_G776insAVMA, A775_G776insSVMA, A775_G776insVAG, A775insV G776C,

A775_G776insI, G776del insVC2, G776del insVV, G776del insLC, G776C V777insC, G776C V777insV, V777_G778insCG, G778_S779insCPG, and P780_Y781insGSP. In some embodiments, the one or more insertions in a *HER2* gene can result, e.g., in the translation of a HER2 protein having one or more of the following exon 20 insertions: Y772_A775dup, A775_G776insYVMA, G776delinsVC, G776delinsVV, V777_G778insGSP, and P780_Y781insGSP. Some embodiments of these methods further include administering to the subject another anticancer agent (e.g., a second HER2 inhibitor, a second compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, or immunotherapy).

In some embodiments of any of the methods or uses described herein, an assay used to determine whether the subject has a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same, using a sample from a subject can include, for example, next generation sequencing, immunohistochemistry, fluorescence microscopy, break apart FISH analysis, Southern blotting, Western blotting, FACS analysis, Northern blotting, and PCR-based amplification (e.g., RT-PCR and quantitative real-time RT-PCR). As is well-known in the art, the assays are typically performed, e.g., with at least one labelled nucleic acid probe or at least one labelled antibody or antigen-binding fragment thereof. Assays can utilize other detection methods known in the art for detecting dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or levels of any of the same (see, e.g., the references cited herein). In some embodiments, the sample is a biological sample or a biopsy sample (e.g., a paraffin-embedded biopsy sample) from the subject. In some embodiments, the subject is a subject suspected of having a HER2-associated cancer, a subject having one or more symptoms of a HER2-associated cancer, and/or a subject that has an increased risk of developing a HER2-associated cancer.

In some embodiments, dysregulation of a *HER2* gene, a HER2 kinase, or the expression or activity or level of any of the same can be identified using a liquid biopsy (variously referred to as a fluid biopsy or fluid phase biopsy). See, e.g., Karachialiou et al., "Real-time liquid biopsies become a reality in cancer treatment", *Ann. Transl. Med.*, 3(3):36, 2016. Liquid biopsy methods can be used to detect total tumor burden and/or the dysregulation of a *HER2* gene, a HER2 kinasev, or the expression or activity or level of any of the same. Liquid biopsies can be performed on biological samples obtained

relatively easily from a subject (e.g., via a simple blood draw) and are generally less invasive than traditional methods used to detect tumor burden and/or dysregulation of a *HER2* gene, a HER2 kinase, or the expression or activity or level of any of the same. In some embodiments, liquid biopsies can be used to detect the presence of dysregulation of a *HER2* gene, a HER2 kinase, or the expression or activity or level of any of the same at an earlier stage than traditional methods. In some embodiments, the biological sample to be used in a liquid biopsy can include, blood, plasma, urine, cerebrospinal fluid, saliva, sputum, broncho-alveolar lavage, bile, lymphatic fluid, cyst fluid, stool, ascites, and combinations thereof. In some embodiments, a liquid biopsy can be used to detect circulating tumor cells (CTCs). In some embodiments, a liquid biopsy can be used to detect cell-free DNA. In some embodiments, cell-free DNA detected using a liquid biopsy is circulating tumor DNA (ctDNA) that is derived from tumor cells. Analysis of ctDNA (e.g., using sensitive detection techniques such as, without limitation, next-generation sequencing (NGS), traditional PCR, digital PCR, or microarray analysis) can be used to identify dysregulation of a *HER2* gene, a HER2 kinase, or the expression or activity or level of any of the same.

Also provided is a method for inhibiting EGFR activity in a cell, comprising contacting the cell with a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof. Also provided is a method for inhibiting HER2 activity in a cell, comprising contacting the cell with a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof. Further provided herein is a method for inhibiting EGFR and HER2 activity in a cell, comprising contacting the cell with a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the contacting is in vitro. In some embodiments, the contacting is in vivo. In some embodiments, the contacting is in vivo, wherein the method comprises administering an effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, to a subject having a cell having aberrant EGFR activity and/or HER2 activity. In some embodiments, the cell is a cancer cell. In some embodiments, the cancer cell is any cancer as described herein. In some embodiments, the cancer cell is an EGFR-associated cancer cell. In some embodiments, the cancer cell is a HER2-associated cancer cell. As used herein, the term "contacting" refers to the bringing

together of indicated moieties in an in vitro system or an in vivo system. For example, "contacting" an EGFR kinase with a compound provided herein includes the administration of a compound provided herein to an individual or subject, such as a human, having an EGFR kinase, as well as, for example, introducing a compound provided herein into a sample containing a cellular or purified preparation containing the EGFR kinase.

Also provided herein is a method of inhibiting cell proliferation, in vitro or in vivo, the method comprising contacting a cell with an effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein.

Further provided herein is a method of increase cell death, in vitro or in vivo, the method comprising contacting a cell with an effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein. Also provided herein is a method of increasing tumor cell death in a subject. The method comprises administering to the subject an effective compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, in an amount effective to increase tumor cell death.

The phrase "therapeutically effective amount" means an amount of compound that, when administered to a subject in need of such treatment, is sufficient to (i) treat an EGFR kinase-associated disease or disorder or a HER2 kinase-associated disease or disorder, (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, condition, or disorder, or (iii) delay the onset of one or more symptoms of the particular disease, condition, or disorder described herein. The amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the subject in need of treatment, but can nevertheless be routinely determined by one skilled in the art.

When employed as pharmaceuticals, the compounds of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), including

pharmaceutically acceptable salts or solvates thereof, can be administered in the form of pharmaceutical compositions as described herein.

Also provided herein is a method of treating a subject having a cancer, wherein the method comprises:

(a) determining that a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first EGFR inhibitor has one or more EGFR inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor that was previously administered to the subject; and

(b) administering a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, as a monotherapy or in conjunction with another anticancer agent to the subject.

Further provided herein is a method of treating a subject having a cancer, wherein the method comprises:

(a) determining that a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first EGFR inhibitor does not have one or more EGFR inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor that was previously administered to the subject; and

(b) administering additional doses of the first EGFR inhibitor to the subject.

Combinations

In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each subject with cancer. In medical oncology the other component(s) of such conjoint treatment or therapy in addition to compositions provided herein may be, for example, surgery, radiotherapy, and chemotherapeutic agents, such as other kinase inhibitors, signal transduction inhibitors and/or monoclonal antibodies. For example, a surgery may be open surgery or minimally invasive surgery. Compounds of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or pharmaceutically acceptable salts or solvates thereof, therefore may also be useful

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

In some embodiments, a subject has a cancer (e.g., a locally advanced or metastatic tumor) that is refractory or intolerant to standard therapy (e.g., administration of a chemotherapeutic agent, such as a first EGFR inhibitor, a first HER2 inhibitor, or a multi-kinase inhibitor, immunotherapy, or radiation (e.g., radioactive iodine)). In some embodiments, a subject has a cancer (e.g., a locally advanced or metastatic tumor) that is refractory or intolerant to prior therapy (e.g., administration of a chemotherapeutic agent, such as a first EGFR inhibitor, a first HER2 inhibitor, or a multi-kinase inhibitor, immunotherapy, or radiation (e.g., radioactive iodine)). In some embodiments, a subject has a cancer (e.g., a locally advanced or metastatic tumor) that has no standard therapy. In some embodiments, a subject is EGFR inhibitor naïve. For example, the subject is naïve to treatment with a selective EGFR inhibitor. In some embodiments, a subject is not EGFR inhibitor naïve. In some embodiments, a subject is HER2 inhibitor naïve. For example, the subject is naïve to treatment with a selective HER2 inhibitor. In some embodiments, a subject is not HER2 inhibitor naïve. In some embodiments, a subject has undergone prior therapy. For example, treatment with a multi-kinase inhibitor (MKI), an EGFR tyrosine

kinase inhibitor (TKI), osimertinib, gefitinib, erlotinib, afatinib, lapatinib, neratinib, AZD-9291, CL-387785, CO-1686, or WZ4002.

In some embodiments of any the methods described herein, the compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**) (or a pharmaceutically acceptable salt thereof) is administered in combination with a therapeutically effective amount of at least one additional therapeutic agent selected from one or more additional therapies or therapeutic (e.g., chemotherapeutic) agents.

Non-limiting examples of additional therapeutic agents include: other EGFR-targeted therapeutic agents (i.e., a first or second EGFR inhibitor), other HER2-targeted therapeutic agents (i.e., a first or second HER2 inhibitor), RAS pathway targeted therapeutic agents, PARP inhibitors, other kinase inhibitors (e.g., receptor tyrosine kinase-targeted therapeutic agents (e.g., Trk inhibitors or multi-kinase inhibitors)), farnesyl transferase inhibitors, signal transduction pathway inhibitors, checkpoint inhibitors, modulators of the apoptosis pathway (e.g., obataclax); cytotoxic chemotherapeutics, angiogenesis-targeted therapies, immune-targeted agents, including immunotherapy, and radiotherapy.

In some embodiments, the other EGFR-targeted therapeutic is a multi-kinase inhibitor exhibiting EGFR inhibition activity. In some embodiments, the other EGFR-targeted therapeutic inhibitor is selective for an EGFR kinase.

Non-limiting examples of EGFR-targeted therapeutic agents (e.g., a first EGFR inhibitor or a second EGFR inhibitor) include an EGFR-selective inhibitor, a panHER inhibitor, and an anti-EGFR antibody. In some embodiments, the EGFR inhibitor is a covalent inhibitor. In some embodiments, the EGFR-targeted therapeutic agent is osimertinib (AZD9291, merelectinib, TAGRISSOTM), erlotinib (TARCEVA®), gefitinib (IRESSA®), cetuximab (ERBITUX®), necitumumab (PORTRAZZATM, IMC-11F8), neratinib (HKI-272, NERLYNX®), lapatinib (TYKERB®), panitumumab (ABX-EGF, VECTIBIX®), vandetanib (CAPRELSA®), rociletinib (CO-1686), olmutinib (OLITATM, HM61713, BI-1482694), naquotinib (ASP8273), nazartinib (EGF816, NVS-816), PF-06747775, icotinib (BPI-2009H), afatinib (BIBW 2992, GILOTRIF®), dacomitinib (PF-00299804, PF-804, PF-299, PF-299804), avitinib (AC0010), AC0010MA EAI045, matuzumab (EMD-7200), nimotuzumab (h-R3, BIOMAb EGFR®), zalutumab,

MDX447, depatuxizumab (humanized mAb 806, ABT-806), depatuxizumab mafodotin (ABT-414), ABT-806, mAb 806, canertinib (CI-1033), shikonin, shikonin derivatives (e.g., deoxyshikonin, isobutyrylshikonin, acetylshikonin, β,β-dimethylacrylshikonin and acetylalkannin), poziotinib (NOV120101, HM781-36B), AV-412, ibrutinib, WZ4002, brigatinib (AP26113, ALUNBRIG®), pelitinib (EKB-569), tarloxotinib (TH-4000, PR610), BPI-15086, Hemay022, ZN-e4, tesevatinib (KD019, XL647), YH25448, epitinib (HMPL-813), CK-101, MM-151, AZD3759, ZD6474, PF-06459988, varlintinib (ASLAN001, ARRY-334543), AP32788, HLX07, D-0316, AEE788, HS-10296, avitinib, GW572016, pyrotinib (SHR1258), SCT200, CPGJ602, Sym004, MAb-425, Modotuximab (TAB-H49), futuximab (992 DS), zalutumumab, KL-140, RO5083945, IMGN289, JNJ-61186372, LY3164530, Sym013, AMG 595, BDTX-189, avatinib, Disruptin, CL-387785, EGFRBi-Armed Autologous T Cells, and EGFR CAR-T Therapy. In some embodiments, the EGFR-targeted therapeutic agent is selected from osimertinib, gefitinib, erlotinib, afatinib, lapatinib, neratinib, AZD-9291, CL-387785, CO-1686, or WZ4002.

Additional EGFR-targeted therapeutic agents (e.g., a first EGFR inhibitor or a second EGFR inhibitor) include those disclosed in WO 2019/246541; WO 2019/165385; WO 2014/176475; and US 9,029,502, each of which is incorporated by reference in its entirety.

In some embodiments, the other HER2-targeted therapeutic is a multi-kinase inhibitor exhibiting HER2 inhibition activity. In some embodiments, the other HER2-targeted therapeutic inhibitor is selective for a HER2 kinase.

Non-limiting examples of HER2-targeted therapeutic agents (e.g., a first HER2 inhibitor or a second HER2 inhibitor) include a HER2-selective inhibitor, a panHER inhibitor, and an anti-HER2 antibody. Exemplary HER2-targeted therapeutic agents include trastuzumab (e.g., TRAZIMERA™, HERCEPTIN®), pertuzumab (e.g., PERJETA®), trastuzumab emtansine (T-DM1 or ado-trastuzumab emtansine, e.g., KADCYLA®), lapatinib, KU004, neratinib (e.g., NERLYNX®), dacomitinib (e.g., VIZIMPRO®), afatinib (GILOTRIF®), tucatinib (e.g., TUKYSA™), erlotinib (e.g., TARCEVA®), pyrotinib, poziotinib, CP-724714, CUDC-101, sapitinib (AZD8931), tanespimycin (17-AAG), IPI-504, PF299, pelitinib, S- 22261 1, and AEE-788.

Additional HER2-targeted therapeutic agents (e.g., a first HER2 inhibitor or a

second HER2 inhibitor) include those disclosed in WO 2019/246541; WO 2019/165385; WO 2014/176475; and US 9,029,502, each of which is incorporated by reference in its entirety.

A "RAS pathway targeted therapeutic agent" as used herein includes any compound exhibiting inactivation activity of any protein in a RAS pathway (e.g., kinase inhibition, allosteric inhibition, inhibition of dimerization, and induction of degradation). Non-limiting examples of a protein in a RAS pathway include any one of the proteins in the RAS-RAF-MAPK pathway or PI3K/AKT pathway such as RAS (e.g., KRAS, HRAS, and NRAS), RAF, BRAF, MEK, ERK, PI3K, AKT, and mTOR. In some embodiments, a RAS pathway modulator can be selective for a protein in a RAS pathway, e.g., the RAS pathway modulator can be selective for RAS (also referred to as a RAS modulator). In some embodiments, a RAS modulator is a covalent inhibitor. In some embodiments, a RAS pathway targeted therapeutic agent is a "KRAS pathway modulator." A KRAS pathway modulator includes any compound exhibiting inactivation activity of any protein in a KRAS pathway (e.g., kinase inhibition, allosteric inhibition, inhibition of dimerization, and induction of degradation). Non-limiting examples of a protein in a KRAS pathway include any one of the proteins in the KRAS-RAF-MAPK pathway or PI3K/AKT pathway such as KRAS, RAF, BRAF, MEK, ERK, PI3K, AKT, and mTOR. In some embodiments, a KRAS pathway modulator can be selective for a protein in a RAS pathway, e.g., the KRAS pathway modulator can be selective for KRAS (also referred to as a KRAS modulator). In some embodiments, a KRAS modulator is a covalent inhibitor. Non-limiting examples of a KRAS-targeted therapeutic agents (e.g., KRAS inhibitors) include BI 1701963, AMG 510, ARS-3248, ARS1620, AZD4785, SML-8-73-1, SML-10-70-1, VSA9, AA12, and MRTX-849.

Further non-limiting examples of RAS-targeted therapeutic agents include BRAF inhibitors, MEK inhibitors, ERK inhibitors, PI3K inhibitors, AKT inhibitors, and mTOR inhibitors. In some embodiments, the BRAF inhibitor is vemurafenib (ZELBORAF®), dabrafenib (TAFINLAR®), and encorafenib (BRAFTOVITM), BMS-908662 (XL281), sorafenib, LGX818, PLX3603, RAF265, RO5185426, GSK2118436, ARQ 736, GDC-0879, PLX-4720, AZ304, PLX-8394, HM95573, RO5126766, LXH254, or a combination thereof.

In some embodiments, the MEK inhibitor is trametinib (MEKINIST®, GSK1120212), cobimetinib (COTELLIC®), binimetinib (MEKTOVI®, MEK162), selumetinib (AZD6244), PD0325901, MSC1936369B, SHR7390, TAK-733, RO5126766, CS3006, WX-554, PD98059, CI1040 (PD184352), hypothemycin, or a combination thereof.

In some embodiments, the ERK inhibitor is FRI-20 (ON-01060), VTX-11e, 25-OH-D3-3-BE (B3CD, bromoacetoxycalcidiol), FR-180204, AEZ-131 (AEZS-131), AEZS-136, AZ-13767370, BL-EI-001, LY-3214996, LTT-462, KO-947, KO-947, MK-8353 (SCH900353), SCH772984, ulixertinib (BVD-523), CC-90003, GDC-0994 (RG-7482), ASN007, FR148083, 5-7-Oxozeaenol, 5-iodotubercidin, GDC0994, ONC201, or a combination thereof.

In some embodiments, PI3K inhibitor is selected from buparlisib (BKM120), alpelisib (BYL719), WX-037, copanlisib (ALIQOPATM, BAY80-6946), dactolisib (NVP-BEZ235, BEZ-235), taselisib (GDC-0032, RG7604), sonolisib (PX-866), CUDC-907, PQR309, ZSTK474, SF1126, AZD8835, GDC-0077, ASN003, pictilisib (GDC-0941), pilaralisib (XL147, SAR245408), gedatolisib (PF-05212384, PKI-587), serabelisib (TAK-117, MLN1117, INK 1117), BGT-226 (NVP-BGT226), PF-04691502, apitolisib (GDC-0980), omipalisib (GSK2126458, GSK458), voxtalisib (XL756, SAR245409), AMG 511, CH5132799, GSK1059615, GDC-0084 (RG7666), VS-5584 (SB2343), PKI-402, wortmannin, LY294002, PI-103, rigosertib, XL-765, LY2023414, SAR260301, KIN-193 (AZD-6428), GS-9820, AMG319, GSK2636771, or a combination thereof.

In some embodiments, the AKT inhibitor is selected from miltefosine (IMPADIVO®), wortmannin, NL-71-101, H-89, GSK690693, CCT128930, AZD5363, ipatasertib (GDC-0068, RG7440), A-674563, A-443654, AT7867, AT13148, uprosertib, afuresertib, DC120, 2-[4-(2-aminoprop-2-yl)phenyl]-3-phenylquinoxaline, MK-2206, edelfosine, miltefosine, perifosine, erucylphophocholine, erufosine, SR13668, OSU-A9, PH-316, PHT-427, PIT-1, DM-PIT-1, triciribine (Triciribine Phosphate Monohydrate), API-1, N-(4-(5-(3-acetamidophenyl)-2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b] pyridin-3-yl)benzyl)-3-fluorobenzamide, ARQ092, BAY 1125976, 3-oxo-tirucallic acid, lactoquinomycin, boc-Phe-vinyl ketone, Perifosine (D-21266), TCN, TCN-P, GSK2141795, ONC201, or a combination thereof.

In some embodiments, the mTOR inhibitor is selected from MLN0128, AZD-2014, CC-223, AZD2014, CC-115, everolimus (RAD001), temsirolimus (CCI-779), ridaforolimus (AP-23573), sirolimus (rapamycin), or a combination thereof.

Non-limiting examples of farnesyl transferase inhibitors include lonafarnib, tipifarnib, BMS-214662, L778123, L744832, and FTI-277.

In some embodiments, a chemotherapeutic agent includes an anthracycline, cyclophosphamide, a taxane, a platinum-based agent, mitomycin, gemcitabine, eribulin (HALAVEN™), or combinations thereof.

Non-limiting examples of a taxane include paclitaxel, docetaxel, abraxane, and taxotere.

In some embodiments, the anthracycline is selected from daunorubicin, doxorubicin, epirubicin, idarubicin, and combinations thereof.

In some embodiments, the platinum-based agent is selected from carboplatin, cisplatin, oxaliplatin, nedplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, satraplatin and combinations thereof

Non-limiting examples of PARP inhibitors include olaparib (LYNPARZA®), talazoparib, rucaparib, niraparib, veliparib, BGB-290 (pamiparib), CEP 9722, E7016, iniparib, IMP4297, NOV1401, 2X-121, ABT-767, RBN-2397, BMN 673, KU-0059436 (AZD2281), BSI-201, PF-01367338, INO-1001, and JPI-289.

Non-limiting examples of immunotherapy include immune checkpoint therapies, atezolizumab (TECENTRIQ®), albumin-bound paclitaxel. Non-limiting examples of immune checkpoint therapies include inhibitors that target CTLA-4, PD-1, PD-L1, BTLA, LAG-3, A2AR, TIM-3, B7-H3, VISTA, IDO, and combinations thereof. In some embodimetnts the CTLA-4 inhibitor is ipilimumab (YERVOY®). In some embodiments, the PD-1 inhibitor is selected from pembrolizumab (KEYTRUDA®), nivolumab (OPDIVO®), cemiplimab (LIBTAYO®), or combinations thereof. In some embodiments, the PD-L1 inhibitor is selected from atezolizumab (TECENTRIQ®), avelumab (BAVENCIO®), durvalumab (IMFINZI®), or combinations thereof. In some embodiments, the LAG-3 inhibitor is IMP701 (LAG525). In some embodiments, the A2AR inhibitor is CPI-444. In some embodiments, the TIM-3 inhibitor is MBG453. In some embodiments, the B7-H3 inhibitor is enoblituzumab. In some embodiments, the

VISTA inhibitor is JNJ-61610588. In some embodiments, the IDO inhibitor is indoximod. See, for example, Marin-Acevedo, et al., *J Hematol Oncol.* 11: 39 (2018).

In some embodiments, the additional therapy or therapeutic agent is a combination of atezolizumab and nab-paclitaxel.

Accordingly, also provided herein is a method of treating cancer, comprising administering to a subject in need thereof a pharmaceutical combination for treating cancer which comprises (a) a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, (b) an additional therapeutic agent, and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent are together effective in treating the cancer.

In some embodiments, the additional therapeutic agent(s) includes any one of the above listed therapies or therapeutic agents which are standards of care in cancers wherein the cancer has a dysregulation of an *EGFR* gene, an EGFR protein, or expression or activity, or level of any of the same.

In some embodiments, the additional therapeutic agent(s) includes any one of the above listed therapies or therapeutic agents which are standards of care in cancers wherein the cancer has a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity, or level of any of the same.

These additional therapeutic agents may be administered with one or more doses of the compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof, as part of the same or separate dosage forms, via the same or different routes of administration, and/or on the same or different administration schedules according to standard pharmaceutical practice known to one skilled in the art.

Also provided herein is (i) a pharmaceutical combination for treating a cancer in a subject in need thereof, which comprises (a) a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, (b) at least one additional therapeutic agent (e.g., any of the exemplary additional therapeutic agents described herein or known in the art), and (c)

optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the compound of Formula **(I)**, or pharmaceutically acceptable salt thereof, and of the additional therapeutic agent are together effective in treating the cancer; (ii) a pharmaceutical composition comprising such a combination; (iii) the use of such a combination for the preparation of a medicament for the treatment of cancer; and (iv) a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of cancer in a subject in need thereof. In some embodiments, the cancer is an EGFR-associated cancer. For example, an EGFR-associated cancer having one or more EGFR inhibitor resistance mutations. In some embodiments, the cancer is a HER2-associated cancer. For example, a HER2-associated cancer having one or more HER2 inhibitor resistance mutations.

The term "pharmaceutical combination", as used herein, refers to a pharmaceutical therapy resulting from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, and at least one additional therapeutic agent (e.g., a chemotherapeutic agent), are both administered to a subject simultaneously in the form of a single composition or dosage. The term "non-fixed combination" means that a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one additional therapeutic agent (e.g., chemotherapeutic agent) are formulated as separate compositions or dosages such that they may be administered to a subject in need thereof simultaneously, concurrently or sequentially with variable intervening time limits, wherein such administration provides effective levels of the two or more compounds in the body of the subject. These also apply to cocktail therapies, e.g., the administration of three or more active ingredients

Accordingly, also provided herein is a method of treating a cancer, comprising administering to a subject in need thereof a pharmaceutical combination for treating cancer which comprises (a) a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or pharmaceutically acceptable salt thereof, and (b) an additional therapeutic agent, wherein the compound of Formula **(I)** and the

additional therapeutic agent are administered simultaneously, separately or sequentially, wherein the amounts of the compound of Formula **(I)**, or pharmaceutically acceptable salt thereof, and the additional therapeutic agent are together effective in treating the cancer. In some embodiments, the compound of Formula **(I)**, or pharmaceutically acceptable salt thereof, and the additional therapeutic agent are administered simultaneously as separate dosages. In some embodiments, the compound of Formula **(I)**, or pharmaceutically acceptable salt thereof, and the additional therapeutic agent are administered as separate dosages sequentially in any order, in jointly therapeutically effective amounts, e.g., in daily or intermittently dosages. In some embodiments, the compound of Formula **(I)**, or pharmaceutically acceptable salt thereof, and the additional therapeutic agent are administered simultaneously as a combined dosage. In some embodiments, the cancer is an EGFR-associated cancer. For example, an EGFR-associated cancer having one or more EGFR inhibitor resistance mutations. In some embodiments, the cancer is a HER2-associated cancer. For example, a HER2-associated cancer having one or more HER2 inhibitor resistance mutations.

In some embodiments, the presence of one or more EGFR inhibitor resistance mutations in a tumor causes the tumor to be more resistant to treatment with a first EGFR inhibitor. Methods useful when an EGFR inhibitor resistance mutation causes the tumor to be more resistant to treatment with a first EGFR inhibitor are described below. For example, provided herein are methods of treating a subject having a cancer that include: identifying a subject having a cancer cell that has one or more EGFR inhibitor resistance mutations; and administering to the identified subject a compound of Formula **(I)** (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered in combination with the first EGFR inhibitor. Also provided are methods of treating a subject identified as having a cancer cell that has one or more EGFR inhibitor resistance mutations that include administering to the subject a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered in combination with the first EGFR inhibitor. In some embodiments, the one or more EGFR inhibitor resistance mutations confer increased

resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor. In some embodiments, the one or more EGFR inhibitor resistance mutations include one or more EGFR inhibitor resistance mutations listed in **Table 2a** and **2b**. For example, the one or more EGFR inhibitor resistance mutations can include a substitution at amino acid position 718, 747, 761, 790, 797, or 854 (e.g., L718Q, L747S, D761Y, T790M, C797S, and T854A).

For example, provided herein are methods for treating an EGFR-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of an *EGFR* gene, an EGFR kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first EGFR inhibitor, wherein the first EGFR inhibitor is selected from the group consisting of osimertinib, gefitinib, erlotinib, afatinib, lapatinib, neratinib, AZD-9291, CL-387785, CO-1686, or WZ4002. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one EGFR inhibitor resistance mutation; and (d) administering a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has been determined to have a cancer cell that has at least one EGFR inhibitor resistance mutation; or (e) administering additional doses of the first EGFR inhibitor of step (b) to the subject if the subject has not been determined to have a cancer cell that has at least one EGFR inhibitor resistance mutation.

Methods useful when a HER2 activating mutation is present in a tumor are described herein. For example, provided herein are methods of treating a subject having a cancer that include: identifying a subject having a cancer cell that has one or more HER2 activating mutations; and administering to the identified subject a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof. Also provided are methods of treating a subject identified as having a cancer that has one or more HER2 activating mutations that include administering to the subject a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof. In some embodiments, the one or more HER2 activating mutations include

one or more HER2 activating mutations listed in **Tables 3-5**.

Methods useful when an activating mutation (e.g., HER2 activating mutation) is present in a tumor in a subject are described herein. For example, provided herein are methods of treating a subject having a cancer that include: identifying a subject having a cancer cell that has one or more HER2 activating mutations; and administering to the identified subject a compound of Formula (I) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof.

Compound Preparation

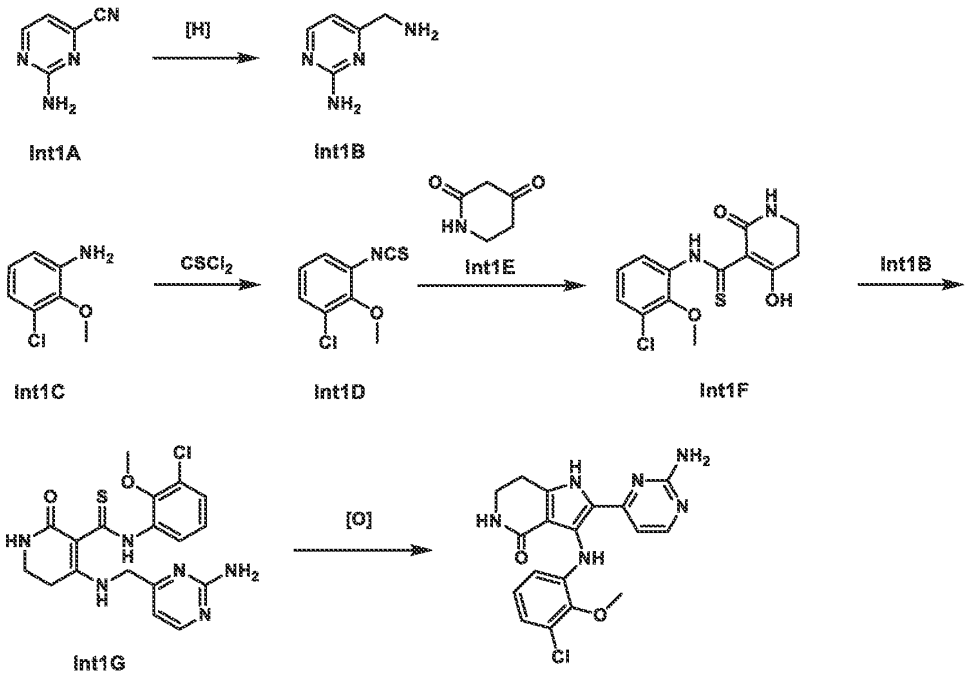
The compounds disclosed herein can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or in light of the teachings herein. The synthesis of the compounds disclosed herein can be achieved by generally following Scheme 1, with modification for specific desired substituents.

Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); Smith, M. B., March, J., March' s Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th edition, John Wiley & Sons: New York, 2001 ; and Greene, T.W., Wuts, P.G. M., Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons: New York, 1999, are useful and recognized reference textbooks of organic synthesis known to those in the art. The following descriptions of synthetic methods are designed to illustrate, but not to limit, general procedures for the preparation of compounds of the present disclosure.

The synthetic processes disclosed herein can tolerate a wide variety of functional groups; therefore, various substituted starting materials can be used. The processes generally provide the desired final compound at or near the end of the overall process,

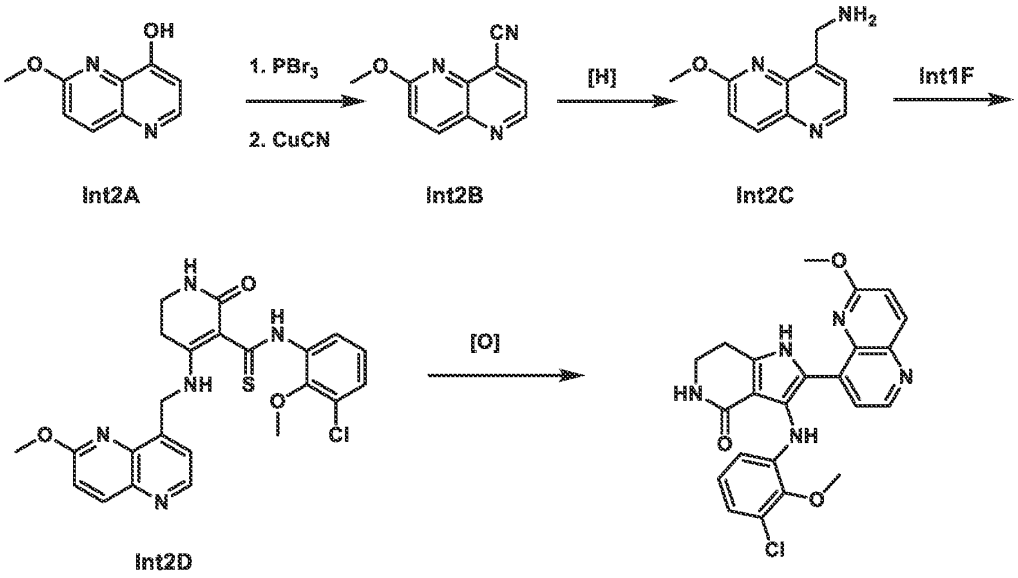
although it may be desirable in certain instances to further convert the compound to a pharmaceutically acceptable salt thereof.

Example 1: Synthesis of 2-(2-aminopyrimidin-4-yl)-3-((3-chloro-2-methoxyphenyl)amino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(Compound 148)**



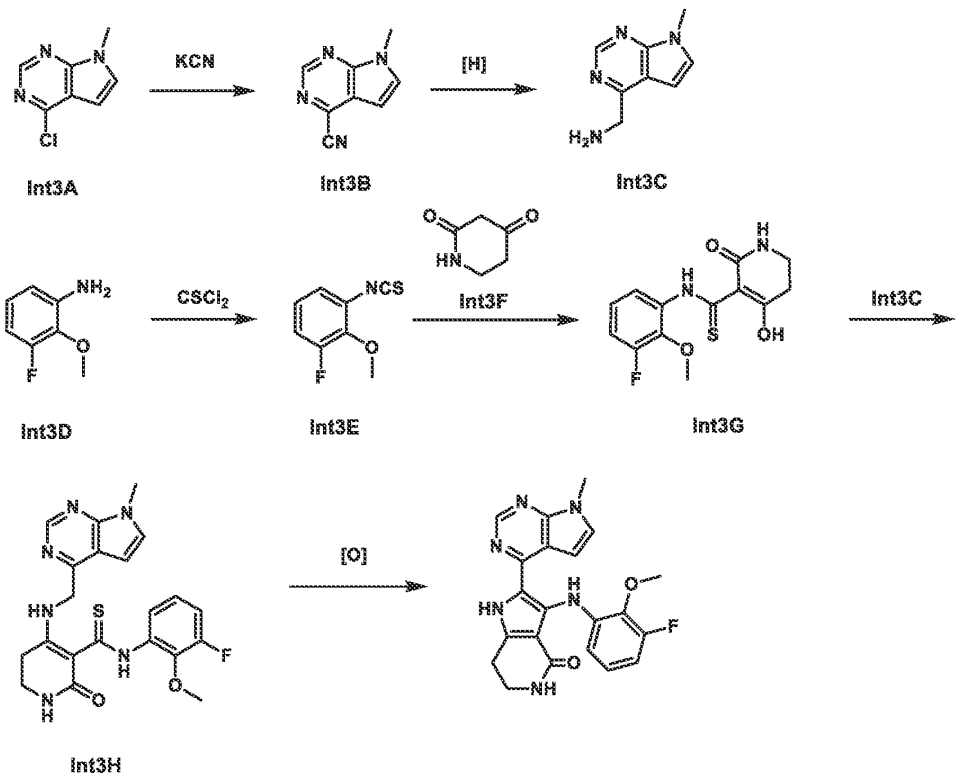
Cyanopyrimidine **Int1A** is hydrogenated in the presence of hydrogen gas and a catalyst, e.g, Raney Ni in a polar protic solvent e.g., MeOH to give **Int1B**. **Int1C** is reacted with thiophosgene under modified Schotten–Baumann conditions, e.g., $NaHCO_3$ in the presence of water/DCM to give the corresponding thioisocyanate **Int1D**. Treatment of **Int1D** with **Int1E** in the presence of a strong base, e.g., DBU in a polar aprotic solvent, e.g., ACN gives **Int1F**. Condensation of **Int1F** with **Int1B** with heating, e.g., at 120 °C in the presence of a dehydrating agent, e.g., 4Å molecular sieves in a polar aprotic solvent, e.g., DMA provides **Int1G**. Oxidative cyclization in the presence of a mild oxidant, e.g., H_2O_2 in and polar protic solvent, e.g., MeOH with heating, e.g., 50 °C gives the title compound.

Example 2: Synthesis of 3-((3-chloro-2-methoxyphenyl)amino)-2-(6-methoxy-1,5-naphthyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(Compound 149)**



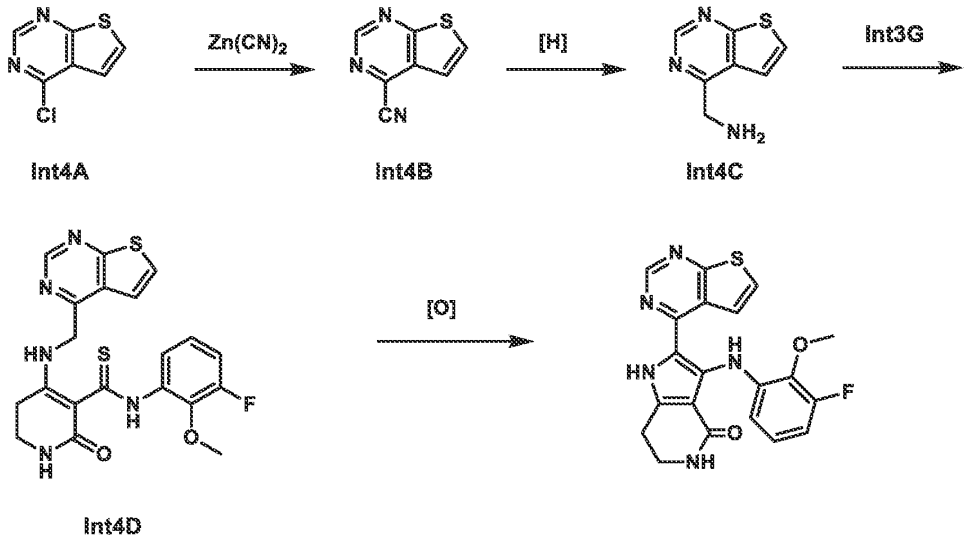
Int2A is treated with a brominating agent, e.g., PBr_3 in a polar aprotic solvent, e.g., DMF to afford the corresponding bromide, which is converted to the corresponding cyano adduct **Int2B** by heating e.g., at 130 °C under copper catalyzed cyanation conditions, e.g., with CuCN in a polar aprotic solvent, e.g., DMF. Hydrogenation of **Int2B** in the presence of hydrogen gas and a catalyst, e.g, Raney Ni in a polar protic solvent e.g., MeOH with acetic acid gives **Int2C**. Condensation of **Int2C** with **Int1F** (from **Example 1**) with heating, e.g.,120 °C in the presence of a dehydrating agent, e.g., 4Å molecular sieves in a polar aprotic solvent, e.g., DMA provides **Int2D**. Oxidative cyclization in the presence of TFA, a mild oxidant, e.g., H_2O_2 in polar protic solvent, e.g., MeOH with heating, e.g., 40 °C gives the title compound.

Example 3: Synthesis of 3-((3-fluoro-2-methoxyphenyl)amino)-2-(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(Compound 150)**



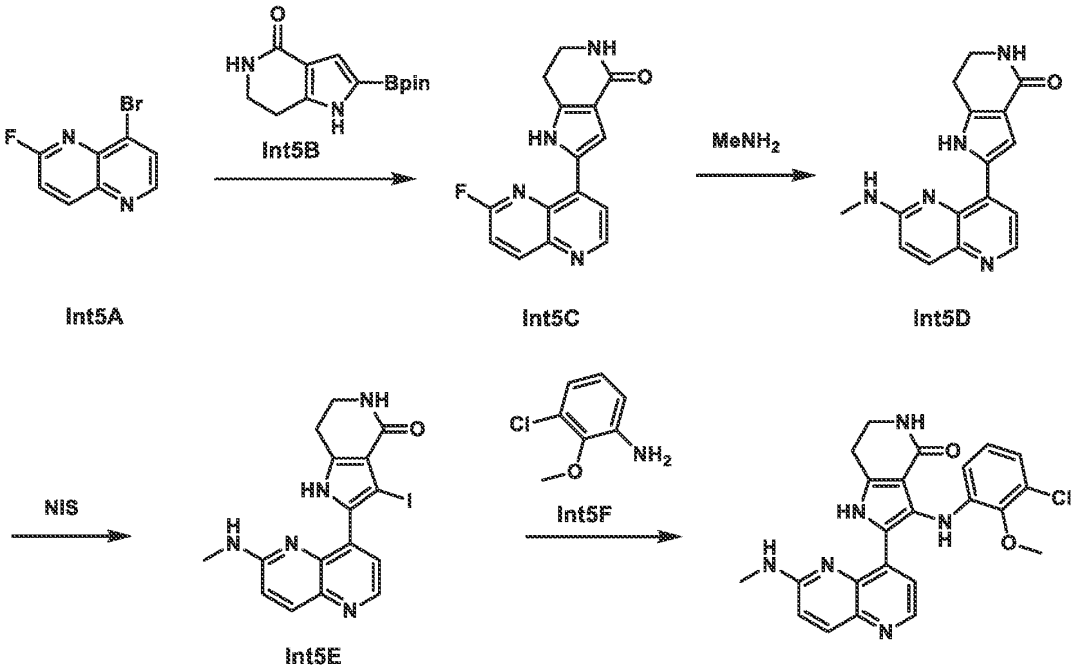
Int3A is converted to the corresponding cyano adduct **Int3B** by heating e.g., 130 °C with a cyanide source, e.g., KCN in a polar aprotic solvent, e.g., DMSO in the presence of SPTS. **Int3B** is hydrogenated in the presence of hydrogen gas and a catalyst, e.g, Pd/C in a polar protic solvent e.g., MeOH to give **Int3C**. **Int3D** is reacted with thiophosgene under modified Schotten–Baumann conditions, e.g., $NaHCO_3$ in the presence of water/DCM to give the corresponding thioisocyanate **Int3E**. Treatment of **Int3E** with **Int3F** in the presence of a strong base, e.g. DBU in a polar aprotic solvent, e.g., ACN gives **Int3G**. Condensation of **Int3G** with **Int3C** under amide coupling conditions, e.g., PyBOP, DIEA in a polar aprotic solvent, e.g., DMF gives **Int3H**. Oxidative cyclization of **Int3H** in the presence of TFA, a mild oxidant, e.g., H_2O_2 in polar protic solvent, e.g., MeOH at room temperature gives the title compound.

Example 4: Synthesis of 3-((3-fluoro-2-methoxyphenyl)amino)-2-(thieno[2,3-d]pyrimidin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(Compound 151)**



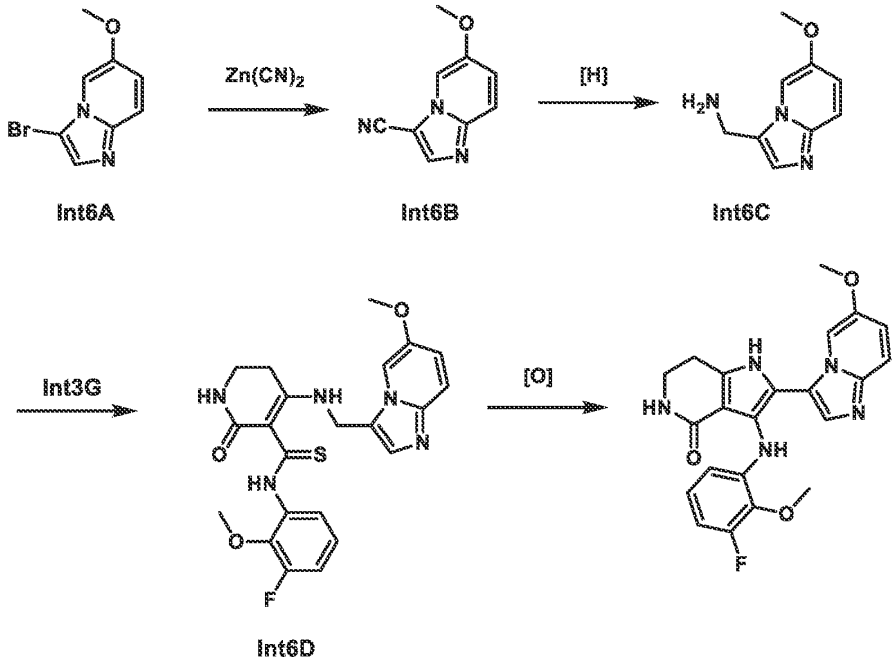
Int4A is converted to the corresponding cyano adduct **Int4B** by Pd-catalyzed cyanation, e.g., $Zn(CN)_2$, Zn, $Pd_2(dba)_3$, $Pd(dppf)Cl_2$ in a polar aprotic solvent, e.g., DMA. Hydrogenation of **Int4B** with a catalyst, e.g., Raney Ni and hydrogen gas in a polar protic solvent e.g., MeOH gives **Int4C**. Condensation of **Int4C** with **Int3G** (from **Example 3**) under amide coupling conditions, e.g., PyBOP, DIEA in a polar aprotic solvent, e.g., DMF gives at 0 °C gives **Int4D**. Oxidative cyclization in the presence of a mild oxidant, e.g., H_2O_2 in polar solvent, e.g., DMSO with heating, e.g., 100 °C gives the title compound.

Example 5: Synthesis of 3-((3-chloro-2-methoxyphenyl)amino)-2-(6-(methylamino)-1,5-naphthyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(Compound 152)**



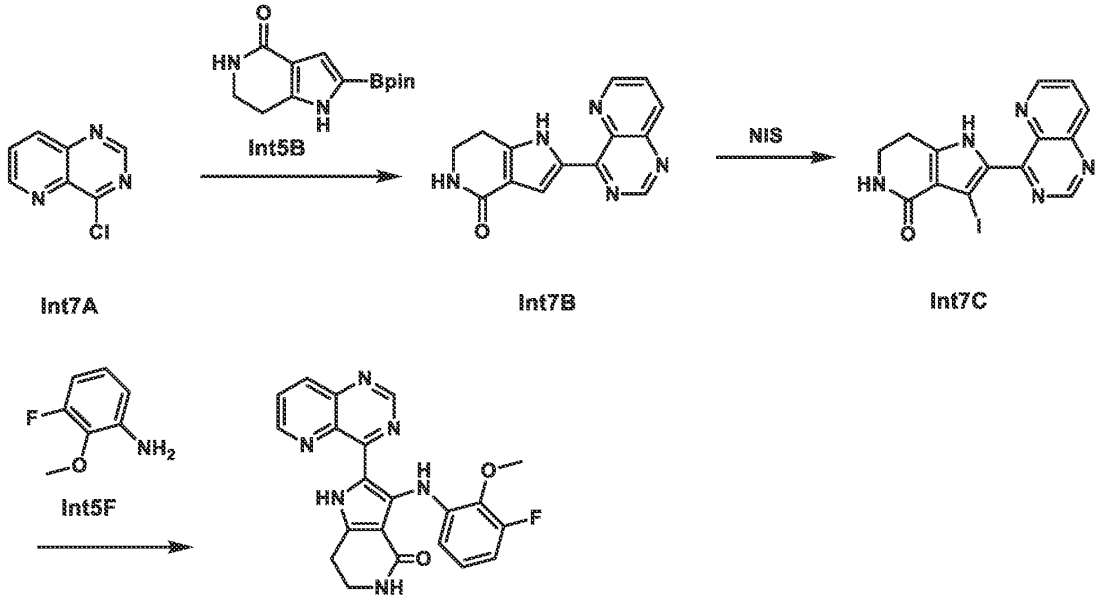
Int5A is treated with **Int5B** under Suzuki cross-coupling conditions, e.g., $Pd(dppf)Cl_2$, with a mild base, e.g., TEA in a polar solvent mixture, e.g., DME/water to give **Int5C**. Displacement of the fluoride of **Int5C** with methylamine gives **Int5D**, which is then iodinated with NIS in a polar aprotic solvent, e.g., DMF to give **Int5E**. Coupling of **Int5E** with of **Int5F** under Buchwald conditions, e.g., Ephos, Ephos Pd G4 in the presence of a base, e.g., Cs_2CO_3 in a polar aprotic solvent e.g., 1,4-dioxane at elevated temperature, e.g., 100 °C gives the title compound.

Example 6: Synthesis of 3-((3-fluoro-2-methoxyphenyl)amino)-2-(6-methoxyimidazo[1,2-a]pyridin-3-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(Compound 153)**



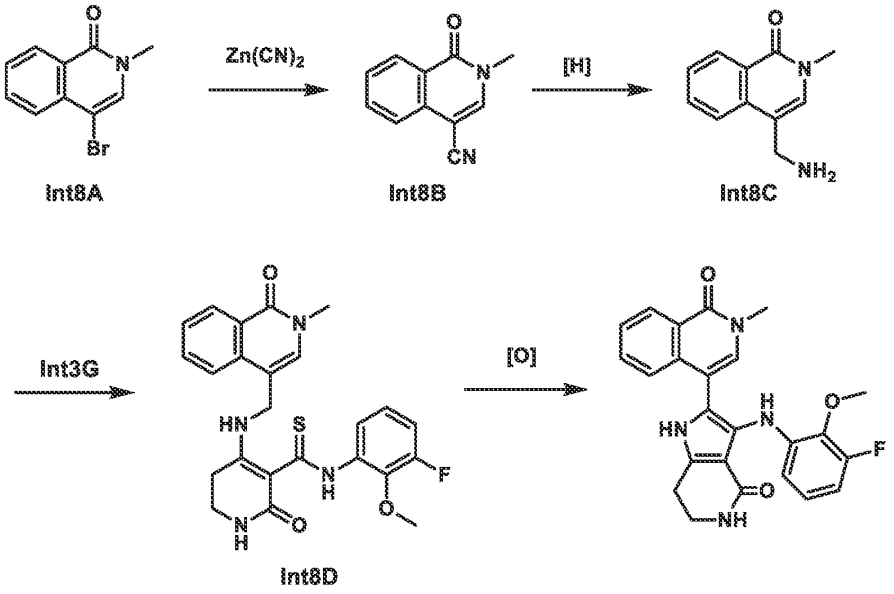
Int6A is converted to the corresponding cyano adduct **Int6B** by Pd-catalyzed cyanation, e.g., $Zn(CN)_2$, $Pd(PPh_3)_4$ in a polar aprotic solvent, e.g., DMA at an elevated temperature, e.g., at 120 °C. Reduction of **Int6B** with a strong reducing agent e.g., LAH in a polar aprotic solvent, e.g., THF at room temperature gives **Int6C**. Condensation of **Int6C** with **Int3G** (from **Example 3**) with heating, e.g., 120 °C in the presence of a dehydrating agent, e.g., 4Å molecular sieves in a polar aprotic solvent, e.g., DMA provides **Int6D**. Oxidative cyclization in the presence of a mild oxidant, e.g., H_2O_2 in a polar protic solvent, e.g., MeOH with heating, e.g., 50 °C gives the title compound.

Example 7: Synthesis of 3-((3-fluoro-2-methoxyphenyl)amino)-2-(pyrido[3,2-d]pyrimidin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(Compound 154)**



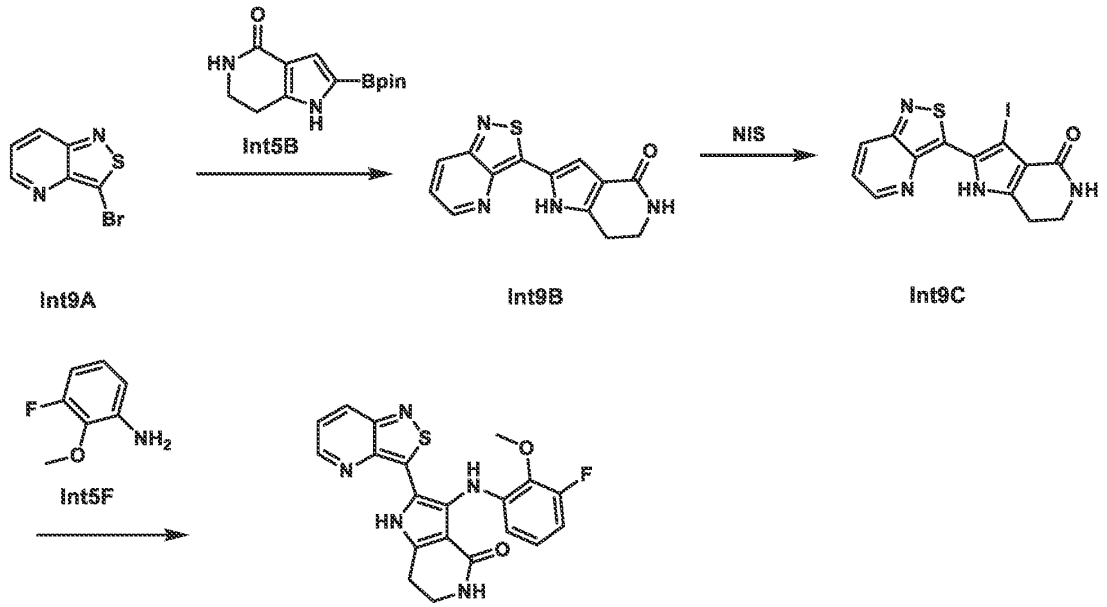
Int7A is treated with **Int5B** under Suzuki cross-coupling conditions, e.g., $Pd(PPh_3)_4$, K_2CO_3, in a polar solvent mixture, e.g., dioxane/water to give **Int7B**, which is iodinated with NIS in a polar aprotic solvent, e.g., DMF to give **Int7C**. Coupling of **Int7C** with of **Int5F** under Buchwald conditions, e.g., Ephos, Ephos Pd G4 in the presence of a base, e.g., Cs_2CO_3 in 1,4-dioxane at elevated temperature, e.g., 50 °C gives the title compound.

Example 8: Synthesis of 4-(3-((3-fluoro-2-methoxyphenyl)amino)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)-2-methylisoquinolin-1(2H)-one **(Compound 155)**



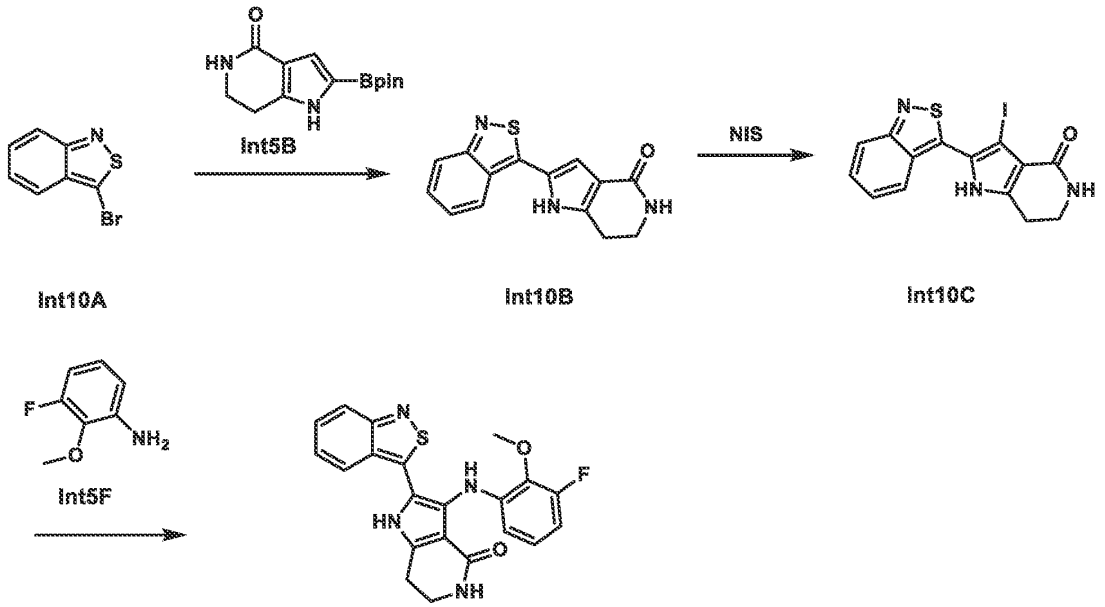
Int8A is converted to the corresponding cyano adduct **Int8B** by Pd-catalyzed cyanation, e.g., $Zn(CN)_2$, $Pd(PPh_3)_4$, in a polar aprotic solvent, e.g., DMF at an elevated temperature, e.g., at 120 °C. Reduction of **Int8B** with a catalyst, e.g., Raney Ni in the presence of hydrogen (e.g., 5 atm) in NH_3/MeOH at room temperature gives **Int8C**. Condensation of **Int8C** with **Int3G** (from **Example 3**) under amide coupling conditions, e.g., PyBOP, DIEA in a polar aprotic solvent, e.g., DMF at 0 °C gives **Int8D**. Oxidative cyclization of **Int8D** in the presence of a mild oxidant, e.g., H_2O_2 in a protic solvent gives the title compound.

Example 9: Synthesis of 3-((3-fluoro-2-methoxyphenyl)amino)-2-(isothiazolo[4,3-b]pyridin-3-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(Compound 156)**



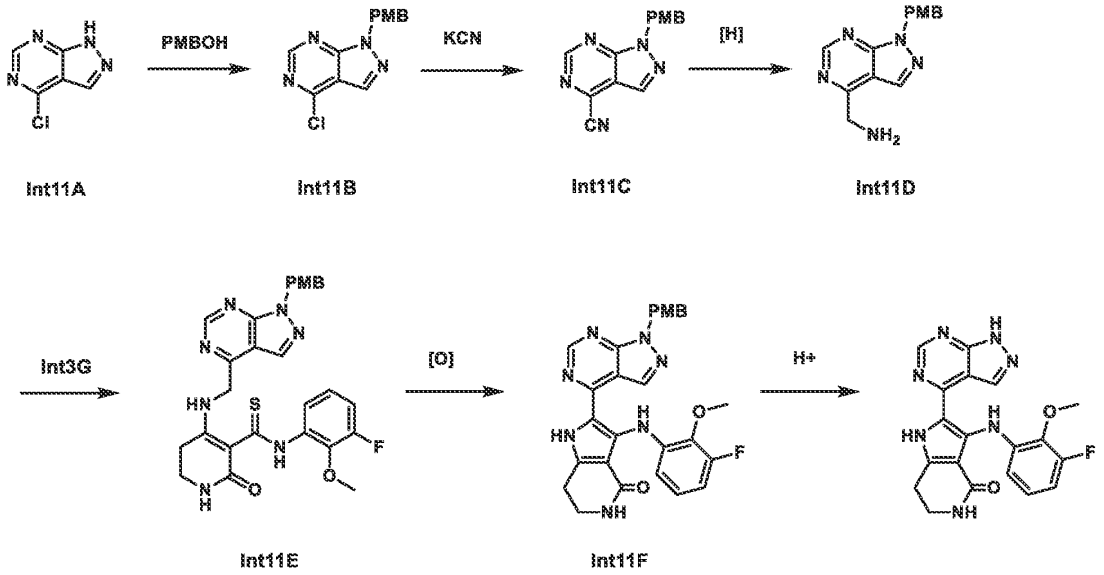
Int9A is treated with **Int5B** under Suzuki cross-coupling conditions, e.g., $Pd(dppf)Cl_2$ in the presence of a mild base, e.g, K_2CO_3 in a polar solvent mixture, e.g., 1,4-dioxane/water to give **Int9B**, which is iodinated with NIS in a polar aprotic solvent, e.g., DMF to give **Int9C**. Coupling of **Int9C** with of **Int5F** under Buchwald conditions, e.g., E-phos Pd G4 in the presence of a strong base, e.g., LiHMDS in 1,4-dioxane at elevated temperature, e.g., 100 °C gives the title compound.

Example 10: Synthesis of 2-(benzo[c]isothiazol-3-yl)-3-((3-fluoro-2-methoxyphenyl)amino)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(Compound 157)**



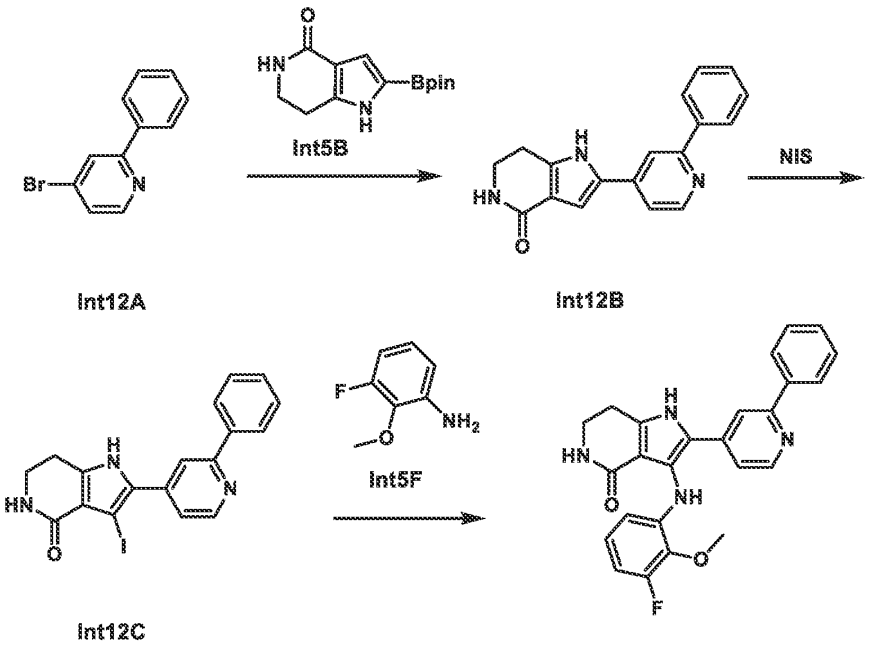
Int10A is treated with **Int5B** under Suzuki cross-coupling conditions, e.g., $Pd(dppf)Cl_2$ in the presence of a mild base, e.g, K_2CO_3 in a polar solvent mixture, e.g., 1,4-dioxane/water to give **Int10B**, which is iodinated with NIS in a polar aprotic solvent, e.g., DMF to give **Int10C**. Coupling of **Int10C** with of **Int5F** under Buchwald conditions, e.g., E-phos Pd G4 in the presence of a base, e.g., Cs_2CO_3 in polar aprotic solvent, e.g., 1,4-dioxane at elevated temperature, e.g., 100 °C gives the title compound.

Example 11: Synthesis of 3-((3-fluoro-2-methoxyphenyl)amino)-2-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(Compound 158)**



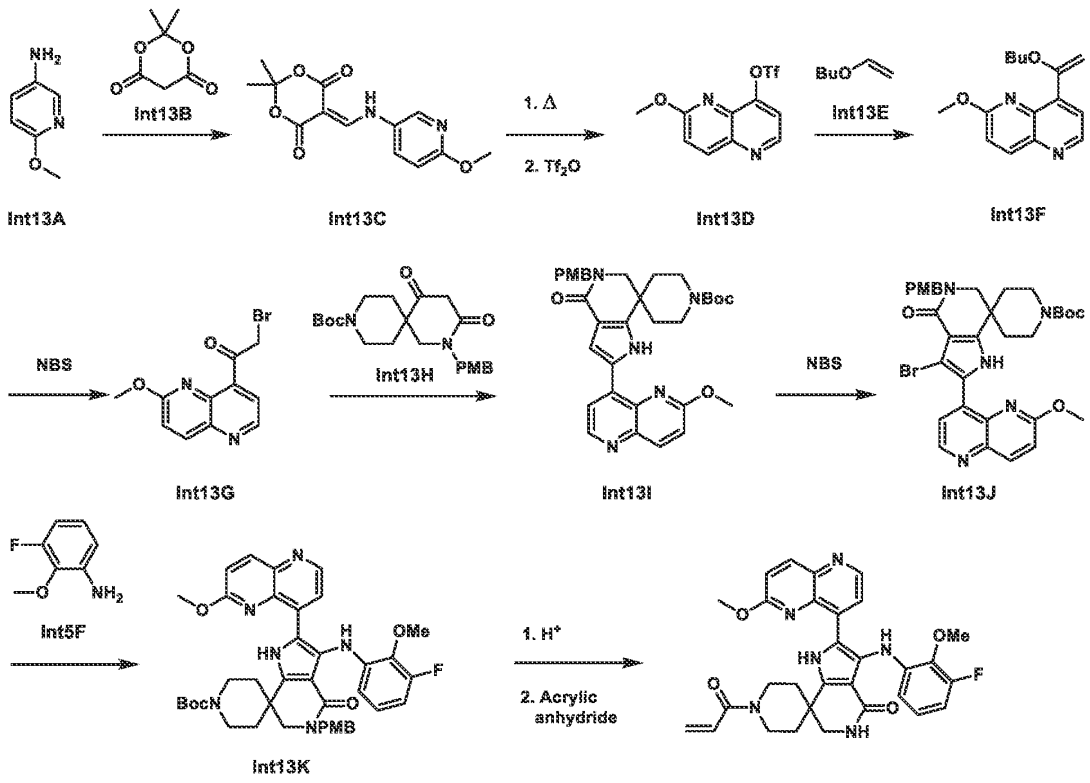
Int11A is PMB-protected by treatment with p-methoxybenzyl alcohol under Mitsunobu conditions, e.g. PPh_3/DIAD in a polar aprotic solvent (e.g., THF) to give **Int11B**, which is cyanated via SNAr with cyanide source, e.g., KCN in a polar aprotic solvent, e.g., DMF at elevated temperature (e.g., 60 °C). Hydrogenation of **Int11C** in the presence of catalytic Pd, e.g., Pd/C under a hydrogen atmosphere in a polar protic solvent, e.g., MeOH gives **Int11D**. Condensation of **Int11D** with **Int3G** (from Example 3) under amide coupling conditions, e.g., PyBOP, DIEA in a polar aprotic solvent, e.g., DMF gives at room temperature gives **Int11E**. Oxidative cyclization of **Int11E** in the presence of a mild oxidant, e.g., H_2O_2 in a polar aprotic solvent, e.g., DMSO with heating, e.g., 100 °C gives **Int11F**, which is deprotected with strong acid, e.g., TFA to give the title compound.

Example 12: Synthesis of 3-((3-fluoro-2-methoxyphenyl)amino)-2-(2-phenylpyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(Compound 159)**



Int12A is treated with **Int5B** under Suzuki cross-coupling conditions, e.g., $Pd(dppf)Cl_2$ in the presence of a mild base, e.g, K_2CO_3 in a polar solvent mixture, e.g., 1,4-dioxane/water to give **Int12B**, which is iodinated with NIS in a polar aprotic solvent, e.g., DMF to give **Int12C**. Coupling of **Int12C** with of **Int5F** under Buchwald conditions, e.g., E-phos Pd G4 in the presence of a base, e.g., Cs_2CO_3 in a polar aprotic solvent, e.g., 1,4-dioxane at elevated temperature, e.g., 100 °C gives the title compound.

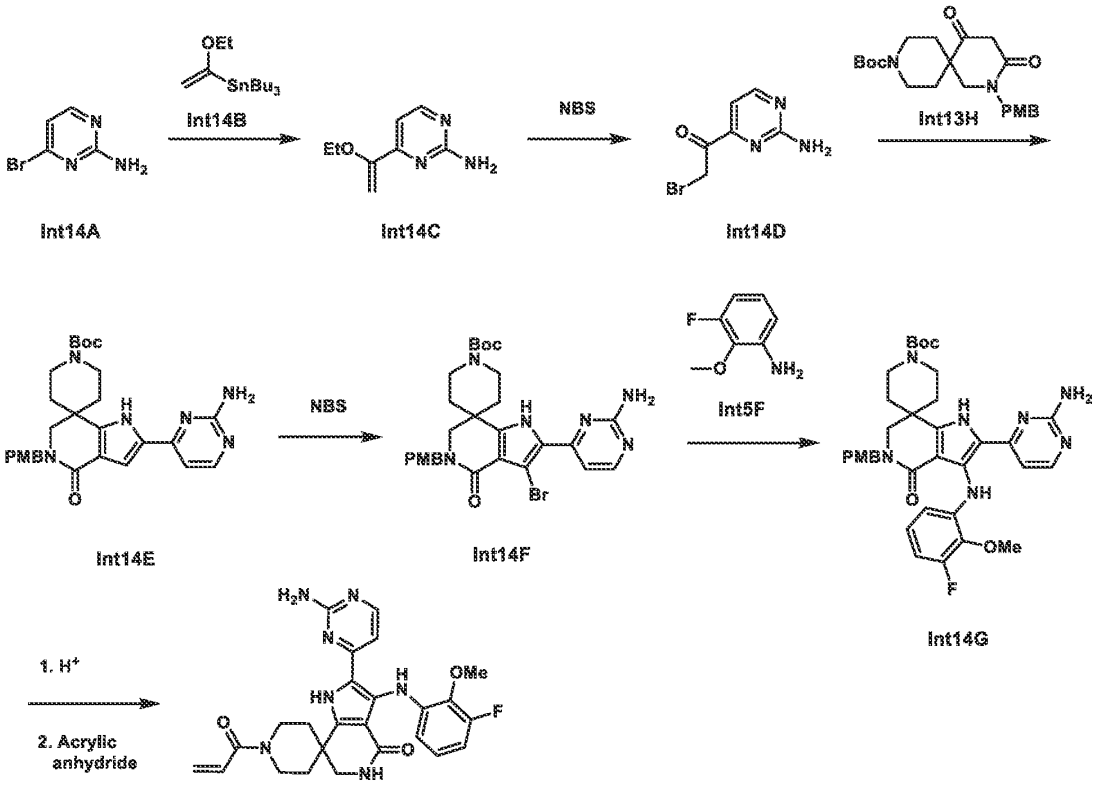
Example 13: Synthesis of 1-acryloyl-3'-((3-fluoro-2-methoxyphenyl)amino)-2'-(6-methoxy-1,5-naphthyridin-4-yl)-5',6'-dihydrospiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'(1'H)-one **(Compound 160)**



Commercially available **Int13A** is condensed with Meldrum's acid **Int13B** in the presence of an orthoformate, e.g., triethylorthoformate in a polar protic solvent, e.g., EtOH at an elevated temperature, e.g., 78 °C to give **Int13C**. Cyclization of **Int13C** at an elevated temperature in a high boiling solvent, e.g., Dowtherm at 220 °C followed by treatment of the resulting phenol with triflic anhydride gives **Int13D**. Coupling of **Int13D** with **Int13E** under Heck conditions, e.g., $Pd(OAc)_2$ and dppp in the presence of a mild base, e.g., TEA with heating, e.g., at 80 °C in a polar aprotic solvent (e.g., DMF, DMA) gives **Int13F**. Bromination of **Int13F** with a brominating agent, e.g., NBS in a halogenated solvent, e.g., DCM at a reduced temperature, e.g., 0 °C affords **Int13G**. Tandem alkylation/cyclization to give pyrrole **Int13I** occurs by treatment of **Int13G** with **Int13H** in the presence of NH_4OAc in a polar protic solvent, e.g., EtOH at room temperature. Bromination of **Int13I** with a brominating agent, e.g., NBS in a halogenated solvent, e.g., DCM affords **Int13J**, which is coupled with **Int5F** under Buchwald conditions, e.g., $Pd_3(dba)_2$, Xphos in the presence of base, e.g., Cs_2CO_3 in a high boiling point aprotic solvent, e.g., Toluene at an

elevated temperature, e.g., 110 °C affords **Int13K**. Deprotection of **Int13K** with a strong acid, e.g., TFA or HCl followed by treatment with acrylic anhydride gives the title compound.

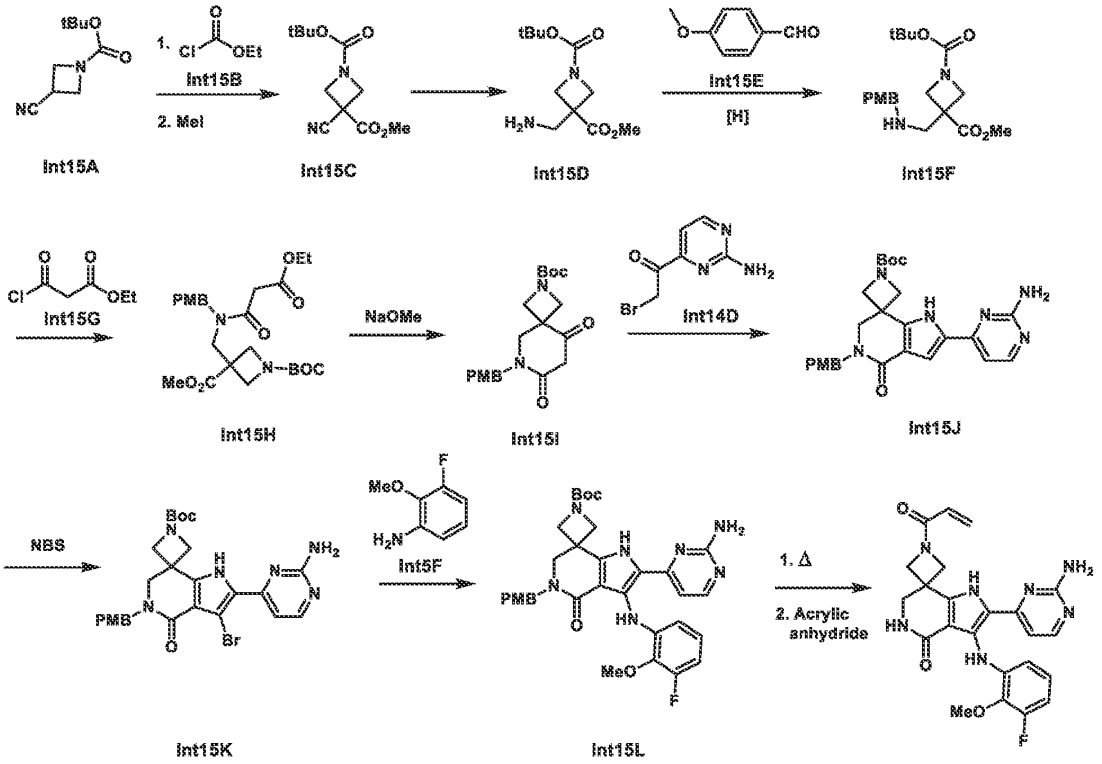
Example 14: Synthesis of 1-acryloyl-2'-(2-aminopyrimidin-4-yl)-3'-((3-fluoro-2-methoxyphenyl)amino)-5',6'-dihydrospiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'(1'H)-one **(Compound 162)**



Commercially available **Int14A** is coupled with commercially available **Int14B** under Stille conditions, e.g., $Pd(dppf)Cl_2$ in a polar aprotic solvent, e.g., DMF with mild heating to give **Int14C**. Treatment of **Int14C** with a brominating agent, e.g., NBS in a polar protic solvent mixture, e.g., THF-water affords **Int14D**. Tandem alkylation/cyclization to give pyrrole **Int14E** occurs by treatment of **Int14D** with **Int13H** in the presence of NH_4OAc in a polar protic solvent, e.g., EtOH at room temperature. Treatment of **Int14E** with a

brominating agent, e.g., NBS in a halogenated solvent, e.g., DCM at reduced temperature (e.g., 0 °C)affords **Int14F**, which is coupled with **Int5F** under Buchwald conditions, e.g., $Pd_3(dba)_2$, Xphos in the presence of base, e.g., Cs_2CO_3 in a high boiling point aprotic solvent, e.g., Toluene at an elevated temperature, e.g., 110 °C affords **Int14G**. Deprotection of **Int14G** with a strong acid, e.g., TFA or HCl followed by treatment with acrylic anhydride gives the title compound.

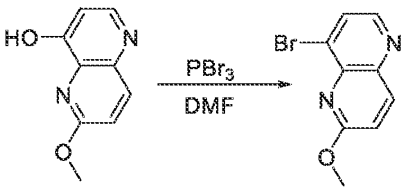
Example 15: Synthesis of 1-acryloyl-2'-(2-aminopyrimidin-4-yl)-3'-((3-fluoro-2-methoxyphenyl)amino)-5',6'-dihydrospiro[azetidine-3,7'-pyrrolo[3,2-c]pyridin]-4'(1'H)-one **(Compound 163)**



Reaction of **Int15A** and **Int15B** in the presence of a strong base, e.g., LiHMDS in a polar aprotic solvent, e.g., THF at reduced temperature (e.g., -78 °C), followed by methylation

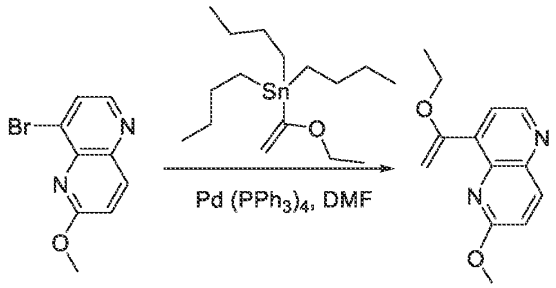
with MeI in the presence of a mild base, e.g., Cs_2CO_3 in a polar aprotic solvent (e.g., DMF) at reduced temperature, e.g., 0 °C- rt gives **Int15C**. Hydrogenation of **Int15C** in the presence of a catalyst, e.g., Pearlman's catalysts $Pd(OH)_2$ under a hydrogen atmosphere in a polar protic solvent, e.g., EtOH at room temperature gives **Int15D**. Protection of the amine with a PMB group occurs via treatment of **Int15D** with **Int15E** (4-methoxybenzaldehyde) followed by a mild reducing agent, e.g., $NaCNBH_3$ in a polar protic solvent, e.g., EtOH at elevated temperature (e.g., 45 °C) over several hours to give **Int15F**. Treatment of **Int15F** with **Int15G** under standard acylation conditions, e.g., pyridine, DMAP in a polar aprotic solvent, e.g., DCM at reduced temperature e.g., 0 °C gives **Int15H**. Dieckmann cyclization of **Int15H** with NaOMe in methanol at elevated temperature, e.g., 60 °C over several hours, followed by decarboxylation gives **Int15I**. Tandem alkylation/cyclization to give pyrrole **Int15J** occurs by treatment of **Int15I** with **Int14D** in the presence of NH_4OAc in a polar protic solvent, e.g., EtOH at room temperature. Treatment of **Int15J** with a brominating agent, e.g., NBS in a halogenated solvent, e.g., DCM at reduced temperature (e.g., 0 °C) affords **Int15K**, which is coupled with **Int5F** under Buchwald conditions, e.g., $Pd_3(dba)_2$, Xphos in the presence of base, e.g., Cs_2CO_3 in a high boiling point aprotic solvent, e.g., toluene at an elevated temperature, e.g., 110 °C to afford **Int15L**. Deprotection of **Int15L** via thermolysis of the BOC and PMB protecting groups by elevated heating (e.g., 140 °C) in a microwave in a high boiling point solvent, e.g., 1,3-xylene followed by treatment with acrylic anhydride under modified Schotten–Baumann conditions, e.g., TEA in the presence of water/THF at reduced temperature (e.g., 0 °C) gives the title compound.

Example 16. (S)-3-((3-chloro-2-methoxyphenyl)amino)-7-(2-fluoroethyl)-2-(6-methoxy-1,5-naphthyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(compound 744)**



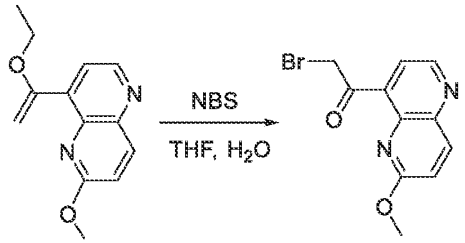
To a stirred mixture of 6-methoxy-1,5-naphthyridin-4-ol (2.0 g, 11.4 mmol, 1.0 equiv) in DMF (39.0 mL, 504 mmol, 44.4 equiv) was added PBr3 (1.1 mL, 11.6 mmol, 1.0 equiv) in portions at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for additional 1 h at 45 degrees C. The resulting mixture was cooled to rt. The precipitation was filtered out and washed with ether (100 mL). The filtrate cake was added water (50 mL) and NaOH (100 mL, 1 M), then extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (2x70 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtO/AcPE (5% to 60%) to afford 8-bromo-2-methoxy-1,5-naphthyridine (1.5 g, 46.0%) as a yellow solid.

LC-MS: M+H found: 239.0.



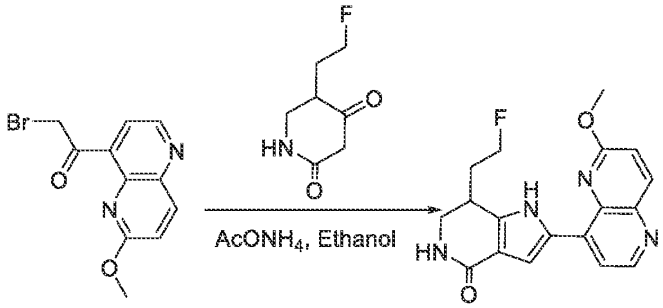
Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, were placed 8-bromo-2-methoxy-1,5-naphthyridine (5.0 g, 20.9 mmol, 1.0 equiv), DMF (60 mL), tributyl(1-ethoxyethenyl)stannane (9.06 g, 25.1 mmol, 1.2 equiv) and $Pd(PPh_3)_4$ (2.42 g, 2.09 mmol, 0.10 equiv) at ambient temperature. The resulting mixture was stirred for 16 h at 100 degrees C. The reaction progress was monitored by LCMS. The reaction was cooled to rt and then diluted by the addition of EA (300 mL). The resulting solution was washed with brine (3 x 200 mL) and the organic layers were combined, dried over anhydrous sodium sulfate, filtrated and the filtrate was concentrated in vacuo to dryness. The residue was applied onto a silica gel column chromatography with ethyl acetate/petroleum ether (0-8%). This resulted in 8-(1-ethoxyethenyl)-2-methoxy-1,5-naphthyridine (4.3 g, 93.9%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 231.1.



Into a 8-mL vial, were placed 8-(1-ethoxyethenyl)-2-methoxy-1,5-naphthyridine (1.0 g, 4.34 mmol, 1.0 equiv), THF (15 mL), water (1.5 mL) and NBS (0.77 g, 4.34 mmol, 1.0 equiv) at ambient temperature. The resulting mixture was stirred for 20 mins at rt. The reaction progress was monitored by LCMS. The reaction was then diluted by the addition of DCM (80 mL). The resulting solution was washed with the solution of $NaHCO_3$ in water (pH = 8) (3 x 50 mL) and the organic layers were combined, dried over anhydrous sodium sulfate, filtrated and the filtrate was concentrated in vacuo to dryness. This resulted in (1.0 g, crude) as a brown solid.

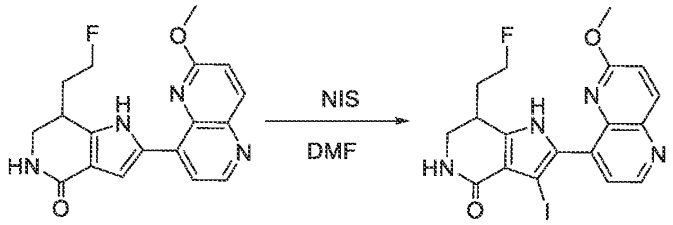
LC-MS: $(M+H)^+$ found: 281.0.



Into a 250-mL round-bottom flask, were placed tert-butyl 5-(2-fluoroethyl)-2,4-dioxopiperidine-1-carboxylate (1.0 g, 6.28 mmol, 1.0 equiv), EtOH (40 mL), 2-bromo-1-(6-methoxy-1,5-naphthyridin-4-yl)ethanone (1.77 g, 6.30 mmol, 1.0 equiv) and NH_4OAc (4.84 g, 62.8 mmol, 10.0 equiv) at ambient temperature. The resulting mixture was stirred for 2 h at rt and then 16 h at 50 degrees C. The reaction progress was monitored by LCMS. LCM showed 62% desired product. The reaction was then diluted by the addition of EA (300 mL). The resulting solution was extracted with brine (2 x 80 mL) and the organic layers were combined, dried over anhydrous sodium sulfate, filtrated and the filtrate was concentrated in vacuo to dryness. The residue was applied onto a silica gel column

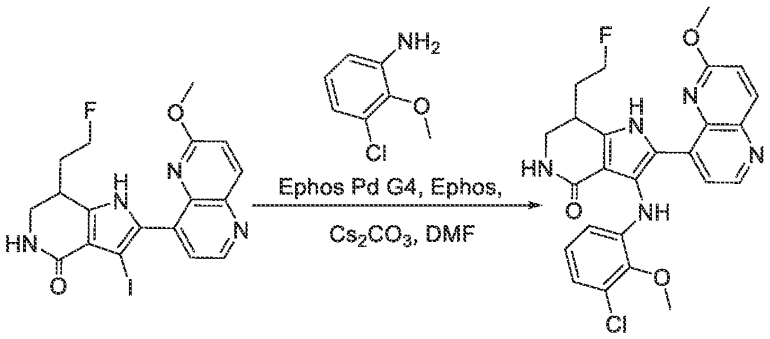
chromatography with dichloromethane/methanol (10/1). This resulted in 7-(2-fluoroethyl)-2-(6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (390 mg, 18.2%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 341.1.



Into a 50-mL round-bottom flask, were placed 7-(2-fluoroethyl)-2-(6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (370 mg, 1.09 mmol, 1.0 equiv), DMF (10 mL) and NIS (318 mg, 1.41 mmol, 1.30 equiv) at ambient temperature. The resulting mixture was stirred for 16 h at rt. The reaction progress was monitored by LCMS. LCMS showed 80% desired product. The reaction was then diluted by the addition of EA (150 mL). The resulting solution was washed with brine (3 x 70 mL) and the organic layers were combined, dried over anhydrous sodium sulfate, filtrated and the filtrate was concentrated in vacuo to dryness. The residue was applied onto a silica gel column chromatography with dichloromethane/methanol (10/1). This resulted in 7-(2-fluoroethyl)-3-iodo-2-(6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (254 mg, 50.1%) as a yellow solid.

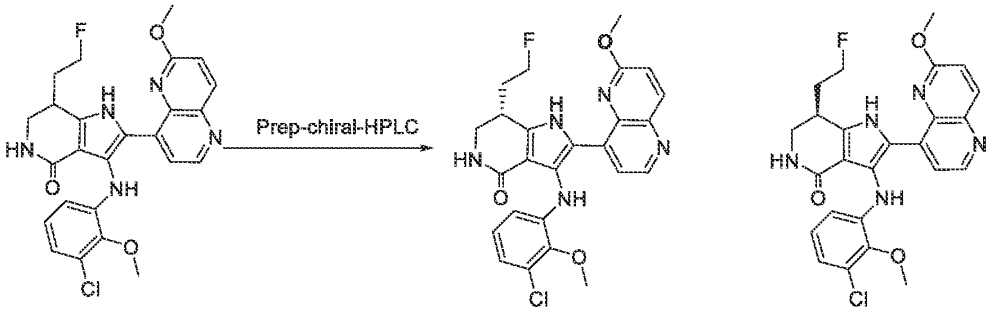
LC-MS: $(M+H)^+$ found: 467.0.



Into a 8-mL vial purged and maintained with an inert atmosphere of nitrogen, were placed

7-(2-fluoroethyl)-3-iodo-2-(6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (239 mg, 0.513 mmol, 1.0 equiv), DMF (10 mL), 3-chloro-2-methoxyaniline (88.9 mg, 0.564 mmol, 1.1 equiv), Ephos Pd G4 (188.3 mg, 0.205 mmol, 0.4 equiv), Ephos (109.7 mg, 0.205 mmol, 0.4 equiv) and Cs_2CO_3 (501 mg, 1.54 mmol, 3.0 equiv) at ambient temperature. The resulting mixture was stirred for 3 h at 50 oC. The reaction progress was monitored by LCMS. The reaction was then diluted by the addition of EA (150 mL). The resulting solution was washed with brine (3 x 80 mL) and the organic layers were combined, dried over anhydrous sodium sulfate, filtrated and the filtrate was concentrated in vacuo to dryness. The residue was applied onto a silica gel column chromatography with dichloromethane/methanol (10/1). This resulted in 3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-fluoroethyl)-2-(6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (240 mg, 94.4%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 496.1.



compound 744

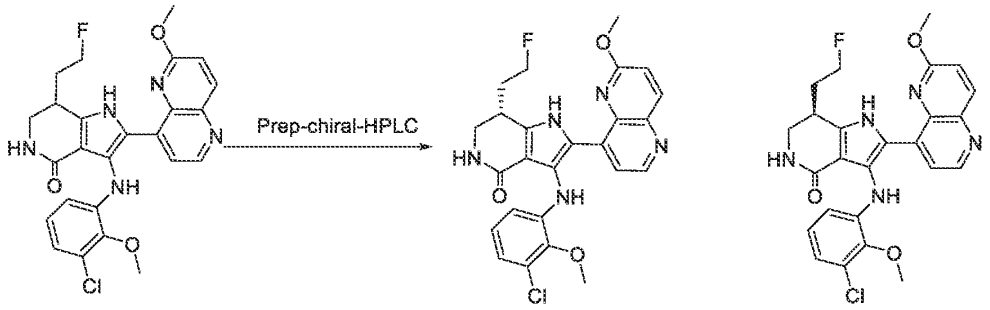
240 mg of 3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-fluoroethyl)-2-(6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one was purified by Chiral-Prep-HPLC. The collected fractions were combined and concentrated under vacuum. The residue was lyophilized to give (S)-3-((3-chloro-2-methoxyphenyl)amino)-7-(2-fluoroethyl)-2-(6-methoxy-1,5-naphthyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (Assumed) (57.9 mg, 0.038 mmol, 48.3 % yield) as a yellow solid.

LC-MS: $(M+H)^+$ found: 496.1.

^{1}H NMR (300 MHz, DMSO-d_6) 12.17 (s, 1H), 8.59 (d, J = 4.8 Hz, 1H), 8.31 (d, J = 9.1 Hz, 1H), 7.82 (s, 1H), 7.53 (d, J = 4.9 Hz, 1H), 7.37 (d, J = 9.1 Hz, 1H), 7.29 (s, 1H), 6.76-

6.61 (m, 2H), 6.17 (dd, *J* = 7.5, 2.2 Hz, 1H), 4.79-4.43 (m, 2H), 4.18 (s, 3H), 3.89 (s, 3H), 3.69-3.51 (m, 1H), 3.29-3.18 (m, 2H), 2.24-1.96 (m, 2H).

Example 17. (R)-3-((3-chloro-2-methoxyphenyl)amino)-7-(2-fluoroethyl)-2-(6-methoxy-1,5-naphthyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(compound 745)**



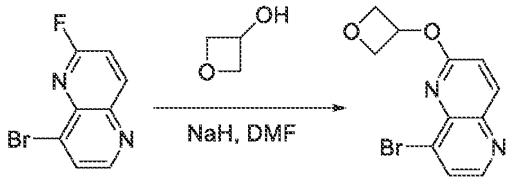
compound 745

240 mg of 3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-fluoroethyl)-2-(6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one was purified by Chiral-Prep-HPLC. The collected fractions were combined and concentrated under vacuum. The residue was lyophilized to give (R)-3-((3-chloro-2-methoxyphenyl)amino)-7-(2-fluoroethyl)-2-(6-methoxy-1,5-naphthyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (Assumed) (65.0 mg, 54.2% yield) as a yellow solid.

LC-MS: $(M+H)^+$ found: 496.1.

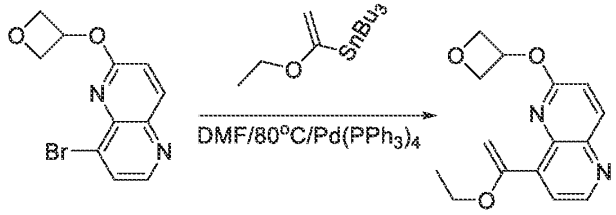
^{1}H NMR (300 MHz, DMSO-d_6) δ 12.17 (s, 1H), 8.59 (d, *J* = 4.8 Hz, 1H), 8.31 (d, *J* = 9.1 Hz, 1H), 7.82 (s, 1H), 7.53 (d, *J* = 4.9 Hz, 1H), 7.37 (d, *J* = 9.1 Hz, 1H), 7.29 (s, 1H), 6.76-6.61 (m, 2H), 6.17 (dd, *J* = 7.5, 2.2 Hz, 1H), 4.79-4.62 (m, 1H), 4.62-4.43 (m, 1H), 4.18 (s, 3H), 3.88 (s, 3H), 3.61 (d, *J* = 10.8 Hz, 1H), 3.33-3.14 (m, 2H), 2.24-1.96 (m, 2H).

Example 18. 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-[6-(oxetan-3-yloxy)-1,5-naphthyridin-4-yl]-5',6'-dihydro-1'H-spiro[cyclopropane-1,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 777)**



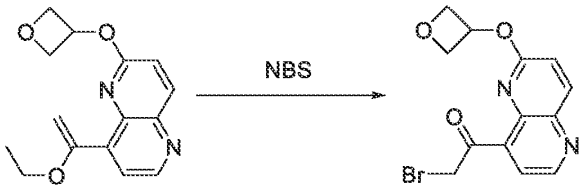
To a solution of cyclopropanol (767.46 mg, 13.213 mmol, 1.5 equiv) in THF (10 mL) was added NaH (704.67 mg, 17.618 mmol, 2 equiv, 60%) at 0 degrees C. The mixture was stirred for 15 min. 8-bromo-2-fluoro-1,5-naphthyridine (2 g, 8.809 mmol, 1.00 equiv) was added and the mixture was allowed to warm to RT and stirred for 2h. The reaction mixture was quenched by water and extracted with DCM (3*25 mL). The aqueous layer was extracted with EtOAc (3x10 mL).The residue was purified by silica gel column chromatography, eluted with PE/EA (10:1) to afford 8-bromo-2-cyclopropoxy-1,5-naphthyridine (1.7 g, 72.79%) as a yellow oil.

LC-MS: M+H found: 282.



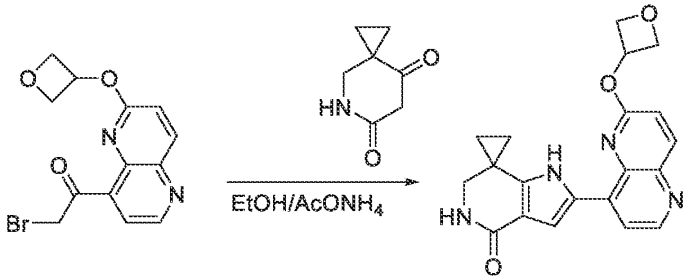
To a stirred solution of 8-bromo-2-(oxetan-3-yloxy)-1,5-naphthyridine (1 g, 3.557 mmol, 1.00 equiv) and tributyl(1-ethoxyethenyl)stannane (1.54 g, 4.268 mmol, 1.2 equiv) in 1,4-dioxane (20 mL) was added $Pd(PPh_3)_4$ (0.62 g, 0.534 mmol, 0.15 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 90°C under nitrogen atmosphere. Desired product could be detected by LCMS. The aqueous layer was extracted with EtOAc (3x10 mL). The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford 8-(1-ethoxyethenyl)-2-(oxetan-3-yloxy)-1,5-naphthyridine (780 mg, 80.52%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 273.



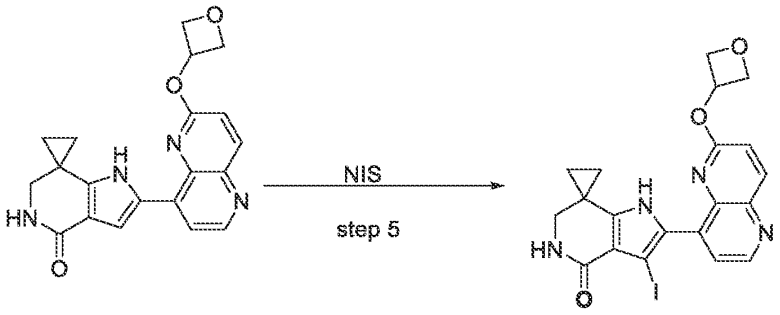
To a stirred solution of 8-(1-ethoxyethenyl)-2-(oxetan-3-yloxy)-1,5-naphthyridine (765 mg, 2.809 mmol, 1.00 equiv) in DMF (10 mL) was added NBS (500.02 mg, 2.809 mmol, 1 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under reduced pressure to afford 2-bromo-1-[6-(oxetan-3-yloxy)-1,5-naphthyridin-4-yl]ethanone (720 mg, 79.31%) as a yellow solid

LC-MS: $(M+H)^+$ found: 324.



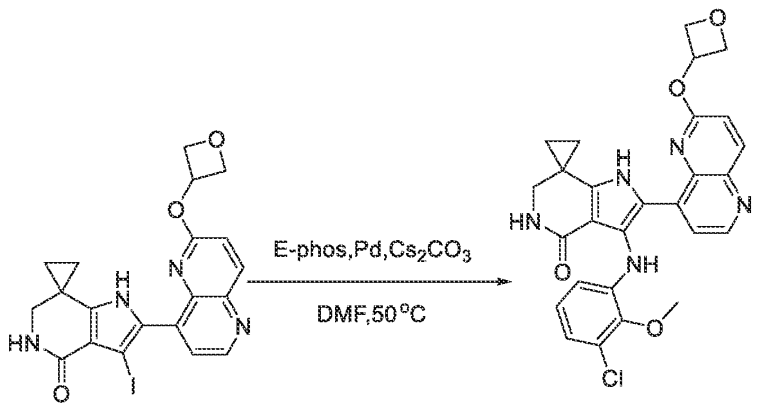
To a stirred solution of 5-azaspiro[2.5]octane-6,8-dione (10 mg, 0.072 mmol, 1.00 equiv) and $AcONH_4$ (33.24 mg, 0.432 mmol, 6 equiv) in EtOH (1 mL) was added 2-bromo-1-[6-(oxetan-3-yloxy)-1,5-naphthyridin-4-yl]ethanone (34.83 mg, 0.108 mmol, 1.5 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 50°C under nitrogen atmosphere. Desired product could be detected by LCMS. The aqueous layer was extracted with EtOAc (3x10 mL). The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 2'-[6-(oxetan-3-yloxy)-1,5-naphthyridin-4-yl]-5',6'-dihydro-1'H-spiro[cyclopropane-1,7'-pyrrolo[3,2-c]pyridin]-4'-one (1.2 g, 42.67%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 363.



To a stirred solution of 2'-[6-(oxetan-3-yloxy)-1,5-naphthyridin-4-yl]-5',6'-dihydro-1'H-spiro[cyclopropane-1,7'-pyrrolo[3,2-c]pyridin]-4'-one (900 mg, 2.484 mmol, 1.00 equiv) in DMF (15 mL) was added NIS (558.75 mg, 2.484 mmol, 1 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature under nitrogen atmosphere .Desired product could be detected by LCMS. The aqueous layer was extracted with EtOAc (3x10 mL).The resulting mixture was concentrated under reduced pressure to afford 3'-iodo-2'-[6-(oxetan-3-yloxy)-1,5-naphthyridin-4-yl]-5',6'-dihydro-1'H-spiro[cyclopropane-1,7'-pyrrolo[3,2-c]pyridin]-4'-one (870 mg, 71.74%) as a brown solid

LC-MS: $(M+H)^+$ found: 489.

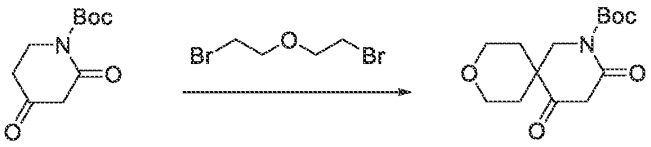


To a stirred mixture of 3'-iodo-2'-[6-(oxetan-3-yloxy)-1,5-naphthyridin-4-yl]-5',6'-dihydro-1'H-spiro[cyclopropane-1,7'-pyrrolo[3,2-c]pyridin]-4'-one (50 mg, 0.102 mmol, 1 equiv) and Cs_2CO_3 (66.73 mg, 0.204 mmol, 2 equiv) in DMF (10 mL) were added 3-chloro-2-methoxyaniline (19.37 mg, 0.122 mmol, 1.2 equiv) and EPhos (10.95 mg, 0.020 mmol, 0.2 equiv) and EPhos Pd G4 (9.41 mg, 0.010 mmol, 0.1 equiv) in portions at room

temperature under nitrogen atmosphere.The resulting mixture was stirred for 3h at 50 degrees C under nitrogen atmosphere.The aqueous layer was extracted with EtOAc (3x10 mL).The resulting mixture was concentrated under reduced pressure.The residue was purified by reverse flash chromatography to afford 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-[6-(oxetan-3-yloxy)-1,5-naphthyridin-4-yl]-5',6'-dihydro-1'H-spiro[cyclopropane-1,7'-pyrrolo[3,2-c]pyridin]-4'-one (6.1 mg, 11.50%) as a yellow solid with the following conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 10 min; detector, UV 254 nm.

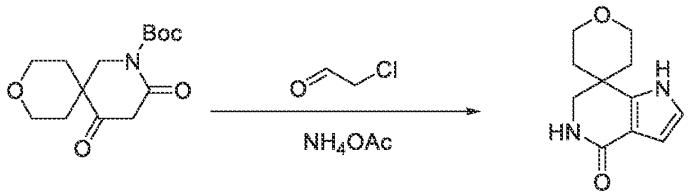
^{1}H NMR (300 MHz, Chloroform-d) δ 11.57 (s, 1H), 8.84 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 7.37 (d, J = 7.9 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.67 (t, J = 7.9 Hz, 1H), 6.12 (d, J = 7.5 Hz, 1H), 5.88 (s, 1H), 5.67 (s, 1H), 5.11 (s, 2H), 4.94 (s, 2H), 4.14 (s, 3H), 3.55 (s, 2H), 1.38 (s, 4H), 1.28 (s, 1H).

Example 19. 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[oxane-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 778)**



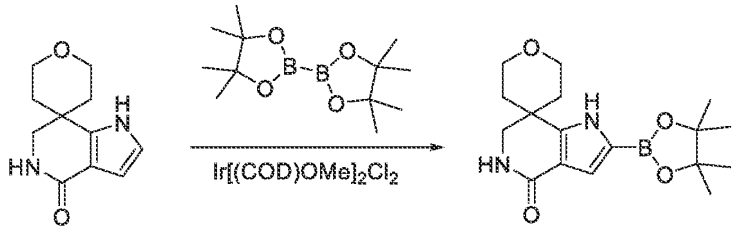
To a solution of tert-butyl 2,4-dioxopiperidine-1-carboxylate (40 g, 187.588 mmol, 1.00 equiv), in dry THF (600 mL) and cooled to -20 degrees C under nitrogen, LiHMDS (188.33 g, 1125.528 mmol, 6 equiv) (0.47 mL of 1 M solution in THF) was added dropwise. After 20 min stirring, 1-bromo-2-(2-bromoethoxy)ethane (174.02 g, 750.352 mmol, 4 equiv) were added and the solution was stirred at -20 °C for 5 hours. The mixture was neutralized to pH 7 with 5% aq $KHSO_4$. The aqueous layer was extracted with DCM (5x1000 mL). The collected organic layers were washed with water, dried over Na2SO4 and evaporated to dryness. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford tert-butyl 3,5-dioxo-9-oxa-2-azaspiro[5.5]undecane-2-carboxylate (5 g, 9.41%) as a light yellow solid.

LC-MS: M+H found: 284.



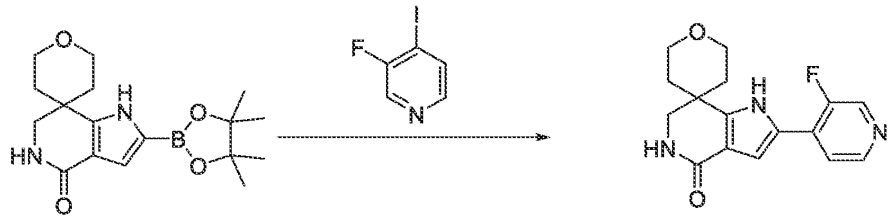
A solution of tert-butyl 3,5-dioxo-9-oxa-2-azaspiro[5.5]undecane-2-carboxylate (1.2 g, 4.235 mmol, 1.00 equiv) and chloroacetaldehyde (0.83 g, 4.235 mmol, 1 equiv), NH_4OAc (8.16 g, 105.875 mmol, 25 equiv) in EtOH (12 mL, 206.562 mmol, 48.77 equiv) was stirred for 24h at 80 degrees C. The aqueous layer was extracted with EA (3x200 mL). The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water; detector, UV 254 nm to afford 5',6'-dihydro-1'H-spiro[oxane-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (600 mg, 68.69%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 207.



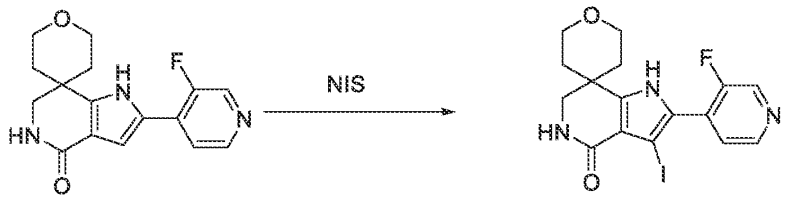
To a solution of 5',6'-dihydro-1'H-spiro[oxane-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (285 mg, 1.382 mmol, 1.00 equiv) and bis(pinacolato)diboron (701.81 mg, 2.764 mmol, 2 equiv) in dioxane (5 mL, 59.020 mmol, 42.71 equiv) were added 4,4'-di-tert-butyl-2,2'-dipyridyl (22.25 mg, 0.083 mmol, 0.06 equiv) and (1,5-cyclooctadiene) (methoxy)iridium (I) dimer (27.48 mg, 0.041 mmol, 0.03 equiv). After stirring for overnight at 50 degrees C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

LC-MS: $(M+H)^+$ found: 333.



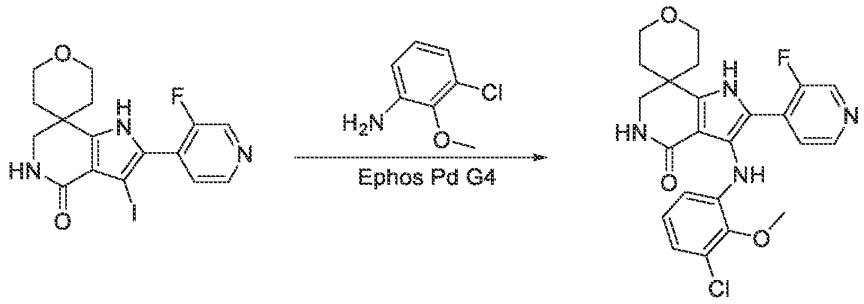
To a solution of 2'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5',6'-dihydro-1'H-spiro[oxane-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (1.1 g, 3.311 mmol, 1.00 equiv) and 3-fluoro-4-iodopyridine (0.81 g, 3.642 mmol, 1.1 equiv) in dioxane (15 mL, 177.061 mmol, 53.47 equiv) were added K_2CO_3 (1.37 g, 9.933 mmol, 3 equiv) and $Pd(dppf)Cl_2$ (0.24 g, 0.331 mmol, 0.1 equiv). After stirring for 3h at 80 degrees C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The aqueous layer was extracted with EA (8x100 mL). The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water; detector, UV 254 nm to afford 2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[oxane-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (280 mg, 28.06%) as a brown solid.

LC-MS: $(M+H)^+$ found: 302.



A solution of 2'-(3-hydroxypyridin-4-yl)-5',6'-dihydro-1'H-spiro[oxane-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (220 mg, 0.735 mmol, 1.00 equiv) and (iodoamino)sulfanyl (127.13 mg, 0.735 mmol, 1 equiv) in DMF (5 mL, 64.609 mmol, 87.91 equiv) was stirred for 1h at rt. The aqueous layer was extracted with EA (8x100 mL). This resulted in 2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[oxane-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (310 mg, 98.73%) as a brown oil.

LC-MS: $(M+H)^+$ found: 428.

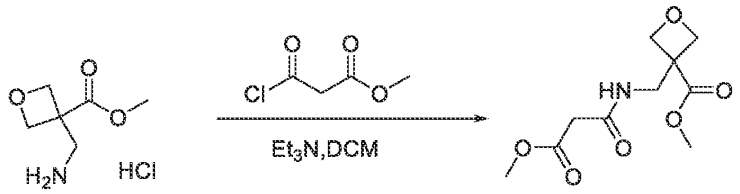


To a solution of 2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[oxane-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (200 mg, 0.468 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (88.54 mg, 0.562 mmol, 1.2 equiv) in DMF (8 mL, 103.374 mmol, 220.82 equiv) were added Cs_2CO_3 (305.06 mg, 0.936 mmol, 2 equiv), EPhos (50.07 mg, 0.094 mmol, 0.2 equiv) and EPhos Pd G4 (43.00 mg, 0.047 mmol, 0.1 equiv). After stirring for 2h at 50 degrees C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The aqueous layer was extracted with EA (5x50 mL). The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water; detector, UV 254 nm to afford 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[oxane-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (24.4 mg, 11.32%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 457.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.46 (s, 1H), 8.49 (d, J = 2.6 Hz, 1H), 8.34 (dd, J = 5.1, 1.2 Hz, 1H), 7.66 (s, 1H), 7.48 (dd, J = 6.7, 5.0 Hz, 1H), 7.30 (s, 1H), 6.68 – 6.57 (m, 2H), 6.09 (dd, J = 7.6, 2.1 Hz, 1H), 3.84 (s, 5H), 3.61 – 3.47 (m, 4H), 2.13 (td, J = 13.0, 4.8 Hz, 2H), 1.63 (d, J = 13.3 Hz, 2H).

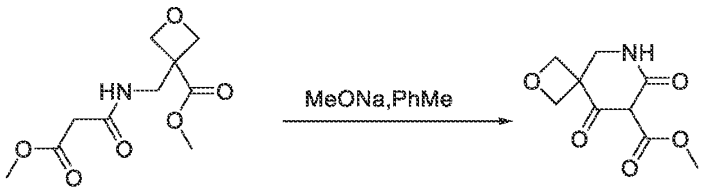
Example 20. 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[oxetane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 748)**



To a stirred mixture of methyl 3-(aminomethyl)oxetane-3-carboxylate hydrochloride (4

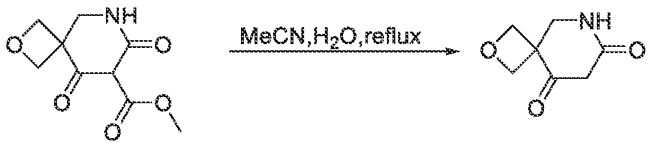
g, 22.024 mmol, 1 equiv) and Et3N (6.68 g, 66.072 mmol, 3 equiv) in DCM (50 mL) was added methyl 3-chloro-3-oxopropanoate (3 g, 22.024 mmol, 1 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was extracted with CH_2Cl_2 (2 x 250 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. to afford methyl 3-[(3-methoxy-3-oxopropanamido)methyl]oxetane-3-carboxylate (5 g, 92.58%) as a light yellow oil.

LC-MS: M+H found: 246.



To a stirred mixture of methyl 3-[(3-methoxy-3-oxopropanamido)methyl]oxetane-3-carboxylate (5 g, 20.389 mmol, 1 equiv) in MeOH (20 mL) in Toluene (30 mL) was added MeONa (2.20 g, 40.778 mmol, 2 equiv) portion-wise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80°C under nitrogen atmosphere. The mixture was acidified to pH 7. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (10:1) to afford methyl 7,9-dioxo-2-oxa-6-azaspiro[3.5]nonane-8-carboxylate (2 g, 46.01%) as an off-white solid.

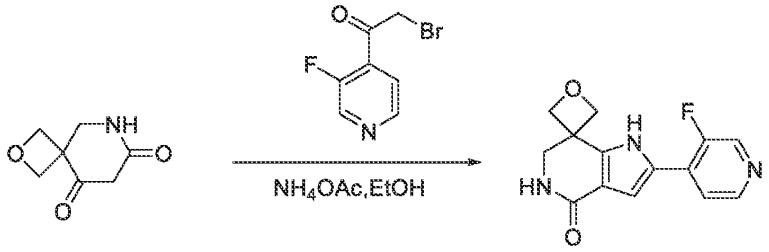
LC-MS: $(M+H)^+$ found: 214.



A mixture of methyl 7,9-dioxo-2-oxa-6-azaspiro[3.5]nonane-8-carboxylate (2 g, 9.381 mmol, 1 equiv) and H_2O (2 mL) in MeCN (20 mL) was stirred for 5 h at 90°C under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure to afford 2-oxa-6-azaspiro[3.5]nonane-7,9-dione (1.4 g, 96.18%) as a yellow solid. The crude product was used in the next step

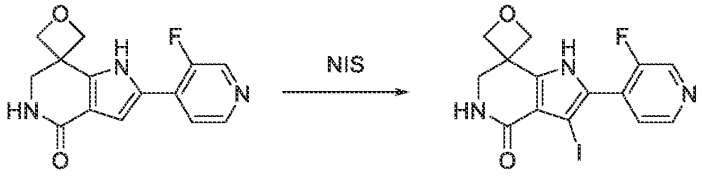
directly without further purification.

LC-MS: $(M+H)^+$ found 156.



To a stirred mixture of 2-oxa-6-azaspiro[3.5]nonane-7,9-dione (1.4 g, 9.023 mmol, 1 equiv) and 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (1.97 g, 9.023 mmol, 1 equiv) in EtOH (15 mL) was added EtOAc (3.18 g, 36.092 mmol, 4 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 50°C under nitrogen atmosphere. The resulting mixture was extracted with EtOAc (2 x 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm. to afford 2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[oxetane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (150 mg, 6.08%) as a yellow solid.

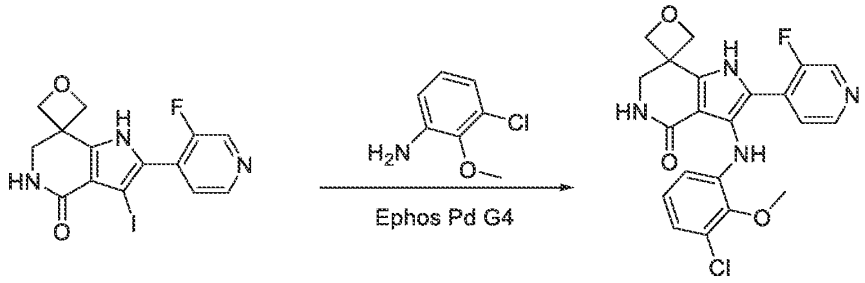
LC-MS: $(M+H)^+$ found: 274.



To a stirred mixture of 2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[oxetane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (150 mg, 0.549 mmol, 1.00 equiv) in DMF (3 mL) was added NIS (123.50 mg, 0.549 mmol, 1 equiv) slowly at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The residue was purified by reverse flash chromatography with the following conditions:

column, silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm. to afford 2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[oxetane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (65 mg, 29.67%) as a yellow solid.

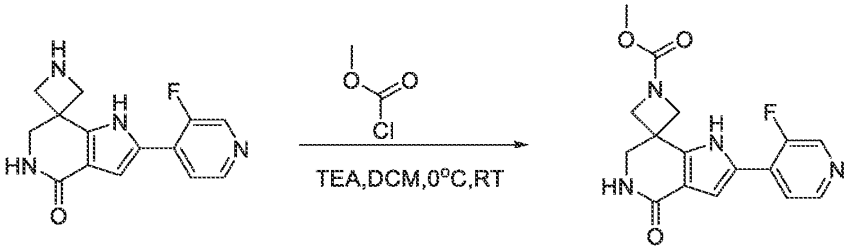
LC-MS: $(M+H)^+$ found: 400.



Into a 2 mL sealed tube were added 2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[oxetane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (60 mg, 0.150 mmol, 1.00 equiv),3-chloro-2-methoxyaniline (28.43 mg, 0.180 mmol, 1.2 equiv), Ephos Pd G4 (20.71 mg, 0.022 mmol, 0.15 equiv), EPhos (24.12 mg, 0.045 mmol, 0.3 equiv), Cs_2CO_3 (97.95 mg, 0.300 mmol, 2 equiv), and DMF (2 mL) at room temperature. The resulting mixture was stirred for 2 h at 50 degrees C under nitrogen atmosphere. Desired product could be detected by LCMS. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 60% gradient in 15 to afford 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[oxetane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (11.1 mg, 17.03%) as a white solid.

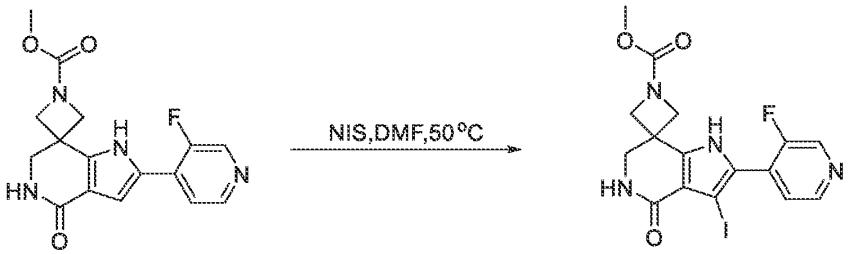
^{1}H NMR (300 MHz, DMSO-d6) δ 3.75 (d, 2H), 3.83 (s, 3H), 4.51 (d, 2H), 4.96 (d, 2H), 6.11 (dd, 1H), 6.55 – 6.70 (m, 2H), 7.38 (s, 1H), 7.49 – 7.59 (m, 2H), 8.38 (dd, 1H), 8.51 (d, 1H), 12.12 (s, 1H).

Example 21. methyl 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate **(compound 490)**



To a stirred mixture of 2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (200 mg, 0.735 mmol, 1.00 equiv) and TEA (222.98 mg, 2.205 mmol, 3 equiv) in DCM (5 mL) was added methyl chloroformate (83.29 mg, 0.882 mmol, 1.2 equiv) dropwise at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of Water at 0 degrees C. The resulting mixture was concentrated under reduced pressure.The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 30% gradient in 30 min; detector, UV 220 nm. This resulted in methyl 2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (120 mg, 49.46%) as a white solid.

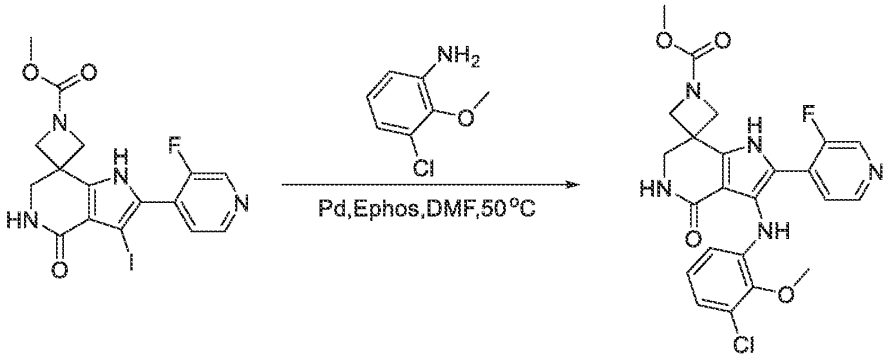
LC-MS: M+H found: 331.



A mixture of methyl 2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c] pyridine]-1-carboxylate (140 mg, 0.424 mmol, 1.00 equiv) and NIS (104.89 mg, 0.466 mmol, 1.1 equiv) in DMF (3 mL) was stirred for overnight at room temperature under nitrogen atmosphere. The resulting mixture was washed with water. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 /

MeOH 20:1) to afford methyl 2'-(3-fluoropyridin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c] pyridine]-1-carboxylate (66 mg, 34.13%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 457.



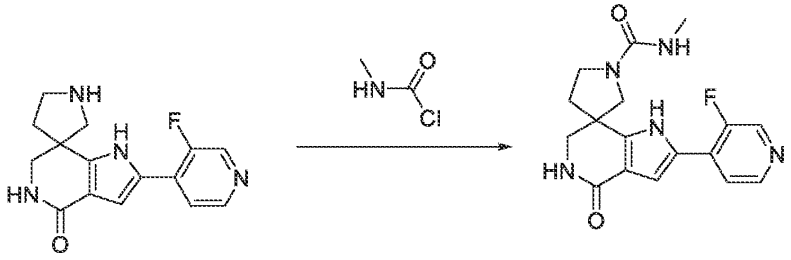
A mixture of methyl 2'-(3-fluoropyridin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (60 mg, 0.132 mmol, 1.00 equiv), 3-chloro-2-methoxyaniline (31.09 mg, 0.198 mmol, 1.5 equiv), EPhos Pd G4 (12.08 mg, 0.013 mmol, 0.1 equiv), EPhos (14.07 mg, 0.026 mmol, 0.2 equiv), and Cs_2CO_3 (128.55 mg, 0.396 mmol, 3 equiv) in DMF (2 mL) was stirred for 1 h at 50 degrees C under nitrogen atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 30 min; detector, UV 254 nm. This resulted in methyl 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (27 mg, 42.25%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 486.

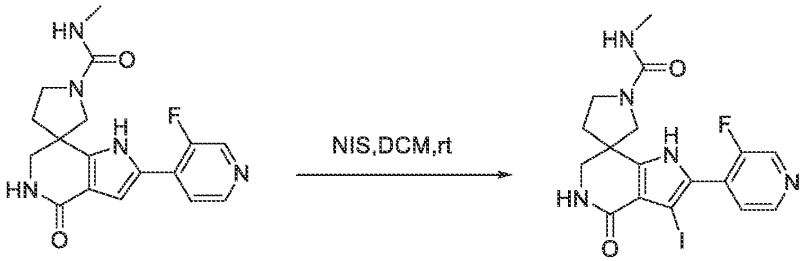
^1H NMR (300 MHz, Chloroform-d) δ 9.74 (d, J = 6.9 Hz, 1H), 8.48 (d, J = 3.6 Hz, 1H), 8.19 (d, J = 5.2 Hz, 1H), 7.56 (s, 1H), 7.37 (dd, J = 7.0, 5.2 Hz, 1H), 6.75 (dd, J = 8.1, 1.5 Hz, 1H), 6.62 (t, J = 8.1 Hz, 1H), 6.16 (dd, J = 8.1, 1.5 Hz, 1H), 5.65 (s, 1H), 4.27 (d, J =

8.9 Hz, 2H), 4.06 (d, J = 19.8 Hz, 5H), 3.74 (d, J = 16.8 Hz, 5H).

Example 22. (3S)-3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-N-methyl-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxamide **(compound 500)**

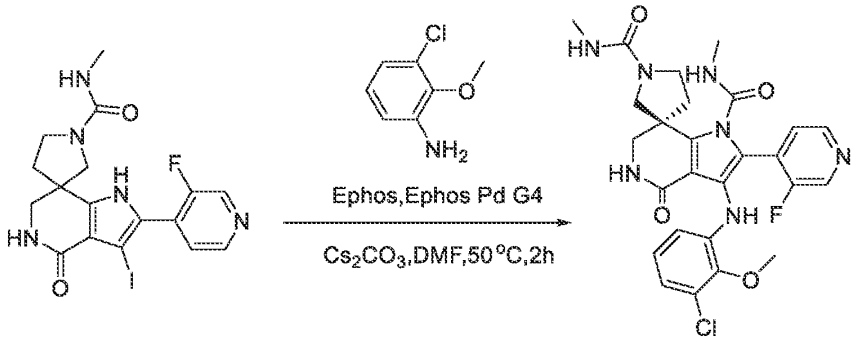


To a stirred mixture of 2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (1 g, 3.493 mmol, 1 equiv) and N-methylcarbamoyl chloride (0.33 g, 3.493 mmol, 1 equiv) in DCM (20 mL) was added TEA (2.43 mL, 17.465 mmol, 5 equiv) in portions at room temperature .The resulting mixture was stirred for 1 h at room temperature .The resulting mixture was concentrated under reduced pressure.The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 100% gradient in 10 min; detector, UV 254 nm.This resulted in 2'-(3-fluoropyridin-4-yl)-N-methyl-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxamide (500 mg, 41.69%) as a yellow solid.



To a stirred mixture of 2'-(3-fluoropyridin-4-yl)-N-methyl-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxamide (400 mg, 1.165 mmol, 1 equiv) in DCM (10 mL) was added NIS (262.10 mg, 1.165 mmol, 1 equiv) in portions at room temperature.The resulting mixture was stirred for 2 h at room temperature. The

resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 100% gradient in 10 min; detector, UV 254 nm. This resulted in 2'-(3-fluoropyridin-4-yl)-3'-iodo-N-methyl-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxamide (260 mg, 47.56%) as a light yellow solid.

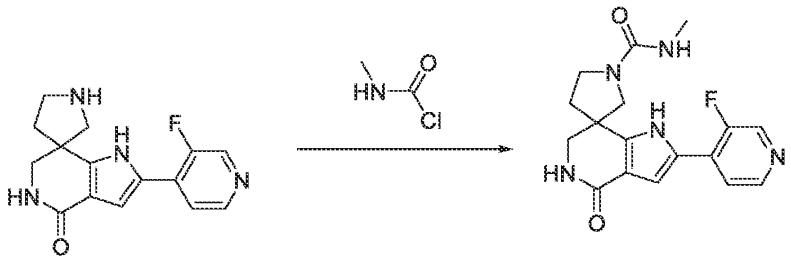


To a stirred mixture of 2'-(3-fluoropyridin-4-yl)-3'-iodo-N-methyl-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxamide (100 mg, 0.213 mmol, 1 equiv) and 3-chloro-2-methoxyaniline (33.58 mg, 0.213 mmol, 1 equiv) in DMF (5 mL) were added Cs_2CO_3 (138.87 mg, 0.426 mmol, 2 equiv), EPhos (22.79 mg, 0.043 mmol, 0.2 equiv)and EPhos Pd G4 (78.30 mg, 0.085 mmol, 0.4 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 50° C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 100% gradient in 20 min; detector, UV 254 nm.The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 17 min; Wave Length: 220/254 nm; RT1(min): 7.27; RT2(min): 13.92; Sample Solvent: ETOH: DCM=1: 1; Injection Volume: 1 mL; Number Of Runs: 8) to afford (3S)-3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-N-methyl-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxamide (39.1 mg, 33.35%) as a white solid.

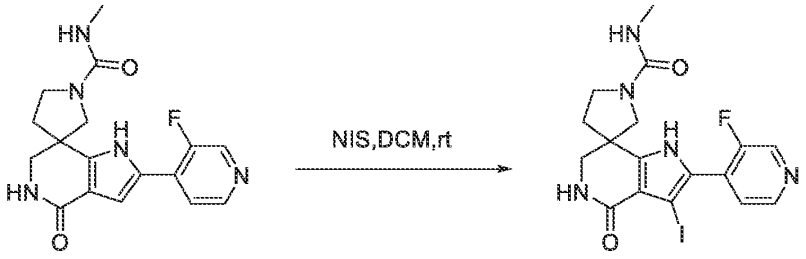
LC-MS: M+H found: 499.

^{1}H NMR (400 MHz, Chloroform-d) δ 9.25 (d, J = 8.6 Hz, 1H), 8.49 – 8.40 (m, 1H), 8.18 (dd, J = 5.3, 1.3 Hz, 1H), 7.59 (s, 1H), 7.33 (dd, J = 7.1, 5.3 Hz, 1H), 6.77 (dd, J = 8.1, 1.5 Hz, 1H), 6.64 (t, J = 8.1 Hz, 1H), 6.18 (dd, J = 8.2, 1.5 Hz, 1H), 5.47 (s, 1H), 4.34 (d, J = 4.9 Hz, 1H), 4.05 (s, 3H), 3.71 (d, J = 10.6 Hz, 1H), 3.68 – 3.47 (m, 4H), 3.47 – 3.33 (m, 1H), 2.89 – 2.80 (m, 3H), 2.42 – 2.31 (m, 1H), 2.26 (ddd, J = 12.9, 7.8, 5.0 Hz, 1H), 1.25 (s, 1H).

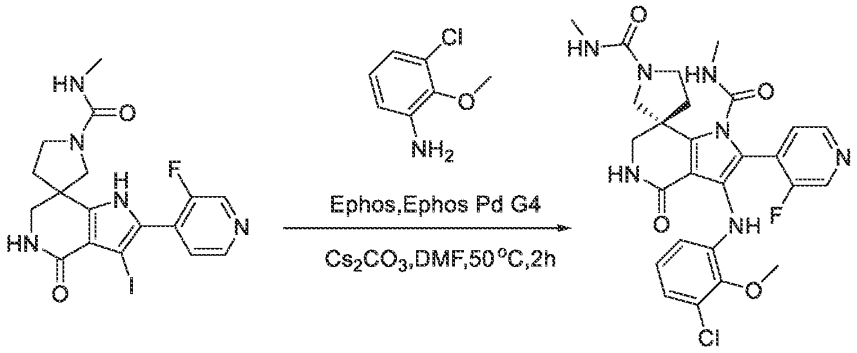
Example 23. (3R)-3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-N-methyl-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxamide **(compound 499)**



To a stirred mixture of 2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (1 g, 3.493 mmol, 1 equiv) and N-methylcarbamoyl chloride (0.33 g, 3.493 mmol, 1 equiv) in DCM (20 mL) was added TEA (2.43 mL, 17.465 mmol, 5 equiv) in portions at room temperature. The resulting mixture was stirred for 1 h at room temperature .The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 100% gradient in 10 min; detector, UV 254 nm. This resulted in 2'-(3-fluoropyridin-4-yl)-N-methyl-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxamide (500 mg, 41.69%) as a yellow solid.



To a stirred mixture of 2'-(3-fluoropyridin-4-yl)-N-methyl-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxamide (400 mg, 1.165 mmol, 1 equiv) in DCM (10 mL) was added NIS (262.10 mg, 1.165 mmol, 1 equiv) in portions at room temperature.The resulting mixture was stirred for 2 h at room temperature.The resulting mixture was concentrated under vacuum.The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 100% gradient in 10 min; detector, UV 254 nm.This resulted in 2'-(3-fluoropyridin-4-yl)-3'-iodo-N-methyl-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxamide (260 mg, 47.56%) as a light yellow solid.



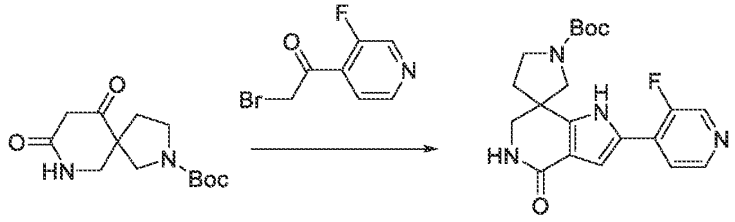
To a stirred mixture of 2'-(3-fluoropyridin-4-yl)-3'-iodo-N-methyl-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxamide (100 mg, 0.213 mmol, 1 equiv) and 3-chloro-2-methoxyaniline (33.58 mg, 0.213 mmol, 1 equiv) in DMF (5 mL) were added Cs2CO3 (138.87 mg, 0.426 mmol, 2 equiv), EPhos (22.79 mg, 0.043 mmol, 0.2 equiv)and EPhos Pd G4 (78.30 mg, 0.085 mmol, 0.4 equiv) in portions at room temperature under nitrogen atmosphere.The resulting mixture was stirred for 2h at 50° C under nitrogen atmosphere.The resulting mixture was concentrated under vacuum.The residue was purified by reverse flash chromatography with the following conditions:

column, C18 silica gel; mobile phase, MeCN in water, 0% to 100% gradient in 20 min; detector, UV 254 nm.The crude product (100mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 17 min; Wave Length: 220/254 nm; RT1(min): 7.27; RT2(min): 13.92; Sample Solvent: ETOH: DCM=1: 1; Injection Volume: 1 mL; Number Of Runs: 8) to afford (3R)-3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-N-methyl-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxamide (24.8 mg, 23.11%) as a white solid.

LC-MS: M+H found: 499.

^{1}H NMR (400 MHz, Chloroform-d) δ 9.23 (d, J = 8.6 Hz, 1H), 8.46 (d, J = 3.9 Hz, 1H), 8.18 (dd, J = 5.3, 1.3 Hz, 1H), 7.59 (s, 1H), 7.33 (dd, J = 7.1, 5.2 Hz, 1H), 6.77 (dd, J = 8.1, 1.5 Hz, 1H), 6.65 (t, J = 8.1 Hz, 1H), 6.18 (dd, J = 8.1, 1.5 Hz, 1H), 5.44 (s, 1H), 4.33 (d, J = 4.9 Hz, 1H), 4.05 (s, 3H), 3.72 (d, J = 10.6 Hz, 1H), 3.68 – 3.49 (m, 4H), 3.42 (dd, J = 12.3, 3.1 Hz, 1H), 2.86 (d, J = 4.6 Hz, 3H), 2.42 – 2.31 (m, 1H), 2.26 (ddd, J = 13.0, 7.9, 4.9 Hz, 1H), 1.25 (s, 1H).

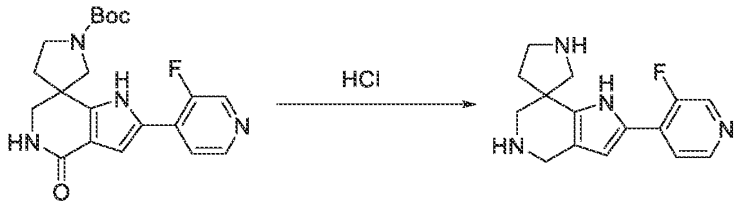
Example 24. methyl (3R)-3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate **(compound 498)**



To a stirred mixture of tert-butyl 8,10-dioxo-2,7-diazaspiro[4.5]decane-2-carboxylate (3 g, 11.181 mmol, 1 equiv) and 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (2.44 g, 11.181 mmol, 1 equiv) in EtOH (20mL) were added NH_4OAc (3.45 g, 44.724 mmol, 4 equiv). The resulting mixture was stirred for 2 h at 50 degrees. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.

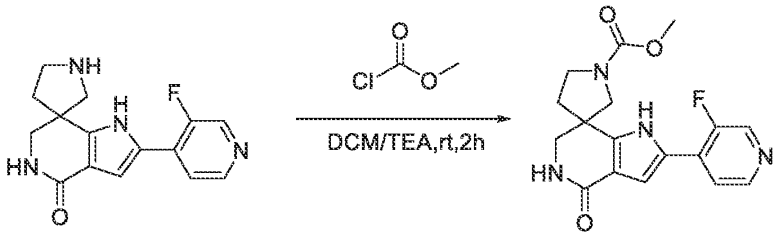
The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 100% gradient in 10 min; detector, UV 254 nm. This resulted in tert-butyl 2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (3.4 g, 78.69%) as a yellow solid.

LC-MS: M+H found: 387.2.



To a stirred mixture of tert-butyl 2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (3 g, 7.763 mmol, 1 equiv) was added HCl(gas) in 1,4-dioxane (50 mL) in portions at room temperature. The final reaction mixture was stirred for 2h. The resulting mixture was concentrated under reduced pressure. The residue was washed with water (2x10 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (2.5 g, 112.47%) as a yellow solid.

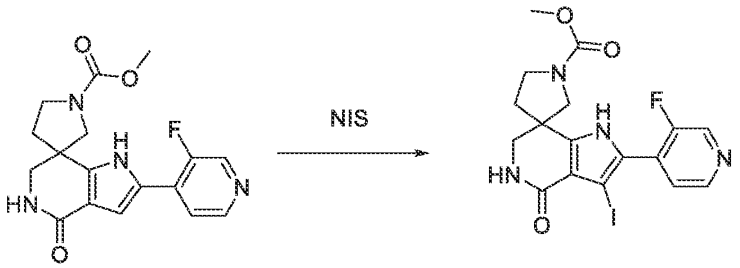
LC-MS: M+H found: 273.1.



A solution of 2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (500 mg, 1.746 mmol, 1.00 equiv) in DCM (10 mL) was treated with TEA (530.14 mg, 5.238 mmol, 3 equiv) for 30 min at 0°C under nitrogen atmosphere followed by the addition ofmethyl chloroformate (165.01 mg, 1.746 mmol, 1

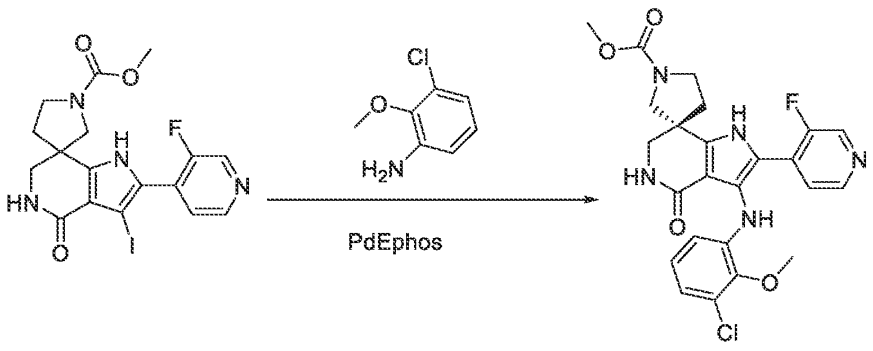
equiv) in portions at rt. The final reaction mixture was stirred for 1h. The resulting mixture was concentrated under vacuum. The aqueous layer was extracted with DCM (3x20 mL). The combined organic phase was concentrated under vacuum to afford methyl 2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (360 mg, 59.87%) as a yellow solid.

LC-MS: M+H found: 345.1.



To a stirred solution of methyl 2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (350 mg, 1.016 mmol, 1.00 equiv) in DMF (4 mL) was added NIS (274.41 mg, 1.219 mmol, 1.2 equiv) in portions at rt. The final reaction mixture was stirred for 3h at rt. The resulting mixture was extracted with EA (3 x 10mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous sodium sulphate. After filtration, the filtrate was concentrated under reduced pressure to afford methyl 2'-(3-fluoropyridin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (335 mg, 70.09%) as a brown yellow solid.

LC-MS: M+H found: 471.0.

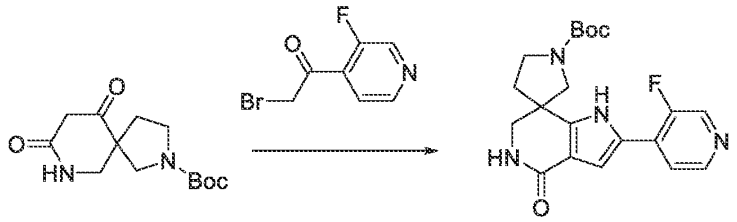


To a stirred solution of methyl 2'-(3-fluoropyridin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (310 mg, 0.659 mmol, 1.00 equiv), EPhos Pd G4 (60.55 mg, 0.066 mmol, 0.1 equiv) and EPhos (70.51 mg, 0.132 mmol, 0.2 equiv) in DMF (4 mL) were added Cs_2CO_3 (429.58 mg, 1.318 mmol, 2 equiv) and 3-chloro-2-methoxyaniline (124.67 mg, 0.791 mmol, 1.2 equiv) under N2 atmosphere. The final reaction mixture was stirred for 5h at 50 degrees. The precipitated solids were collected by filtration and washed with MeOH (3x1mL). The crude product was purified by Pre-Chriral HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 23 min; Wave Length: 220/254 nm; RT1(min): 12.71; RT2(min): 19.13; Sample Solvent: ETOH: DCM=1: 1; Injection Volume: 0.8 mL; Number Of Runs: 6) to afford methyl (3R)-3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (25.1 mg, 7.57%) as a white solid.

LC-MS: (M+H) found: 500.0.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.58 (s, 1H), 8.50 (d, J = 2.5 Hz, 1H), 8.35 – 8.28 (m, 1H), 7.62 (s, 1H), 7.52 – 7.44 (m, 1H), 7.38 (s, 1H), 6.69 – 6.54 (m, 2H), 6.11 (dd, J = 7.8, 1.8 Hz, 1H), 3.84 (s, 3H), 3.62 (s, 3H), 3.57 (d, J = 11.5 Hz, 3H), 3.44 (dd, J = 7.0, 5.1 Hz, 3H), 2.40 (s, 1H), 2.08 (s, 1H).

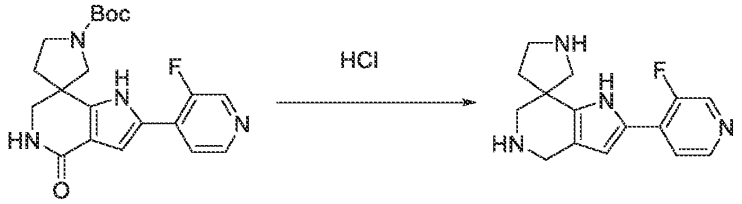
Example 25. methyl (3S)-3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate **(compound 497)**



To a stirred mixture of tert-butyl 8,10-dioxo-2,7-diazaspiro[4.5]decane-2-carboxylate (3 g, 11.181 mmol, 1 equiv) and 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (2.44 g, 11.181

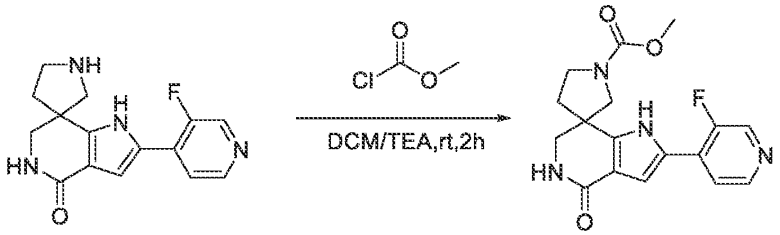
mmol, 1 equiv) in EtOH (20 mL) were added NH_4OAc (3.45 g, 44.724 mmol, 4 equiv). The resulting mixture was stirred for 2 h at 50°C. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 100% gradient in 10 min; detector, UV 254 nm. This resulted in tert-butyl 2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (3.4 g, 78.69%) as a yellow solid.

LC-MS: M+H found: 387.2.



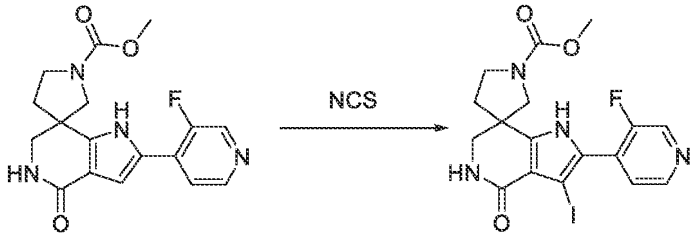
To a stirred mixture of tert-butyl 2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (3 g, 7.763 mmol, 1 equiv) was added HCl(gas) in 1,4-dioxane (50 mL) in portions at room temperature . The final reaction mixture was striied for 2h. The resulting mixture was concentrated under reduced pressure. The residue was washed with water (2x10 mL).The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (2.5 g, 112.47%) as a yellow solid.

LC-MS: M+H found: 273.1.



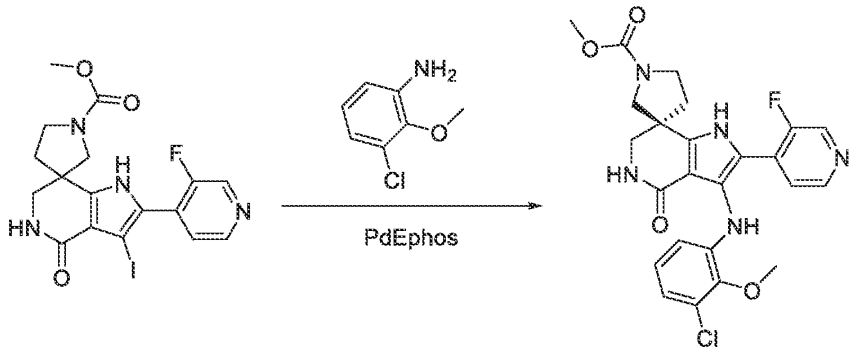
A solution of 2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (500 mg, 1.746 mmol, 1.00 equiv) in DCM (10 mL) was treated with TEA (530.14 mg, 5.238 mmol, 3 equiv) for 30 min at 0°C under nitrogen atmosphere followed by the addition of methyl chloroformate (165.01 mg, 1.746 mmol, 1 equiv) in portions at rt. The reaction mixture was stirred for 1h, then concentrated under vacuum. The aqueous layer was extracted with DCM (3x20 mL). The combined organic phase were concentrated under vacuum to afford methyl 2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (360 mg, 59.87%) as a yellow solid.

LC-MS: M+H found: 345.1.



To a stirred solution of methyl 2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (350 mg, 1.016 mmol, 1.00 equiv) in DMF (4 mL) was added NIS (274.41 mg, 1.219 mmol, 1.2 equiv) in portions at rt. The final reaction mixture was striied for 3h at rt. The resulting mixture was extracted with EA (3 x 10mL). The combined organic layers were washed with brine (3x30mL), dried over anhydrous sodium sulphate. After filtration, the filtrate was concentrated under reduced pressureto afford methyl 2'-(3-fluoropyridin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (335 mg, 70.09%) as a brown yellow solid.

LC-MS: M+H found: 471.0.



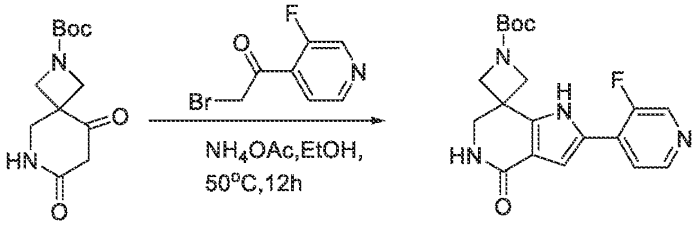
To a stirred solution of methyl 2'-(3-fluoropyridin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (310 mg, 0.659 mmol, 1.00 equiv), EPhos Pd G4 (60.55 mg, 0.066 mmol, 0.1 equiv), and EPhos (70.51 mg, 0.132 mmol, 0.2 equiv) in DMF (4 mL) were added Cs_2CO_3 (429.58 mg, 1.318 mmol, 2 equiv) and 3-chloro-2-methoxyaniline (124.67 mg, 0.791 mmol, 1.2 equiv) under N_2 atmosphere. The final reaction mixture was stirred for 5h at 50 degrees. The precipitated solids were collected by filtration and washed with MeOH (3x1mL). The crude product was purified by Pre-Chriral HPLC with the following conditions (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 23 min; Wave Length: 220/254 nm; RT1(min): 12.71; RT2(min): 19.13; Sample Solvent: ETOH: DCM=1: 1; Injection Volume: 0.8 mL; Number Of Runs: 6) to afford methyl (3S)-3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[pyrrolidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (25.7 mg, 7.74%) as a white solid.

LC-MS: $(M+H)^+$ found: 500.0.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.58 (s, 1H), 8.50 (d, J = 2.5 Hz, 1H), 8.34 (dd, J = 5.1, 1.1 Hz, 1H), 7.62 (s, 1H), 7.48 (t, J = 5.8 Hz, 1H), 7.38 (s, 1H), 6.68 – 6.57 (m, 2H), 6.11 (dd, J = 7.8, 1.9 Hz, 1H), 3.84 (s, 3H), 3.62 (s, 3H), 3.57 (d, J = 11.6 Hz, 3H), 3.44 (dd, J = 7.0, 5.1 Hz, 3H), 2.40 (s, 1H), 2.08 (s, 1H).

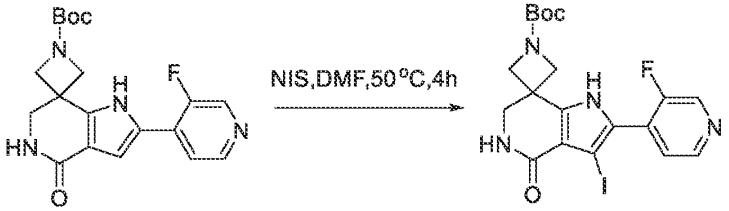
Example 26 3'-[(3-chloro-2-methoxyphenyl)amino]-1-(2,2-difluoroethyl)-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c]pyridin]-4'-one

(compound 519)



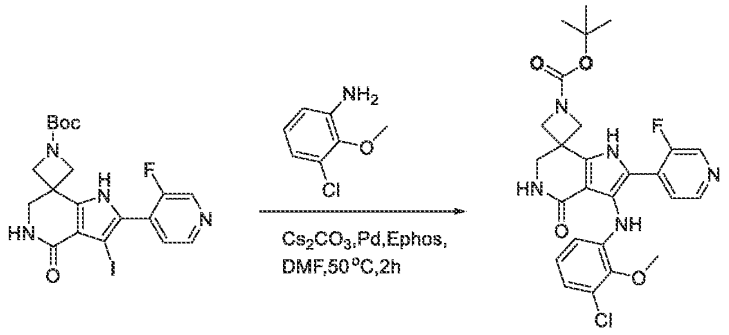
A mixture of tert-butyl 7,9-dioxo-2,6-diazaspiro[3.5]nonane-2-carboxylate (500 mg, 1.966 mmol, 1.00 equiv) and NH_4OAc (606.27 mg, 7.864 mmol, 4 equiv) in EtOH (10 mL) was stirred for overnight at 50 degrees C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with water. The precipitated solids were collected by filtration and washed with water. This resulted in tert-butyl 2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (470 mg, 64.19%) as a white solid.

LC-MS: M+H found: 373.



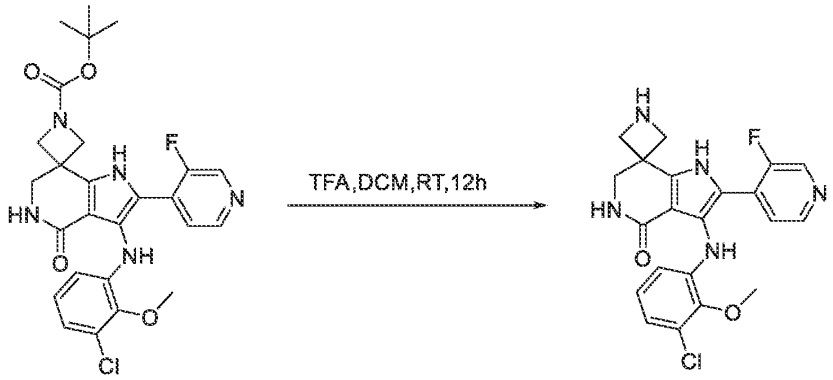
A mixture of tert-butyl 2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (300 mg, 0.806 mmol, 1.00 equiv) and NIS (199.37 mg, 0.887 mmol, 1.1 equiv) in DMF (6 mL) was stirred for overnight at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with CH2Cl2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 30 min; detector, UV 254 nm. This resulted in tert-butyl 2'-(3-fluoropyridin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (300 mg, 74.73%) as a white solid.

LC-MS: $(M+H)^+$ found: 499.

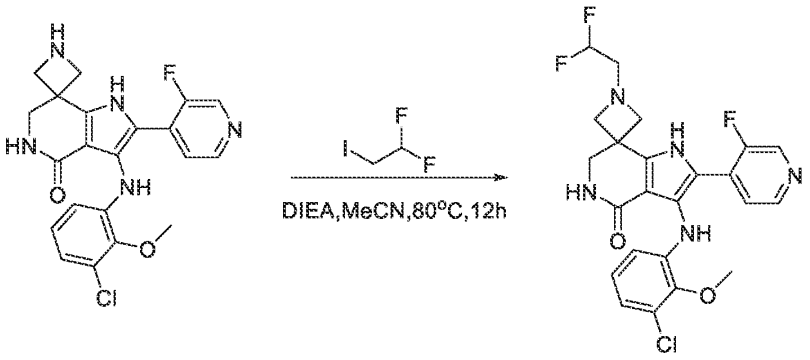


A mixture of tert-butyl 2'-(3-fluoropyridin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (300 mg, 0.602 mmol, 1.00 equiv), 3-chloro-2-methoxyaniline (142.32 mg, 0.903 mmol, 1.5 equiv), EPhos Pd G4 (55.30 mg, 0.060 mmol, 0.1 equiv), EPhos (64.39 mg, 0.120 mmol, 0.2 equiv) and Cs_2CO_3 (588.48 mg, 1.806 mmol, 3 equiv) in DMF (6 mL) was stirred for 1 h at 50 degrees C under nitrogen atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 30 min; detector, UV 254 nm. This resulted in tert-butyl 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (300 mg, 94.38%) as a white solid.

LC-MS: $(M+H)^+$ found: 528.



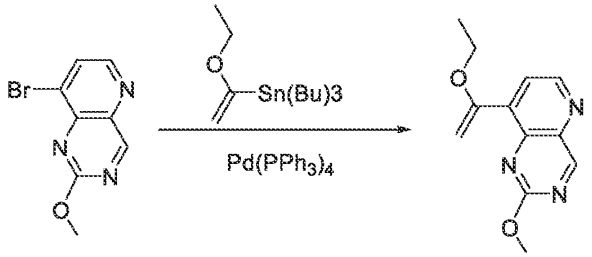
A mixture of tert-butyl 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (300 mg, 0.568 mmol, 1.00 equiv) in HCl(gas)in 1,4-dioxane (6 mL) was stirred for overnight at room temperature under air atmosphere. The resulting mixture was concentrated under reduced pressure. The mixture was basified to pH 8 with saturated $NaHCO_3$ (aq.). The precipitated solids were collected by filtration and washed with water. The crude product/ resulting mixture was used in the next step directly without further purification. This resulted in 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (200 mg, 82.27%) as a brown solid.
LC-MS: $(M+H)^+$ found: 428.



A mixture of 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (200 mg, 0.467 mmol, 1 equiv), 1,1-difluoro-2-iodoethane (107.67 mg, 0.560 mmol, 1.2 equiv), and DIEA (181.24 mg, 1.401 mmol, 3 equiv) in MeCN (4 mL) was stirred for overnight at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 30 min; detector, UV 254 nm. This resulted in 3'-[(3-chloro-2-methoxyphenyl)amino]-1-(2,2-difluoroethyl)-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[azetidine-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (50 mg, 21.64%) as a light yellow solid.
LC-MS: $(M+H)^+$ found: 492.

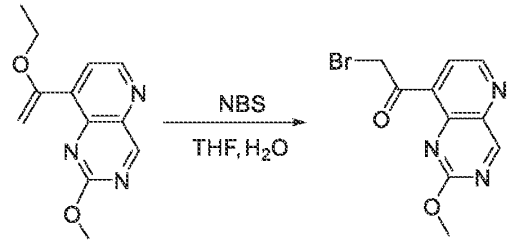
^{1}H NMR (300 MHz, Methanol-d4) δ 8.44 (d, J = 3.2 Hz, 1H), 8.24 (dd, J = 5.3, 0.9 Hz, 1H), 7.54 (dd, J = 6.7, 5.2 Hz, 1H), 6.73 – 6.48 (m, 2H), 6.27 – 5.77 (m, 2H), 4.03 – 3.79 (m, 9H), 3.36 (d, J = 3.7 Hz, 1H), 3.26 (d, J = 3.7 Hz, 1H).

Example 27. (6S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-6-(trifluoromethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 508)**



To a stirred solution of tributyl(1-ethoxyethenyl)stannane (12.04 g, 33.326 mmol, 2.0 equiv) and 8-bromo-2-methoxypyrido[3,2-d]pyrimidine (4 g, 16.663 mmol, 1.00 equiv) in 1,4-dioxane (30 mL) was added PPh_3 (2.19 g, 8.332 mmol, 0.5 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 90 ° C under nitrogen atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (1x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (5:1) to afford 8-(1-ethoxyethenyl)-2-methoxypyrido[3,2-d]pyrimidine (3.2 g, 83.05%) as a off-white solid.

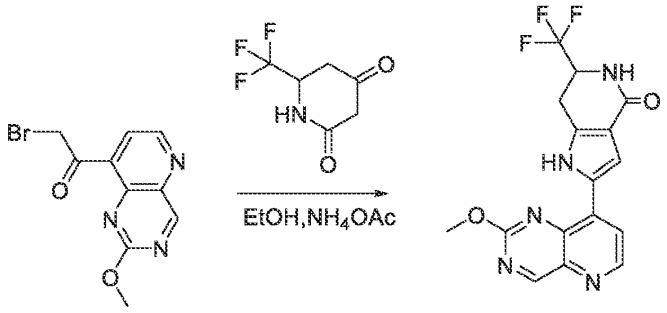
LC-MS: M+H found: 232.



To a stirred solution of 8-(1-ethoxyethenyl)-2-methoxypyrido[3,2-d]pyrimidine (3 g, 12.973 mmol, 1.00 equiv) in THF (25 mL) and H_2O (5 mL) was added NBS (2.31 g,

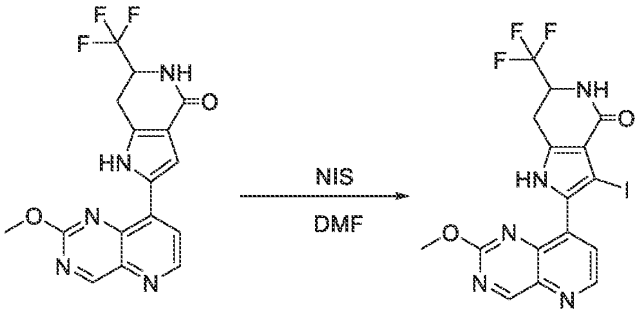
12.973 mmol, 1.0 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 1 h at 50 ° C under air atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (7:1) to afford 2-bromo-1-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}ethanone (2.6 g, 71.05%) as a white solid.

LC-MS: M+H found: 282.



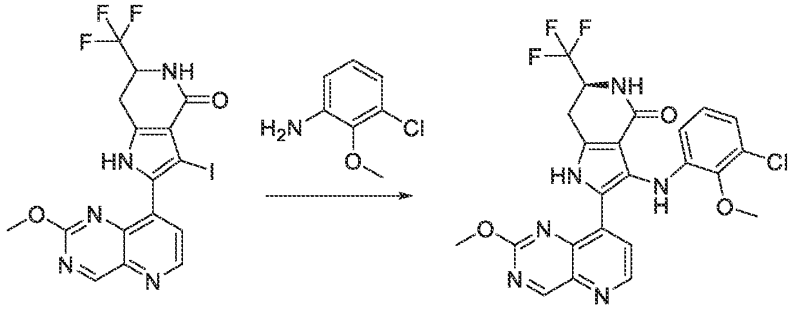
To a stirred solution of 2-bromo-1-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}ethanone (1 g, 3.545 mmol, 1.0 equiv) and 6-(trifluoromethyl)piperidine-2,4-dione (0.71 g, 3.900 mmol, 1.1 equiv) in EtOH (15 mL) was added NH_4OAc (1.37 g, 17.725 mmol, 5.0 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 6 h at 50 ° C under nitrogen atmosphere. The resulting mixture was diluted with water. The aqueous layer was extracted with EtOAc (3x30 mL). The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford 2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-6-(trifluoromethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (850 mg, 66.00%) as a light yellow solid.

LC-MS: M+H found: 364.



To a stirred solution of 2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-6-(trifluoromethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (500 mg, 1.376 mmol, 1.0 equiv) in DMF (10 mL) was added NIS (340.60 mg, 1.514 mmol, 1.1 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2 h at 50 °C under air atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3x50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (40:1) to afford 3-iodo-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-6-(trifluoromethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (450 mg, 66.84%) as a light yellow solid.

LC-MS: M+H found: 490.



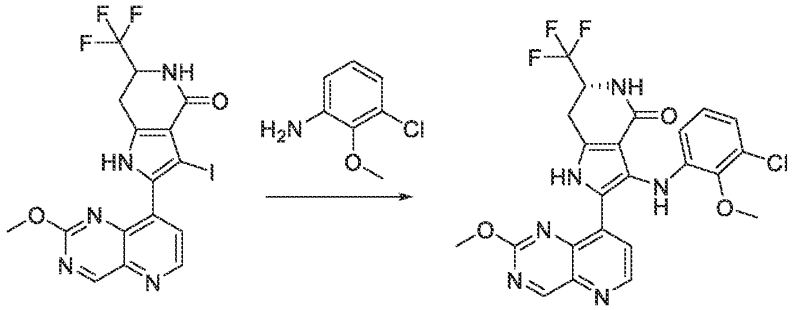
To a stirred solution of 3-iodo-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-6-(trifluoromethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (40 mg, 0.082 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (25.77 mg, 0.164 mmol, 2.0 equiv) in DMF (2 mL) were added EPhos (21.86 mg, 0.041 mmol, 0.5 equiv), EPhos Pd G4 (37.55 mg, 0.041

mmol, 0.5 equiv) and Cs_2CO_3 (79.92 mg, 0.246 mmol, 3.0 equiv) at room temperature in portions under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 50 °C under nitrogen atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IG-3, 4.6*50mm, 3um; Mobile Phase A: Hex: DCM=3: 1)(0.1%DEA): EtOH=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (6S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-6-(trifluoromethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (8.1 mg, 18.98%) as a white solid.

LC-MS: M+H found: 520.

^{1}H NMR (300 MHz, DMSO-d6) δ 12.06 (s, 1H), 9.51 (s, 1H), 8.73 (d, J = 4.8 Hz, 1H), 7.94 (d, J = 4.3 Hz, 1H), 7.76 – 7.64 (m, 2H), 6.75 – 6.62 (m, 2H), 6.15 (dd, J = 6.9, 2.8 Hz, 1H), 4.46 (s, 1H), 4.21 (s, 3H), 3.86 (s, 3H), 3.34 (s, 1H), 3.24 (s, 1H).

Example 28. (6R)-3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-6-(trifluoromethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 507)**



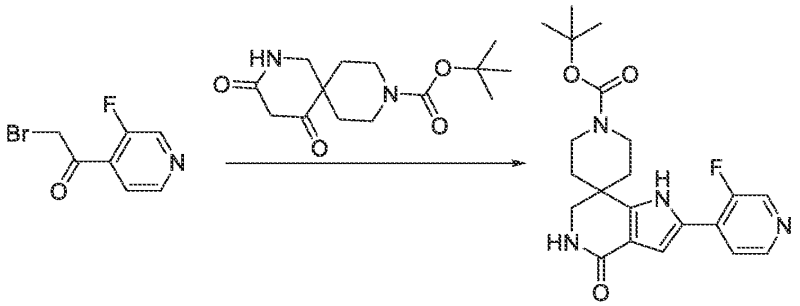
To a stirred solution of 3-iodo-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-6-(trifluoromethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (40 mg, 0.082 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (25.77 mg, 0.164 mmol, 2.0 equiv) in DMF (2 mL) were added EPhos (21.86 mg, 0.041 mmol, 0.5 equiv), EPhos Pd G4 (37.55 mg, 0.041 mmol, 0.5 equiv) and Cs_2CO_3 (79.92 mg, 0.246 mmol, 3.0 equiv) at room temperature in

portions under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 50 ° C under nitrogen atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with CH_2Cl2 (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IG-3, 4.6*50mm, 3um; Mobile Phase A: Hex: DCM=3: 1)(0.1%DEA): EtOH=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (6R)-3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-6-(trifluoromethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (13.6 mg, 25.44%) as a yellow solid.

LC-MS: M+H found: 520.

^{1}H NMR (300 MHz, DMSO-d6) δ 12.06 (s, 1H), 9.51 (s, 1H), 8.73 (d, J = 4.8 Hz, 1H), 7.94 (d, J = 4.3 Hz, 1H), 7.76 – 7.64 (m, 2H), 6.75 – 6.62 (m, 2H), 6.15 (dd, J = 6.9, 2.8 Hz, 1H), 4.46 (s, 1H), 4.21 (s, 3H), 3.86 (s, 3H), 3.34 (s, 1H), 3.24 (s, 1H).

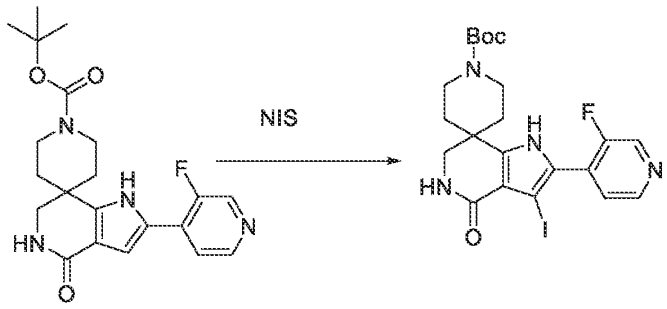
Example 29. 3'-[(3-bromo-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 561)**



To a stirred solution of 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (5 g, 22.933 mmol, 1 equiv) and tert-butyl 3,5-dioxo-2,9-diazaspiro[5.5]undecane-9-carboxylate (6.47 g, 22.933 mmol, 1 equiv) in EtOH (50 mL) was added NH_4OAc (10.61 g, 137.598 mmol, 6 equiv) in portions at 50°C under N_2 atmosphere. The final reaction mixture was stirred for 2h. The resulting mixture was concentrated under vacuum. The aqueous layer was extracted with EA (3x20mL) to afford tert-butyl 2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-

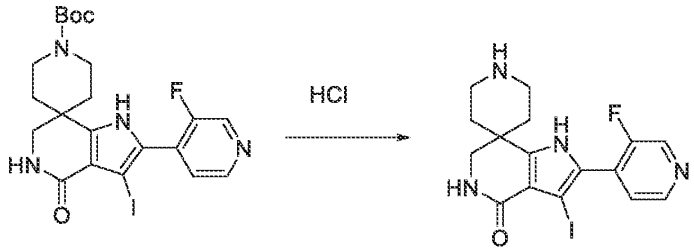
dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (7 g, 76.22%) as a yellow solid.

LC-MS: M+H found: 401.4.



To a stirred solution of isopropyl 2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (5 g, 12.939 mmol, 1 equiv) in DMF (50 mL) was added NIS (3.49 g, 15.527 mmol, 1.2 equiv) in portions at RT. The final reaction mixture was stirred for 2h. The resulting mixture was extracted with EA (3 x 50mL). The combined organic layers were washed with brine (3x150mL), dried over anhydrous sodium sulphate. After filtration, the filtrate was concentrated under reduced pressure to afford tert-butyl 2'-(3-fluoropyridin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (6 g, 88.10%) as a yellow solid.

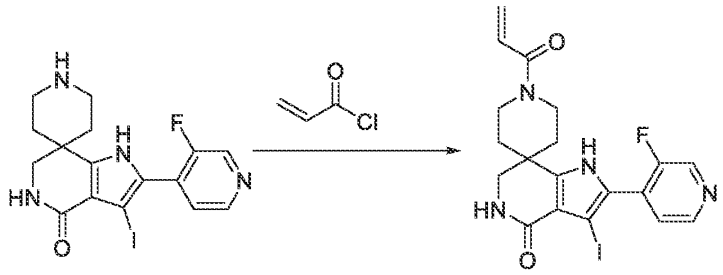
LC-MS: M+H found: 527.1.



To a stirred solution oftert-butyl 2'-(3-fluoropyridin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (5 g, 1 equiv) in reaction vessel was added HCl(gas)in 1,4-dioxane (50 mL) in portions at rt under N_2 atmosphere. The final reaction mixture was stirred for 2h. The resulting mixture was concentrated

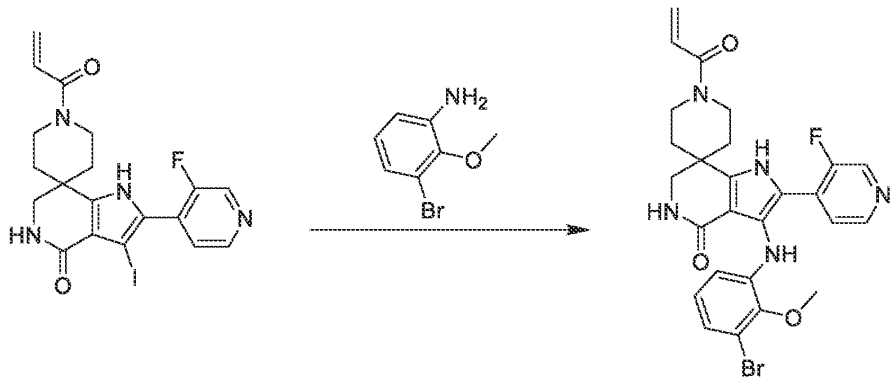
under vacuum. The residue was acidified to pH=7 with $NaHCO_3$.The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 25 mL). The filtrate was concentrated under reduced pressureto afford 2'-(3-fluoropyridin-4-yl)-3'-iodo-1',4',5',6'-tetrahydrospiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine] (3 g, 75.38%) as a yellow solid.

LC-MS: M+H found: 426.9.



A solution of 2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (1.6 g, 3.754 mmol, 1 equiv) in DCM (20 mL) was treated with TEA (1.14 g, 11.262 mmol, 3 equiv) for 30 min at 0°C under nitrogen atmosphere followed by the addition of acryloyl chloride (509.64 mg, 5.631 mmol, 1.5 equiv) in portions at rt. The final reaction mixture was stirred for 1h. The reaction was quenched with isopropanol at rt. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM : EtOH (10:1) to afford 2'-(3-fluoropyridin-4-yl)-3'-iodo-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (1.63 g, 90.56%) as a yellow solid.

LC-MS: M+H found: 481.2.



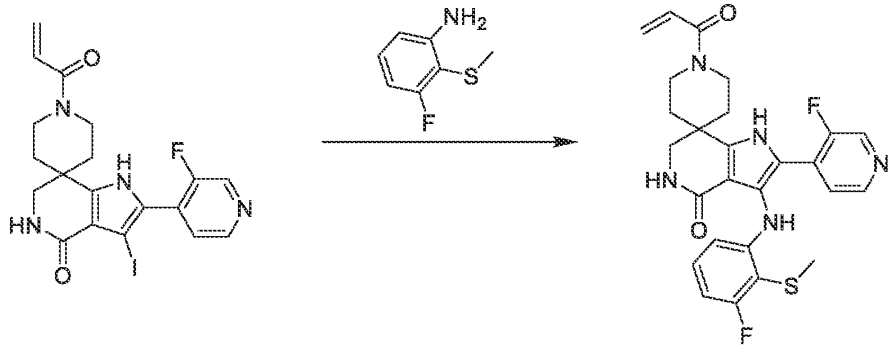
To a stirred solution of 2'-(3-fluoropyridin-4-yl)-3'-iodo-1-(prop-2-enoyl)-5',6'-dihydro-

1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (1 g, 2.082 mmol, 1 equiv) and 3-bromo-2-methoxyaniline (546.90 mg, 2.707 mmol, 1.3 equiv) in DMF (15 mL) were added EPhos Pd G4 (382.50 mg, 0.416 mmol, 0.2 equiv), EPhos (222.70 mg, 0.416 mmol, 0.2 equiv) and Cs_2CO_3 (1.36 g, 4.164 mmol, 2 equiv) under N_2 atmosphere. The final reaction mixture was stirred for 2h at 50 degrees. The resulting mixture was filtered, the filter cake was washed with EA (3x5mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH=12:1) to afford crude product. The crude product (130mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO3+0.1%NH_3*H_2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 24% B to 54% B in 8 min, 54% B; Wave Length: 254; 220 nm; RT1(min): 7.17) to afford 3'-[(3-bromo-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (24.4 mg, 2.11%) as a white solid.

LC-MS: (M+H) found: 554.3.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.43 (s, 1H), 8.47 (d, J = 2.6 Hz, 1H), 8.31 (dd, J = 5.0, 1.2 Hz, 1H), 7.68 (s, 1H), 7.44 (dd, J = 6.7, 5.1 Hz, 1H), 7.34 (s, 1H), 6.93 – 6.74 (m, 2H), 6.55 (t, J = 8.1 Hz, 1H), 6.20 – 6.08 (m, 2H), 5.71 (dd, J = 10.4, 2.5 Hz, 1H), 4.42 (d, J = 13.2 Hz, 1H), 4.05 (d, J = 14.0 Hz, 1H), 3.83 (s, 3H), 3.52 (s, 2H), 3.32-3.25 (m, 1H),2.85 (t, J = 12.6 Hz, 1H), 1.97 (s, 2H), 1.76 (s, 2H).

Example 30. 3'-{[3-fluoro-2-(methylsulfanyl)phenyl]amino}-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 560)**

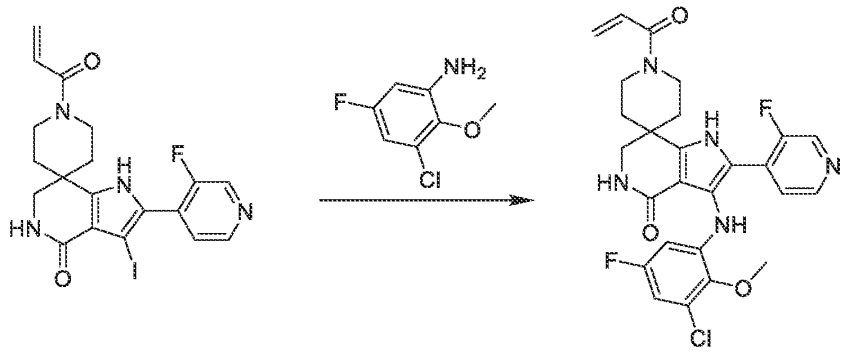


To a solution of 2'-(3-fluoropyridin-4-yl)-3'-iodo-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (500 mg, 1.041 mmol, 1 equiv) and 3-fluoro-2-(methylsulfanyl)aniline (196.40 mg, 1.249 mmol, 1.2 equiv) in DMF (10 mL) were added Cs_2CO_3 (678.39 mg, 2.082 mmol, 2 equiv) and EPhos Pd G4 (191.25 mg, 0.208 mmol, 0.2 equiv) and EPhos (111.35 mg, 0.208 mmol, 0.2 equiv). After stirring for 3h at 50 °C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The aqueous layer was extracted with EA (6x100 mL). The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water; detector, UV 254 nm to afford 3'-{[3-fluoro-2-(methylsulfanyl)phenyl]amino}-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (8.3 mg, 1.56%) as a light yellow solid.

LC-MS: M+H found: 510.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.48 (s, 1H), 8.47 (d, J = 2.5 Hz, 1H), 8.32 (dd, J = 5.0, 1.1 Hz, 1H), 8.15 (s, 1H), 7.43 (dd, J = 6.7, 5.0 Hz, 1H), 7.34 (s, 1H), 6.93 – 6.80 (m, 2H), 6.50 – 6.42 (m, 1H), 6.15 (dd, J = 16.7, 2.5 Hz, 1H), 6.02 (d, J = 8.4 Hz, 1H), 5.72 (dd, J = 10.4, 2.5 Hz, 1H), 4.43 (d, J = 13.3 Hz, 1H), 4.14 – 4.02 (m, 1H), 3.53 (s, 2H), 3.17 (d, J = 5.2 Hz, 1H), 2.87 (dd, J = 23.4, 10.3 Hz, 1H), 2.34 (s, 3H), 1.98 (q, J = 12.6 Hz, 2H), 1.76 (t, J = 12.1 Hz, 2H).

Example 31. 3'-[(3-chloro-5-fluoro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 559)**

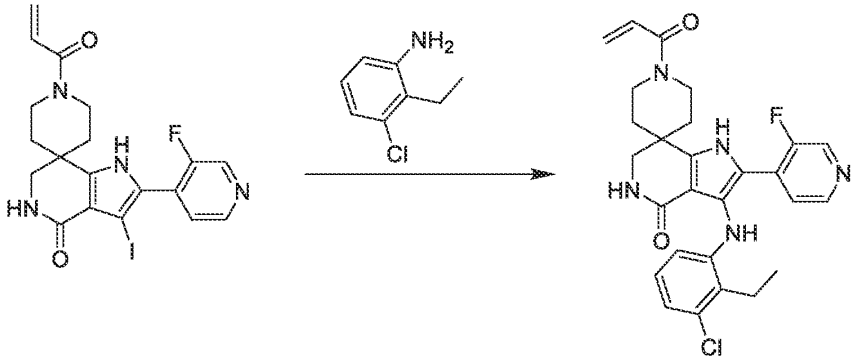


To a stirred solution of 2'-(3-fluoropyridin-4-yl)-3'-iodo-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (500 mg, 1.041 mmol, 1 equiv) and 3-chloro-5-fluoro-2-methoxyaniline (219.36 mg, 1.249 mmol, 1.2 equiv) in DMF (6 mL) were added EPhos Pd G4 (191.25 mg, 0.208 mmol, 0.2 equiv),EPhos (111.35 mg, 0.208 mmol, 0.2 equiv) and Cs_2CO_3 (678.39 mg, 2.082 mmol, 2 equiv) under N_2 atmosphere. The final reaction mixture was stirred for 2h at 50 degrees. The resulting mixture was filtered, the filter cake was washed with EA (3 x 5 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH=15:1) to afford crude product. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%NH_3*H_2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 24% B to 54% B in 8 min, 54% B; Wave Length: 254; 220 nm; RT1(min): 7.32) to afford 3'-[(3-chloro-5-fluoro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (21.9 mg, 3.95%) as a white solid.

LC-MS: (M+H) found: 528.2.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.53 (s, 1H), 8.52 (d, J = 2.5 Hz, 1H), 8.37 (dd, J = 5.1, 1.2 Hz, 1H), 7.79 (d, J = 1.5 Hz, 1H), 7.49 (dd, J = 6.6, 5.0 Hz, 1H), 7.32 (s, 1H), 6.87 (dd, J = 16.6, 10.4 Hz, 1H), 6.56 – 6.47 (m, 1H), 6.15 (dd, J = 16.6, 2.5 Hz, 1H), 5.81 (dd, J = 11.1, 3.0 Hz, 1H), 5.71 (dd, J = 10.4, 2.5 Hz, 1H), 4.42 (d, J = 13.2 Hz, 1H), 4.05 (d, J = 13.9 Hz, 1H), 3.79 (s, 3H), 3.53 (s, 2H), 3.32 – 3.25 (m, 1H),2.85 (t, J = 12.7 Hz, 1H), 1.95 (s, 2H), 1.77 (s, 2H).

Example 32. 3'-[(3-chloro-2-ethylphenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 558)**

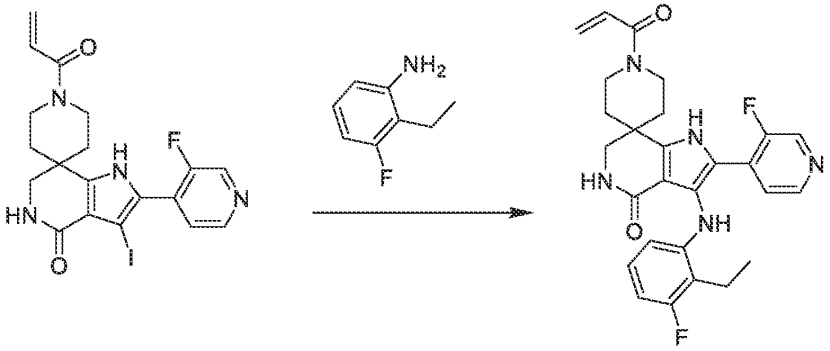


To a solution of 2'-(3-fluoropyridin-4-yl)-3'-iodo-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (300 mg, 0.625 mmol, 1 equiv) and 3-chloro-2-ethylaniline (116.65 mg, 0.750 mmol, 1.2 equiv) in DMF (10 mL) were added Cs_2CO_3 (407.04 mg, 1.250 mmol, 2 equiv) and EPhos Pd G4 (114.75 mg, 0.125 mmol, 0.2 equiv), EPhos (66.81 mg, 0.125 mmol, 0.2 equiv). After stirring for 5h at 50 °C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The aqueous layer was extracted with EA (6x50 mL). The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in wate; detector, UV 254 nm to afford 3'-[(3-chloro-2-ethylphenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (10.8 mg, 3.32%) as a light yellow solid.

LC-MS: M+H found: 508.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.39 (s, 1H), 8.43 (d, J = 2.6 Hz, 1H), 8.26 (d, J = 5.0 Hz, 1H), 7.62 (s, 1H), 7.40 – 7.31 (m, 2H), 6.88 (dd, J = 16.7, 10.4 Hz, 1H), 6.74 – 6.63 (m, 2H), 6.18 (dd, J = 7.2, 2.3 Hz, 1H), 6.13 (d, J = 2.5 Hz, 1H), 5.72 (dd, J = 10.4, 2.5 Hz, 1H), 4.43 (d, J = 13.2 Hz, 1H), 4.06 (d, J = 14.0 Hz, 1H), 3.54 (t, J = 2.7 Hz, 4H), 2.82 (q, J = 7.4 Hz, 2H), 1.98 (d, J = 12.6 Hz, 2H), 1.81 – 1.71 (m, 2H), 1.21 (q, J = 7.9 Hz, 3H).

Example 33. 3'-[(2-ethyl-3-fluorophenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 557)**

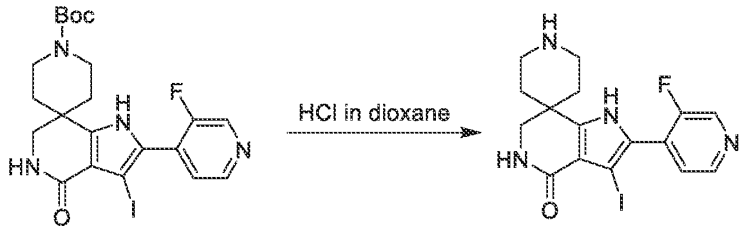


To a stirred solution of 2'-(3-fluoropyridin-4-yl)-3'-iodo-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (100 mg, 0.208 mmol, 1 equiv) and 2-ethyl-3-fluoroaniline (34.77 mg, 0.250 mmol, 1.2 equiv) in DMF (1.5 mL) were added EPhos Pd G4 (38.25 mg, 0.042 mmol, 0.2 equiv), EPhos (22.27 mg, 0.042 mmol, 0.2 equiv) and Cs_2CO_3 (135.68 mg, 0.416 mmol, 2 equiv) under N_2 atmosphere. The final reaction mixture was stirred for 2h at 50 degrees. The resulting mixture was filtered, the filter cake was washed with MeOH. The filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase flash with the following conditions (MeCN:H_2O=47:53) to afford 3'-[(2-ethyl-3-fluorophenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (8.7 mg, 8.08%) as a white solid.

LC-MS: (M+H) found: 492.0.

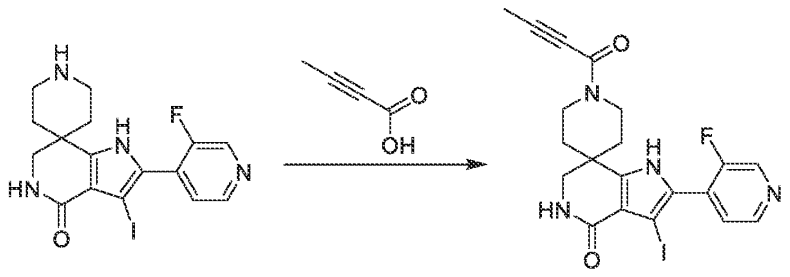
^{1}H NMR (300 MHz, DMSO-d6) δ 11.35 (s, 1H), 8.41 (d, J = 2.6 Hz, 1H), 8.24 (d, J = 5.1 Hz, 1H), 7.59 (s, 1H), 7.35 (dd, J = 6.8, 4.7 Hz, 2H), 6.94 – 6.82 (m, 1H), 6.66 (q, J = 7.8 Hz, 1H), 6.42 (t, J = 8.9 Hz, 1H), 6.14 (dd, J = 16.7, 2.6 Hz, 1H), 6.04 (d, J = 8.2 Hz, 1H), 5.71 (dd, J = 10.4, 2.6 Hz, 1H), 4.42 (d, J = 13.1 Hz, 1H), 4.05 (d, J = 14.2 Hz, 1H), 3.53 (s, 2H), 3.32 – 3.25 (m, 1H), 2.85 (t, J = 12.9 Hz, 1H), 2.67 (d, J = 8.0 Hz, 2H), 2.01 (d, J = 19.0 Hz, 2H), 1.76 (s, 2H), 1.18 (q, J = 7.2 Hz, 3H).

Example 34. 1-(but-2-ynoyl)-3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 555)**



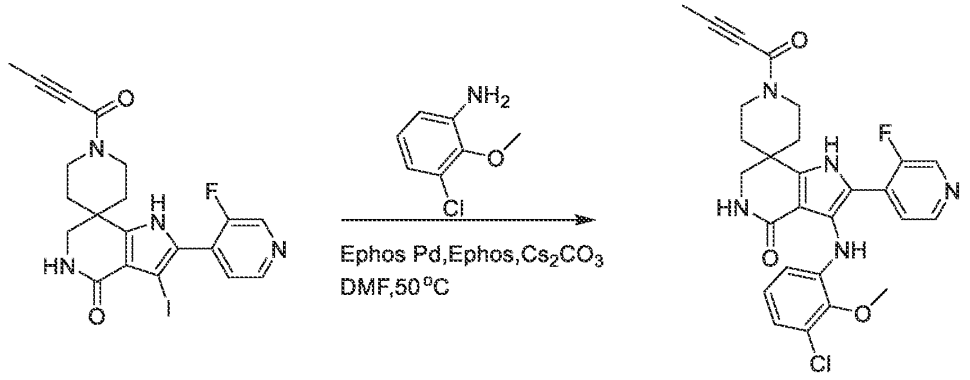
Into a 5 mL round-bottom flask were added tert-butyl 2'-(3-fluoropyridin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (4.9 g, 9.309 mmol, 1 equiv) and HCl(gas)in 1,4-dioxane (6.12 mL, 201.540 mmol, 21.65 equiv) at room temperature.The resulting mixture was stirred for 1h at room temperature. The resulting mixture was concentrated under reduced pressure to afford 2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (3.9 g, 98.29%) as a light yellow solid.

LC-MS: M+H found: 427.



To a stirred solution of 2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (200 mg, 0.469 mmol, 1 equiv) and 2-butynoic acid (43.39 mg, 0.516 mmol, 1.1 equiv) in Pyridine (4 mL) were added HOBT (76.08 mg, 0.563 mmol, 1.2 equiv) and EDC*HCl (107.94 mg, 0.563 mmol, 1.2 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperatur. The reaction was quenched with Water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 1-(but-2-ynoyl)-2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (160 mg, 69.27%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 493.

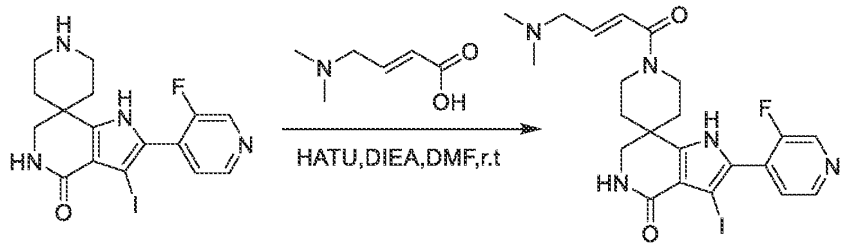


To a stirred solution of 1-(but-2-ynoyl)-2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (150 mg, 0.305 mmol, 1 equiv) and 3-chloro-2-methoxyaniline (144.06 mg, 0.915 mmol, 3 equiv) in DMF (3 mL) were added EPhos Pd G4 (55.98 mg, 0.061 mmol, 0.2 equiv) and EPhos (32.59 mg, 0.061 mmol, 0.2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at 50°C under nitrogen atmosphere. The reaction was quenched with Water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (mg) was purified by Prep-HPLC with the following conditions to afford 1-(but-2-ynoyl)-3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one as a light yellow solid.

LC-MS: $(M+H)^+$ found: 522.

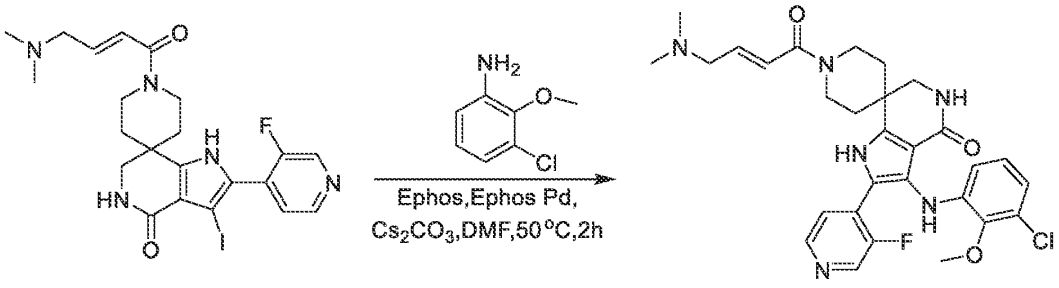
^{1}H NMR 11.42(s, 1H), 8.48(d, 1H), 8.32(d, 1H), 7.69(s, 1H), 7.43-7.47(dd, 1H, J1=5.4Hz, J2=6.6Hz), 7.35 (s,1H), 6.58-6.67(m, 2H), 6.07-6.10(dd, 1H, J1=1.8Hz, J2=7.5Hz), 4.18-4.32(m, 2H), 3.84(s, 3H), 3.51(s, 2H), 2.84-2.92(t, 1H, J=18H), 2.04(s, 3H), 1.76-1.82(m, 3H), 1.24(s, 1H), 0.83-0.85(d, 1H, J=6H).

Example 35. 3'-[(3-chloro-2-methoxyphenyl)amino]-1-[4-(dimethylamino)but-2-enoyl]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 522)**



To a stirred solution of 2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (200 mg, 0.469 mmol, 1 equiv) and (2E)-4-(dimethylamino)but-2-enoic acid (66.67 mg, 0.516 mmol, 1.1 equiv) in DMF (5 mL, 64.609 mmol, 137.69 equiv) were added HATU (214.10 mg, 0.563 mmol, 1.2 equiv) and DIEA (90.97 mg, 0.704 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperature. The reaction was quenched with Water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (30:1) to afford 1-[(2E)-4-(dimethylamino)but-2-enoyl]-2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (210 mg, 83.28%) as a light yellow solid.

LC-MS: M+H found: 538.



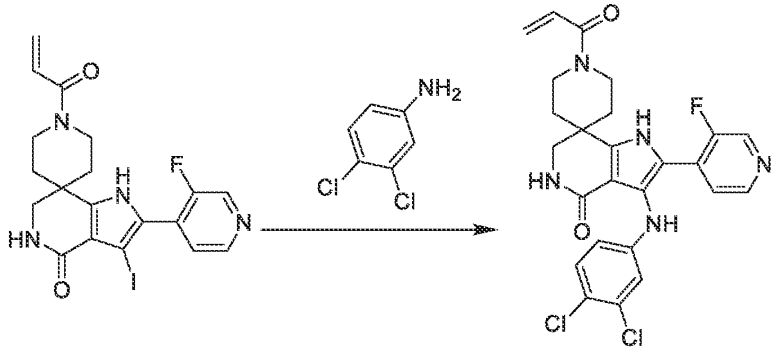
To a stirred solutio of 1-[4-(dimethylamino)but-2-enoyl]-2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (200 mg, 0.372 mmol, 1 equiv) and 3-chloro-2-methoxyaniline (175.97 mg, 1.116 mmol, 3 equiv) in DMF (5 mL) were added EPhos Pd G4 (68.37 mg, 0.074 mmol, 0.2 equiv) and Cs_2CO_3 (363.79 mg, 1.116 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting

mixture was stirred for 2h at 50°C under nitrogen atmosphere. The reaction was quenched with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%NH_3*H_2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 45% B in 8 min, 45% B; Wave Length: 254; 220 nm; RT1(min): 7.82) to afford 3'-[(3-chloro-2-methoxyphenyl)amino]-1-[4-(dimethylamino)but-2-enoyl]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (15.9 mg, 8.95%) as a light yellow solid.

LC-MS: $(M+H)^+$ found 567.

^{1}H NMR 11.43(s, 1H), 8.48(d, 1H, J=2.4Hz), 8.32(d, 1H, J=4.8Hz), 7.69(s, 1H), 7.42-7.46(dd, 1H, J1=5.1Hz, J2=6.6Hz), 7.34(s, 1H), 6.60-6.66(m, 4H), 6.07-6.10(dd, 1H, J1=1.8Hz, J2=7.8Hz), 4.42(d, 1H, J=2.4Hz), 4.03(d, 1H, J=1.8Hz), 3.84(s, 3H), 3.52(s, 2H), 3.21-3.30(m, 1H), 3.03-3.04(m, 2H), 2.79-2.87(m, 1H), 2.15(s, 6H), 1.92-1.97(m, 2H), 1.70-1.77(m, 2H).

Example 36. 3'-[(3,4-dichlorophenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 590)**



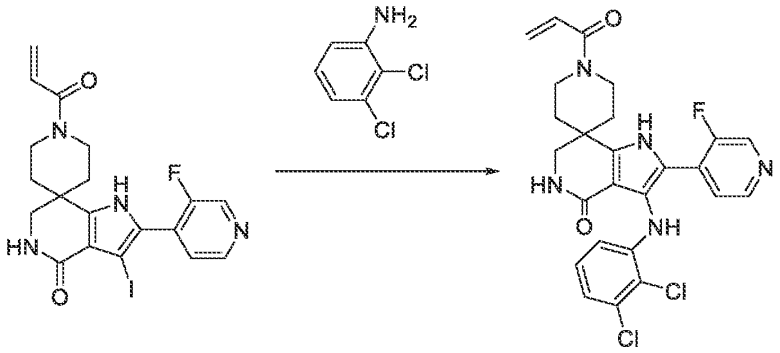
To a stirred solution of 2'-(3-fluoropyridin-4-yl)-3'-iodo-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (300 mg, 0.625 mmol, 1 equiv) and 3,4-dichloroaniline (121.44 mg, 0.750 mmol, 1.2 equiv) in DMF (4 mL) were added

EPhos Pd G4 (114.75 mg, 0.125 mmol, 0.2 equiv), EPhos (66.81 mg, 0.125 mmol, 0.2 equiv) and Cs_2CO_3 (407.04 mg, 1.250 mmol, 2 equiv) under N_2 atmosphere. The final reaction mixture was stirred for 2h at 50 degrees. The resulting mixture was extracted with EA (3 x 10mL). The combined organic layers were washed with brine (3x50 mL), dried over anhydrous sodium sulphate. After filtration, the filtrate was concentrated under reduced pressure. The crude product (90 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%NH_3*H_2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 50% B in 8 min, 50% B; Wave Length: 254/220 nm; RT1(min): 7.43) to afford 3'-[(3,4-dichlorophenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (12.5 mg, 3.86%) as a white solid.

LC-MS: (M+H) found: 514.1.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.47 (s, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.34 (dd, J = 5.1, 1.1 Hz, 1H), 7.80 (s, 1H), 7.42 (dd, J = 6.6, 5.1 Hz, 1H), 7.26 – 7.14 (m, 2H), 6.87 (dd, J = 16.7, 10.5 Hz, 1H), 6.66 (d, J = 2.7 Hz, 1H), 6.51 (dd, J = 8.8, 2.7 Hz, 1H), 6.15 (dd, J = 16.7, 2.5 Hz, 1H), 5.79 – 5.67 (m, 1H), 4.42 (d, J = 13.4 Hz, 1H), 4.05 (d, J = 14.0 Hz, 1H), 3.51 (s, 2H), 3.32 – 3.25 (m, 1H),2.84 (t, J = 13.0 Hz, 1H), 2.04 – 1.89 (m, 2H), 1.76 (t, J = 12.3 Hz).

Example 37. 3'-[(2,3-dichlorophenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 589)**



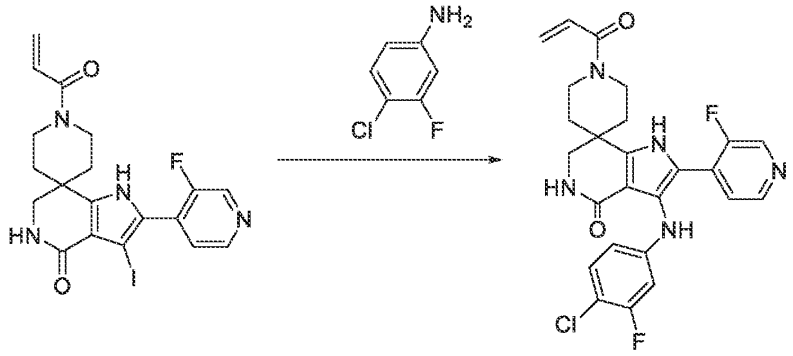
To a stirred solution of 2'-(3-fluoropyridin-4-yl)-3'-iodo-1-(prop-2-enoyl)-5',6'-dihydro-

1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (300 mg, 0.625 mmol, 1.0 equiv) and 2,3-dichloroaniline (202.39 mg, 1.250 mmol, 2.0 equiv) in DMF (10 mL) were added Cs_2CO_3 (407.04 mg, 1.250 mmol, 2.0 equiv), EPhos (66.81 mg, 0.125 mmol, 0.2 equiv) and EPhos Pd G4 (114.75 mg, 0.125 mmol, 0.2 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 50 ° C under nitrogen atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (200 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30*150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3+0.1%NH_3*H_2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 37% B to 48% B in 8 min, 48% B; Wave Length: 254; 220 nm; RT1(min): 8.05) to afford 3'-[(2,3-dichlorophenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (46.4 mg, 14.39%) as a off-white solid.

LC-MS: M+H found: 514.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.51 (s, 1H), 8.48 (d, J = 2.6 Hz, 1H), 8.36 – 8.28 (m, 1H), 7.75 (s, 1H), 7.47 – 7.32 (m, 2H), 6.94 – 6.80 (m, 3H), 6.30 – 6.21 (m, 1H), 6.15 (dd, J = 16.7, 2.5 Hz, 1H), 5.71 (dd, J = 10.3, 2.5 Hz, 1H), 4.42 (d, J = 12.6 Hz, 1H), 4.05 (d, J = 13.1 Hz, 1H), 3.53 (s, 2H), 2.88 – 2.78 (m, 1H), 1.96 (s, 2H), 1.77 (s, 2H).

Example 38. 3'-[(4-chloro-3-fluorophenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 588)**



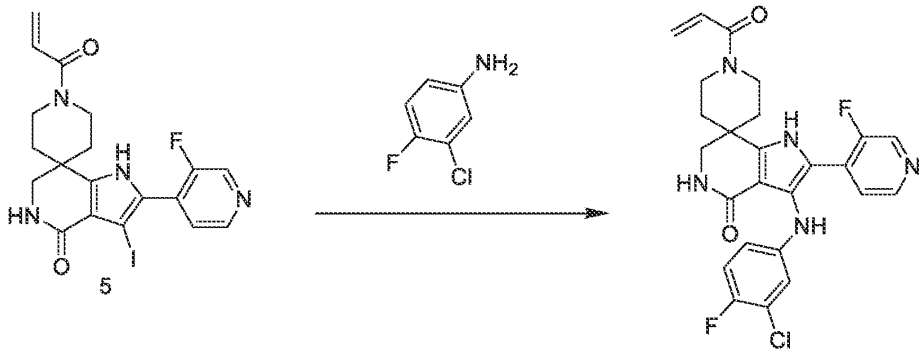
To a stirred solution of 2'-(3-fluoropyridin-4-yl)-3'-iodo-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (300 mg, 0.625 mmol, 1.0 equiv) and 4-chloro-3-fluoroaniline (181.84 mg, 1.250 mmol, 2.0 equiv) in DMF (10 mL) were added Cs_2CO_3 (407.04 mg, 1.250 mmol, 2.0 equiv), EPhos (66.81 mg, 0.125 mmol, 0.2 equiv) and EPhos Pd G4 (114.75 mg, 0.125 mmol, 0.2 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 50 ° C under nitrogen atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (200 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30*150 mm, 5 μ m; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%NH_3*H_2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 47% B in 8 min, 47% B; Wave Length: 254; 220 nm; RT1(min): 7.7) to afford 3'-[(4-chloro-3-fluorophenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (51.1 mg, 16.41%) as a white solid.

LC-MS: M+H found: 498.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.49 (s, 1H), 8.51 (d, J = 2.5 Hz, 1H), 8.37 – 8.31 (m, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.46 (dd, J = 6.7, 5.0 Hz, 1H), 7.33 (s, 1H), 6.88 (dd, J = 16.6, 10.5 Hz, 1H), 6.78 – 6.68 (m, 2H), 6.30 – 6.21 (m, 1H), 6.15 (dd, J = 16.6, 2.5 Hz, 1H), 5.72 (dd, J = 10.5, 2.5 Hz, 1H), 4.43 (d, J = 13.2 Hz, 1H), 4.06 (d, J = 14.1 Hz, 1H),

3.52 (s, 2H), 3.27 (d, J = 13.3 Hz, 1H), 2.85 (t, J = 12.9 Hz, 1H), 1.98 (d, J = 13.5 Hz, 2H), 1.76 (t, J = 11.9 Hz, 2H).

Example 39. 3'-[(3-chloro-4-fluorophenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 587)**

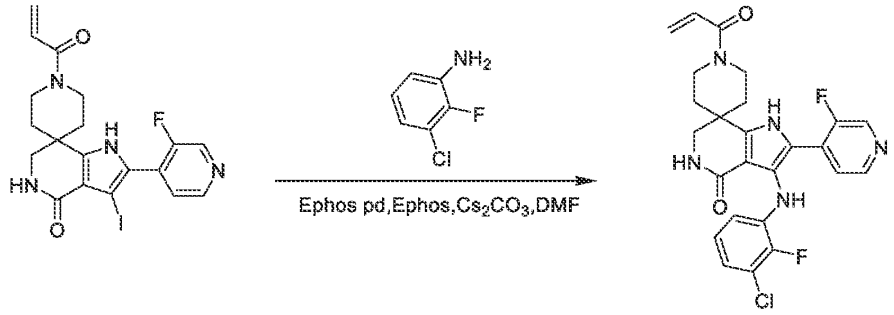


To a stirred solution of 2'-(3-fluoropyridin-4-yl)-3'-iodo-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (300 mg, 0.625 mmol, 1 equiv) and 3-chloro-4-fluoroaniline (109.11 mg, 0.750 mmol, 1.2 equiv) in DMF (5 mL) were added EPhos Pd G4 (114.75 mg, 0.125 mmol, 0.2 equiv) ,EPhos (66.81 mg, 0.125 mmol, 0.2 equiv) and Cs_2CO_3 (407.04 mg, 1.250 mmol, 2 equiv) under N_2 atmosphere. The final reaction mixture was irradiated with microwave radiation for 2h at 50 degrees. The resulting mixture was filtered, the filter cake was washed with EA (3x5mL). The filtrate was concentrated under reduced pressure. The resulting mixture was extracted with EA (3 x20mL). The combined organic layers were washed with brine (3x50mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (60 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%NH_3*H_2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 45% B in 8 min, 45% B; Wave Length: 254； 220 nm; RT1(min): 7.45) to afford 3'-[(3-chloro-4-fluorophenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (28.0 mg, 8.98%) as a white solid.

LC-MS: (M+H) found: 498.1.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.41 (s, 1H), 8.51 (d, J = 2.5 Hz, 1H), 8.32 (dd, J = 5.0, 1.1 Hz, 1H), 7.63 (s, 1H), 7.41 (dd, J = 6.7, 5.0 Hz, 1H), 7.27 (d, J = 2.9 Hz, 1H), 7.01 (t, J = 9.1 Hz, 1H), 6.88 (dd, J = 16.7, 10.5 Hz, 1H), 6.60 (dd, J = 6.4, 2.8 Hz, 1H), 6.52 – 6.47 (m, 1H), 6.15 (dd, J = 16.7, 2.5 Hz, 1H), 5.71 (dd, J = 10.4, 2.5 Hz, 1H), 4.42 (d, J = 13.4 Hz, 1H), 4.06 (d, J = 14.0 Hz, 1H), 3.51 (t, J = 2.9 Hz, 2H), 3.24 (s, 1H), 2.85 (t, J = 13.0 Hz, 1H), 1.97 (q, J = 11.8 Hz, 2H), 1.76 (t, J = 12.1 Hz, 2H).

Example 40. 3'-[(3-chloro-2-fluorophenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 586)**

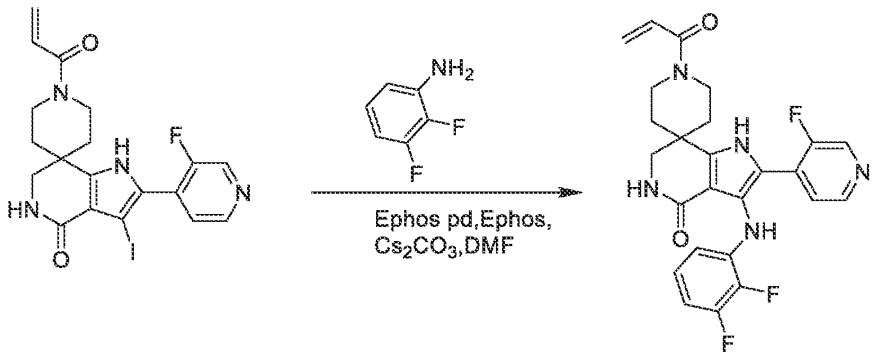


To a stirred mixture of 2'-(3-fluoropyridin-4-yl)-3'-iodo-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (300 mg, 0.625 mmol, 1 equiv) and 3-chloro-2-fluoroaniline (181.84 mg, 1.250 mmol, 2 equiv) in DMF (5 mL) were added EPhos Pd G4 (86.06 mg, 0.094 mmol, 0.15 equiv), EPhos (100.22 mg, 0.188 mmol, 0.3 equiv) and Cs_2CO_3 (407.04 mg, 1.250 mmol, 2 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 50 °C under nitrogen atmosphere. The resulting mixture was extracted with EtOAc (2 x 100mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm. To afford 3'-[(3-chloro-2-fluorophenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one(100 mg), then the crude product (60 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep

OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%NH_3*H_2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 45% B in 8 min, 45% B; Wave Length: 254; 220 nm; RT1(min): 6.57) to afford 3'-[(3-chloro-2-fluorophenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (19.1 mg, 6.09%) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 1.75 (t, 2H), 1.91 – 2.03 (q, 2H), 2.85 (t, 1H), 3.28 (t, 1H), 3.49 – 3.55 (m, 2H), 4.05 (d, 1H), 4.42 (d, 1H), 5.71 (dd, 1H), 6.15 (dd, 1H), 6.19 – 6.30 (m, 1H), 6.67 – 6.77 (m, 2H), 6.87 (dd, 1H), 7.33 (d, 1H), 7.46 (dd, 1H), 7.62 (d, 1H), 8.33 (dd, 1H), 8.50 (d, 1H), 11.49 (s, 1H).

Example 41. 3'-[(2,3-difluorophenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 585)**

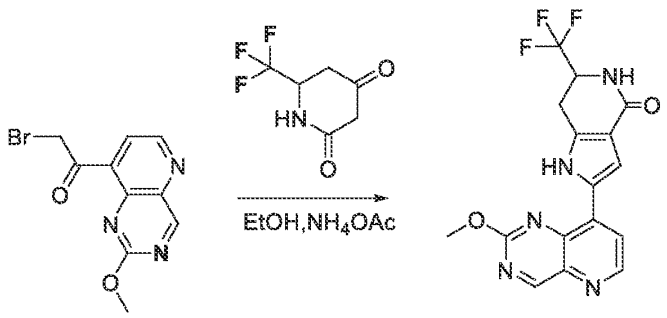


To a stirred mixture of 2'-(3-fluoropyridin-4-yl)-3'-iodo-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (300 mg, 0.625 mmol, 1 equiv) and 2,3-difluoroaniline (161.29 mg, 1.250 mmol, 2 equiv) in DMF (5 mL) were added EPhos Pd G4 (86.06 mg, 0.094 mmol, 0.15 equiv), EPhos (100.22 mg, 0.188 mmol, 0.3 equiv) and Cs_2CO_3 (407.04 mg, 1.250 mmol, 2 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 50 °C under nitrogen atmosphere.The resulting mixture was extracted with EtOAc (2 x 100mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN

in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford 3'-[(3-chloro-2-fluorophenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one(100 mg). The semi-pure product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%NH_3*H_2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 45% B in 8 min, 45% B; Wave Length: 254; 220 nm; RT1(min): 6.57) to afford 3'-[(2,3-difluorophenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (41.6 mg, 13.75%) as a off-white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 1.75 (t, 2H), 1.90 – 2.03 (m, 2H), 2.85 (t, 1H), 3.28 (t, 1H), 3.52 (t, 2H), 4.05 (d, 1H), 4.42 (d, 1H), 5.71 (dd, 1H), 6.07 – 6.15 (m, 1H), 6.11 – 6.19 (m, 1H), 6.52 – 6.63 (m, 1H), 6.64 – 6.74 (m, 1H), 6.87 (dd, 1H), 7.33 (t, 1H), 7.46 (dd, 1H), 7.62 (d, 1H), 8.33 (dd, 1H), 8.49 (d, 1H), 11.48 (s, 1H).

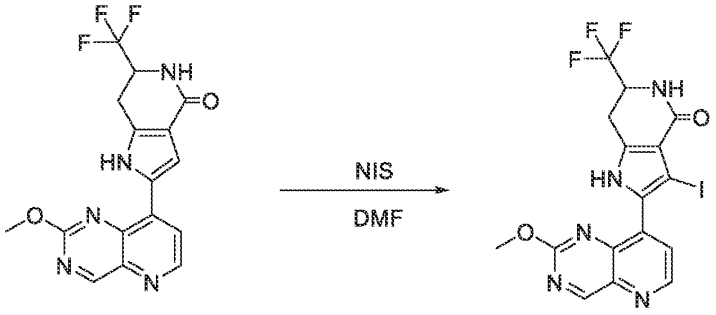
Example 42. 3-[(3-fluoro-2-methoxyphenyl)amino]-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-6-(trifluoromethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 595)**



To a stirred solution of 2-bromo-1-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}ethanone (1 g, 3.545 mmol, 1.0 equiv) and 6-(trifluoromethyl)piperidine-2,4-dione (0.71 g, 3.900 mmol, 1.1 equiv) in EtOH (15 mL) was added NH_4OAc (1.37 g, 17.725 mmol, 5.0 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 6 h at 50 °C under nitrogen atmosphere. The aqueous layer was extracted with EtOAc (3x30 mL). The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford 2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-6-(trifluoromethyl)-

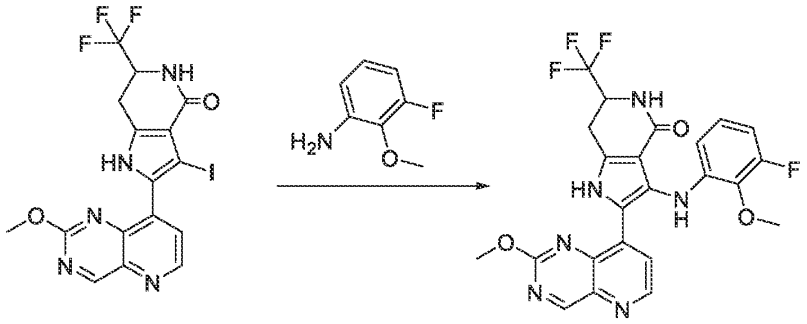
1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (850 mg, 66.00%) as a light yellow solid.

LC-MS: M+H found: 364.



A solution of 2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-6-(trifluoromethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (300 mg, 0.826 mmol, 1.00 equiv) and NIS (222.94 mg, 0.991 mmol, 1.2 equiv) in DMF (5 mL) was stirred for 1h at 40 degrees C. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water; detector, UV 254 nm to afford 3-iodo-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-6-(trifluoromethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (90 mg, 22.28%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 490.



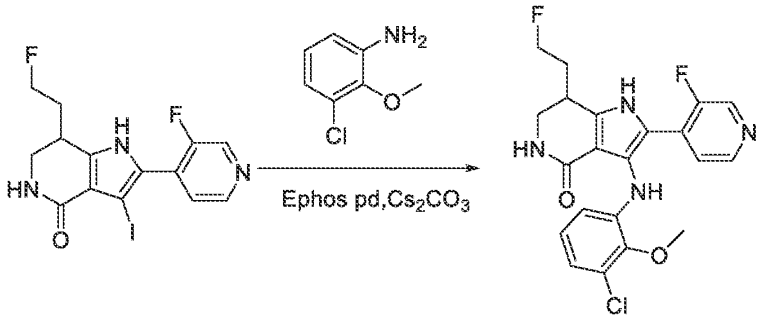
To a solution of 3-iodo-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-6-(trifluoromethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70 mg, 0.143 mmol, 1 equiv) and 3-fluoro-2-methoxyaniline (40.39 mg, 0.286 mmol, 2 equiv) in DMF (2 mL) were added Cs_2CO_3 (139.87 mg, 0.429 mmol, 3 equiv) and EPhos Pd G4 (26.29 mg, 0.029 mmol, 0.2 equiv), EPhos (15.30 mg, 0.029 mmol, 0.2 equiv). After stirring for 3h at 50 °C under a nitrogen

atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water; detector, UV 254 nm to afford 3-[(3-fluoro-2-methoxyphenyl)amino]-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-6-(trifluoromethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (5 mg, 6.27%) as an orange solid.

LC-MS: $(M+H)^+$ found 503.

^{1}H NMR (400 MHz, Chloroform-d) δ 14.26 (s, 1H), 13.48 (d, J = 4.8 Hz, 1H), 12.69 (d, J = 4.3 Hz, 1H), 12.50 (s, 1H), 12.43 (s, 1H), 12.42 (s, 1H), 11.40 – 11.35 (m, 1H), 11.27 (dd, J = 10.7, 1.7 Hz, 1H), 10.76 (d, J = 8.2 Hz, 1H), 9.22 (s, 1H), 8.97 (s, 3H), 8.63 (d, J = 0.9 Hz, 3H), 5.99 (s, 2H).

Example 43. 3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-fluoroethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 473)**

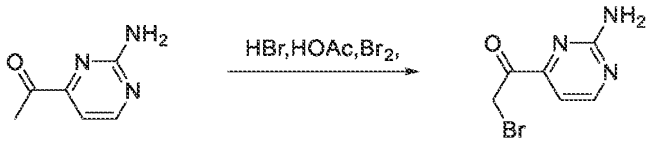


To a stirred mixture of 7-(2-fluoroethyl)-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 0.992 mmol, 1 equiv), Cs_2CO_3 (646.51 mg, 1.984 mmol, 2 equiv) and 3-chloro-2-methoxyaniline (234.54 mg, 1.488 mmol, 1.5 equiv) in DMF (5 mL) were added EPhos Pd G4 (91.13 mg, 0.099 mmol, 0.1 equiv) and EPhos (106.12 mg, 0.198 mmol, 0.2 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 50°C under nitrogen atmosphere. The resulting mixture was extracted with EtOAc (2 x100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 10% to100% gradient in 20 min; detector, UV 254 nm. to afford 3-[(3-chloro-2-

methoxyphenyl)amino]-7-(2-fluoroethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (12.6 mg, 39.04%) as an off-white solid.

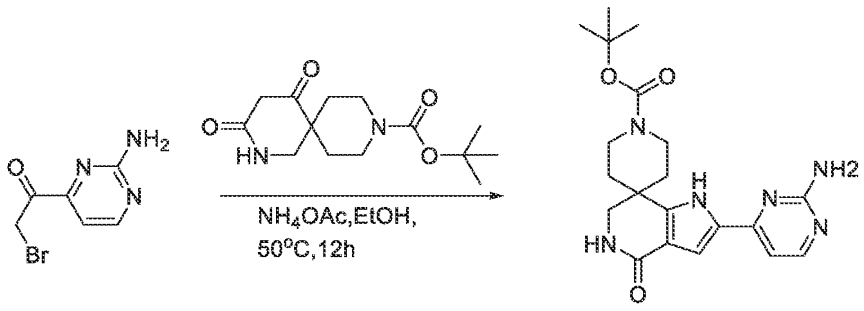
^{1}H NMR (400 MHz, DMSO-d6) δ 1.89 – 2.05 (m, 1H), 2.09 – 2.26 (m, 1H), 3.15 (dq, 1H), 3.23 – 3.32 (m, 1H), 3.54 – 3.61 (m, 1H), 3.86 (s, 3H), 4.55 (t, 1H), 4.67 (t, 1H), 6.13 (dd, 1H), 6.61 – 6.70 (m, 2H), 7.21 (t, 1H), 7.46 (dd, 1H), 7.60 (s, 1H), 8.31 (dd, 1H), 8.51 (d, 1H), 11.61 (s, 1H).

Example 44. 2'-(2-aminopyrimidin-4-yl)-3'-[(3-chloro-2-methoxyphenyl)amino]-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 556)**



To a stirred mixture of 1-(2-aminopyrimidin-4-yl) ethanone (8.3 g, 60.521 mmol, 1 equiv) and HBr in water (2.45 g, 30.261 mmol, 0.5 equiv) in HOAc (50 mL) was added Br_2 (9.67 g, 60.521 mmol, 1 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The resulting mixture was diluted with EtOAc. The precipitated solids were collected by filtration and washed with EtOAc. This resulted in 1-(2-aminopyrimidin-4-yl)-2-bromoethanone (12.3 g, 94.07%) as a yellow solid.

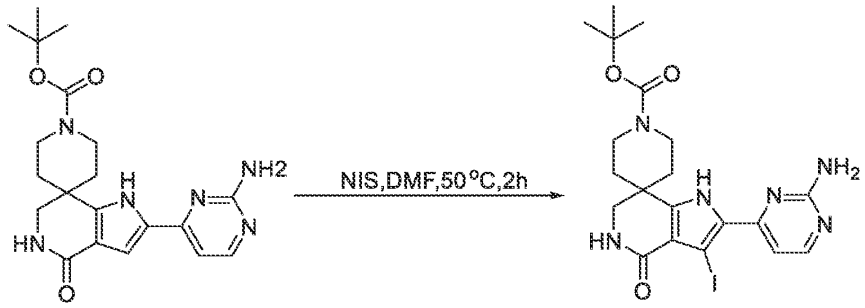
LC-MS: M+H found: 216.



A mixture of 1-(2-aminopyrimidin-4-yl)-2-bromoethanone (1 g, 4.629 mmol, 1 equiv) and NH_4OAc (1.43 g, 18.516 mmol, 4 equiv) in EtOH (20 mL) was stirred for overnight

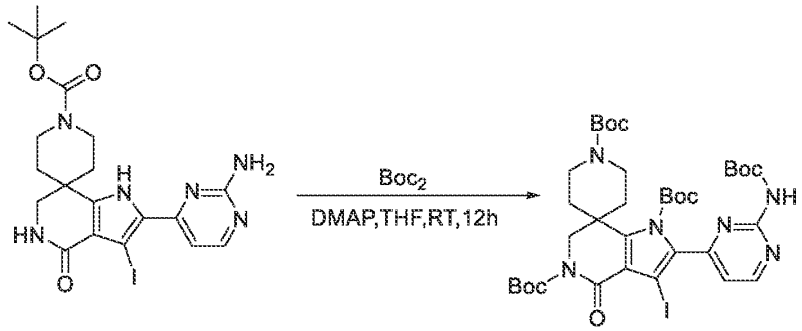
at 60 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with water. The precipitated solids were collected by filtration and washed with MeOH. This resulted in tert-butyl 2'-(2-aminopyrimidin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (1.2 g, 65.06%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 399.



A mixture of tert-butyl 2'-(2-aminopyrimidin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c] pyridine]-1-carboxylate (850 mg, 2.133 mmol, 1 equiv) and NIS (527.92 mg, 2.346 mmol, 1.1 equiv) in DMF (20 mL) was stirred for 2 h at 50 °C under nitrogen atmosphere. The resulting mixture was diluted with water. The precipitated solids were collected by filtration and washed with water. This resulted in tert-butyl 2'-(2-aminopyrimidin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c] pyridine]-1-carboxylate (1.1 g, 98.34%) as a white solid.

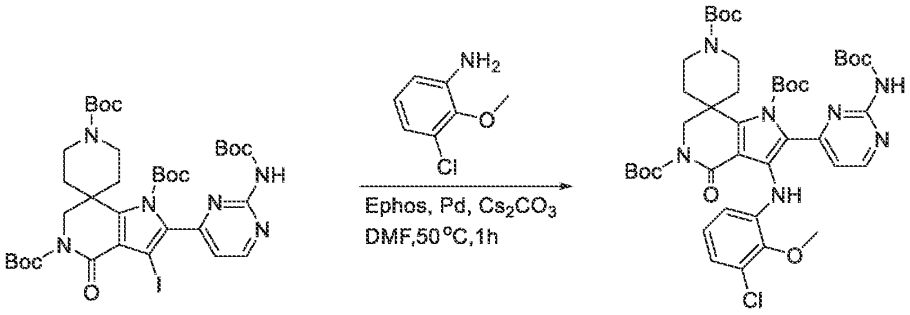
LC-MS: $(M+H)^+$ found: 525.



A mixture of tert-butyl 2'-(2-aminopyrimidin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (2 g, 3.814 mmol, 1 equiv)

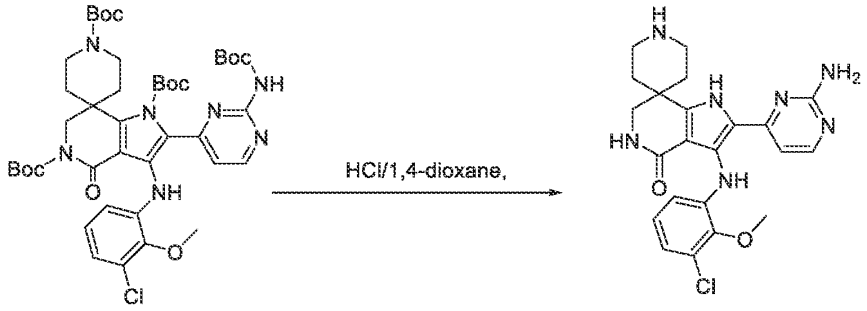
and DMAP (46.60 mg, 0.381 mmol, 0.1 equiv) in THF (20 mL) was stirred for overnight at room temperature under air atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (5:1) to afford 1,1',5'-tri-tert-butyl 2'-{2-[(tert-butoxycarbonyl)amino]pyrimidin-4-yl}-3'-iodo-4'-oxo-6'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1,1',5'-tricarboxylate (2 g, 63.58%) as a white solid.

LC-MS: $(M+H)^+$ found: 825.



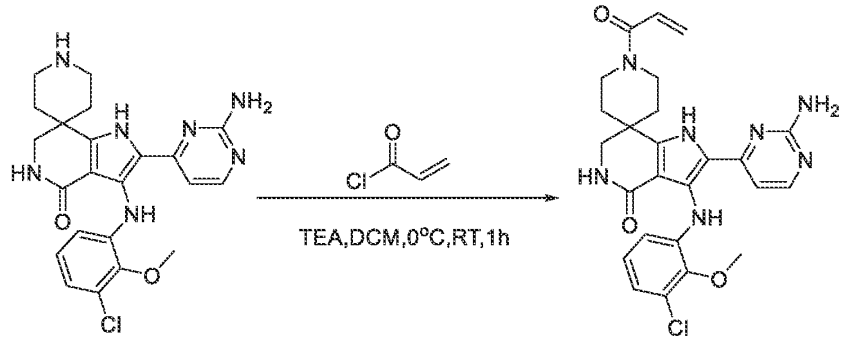
A mixture of 1,1',5'-tri-tert-butyl 2'-{2-[(tert-butoxycarbonyl)amino]pyrimidin-4-yl}-3'-iodo-4'-oxo-6'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1,1',5'-tricarboxylate (380 mg, 0.461 mmol, 1 equiv), 3-chloro-2-methoxyaniline (217.85 mg, 1.383 mmol, 3 equiv), EPhos Pd G4 (42.32 mg, 0.046 mmol, 0.1 equiv), EPhos (49.28 mg, 0.092 mmol, 0.2 equiv) and Cs_2CO_3 (450.38 mg, 1.383 mmol, 3 equiv) in DMF (9 mL) was stirred for 2 h at 50 °C under nitrogen atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (5:1) to afford 1,1',5'-tri-tert-butyl 2'-{2-[(tert-butoxycarbonyl)amino]pyrimidin-4-yl}-3'-[(3-chloro-2-methoxyphenyl)amino]-4'-oxo-6'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1,1',5'-tricarboxylate (160 mg, 40.64%) as a white solid.

LC-MS: $(M+H)^+$ found: 854.



A mixture of 1,1',5'-tri-tert-butyl 2'-{2-[(tert-butoxycarbonyl)amino]pyrimidin-4-yl}-3'-[(3-chloro-2-methoxyphenyl)amino]-4'-oxo-6'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1,1',5'-tricarboxylate (160 mg, 0.187 mmol, 1 equiv) in HCl(gas) in 1,4-dioxane (4 mL) was stirred for 2 h at room temperature under air atmosphere. The resulting mixture was concentrated under reduced pressure. The mixture/residue was acidified/basified/neutralized to pH 8 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. This resulted in 2'-(2-aminopyrimidin-4-yl)-3'-[(3-chloro-2-methoxyphenyl)amino]-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (70 mg, 82.35%) as a brown solid.

LC-MS: $(M+H)^+$ found: 454.



To a stirred mixture of 2'-(2-aminopyrimidin-4-yl)-3'-[(3-chloro-2-methoxyphenyl)amino]-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (60 mg, 0.132 mmol, 1 equiv) and TEA (40.13 mg, 0.396 mmol, 3 equiv) in DCM

(2 mL) was added acryloyl chloride (14.36 mg, 0.158 mmol, 1.2 equiv) dropwises at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of Water/Ice at 0 °C. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30*150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%NH_3*H_2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 42% B in 8 min, 42% B; Wave Length: 254; 220 nm; RT1(min): 7.58) to afford 2'-(2-aminopyrimidin-4-yl)-3'-[(3-chloro-2-methoxyphenyl)amino]-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (9.3 mg, 13.85%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 508.

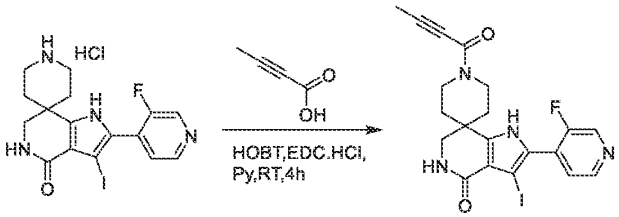
^{1}H NMR (300 MHz, DMSO-d6) δ 11.40 (s, 1H), 8.31 (s, 1H), 8.08 (d, J = 5.4 Hz, 1H), 7.29 (s, 1H), 6.94 – 6.68 (m, 3H), 6.56 (d, J = 5.3 Hz, 1H), 6.38 (dd, J = 7.8, 1.9 Hz, 1H), 6.24 (s, 2H), 6.16 (dd, J = 16.7, 2.5 Hz, 1H), 5.79 – 5.66 (m, 1H), 4.45 (d, J = 13.3 Hz, 1H), 4.05 (d, J = 13.8 Hz, 1H), 3.89 (s, 3H), 3.50 (d, J = 3.0 Hz, 2H), 3.28 – 3.13 (m, 1H), 2.81 (t, J = 13.0 Hz, 1H), 2.12 (s, 2H), 1.69 (d, J = 13.2 Hz, 2H).

Example 45. 1-(but-2-ynoyl)-3'-[(3-fluoro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 609)**



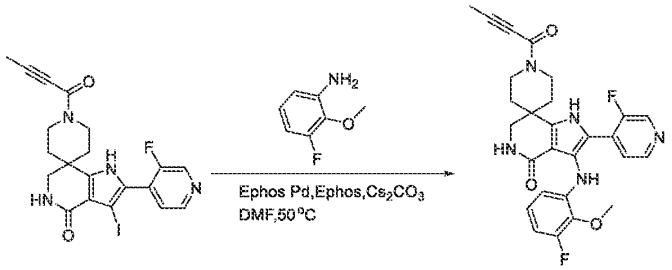
A mixture of tert-butyl 2'-(3-fluoropyridin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (500 mg, 0.950 mmol, 1 equiv)in HCl(gas)in 1,4-dioxane (10 mL) was stirred for 2 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. This resulted in 2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (350 mg, 86.44%) as a brown solid.

LC-MS: M+H found: 427.



A mixture of 2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (300 mg, 0.704 mmol, 1 equiv) and EDC*HCl (202.39 mg, 1.056 mmol, 1.5 equiv) in Pyridine (6 mL) was stirred for overnight at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH 15:1) to afford 1-(but-2-ynoyl)-2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (300 mg, 86.58%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 493.

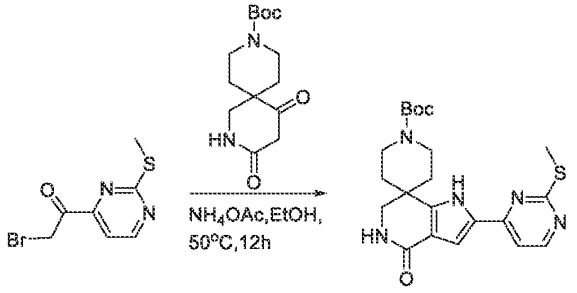


A mixture of 1-(but-2-ynoyl)-2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (280 mg, 0.569 mmol, 1 equiv), 3-fluoro-2-methoxyaniline (240.84 mg, 1.707 mmol, 3 equiv), EPhos Pd G4 (52.24 mg, 0.057 mmol, 0.1 equiv), EPhos (60.83 mg, 0.114 mmol, 0.2 equiv) and Cs_2CO_3 (555.95 mg, 1.707 mmol, 3 equiv) in DMF (6 mL) was stirred for 2 h at 50 °C under nitrogen atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (mg) was purified by Prep-HPLC with the following conditions to afford 1-(but-2-ynoyl)-3'-[(3-fluoro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (120 mg, 41.74%) as a white solid.

LC-MS: $(M+H)^+$ found: 506.

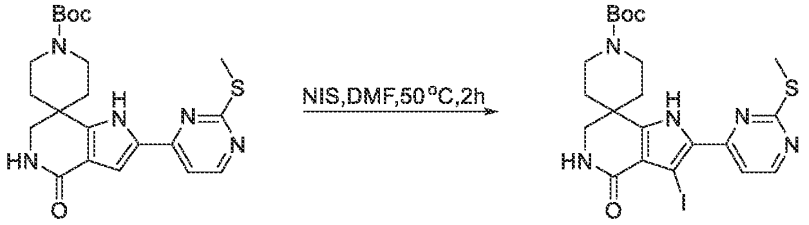
^{1}H NMR (400 MHz, DMSO-d6) δ 11.39 (s, 1H), 8.48 (d, J = 2.6 Hz, 1H), 8.32 (dd, J = 5.1, 1.2 Hz, 1H), 7.68 (s, 1H), 7.45 (dd, J = 6.7, 5.1 Hz, 1H), 7.36 (d, J = 2.7 Hz, 1H), 6.57 (td, J = 8.3, 6.1 Hz, 1H), 6.46 (ddd, J = 10.8, 8.3, 1.5 Hz, 1H), 5.94 (dt, J = 8.2, 1.4 Hz, 1H), 4.29 (d, J = 13.3 Hz, 1H), 4.22 (d, J = 13.5 Hz, 1H), 3.88 (s, 3H), 3.52 (t, J = 2.6 Hz, 2H), 2.94 – 2.83 (m, 1H), 2.12 – 2.00 (m, 1H), 2.05 (s, 3H), 1.92 (td, J = 13.2, 4.7 Hz, 1H), 1.80 (d, J = 13.3 Hz, 1H), 1.74 (d, J = 13.3 Hz, 1H).

Example 46. 3'-[(3-fluoro-2-methoxyphenyl)amino]-1-(prop-2-enoyl)-2'-(pyrimidin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 611)**



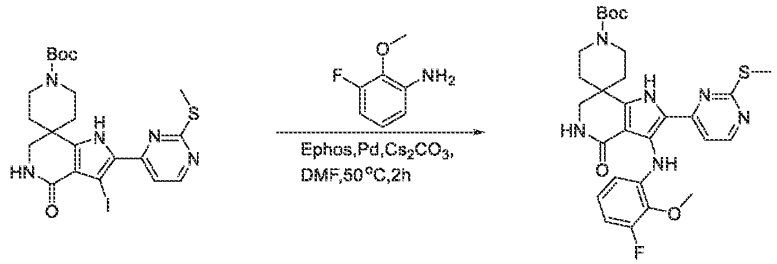
A mixture of 2-bromo-1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone (1.7 g, 6.880 mmol, 1 equiv), tert-butyl 3,5-dioxo-2,9-diazaspiro[5.5]undecane-9-carboxylate (2.14 g, 7.568 mmol, 1.1 equiv) and NH_4OAc (2.12 g, 27.520 mmol, 4 equiv) in EtOH (50 mL) was stirred for overnight at 50 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with water. The precipitated solids were collected by filtration and washed with acetonitrile. The crude product mixture was used in the next step directly without further purification.

LC-MS: M+H found: 430.



A mixture of tert-butyl 2'-[2-(methylsulfanyl)pyrimidin-4-yl]-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (6.3 g, 14.667 mmol, 1 equiv) and NIS (3.63 g, 16.134 mmol, 1.1 equiv) in DMF (100 mL) was stirred for 2 h at 50 °C under nitrogen atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (50:1) to afford tert-butyl 3'-iodo-2'-[2-(methylsulfanyl)pyrimidin-4-yl]-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (7.8 g, 95.75%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 556.



A mixture of tert-butyl 3'-iodo-2'-[2-(methylsulfanyl)pyrimidin-4-yl]-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (1.5 g, 2.701 mmol, 1 equiv) and Cs_2CO_3 (2.64 g, 8.103 mmol, 3 equiv) in DMF (30 mL) was stirred for 2 h at 50 °C under nitrogen atmosphere. The resulting mixture was diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (50:1) to afford tert-butyl 3'-[(3-fluoro-2-methoxyphenyl)amino]-2'-[2-(methylsulfanyl)pyrimidin-4-yl]-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (1.1 g, 71.63%) as a yellow solid.

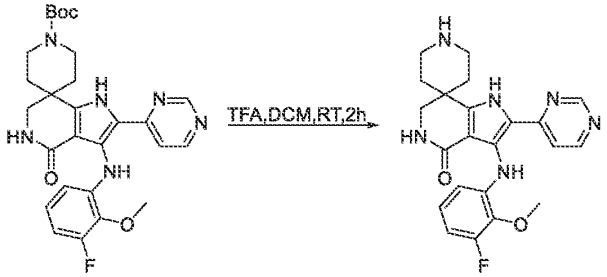
LC-MS: $(M+H)^+$ found: 569.



A mixture of tert-butyl 3'-[(3-fluoro-2-methoxyphenyl)amino]-2'-[2-(methylsulfanyl)pyrimidin-4-yl]-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (800 mg, 1.407 mmol, 1 equiv) and Raney Nickel (180.79 mg, 2.111 mmol, 1.5 equiv) in EtOH (16 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with EtOAc. The filtrate was concentrated under reduced pressure. The resulting mixture was

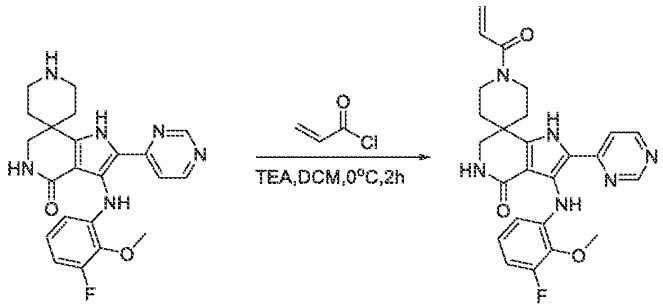
concentrated under reduced pressure. The crude product mixture was used in the next step directly without further purification. This resulted in tert-butyl 3'-[(3-fluoro-2-methoxyphenyl)amino]-4'-oxo-2'-(pyrimidin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (670 mg, 91.14%) as a brown solid.

LC-MS: $(M+H)^+$ found: 523.



A mixture of tert-butyl 3'-[(3-fluoro-2-methoxyphenyl)amino]-4'-oxo-2'-(pyrimidin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (800 mg, 1.531 mmol, 1 equiv) and TFA (1.75 g, 15.310 mmol, 10 equiv) in DCM (16 mL) was stirred for 2 h at room temperature under air atmosphere. The resulting mixture was concentrated under reduced pressure. The mixture was basified to pH 8 with saturated NaHCO3 (aq.). The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 3'-[(3-fluoro-2-methoxyphenyl)amino]-2'-(pyrimidin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (500 mg, 77.31%) as a brown solid.

LC-MS: $(M+H)^+$ found: 423.

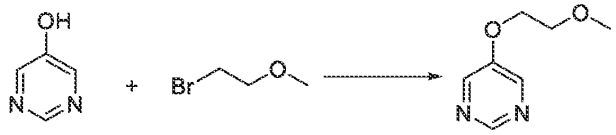


To a stirred mixture of 3'-[(3-fluoro-2-methoxyphenyl)amino]-2'-(pyrimidin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (300 mg, 0.710 mmol, 1 equiv) and TEA (215.57 mg, 2.130 mmol, 3 equiv) in DCM (6 mL) was added acryloyl

chloride (70.70 mg, 0.781 mmol, 1.1 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction was quenched with Water/Ice at 0 °C. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (mg) was purified by Prep-HPLC with the following conditions to afford 3'-[(3-fluoro-2-methoxyphenyl)amino]-1-(prop-2-enoyl)-2'-(pyrimidin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (110 mg, 32.51%) as a yellow solid. LC-MS: $(M+H)^+$ found: 477.

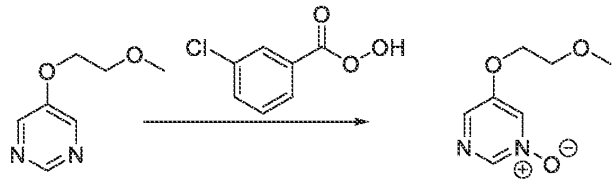
^{1}H NMR (300 MHz, DMSO-d6) δ 11.82 (s, 1H), 9.03 (d, J = 1.4 Hz, 1H), 8.56 (d, J = 5.6 Hz, 1H), 8.31 (s, 1H), 7.36 (d, J = 3.0 Hz, 1H), 7.29 (dd, J = 5.6, 1.4 Hz, 1H), 6.87 (dd, J = 16.7, 10.4 Hz, 1H), 6.77 (td, J = 8.3, 6.0 Hz, 1H), 6.60 (ddd, J = 11.0, 8.3, 1.4 Hz, 1H), 6.22 (dd, J = 8.3, 1.4 Hz, 1H), 6.16 (dd, J = 16.7, 2.6 Hz, 1H), 5.72 (dd, J = 10.4, 2.5 Hz, 1H), 4.45 (d, J = 13.2 Hz, 1H), 4.06 (d, J = 14.1 Hz, 1H), 3.95 (d, J = 0.9 Hz, 3H), 3.52 (d, J = 2.9 Hz, 2H), 3.26 (t, J = 13.3 Hz, 1H), 2.81 (t, J = 13.1 Hz, 1H), 2.14 (d, J = 8.4 Hz, 2H), 1.71 (d, J = 13.2 Hz, 2H).

Example 47. 3-[(3-fluoro-2-methoxyphenyl)amino]-2-[5-(2-methoxyethoxy)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 676)**



To a stirred mixture of pyrimidin-5-ol (2.00 g, 20.814 mmol, 1.00 equiv) and 2-bromoethyl methyl ether (3.47 g, 0.025 mmol, 1.2 equiv) in DMF (15.00 mL) was added K_2CO_3 (5.75 g, 0.042 mmol, 2.0 equiv) at rt under N_2 atmosphere. Then, the solution was stirred at 60 degrees C for 3h. The resulting mixture was diluted with water (50 mL) and extracted with 6x60 mL of EA. The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeOH in DCM, 0% to 5% gradient in 10 min; detector, UV 254 nm to afford 5-(2-methoxyethoxy) pyrimidine (0.848 g, 26.4%) as a yellow oil.

LC-MS: M+H found: 155.1.



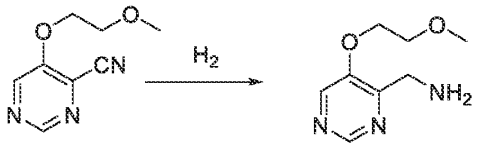
To a stirred solution of 5-(2-methoxyethoxy) pyrimidine (848.00 mg, 5.500 mmol, 1.00 equiv) in CHCl3 (8.00 mL) were added m-CPBA (1423.74 mg, 8.251 mmol, 1.5 equiv) at rt under N_2 atmosphere. The solution was stirred at rt for 1h first, and then stirred at 60 degrees C for 1.5h. The resulting mixture was diluted with saturated $NaHCO_3$ (30 mL) and extracted with 3x20 mL of EA. The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeOH in DCM, 0% to 10% gradient in 10 CV; detector, UV 254 nm to afford 5-(2-methoxyethoxy) pyrimidin-1-ium-1-olate (400mg, 43.2%) as a white solid.

LC-MS: M+H found: 171.0.



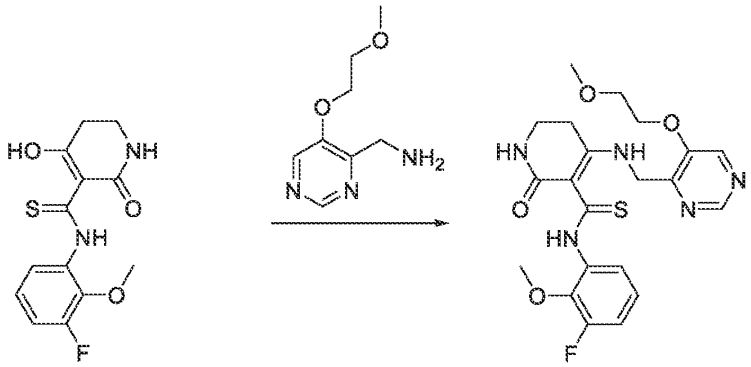
To a stirred solution of 5-(2-methoxyethoxy) pyrimidin-1-ium-1-olate (1.26 g, 7.404 mmol, 1.00 equiv) and Et3N (1.51 g, 0.015 mmol, 2.00 equiv) in ACN (6.00 mL) was addedtrimethylsilyl cyanide (0.73 g, 7.404 mmol, 1.00 equiv) at rt. The solution was stirred at rt for 16h. The solution was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeOH in DCM 0% to 10% gradient in 10 CV; detector, UV 254 nm to afford the surplus of 5-(2-methoxyethoxy)pyrimidine-4-carbonitrile (523 mg, 39.42%) as a yellow oil.

LC-MS: M+H found: 180.15.



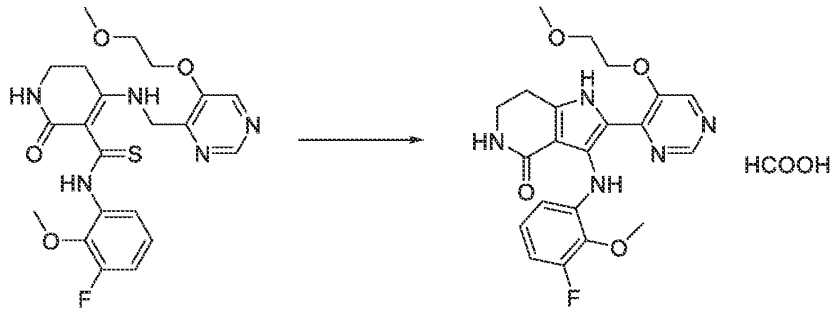
Into a 100 mL stand-up flask were added 5-(2-methoxyethoxy) pyrimidine-4-carbonitrile (523.00 mg, 2.919 mmol, 1.00 equiv), Raney Ni (55.00 mg, 0.642 mmol, 0.22 equiv) and NH3(g) in MeOH (15.00 mL) at rt. Then, the resulting solution was backfilled with the hydrogen. The solution was stirred at rt for 16h. The resulting mixture was filtered, the filtrate was concentrated under reduced pressure to afford 1-[5-(2-methoxyethoxy) pyrimidin-4-yl] methanamine (534 mg, 100%) as a blue oil.

LC-MS: M+H found: 171.05.



To a stirred solution of 1-[5-(2-methoxyethoxy) pyrimidin-4-yl] methanamine (534.00 mg, 2.915 mmol, 1.00 equiv) and N-(3-fluoro-2-methoxyphenyl)-4-hydroxy-2-oxo-5,6-dihydro-1H-pyridine-3-carbothioamide (863.68 mg, 2.915 mmol, 1.0 equiv) in DMA (15.00 mL) were added 4A molecular sieves (640.00 mg) at rt under N_2 atmosphere. Then, the solution was stirred at 120 degrees C for 2h. The resulting mixture was diluted with water (50 mL) and washed with EA (4x50 mL). Then, the organic layer was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeOH in DCM, 0% to 10% gradient in 10 CV; detector, UV 254 nm to afford N-(3-fluoro-2-methoxyphenyl)-4-([[5-(2-methoxyethoxy) pyrimidin-4-yl] methyl]amino)-2-oxo-5,6-dihydro-1H-pyridine-3-carbothioamide (299 mg, 22.2%) as a yellow solid.

LC-MS: M+H found: 462.15.

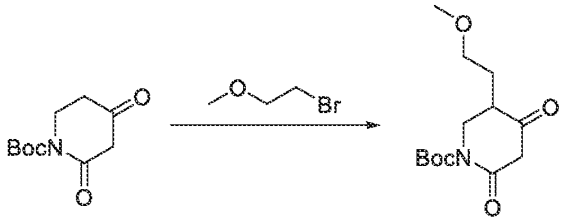


To a stirred solution of N-(3-fluoro-2-methoxyphenyl)-4-([[5-(2-methoxyethoxy)pyrimidin-4-yl]methyl]amino)-2-oxo-5,6-dihydro-1H-pyridine-3-carbothioamide (220.00 mg, 0.477 mmol, 1.00 equiv) and H_2O_2(30%) (81.10 mg, 2.384 mmol, 5.00 equiv) in DMSO (13.00 mL) were added TFA (59.80 mg, 0.524 mmol, 1.10 equiv) at rt under N_2 atmosphere. Then, the solution was stirred at 80 degrees C for 2h. The resulting mixture was diluted with water (60 mL) and extracted with 4x60 mL of EA.The filtrate was concentrated under reduced pressure. The residue was purified by re verse flash chromatography with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 35% B in 8 min; Wave Length: 254 nm; RT1(min): 6; to afford 3-[(3-fluoro-2-methoxyphenyl)amino]-2-[5-(2-methoxyethoxy)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (19.0 mg, 9.04%) as a yellow solid.

LC-MS: $(M+H)^+$ found 428.15.

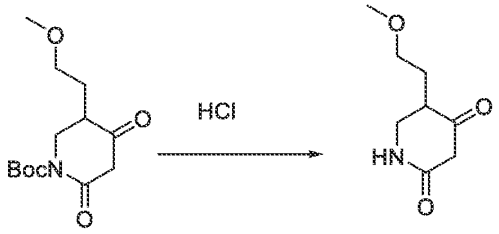
^{1}H NMR (300 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.12 (s, 1H), 8.70 (s, 1H), 8.51 (s, 1H), 7.16 (s, 1H), 6.73 (td, J = 8.3, 6.0 Hz, 1H), 6.55 (ddd, J = 11.1, 8.3, 1.5 Hz, 1H), 6.41 – 6.32 (m, 1H), 4.33 – 4.24 (m, 2H), 3.94 (d, J = 1.0 Hz, 3H), 3.84 – 3.69 (m, 2H), 3.45 (q, J = 4.5 Hz, 2H), 2.89 (t, J = 6.7 Hz, 2H).

Example 48. (7R)-2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4 one **(compound 726)**

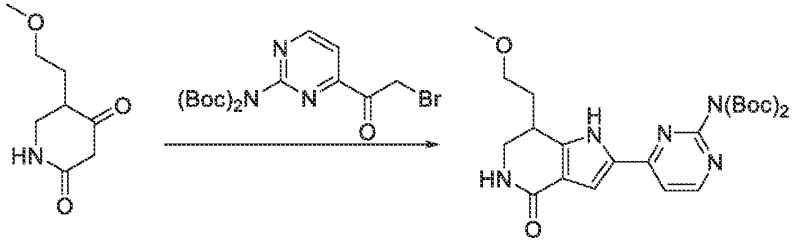


To a stirred solution of tert-butyl 2,4-dioxopiperidine-1-carboxylate (5.00 g, 23.449 mmol, 1.00 equiv) and 2-bromoethyl methyl ether (8.15 g, 58.623 mmol, 2.50 equiv) in THF (20.00 mL) were added LiHMDS (70.00 mL, 418.345 mmol, 17.84 equiv) at -20 degrees C under N2 atmosphere. Then, the solution was stirred at -20 degrees C for 1h. The mixture was diluted with water (50 ml) and added 2M HCl to ajust PH to 4, then extracted with 3×40 ml of EA. The filtrate was concentrated under reduced pressure to afford crude 5-(2-methoxyethyl)piperidine-2,4-dione (6.0 g, 149.47%) as a yellow oil.

LC-MS: M-57 found: 216.2.



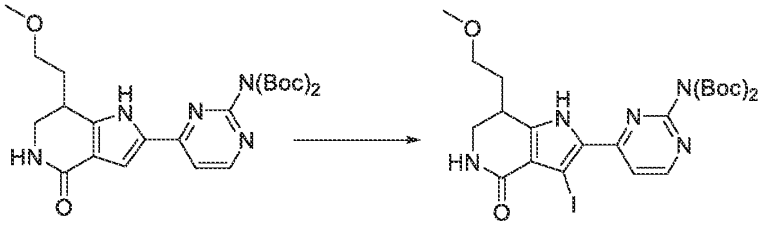
To a stirred solution of tert-butyl 5-(2-methoxyethyl)-2,4-dioxopiperidine-1-carboxylate (3.00 mg, 0.011 mmol, 1.00 equiv) in DCM (15.00 mL) were added HCl(gas)in 1,4-dioxane (15.00 mg, 0.219 mmol, 19.80 equiv) at 0 degrees C under N_2 atmosphere. Then, the solution was stirred at rt for 2h. The resulting mixture was concentrate under reduced pressure to afford about 3.2 g of crude product as a yellow oil. LC-MS: M+CH_3 found: 186.1.



To a stirred solution of 5-(2-methoxyethyl)piperidine-2,4-dione (1.90 mg, 0.011 mmol,

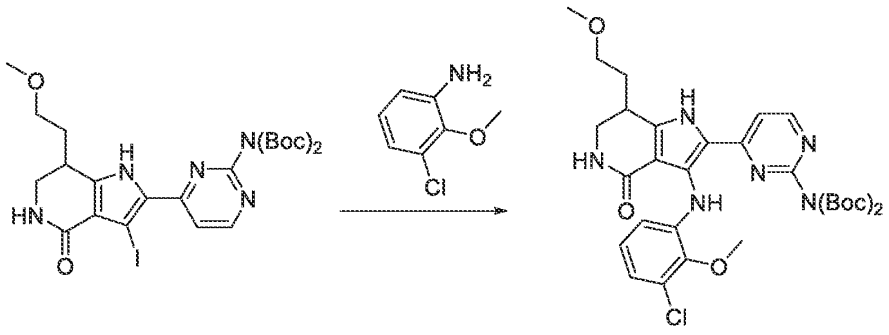
1.00 equiv) and NH_4OAc (5.13 mg, 0.066 mmol, 6.00 equiv) in EtOH (15.00 mL) were added tert-butyl N-[4-(2-bromoacetyl)pyrimidin-2-yl]-N-(tert-butoxycarbonyl)carbamate (4.62 mg, 0.011 mmol, 1.00 equiv) at rt under N_2 atmosphere. Then, the solution was stirred at 50 degrees C for 2h. The resulting mixture was diluted with water (50 ml), some solid was get by filtrated to afford crude product about 2.6g as a yellow solid.

LC-MS: M+H found: 488.15.



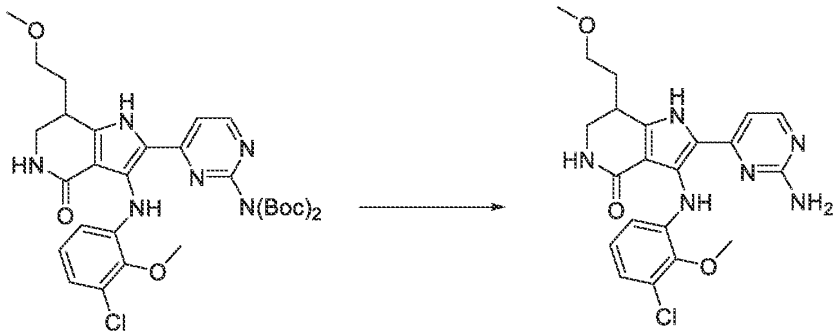
To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-[4-[7-(2-methoxyethyl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl]carbamate (1500.00 mg, 3.077 mmol, 1.00 equiv) in DMF (30.00 mL) were added NIS (969.05 mg, 4.307 mmol, 1.40 equiv) at rt under N_2 atmosphere. The solution was stirred at rt for 16h. The resulting mixture was diluted with water (80 ml) and extracted with 2×70 ml of EA. The combined organic layer was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeOH in DCM, 0% to 7% gradient in 10 min; detector, UV 254 nm to afford tert-butyl N-(tert-butoxycarbonyl)-N-[4-[3-iodo-7-(2-methoxyethyl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl]carbamate (650 mg, 34.44%) as a yellow oil.

LC-MS: M+H found: 614.05.



To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-[4-[3-iodo-7-(2-methoxyethyl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl]carbamate (650.00 mg, 1.060 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (250.48 mg, 1.589 mmol, 1.50 equiv) in dioxane (20.00 mL) were added Cs_2CO_3 (690.46 mg, 2.119 mmol, 2.00 equiv) and EPhos Pd G4 (145.99 mg, 0.159 mmol, 0.15 equiv) at rt under N_2 atmosphere. Then, the solution was stirred at 50 degrees C for 2h. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM: MeOH= 20:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (184 mg, 27.00%) as a yellow oil.

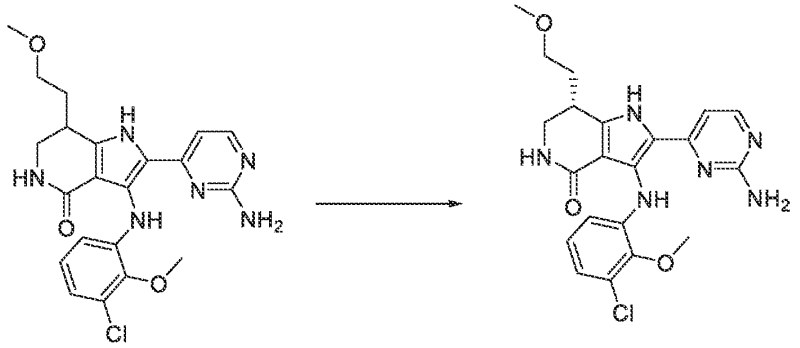
LC-MS: M-53 found: 589.1.



To a stirred solution of tert-butyl 4-[(3-chloro-2-methoxyphenyl)carbamothioyl]-3-([[3-(2-methoxy-2-methylpropoxy)pyridin-4-yl]methyl]amino)-5-oxo-2,6-dihydropyridine-1-carboxylate (100.00 mg, 0.165 mmol, 1.00 equiv) and H_2O_2 (11.24 mg, 0.330 mmol, 2.00 equiv) in EtOH (2.5. mL) were added TFA (20.73 mg, 0.182 mmol, 1.10 equiv) at rt under N_2 atmosphere. Then, the solution was stirred at 80 degrees C for 2h. The resulting mixture was diluted with water (20ml) and extracted with EA (3x20 ml). Then, the organic layer was concentrated under reduced pressure. The crude product (mg) was purified by Prep-HPLC with the following conditions Column: CHIRAL ART Cellulose-SC, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH3-MeOH), Mobile Phase B: IPA; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 14 min; Wave Length: 220/254 nm; RT1(min): 8.26; RT2(min): 11.54; to afford tert-butyl 3-[(3-chloro-2-methoxyphenyl)amino]-2-[3-(2-methoxy-2-methylpropoxy)pyridin-4-yl]-4-

oxo-1H,5H,7H-pyrrolo[2,3-c]pyridine-6-carboxylate(22.7 mg) as a yellow solid.

LC-MS: $(M+H)^+$ found 443.2.

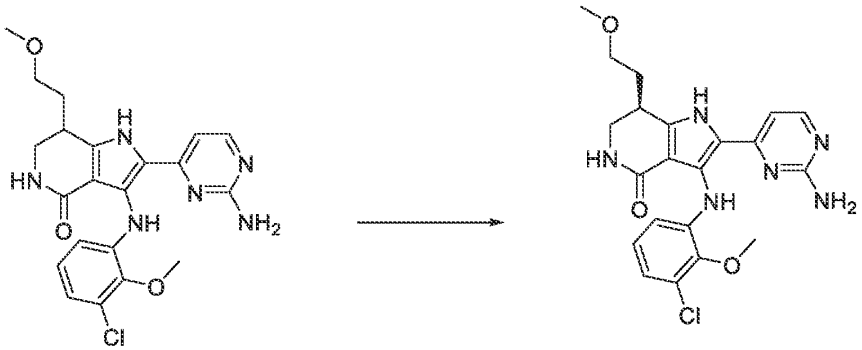


The 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (213.00 mg) was split into (7R)-2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4 one (44.5 mg, 20.89%) as a yellow solid.

LC-MS: $(M+H)^+$ found 443.2.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.46 (s, 1H), 8.07 (d, J = 5.3 Hz, 1H), 7.98 (s, 1H), 7.12 (s, 1H), 6.88 – 6.72 (m, 2H), 6.50 (d, J = 5.3 Hz, 1H), 6.36 (dd, J = 7.8, 1.9 Hz, 1H), 6.21 (s, 2H), 3.90 (s, 3H), 3.50 (d, J = 5.7 Hz, 3H), 3.35 (s, 3H), 3.23(m, 1H), 3.07(M, 1H), 2.04 – 1.93 (m, 1H), 1.77 (dd, J = 13.7, 7.7 Hz, 1H).

Example 49. (7S)-2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 727)**

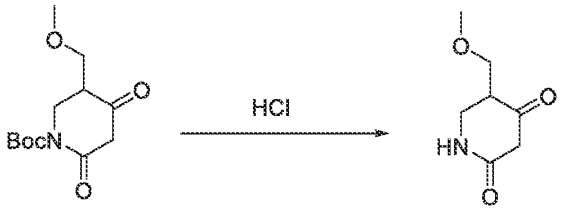


The 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (213.00 mg) was split(HPLC conditions: Column: CHIRAL ART Cellulose-SC, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH3-MeOH), Mobile Phase B: IPA; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 14 min; Wave Length: 220/254 nm; RT1(min): 8.26; RT2(min): 11.54㊣ into (7S)-2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (34.4 mg, 16.15%) as a yellow solid.

LC-MS: $(M+H)^+$ found 443.2.

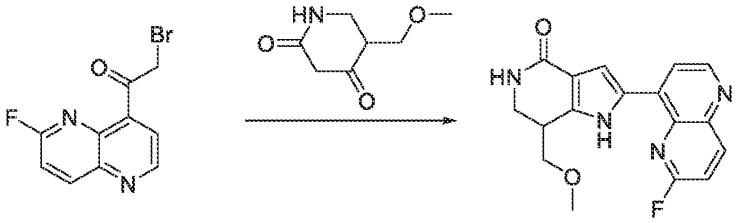
^{1}H NMR (300 MHz, DMSO-d6) δ 11.46 (s, 1H), 8.07 (d, J = 5.3 Hz, 1H), 7.98 (s, 1H), 7.12 (s, 1H), 6.88 – 6.72 (m, 2H), 6.50 (d, J = 5.3 Hz, 1H), 6.36 (dd, J = 7.8, 1.9 Hz, 1H), 6.21 (s, 2H), 3.90 (s, 3H), 3.50 (d, J = 5.7 Hz, 3H), 3.35 (s, 3H), 3.23(m, 1H), 3.07(M, 1H), 2.04 – 1.93 (m, 1H), 1.77 (dd, J = 13.7, 7.7 Hz, 1H).

Example 50. (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-methoxy-1,5-naphthyridin-4-yl)-7-(methoxymethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 765)**



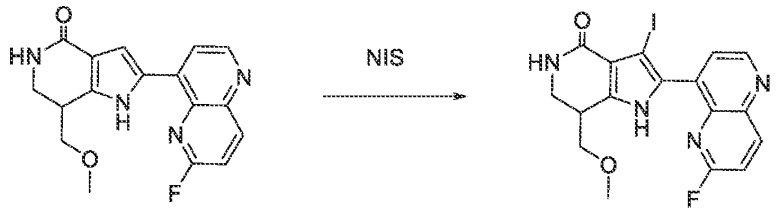
To a stirred solution of tert-butyl 5-(methoxymethyl)-2,4-dioxopiperidine-1-carboxylate (1.00 g, 3.887 mmol, 1.00 equiv) in DCM (5.00 mL) was added HCl(gas) in 1,4-dioxane (5.00 mL) at rt. The solution was stirred at rt about 2h. The resulting mixture was concentrated under reduced pressure to obtain 5-(methoxymethyl)piperidine-2,4-dione (1.04 g, 170.25%) as a yellow oil.

LC-MS: M+H found: 158.10.



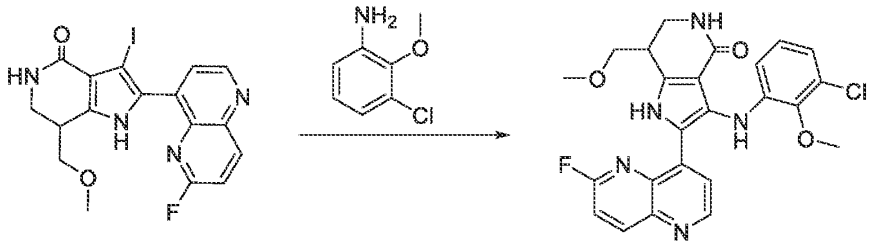
To a stirred solution of 5-(methoxymethyl)piperidine-2,4-dione (611.00 mg, 3.888 mmol, 1.00 equiv) and 2-bromo-1-(6-fluoro-1,5-naphthyridin-4-yl)ethanone (1046.03 mg, 3.888 mmol, 1.00 equiv) in EtOH (10.00 mL) were added NH_4OAc (1498.30 mg, 19.438 mmol, 5.00 equiv) at rt . Then the solution was stirred at 50 degrees C about 16h. The resulting mixture was diluted with water (200mL) and was filtered, and the filter cake was washed with 50 mL of EA. After filtration, the filtrate was concentrated under reduced pressure to obtain 22-(6-fluoro-1,5-naphthyridin-4-yl)-7-(methoxymethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (474.7 mg, 37.42%) as a red solid.

LC-MS: M+H found: 327.05.



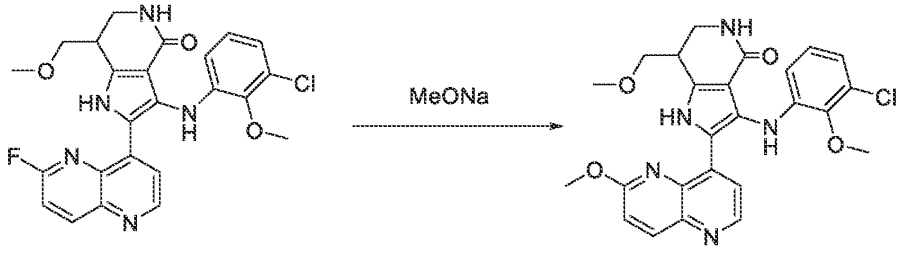
To a stirred solution of 2-(6-fluoro-1,5-naphthyridin-4-yl)-7-(methoxymethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (348.40 mg, 1.068 mmol, 1.00 equiv) in DMF (12.00 mL) and was added NIS (360.30 mg, 1.601 mmol, 1.50 equiv) at rt. The solution was stirred at rt about 16h. The resulting mixture was diluted with water (100mL) and filtered. The filterate was concentrated under reduced pressure to obtain 2-(6-fluoro-1,5-naphthyridin-4-yl)-3-iodo-7-(methoxymethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (392.6 mg, 81.32%) as a red solid.

LC-MS: M+H found: 453.05.



To a stirred solution of 2-(6-fluoro-1,5-naphthyridin-4-yl)-3-iodo-7-(methoxymethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100.00 mg, 0.221 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (52.27 mg, 0.332 mmol, 1.50 equiv) in dioxane (6.00 mL, 70.825 mmol, 320.29 equiv) in DMF (2.00mL) were added Cs_2CO_3 (144.10 mg, 0.442 mmol, 2.00 equiv), and EPhos Pd G4 (40.62 mg, 0.044 mmol, 0.20 equiv) at rt. The solution was stirred at 50 degrees C about 16h. The resulting mixture was diluted with water (50mL) and washed with 2x40 mL of EA. The combined organic layers were washed with saturated salt solution (2x40mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (MeOH : DCM= 30:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-7-(methoxymethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (85 mg, 79.76%) as a yellow solid.

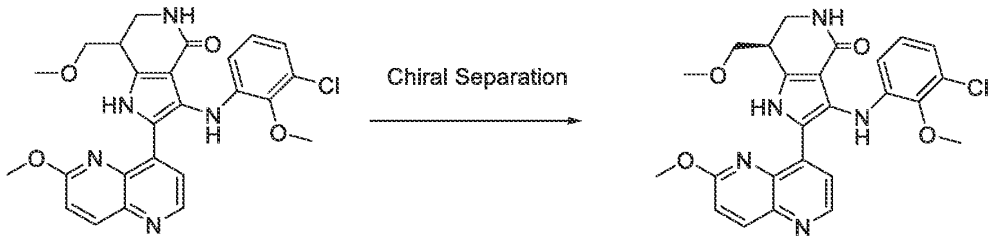
LC-MS: M+H found: 482.15.



To a stirred solution 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-7-(methoxymethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80.00 mg, 0.166 mmol, 1.00 equiv) in MeOH (4.00 mL) was added MeONa (10.76 mg, 0.199 mmol, 1.20 equiv) at rt. The solution was stirred at 80 degrees C under N_2 atmosphere about 1h. The resulting mixture was diluted with water (50mL) and was washed with 3x40 mL of EA. The combined organic layers were washed with saturated

salt solution (2x40mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to obtain 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-methoxy-1,5-naphthyridin-4-yl)-7-(methoxymethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (58.8 mg, 71.71%) as a yellow solid.

LC-MS: M+H found: 494.2.

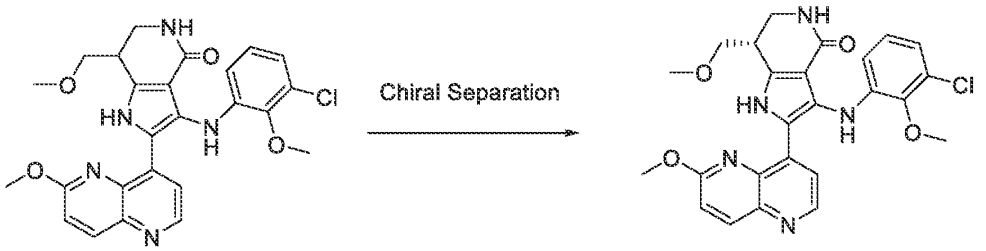


The 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-methoxy-1,5-naphthyridin-4-yl)-7-(methoxymethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (30 mg, 0.061 mmol, 1.00 equiv) was split into (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-methoxy-1,5-naphthyridin-4-yl)-7-(methoxymethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (10.8 mg, 36.00%) as a yellow solid.

LC-MS: M+H found 494.0.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.12 (s, 1H), 8.58 (d, J = 4.8 Hz, 1H), 8.31 (d, J = 9.1 Hz, 1H), 7.80 (s, 1H), 7.52 (d, J = 4.8 Hz, 1H), 7.37 (d, J = 9.1 Hz, 1H), 7.19 (s, 1H), 6.77 – 6.62 (m, 2H), 6.17 (dd, J = 7.7, 2.0 Hz, 1H), 4.20 (s, 3H), 3.89 (s, 3H), 3.62 (d, J = 6.5 Hz, 2H), 3.56 – 3.49 (m, 1H), 3.38 (d, J = 10.1 Hz, 2H), 2.68 (s, 3H).

Example 51. (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-methoxy-1,5-naphthyridin-4-yl)-7-(methoxymethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 764)**

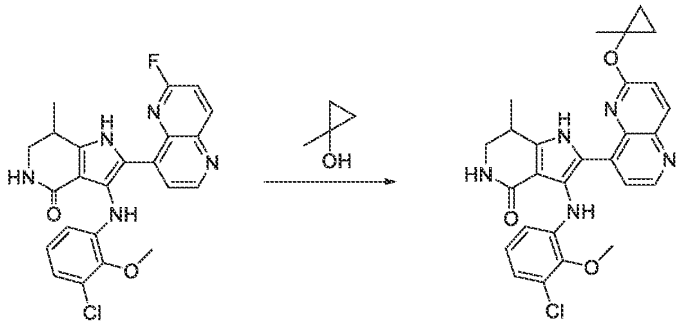


The 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-methoxy-1,5-naphthyridin-4-yl)-7-(methoxymethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (30 mg, 0.061 mmol, 1 equiv) was split into (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-methoxy-1,5-naphthyridin-4-yl)-7-(methoxymethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (7.8 mg, 26.00%) as a yellow solid.

LC-MS: M+H found 494.0.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.12 (s, 1H), 8.58 (d, J = 4.8 Hz, 1H), 8.31 (d, J = 9.1 Hz, 1H), 7.80 (s, 1H), 7.52 (d, J = 4.8 Hz, 1H), 7.37 (d, J = 9.1 Hz, 1H), 7.19 (s, 1H), 6.77 – 6.62 (m, 2H), 6.17 (dd, J = 7.7, 2.0 Hz, 1H), 4.20 (s, 3H), 3.89 (s, 3H), 3.62 (d, J = 6.5 Hz, 2H), 3.56 – 3.49 (m, 1H), 3.38 (d, J = 10.1 Hz, 2H), 2.68 (s, 3H).

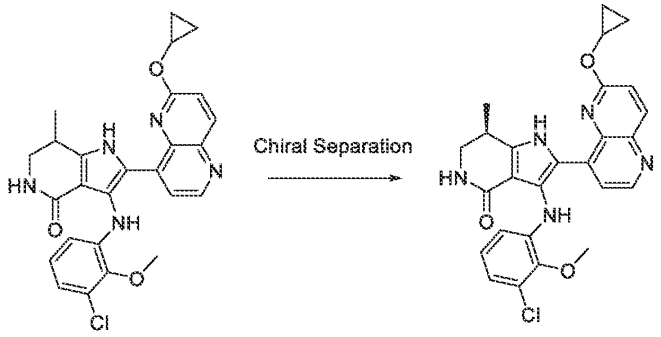
Example 52. (R)-3-((3-chloro-2-methoxyphenyl)amino)-2-(6-cyclopropoxy-1,5-naphthyridin-4-yl)-7-methyl-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(compound 769)**



A solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-7-methyl-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (700.24 mg, 1.550 mmol, 0.9 equiv) in DMF (1.5 mL) was treated with NaH (82.64 mg, 3.444 mmol, 2 equiv) for 30min at 0oC under nitrogen atmosphere followed by the addition of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-7-methyl-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (700.24 mg, 1.550 mmol, 0.9 equiv) in portions at RT for 2h .The reaction was ok. The aqueous layer was extracted with EA (3x10ml). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM/MeOH=10:1) to afford3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-cyclopropoxy-1,5-naphthyridin-4-yl)-7-methyl-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-

one as a yellow solid.

LC-MS: M+H found: 490.

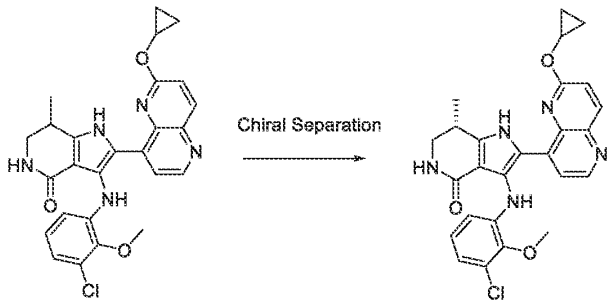


The crude product 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-cyclopropoxy-1,5-naphthyridin-4-yl)-7-methyl-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (58.00 mg) was purified by Prep-chiral-HPLC with the following conditions (Column: CHIRALPAK IG-3, 4.6*50mm, 3um; Mobile Phase A: (Hex: DCM=3: 1)(0.1% DEA): EtOH=50: 50; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) fractions containing the desired compound were evaporated to dryness to afford (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-cyclopropoxy-1,5-naphthyridin-4-yl)-7-methyl-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (12.1 mg) as a yellow solid and (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-cyclopropoxy-1,5-naphthyridin-4-yl)-7-methyl-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (12.1 mg) as a yellow solid

LC-MS: M+H found: 490.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.43 (s, 1H), 8.59 (d, J = 4.9 Hz, 1H), 8.32 (d, J = 9.0 Hz, 1H), 7.87 (s, 1H), 7.52 (d, J = 4.9 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 7.26 (d, J = 2.9 Hz, 1H), 6.79 – 6.67 (m, 2H), 6.18 (dd, J = 7.7, 1.9 Hz, 1H), 4.68 – 4.59 (m, 1H), 3.92 (s, 3H), 3.57 – 3.49 (m, 1H), 3.28 – 3.01 (m, 2H), 1.28 (d, J = 6.6 Hz, 3H), 0.98 – 0.86 (m, 4H).

Example 53. (S)-3-((3-chloro-2-methoxyphenyl)amino)-2-(6-cyclopropoxy-1,5-naphthyridin-4-yl)-7-methyl-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(compound 770)**

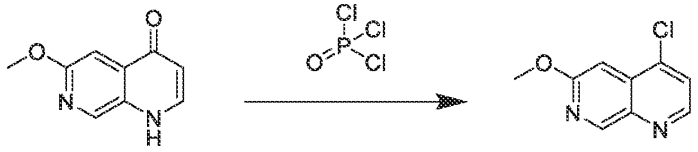


The crude product 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-cyclopropoxy-1,5-naphthyridin-4-yl)-7-methyl-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (58.00 mg) was purified by Prep-chiral-HPLC with the following conditions (Column: CHIRALPAK IG-3, 4.6*50mm, 3um; Mobile Phase A: (Hex: DCM=3: 1)(0.1% DEA): EtOH=50: 50; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) fractions containing the desired compound were evaporated to dryness to afford (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-cyclopropoxy-1,5-naphthyridin-4-yl)-7-methyl-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (12.1 mg) as a yellow solid and (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-cyclopropoxy-1,5-naphthyridin-4-yl)-7-methyl-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (12.1 mg) as a yellow solid

LC-MS: M+H found: 490.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.43 (s, 1H), 8.59 (d, J = 4.9 Hz, 1H), 8.32 (d, J = 9.1 Hz, 1H), 7.87 (s, 1H), 7.52 (d, J = 4.9 Hz, 1H), 7.34 (d, J = 9.1 Hz, 1H), 7.26 (d, J = 2.6 Hz, 1H), 6.79 – 6.67 (m, 2H), 6.18 (dd, J = 7.7, 1.9 Hz, 1H), 4.68 – 4.59 (m, 1H), 3.92 (s, 3H), 3.57 – 3.48 (m, 1H), 3.25 – 3.09 (m, 2H), 1.28 (d, J = 6.6 Hz, 3H), 0.97 – 0.88 (m, 4H).

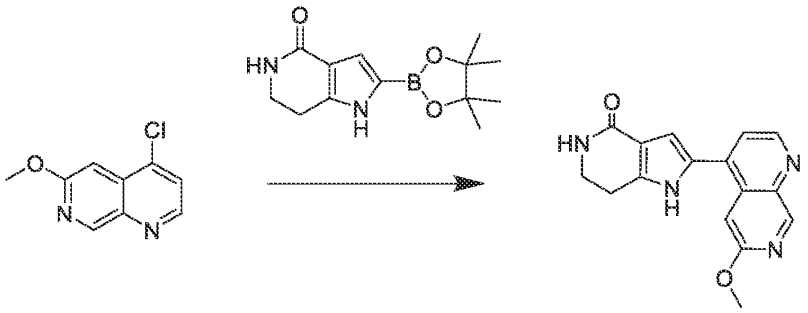
Example 54. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-methoxy-1,7-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 772)**



To a stirred mixture of 6-methoxy-1H-1,7-naphthyridin-4-one (400 mg, 2.270 mmol, 1.00

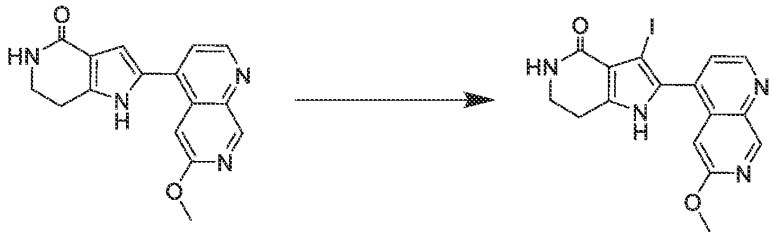
equiv) and phosphorus oxychloride (4 mL, 26.089 mmol, 11.49 equiv) for 2 hours at 100 degrees C under N_2 atmosphere. The reaction was quenched with H2O at 0 degrees C. The aqueous layer was extracted with EA and H2O 3x1 150 mL). The residue was purified by Prep-TLC (DCM:MeOH=18:1) to afford 4-chloro-6-methoxy-1,7-naphthyridine (420 mg, 95.05%) as a light yellow oil.

LC-MS: M+H found: 194.8.



To a stirred mixture of 4-chloro-6-methoxy-1,7-naphthyridine (60 mg, 0.308 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (105.05 mg, 0.400 mmol, 1.3 equiv) in dioxane (1.2 mL, 14.165 mmol, 45.95 equiv) and H_2O (0.3 mL, 16.653 mmol, 54.02 equiv) were added XPhos Pd G3 (26.10 mg, 0.031 mmol, 0.1 equiv) and K_2CO_3 (85.22 mg, 0.616 mmol, 2 equiv) in portions at RT. The resulting mixture was stirred for 2 hours at 80 degrees C under N2 atmosphere. The resulting mixture was filtered, then the filter cake was washed with EA (10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM and MeOH 10:1) to afford 2-(6-methoxy-1,7-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (88 mg, 96.99%) as a light yellow solid.

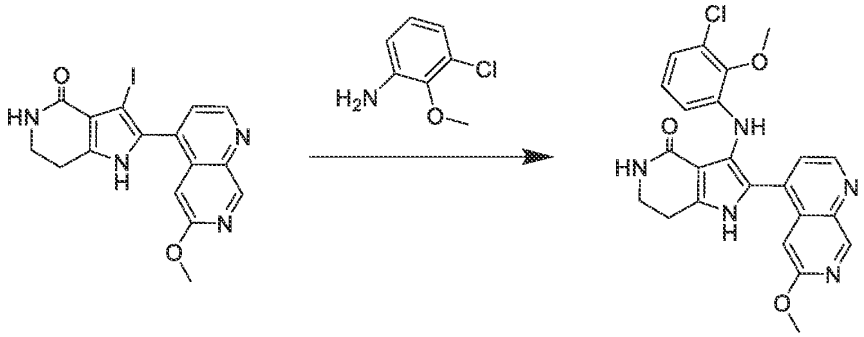
LC-MS: M+H found: 295.0.



To a stirred solution of 2-(6-methoxy-1,7-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-

c]pyridin-4-one (100 mg, 0.340 mmol, 1.00 equiv) in DMF (1 mL, 12.922 mmol, 38.03 equiv) was added NIS (91.73 mg, 0.408 mmol, 1.2 equiv) in portions at RT. The resulting mixture was stirred for 1 hour at RT. The resulting mixture was extracted with EA (3 x 10 mL). The combined organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM and MeOH 15:1) to afford 3-iodo-2-(6-methoxy-1,7-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (96 mg, 67.24%) as a light yellow solid.

LC-MS: M+H found: 420.95.



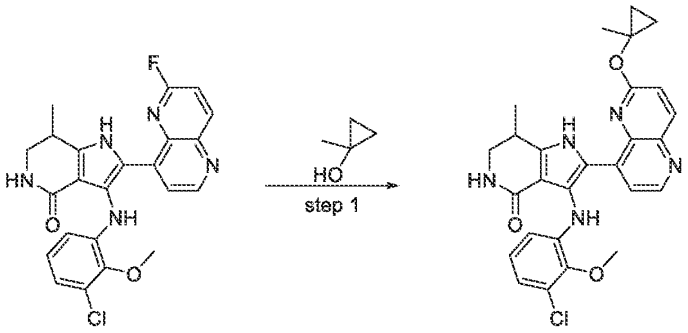
To a stirred mixture of 3-iodo-2-(6-methoxy-1,7-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (20.00 mg, 0.048 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (22.50 mg, 0.143 mmol, 3 equiv) in dioxane (0.50 mL) were added Cs2CO3 (46.52 mg, 0.143 mmol, 3 equiv) and EPhos Pd G4 (8.74 mg, 0.010 mmol, 0.2 equiv) in portions at RT under N2 atmosphere. The resulting mixture was stirred for 16 hours at 50 degrees C under N_2 atmosphere. The resulting mixture was filtered, then the filter cake was washed with EA (1x1 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM and MeOH 25:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-methoxy-1,7-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.8 mg, 8.11%) as a yellow solid.

LC-MS: $(M+H)^+$ found 449.95.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.80 (s, 1H), 9.08 (s, 1H), 8.82 (d, J = 4.4 Hz, 1H), 7.74 (s, 1H), 7.63 – 7.56 (m, 1H), 7.25 (d, J = 14.4 Hz, 2H), 6.51 (d, J = 8.3 Hz, 1H), 6.38 (t, J = 8.1 Hz, 1H), 6.05 (d, J = 8.2 Hz, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.49 (s, 2H), 2.92

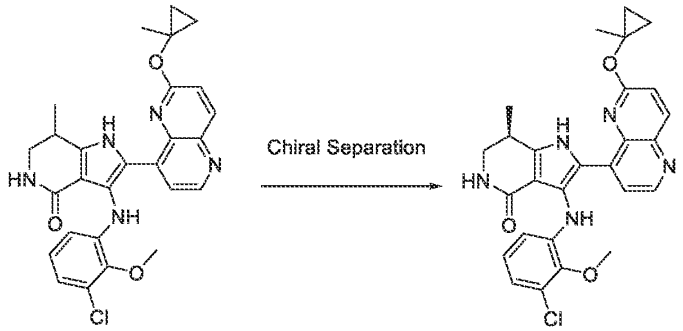
(d, J = 7.4 Hz, 2H).

Example 55. (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-methyl-2-[6-(1-methylcyclopropoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (23 mg)as a yellow solid and (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-7-methyl-2-[6-(1-methylcyclopropoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 774)**



A solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-7-methyl-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (564.02 mg, 1.248 mmol, 0.9 equiv) in DMF was treated with NaH (66.56 mg, 2.774 mmol, 2 equiv) for 30min at 0oC under nitrogen atmosphere followed by the addition of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-7-methyl-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (564.02 mg, 1.248 mmol, 0.9 equiv) dropwise/ in portions at RT for 2h .The reaction was ok. The aqueous layer was extracted with EA (3x10ml). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM/MeOH=10:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-7-methyl-2-[6-(1-methylcyclopropoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50 mg, 7.15%) as a light yellow solid.

LC-MS: M+H found: 504.

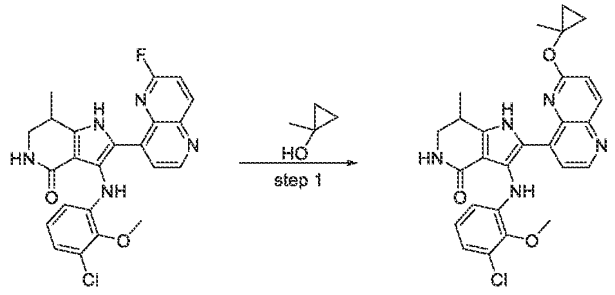


The crude product 3-[(3-chloro-2-methoxyphenyl)amino]-7-methyl-2-[6-(1-methylcyclopropoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50.00 mg) was purified by Prep-chiral-HPLC with the following conditions (Column: CHIRALPAK IG-3, 4.6*50mm, 3um; Mobile Phase A: (Hex: DCM=3: 1)(0.1% DEA): EtOH=50: 50; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) fractions containing the desired compound were evaporated to dryness to afford (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-methyl-2-[6-(1-methylcyclopropoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (23 mg)as a yellow solid and (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-7-methyl-2-[6-(1-methylcyclopropoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (23 mg) as a yellow solid.

LC-MS: M+H found: 504.

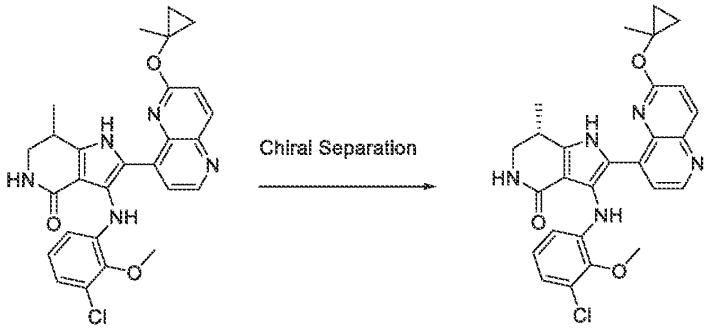
^{1}H NMR (400 MHz, DMSO-d6) δ 12.56 (s, 1H), 8.58 (d, J = 4.9 Hz, 1H), 8.31 (d, J = 9.1 Hz, 1H), 7.81 (s, 1H), 7.52 (d, J = 4.9 Hz, 1H), 7.31 (d, J = 9.1 Hz, 1H), 7.25 (d, J = 3.5 Hz, 1H), 6.79 – 6.67 (m, 2H), 6.20 (dd, J = 7.9, 1.8 Hz, 1H), 3.95 (s, 3H), 3.64 (dd, J = 12.1, 4.7 Hz, 1H), 3.17 (ddt, J = 15.9, 12.1, 4.1 Hz, 2H), 2.08 (s, 1H), 1.79 (s, 3H), 1.30 (d, J = 6.7 Hz, 3H), 1.20 (dp, J = 18.0, 6.3, 5.6 Hz, 2H), 0.96 (q, J = 4.8 Hz, 2H).

Example 56. (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-methyl-2-[6-(1-methylcyclopropoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 775)**



A solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-7-methyl-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (564.02 mg, 1.248 mmol, 0.9 equiv) in DMF was treated with NaH (66.56 mg, 2.774 mmol, 2 equiv) for 30min at 0oC under nitrogen atmosphere followed by the addition of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-7-methyl-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (564.02 mg, 1.248 mmol, 0.9 equiv) dropwise/ in portions at RT for 2h .The reaction was ok. The aqueous layer was extracted with EA (3x10ml). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM/MeOH=10:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-7-methyl-2-[6-(1-methylcyclopropoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50 mg, 7.15%) as a light yellow solid.

LC-MS: M+H found: 504.



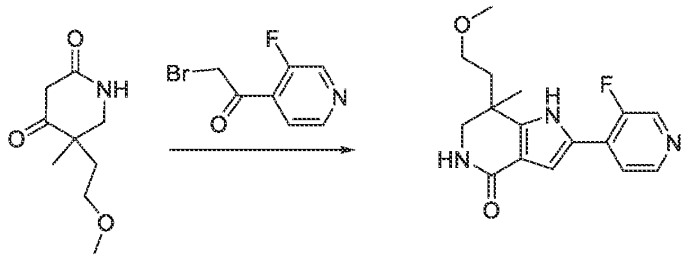
The crude product 3-[(3-chloro-2-methoxyphenyl)amino]-7-methyl-2-[6-(1-methylcyclopropoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50.00 mg) was purified by Prep-chiral-HPLC with the following conditions (Column: CHIRALPAK IG-3, 4.6*50mm, 3um; Mobile Phase A: (Hex: DCM=3: 1)(0.1% DEA):

EtOH=50: 50; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) fractions containing the desired compound were evaporated to dryness to afford (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-methyl-2-[6-(1-methylcyclopropoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (23 mg) as a yellow solid and (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-7-methyl-2-[6-(1-methylcyclopropoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (23 mg) as a yellow solid.

LC-MS: M+H found: 504.

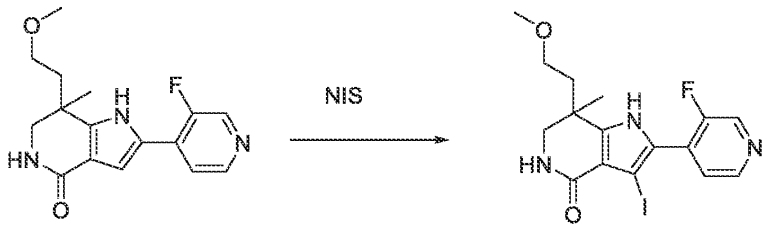
^{1}H NMR (400 MHz, DMSO-d6) δ 12.56 (s, 1H), 8.58 (d, J = 4.9 Hz, 1H), 8.31 (d, J = 9.1 Hz, 1H), 7.81 (s, 1H), 7.52 (d, J = 4.9 Hz, 1H), 7.31 (d, J = 9.1 Hz, 1H), 7.25 (d, J = 3.5 Hz, 1H), 6.79 – 6.67 (m, 2H), 6.20 (dd, J = 7.9, 1.8 Hz, 1H), 3.95 (s, 3H), 3.64 (dd, J = 12.0, 4.8 Hz, 1H), 3.17 (ddt, J = 15.9, 12.2, 4.1 Hz, 2H), 2.08 (s, 1H), 1.79 (s, 3H), 1.30 (d, J = 6.7 Hz, 3H), 1.20 (tt, J = 10.5, 5.6 Hz, 2H), 0.96 (q, J = 4.9 Hz, 2H).

Example 57. (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-7-methyl-1H,5H,6H-pyrrolo[3,2-c]pyridin-4-one **(compound 780)**



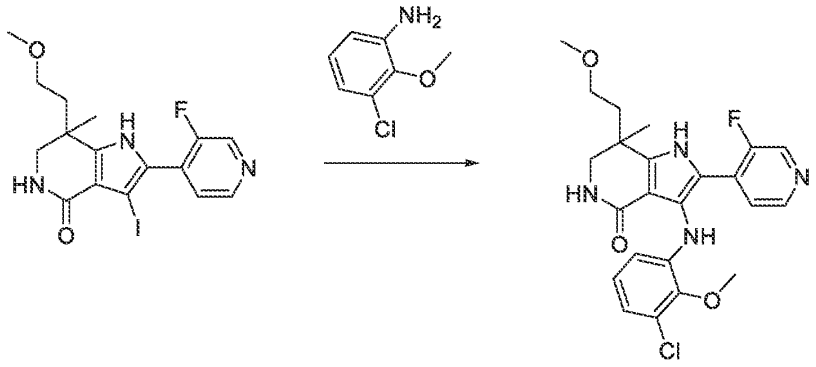
To a stirred solution of 5-(2-methoxyethyl)-5-methylpiperidine-2,4-dione (705 mg, 3.806 mmol, 1.00 equiv) and 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (829.85 mg, 3.806 mmol, 1 equiv) in EtOH (10 mL, 172.135 mmol, 45.22 equiv) was added NH4OAc (1466.97 mg, 19.030 mmol, 5 equiv) in portions at RT. The resulting mixture was stirred for 10 hours at 50 degrees C under N2 atmosphere. The mixture was allowed to cool down to RT. Desired product could be detected by LCMS. The crude resulting mixture was used in the next step directly without further purification.

LC-MS: M+H found: 304.25.



To a stirred solution of bis(2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-7-methyl-1H,5H,6H-pyrrolo[3,2-c]pyridin-4-one) (1000 mg, 1.648 mmol, 1.00 equiv) in DMF (10 mL, 129.218 mmol, 78.39 equiv) was added NIS (556.27 mg, 2.472 mmol, 1.5 equiv) in portions at RT. The resulting mixture was stirred for 1 hour at RT. The resulting mixture was extracted with EA (3 x 10 mL). The combined organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM :MeOH 15:1) to afford bis(2-(3-fluoropyridin-4-yl)-3-iodo-7-(2-methoxyethyl)-7-methyl-1H,5H,6H-pyrrolo[3,2-c]pyridin-4-one) (960 mg, 67.84%) as a light yellow solid.

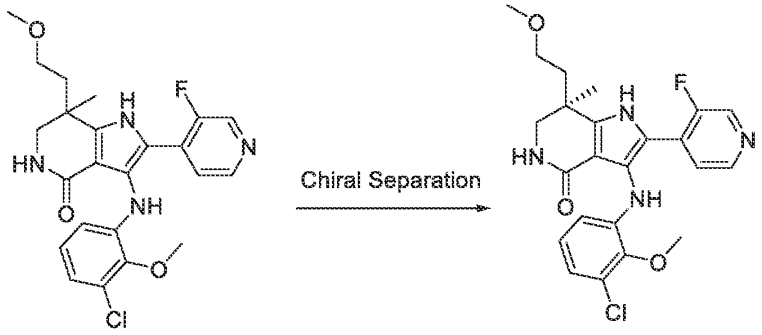
LC-MS: M+H found: 430.15.



To a stirred mixture of 2-(3-fluoropyridin-4-yl)-3-iodo-7-(2-methoxyethyl)-7-methyl-1H,5H,6H-pyrrolo[3,2-c]pyridin-4-one (480 mg, 1.118 mmol, 1.00 equiv) and EPhos Pd G4 (205.44 mg, 0.224 mmol, 0.2 equiv) and Cs2CO3 (1093.06 mg, 3.354 mmol, 3 equiv) in DMF (5 mL) was added 3-chloro-2-methoxyaniline (528.72 mg, 3.354 mmol, 3 equiv) in portions at RT under N2 atmosphere. The resulting mixture was stirred for 2 hours at 50 degrees C under N2 atmosphere. The resulting mixture was filtered, then the filter cake was washed with EA (1x1 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM and MeOH 20:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-7-methyl-

1H,5H,6H-pyrrolo[3,2-c]pyridin-4-one (275 mg, 53.59%) as a light yellow solid.

LC-MS: M+H found: 459.15.

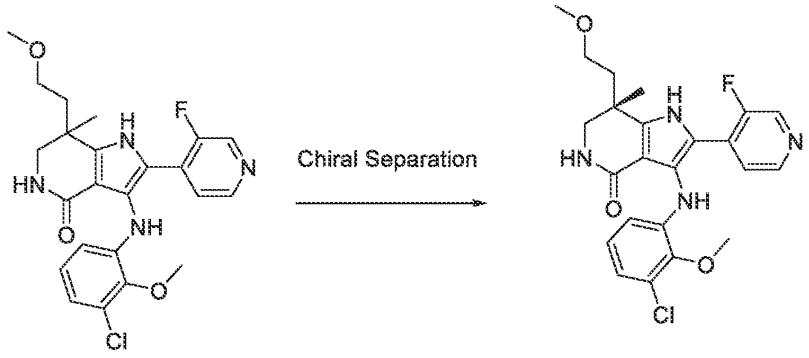


The crude product 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-7-methyl-1H,5H,6H-pyrrolo[3,2-c]pyridin-4-one (300.00 mg, 0.654 mmol, 1.00 equiv) was purified by Prep-Chiral-HPLC to afford (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-7-methyl-1H,5H,6H-pyrrolo[3,2-c]pyridin-4-one (117 mg, 38.81%) as a off-white solid.

LC-MS: $(M+H)^+$ found 459.0.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.37 (s, 1H), 8.50 (d, J = 2.8 Hz, 1H), 8.32 (dd, J = 5.0, 1.1 Hz, 1H), 7.65 (s, 1H), 7.45 (dd, J = 6.8, 5.1 Hz, 1H), 7.28 (d, J = 2.7 Hz, 1H), 6.70 – 6.59 (m, 2H), 6.11 (dd, J = 7.6, 2.1 Hz, 1H), 3.85 (s, 3H), 3.43 (td, J = 6.7, 2.8 Hz, 2H), 3.29 – 3.24 (m, 4H), 3.17 (dd, J = 12.5, 2.4 Hz, 1H), 1.99 (dt, J = 14.0, 7.0 Hz, 1H), 1.84 (dt, J = 13.6, 6.5 Hz, 1H), 1.33 (s, 3H).

Example 58. (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-7-methyl-1H,5H,6H-pyrrolo[3,2-c]pyridin-4-one **(compound 779)**

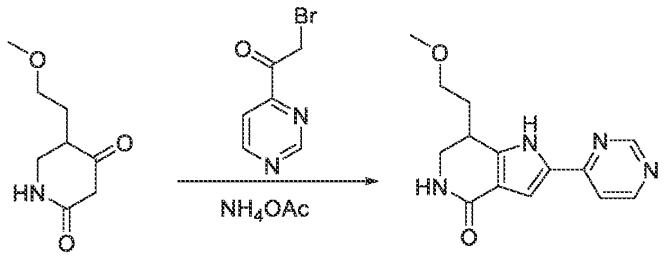


The crude product 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-7-methyl-1H,5H,6H-pyrrolo[3,2-c]pyridin-4-one (300.00 mg, 0.654 mmol, 1.00 equiv) was purified by Prep-Chiral-HPLC to afford (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-7-methyl-1H,5H,6H-pyrrolo[3,2-c]pyridin-4-one (111.5 mg, 36.98%) as a off-white solid.

LC-MS: $(M+H)^+$ found: 459. 0.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.37 (s, 1H), 8.50 (d, J = 2.7 Hz, 1H), 8.32 (dd, J = 5.0, 1.1 Hz, 1H), 7.66 (s, 1H), 7.45 (dd, J = 6.8, 5.1 Hz, 1H), 7.28 (t, J = 2.7 Hz, 1H), 6.70 – 6.59 (m, 2H), 6.11 (dd, J = 7.6, 2.1 Hz, 1H), 3.85 (s, 3H), 3.43 (dt, J = 6.8, 3.3 Hz, 2H), 3.31 – 3.24 (m, 4H), 3.17 (dd, J = 12.5, 2.4 Hz, 1H), 1.99 (dt, J = 13.9, 6.9 Hz, 1H), 1.84 (dt, J = 13.6, 6.5 Hz, 1H), 1.33 (s, 3H).

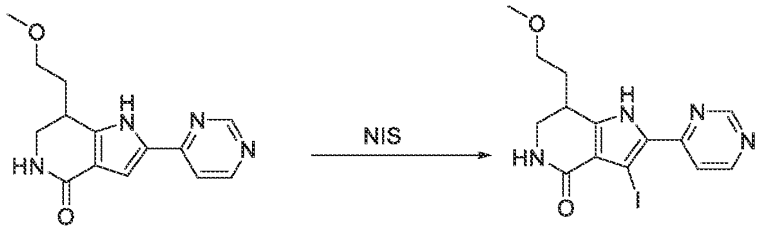
Example 59. (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-1-methyl-2-(pyrimidin-4-yl)-5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (13.9 mg) as a white solid and (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-1-methyl-2-(pyrimidin-4-yl)-5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 797)**



To a mixture of 5-(2-methoxyethyl)piperidine-2,4-dione (1.5 g, 8.762 mmol, 1 equiv) in

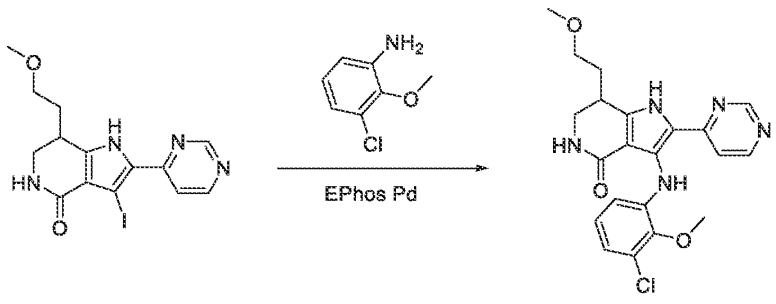
EtOH (2 mL) was added ammonium acetate (1350.79 mg, 17.524 mmol, 2 equiv) and 2-bromo-1-(pyrimidin-4-yl)ethanone (2113.61 mg, 10.514 mmol, 1.2 equiv) , the reaction mixture was stirred at 50°C for 16h, LCMS was OK. The reaction mixture was concentrated under vacuum. The residue was purified by flash chromatography (9%MeoH in DCM) to give 7-(2-methoxyethyl)-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (750 mg, 31.43%) as a red solid.

LC-MS: M+H found: 273.



To a mixture of 7-(2-methoxyethyl)-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (750 mg, 2.754 mmol, 1 equiv) in DMF (7 mL) was added iodo(sulfanyl)amine (575.02 mg, 3.305 mmol, 1.2 equiv) , the reaction mixture was stirred at 50°C for 2h. LCMS was ok. The reaction mixture was added to the saturated and extracted with DCM. The organic phase was concentrated under vacuum. The residue was purified by flash chromatography (9% MeOH in DCM) to give 3-iodo-7-(2-methoxyethyl)-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (700 mg, 63.83%) as a red solid.

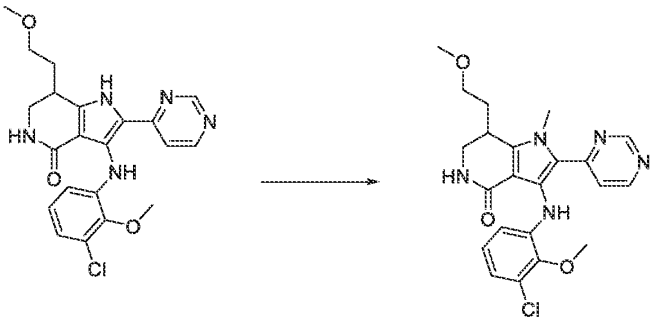
LC-MS: M+H found: 399.



Into a 20-mL sealed tube was placed 3-iodo-7-(2-methoxyethyl)-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (750 mg, 1.883 mmol, 1 equiv) in DMF(7mL),

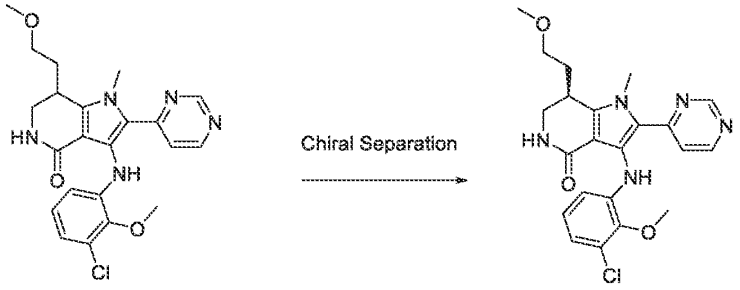
3-chloro-2-methoxyaniline (890.50 mg, 5.649 mmol, 3 equiv) ,EPhos Pd G4 (692.02 mg, 0.753 mmol, 0.4 equiv) and CS2CO3 (1227.33 mg, 3.766 mmol, 2 equiv). The resulting solution was stirred at 50oC for 2h. The reaction mixture was added to the ice water and extracted with EA. The organic phase was concentrated under vacuum. the residue was purified by Prep-Flash-HPLC with following conditions (9% MeOH in DCM). This resulted in 3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (160 mg, 19.85%) as a light yellow solid.

LC-MS: M+H found: 428



The reaction mixture was added to the saturated and extracted with DCM. The organic phase was concentrated under vacuum. The residue was purified by flash chromatography (9% MeOH in DCM) to give 3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-1-methyl-2-(pyrimidin-4-yl)-5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50 mg, 30.26%) as a light yellow solid.

LC-MS: M+H found: 428.



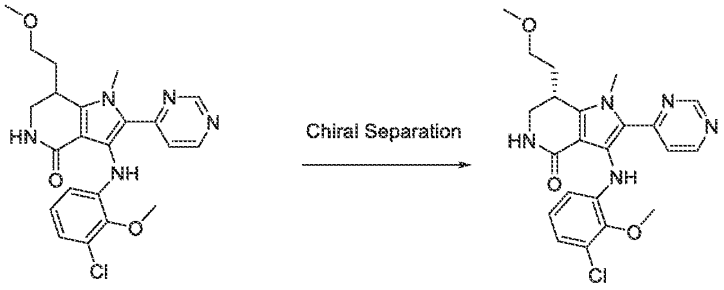
The crude product 3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-1-methyl-2-(pyrimidin-4-yl)-5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one)was purified by Prep-chiral-

HPLC with the following conditions (Column: CHIRALPAK IG-3, 4.6*50mm 3um; Mobile Phase A: (Hex: DCM=3: 1)(0.1%DEA): IPA=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) fractions containing the desired compound were evaporated to dryness to afford (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-1-methyl-2-(pyrimidin-4-yl)-5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (13.9 mg) as a white solid and (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-1-methyl-2-(pyrimidin-4-yl)-5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (16.9 mg) as a white solid.

LC-MS: M+H found: 442.

^{1}H NMR (300 MHz, DMSO-d6) δ 9.14 (s, 1H), 8.56 (d, J = 5.4 Hz, 1H), 7.69 (s, 1H), 7.42 (d, J = 5.5 Hz, 1H), 7.17 (s, 1H), 6.69 (d, J = 5.2 Hz, 2H), 6.13 (dd, J = 6.1, 3.2 Hz, 1H), 3.88 (d, J = 6.2 Hz, 6H), 3.55 – 3.35 (m, 4H), 3.28 (s, 3H), 3.18 (s, 1H), 1.88 – 1.71 (m, 2H).

Example 60. (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-1-methyl-2-(pyrimidin-4-yl)-5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **Compound 796)**



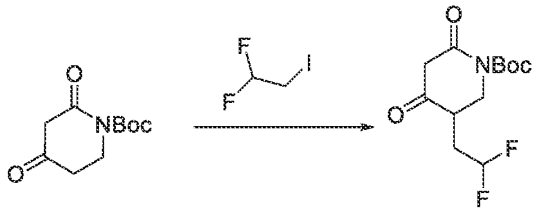
The crude product 3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-1-methyl-2-(pyrimidin-4-yl)-5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one)was purified by Prep-chiral-HPLC with the following conditions (Column: CHIRALPAK IG-3, 4.6*50mm 3um; Mobile Phase A: (Hex: DCM=3: 1)(0.1%DEA): IPA=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) fractions containing the desired compound were evaporated to dryness to afford (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-(2-methoxyethyl)-1-methyl-2-(pyrimidin-4-yl)-5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (13.9 mg) as a white solid and (7S)-3-[(3-chloro-2-

methoxyphenyl)amino]-7-(2-methoxyethyl)-1-methyl-2-(pyrimidin-4-yl)-5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (16.9 mg) as a white solid.

LC-MS: M+H found: 442.

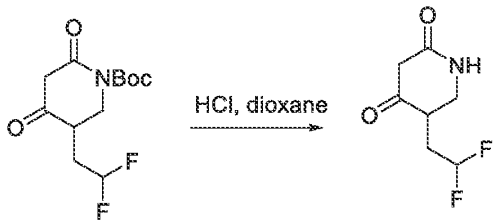
^{1}H NMR (300 MHz, DMSO-d6) δ 9.14 (s, 1H), 8.56 (d, J = 5.6 Hz, 1H), 7.69 (s, 1H), 7.42 (d, J = 5.6 Hz, 1H), 7.18 (s, 1H), 6.72 – 6.64 (m, 2H), 6.13 (dd, J = 6.7, 3.3 Hz, 1H), 3.88 (d, J = 6.2 Hz, 6H), 3.54 – 3.37 (m, 4H), 3.28 (s, 3H), 3.18 (s, 1H), 1.83 - 1.74 (m, 2H).

Example 61. (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-(2,2-difluoroethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 820)**



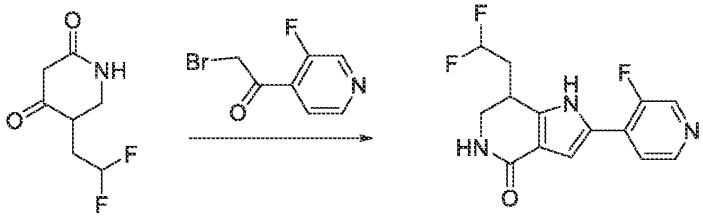
To a stirred mixture of pyrimidin-5-ol (2.00 g, 20.814 mmol, 1.00 equiv) and 2-bromoethyl methyl ether (3.47 g, 0.025 mmol, 1.2 equiv) in DMF (15.00 mL, 193.826 mmol, 9.31 equiv) was added K2CO3 (5.75 g, 0.042 mmol, 2.0 equiv) at rt under N2 atmosphere. Then, the solution was stirred at 60 degrees C for 3h. TLC: DCM: MeOH= 15:1. The resulting mixture was diluted with water (50 mL) and washed with 6x60 mL of EA. The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeOH in DCM, 0% to 5% gradient in 10 min; detector, UV 254 nm to afford 5-(2-methoxyethoxy) pyrimidine (0.848g) as a yellow oil.

LC-MS: M+H found: 221.95.



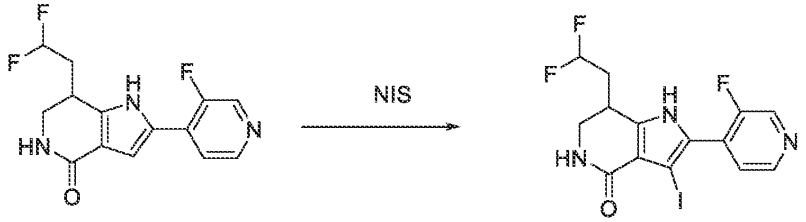
To a stirred solution of tert-butyl 5-(2,2-difluoroethyl)-2,4-dioxopiperidine-1-carboxylate (1.05 g, 3.787 mmol, 1.00 equiv) in DCM (7.5 mL, 117.975 mmol, 31.15 equiv) was added HCl(gas)in 1,4-dioxane (2.5 mL, 82.280 mmol, 21.73 equiv) dropwise at RT. Desired product could be detected by LCMS. The crude resulting mixture was used in the next step directly without further purification.

LC-MS: M+H found: 178.1.



To a stirred solution of 5-(2,2-difluoroethyl)piperidine-2,4-dione (800 mg, 4.516 mmol, 1.00 equiv) and NH4OAc (1740.49 mg, 22.580 mmol, 5 equiv) in EtOH (8 mL, 137.708 mmol, 30.49 equiv) was added 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (1181.50 mg, 5.419 mmol, 1.2 equiv) dropwise at RT. The resulting mixture was stirred for 16 hours at 50 degrees C under N2 atmosphere. The aqueous layer was extracted with EA and H2O (3x150 mL). The combined organic phase was concentrated to afford 7-(2,2-difluoroethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (825 mg, 61.87%) as a light yellow solid.

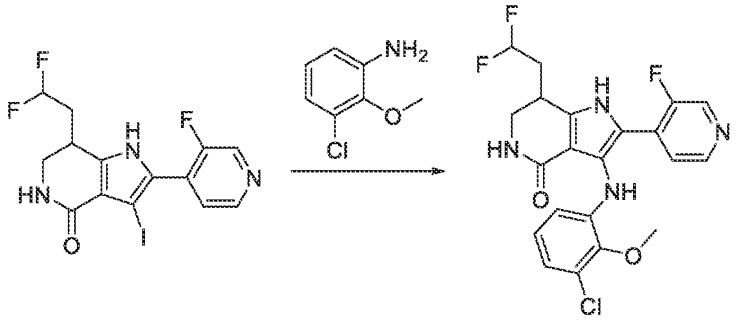
LC-MS: M+H found: 296.2.



To a stirred solution of 7-(2,2-difluoroethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (800 mg, 2.709 mmol, 1.00 equiv) in DMF (8 mL, 103.374 mmol, 38.15 equiv) was added NIS (914.37 mg, 4.064 mmol, 1.5 equiv) in portions at RT. The resulting mixture was stirred for 1 hour at RT. The resulting mixture was

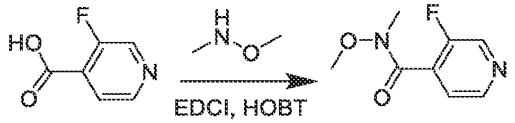
extracted with EA (3 x 10 mL). The combined organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM and MeOH 25:1) to afford 7-(2,2-difluoroethyl)-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (358 mg, 31.37%) as a light yellow solid.

LC-MS: M+H found: 243.05.



To a stirred mixture of 2-(3-fluoropyridin-4-yl)-3-iodo-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (500 mg, 1.204 mmol, 1.00 equiv) and EPhos (128.80 mg, 0.241 mmol, 0.2 equiv) and EPhos Pd G4 (221.23 mg, 0.241 mmol, 0.2 equiv) and Cs2CO3 (1177.07 mg, 3.612 mmol, 3 equiv) in DMF (5 mL) was added 3-fluoro-2-methoxyaniline (509.91 mg, 3.612 mmol, 3 equiv) in portions at RT under N2 atmosphere. The resulting mixture was stirred for 2 hours at 50 degrees C under N2 atmosphere. The resulting mixture was filtered, then the filter cake was washed with EA (1x1 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM and MeOH 20:1) to afford 3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (410 mg, 79.47%) as a light yellow solid.

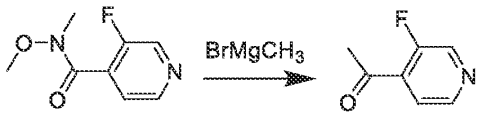
LC-MS: M+H found: 450.95.



To a stirred mixture of 3-fluoropyridine-4-carboxylic acid (6 g, 42.523 mmol, 1.00 equiv) and N,O-dimethylhydroxylamine (3.90 g, 63.785 mmol, 1.5 equiv) and EDCI (8.97 g, 46.775 mmol, 1.1 equiv) and HOBT (6.32 g, 46.775 mmol, 1.1 equiv) in DCM (150 mL,

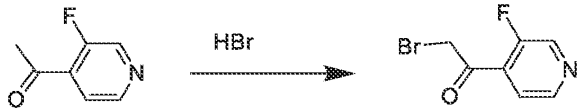
2359.507 mmol, 55.49 equiv) was added TEA (17.21 g, 170.092 mmol, 4 equiv) dropwise at RT. The resulting mixture was stirred for 16 hours at RT under N2 atmosphere. The aqueous layer was extracted with DCM and H2O (1x1 500 mL). The crude product was purified by Prep-HPLC to afford 3-fluoro-N-methoxy-N-methylpyridine-4-carboxamide (4.37 g, 55.80%) as a light yellow oil.

LC-MS: M+H found: 185.1.



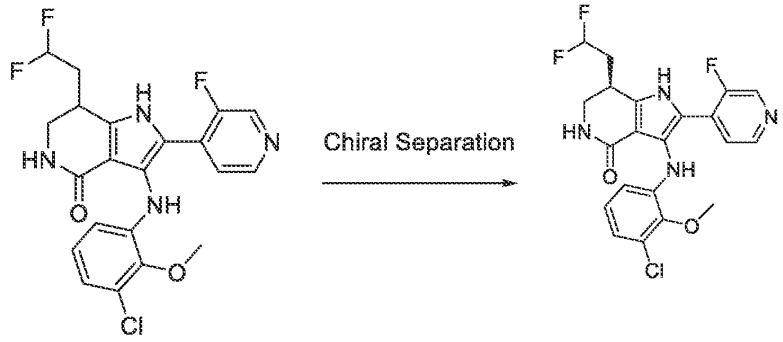
To a stirred solution of 3-fluoro-N-methoxy-N-methylpyridine-4-carboxamide; bromo(methyl)magnesium (3.87 g, 12.755 mmol, 1.00 equiv) in THF (40 mL) was added bromo(methyl)magnesium (2.28 g, 19.133 mmol, 1.5 equiv) dropwise at 0℃ under N2 atmosphere. The resulting mixture was stirred for 0.5 hour at rt under N2 atmosphere. The reaction was quenched with NH4Cl at 0℃. The aqueous layer was extracted with EA and H2O (1x1 300 mL). To afford 1-(3-fluoropyridin-4-yl)ethanone (2.5 g, 91.57%) as a light yellow oil.

LC-MS: M+H found: 140.05.



To a stirred solution of 1-(3-fluoropyridin-4-yl)ethanone (3 g, 21.563 mmol, 1.00 equiv) and hydrogen bromide (3 mL, 37.077 mmol, 1.72 equiv) in HAc (11 mL, 191.967 mmol, 8.90 equiv) was added Br2 (1.13 mL, 22.054 mmol, 1.02 equiv) dropwise at RT. The resulting mixture was stirred for 2.5 hours at 60℃ under N2 atmosphere. Desired product could be detected by LCMS. The mixture was allowed to cool down to RT. The product was precipitated by the addition of EA. The precipitated solids were collected by filtration to afford 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (4.4 g, 93.59%) as a light yellow solid.

LC-MS: M+H found: 450.95.

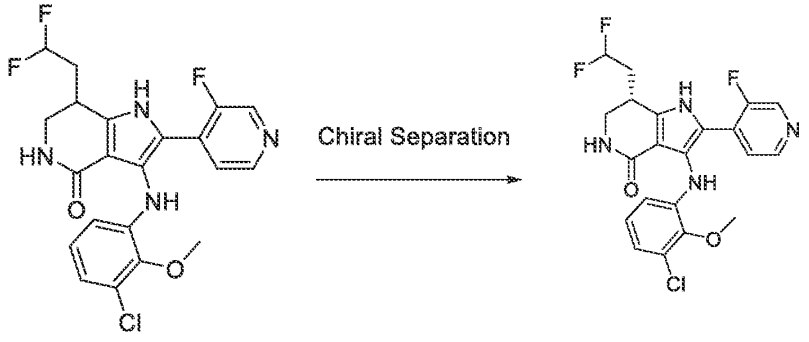


The crude product 3-[(3-chloro-2-methoxyphenyl)amino]-7-(2,2-difluoroethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.222 mmol, 1.00 equiv) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IA-3, 4.6*50mm 3um; Mobile Phase A: MtBE(0.1%DEA): EtOH=90: 10; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-(2,2-difluoroethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (33.4 mg, 33.30%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 450.95.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.63 (s, 1H), 8.52 (d, J = 2.9 Hz, 1H), 8.32 (dd, J = 5.1, 1.2 Hz, 1H), 7.60 (s, 1H), 7.47 (dd, J = 6.8, 5.1 Hz, 1H), 7.27 (s, 1H), 6.73 – 6.59 (m, 2H), 6.29 (t, J = 4.5 Hz, 1H), 6.12 (td, J = 8.0, 7.6, 3.5 Hz, 1H), 3.86 (s, 3H), 3.58 (d, J = 9.6 Hz, 1H), 2.39 (q, J = 17.8, 17.0 Hz, 2H).

Example 62. (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-7-(2,2-difluoroethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 819)**



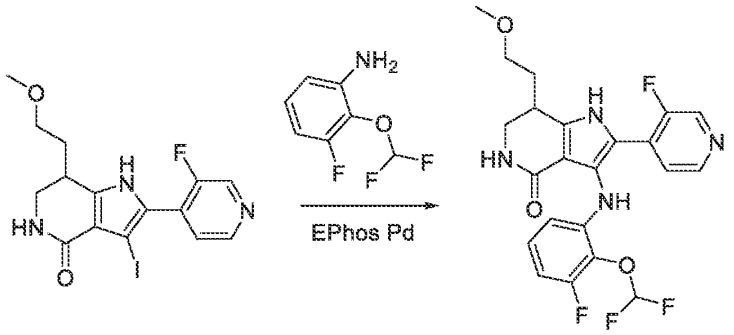
The crude product 3-[(3-chloro-2-methoxyphenyl)amino]-7-(2,2-difluoroethyl)-2-(3-

fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.222 mmol, 1.00 equiv) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IA-3, 4.6*50mm 3um; Mobile Phase A: MtBE(0.1%DEA): EtOH=90: 10; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-7-(2,2-difluoroethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (35.4 mg, 35.29%) as a light yellow solid.

LC-MS: $(M+H)^+$ found 450.95.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.63 (s, 1H), 8.52 (d, J = 2.9 Hz, 1H), 8.32 (d, J = 5.0 Hz, 1H), 7.60 (s, 1H), 7.47 (dd, J = 6.8, 5.1 Hz, 1H), 7.27 (s, 1H), 6.72 – 6.59 (m, 2H), 6.50 – 6.06 (m, 2H), 3.86 (s, 3H), 3.59 (d, J = 9.4 Hz, 1H), 2.37 – 2.03 (m, 2H).

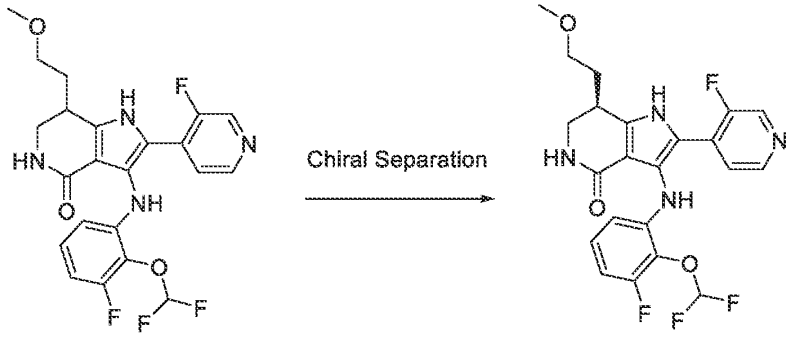
Example 63. (7R)-3-{[2-(difluoromethoxy)-3-fluorophenyl]amino}-2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 470)**



To a stirred mixture of 2-(3-fluoropyridin-4-yl)-3-iodo-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (300 mg, 0.723 mmol, 1.00 equiv) and EPhos (77.28 mg, 0.145 mmol, 0.2 equiv) and EPhos Pd G4 (132.74 mg, 0.145 mmol, 0.2 equiv) and Cs2CO3 (706.24 mg, 2.169 mmol, 3 equiv) in DMF (3 mL) was added 2-(difluoromethoxy)-3-fluoroaniline (383.94 mg, 2.169 mmol, 3 equiv) in portions at RT under N2 atmosphere. The resulting mixture was stirred for 2 hours at 50 degrees C under N2 atmosphere. The resulting mixture was filtered, then the filter cake was washed with EA (1x1 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM and MeOH 20:1) to afford 3-{[2-(difluoromethoxy)-3-fluorophenyl]amino}-2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-1H,5H,6H,7H-

pyrrolo[3,2-c]pyridin-4-one (263 mg, 78.38%) as a light yellow solid.

LC-MS: M+H found: 464.95.

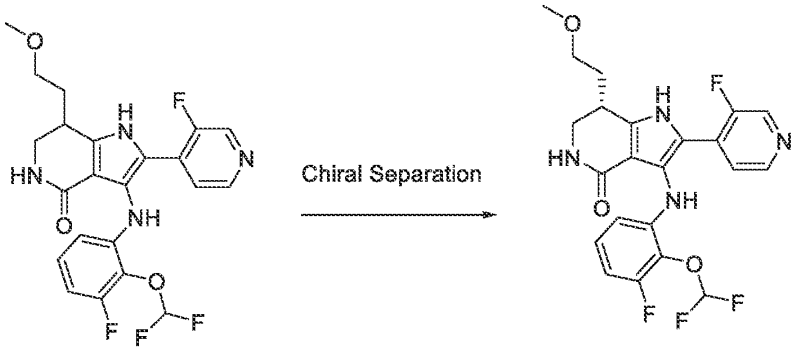


The crude product 3-{[2-(difluoromethoxy)-3-fluorophenyl]amino}-2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.215 mmol, 1.00 equiv) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 11 min; Wave Length: 220/254 nm; RT1(min): 7.57; RT2(min): 9.68; Sample Solvent: EtOH--HPLC; Injection Volume: 0.8 mL; Number Of Runs: 5) to afford (7R)-3-{[2-(difluoromethoxy)-3-fluorophenyl]amino}-2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (28.9 mg, 27.66%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 464.95.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.55 (s, 1H), 8.53 (d, J = 2.8 Hz, 1H), 8.29 (dd, J = 5.0, 1.1 Hz, 1H), 7.54 (s, 1H), 7.49 (dd, J = 6.8, 5.1 Hz, 1H), 7.35 – 6.96 (m, 2H), 6.86 – 6.79 (m, 1H), 6.58 (ddd, J = 9.9, 8.3, 1.4 Hz, 1H), 6.13 (dd, J = 8.4, 1.6 Hz, 1H), 3.56 – 3.43 (m, 3H), 3.31 (s, 3H), 3.26 – 3.20 (m, 1H), 3.09 (dt, J = 8.3, 5.4 Hz, 1H), 2.00 (dp, J = 17.5, 6.2, 5.6 Hz, 1H), 1.78 (ddt, J = 13.9, 8.3, 5.6 Hz, 1H).

Example 64. (7S)-3-{[2-(difluoromethoxy)-3-fluorophenyl]amino}-2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 471)**



The crude product 3-{[2-(difluoromethoxy)-3-fluorophenyl]amino}-2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.215 mmol, 1.00 equiv) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 25% B to 25% B in 11 min; Wave Length: 220/254 nm; RT1(min): 7.57; RT2(min): 9.68; Sample Solvent: EtOH--HPLC; Injection Volume: 0.8 mL; Number Of Runs: 5) to afford (7S)-3-{[2-(difluoromethoxy)-3-fluorophenyl]amino}-2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (38.2 mg, 37.93%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 464.95.

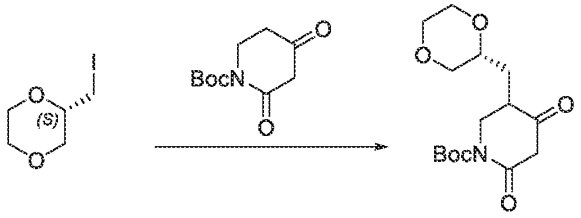
^{1}H NMR (400 MHz, DMSO-d6) δ 11.55 (s, 1H), 8.52 (d, J = 2.8 Hz, 1H), 8.29 (dd, J = 5.1, 1.1 Hz, 1H), 7.54 (s, 1H), 7.49 (dd, J = 6.8, 5.1 Hz, 1H), 7.36 – 6.97 (m, 2H), 6.84 (td, J = 8.4, 6.0 Hz, 1H), 6.58 (ddd, J = 9.9, 8.3, 1.4 Hz, 1H), 6.12 (dt, J = 8.5, 1.4 Hz, 1H), 3.55 – 3.43 (m, 3H), 3.24 (ddd, J = 12.4, 5.9, 3.1 Hz, 1H), 3.08 (dq, J = 11.2, 5.5 Hz, 1H), 2.01 (dq, J = 13.1, 6.7 Hz, 1H), 1.84 – 1.71 (m, 1H).

Example 65. (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 483)**



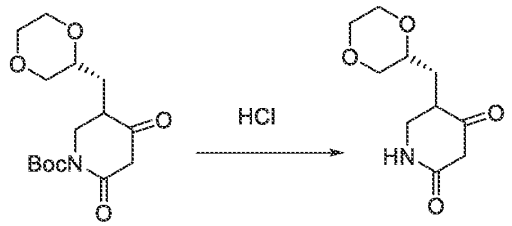
To a stirred solution of 1,4-dioxan-2-ylmethanol (1400 mg, 11.851 mmol, 1.00 equiv) in Toluene (70.0 mL) was added 1H-imidazole (1678.13 mg, 24.650 mmol, 2.08 equiv) and I2 (3158.32 mg, 12.444 mmol, 1.05 equiv) at rt. After stirring the solution at rt for 1h under N2 atmosphere, THF (35.00 mL) was added. Then, the solution was stirred at rt for 2h under N2 atmosphere. The reaction was quenched with NaS2O3 at rt and extracted with 3x20 ml of diethyl ether. The extracts were washed with brine (1×30 ml), dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE: EA=6:1 to afford 2-(iodomethyl)-1,4-dioxane (1150 mg, 42.55%) as a white oil.

LC-MS: M-56 found: 228.85.



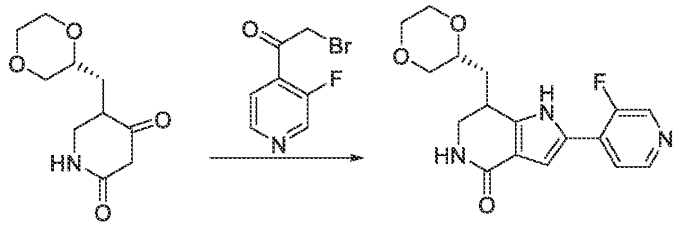
To a stirred solution of tert-butyl 2,4-dioxopiperidine-1-carboxylate (600 mg, 2.814 mmol, 1.00 equiv) in THF (18.00 mL) were added LDA (904.28 mg, 8.442 mmol, 3 equiv) at -80 degrees C under N2 atmosphere. Then, then the solution was added 2-(iodomethyl)-1,4-dioxane (769.96 mg, 3.377 mmol, 1.2 equiv) at -80 degrees C under N2 atmosphere. The solution was stirred at rt for 16h. The mixture was acidified to pH 3-4 with HCl. The residue was washed with EA (3x40 ml). The extracts was concentrated under reduced pressure and purified by Prep-TLC (PE:EA=1:1) by 3 times to afford tert-butyl 5-(1,4-dioxan-2-ylmethyl)-2,4-dioxopiperidine-1-carboxylate (230 mg, 26.09%) as a yellow solid.

LC-MS: M-56 found: 257.95.



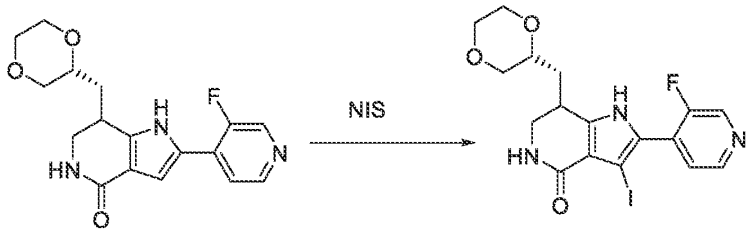
To a stirred solution of tert-butyl 5-(1,4-dioxan-2-ylmethyl)-2,4-dioxopiperidine-1-carboxylate (690 mg, 2.202 mmol, 1.00 equiv) in DCM (15 mL) was added HCl(gas)in 1,4-dioxane (7.89 mL, 259.528 mmol, 117.86 equiv) at rt under N2 atmosphere. Then, the solution was stirred at rt for 2h. The resulting mixture was concentrated under reduced pressure to afford crude 5-(1,4-dioxan-2-ylmethyl)piperidine-2,4-dione (470 mg, 100.10%) as a yellow oil.

LC-MS: M+41 found: 254.2.



To a stirred solution of 5-(1,4-dioxan-2-ylmethyl)piperidine-2,4-dione (470 mg, 2.204 mmol, 1.00 equiv) and NH4OAc (849.51 mg, 11.020 mmol, 5.0 equiv) in EtOH (13 mL) were added 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (480.56 mg, 2.204 mmol, 1.0 equiv) at rt under N2 atmosphere. Then, the solution was stirred at 50 degrees C for 16h. The resulting mixture was concentrated under reduced pressure and purified by Prep-TLC (DCM: MeOH=12:1) to afford 7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (620 mg, 84.89%) as a pink solid.

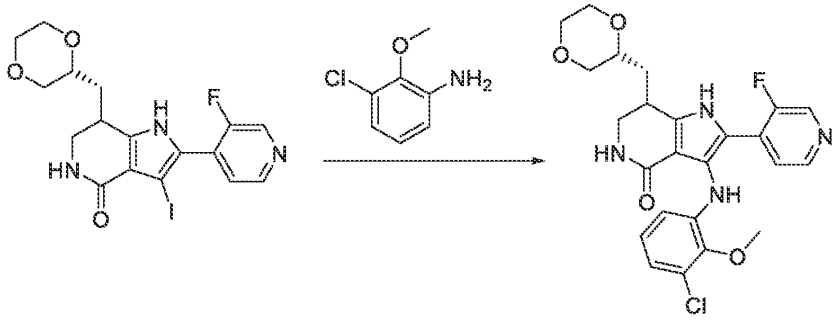
LC-MS: M+H found: 332.1.



To a stirred solution of 7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (375 mg, 1.132 mmol, 1.00 equiv) in DMF (14 mL) was added NIS (305.55 mg, 1.358 mmol, 1.2 equiv) at rt under N2 atmosphere. Then, the solution was stirred at rt for1h. The resulting mixture was concentrated under reduced pressure and purified by Prep-TLC (DCM:MeOH=15:1) to afford 7-(1,4-dioxan-

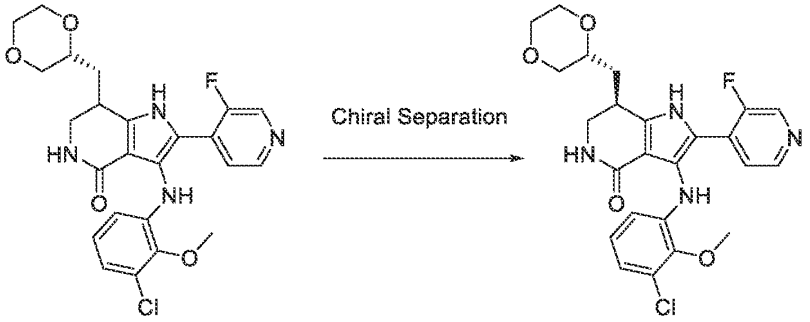
2-ylmethyl)-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (485 mg, 93.72%) as a yellow solid.

LC-MS: M+H found: 458.0.



To a stirred solution of 7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (110 mg, 0.241 mmol, 1.00 equiv) and Cs2CO3 (36.63 mg, 0.482 mmol, 2.0 equiv) in DMF (4.40 mL) was added EPhos Pd G4 (44.20 mg, 0.048 mmol, 0.2 equiv) and 3-chloro-2-methoxyaniline (113.74 mg, 0.723 mmol, 3.0 equiv) at rt under N2 atmosphere. Then, the solution was stirred at 50 degrees C for 2h. The resulting mixture was concentrated under reduced pressure and purified by Prep-TLC (DCM: MeOH=20:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (68 mg, 58.05%) as a yellow oil.

LC-MS: M+H found: 487.1.



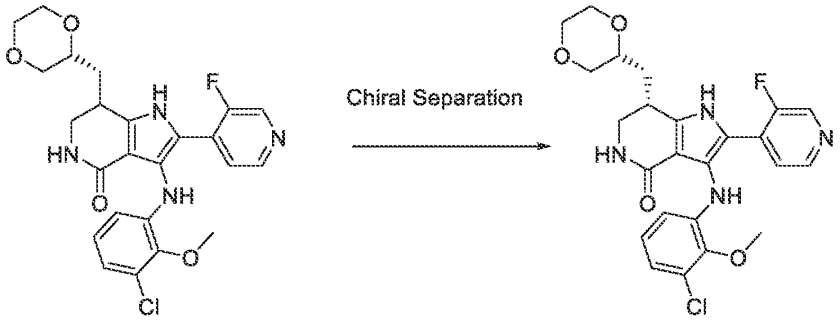
The 3-[(3-chloro-2-methoxyphenyl)amino]-7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (103 mg, 0.212 mmol, 1.00 equiv) was purified by reverse flash chromatography with the following

conditions: Column: YMC-Actus Triart C18, 30*150 mm, 5 μ m; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 45% B in 10 min, 45% B; Wave Length: 254/220 nm; RT1(min): 10.05 to afford (R)-7-(((R)-1,4-dioxan-2-yl)methyl)-3-((3-chloro-2-methoxyphenyl)amino)-2-(3-fluoropyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (26.4 mg, 25.63%) as a yellow solid.

LC-MS: M+H found: 487.0.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.45 (s, 1H), 8.51 (d, J = 2.8 Hz, 1H), 8.30 (d, J = 5.1 Hz, 1H), 7.57 (s, 1H), 7.45 (dd, J = 6.8, 5.1 Hz, 1H), 7.18 (s, 1H), 6.70 – 6.60 (m, 2H), 6.13 (dd, J = 7.1, 2.5 Hz, 1H), 3.86 (s, 3H), 3.77 (dd, J = 10.5, 2.3 Hz, 1H), 3.73 – 3.53 (m, 5H), 3.53 – 3.42 (m, 1H), 3.28 (q, J = 4.3 Hz, 1H), 3.26 – 3.15 (m, 1H), 3.10 (dd, J = 8.1, 5.1 Hz, 1H), 1.76 (dt, J = 14.1, 5.0 Hz, 1H), 1.60 (dt, J = 14.6, 8.0 Hz, 1H).

Example 66. (S)-7-(((R)-1,4-dioxan-2-yl)methyl)-3-((3-chloro-2-methoxyphenyl)amino)-2-(3-fluoropyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(compound 482)**



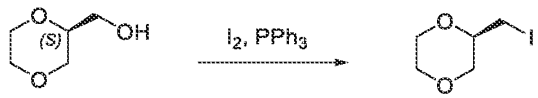
The 3-[(3-chloro-2-methoxyphenyl)amino]-7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (103 mg, 0.212 mmol, 1.00 equiv) was purified by reverse flash chromatography with the following conditions: Column: YMC-Actus Triart C8, 20*250 mm, 5 μ m; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 45% B in 10 min, 45% B; Wave Length: 254/220 nm; RT1(min): 9.56 to afford (S)-7-(((R)-1,4-dioxan-2-yl)methyl)-3-((3-chloro-2-

methoxyphenyl)amino)-2-(3-fluoropyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (23.1 mg, 22.43%) as a yellow solid.

LC-MS: M+H found: 487.0.

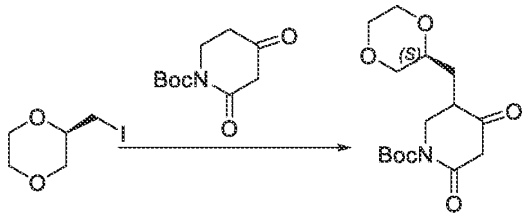
^{1}H NMR (400 MHz, DMSO-d6) δ 11.52 (s, 1H), 8.50 (d, J = 2.9 Hz, 1H), 8.29 (d, J = 5.1 Hz, 1H), 7.59 (s, 1H), 7.44 (dd, J = 6.8, 5.1 Hz, 1H), 7.18 (d, J = 3.2 Hz, 1H), 6.72 – 6.61 (m, 2H), 6.13 (dd, J = 7.4, 2.3 Hz, 1H), 3.84 – 3.74 (m, 2H), 3.68 (ddt, J = 18.8, 11.3, 5.6 Hz, 4H), 3.50 (t, J = 10.5 Hz, 2H), 3.33 (s, 1H), 3.29 – 3.19 (m, 3H), 3.18 (d, J = 5.0 Hz, 1H), 1.79 (ddd, J = 14.1, 9.5, 4.9 Hz, 1H), 1.59 (ddd, J = 13.9, 8.6, 3.0 Hz, 1H).

Example 67. (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 481)**



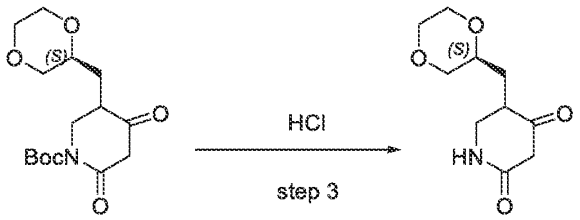
I_2 (6.78 g, 26.713 mmol, 1.05 equiv), Ph_3P (7.02 g, 26.765 mmol, 1.05 equiv), and imidazole (3.54 g, 52.000 mmol, 2.06 equiv) were added to a solution of 1,4-dioxan-2-ylmethanol (3g, 25.4 mmol, 1.00 equiv) in Toluene (120 mL). After stirring for 10 min at rt, THF (60 mL) was added, and the solution was allowed to stir 10h. The resulting solution was quenched with saturated sodium thiosulfate solution (120 mL) and extracted with diethyl ether (3x120mL). The extracts were washed with brine(180mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was extracted with ether-hexane(18ml:120mL) to remove solid triphenylphosphine oxide. The extract was concentrated and purified by column chromatography (PE: EA=6:1) to give a clear liquid 2-(iodomethyl)-1,4-dioxane (2.8 g, 48.27.%) as a white oil.

GC-MS: M+H found: 228.



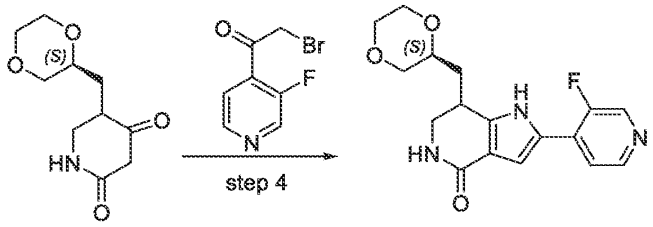
A solution of tert-butyl 2,4-dioxopiperidine-1-carboxylate (800 mg, 3.752 mmol, 1.00 equiv) in THF (24 mL) was treated under nitrogen atmosphere, when the temperature was got -70 degrees C ,followed by the addition of LDA (5.6 mL, 41.298 mmol) dropwise at -70 degrees C and remained the temperature about 30min, then added the(2R)-2-(iodomethyl)-1,4-dioxane (1026.61 mg, 4.502 mmol, 1.20 equiv) ,finally the mixture was stirred at rt about 16h.The reaction was quenched by the addition of H2O(5mL) at RT.The mixture was acidified to pH 3 with HCl. The resulting mixture was extracted with EA(3x15mL). The combined organic layers were washed with saturated salt solution(3x15mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE:EA=1:1) to afford tert-butyl 5-(1,4-dioxan-2-ylmethyl)-2,4-dioxopiperidine-1-carboxylate (306 mg, 26.03%) as a yellow solid.

LC-MS: 2M+Na found: 649.5.



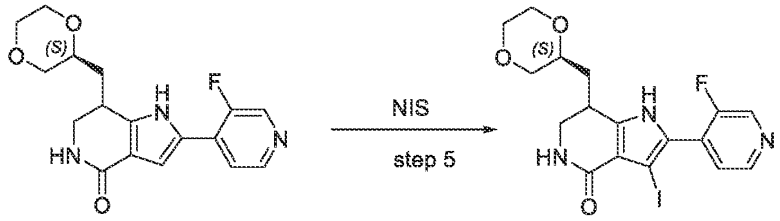
To a stirred solution of tert-butyl 5-(1,4-dioxan-2-ylmethyl)-2,4-dioxopiperidine-1-carboxylate (306 mg, 0.977 mmol, 1.00 equiv) in DCM (3.6 mL) was added HCl(gas)in 1,4-dioxane (1.8 mL, 59.241 mmol, 60.66 equiv) at rt. Then the solution was stirred at rt about 2h. The resulting mixture was concentrated under reduced pressure and get the 5-(1,4-dioxan-2-ylmethyl)piperidine-2,4-dione (200 mg, 96.05%) as a yellow oil.

LC-MS: M+H found: 214.2.



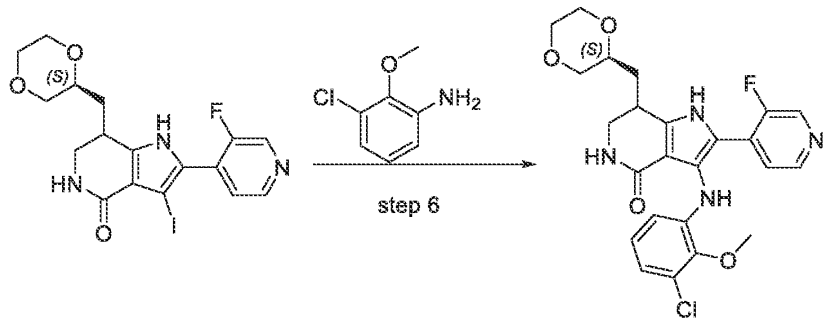
To a stirred solution of 5-(1,4-dioxan-2-ylmethyl)piperidine-2,4-dione (306 mg, 1.435 mmol, 1.00 equiv) and 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (375.45 mg, 1.722 mmol, 1.2 equiv) in EtOH (5.98 mL) were added NH4OAc (553.09 mg, 7.175 mmol, 5.00 equiv) at rt. Then the solution was stirred at 50degrees C about 16h.The residue was purified by Prep-TLC (MeOH: DCM=20:1) to afford 7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (340 mg, 71.50%) as a yellow solid.

LC-MS: M+H found: 332.0.



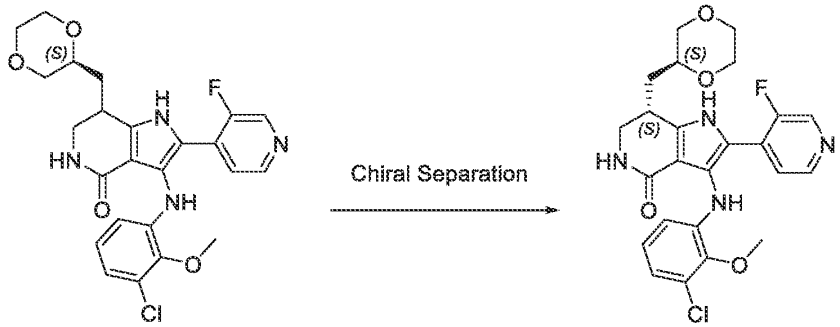
To a stirred solution of7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (270 mg, 0.815 mmol, 1.00 equiv) in DMF (5.40 mL) was added (iodoamino)sulfanyl (211.42 mg, 1.222 mmol, 1.5 equiv) at rt, then the solution was stirred at rt about 2h.The resulting mixture was concentrated under reduced pressure and then was purified by Prep-TLC (DCM: MeOH=20:1) to afford 7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (230 mg, 61.73%) as a yellow solid.

LC-MS: M+H found: 457.9.



To a stirred solution of 7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (235 mg, 0.514 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (242.99 mg, 1.542 mmol, 3 equiv) in DMF (5.0 mL) were added Cs2CO3 (334.91 mg, 1.028 mmol, 2.00 equiv) and EPhos Pd G4 (94.42 mg, 0.103 mmol, 0.2 equiv) at rt, then the solution was stirred at 50 degrees C under N2 atmosphere about 3h .The resulting mixture was extracted with EA(3x20mL). The combined organic layers were washed with saturated salt solution (3x20mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM: MeOH=20:1) to afford 3-[(3-chloro-2-methoxyphenyl) amino]-7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (130 mg, 51.95%) as a yellow solid.

LC-MS: M+H found: 487.3.



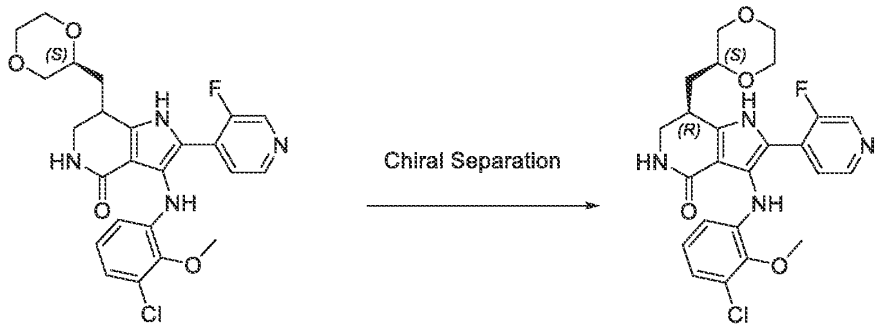
The 3-[(3-chloro-2-methoxyphenyl)amino]-7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (140 mg, 0.288 mmol, 1.00 equiv) was purified by reverse flash chromatography with the following conditions: Column: YMC-Actus Triart C18, 30*150 mm, 5 μ m; Mobile Phase A: Water(10 mmol/L

NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 55% B in 8 min, 55% B; Wave Length: 254/220 nm; RT1(min): 7.10/8.48 to afford (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (11.2 mg, 7.94%) as a yellow solid.

LC-MS: M+H found: 486.9.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.45 (s, 1H), 8.51 (d, J = 2.8 Hz, 1H), 8.30 (d, J = 5.1 Hz, 1H), 7.57 (s, 1H), 7.49 – 7.41 (m, 1H), 7.18 (s, 1H), 6.72 – 6.62 (m, 2H), 6.13 (dd, J = 7.1, 2.6 Hz, 1H), 3.81 – 3.66 (m, 3H), 3.66 – 3.33 (m, 7H), 3.30 – 3.09 (m, 3H), 1.77 (dd, J = 14.2, 5.3 Hz, 1H), 1.60 (dt, J = 15.0, 8.1 Hz, 1H).

Example 68. (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 480)**

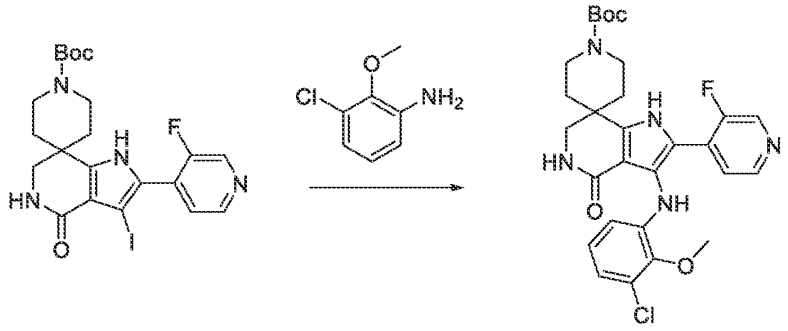


The 3-[(3-chloro-2-methoxyphenyl)amino]-7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (140 mg, 0.288 mmol, 1.00 equiv) was purified by reverse flash chromatography with the following conditions: Column: YMC-Actus Triart C18, 30*150 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 55% B in 8 min, 55% B; Wave Length: 254/220 nm; RT1(min): 7.10/8.48 to afford (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (12.1 mg, 8.46%) as a yellow solid.

LC-MS: M+H found: 486.9.

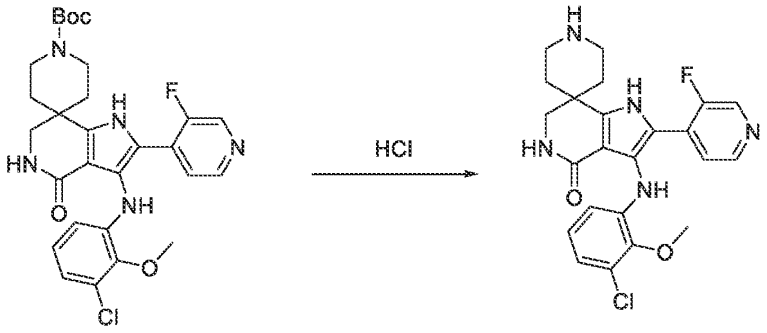
^{1}H NMR (400 MHz, DMSO-d6) δ 11.45 (s, 1H), 8.51 (d, J = 2.8 Hz, 1H), 8.30 (d, J = 5.1 Hz, 1H), 7.57 (s, 1H), 7.49 – 7.41 (m, 1H), 7.18 (s, 1H), 6.72 – 6.62 (m, 2H), 6.13 (dd, J = 7.1, 2.6 Hz, 1H), 3.81 – 3.66 (m, 3H), 3.66 – 3.33 (m, 7H), 3.30 – 3.09 (m, 3H), 1.77 (dd, J = 14.2, 5.3 Hz, 1H), 1.60 (dt, J = 15.0, 8.1 Hz, 1H).

Example 69. methyl 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate **(compound 479)**



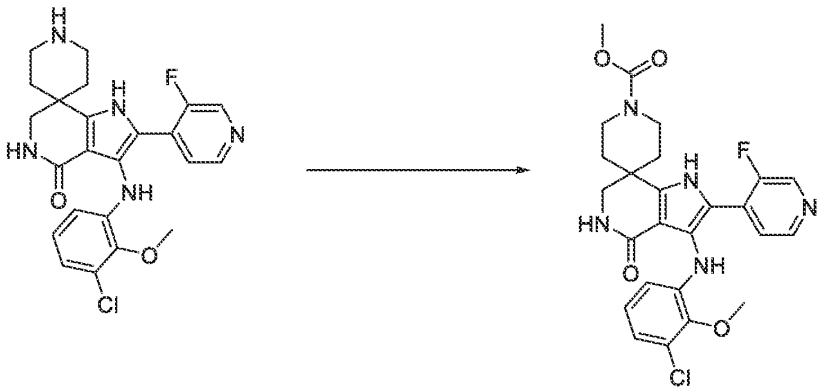
To a stirred solution of tert-butyl 2'-(3-fluoropyridin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (500 mg, 0.950 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (449.13 mg, 2.850 mmol, 3 equiv) in DMF (4 mL) were added Cs2CO3 (619.02 mg, 1.900 mmol, 2 equiv) and EPhos Pd G4 (174.51 mg, 0.190 mmol, 0.2 equiv) at rt, then teh solution was stirred at 50 degrees C under N2 atmosphere about 2h. The resulting mixture was extracted with EA (3 x 20mL). The combined organic layers were washed with saturated salt solution (3x20mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM: MeOH =20:1) to afford tert-butyl 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (332 mg, 62.85%) as a yellow solid.

GC-MS: M +H found: 556.1.



A solution of tert-butyl 2,4-dioxopiperidine-1-carboxylate (800 mg, 3.752 mmol, 1.00 equiv) in THF (24 mL) was treated under nitrogen atmosphere, when the temperature was got -70 degrees C ,followed by the addition of LDA (5.6 mL, 41.298 mmol) dropwise at -70 degrees C and remained the temperature about 30min, then added the(2R)-2-(iodomethyl)-1,4-dioxane (1026.61 mg, 4.502 mmol, 1.20 equiv), finally the mixture was stirred at rt about 16h. The reaction was quenched by the addition of H2O(5mL) at RT. The mixture was acidified to pH 3 with HCl. The resulting mixture was extracted with EA(3x15mL). The combined organic layers were washed with saturated salt solution(3x15mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE:EA=1:1) to afford tert-butyl 5-(1,4-dioxan-2-ylmethyl)-2,4-dioxopiperidine-1-carboxylate (306 mg, 26.03%) as a yellow solid.

LC-MS: M+H found: 455.9.



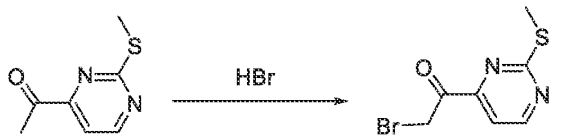
To a stirred solution of 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (400 mg, 0.877

mmol, 1.00 equiv) and Et3N (177.56 mg, 1.754 mmol, 2 equiv) in DCM (5 mL) were added methyl chloroformate (99.48 mg, 1.052 mmol, 1.2 equiv) at rt, then the solution was stirred at rt about 2h. The residue was purified by Prep-TLC (DCM: MeOH= 15:1) to afford crude product as a yellow solid.The residue was purified by reverse flash chromatography with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 56% B in 8 min, 56% B; Wave Length: 254; 220 nm; RT1(min): 7.25; Number Of Runs: to afford methyl 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (53.7 mg, 11.85%) as a yellow solid.

LC-MS: M+H found: 514.0.

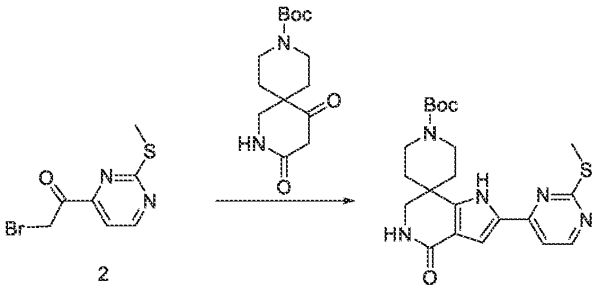
^{1}H NMR (400 MHz, DMSO-d6) δ 11.38 (s, 1H), 8.47 (d, J = 2.6 Hz, 1H), 8.32 (dd, J = 5.0, 1.2 Hz, 1H), 7.67 (s, 1H), 7.45 (dd, J = 6.7, 5.0 Hz, 1H), 7.30 (s, 1H), 6.73 – 6.52 (m, 2H), 6.09 (dd, J = 7.9, 1.8 Hz, 1H), 3.84 (s, 5H), 3.62 (s, 3H), 3.48 (d, J = 2.8 Hz, 2H), 3.02 (s, 2H), 1.98 (s, 2H), 1.70 (d, J = 13.3 Hz, 2H).

Example 70. 3'-[(3-chloro-2-methoxyphenyl)amino]-1-(prop-2-enoyl)-2'-(pyrimidin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 478)**



To a stirred solution/mixture of 1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone (1000 mg, 5.945 mmol, 1.00 equiv) in AcOH/HBr(0.6mL;0.5:0.1) were added Br2 (950.05 mg, 5.945 mmol, 1.00 equiv) in AcOH (0.1mL) . The resulting mixture was stirred for 2.5H at 60°C under nitrogen atmosphere. The resulting mixture was wished with EA. The precipitated solids were collected by filtration and washed with EA (3x5mL).to afford 2-bromo-1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone (1100 mg, 74.88%) as a yellow solid.

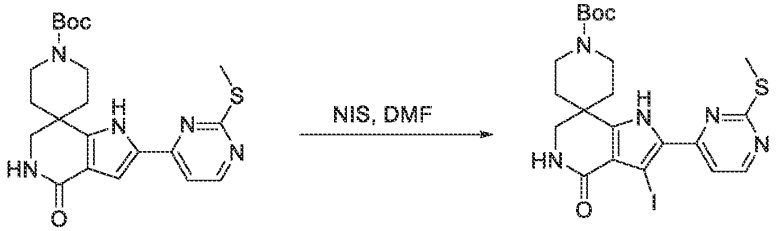
LC-MS: M+H found: 247.



2

To a stirred solution/mixture of 2-bromo-1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone (1.1 g, 4.451 mmol, 1 equiv), tert-butyl 3,5-dioxo-2,9-diazaspiro[5.5]undecane-9-carboxylate (1256.82 mg, 4.451 mmol, 1 equiv) and AcONH4 (1715.65 mg, 22.255 mmol, 5 equiv) in EtOH(11mL). The resulting mixture was stirred for 16h at 50°C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was diluted with MeOH (10 mL). The resulting mixture was filtered; the filter cake was washed with MeOH (2x5 ml). The filter cake was collected to afford tert-butyl 2'-[2-(methylsulfanyl)pyrimidin-4-yl]-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (1.1 g, 57.53%) as an off-white solid.

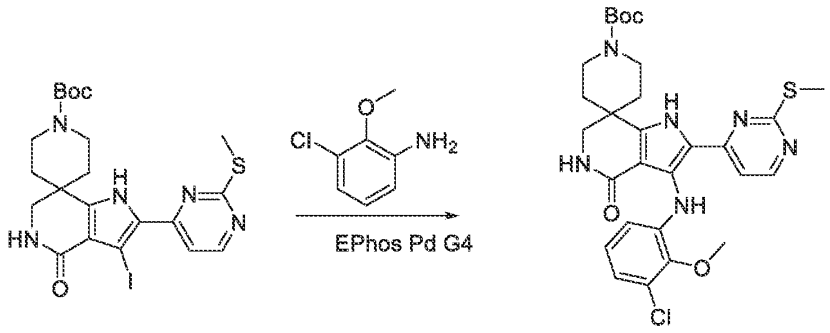
LC-MS: M+H found: 430.



Into a 40-mL vial, was placed tert-butyl 2'-[2-(methylsulfanyl)pyrimidin-4-yl]-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (1.1 g, 2.561 mmol, 1 equiv)and NIS (864.24 mg, 3.841 mmol, 1.5 equiv) in DMF(10mL). The resulting solution was stirred for 2H at 50 degrees C. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was diluted with H2O (60 mL). The resulting mixture was filtered; the filter cake was washed with

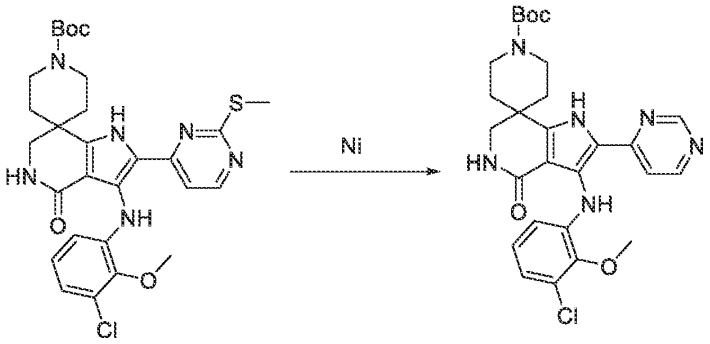
H2O (2x5 ml). The filter cake was collected. The crude product was purified by Prep-Flash (DCM/MEOH; 20:1) to afford tert-butyl 3'-iodo-2'-[2-(methylsulfanyl)pyrimidin-4-yl]-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (1.1 g, 77.33%) as an off-white solid.

LC-MS: M+H found: 556.



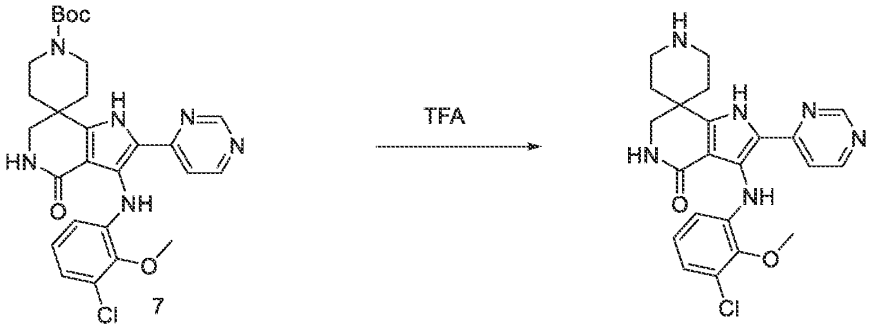
Into a 8-mL vial, was placed tert-butyl 3'-iodo-2'-[2-(methylsulfanyl)pyrimidin-4-yl]-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (1.1 g, 1.980 mmol, 1 equiv), 3-chloro-2-methoxyaniline (936.34 mg, 5.940 mmol, 3 equiv), EPhos Pd G4 (545.73 mg, 0.594 mmol, 0.3 equiv) and EPhos (635.47 mg, 1.188 mmol, 0.6 equiv)) in DMF(0.5mL). The resulting solution was stirred for 2h at 50 degrees C. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was diluted with H2O (60 mL). The resulting mixture was filtered; the filter cake was washed with H2O (2x5 ml). The filter cake was collected. The crude product was purified by Prep-Flash (DCM/MEOH; 20:1) to afford tert-butyl 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-[2-(methylsulfanyl)pyrimidin-4-yl]-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (1.0 g) as an off-white solid.

LC-MS: M+H found: 585.



Into a 8-mL vial, was placed tert-butyl 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-[2-(methylsulfanyl)pyrimidin-4-yl]-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (350 mg, 0.598 mmol, 1 equiv) and Raney Ni (2562.40 mg, 29.900 mmol, 50 equiv) in EtOH(1 mL). The resulting solution was stirred for 2h at 90 degrees C. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was diluted with MeOH (10 mL). The resulting mixture was filtered; the filter cake was washed with MeOH (2x5 ml). The filtrate was concentrated under reduced pressure. The crude product was purified by Prep-Flash(DCM/MeOH: 20:1) to afford tert-butyl 3'-[(3-chloro-2-methoxyphenyl)amino]-4'-oxo-2'-(pyrimidin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (160 mg, 49.62%) as an off-white solid.

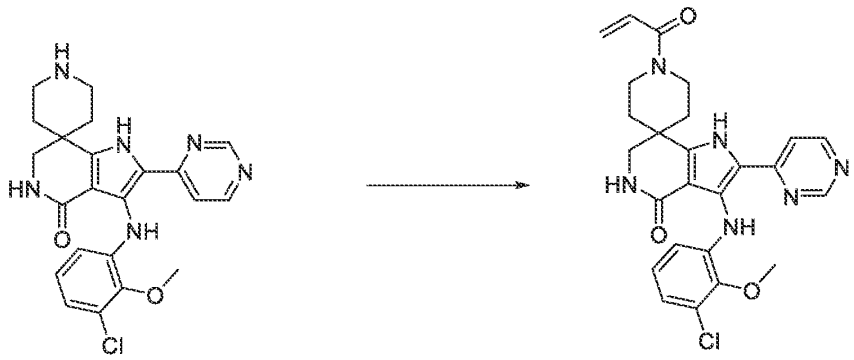
LC-MS: M+H found: 539.



Into a 8-mL vial, was placed tert-butyl 3'-[(3-chloro-2-methoxyphenyl)amino]-4'-oxo-2'-(pyrimidin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (150 mg, 0.278 mmol, 1 equiv) in DCM(4mL), then added TFA(1mL) dropwise. The resulting solution was stirred for 2h at rt. The reaction was monitored by

LCMS. Desired product could be detected by LCMS. The mixture was neutralized to pH 7~8 with NaHCO3(aq).The aqueous layer was extracted with EA (3x10mL).The resulting mixture was concentrated under reduced pressure. The crude product/ resulting mixture was used in the next step directly without further purification.

LC-MS: M+H found: 439.



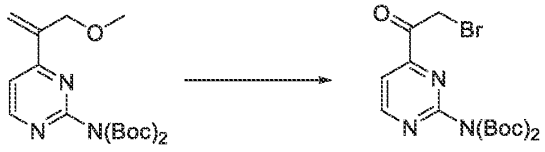
Into a 8 mL round-bottom flask were added 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(pyrimidin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (150 mg, 0.342 mmol, 1 equiv) in THF/NaHCO3(aq)(4ml;1： 1)at 0 °C, to the above mixture was added acryloyl chloride (46.40 mg, 0.513 mmol, 1.5 equiv) dropwise / in portions over 1 min at 0°C. The resulting mixture was stirred for additional 15 min at 0°C. The reaction was OK. The aqueous layer was extracted with EA (3x10mL). The solution was concentrated under reduced pressure. The crude product/ resulting mixture got 3'-[(3-chloro-2-methoxyphenyl)amino]-1-(prop-2-enoyl)-2'-(pyrimidin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one (100 mg, 59.36%)

LC-MS: M+H found: 493.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.82 (s, 1H), 9.03 (d, J = 1.4 Hz, 1H), 8.57 (d, J = 5.6 Hz, 1H), 8.33 (s, 1H), 7.38 – 7.27 (m, 2H), 6.93 – 6.73 (m, 3H), 6.37 (dd, J = 6.9, 2.8 Hz, 1H), 6.16 (dd, J = 16.7, 2.5 Hz, 1H), 5.72 (dd, J = 10.5, 2.5 Hz, 1H), 4.45 (d, J = 13.1 Hz, 1H), 4.06 (d, J = 13.8 Hz, 1H), 3.92 (s, 3H), 3.52 (d, J = 2.9 Hz, 2H), 3.26 (t, J = 13.4 Hz, 1H), 2.81 (t, J = 13.1 Hz, 1H), 2.14 (d, J = 12.9 Hz, 2H), 1.71 (d, J = 13.3 Hz, 2H).

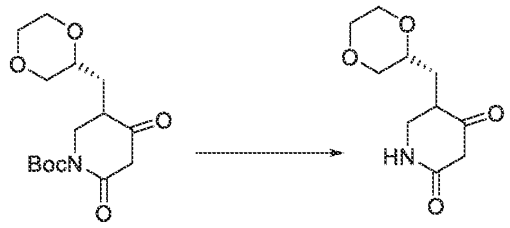
Example 71. (7S)-2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-

[(2S)-1,4-dioxan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 531)**



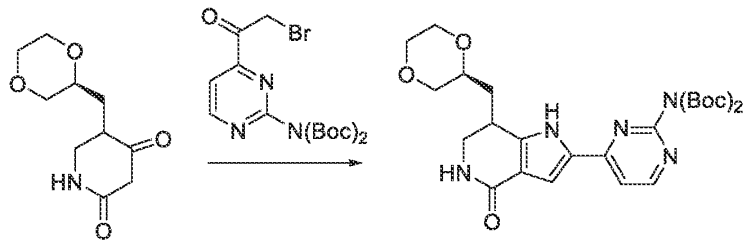
To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-[4-(1-ethoxyethenyl)pyrimidin-2-yl]carbamate (1250 mg, 3.421 mmol, 1.00 equiv) in THF (15 mL) and H2O (1 mL) were added NBS (730.58 mg, 4.105 mmol, 1.2 equiv) at rt under N2 atmosphere. Then, the solution was stirred at rt for 2h. The resulting mixture was diluted with water (30ml) and extracted with 3x40ml of EA. The extract was concentrated under reduce pressure to afford crude tert-butyl N-[4-(2-bromoacetyl)pyrimidin-2-yl]-N-(tert-butoxycarbonyl)carbamate (1300 mg, 91.30%) as a yellow oil.

LC-MS: M+35 found: 450.0.



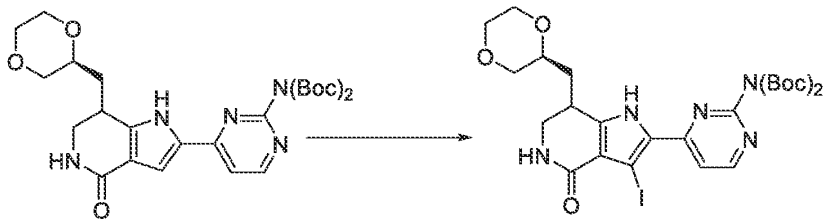
To a stirred solution of tert-butyl 5-(1,4-dioxan-2-ylmethyl)-2,4-dioxopiperidine-1-carboxylate (690 mg, 2.202 mmol, 1.00 equiv) in DCM (15 mL) was added HCl(gas)in 1,4-dioxane (7.89 mL, 259.528 mmol, 117.86 equiv) at rt under N2 atmosphere. Then, the solution was stirred at rt for 2h. The resulting mixture was concentrated under reduced pressure to afford crude 5-(1,4-dioxan-2-ylmethyl)piperidine-2,4-dione (470 mg, 100.10%) as a yellow oil.

LC-MS: M+15 found: 228.1.



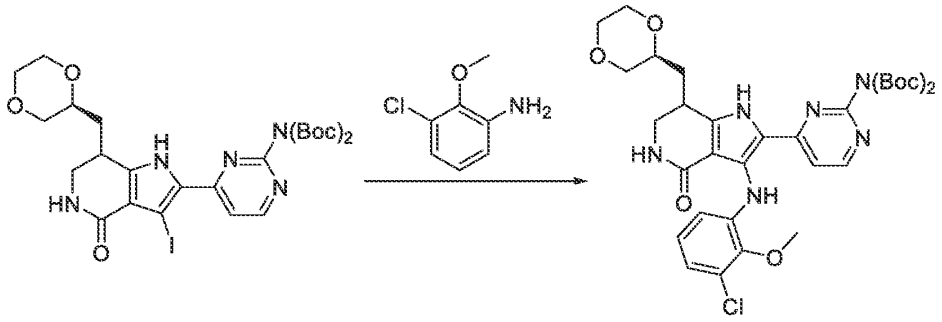
To a stirred solution of 5-[(2R)-1,4-dioxan-2-ylmethyl]piperidine-2,4-dione (680.5 mg, 3.191 mmol, 1.00 equiv) and NH4OAc (1475.98 mg, 19.146 mmol, 6.0 equiv) in EtOH (10 mL) were added tert-butyl N-[4-(2-bromoacetyl)pyrimidin-2-yl]-N-(tert-butoxycarbonyl)carbamate (1328.47 mg, 3.191 mmol, 1.00 equiv) at rt under N2 atmosphere. Then, the solution was stirred at 50° C for 16h. The resulting mixture was concentrated under reduced pressure and purified by silica gel column chromatography, eluted with DCM: MeOH=15:1 to afford tert-butyl N-(tert-butoxycarbonyl)-N-{4-[7-(1,4-dioxan-2-ylmethyl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl}carbamate (520 mg, 30.77%) as a yellow solid.

LC-MS: M+H found: 530.0.



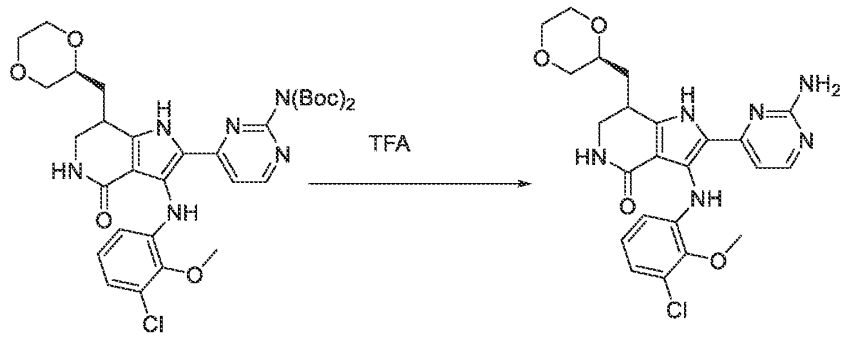
To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-{4-[7-(1,4-dioxan-2-ylmethyl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl}carbamate (520 mg, 0.982 mmol, 1.00 equiv) in DMF (5 mL) was added NIS (287.18 mg, 1.277 mmol, 1.30 equiv) at RT under N2 atmosphere. Then, the solution was stirred at rt for 2h. The resulting mixture was concentrated under reduced pressure and purified by Prep-TLC (DCM: MeOH=15:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-{4-[7-(1,4-dioxan-2-ylmethyl)-3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl}carbamate (530 mg, 82.35%) as a yellow solid.

LC-MS: M+H found: 656.2.



To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-{7-[(2S)-1,4-dioxan-2-ylmethyl]-3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}pyrimidin-2-yl)carbamate (400 mg, 0.610 mmol, 1 equiv) and Cs2CO3 (397.65 mg, 1.220 mmol, 2.00 equiv) in DMF (1.5 mL) were added 3-chloro-2-methoxyaniline (384.69 mg, 2.441 mmol, 4.00 equiv)and EPhos Pd G4 (112.11 mg, 0.122 mmol, 0.20 equiv) at RT under N2 atmosphere. The solution was stirred at 50°C for 16h. The resulting mixture was concentrated under reduced pressure and purified by Prep-TLC (DCM: MeOH=10:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(4-{3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}pyrimidin-2-yl)carbamate (350 mg, 83.71%) as a yellow solid.

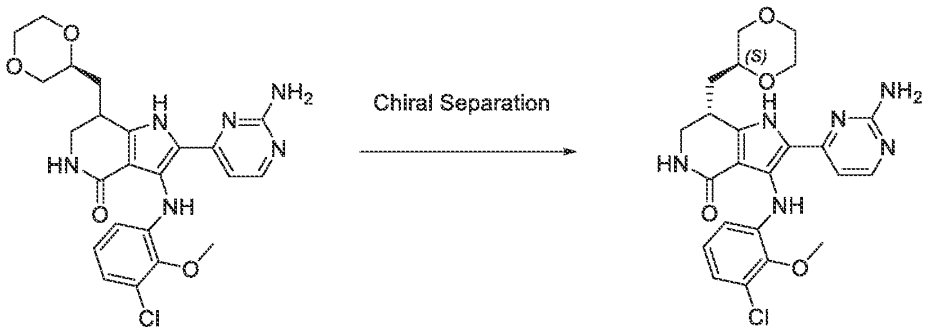
LC-MS: M+H found: 685.25.



To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-{3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}pyrimidin-2-yl)carbamate (90 mg, 0.131 mmol, 1 equiv) in DCM (0.5 mL) were added TFA (0.75 mL, 10.070 mmol, 76.87 equiv) at RT under N2 atmosphere. Then, the solution was stirred at rt for 30 min. The

resulting mixture was concentrated under reduced pressure and purified by Prep-TLC (DCM: MeOH=15:1) to afford 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (60 mg, 94.19%) as a light yellow solid.

LC-MS: M+H found: 485.15.



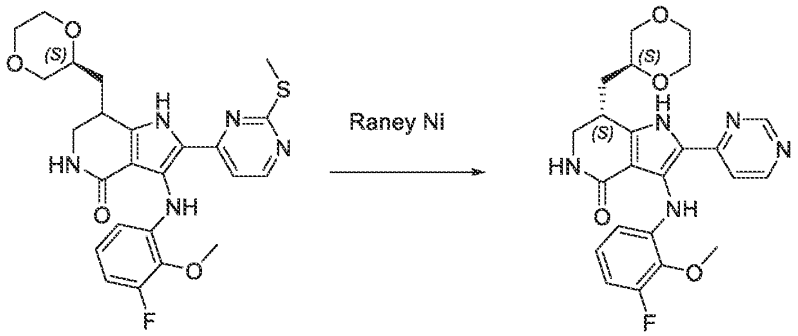
The crude product 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (300 mg, 0.619 mmol, 1 equiv) was purified by Prep-HPLC as the following Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5 μ m; Mobile Phase A: Water (10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 50% B in 11 min, 50% B; Wave Length: 254/220 nm; RT1(min): 7.25/10.2 to afford (7S)-2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (57.6 mg, 19.20%) as a light yellow solid.

LC-MS: M+H found 485.1.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.40 (s, 1H), 8.06 (d, J = 5.3 Hz, 1H), 7.93 (s, 1H), 7.14 (s, 1H), 6.87 – 6.72 (m, 2H), 6.49 (d, J = 5.3 Hz, 1H), 6.33 (dd, J = 7.9, 1.9 Hz, 1H), 6.24 (s, 1H), 3.89 (s, 3H), 3.79 (d, J = 12.2 Hz, 1H), 3.65 (q, J = 10.8, 9.9 Hz, 5H), 3.48 (d, J = 11.8 Hz, 2H), 3.21 (dd, J = 11.2, 9.7 Hz, 2H), 3.08 (s, 1H), 1.76 (d, J = 14.4 Hz, 1H), 1.59 (dt, J = 14.7, 7.8 Hz, 1H).

Example 72. afford (7R*)-7-[(2S)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one

(compound 530)

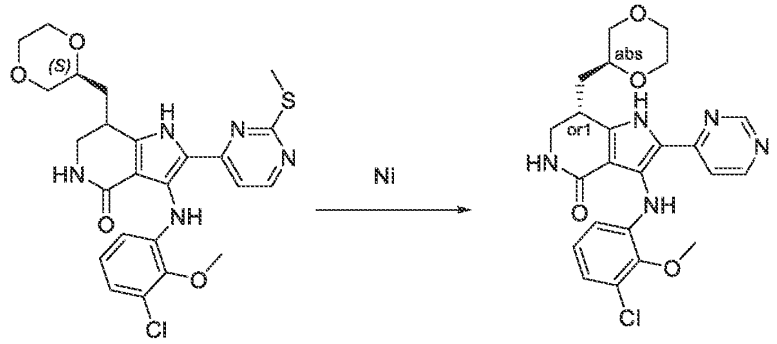


To a stirred solution of 7-[(2S)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (200 mg, 0.400 mmol, 1 equiv)in EtOH (2 mL) was added Raney Ni (51.45 mg, 0.600 mmol, 1.5 equiv) in portions at RT under N2 atmosphere. The resulting mixture was stirred for 2 hours at 90°C under N2 atmosphere. The mixture was allowed to cool down to RT. The resulting mixture was filtered, then the filter cake was washed with MeOH (3*10 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 24% B to 44% B in 9 min, 44% B; Wave Length: 254;220 nm; RT1(min): 7.58/8.72) to afford (7R*)-7-[(2S)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (47.4 mg, 26.00%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 454.1.

^{1}H NMR (300 MHz, DMSO-d6) δ 12.01 (s, 1H), 9.03 (d, J = 1.4 Hz, 1H), 8.54 (d, J = 5.6 Hz, 1H), 8.03 (s, 1H), 7.20 (dd, J = 5.6, 1.4 Hz, 2H), 6.77 (td, J = 8.3, 6.1 Hz, 1H), 6.67 – 6.54 (m, 1H), 6.18 (d, J = 8.2 Hz, 1H), 3.95 (d, J = 0.9 Hz, 3H), 3.80 (d, J = 12.3 Hz, 2H), 3.66 (t, J = 10.0 Hz, 3H), 3.51 (d, J = 11.0 Hz, 2H), 3.20 (d, J = 9.7 Hz, 3H), 1.86 – 1.75 (m, 1H), 1.59 (t, J = 10.2 Hz, 1H).

Example 73. (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 527)**



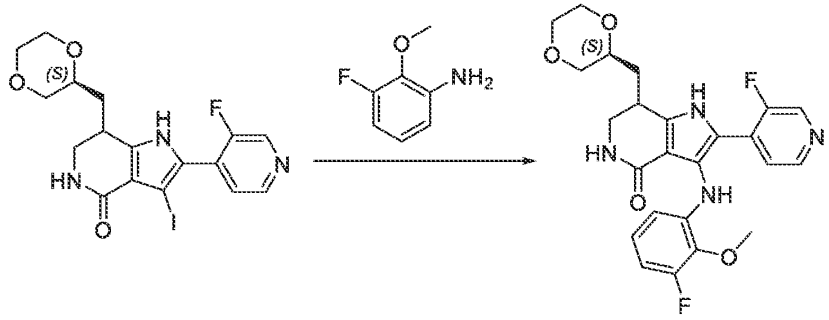
To a stirred mixture of Raney Nickel (99.62 mg, 1.162 mmol, 2 equiv) in EtOH (3 mL) was added 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (300 mg, 0.581 mmol, 1 equiv) in portions at RT under N2 atmosphere. The resulting mixture was stirred for 2 hours at 90°C under N2 atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH. The filtrate was concentrated under reduced pressure. The crude product (200 mg) was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Fluoro Phenyl, 30*150 mm, 5μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 40% B in 10 min, 40% B; Wave Length: 254/220 nm; RT1(min): 7.65/8.83) to afford (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (113.6 mg, 41.21%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 470.4.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.97 (s, 1H), 8.99 (d, J = 1.4 Hz, 1H), 8.51 (d, J = 5.6 Hz, 1H), 8.00 (s, 1H), 7.17 (dd, J = 5.6, 1.5 Hz, 1H), 7.13 (s, 1H), 6.82 – 6.71 (m, 2H), 6.29 (dd, J = 6.9, 2.7 Hz, 1H), 3.88 (s, 3H), 3.74 (ddd, J = 18.8, 11.0, 2.0 Hz, 2H), 3.68 – 3.54 (m, 3H), 3.45 (ddd, J = 12.8, 9.3, 3.6 Hz, 2H), 3.22 – 3.12 (m, 3H), 1.79 (ddd, J = 14.3, 9.2, 5.4 Hz, 1H), 1.61 – 1.50 (m, 1H).

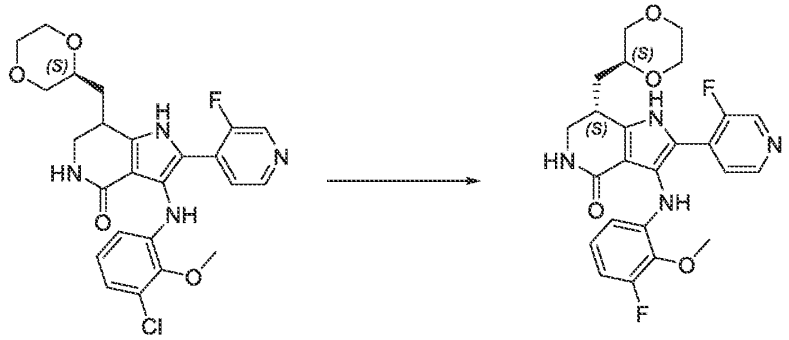
Example 74. (7S)-7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (35.3 mg, 22.83%) (7S)-7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-

methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 525)**



To a stirred solution of 7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (600 mg, 1.312 mmol, 1.00 equiv) and 3-fluoro-2-methoxyaniline (555.64 mg, 3.936 mmol, 3.00 equiv) in DMF (7 mL) were added Cs2CO3 (855.09 mg, 2.624 mmol, 2.0 equiv) and EPhos Pd G4 (241.07 mg, 0.262 mmol, 0.2 equiv) and EPhos (140.35 mg, 0.262 mmol, 0.20 equiv) at rt, then the solution was stirred at 50 ° C under N2 atmosphere about 3h. The resulting mixture was extracted with EA (3 x 20mL). The combined organic layers were washed with saturated salt solution (3x20mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM: MeOH=20:1) to afford crude product 7-(1,4-dioxan-2-ylmethyl)-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (160 mg, 25.92%) as a yellow solid.

LC-MS: M+H found: 471.0.

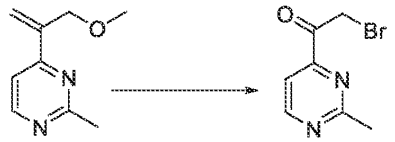


The crude product 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (160 mg, 0.329 mmol, 1.00 equiv) was purified by Prep-HPLC with the following conditions (Column: X Bridge Prep Phenyl OBD Column, 19 250 mm, 5 μ m; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3 H2O), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 60% B to 74% B in 10 min, 74% B; Wave Length: 254; 220 nm) to afford (7S)-7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (35.3 mg, 22.83%) (7S)-7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (35.3 mg, 22.83%) as a light yellow solid.

LC-MS: M+H found: 471.0.

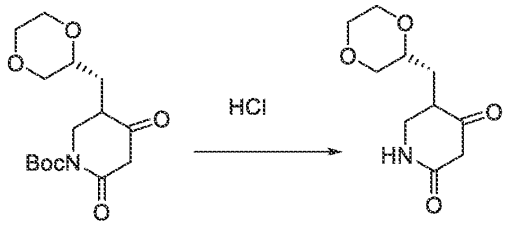
^{1}H NMR (300 MHz, DMSO-d6) δ 11.39 (s, 1H), 8.50 (d, J = 3.0 Hz, 1H), 8.28 (d, J = 5.2 Hz, 1H), 7.53 (s, 1H), 7.46 – 7.40 (m, 1H), 7.16 (s, 1H), 6.65 – 6.55 (m, 1H), 6.52 – 6.44 (m, 1H), 5.98 (d, J = 8.2 Hz, 1H), 3.88 (s, 3H), 3.81 – 3.73 (m, 1H), 3.69 – 3.58 (m, 4H), 3.56 – 3.40 (m, 2H), 3.17 (dd, J = 25.1, 14.8 Hz, 3H), 1.81 – 1.70 (m, 1H), 1.66 – 1.53 (m, 1H).

Example 75. (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 551)**



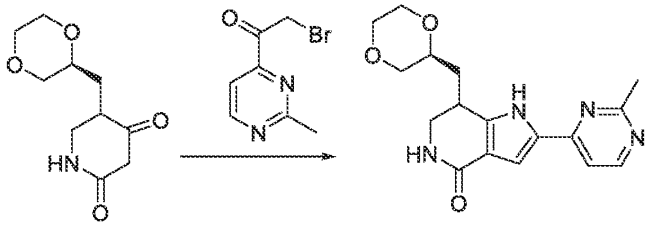
To a stirred solution of 4-(1-ethoxyethenyl)-2-methylpyrimidine (250 mg, 1.522 mmol, 1.00 equiv) in THF (3 mL, 30.851 mmol, 20.27 equiv) was added NBS (325.17 mg, 1.826 mmol, 1.2 equiv) at rt under N2 atmosphere. Then, the solution was stirred at rt for 2h. The resulting mixture was diluted with water (100 ml) and extracted with EA(3x100 ml). The extracts was concentrated under reduced pressure to afford 2-bromo-1-(2-methylpyrimidin-4-yl)ethanone (283 mg, 86.44%) as a yellow oil.

LC-MS: M-18 found: 232.95.



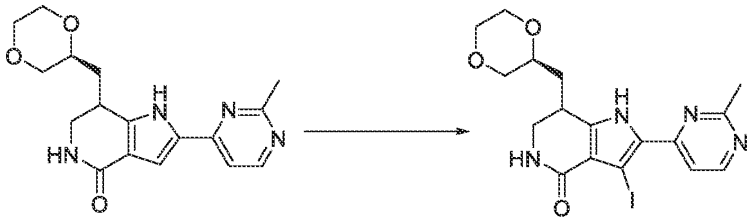
To a stirred solution of tert-butyl 5-(1,4-dioxan-2-ylmethyl)-2,4-dioxopiperidine-1-carboxylate (690 mg, 2.202 mmol, 1.00 equiv) in DCM (14.79 mL, 232.575 mmol, 105.62 equiv) was added HCl(gas) in 1,4-dioxane (7.89 mL, 259.528 mmol, 117.86 equiv) at rt under N2 atmosphere. Then, the solution was stirred at rt for 2h. The resulting mixture was concentrated under reduced pressure to afford crude 5-(1,4-dioxan-2-ylmethyl)piperidine-2,4-dione (470 mg, 100.10%) as a yellow oil.

LC-MS: M+1 found: 214.25.



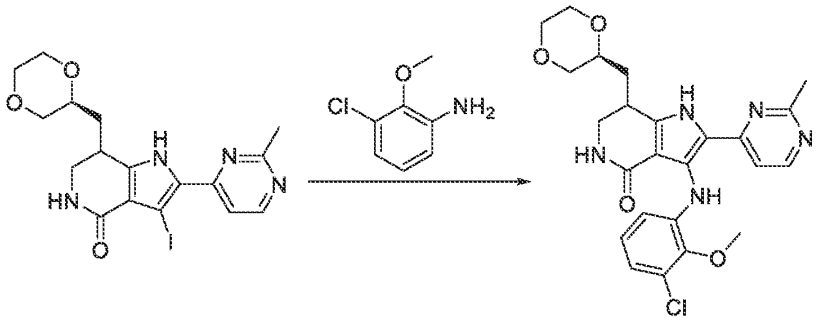
To a stirred solution of 5-[(2R)-1,4-dioxan-2-ylmethyl]piperidine-2,4-dione (272 mg, 1.276 mmol, 1.00 equiv) and NH4OAc (589.96 mg, 7.656 mmol, 6.0 equiv) in EtOH (5 mL) were added 2-bromo-1-(2-methylpyrimidin-4-yl)ethanone (274.32 mg, 1.276 mmol, 1.0 equiv) at RT under N2 atmosphere. Then, the solution was stirred at 50° C for 16h. The resulting mixture was concentrated under reduced pressure and purified by silica gel column chromatography, eluted with DCM: MeOH=7% to afford 7-(1,4-dioxan-2-ylmethyl)-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (140 mg, 33.42%) as a yellow oil.

LC-MS: M+H found: 329.0.



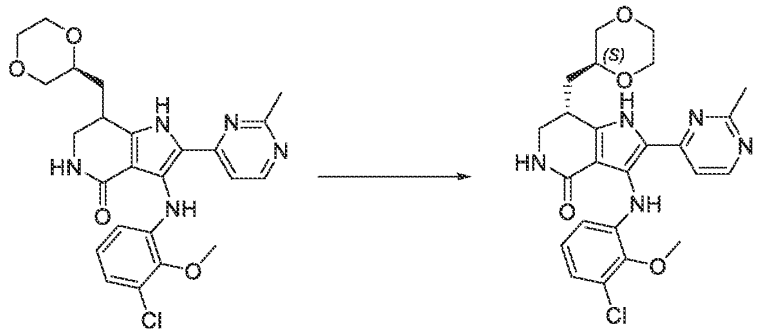
To a stirred solution of 7-(1,4-dioxan-2-ylmethyl)-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (140 mg, 0.426 mmol, 1.00 equiv) in DMF (3 mg) were added NIS (124.70 mg, 0.554 mmol, 1.3 equiv) at rt under N2 atmosphere. Then, the solution was stirred at rt for 2h. The resulting mixture was concentrated under reduced pressure and purified by Prep-TLC (DCM: MeOH=15:1) to afford 7-(1,4-dioxan-2-ylmethyl)-3-iodo-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (130 mg, 67.12%) as a yellow solid.

LC-MS: M+H found: 454.85.



To a stirred solution of 7-[(2S)-1,4-dioxan-2-ylmethyl]-3-iodo-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (130 mg, 0.286 mmol, 1 equiv) and Cs2CO3 (186.48 mg, 0.572 mmol, 2.0 equiv) in DMF (1.5 mL) were added 3-chloro-2-methoxyaniline (180.40 mg, 1.144 mmol, 4.0 equiv) and EPhos Pd G4 (52.57 mg, 0.057 mmol, 0.2 equiv) at RT under N2 atmosphere. The solution was stirred at 50° C for 16h. The resulting mixture was concentrated under reduced pressure and purified by Prep-TLC (DCM: MeOH=15:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70 mg, 50.54%) as a yellow solid.

LC-MS: M+H found: 484.0.

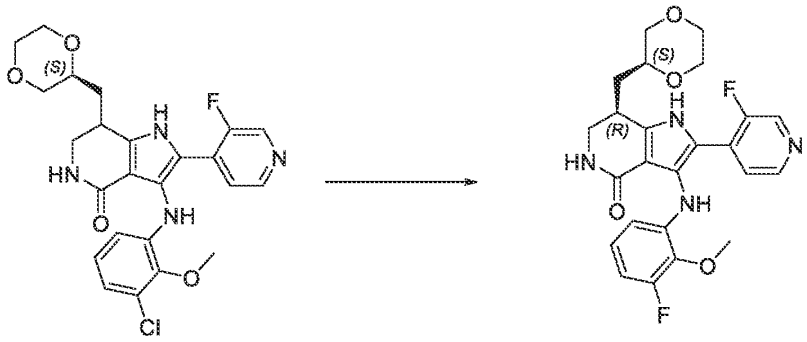


The crude product 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70 mg, 0.145 mmol, 1 equiv) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column, 19*250 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 68% B to 78% B in 8 min, 78% B; Wave Length: 254; 220 nm; RT1(min): 6.42, 7.18) to afford (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (14.2 mg, 20.29%) as a light yellow solid.

LC-MS: M found 484.0.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.74 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.21 (s, 1H), 7.19 (s, 1H), 7.07 (d, J = 5.6 Hz, 1H), 6.87 – 6.74 (m, 2H), 6.33 (dd, J = 6.8, 2.7 Hz, 1H), 3.90 (s, 3H), 3.82 – 3.70 (m, 2H), 3.66 (d, J = 11.1 Hz, 4H), 3.49 (dd, J = 12.5, 3.8 Hz, 2H), 3.19 (d, J = 10.0 Hz, 1H), 3.09 (s, 1H), 2.60 (s, 3H), 1.75 (d, J = 13.8 Hz, 1H), 1.65 (t, J = 7.8 Hz, 1H).

Example 76. (7R)-7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 575)**

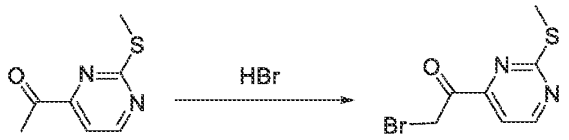


The crude product 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (160 mg, 0.329 mmol, 1.00 equiv) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column, 19*250 mm, 5 μ m; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 60% B to 74% B in 10 min, 74% B; Wave Length: 254； 220 nm; RT1(min): 7.18， 8.9) to afford (7R)-7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (26.6 mg, 17.21%) as a light yellow solid.

LC-MS: M+H found: 471.0.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.49 (s, 1H), 8.51 (d, J = 3.0 Hz, 1H), 8.31 – 8.26 (m, 1H), 7.57 (s, 1H), 7.44 (dd, J = 6.9, 5.1 Hz, 1H), 7.17 (s, 1H), 6.68 – 6.59 (m, 1H), 6.56 – 6.46 (m, 1H), 6.00 (d, J = 8.2 Hz, 1H), 3.92 – 3.89 (m, 3H), 3.83 – 3.66 (m, 5H), 3.51 (t, J = 10.0 Hz, 2H), 3.26 – 3.17 (m, 3H), 1.80 (dd, J = 14.8, 9.6 Hz, 1H), 1.68 – 1.54 (m, 1H).

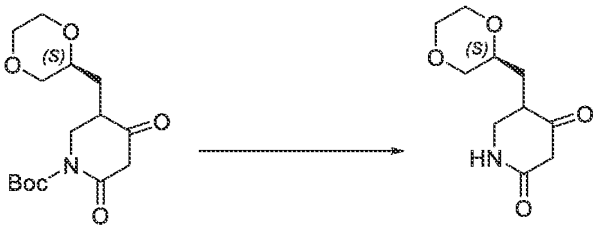
Example 77. (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 574)**



To a stirred solution of 1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone (3 g, 17.835 mmol, 1 equiv) in HBr in AcOH(40%) (3 mL, 102.704 mmol, 5.76 equiv) and HAc (10 mL) was

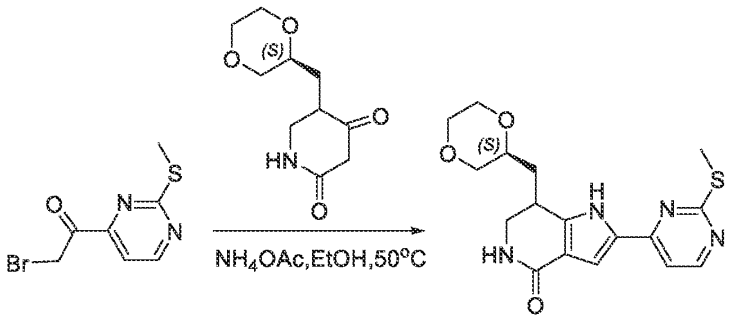
added Br2 (1.13 mL, 22.054 mmol, 1.24 equiv) dropwise at 0°C under N2 atmosphere. The resulting mixture was stirred for 2.5 hours at 80°C under N2 atmosphere. The mixture was allowed to cool down to RT. The resulting mixture was re-crystallized from EA 200 mL . The precipitated solids were collected by filtration to afford 2-bromo-1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone (4 g, 90.76%) as a yellow solid.

LC-MS: M+H found: 246.95.



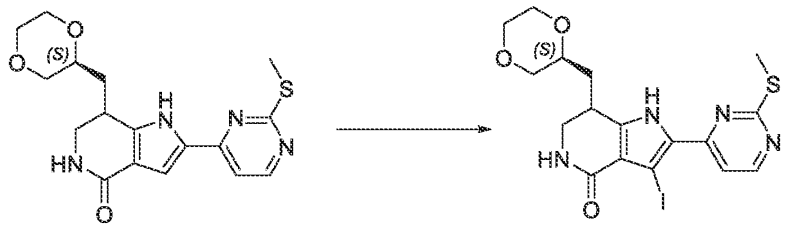
To a stirred solution of tert-butyl 5-[(2S)-1,4-dioxan-2-ylmethyl]-2,4-dioxopiperidine-1-carboxylate (4 g, 12.765 mmol, 1 equiv) in DCM (40 mL) was added TFA (20 mL, 269.261 mmol, 21.09 equiv) dropwise at RT. The resulting mixture was stirred for 1.5 hour at RT. The aqueous layer was extracted with DCM and H2O (3x1 150 mL). To afford 5-[(2S)-1,4-dioxan-2-ylmethyl]piperidine-2,4-dione (2.6 g, 95.52%) as a light yellow solid.

LC-MS: M-H found: 212.05.



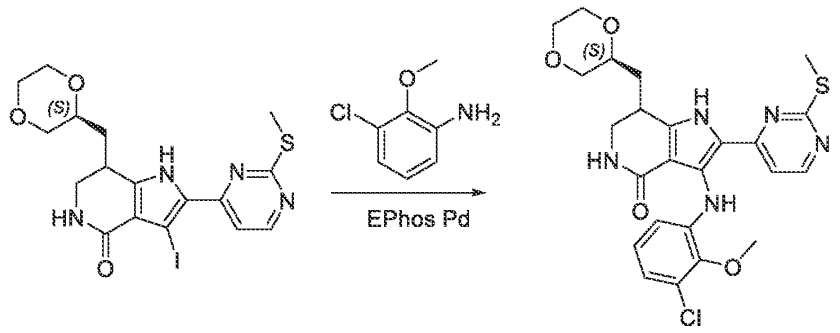
To a stirred solution of 2-bromo-1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone (2.4 g, 9.712 mmol, 1 equiv) and 5-[(2S)-1,4-dioxan-2-ylmethyl]piperidine-2,4-dione (2.07 g, 9.712 mmol, 1 equiv) in EtOH (20 mL) was added NH4OAc (3.74 g, 48.560 mmol, 5 equiv) in portions at RT. The resulting mixture was stirred for 20 hours at 50°C under N2 atmosphere. The mixture was allowed to cool down to RT. The resulting mixture was

extracted with EA and Water (3 x 150 mL). The combined organic dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM and MeOH (95:5) to afford 7-[(2S)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.15 g, 32.85%) as a yellow solid.



To a stirred solution of 7-[(2S)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.4 g, 3.884 mmol, 1 equiv) in DMF (20 mL) was added NIS (1.31 g, 5.826 mmol, 1.5 equiv) in portions at RT. The resulting mixture was stirred for 1 hour at RT. The resulting mixture was extracted with EA (3 x 50 mL). The combined organic layer was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM and MeOH 15:1) to afford 7-[(2S)-1,4-dioxan-2-ylmethyl]-3-iodo-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.65 g, 87.35%) as a yellow solid.

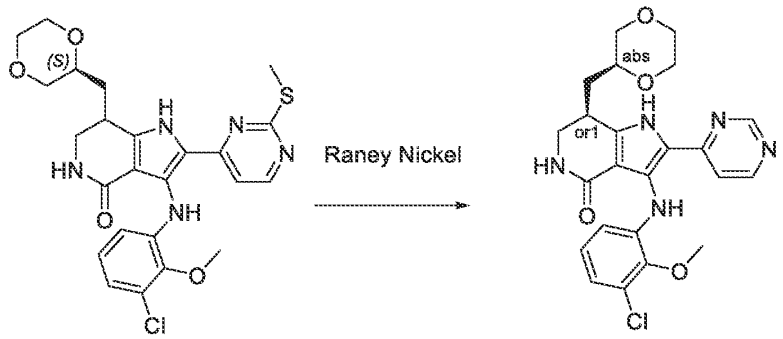
LC-MS: M-H found: 487.0.



To a stirred mixture of 7-[(2S)-1,4-dioxan-2-ylmethyl]-3-iodo-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1 g, 2.056 mmol, 1 equiv) and 3-chloro-2-methoxyaniline (0.97 g, 6.168 mmol, 3 equiv) in DMF (10 mL) were added Cs2CO3 (2.01 g, 6.168 mmol, 3 equiv) and EPhos Pd G4 (0.19 g,

0.206 mmol, 0.1 equiv) in portions at RT under N2 atmosphere. The resulting mixture was stirred for 2 hours at 50 degrees C under N2 atmosphere. The resulting mixture was filtered, then the filter cake was washed with EA (1x1 100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM and MeOH 20:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.04 g, 98.02%) as a light yellow solid.

LC-MS: M+H found: 516.1.



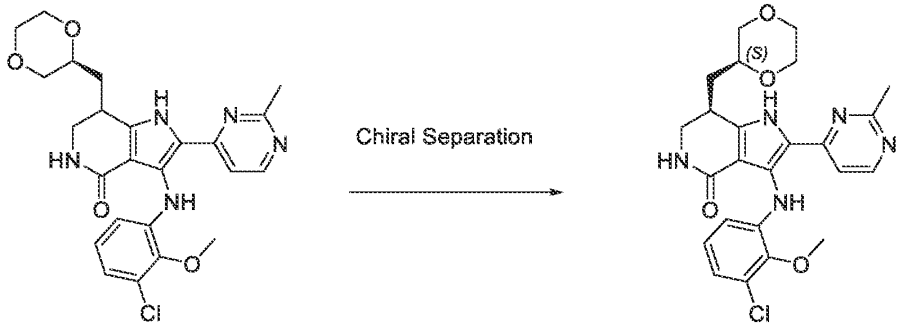
To a stirred mixture of Raney Nickel (99.62 mg, 1.162 mmol, 2 equiv) in EtOH (3 mL) was added 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (300 mg, 0.581 mmol, 1 equiv) in portions at RT under N2 atmosphere. The resulting mixture was stirred for 2 hours at 90°C under N2 atmosphere. The resulting mixture was filtered, then the filter cake was washed with MeOH. The filtrate was concentrated under reduced pressure. The crude product (200 mg) was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Fluoro Phenyl, 30*150 mm, 5μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 40% B in 10 min, 40% B; Wave Length: 254/220 nm; RT1(min): 7.65/8.83) to afford (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (109.8 mg, 39.34%) as a yellow solid.

LC-MS: $(M+H)^+$ found 470.4.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.97 (s, 1H), 8.99 (d, J = 1.4 Hz, 1H), 8.51 (d, J = 5.6 Hz, 1H), 8.00 (s, 1H), 7.17 (dd, J = 5.6, 1.5 Hz, 1H), 7.13 (s, 1H), 6.82 – 6.71 (m, 2H),

6.29 (dd, J = 6.9, 2.7 Hz, 1H), 3.88 (s, 3H), 3.74 (ddd, J = 18.8, 11.0, 2.0 Hz, 2H), 3.68 – 3.54 (m, 3H), 3.45 (ddd, J = 12.8, 9.3, 3.6 Hz, 2H), 3.22 – 3.12 (m, 3H), 1.79 (ddd, J = 14.3, 9.2, 5.4 Hz, 1H), 1.61 – 1.50 (m, 1H).

Example 78 (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 573)**



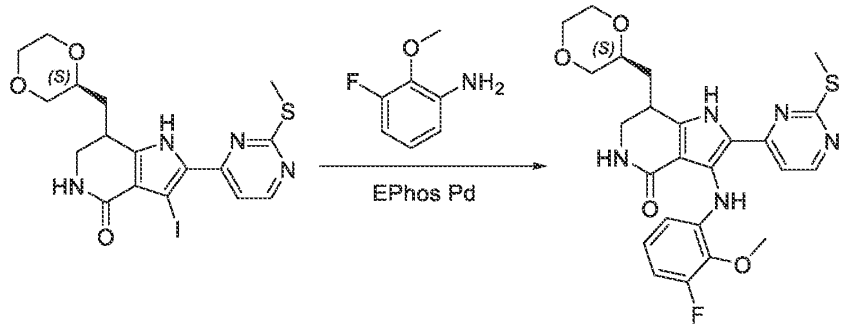
The crude product 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70 mg, 0.145 mmol, 1 equiv) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column, 19*250 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 68% B to 78% B in 8 min, 78% B; Wave Length: 254; 220 nm; RT1(min): 6.42, 7.18) to afford (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (17.3 mg, 24.71%) as a light yellow solid.

LC-MS: M+H found: 484.0.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.83 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.27 (s, 1H), 7.18 (s, 1H), 7.06 (d, J = 5.5 Hz, 1H), 6.87 – 6.74 (m, 2H), 6.36 (dd, J = 6.8, 2.8 Hz, 1H), 3.90 (s, 3H), 3.84 (d, J = 11.7 Hz, 2H), 3.70 (q, J = 11.7 Hz, 4H), 3.53 (d, J = 11.3 Hz, 1H), 3.46 (s, 1H), 3.22 (d, J = 6.1 Hz, 2H), 2.58 (s, 3H), 1.77 (s, 1H), 1.59 (s, 1H).

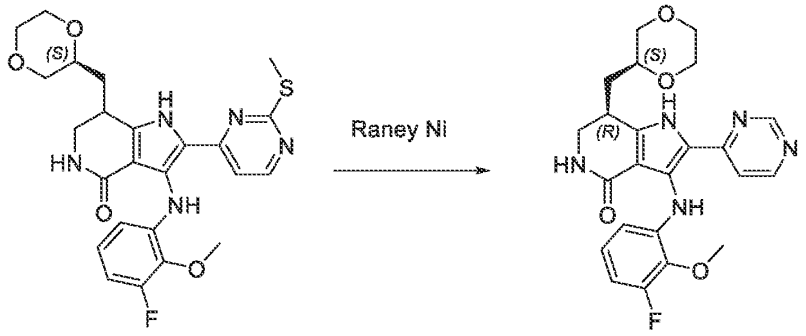
Example 79. (7R*)-7-[(2S)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one

(compound 572)



To a stirred mixture of 7-[(2S)-1,4-dioxan-2-ylmethyl]-3-iodo-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 0.822 mmol, 1 equiv) and 3-fluoro-2-methoxyaniline (348.27 mg, 2.466 mmol, 3 equiv) in DMF (5 mL) were added Cs2CO3 (803.95 mg, 2.466 mmol, 3 equiv) and EPhos Pd G4 (75.55 mg, 0.082 mmol, 0.1 equiv) in portions at RT under N2 atmosphere. The resulting mixture was stirred for 2 hours at 50 degrees C under N2 atmosphere. The resulting mixture was filtered, then the filter cake was washed with EA (1x1 30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM and MeOH 20:1) to afford 7-[(2S)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (363 mg, 88.35%) as a light yellow solid.

LC-MS: M+H found: 500.45.



To a stirred solution of 7-[(2S)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (200 mg, 0.400 mmol, 1 equiv)in EtOH (2 mL) was added

Raney Ni (51.45 mg, 0.600 mmol, 1.5 equiv) in portions at RT under N2 atmosphere. The resulting mixture was stirred for 2 hours at 90°C under N2 atmosphere. The mixture was allowed to cool down to RT. The resulting mixture was filtered, then the filter cake was washed with MeOH (3*10 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 24% B to 44% B in 9 min, 44% B; Wave Length: 254;220 nm; RT1(min): 7.58/8.72) to afford (7R*)-7-[(2S)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (42.9 mg, 23.37%) as a yellow solid.

LC-MS: $(M+H)^+$ found 454.1.

^{1}H NMR (300 MHz, DMSO-d6) δ 12.01 (s, 1H), 9.03 (d, J = 1.4 Hz, 1H), 8.54 (d, J = 5.6 Hz, 1H), 8.03 (s, 1H), 7.20 (dd, J = 5.6, 1.4 Hz, 2H), 6.77 (td, J = 8.3, 6.1 Hz, 1H), 6.67 – 6.54 (m, 1H), 6.18 (d, J = 8.2 Hz, 1H), 3.95 (d, J = 0.9 Hz, 3H), 3.80 (d, J = 12.3 Hz, 2H), 3.66 (t, J = 10.0 Hz, 3H), 3.51 (d, J = 11.0 Hz, 2H), 3.20 (d, J = 9.7 Hz, 3H), 1.86 – 1.75 (m, 1H), 1.59 (t, J = 10.2 Hz, 1H).

Example 80. (7R)-2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 571)**



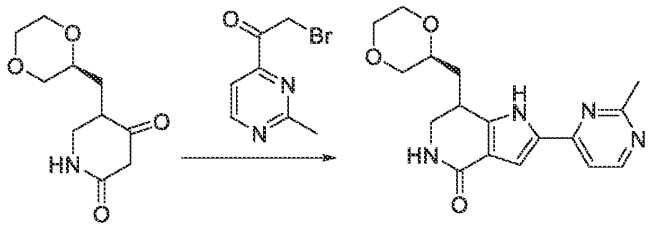
The crude product 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (300 mg, 0.619 mmol, 1 equiv) was purified by Prep-HPLC as the following Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5 μ m; Mobile Phase A: Water(10 mmol/L

NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 50% B in 11 min, 50% B; Wave Length: 254/220 nm; RT1(min): 7.25/10.2; to afford (7R)-2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2S)-1,4-dioxan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (54.0 mg, 18.00%) as a light yellow solid.

LC-MS: M found 485.1.

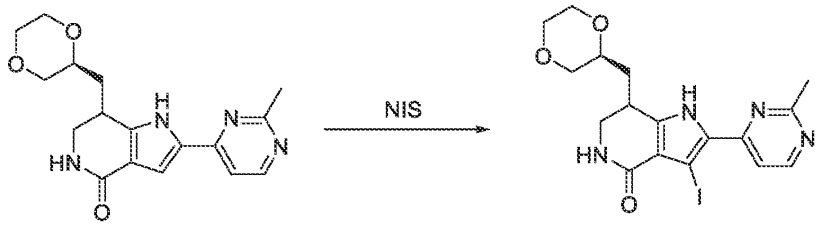
^{1}H NMR (300 MHz, DMSO-d6) δ 11.52 (s, 1H), 8.06 (d, J = 5.3 Hz, 1H), 7.96 (s, 1H), 7.15 (s, 1H), 6.87 – 6.69 (m, 2H), 6.47 (d, J = 5.3 Hz, 1H), 6.35 (dd, J = 7.8, 1.9 Hz, 1H), 6.24 (s, 2H), 3.90 (s, 4H), 3.78 – 3.38 (m, 6H), 3.20 (d, J = 13.5 Hz, 3H), 1.72 (d, J = 10.6 Hz, 1H), 1.56 (t, J = 7.8 Hz, 1H).

Example 81. (7R)-7-[(2S)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 606)**



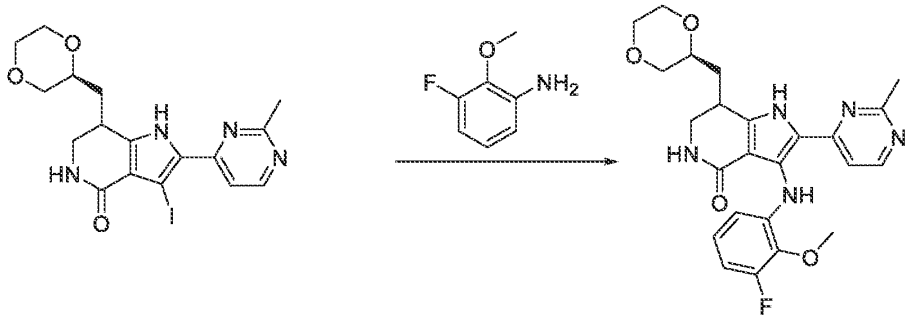
To a stirred solution of 5-[(2S)-1,4-dioxan-2-ylmethyl]piperidine-2,4-dione (1 g, 4.690 mmol, 1 equiv) and 2-bromo-1-(2-methylpyrimidin-4-yl)ethanone (1.21 g, 5.628 mmol, 1.2 equiv) in EtOH (10 mL) was added NH4OAc (1.81 g, 23.450 mmol, 5 equiv) at rt, then the solution was stirred at 50° C about 16h. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with MeOH: DCM=15:1 to afford 7-[(2S)-1,4-dioxan-2-ylmethyl]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 25.97%) as a yellow solid.

LC-MS: M+H found: 329.2.



To a stirred solution of 7-[(2S)-1,4-dioxan-2-ylmethyl]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 1.218 mmol, 1 equiv) in DMF (10 mL) was added NIS (356.28 mg, 1.583 mmol, 1.3 equiv)) at rt, Then the solution was stirred at rt about 2h. The resulting mixture was concentrated under reduced pressure. The residue was purified by column chromatography with the following conditions (MeOH: DCM=15:1) to afford 7-[(2S)-1,4-dioxan-2-ylmethyl]-3-iodo-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 72.29%) as a yellow solid.

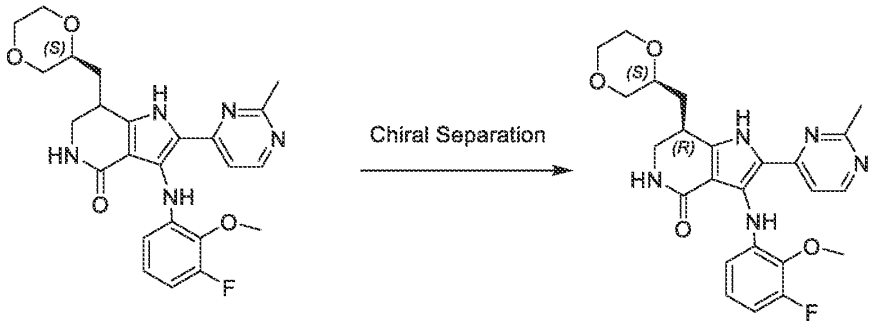
LC-MS: M+H found: 455.0.



To a stirred solution of 7-[(2S)-1,4-dioxan-2-ylmethyl]-3-iodo-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 0.881 mmol, 1 equiv) and 3-fluoro-2-methoxyaniline (149.14 mg, 1.057 mmol, 1.2 equiv) in DMF (4 mL) were added EPhos Pd G4 (80.88 mg, 0.088 mmol, 0.1 equiv) and EPhos (94.18 mg, 0.176 mmol, 0.2 equiv) at rt. Then the solution was stirred 50 ° C under N2 atmosphere for 2h. The resulting mixture was extracted with EA (3 x 20 mL). The combined organic layers were washed with saturated salt solution (3x20 mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM: MeOH=20:1) to afford 7-[(2S)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-

pyrrolo[3,2-c]pyridin-4-one (350 mg, 85.02%) as a yellow solid.

LC-MS: M+H found: 468.4.

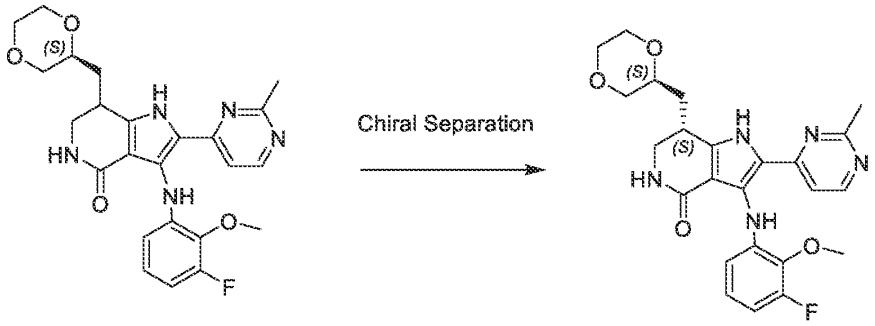


The residue 7-[(2S)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 0.856 mmol, 1 equiv) was purified by reverse flash chromatography with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μ m; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: MeOH--HPLC; Flow rate: 60 mL/min; Gradient: 65% B to 77% B in 10 min, 77% B; Wave Length: 254; 220 nm; RT1(min): 8.4, 9.43(min), to afford (7R)-7-[(2S)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (71.1 mg, 17.74%) as a yellow solid.

LC-MS: M+H found: 468.1.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.72 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.14 (s, 1H), 7.19 (s, 1H), 7.06 (d, J = 5.5 Hz, 1H), 6.76 (td, J = 8.2, 5.9 Hz, 1H), 6.59 (dd, J = 10.7, 8.5 Hz, 1H), 6.18 (d, J = 8.3 Hz, 1H), 3.94 (s, 3H), 3.81 – 3.69 (m, 2H), 3.69 – 3.63 (m, 3H), 3.63 – 3.50 (m, 2H), 3.50 – 3.42 (m, 1H), 3.21 (t, J = 10.6 Hz, 1H), 3.14 – 3.07 (m, 1H), 2.60 (s, 3H), 1.75 (dt, J = 14.2, 4.7 Hz, 1H), 1.62 (dt, J = 14.7, 8.0 Hz, 1H).

Example 82. (7S)-7-[(2S)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 603)**

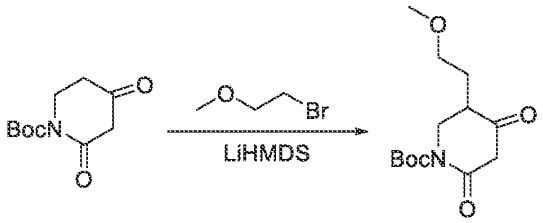


The residue 7-[(2S)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 0.856 mmol, 1 equiv) was purified by reverse flash chromatography with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: MeOH--HPLC; Flow rate: 60 mL/min; Gradient: 65% B to 77% B in 10 min, 77% B; Wave Length: 254; 220 nm; RT1(min): 8.4, 9.43(min); to afford (7S)-7-[(2S)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (85.5 mg, 21.31%) as a yellow solid.

LC-MS: M+H found: 468.1.

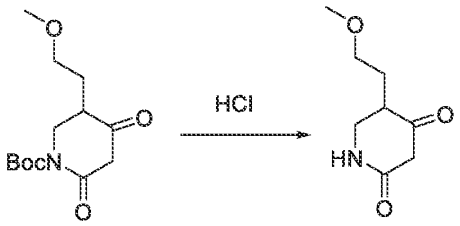
^{1}H NMR (400 MHz, DMSO-d6) δ 11.72 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.14 (s, 1H), 7.19 (s, 1H), 7.06 (d, J = 5.5 Hz, 1H), 6.76 (td, J = 8.2, 5.9 Hz, 1H), 6.59 (dd, J = 10.7, 8.5 Hz, 1H), 6.18 (d, J = 8.3 Hz, 1H), 3.94 (s, 3H), 3.81 – 3.69 (m, 2H), 3.69 – 3.63 (m, 3H), 3.63 – 3.50 (m, 2H), 3.50 – 3.42 (m, 1H), 3.21 (t, J = 10.6 Hz, 1H), 3.14 – 3.07 (m, 1H), 2.60 (s, 3H), 1.75 (dt, J = 14.2, 4.7 Hz, 1H), 1.62 (dt, J = 14.7, 8.0 Hz, 1H).

Example 83. (7S)-3-[(3-chloro-2-methoxyphenyl) amino]-7-(methoxymethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 747)**



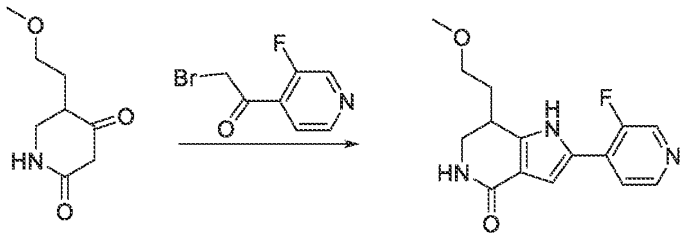
To a stirred solution of tert-butyl 2,4-dioxopiperidine-1-carboxylate (5 g, 23.449 mmol, 1.00 equiv) and 2-bromoethyl methyl ether (6.52 g, 46.898 mmol, 2.00 equiv) in THF (50 mL, 234.490 mmol) were added LiHMDS (9.81 g, 58.623 mmol, 2.50 equiv) dropwise at -70 degrees C under N2 atmosphere. The mixture was stirred for 1.5h at -70°C ~ -10°C. Then the mixture solution was adjusted to pH=5. The resulting mixture was extracted with EA (3 x 50 ml). The combined organic layers were washed with saturated NaCl solution (2x100 ml), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (99:1~15:1) to afford tert-butyl 5-(2-methoxyethyl)-2,4-dioxopiperidine-1-carboxylate (4.7 g, 73.88%) as a yellow oil.

LC-MS: 2M+Na found: 565.15.



To a stirred solution of tert-butyl 5-(2-methoxyethyl)-2,4-dioxopiperidine-1-carboxylate (1.5 g, 5.529 mmol, 1 equiv) in DCM (15 mL) was added HCl (gas)in 1,4-dioxane (7 mL, 230.389 mmol, 41.67 equiv) dropwise at 0°C. The resulting mixture was concentrated under reduced pressure to afford 5-(2-methoxyethyl) piperidine-2,4-dione (1.5 g, 158.48%), which was used directly in next step without further purification.

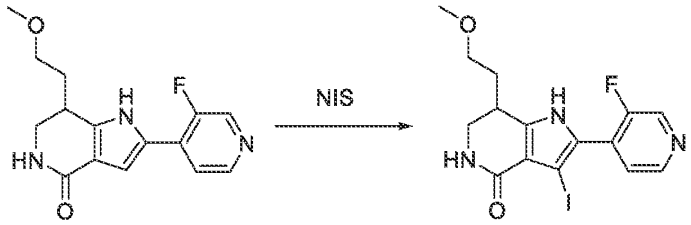
LC-MS: M+H found: 172.01.



A solution of 5-(2-methoxyethyl) piperidine-2,4-dione (1.5 g, 8.762 mmol, 1.00 equiv), 2-bromo-1-(3-fluoropyridin-4-yl) ethanone (2.10 g, 9.632 mmol, 1.10 equiv) and NH4OAc (4.73 g, 61.334 mmol, 7 equiv) in EtOH (20 mL) was stirred for 16h at 50

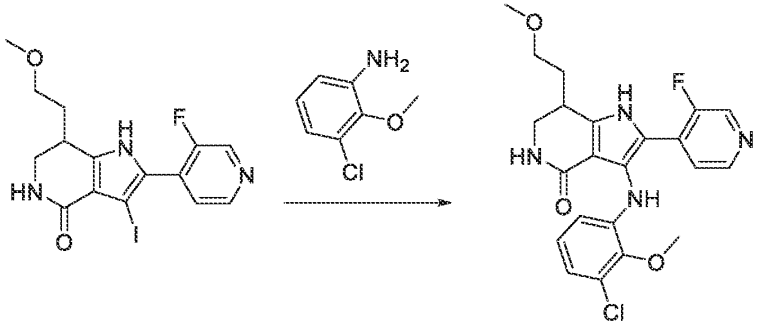
degrees C. The mixture was allowed to cool down to RT. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (15:1) to afford 2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (1.6 g, 63.12%) as a yellow solid.

LC-MS: M+H found: 290.05.



To a stirred solution of 2-(3-fluoropyridin-4-yl)-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (1000 mg, 3.456 mmol, 1.00 equiv) in DMF (10 mL) was added NIS (1166.49 mg, 5.184 mmol, 1.50 equiv) in portions at RT. The reaction was monitored by LCMS. When the reaction was complete, the resulting mixture was extracted with EA (3 x 20 ml). The combined organic layers were washed with saturated NaCl solution (2 x 40 ml), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (99:1~15:1) to afford 2-(3-fluoropyridin-4-yl)-3-iodo-7-(2-methoxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (1.1g, 76.65%) as a yellow solid.

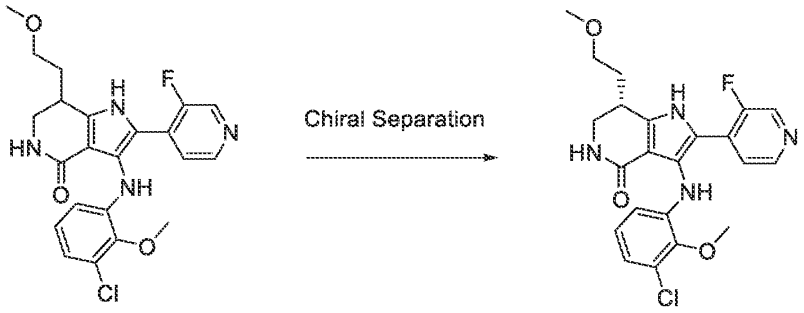
LC-MS: M+H found: 416.10.



A mixture of 3-iodo-7-(2-methoxyethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]

pyridin-4-one (400 mg, 1.007 mmol, 1 equiv) and 3-chloro-2-methoxyaniline (317.41 mg, 2.014 mmol, 2 equiv) in DMF (4 mL) was treated with Cs2CO3 (984.31 mg, 3.021 mmol, 3 equiv) and EPhos Pd G4 (185.00 mg, 0.201 mmol, 0.2 equiv) for 3h at 50°C under nitrogen atmosphere. The mixture was allowed to cool down to RT. The resulting mixture was extracted with EA (3 x 10ml). The combined organic layers were washed with saturated NaCl solution (2x20ml), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (99:1~15:1) to afford 3-[(3-chloro-2-methoxyphenyl) amino]-7-(2-methoxyethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (370 mg). The residue was purified by reverse flash chromatography with the following conditions: Column: YMC-Actus Triart C18, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 8 min, 60% B; Wave Length: 254/220 nm; RT1(min): 7.48 to afford 3-[(3-chloro-2-methoxyphenyl) amino]-7-(2-methoxyethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (120 mg, 27.91%).

LC-MS: M+H found: 445.10.

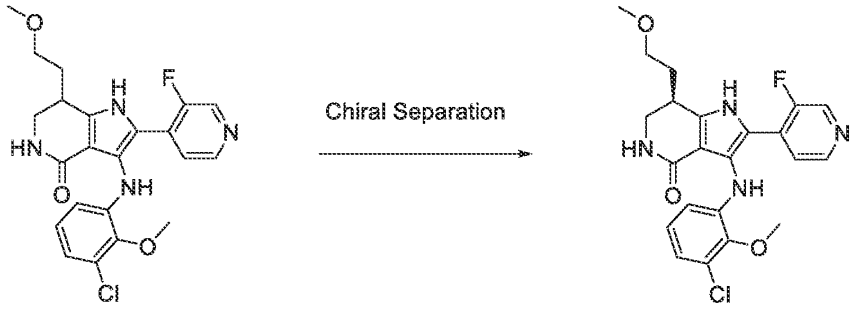


The crude product (170 mg, 0.383 mmol, 1.00 equiv) was purified by Prep-Chiral-HPLC (Column: CHIRALPAK IG-3, 4.6*50mm 3um; Mobile Phase A: (Hex: DCM=3: 1) (0.1% DEA): IPA=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (7S)-3-[(3-chloro-2-methoxyphenyl) amino]-7-(methoxymethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (47.8 mg, 28.1%) as a light yellow solid.

LC-MS: M+H found 445.00.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.49 (s, 1H), 8.51 (d, J = 2.9 Hz, 1H), 8.29 (dd, J = 5.1, 1.2 Hz, 1H), 7.59 (s, 1H), 7.45 (dd, J = 6.8, 5.1 Hz, 1H), 7.19 (d, J = 2.7 Hz, 1H), 6.73 – 6.57 (m, 2H), 6.13 (dd, J = 7.3, 2.4 Hz, 1H), 3.86 (s, 3H), 3.59 – 3.40 (m, 3H), 3.30 (s, 3H), 3.24 (ddd, J = 12.5, 6.0, 3.1 Hz, 1H), 3.09 (dt, J = 8.4, 5.4 Hz, 1H), 2.09 – 1.95 (m, 1H), 1.78 (ddt, J = 13.8, 8.1, 5.5 Hz, 1H).

Example 84. (7S)-3-[(3-chloro-2-methoxyphenyl) amino]-7-(methoxymethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one **(compound 746)**

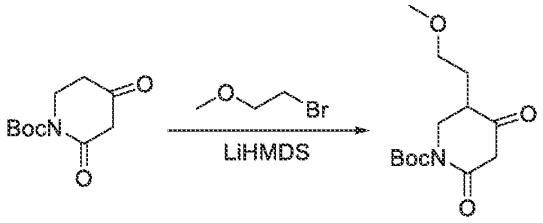


The crude product (170 mg, 0.383 mmol, 1.00 equiv) was purified by Prep-Chiral-HPLC (Column: CHIRALPAK IG-3, 4.6*50mm 3um; Mobile Phase A: (Hex: DCM=3: 1) (0.1% DEA): IPA=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (7S)-3-[(3-chloro-2-methoxyphenyl) amino]-7-(methoxymethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (55.1 mg, 32.4%) as a light yellow solid.

LC-MS: M+H found 445.00.

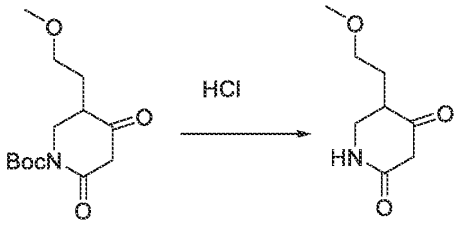
^{1}H NMR (400 MHz, DMSO-d6) δ 11.49 (s, 1H), 8.51 (d, J = 3.0 Hz, 1H), 8.29 (dd, J = 5.1, 1.2 Hz, 1H), 7.59 (s, 1H), 7.44 (dd, J = 6.8, 5.1 Hz, 1H), 7.18 (t, J = 2.7 Hz, 1H), 6.73 – 6.60 (m, 2H), 6.13 (dd, J = 7.3, 2.3 Hz, 1H), 3.86 (s, 3H), 3.57 – 3.41 (m, 3H), 3.30 (s, 3H), 3.24 (ddd, J = 12.5, 6.1, 3.1 Hz, 1H), 3.09 (dq, J = 11.0, 5.5 Hz, 1H), 2.07 – 1.95 (m, 1H), 1.78 (td, J = 13.9, 5.6 Hz, 1H).

Example 85. (7S)-3-[(3-chloro-2-methoxyphenyl) amino]-7-(methoxymethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one **(compound 447a)**



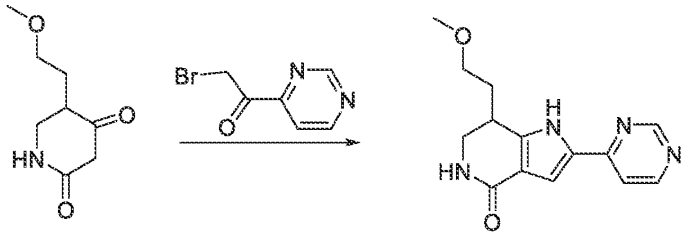
To a stirred solution of tert-butyl 2,4-dioxopiperidine-1-carboxylate (5 g, 23.449 mmol, 1.00 equiv) and 2-bromoethyl methyl ether (6.52 g, 46.898 mmol, 2.00 equiv) in THF (50 mL) were added LiHMDS (9.81 g, 58.623 mmol, 2.50 equiv) dropwise at -70 degrees C under N2 atmosphere. The mixture was stirred for 1.5h at -70°C ~ -10°C. Then the mixture solution was adjusted to pH=5. The resulting mixture was extracted with EA (3 x 50 ml). The combined organic layers were washed with saturated NaCl solution (2x100 ml), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (99:1~15:1) to afford tert-butyl 5-(2-methoxyethyl)-2,4-dioxopiperidine-1-carboxylate (4.7 g, 73.88%) as a yellow oil.

LC-MS: 2M+Na found: 565.15.



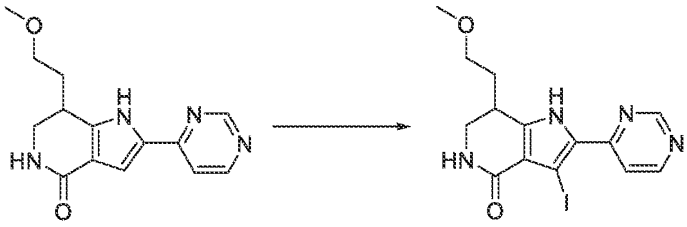
To a stirred solution of tert-butyl 5-(2-methoxyethyl)-2,4-dioxopiperidine-1-carboxylate (1.5 g, 5.529 mmol, 1 equiv) in DCM (15 mL) was added HCl (gas)in 1,4-dioxane (7 mL, 230.389 mmol, 41.67 equiv) dropwise at 0°C. The resulting mixture was concentrated under reduced pressure to afford 5-(2-methoxyethyl) piperidine-2,4-dione (1.5 g, 158.48%), which was used directly in next step without further purification.

LC-MS: M+H found: 172.01.



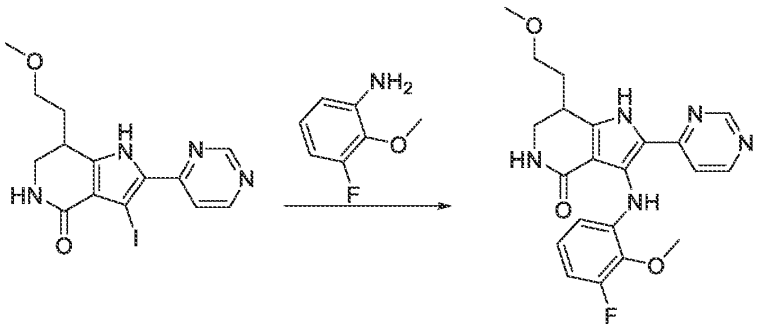
A solution of 5-(2-methoxyethyl) piperidine-2,4-dione (1000 mg, 5.841 mmol, 1 equiv), 2-bromo-1-(pyrimidin-4-yl) ethanone (1291.65 mg, 6.425 mmol, 1.1 equiv) and NH4OAc (3151.83 mg, 40.887 mmol, 7 equiv) in EtOH (10 mL,) was stirred for 16h at 50 degrees C. The mixture was allowed to cool down to RT. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (15:1) to afford 7-(2-methoxyethyl)-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (520 mg, 32.69%) as a yellow solid.

LC-MS: M+H found: 290.05.



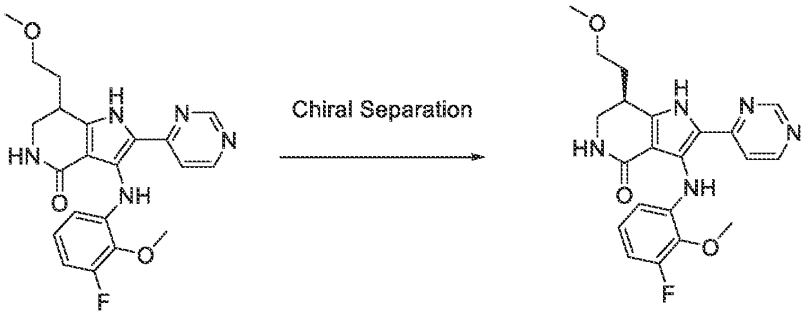
To a stirred solution of 7-(2-methoxyethyl)-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (520 mg, 1.910 mmol, 1 equiv) in DMF (5 mL) was added NIS (644.45 mg, 2.865 mmol, 1.5 equiv) in portions at RT. The reaction was monitored by LCMS. When the reaction was complete, the resulting mixture was extracted with EA (3 x 20 ml). The combined organic layers were washed with saturated NaCl solution (2 x 40 ml), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (99:1~15:1) to afford 3-iodo-7-(2-methoxyethyl)-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (530 mg, 69.70%) as a yellow solid.

LC-MS: M+H found: 398.85.



A solution of 3-iodo-7-(2-methoxyethyl)-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (200 mg, 0.502 mmol, 1 equiv) and 3-fluoro-2-methoxyaniline (141.78 mg, 1.004 mmol, 2 equiv) in DMF (2.5 mL) was treated with Cs2CO3 (490.93 mg, 1.506 mmol, 3 equiv) and EPhos Pd G4 (92.27 mg, 0.100 mmol, 0.2 equiv) for 3h at 50°C under nitrogen atmosphere. The mixture was allowed to cool down to RT. The resulting mixture was extracted with EA (3 x 10ml). The combined organic layers were washed with saturated NaCl solution (2x20ml), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (99:1~15:1) to afford the crude product. The residue was purified by reverse flash chromatography with the following conditions: Column: XBridge Prep Amide OBD Column, 19*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 98% B to 50% B in 7 min, 50% B; RT1(min): 3.82 to afford 3-[(3-fluoro-2-methoxyphenyl) amino]-7-(2-methoxyethyl)-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (35 mg, 16.94%) as a white solid.

LC-MS: M+H found: 412.30.

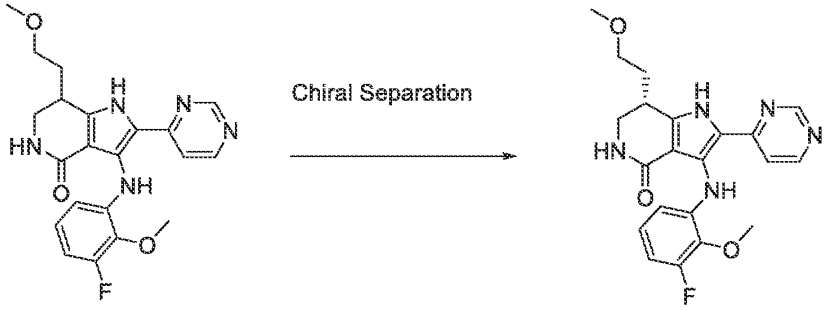


The product 5(35 mg, 0.079 mmol, 1.00 equiv) was purified by Prep-Chiral-HPLC (Column: CHIRALPAK IC-3, 4.6*50mm 3um; Mobile Phase A: Hex(0.1%DEA): EtOH=60: 40; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (7S)-3-[(3-chloro-2-methoxyphenyl) amino]-7-(methoxymethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (8.9 mg, 25.4%) as a white solid.

LC-MS: M+H found: 412.30.

^{1}H NMR (300 MHz, DMSO-d6) δ 12.00 (s, 1H), 9.05 (d, J = 1.4 Hz, 1H), 8.55 (d, J = 5.6 Hz, 1H), 8.01 (s, 1H), 7.20 (d, J = 5.9 Hz, 2H), 6.89 – 6.70 (m, 1H), 6.67 – 6.47 (m, 1H), 6.29 – 6.03 (m, 1H), 3.96 (s, 3H), 3.48 (d, J = 21.4 Hz, 3H), 3.33 – 3.16 (m, 4H), 3.08 (s, 1H), 2.13 – 1.88 (m, 1H), 1.88 – 1.66 (m, 1H).

Example 86. (7S)-3-[(3-chloro-2-methoxyphenyl) amino]-7-(methoxymethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one **(compound 447b)**

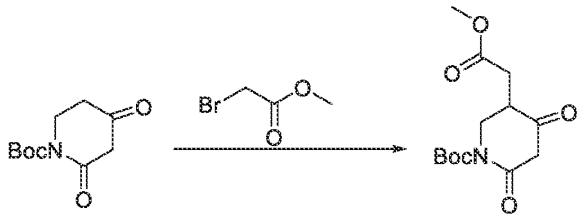


The product 5 (35 mg, 0.079 mmol, 1.00 equiv) was purified by Prep-Chiral-HPLC (Column: CHIRALPAK IC-3, 4.6*50mm 3um; Mobile Phase A: Hex(0.1%DEA): EtOH=60: 40; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (7S)-3-[(3-chloro-2-methoxyphenyl) amino]-7-(methoxymethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (8.4 mg, 24.0%) as a white solid.

LC-MS: M+H found 412.30.

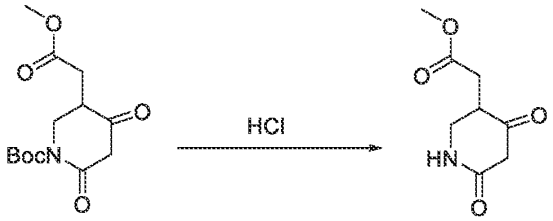
^{1}H NMR (300 MHz, DMSO-d6) δ 12.00 (s, 1H), 9.05 (s, 1H), 8.56 (s, 1H), 8.01 (s, 1H), 7.20 (d, J = 6.0 Hz, 2H), 6.88 – 6.70 (m, 1H), 6.62 (ddd, J = 10.0, 8.4, 1.5 Hz, 1H), 6.18 (dt, J = 8.2, 1.3 Hz, 1H), 3.96 (s, 3H), 3.48 (d, J = 5.8 Hz, 3H), 3.25 (s, 4H), 3.09 (d, J = 7.9 Hz, 1H), 2.02 (dt, J = 12.8, 6.8 Hz, 1H), 1.85 – 1.69 (m, 1H).

Example 87. (7S)-3-[(3-chloro-2-methoxyphenyl) amino]-7-(methoxymethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one **(compound 489)**



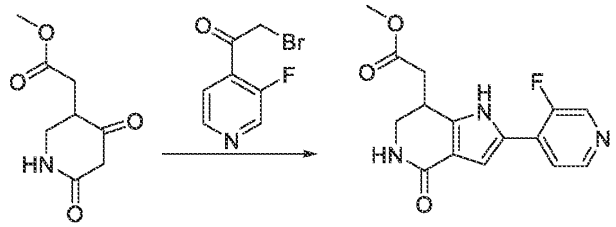
To a stirred solution of tert-butyl 2,4-dioxopiperidine-1-carboxylate (2500 mg, 11.724 mmol, 1.00 equiv) in THF (30 ml) was added LDA (3767.82 mg, 35.172 mmol, 3 equiv) dropwise at -70°C under N2 atmosphere. After stirring for additional 30 min, methyl 2-bromoacetate (2690.28 mg, 17.586 mmol, 1.5 equiv) was added and continued to react for 2h at -70°C. Then the mixture solution was adjusted to pH=5. The resulting mixture was extracted with EA (3 x 100ml). The combined organic layers were washed with saturated NaCl solution (2x150ml), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (99:1~15:1) to afford tert-butyl 5-(2-methoxy-2-oxoethyl)-2,4-dioxopiperidine-1-carboxylate (820 mg, 24.52%) as a yellow oil.

LC-MS: 2M+Na found: 593.45.



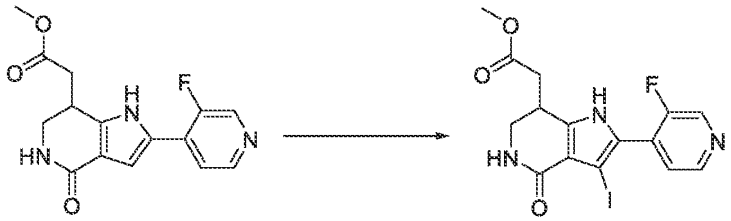
To a stirred solution of tert-butyl 5-(2-methoxy-2-oxoethyl)-2,4-dioxopiperidine-1-carboxylate (820 mg, 2.874 mmol, 1 equiv) in DCM (8 mL) was added HCl (gas) in 1,4-dioxane (4 mL, 109.709 mmol, 38.17 equiv) dropwise at 0°C. The resulting mixture was concentrated under reduced pressure to afford methyl 2-(4,6-dioxopiperidin-3-yl) acetate (850 mg, 159.70%), which was used directly in next step without purification.

LC-MS: M+H found: 186.15.



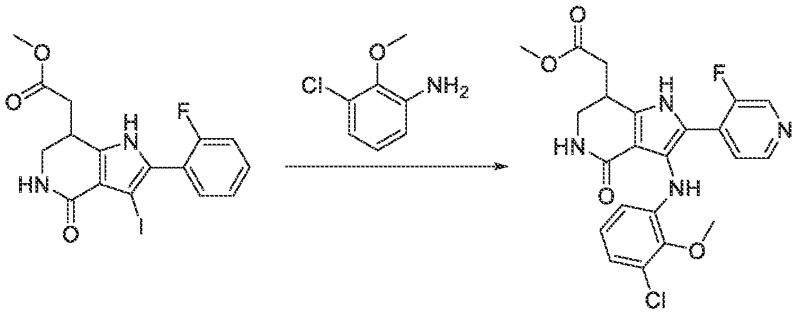
A solution of methyl 2-(4,6-dioxopiperidin-3-yl)acetate (850 mg, 4.590 mmol, 1 equiv) , 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (1200.92 mg, 5.508 mmol, 1.2 equiv) and NH4OAc (2476.76 mg, 32.130 mmol, 7 equiv) in EtOH (10 mL) was stirred for 16h at 50 degrees C. The mixture was allowed to cool down to RT. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (15:1) to afford methyl 2-[2-(2-fluorophenyl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-7-yl]acetate (350 mg, 25.22%) as a yellow solid.

LC-MS: M+H found: 304.00.



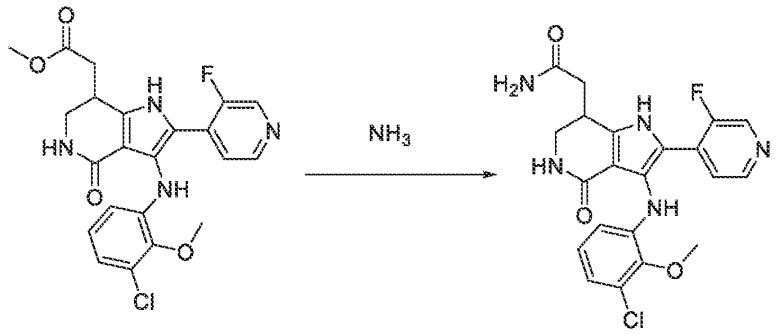
To a stirred solution of methyl 2-[2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-7-yl] acetate (410 mg, 1.352 mmol, 1 equiv) in DMF (4 mL) was added NIS (456.21 mg, 2.028 mmol, 1.5 equiv) in portions at RT. The reaction was monitored by LCMS. When the reaction was complete, the resulting mixture was extracted with EA (3 x 20 ml). The combined organic layers were washed with saturated NaCl solution (2 x 40 ml), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (99:1~15:1) to afford methyl 2-[2-(3-fluoropyridin-4-yl)-3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-7-yl] acetate (420 mg, 72.39%) as a yellow solid.

LC-MS: M+H found: 430.15.



A solution of methyl 2-[2-(2-fluorophenyl)-3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-7-yl] acetate (420 mg, 0.981 mmol, 1 equiv) and 3-chloro-2-methoxyaniline (309.16 mg, 1.962 mmol, 2 equiv) in DMF (4 mL) was treated with Cs2CO3 (958.73 mg, 2.943 mmol, 3 equiv) and EPhos Pd G4 (180.20 mg, 0.196 mmol, 0.2 equiv) for 3h at 50°C under nitrogen atmosphere. The mixture was allowed to cool down to RT. The resulting mixture was extracted with EA (3 x 10ml). The combined organic layers were washed with saturated NaCl solution (2x20ml), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (99:1~15:1) to afford methyl 2-{3-[(3-chloro-2-methoxyphenyl) amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-7-yl} acetate (400 mg, 88.87%) as a yellow solid.

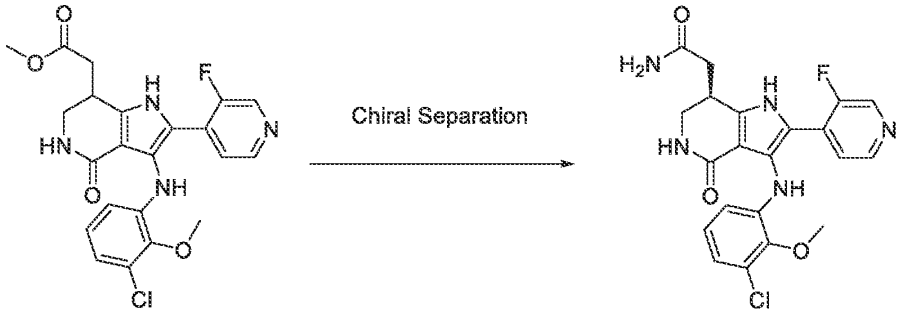
LC-MS: M+H found: 459.00.



A solution of methyl 2-{3-[(3-chloro-2-methoxyphenyl) amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-7-yl} acetate (190 mg, 0.414 mmol, 1 equiv) in NH3(g) in MeOH (0.2 mL, 7.046 mmol, 17.02 equiv) was stirred for 3h at RT. The resulting mixture was concentrated under reduced pressure. The residue was

purified by reverse flash chromatography with the following conditions: Column: YMC-Actus Triart C18, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 42% B in 10 min, 42% B; Wave Length: 254/220 nm; RT1(min): 9.56 to afford 2-[(7R)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-7-yl]acetamide (50 mg, 27.21%) as a white solid.

LC-MS: M+H found 443.95.

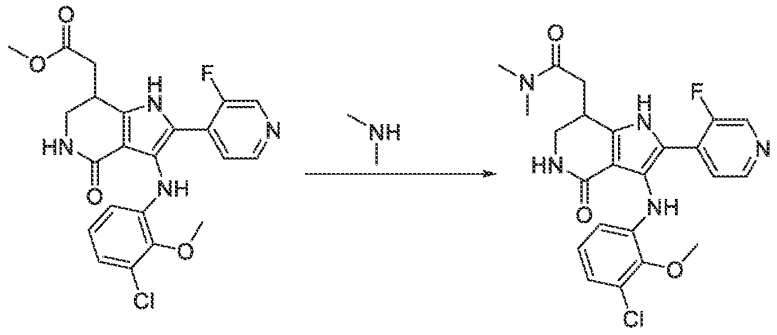


The product 6 (50 mg, 0.113 mmol, 1.00 equiv) was purified by Prep-Chiral-HPLC (Column: CHIRALPAK IG-3, 4.6*50mm, 3um; Mobile Phase A: (Hex: DCM=3: 1) (0.1%DEA): EtOH=80: 20; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (7S)-3-[(3-chloro-2-methoxyphenyl) amino]-7-(methoxymethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (19.9 mg, 39.8%) as a white solid.

LC-MS: M+H found: 443.90.

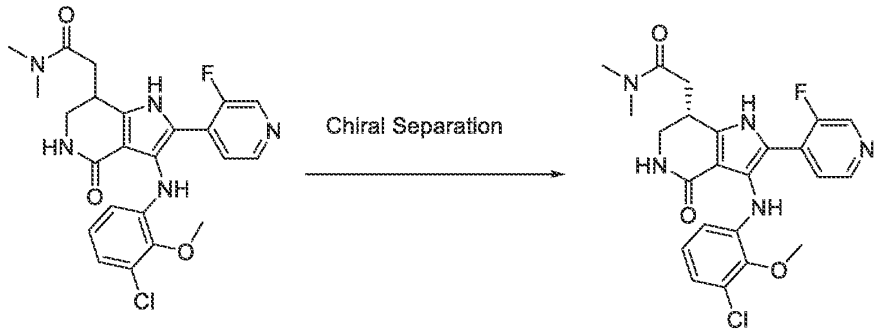
^{1}H NMR (300 MHz, DMSO-d6) δ 11.62 (s, 1H), 8.51 (d, J = 3.0 Hz, 1H), 8.29 (dd, J = 5.1, 1.2 Hz, 1H), 7.70 – 7.38 (m, 3H), 7.19 (s, 1H), 7.08 (s, 1H), 6.74 – 6.58 (m, 2H), 6.14 (dd, J = 6.8, 2.8 Hz, 1H), 3.87 (s, 3H), 3.55 – 3.36 (m, 2H), 3.24 – 3.13 (m, 1H), 2.46 – 2.38 (m, 2H).

Example 88. (7S)-3-[(3-chloro-2-methoxyphenyl) amino]-7-(methoxymethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one **(compound 488)**



A solution of methyl 2-{3-[(3-chloro-2-methoxyphenyl) amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-7-yl} acetate (170 mg, 0.370 mmol, 1 equiv) and dimethylamine (2 M in aqueous) (0.1 mL, 1.508 mmol, 4.07 equiv) in MeOH (1 mL) was stirred for 3h at 50°C. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 52% B in 8 min, 52% B; Wave Length: 254; 220 nm; RT1(min): 7.17 to afford 2-{3-[(3-chloro-2-methoxyphenyl) amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-7-yl}acetamide (50 mg, 30.41%)

LC-MS: M+H found 472.10.



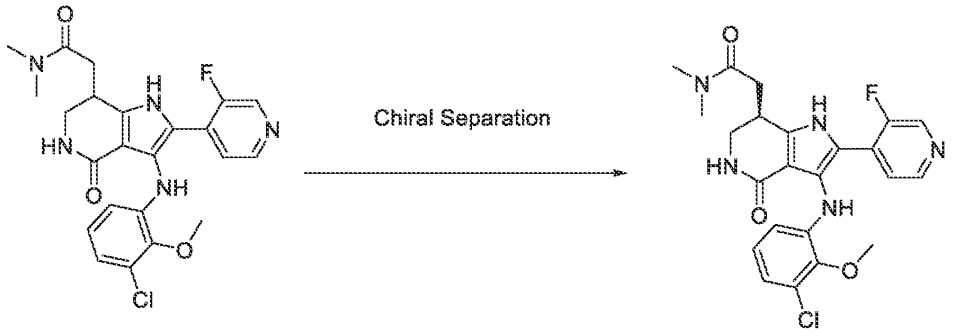
The product 6 (50 mg, 0.106 mmol, 1.00 equiv) was purified by Prep-Chiral-HPLC (Column: CHIRALPAK IC-3, 4.6*50mm 3um; Mobile Phase A: Hex(0.1%DEA): EtOH=50: 50; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (7S)-3-[(3-chloro-2-methoxyphenyl) amino]-7-(methoxymethyl)-2-(pyridin-4-

yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (9.7 mg, 19.4%) as a white solid.

LC-MS: M+H found 472.10.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.46 (s, 1H), 8.51 (d, J = 3.0 Hz, 1H), 8.29 (d, J = 5.1 Hz, 1H), 7.62 (s, 1H), 7.44 (t, J = 5.9 Hz, 1H), 7.16 (s, 1H), 6.67 (d, J = 7.9 Hz, 2H), 6.24 – 6.05 (m, 1H), 3.87 (s, 3H), 3.64 – 3.52 (m, 1H), 3.43 (s, 1H), 3.20 (d, J = 13.1 Hz, 1H), 2.98 (s, 3H), 2.88 (s, 3H), 2.71 (d, J = 6.9 Hz, 2H).

Example 89. (7S)-3-[(3-chloro-2-methoxyphenyl) amino]-7-(methoxymethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one **(compound 487)**

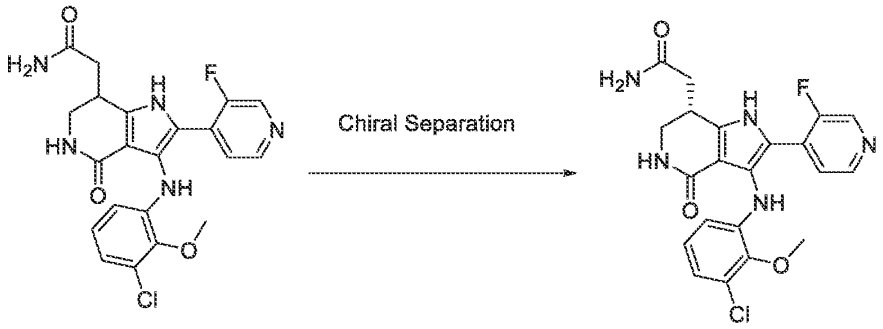


The product 6 (50 mg, 0.106 mmol, 1.00 equiv) was purified by Prep-Chiral-HPLC (Column: CHIRALPAK IC-3, 4.6*50mm 3um; Mobile Phase A: Hex(0.1%DEA): EtOH=50: 50; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (7S)-3-[(3-chloro-2-methoxyphenyl) amino]-7-(methoxymethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (9.7 mg, 19.4%) as a white solid.

LC-MS: M+H found 472.15.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.46 (s, 1H), 8.52 (d, J = 2.9 Hz, 1H), 8.29 (d, J = 5.2 Hz, 1H), 7.62 (s, 1H), 7.44 (t, J = 6.0 Hz, 1H), 7.16 (s, 1H), 6.67 (d, J = 7.9 Hz, 2H), 6.15 (d, J = 7.3 Hz, 1H), 3.87 (s, 3H), 3.57 (d, J = 12.6 Hz, 1H), 3.43 (s, 1H), 3.22 (s, 1H), 2.98 (s, 3H), 2.88 (s, 3H), 2.71 (d, J = 6.9 Hz, 2H).

Example 90. (7S)-3-[(3-chloro-2-methoxyphenyl) amino]-7-(methoxymethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one **(compound 474)**

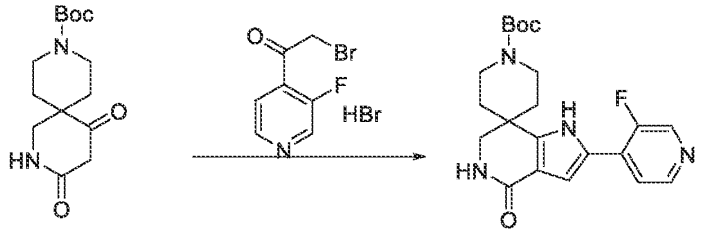


The product 6 (50 mg, 0.113 mmol, 1.00 equiv) was purified by Prep-Chiral-HPLC (Column: CHIRALPAK IG-3, 4.6*50mm, 3um; Mobile Phase A: (Hex: DCM=3: 1) (0.1%DEA): EtOH=80: 20; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (7S)-3-[(3-chloro-2-methoxyphenyl) amino]-7-(methoxymethyl)-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (19.7 mg, 39.4%) as a white solid.

LC-MS: M+H found: 443.90.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.62 (s, 1H), 8.51 (d, J = 3.0 Hz, 1H), 8.29 (dd, J = 5.2, 1.2 Hz, 1H), 7.60 (s, 1H), 7.56 – 7.49 (m, 1H), 7.44 (dd, J = 6.9, 5.1 Hz, 1H), 7.19 (s, 1H), 7.08 (s, 1H), 6.75 – 6.59 (m, 2H), 6.14 (dd, J = 6.9, 2.8 Hz, 1H), 3.87 (s, 3H), 3.54 – 3.37 (m, 2H), 3.18 (dt, J = 11.9, 4.5 Hz, 1H), 2.45 – 2.31 (m, 2H).

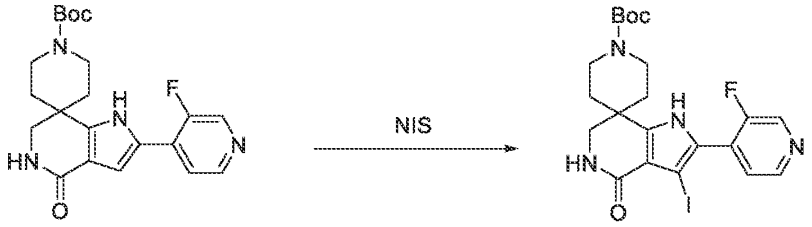
Example 91. 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,4'-pyrrolo[2,3-c]pyridin]-7'-one **(compound 831)**



A solution of tert-butyl 3,5-dioxo-2,9-diazaspiro[5.5]undecane-9-carboxylate (20 mg, 0.071 mmol, 1 equiv) and ammonium acetate (18.82 mg, 0.319 mmol, 4.5 equiv), 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (23.17 mg, 0.106 mmol, 1.5 equiv) in EtOH (3

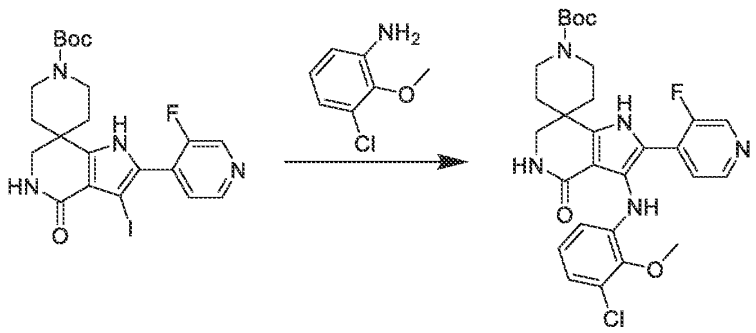
mL) was stirred at 50°C under N2 atmosphere for 6h. The resulting mixture was extracted with EA (3 x 35ml). The combined organic layers were washed with brine (3x 20ml), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH = 15:1) to afford tert-butyl 2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (15 mg, 53.86%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 401.95.



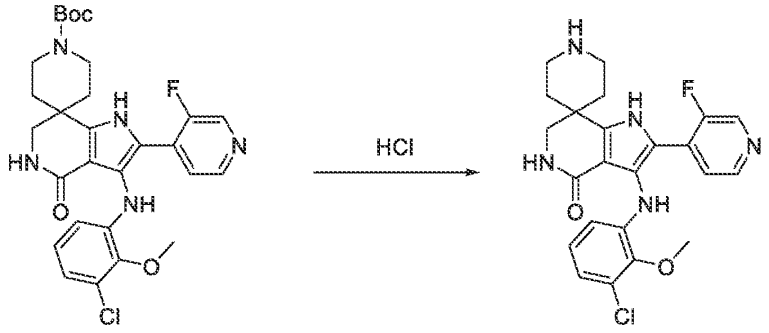
To a solution of tert-butyl 2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (500 mg, 1.249 mmol, 1.0 equiv) in DMF (2.3 mL) was added NIS (337.09 mg, 1.499 mmol, 1.2 equiv) in portions at RT, the resulting mixture was stirred for 2h at RT under nitrogen atmosphere. The resulting mixture was diluted with water (20 mL), extracted with EA (3 x 30ml). The combined organic layers were washed with brine (1x30ml), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM: MeOH= 20:1) to afford tert-butyl 2'-(3-fluoropyridin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (406 mg, 61.86%) as a yellow solid.

LC-MS: $(M-H)^-$ found: 526.95.



To a mixture of tert-butyl 2'-(3-fluoropyridin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (30 mg, 0.057 mmol, 1 equiv) and 3-chloro-2-methoxyaniline (17.97 mg, 0.114 mmol, 2 equiv) and Cs2CO3 (46.43 mg, 0.143 mmol, 2.5 equiv) in DMF (1 mL) were added EPhos Pd G4 (10.47 mg, 0.011 mmol, 0.2 equiv) and EPhos (6.10 mg, 0.011 mmol, 0.2 equiv), the resulting mixture was stirred at 50°C under N2 atmosphere for 3h. The resulting mixture was diluted with water (20 mL), extracted with EA (3 x 30mL). The combined organic layers were washed with brine (1x120ml), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM: MeOH= 20: 1) to afford tert-butyl 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (17 mg, 54.55%) as a brown solid.

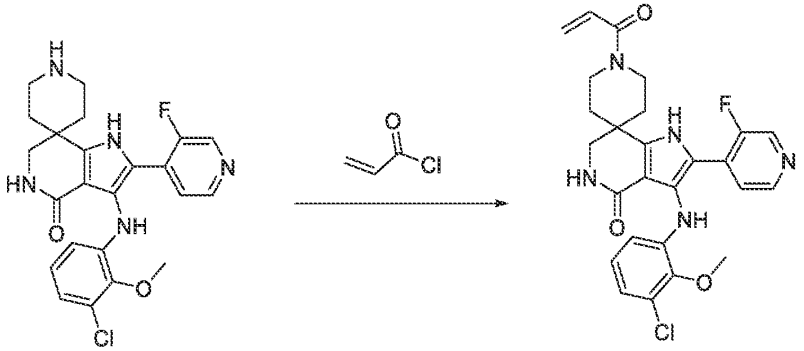
LC-MS: $(M+H)^+$ found: 556.20.



A solution of tert-butyl 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (300 mg, 0.540 mmol, 1 equiv) in hydrogen chloride in 1,4-dioxane (50.00 mL, 4M) was stirred

at 25°C for 1h. The resulting mixture was concentrated under vacuum. The residue was basified to pH=8 with $NaHCO_3$. The resulting mixture was extracted with EA (3 x 20ml). The combined organic layers were washed with brine (50ml), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one) (206 mg, 84.86%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 412.90.



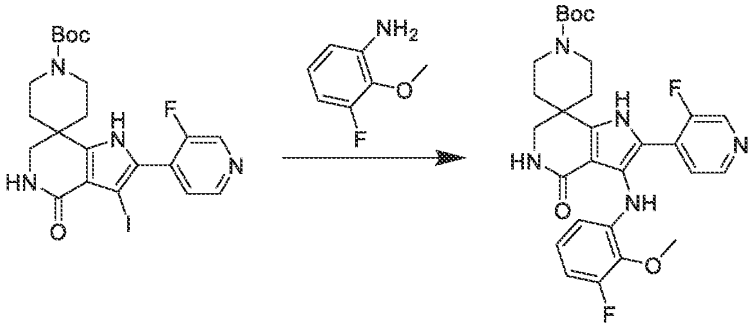
To a stirred solution of 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,4'-pyrrolo[2,3-c]pyridin]-7'-one (70 mg, 0.154 mmol, 1.00 equiv) in THF (3.5 mL)/aqueous NaHCO3 solution (3.5 mL) was added prop-2-enoyl bromide (12.43 mg, 0.092 mmol, 0.60 equiv) dropwise at 0℃, the resulting mixture was stirred for 2h. The resulting mixture was extracted with EA (3 x 20ml). The combined organic layers were washed with brine (50ml), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure, the crude product was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30*150 mm, 5 μ m; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 60% B in 10 min, 60% B; Wave Length: 254/220 nm; RT1(min): 8.47) to afford 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,4'-pyrrolo[2,3-c]pyridin]-7'-one (5.5 mg, 6.93%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 509.95.

^1H NMR (300 MHz, DMSO-d6) δ 11.44 (s, 1H), 8.42 (d, J = 49.1 Hz, 1H), 7.70 (s, 1H), 7.41 (d, J = 28.5 Hz, 1H), 6.88 (dd, J = 16.6, 10.4 Hz, 1H), 6.73 – 6.54 (m, 2H), 6.20 – 6.03

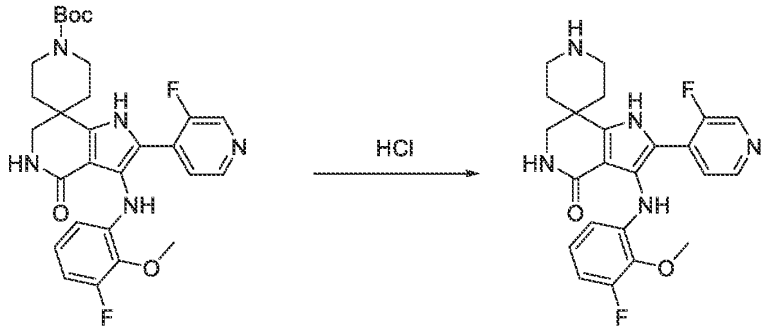
(m, 2H), 5.71 (dd, J = 10.4, 2.5 Hz, 1H), 4.43 (d, J = 12.2 Hz, 1H), 4.06 (d, J = 13.5 Hz, 1H), 3.84 (s, 3H), 3.53 (s, 2H), 2.85 (s, 1H), 1.95 (s, 2H), 1.77 (s, 2H).

Example 92. 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,4'-pyrrolo[2,3-c]pyridin]-7'-one **(compound 830)**



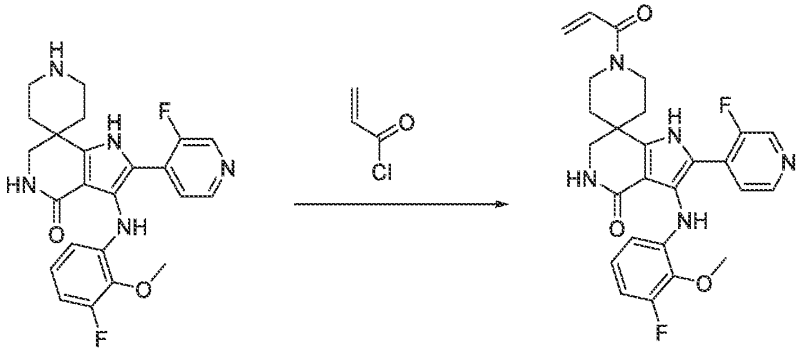
A mixture of tert-butyl 2'-(3-fluoropyridin-4-yl)-3'-iodo-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (50 mg, 0.097 mmol, 1 equiv) and 3-chloro-2-methoxyaniline (17.97 mg, 0.194 mmol, 2 equiv) and Cs_2CO_3 (88.43 mg, 0.243 mmol, 2.5 equiv), EPhos Pd G4 (10.47 mg, 0.011 mmol, 0.2 equiv) and EPhos (6.10 mg, 0.011 mmol, 0.2 equiv) in DMF (1 mL) were stirred at 50°C under N_2 atmosphere for 2h. The resulting mixture was extracted with EA (3 x 30). The combined organic layers were washed with brine (3x20ml), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM: MeOH = 20: 1) to afford tert-butyl 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (25mg, 49.55%) as a brown solid.

LC-MS: $(M+H)^+$ found: 541.32.



A solution of tert-butyl 3'-[(3-chloro-2-methoxyphenyl) amino]-2'-(3-fluoropyridin-4-yl)-4'-oxo-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridine]-1-carboxylate (300 mg, 0.540 mmol, 1 equiv) in hydrogen chloride dioxane (5.00 mL) was stirred at 25°C for 2h. The resulting mixture was concentrated under vacuum. The residue was basified to pH 8 with $NaHCO_3$. The resulting mixture was extracted with EA (3 x 20ml). The combined organic layers were washed with brine (50ml), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure, to afford 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,7'-pyrrolo[3,2-c]pyridin]-4'-one) (210.0mg, 87.55%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 440.10.



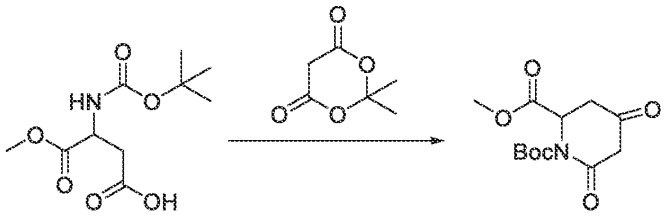
To a stirred solution of 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[piperidine-4,4'-pyrrolo[2,3-c]pyridin]-7'-one (90 mg, 0.174 mmol, 1.00 equiv)in THF (3.5 mL)/NaHCO3(aq, 3.5mL) was added prop-2-enoyl bromide (12.43 mg, 0.092 mmol, 0.60 equiv) dropwise at 0℃ under N2 atmosphere. The resulting mixture was extracted with EA (3 x 20ml). The combined organic layers were washed with brine (50ml), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure, the crude product was purified by Prep-HPLC with the following

conditions (Column: YMC-Actus Triart C18, 30*150 mm, 5 μ m; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 60% B in 10 min, 60% B; Wave Length: 254/220 nm; RT1(min): 8.47) to afford 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-1-(prop-2-enoyl)-5',6'-dihydro-1'H-spiro[piperidine-4,4'-pyrrolo[2,3-c]pyridin]-7'-one (19.1 mg, 21.23%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 509.95.

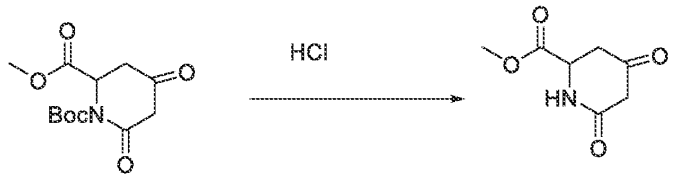
^{1}H NMR (300 MHz, DMSO-d6) δ 11.44 (s, 1H), 8.42 (d, J = 49.1 Hz, 1H), 7.70 (s, 1H), 7.41 (d, J = 28.5 Hz, 1H), 6.88 (dd, J = 16.6, 10.4 Hz, 1H), 6.73 – 6.54 (m, 2H), 6.20 – 6.03 (m, 2H), 5.71 (dd, J = 10.4, 2.5 Hz, 1H), 4.43 (d, J = 12.2 Hz, 1H), 4.06 (d, J = 13.5 Hz, 1H), 3.84 (s, 3H), 3.53 (s, 2H), 2.85 (s, 1H), 1.95 (s, 2H), 1.77 (s, 2H).

Example 93. 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-6-(hydroxymethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 751)**



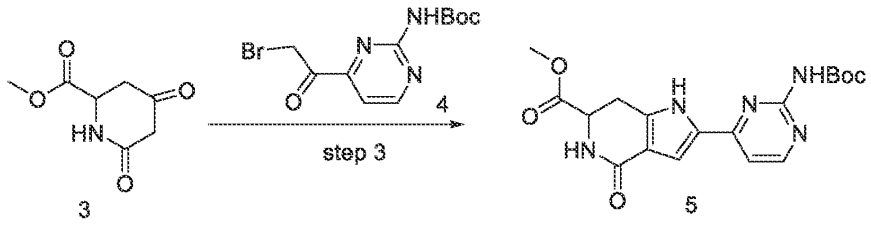
A solution of 3-[(tert-butoxycarbonyl)amino]-4-methoxy-4-oxobutanoic acid (8 g, 32.356 mmol, 1 equiv), DMAP (5929.50 mg, 48.534 mmol, 1.5 equiv), EDCI (9304.06 mg, 48.534 mmol, 1.5 equiv) and meldrum's acid (4663.39 mg, 32.356 mmol, 1.0 equiv) in DCM (80mL) was stirred for RT at 3h and washed with KHSO4 solution(1M, 200 mL X 2),The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in EA(200mL) and heated to reflux for 5 hours. After cooling down to room temperature, the mixture was washed with 1N KHSO4 solution (100 mL) and brine (10mL), dried over sodium sulfate, filtered and evaporated to give a crude product, which was slurred in a mixture of EA and PE (100mL,10%V/V) to yield 1-tert-butyl 2-methyl 4,6-dioxopiperidine-1,2-dicarboxylate (4 g, 45.57%).

LC-MS: M+H found: 216.



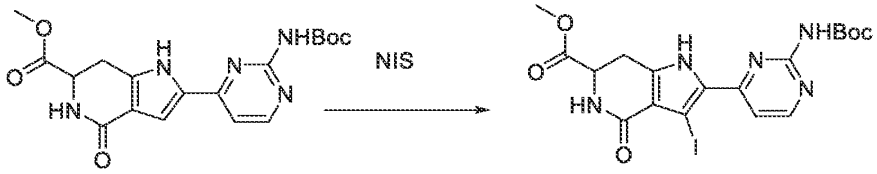
A solution of 1-tert-butyl 2-methyl 4,6-dioxopiperidine-1,2-dicarboxylate (4 g, 14.746 mmol, 1 equiv) in DCM (10mL) was treated with HCl (gas) in 1,4-dioxane (10mL) for 2h at rt. The resulting mixture was concentrated under reduced pressure. The crude product was used directly in next step.

LC-MS: M+H found: 171.



A solution of methyl 4,6-dioxopiperidine-2-carboxylate (2.5 g, 14.607 mmol, 1 equiv),tert-butyl N-[4-(2-bromoacetyl)pyrimidin-2-yl]carbamate (5541.65 mg, 17.528 mmol, 1.2 equiv) and NH4OAc (5629.72 mg, 73.035 mmol, 5.00 equiv) in EtOH (25 mL) was stirred for 16h at 50oC. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (20:1) to afford methyl 2-{2-[(tert-butoxycarbonyl)amino]pyrimidin-4-yl}-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridine-6-carboxylate (2.0 g, 35.34%) as a yellow solid.

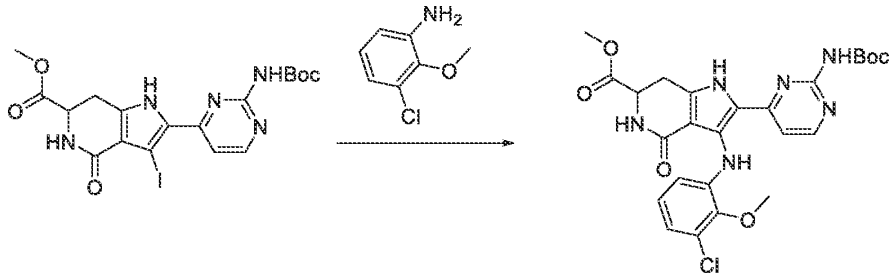
LC-MS: M+H found: 488.



To a mixture of methyl 2-{2-[(tert-butoxycarbonyl)amino]pyrimidin-4-yl}-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridine-6-carboxylate (2 g, 5.163 mmol, 1 equiv) in DMF (20 mL) was added NIS (1742.29 mg, 7.745 mmol, 1.5 equiv), the reaction mixture was

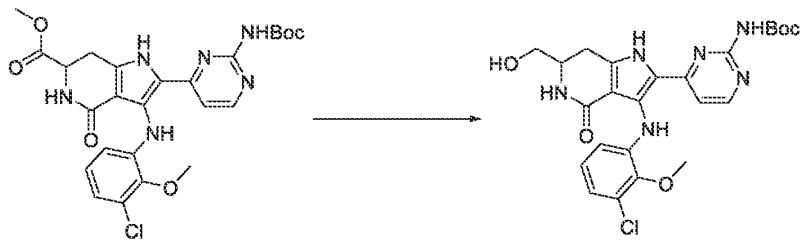
stirred at 50°C for 2h. The reaction was quenched with saturated Na2S2O3, then extracted with DCM. The organic phase was concentrated under vacuum. The residue was purified by flash chromatography (9% MeOH in DCM) to give methyl 2-{2-[(tert-butoxycarbonyl)amino]pyrimidin-4-yl}-3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridine-6-carboxylate (1.7 g, 64.15%) as a light yellow solid.

LC-MS: M+H found: 514.



Into a 20-mL sealed tube was placed methyl 2-{2-[(tert-butoxycarbonyl)amino]pyrimidin-4-yl}-3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridine-6-carboxylate (1.7 g, 3.312 mmol, 1.0 equiv) in dioxane(17mL), 3-chloro-2-methoxyaniline (0.57 g, 3.643 mmol, 1.1 equiv) ,EPhos (0.89 g, 1.656 mmol, 0.5 equiv) ,EPhos Pd G4 (1.52 g, 1.656 mmol, 0.5 equiv) and Cs2CO3 (2.16 g, 6.624 mmol, 2 equiv). The resulting solution was stirred at 50oC for 2h. The reaction mixture was added to the ice water and extracted with EA. The organic phase was concentrated under vacuum, the residue was purified by Prep-Flash-HPLC with following conditions (9% MeOH in DCM). This resulted in methyl 2-{2-[(tert-butoxycarbonyl)amino]pyrimidin-4-yl}-3-[(3-chloro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridine-6-carboxylate (1.4 g, 77.85%) as a light yellow solid.

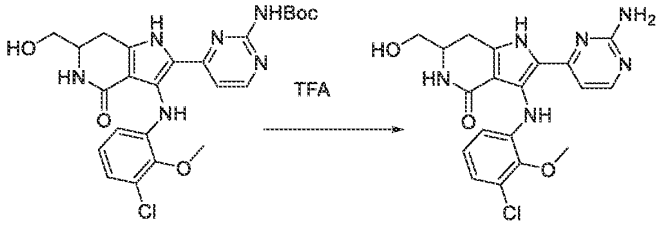
LC-MS: M+H found: 543.



A solution of methyl 2-{2-[(tert-butoxycarbonyl)amino]pyrimidin-4-yl}-3-[(3-chloro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridine-6-carboxylate (900

mg, 1.658 mmol, 1 equiv) in THF(10 mL) at -50oC under nitrogen atmosphere followed by the addition of Diisobutylaluminium hydride (1.2M, 9eq, 10.44mL) dropwise at -50oC. The resulting mixture was stirred for 1h at RT under N2 atmosphere. The reaction was quenched with saturated NH4Cl and 10%NaOH(aq). The aqueous layer was extracted with EA (3x10 mL). The residue was purified by silica gel column chromatography, eluted with DCM/MEOH (5:1) to afford tert-butyl N-(4-{3-[(3-chloro-2-methoxyphenyl)amino]-6-(hydroxymethyl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}pyrimidin-2-yl)carbamate (300 mg, 35.15%) as a light yellow solid.

LC-MS: M+H found: 515.



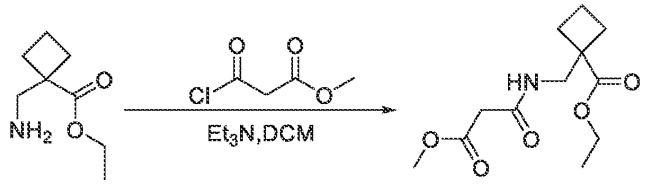
Into a 8 mL-sealed tube was placed tert-butyl N-(4-[3-[(3-chloro-2-methoxyphenyl)amino]-6-(hydroxymethyl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (25.00 mg) in CH2Cl2 (1.00 mL), then added TFA (0.30 mL). The resulting mixture was stirred for 2h at room temperature. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 19*250 mm, 10μm; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 47% B to 72% B in 7 min, 72% B; Wave Length: 254£»220 nm; RT1(min): 6.4) to afford 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-6-(hydroxymethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (8.3 mg) as a yellow solid.

LC-MS: M+H found: 415.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.65 (s, 1H), 8.06 (d, J = 5.3 Hz, 1H), 7.92 (s, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.82 (t, J = 8.0 Hz, 2H), 6.50 (d, J = 5.4 Hz, 1H), 6.36 (dd, J = 8.0, 1.7 Hz, 1H), 6.18 (s, 2H), 4.93 (t, J = 5.6 Hz, 1H), 3.90 (s, 3H), 3.69 – 3.56 (m, 1H), 3.55 – 3.36 (m, 2H), 2.95 (dd, J = 16.6, 5.7 Hz, 1H), 2.81 (dd, J = 16.6, 8.3 Hz, 1H).

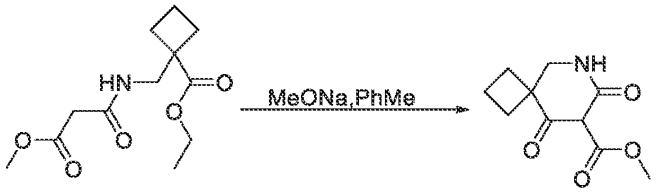
Example 94. 3'-((3-chloro-2-methoxyphenyl)amino)-2'-(6-methoxy-1,5-naphthyridin-4-

yl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[3,2-c]pyridin]-4'(1'*H*)-one **(compound 760)**



To a mixture of ethyl 1-(aminomethyl)cyclobutane-1-carboxylate (9.00 g, 57.3 mmol, 1.00 equiv) and Et3N (7.00 g, 68.7 mmol, 1.20 equiv) in DCM (90.00 mL) was added methyl 3-chloro-3-oxopropanoate (7.85 g, 57.3 mmol, 1.00 equiv) dropwise at 0 degrees C. The resulting mixture was stirred for additional 1h at room temperature. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2:1) to afford ethyl 1-((3-methoxy-3-oxopropanamido)methyl)cyclobutane-1-carboxylate (7.0 g, 50%) as yellow oil.

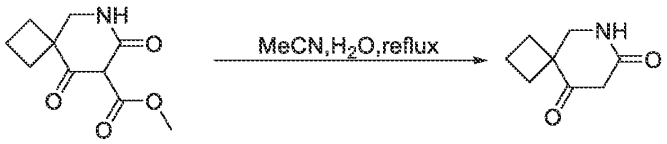
LC-MS: M+H found: 258.0.



A mixture of ethyl 1-((3-methoxy-3-oxopropanamido)methyl)cyclobutane-1-carboxylate (7.00 g, 27.1 mmol, 1.00 equiv) and MeONa (1.46 g, 27.1 mmol, 1.00 equiv) in PhMe (70.00 mL) was stirred for 3 h at 110 degrees C. The reaction was quenched with Water at room temperature. The mixture was acidified to pH 5 with concentrated HCl. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography (with the following conditions: column, C18

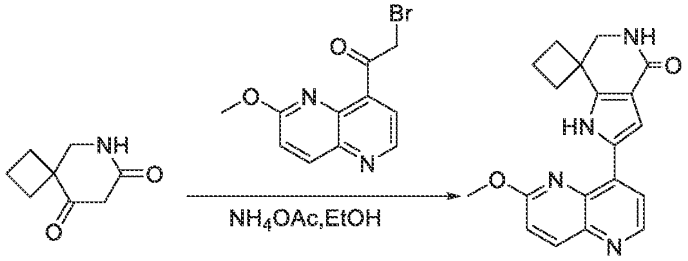
silica gel; mobile phase, MeCN in water, 0% to 10% gradient in 15 min; detector, UV 220 nm) to afford methyl 7,9-dioxo-6-azaspiro[3.5]nonane-8-carboxylate 4 g (69.4%) as an oil.

LC-MS: $(M+H)^+$ found: 212.



A mixture of methyl 7,9-dioxo-6-azaspiro[3.5]nonane-8-carboxylate (4.00 g, 18.8 mmol, 1.00 equiv) in MeCN (40.00 mL) and Water (4.00 mL) was stirred at 80 degrees C for overnight. The reaction was quenched with Water at room temperature and concentrated under reduced pressure. The residue was purified by reversed phase flash chromatography (with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 20% gradient in 15 min; detector, UV 220 nm) to afford 6-azaspiro[3.5]nonane-7,9-dione 2 g (68.9%) as a white solid.

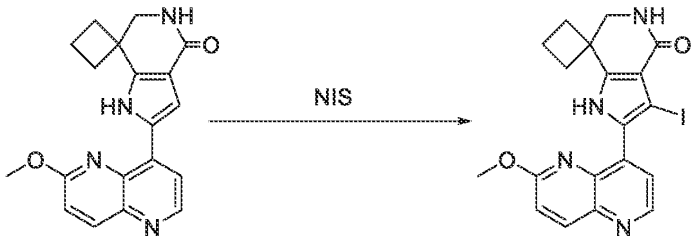
LC-MS: $(M+H)^+$ found: 154.



A mixture of 6-azaspiro[3.5]nonane-7,9-dione (300 mg, 1.94 mmol, 1.00 equiv), 2-bromo-1-(6-methoxy-1,5-naphthyridin-4-yl)ethan-1-one (656 mg, 2.33 mmol, 1.20 equiv),and NH_4OAc (900 mg, 11.64 mmol, 6.00 equiv) in EtOH (15.00 mL) was stirred at 50 degrees C for 3 h. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH (10:1)) to afford 2'-(6-methoxy-1,5-naphthyridin-4-yl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[3,2-c]pyridin]-4'(1'*H*)-one (360 mg, 55%) as a

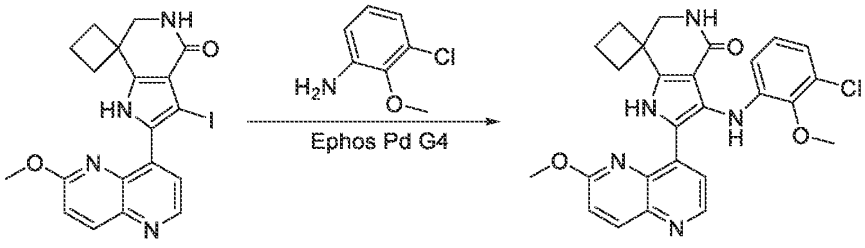
yellow solid.

LC-MS: $(M+H)^+$ found 335.



To a stirred mixture of 2'-(6-methoxy-1,5-naphthyridin-4-yl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[3,2-c]pyridin]-4'(1'*H*)-one (360 mg, 1.07 mmol, 1.00 equiv) in DMF (2.00 mL) was added NIS (186 mg, 1.07 mmol, 1.00 equiv) at 0 degrees C. The mixture was stirred at room temperature for 2 h. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH (20:1)) to afford 3'-iodo-2'-(6-methoxy-1,5-naphthyridin-4-yl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[3,2-c]pyridin]-4'(1'*H*)-one (200 mg, 40%) as yellow solid.

LC-MS: $(M+H)^+$ found 461.



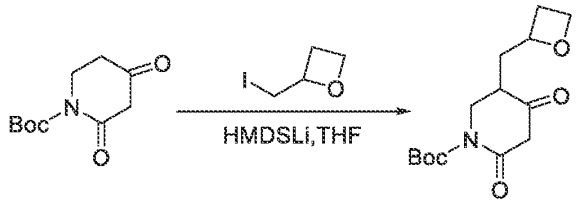
To a stirred solution of 3'-iodo-2'-(6-methoxy-1,5-naphthyridin-4-yl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[3,2-c]pyridin]-4'(1'*H*)-one (200.00 mg, 0.433 mmol, 1.00 equiv), 3-chloro-2-methoxyaniline(89.1 mg, 0.563 mmol, 1.3 equiv), and Cs_2CO_3 (282 mg, 0.867 mmol, 2.00 equiv) in 1,4-dioxane(5.00 mL) were added EPhos (48.8 mg, 0.086 mmol, 0.20 equiv) and EPhos Pd G4 (41.12 mg, 0.043 mmol, 0.10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h

at 50 °C under nitrogen atmosphere. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 58% B to 65% B in 10 min, 65% B; Wave Length: 220/254 nm; RT1(min): 9.30;) to afford 3'-((3-chloro-2-methoxyphenyl)amino)-2'-(6-methoxy-1,5-naphthyridin-4-yl)-5',6'-dihydrospiro[cyclobutane-1,7'-pyrrolo[3,2-c]pyridin]-4'(1'*H*)-one 100 mg crude as a yellow solid.

LC-MS: $(M+H)^+$ found: 490.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.14 – 12.02 (m, 1H), 8.64 – 8.59 (m, 1H), 8.40 – 8.27 (m, 1H), 7.86 – 7.77 (m, 1H), 7.58 – 7.51 (m, 1H), 7.42 – 7.26 (m, 2H), 6.72 – 6.60 (m, 2H), 6.20 – 6.09 (m, 1H), 4.28 – 4.18 (m, 3H), 3.92 – 3.82 (m, 3H), 3.56 – 3.47 (m, 2H), 2.72 – 2.63 (m, 1H), 2.39 – 2.27 (m, 1H), 2.14 – 2.02 (m, 3H), 1.99 – 1.90 (m, 1H).

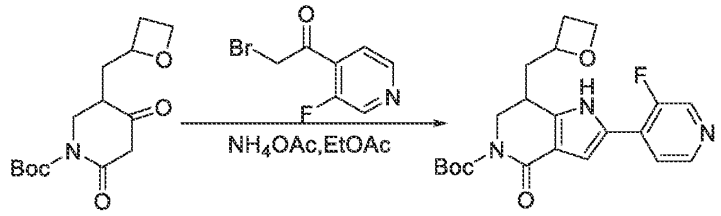
Example 95. (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[(2S)-oxetan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 786)**



To a stirred solution of tert-butyl 2,4-dioxopiperidine-1-carboxylate (3.59 g, 16.836 mmol, 1.00 equiv) in THF (50 mL) was added LiHMDS (42.09 mL, 42.090 mmol, 2.5 equiv) dropwise at -20 degrees C under nitrogen atmosphere. To the above mixture was added 2-(iodomethyl)oxetane (5.00 g, 25.254 mmol, 1.5 equiv) dropwise at -20 degrees C. The resulting mixture was stirred for additional 3 h at -20 degrees C. The mixture was acidified to pH 5 with 5% KHSO4 (aq.). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.

The residue was purified by silica gel column chromatography, eluted with PE / EtOAc (2:1) to afford tert-butyl 5-(oxetan-2-ylmethyl)-2,4-dioxopiperidine-1-carboxylate (2.5 g, 52.41%) as a light yellow solid.

LC-MS $(M+H)^+$ found: 284.



A solution of tert-butyl 5-(oxetan-2-ylmethyl)-2,4-dioxopiperidine-1-carboxylate (2 g, 7.059 mmol, 1.00 equiv) in EtOH (30 mL) was treated with 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (1.85 g, 8.471 mmol, 1.2 equiv) for 2 min at room temperature under nitrogen atmosphere followed by the addition of NH4OAc (3.26 g, 42.354 mmol, 6 equiv) in portions at 60 degrees C. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 10 min; detector, UV 220 nm. This resulted in tert-butyl 2-(3-fluoropyridin-4-yl)-7-(oxetan-2-ylmethyl)-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (1 g, 35.29%) as a yellow oil.

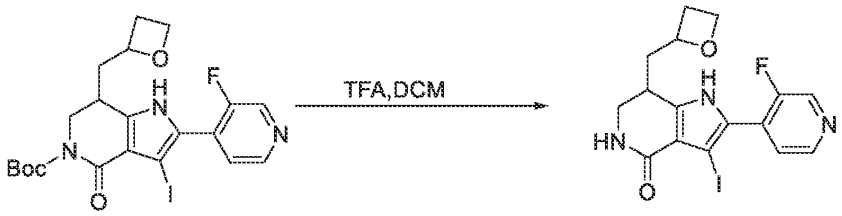
LC-MS $(M+H)^+$ found: 402.



A solution of tert-butyl 2-(3-fluoropyridin-4-yl)-7-(oxetan-2-ylmethyl)-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (1 g, 2.491 mmol, 1.00 equiv) in DMF (15 mL) was treated with NIS (0.56 g, 2.491 mmol, 1 equiv) for 30 min at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined

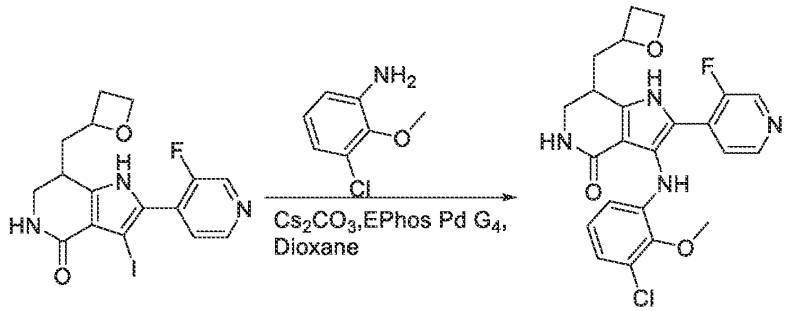
organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (12:1) to afford tert-butyl 2-(3-fluoropyridin-4-yl)-3-iodo-7-(oxetan-2-ylmethyl)-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (900 mg, 68.51%) as a yellow solid.

LC-MS $(M+H)^+$ found: 528.



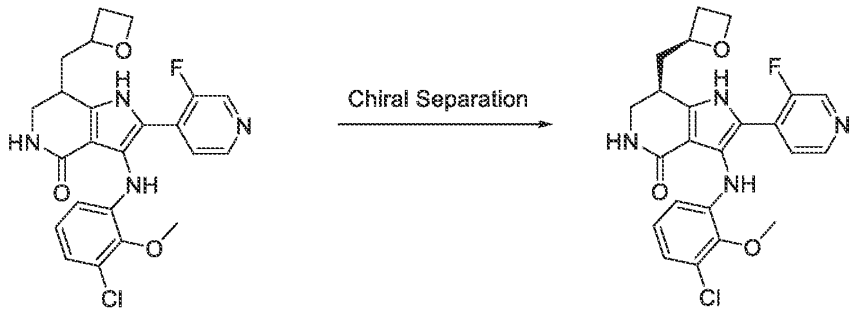
A solution of tert-butyl 2-(3-fluoropyridin-4-yl)-3-iodo-7-(oxetan-2-ylmethyl)-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (900 mg, 1.707 mmol, 1.00 equiv) in DCM (7 mL) was treated with TFA (3 mL) for 2 min at 0 degrees C under nitrogen atmosphere followed by the addition of TFA (3 mL) dropwise at 0 degrees C. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The resulting mixture was extracted with CH2Cl2 (3 x 50 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (12:1) to afford 2-(3-fluoropyridin-4-yl)-3-iodo-7-(oxetan-2-ylmethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (580 mg, 79.55%) as a yellow solid.

LC-MS $(M+H)^+$ found: 428.



To a stirred mixture of tert-butyl 2-(3-fluoropyridin-4-yl)-3-iodo-7-(oxetan-2-ylmethyl)-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (500 mg, 0.948 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (373.58 mg, 2.370 mmol, 2.50 equiv) in dioxane (10 mL) were added Ephos Pd G4 (87.09 mg, 0.095 mmol, 0.10 equiv) and Ephos (101.41 mg, 0.190 mmol, 0.2 equiv) and Cs2CO3 (617.86 mg, 1.896 mmol, 2 equiv) in portions at room temperature under nitrogen atmosphere.The resulting mixture was stirred for 1 h at 50 degrees C under nitrogen atmosphere.The resulting mixture was concentrated under vacuum.The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (10:1) to afford tert-butyl 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(oxetan-2-ylmethyl)-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (300 mg, 56.80%) as a yellow solid.

LC-MS $(M+H)^+$ found: 457.



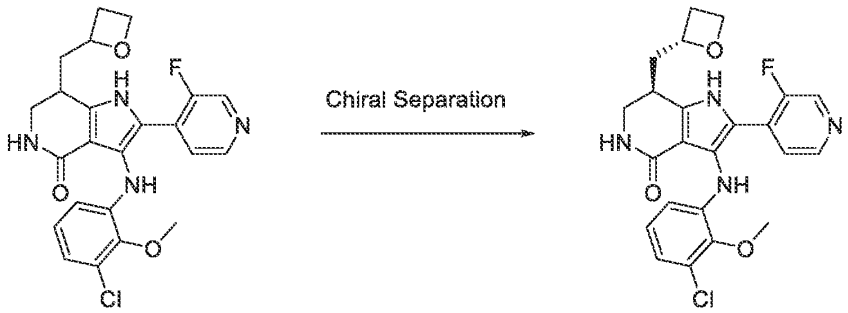
The product was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 18 min; Wave Length: 220/254 nm; RT1(min): 7.112; RT2(min): 13.349; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 4). This resulted in (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[(2S)-oxetan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (5.6 mg) as a white solid.

LC-MS: $(M+H)^+$ found: 457.00.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.56 (s, 1H), 8.52 (d, J = 3.1 Hz, 1H), 8.29 (d, J = 5.2 Hz, 1H), 7.62 (s, 1H), 7.44 (dd, J = 6.8, 5.1 Hz, 1H), 7.24 (d, J = 2.5 Hz, 1H), 6.74 – 6.63

(m, 2H), 6.14 (dd, J = 7.2, 2.4 Hz, 1H), 5.02 – 4.91 (m, 1H), 4.62 (td, J = 7.9, 5.8 Hz, 1H), 4.52 (dt, J = 9.1, 5.8 Hz, 1H), 3.87 (s, 3H), 3.48 – 3.39 (m, 1H), 3.27 – 3.07 (m, 2H), 2.81 – 2.70 (m, 1H), 2.44 – 2.33 (m, 1H), 2.23 (m, 1H), 1.91 (m, 1H).

Example 96. (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[(2R)-oxetan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 785)**

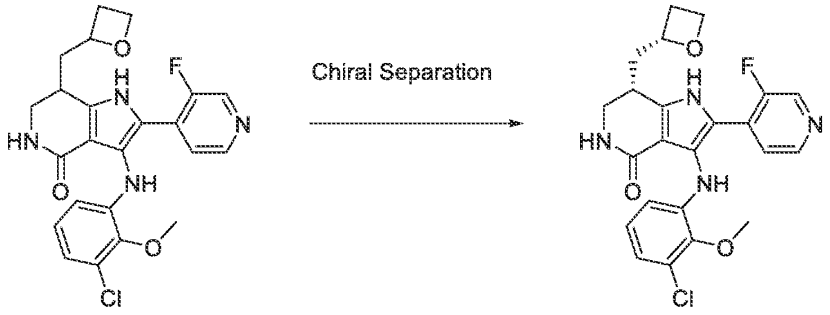


The product was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 18 min; Wave Length: 220/254 nm; RT1(min): 7.112; RT2(min): 13.349; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 4). This resulted in (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[(2R)-oxetan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (23.7 mg) as a yellow solid.

LC-MS: $(M+H)^+$ found: 457.00.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.55 (s, 1H), 8.51 (d, J = 2.9 Hz, 1H), 8.30 (dd, J = 5.1, 1.1 Hz, 1H), 7.60 (s, 1H), 7.45 (dd, J = 6.8, 5.1 Hz, 1H), 7.22 (s, 1H), 6.72 – 6.61 (m, 2H), 6.13 (dd, J = 7.3, 2.4 Hz, 1H), 4.93 (p, J = 6.8 Hz, 1H), 4.55 (td, J = 8.0, 5.7 Hz, 1H), 4.42 (dt, J = 9.0, 5.7 Hz, 1H), 3.86 (s, 3H), 3.50 (m, 1H), 3.30 – 3.20 (m, 1H), 3.05 (m, 1H), 2.68 – 2.58 (m, 1H), 2.33 – 2.24 (m, 1H), 2.16 – 1.97 (m, 2H).

Example 97. (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[(2R)-oxetan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 784)**

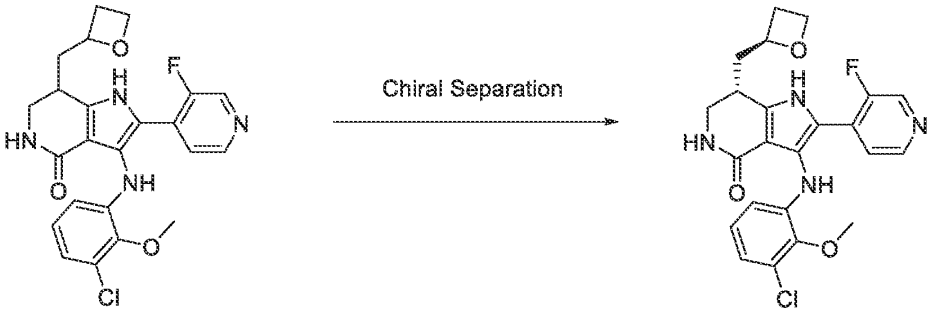


The product was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 18 min; Wave Length: 220/254 nm; RT1(min): 7.112; RT2(min): 13.349; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 4). The product was separated by Chiral-Sep. This resulted in (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[(2R)-oxetan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (20.7 mg) as a white solid.

LC-MS: $(M+H)^+$ found: 457.00.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.55 (s, 1H), 8.51 (d, J = 2.9 Hz, 1H), 8.30 (d, J = 5.1 Hz, 1H), 7.60 (s, 1H), 7.45 (dd, J = 6.8, 5.1 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 6.72 – 6.61 (m, 2H), 6.13 (dd, J = 7.3, 2.4 Hz, 1H), 4.93 (p, J = 6.7 Hz, 1H), 4.55 (td, J = 8.0, 5.8 Hz, 1H), 4.42 (dt, J = 9.1, 5.7 Hz, 1H), 3.86 (s, 3H), 3.50 (ddd, J = 12.7, 5.3, 1.9 Hz, 1H), 3.25 (ddd, J = 12.6, 5.6, 3.5 Hz, 1H), 3.05 (dd, J = 7.7, 5.2 Hz, 1H), 2.68 – 2.58 (m, 1H), 2.30 (dd, J = 13.5, 6.2 Hz, 1H), 2.07 (ddt, J = 26.5, 13.9, 6.4 Hz, 2H).

Example 98. (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[(2S)-oxetan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 783)**

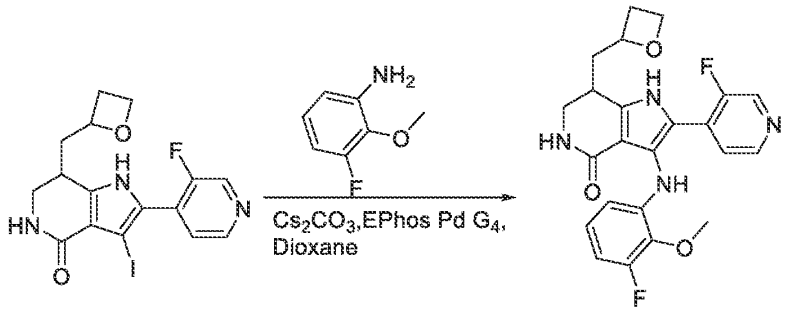


The product was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2*25 cm, 5 μm; Mobile Phase A: MtBE(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 18 min; Wave Length: 220/254 nm; RT1(min): 7.112; RT2(min): 13.349; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 4). This resulted in (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[(2S)-oxetan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (6.1 mg) as a white solid.

LC-MS: $(M+H)^+$ found: 457.00.

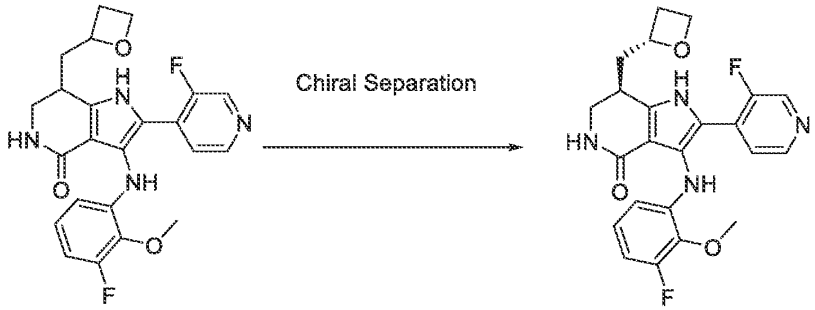
^{1}H NMR (400 MHz, DMSO-d6) δ 11.56 (s, 1H), 8.52 (d, J = 3.0 Hz, 1H), 8.29 (d, J = 5.2 Hz, 1H), 7.62 (s, 1H), 7.44 (dd, J = 6.9, 5.1 Hz, 1H), 7.24 (d, J = 2.6 Hz, 1H), 6.74 – 6.63 (m, 2H), 6.14 (dd, J = 7.2, 2.4 Hz, 1H), 4.96 (m, 1H), 4.62 (td, J = 8.0, 5.8 Hz, 1H), 4.52 (dt, J = 9.0, 5.8 Hz, 1H), 3.88 (s, 3H), 3.44 (m, 1H), 3.27 – 3.07 (m, 2H), 2.81 – 2.69 (m, 1H), 2.44 – 2.33 (m, 1H), 2.23 (m, 1H), 1.91 (m, 1H).

Example 99. (7R)-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[(2R)-oxetan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 422a)**



To a stirred mixture of tert-butyl 2-(3-fluoropyridin-4-yl)-3-iodo-7-(oxetan-2-ylmethyl)-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (500 mg, 0.948 mmol, 1.00 equiv) and 3-fluoro-2-methoxyaniline (330.38 mg, 2.340 mmol, 2 equiv) in dioxane (10 mL) were added Ephos Pd G4 (87.09 mg, 0.095 mmol, 0.10 equiv) and Ephos (101.41 mg, 0.190 mmol, 0.2 equiv) and Cs2CO3 (617.86 mg, 1.896 mmol, 2 equiv) in portions at room temperature under nitrogen atmosphere.The resulting mixture was stirred for 1 h at 50 degrees C under nitrogen atmosphere.The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (10:1) to afford 3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(oxetan-2-ylmethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (300 mg, 58.20%) as a yellow solid.

LC-MS $(M+H)^+$ found: 441.



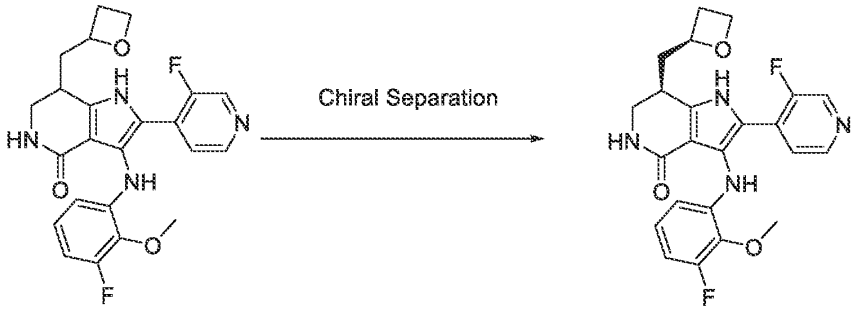
3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(oxetan-2-ylmethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (300 mg) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IA-3, 4.6*50mm, 3um; Mobile Phase A: MtBE(0.1%DEA): EtOH=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL). This resulted in (7R)-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[(2R)-oxetan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.3 mg) as a white solid.

LC-MS: $(M+H)^+$ found: 440.95.

^{1}H NMR (300 MHz, Chloroform-d) δ 11.45 (s, 1H), 8.44 (d, J = 4.4 Hz, 1H), 8.13 (d, J = 5.6 Hz, 1H), 7.74 (s, 1H), 7.44 (t, J = 6.4 Hz, 1H), 6.71 – 6.49 (m, 2H), 6.08 (d, J = 8.0 Hz, 1H), 5.30 (s, 1H), 5.20 – 5.08 (m, 1H), 5.00 – 4.78 (m, 2H), 4.13 (d, J = 1.4 Hz, 3H),

3.49 – 3.39 (m, 2H), 3.27 (q, J = 9.7 Hz, 1H), 2.97 (s, 1H), 2.53 (s, 1H), 2.37 (m, 1H), 1.83 (d, J = 14.4 Hz, 1H).

Example 100. (7R)-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[(2S)-oxetan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 422d)**

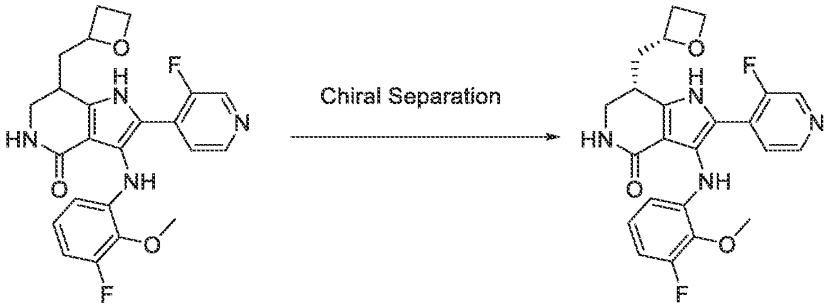


3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(oxetan-2-ylmethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (300 mg) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IA-3, 4.6*50mm, 3um; Mobile Phase A: MtBE(0.1%DEA): EtOH=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL). This resulted in (7R)-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[(2S)-oxetan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (5 mg) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 440.95.

^{1}H NMR (300 MHz, Chloroform-d) δ 10.97 (s, 1H), 8.45 (d, J = 4.3 Hz, 1H), 8.15 (d, J = 5.4 Hz, 1H), 7.69 (s, 1H), 7.49 – 7.38 (m, 1H), 6.72 – 6.49 (m, 2H), 6.10 (d, J = 8.1 Hz, 1H), 5.33 – 5.20 (m, 2H), 4.89 (q, J = 7.7 Hz, 1H), 4.61 (m, 1H), 4.14 (d, J = 1.4 Hz, 3H), 3.75 – 3.40 (m, 3H), 2.85 – 2.61 (m, 2H), 2.23 (m, 1H), 1.90 – 1.78 (m, 1H).

Example 101. (7S)-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[(2R)-oxetan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 422b)**

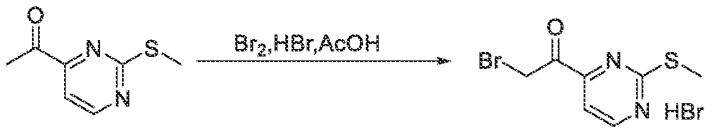


3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(oxetan-2-ylmethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (300 mg) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IA-3, 4.6*50mm, 3um; Mobile Phase A: MtBE(0.1%DEA): EtOH=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL). This resulted in (7S)-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[(2R)-oxetan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (4.4 mg) as a white solid.

LC-MS: $(M+H)^+$ found: 440.95.

^{1}H NMR (300 MHz, Chloroform-d) δ 11.44 (s, 1H), 8.44 (d, J = 4.3 Hz, 1H), 8.13 (d, J = 5.5 Hz, 1H), 7.73 (s, 1H), 7.44 (t, J = 6.4 Hz, 1H), 6.71 – 6.58 (m, 1H), 6.55 (t, J = 9.6 Hz, 1H), 6.09 (d, J = 8.1 Hz, 1H), 5.30 (s, 1H), 5.23 – 5.11 (m, 1H), 5.00 – 4.78 (m, 2H), 4.13 (d, J = 1.4 Hz, 3H), 3.44 (d, J = 10.6 Hz, 2H), 3.35 – 3.23 (m, 1H), 2.97 (s, 1H), 2.58 – 2.46 (m, 1H), 2.36 (dt, J = 14.8, 10.6 Hz, 1H), 1.83 (d, J = 14.5 Hz, 1H).

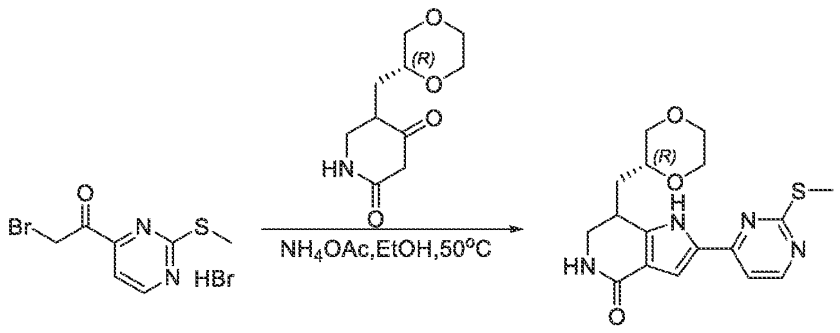
Example 102. (7S)-2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 532)**



To a stirred mixture of 1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone (20 g, 118.899 mmol, 1 equiv.) and HBr (20.00 mL, 684.858 mmol, 5.76 equiv.) in AcOH (60 mL) was added Br2 (24.70 g, 154.569 mmol, 1.3 equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 60 °C. Desired product could be detected by

LCMS. The precipitated solids were collected by filtration and washed with ethyl acetate (3x20 mL). This resulted in 2-bromo-1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone hydrobromide (28 g, 71.79%) as a yellow solid.

LC-MS: $(M+H)^+$ found 246.95.



To a stirred solution of 5-[(2R)-1,4-dioxan-2-ylmethyl]piperidine-2,4-dione (3.2 g, 15.007 mmol, 1 equiv.) in EtOH (30 mL) were added 2-bromo-1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone hydrobromide (5.91 g, 18.008 mmol, 1.2 equiv.) and NH_4OAc (11.57 g, 150.070 mmol, 10 equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 60 °C. Desired product could be detected by LCMS. The aqueous layer was extracted with CH_2Cl_2 (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (25:1) to afford 7-[(2R)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (2 g, 36.98%) as a brown solid.

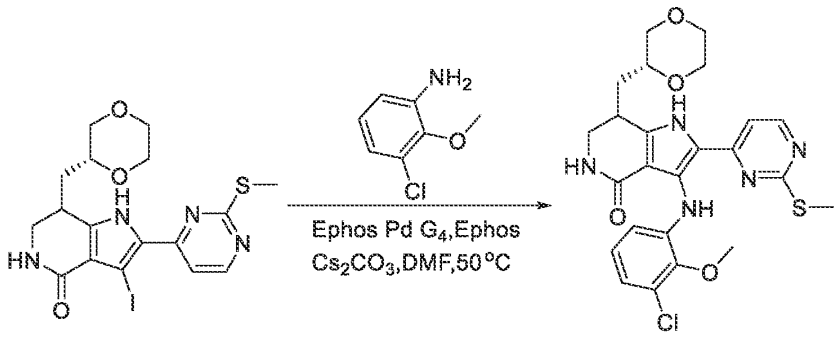
LC-MS: $(M+H)^+$ found: 361.30.



To a stirred solution of 7-[(2R)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (2 g, 5.549 mmol, 1 equiv.) in DMF (20 mL)

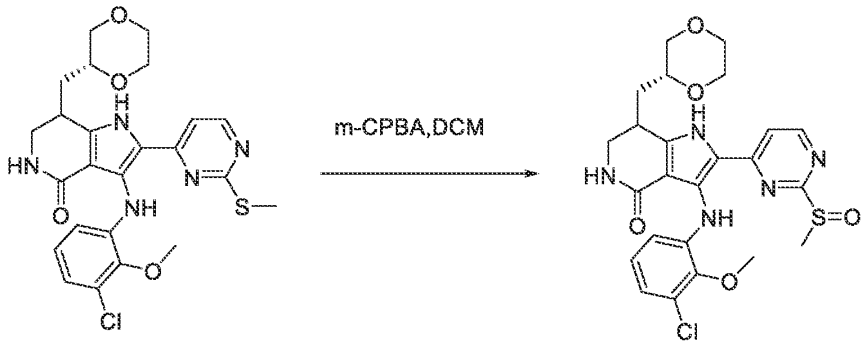
was added NIS (1.50 g, 6.659 mmol, 1.2 equiv.) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature. Desired product could be detected by LCMS. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was washed with 2x50 mL of water. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (30:1) to afford 7-[(2R)-1,4-dioxan-2-ylmethyl]-3-iodo-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.65 g, 61.14%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 487.15.



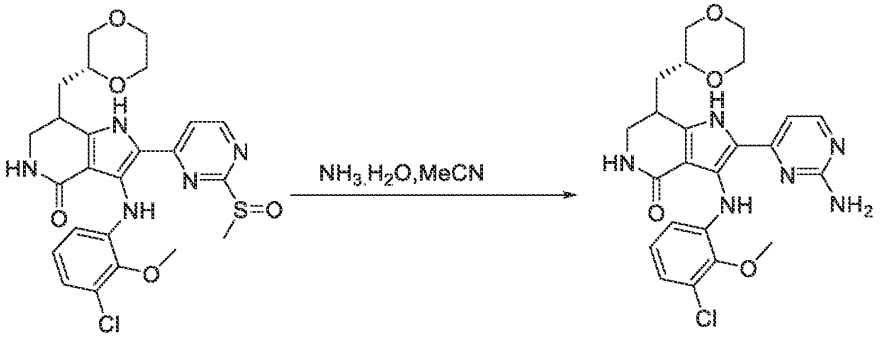
To a stirred mixture of 7-[(2R)-1,4-dioxan-2-ylmethyl]-3-iodo-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.5 g, 3.084 mmol, 1 equiv.) and 3-chloro-2-methoxyaniline (1.46 g, 9.252 mmol, 3 equiv.) in DMF (20 mL) were added Cs_2CO_3 (3.01 g, 9.252 mmol, 3 equiv.) and Ephos Pd G4 (0.28 g, 0.308 mmol, 0.1 equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 50 °C. Desired product could be detected by LCMS. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 40% to 60% gradient in 10 min; detector, UV 254 nm. This resulted in 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1 g, 62.83%) as a yellow solid.

LC-MS: $(M+H)^+$ found 516.30.



To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (350 mg, 0.678 mmol, 1 equiv.) in DCM (5 mL) was added m-CPBA (234.10 mg, 1.356 mmol, 2 equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature. Desired product could be detected by LCMS. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was washed with 3x10 mL of sat.$NaHCO_3$. The resulting mixture was concentrated under reduced pressure. This resulted in 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (370 mg, 92.28%) as a reddish solid.

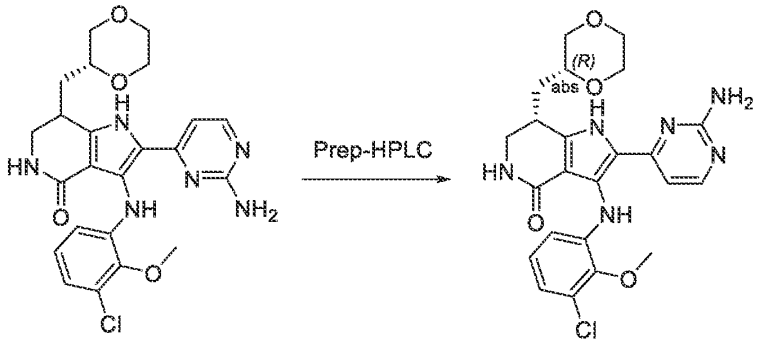
LC-MS: $(M+H)^+$ found: 532.45.



To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (370 mg, 0.626 mmol, 1 equiv, 90%) in ACN (4 mL) was added NH3.H2O (2 mL, 15.408 mmol, 24.62 equiv, 30%) at room temperature under nitrogen atmosphere. The

resulting mixture was stirred for overnight at 80 °C. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. This resulted in 150 mg crude product.

LC-MS: $(M+H)^+$ found: 485.2.

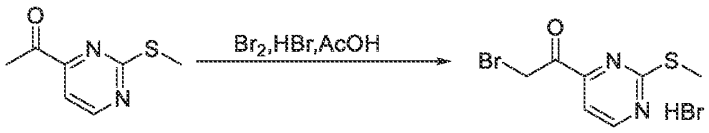


The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 35% B in 10 min, 35% B; Wave Length: 254/220 nm; RT1(min): 9.92 to afford (7S)-2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (19.6 mg, 12.81%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 485.2.

^{1}H NMR (300 MHz, Chloroform-d) δ 10.17 (s, 1H), 8.01 (d, J = 5.7 Hz, 1H), 7.65 (s, 1H), 6.87 – 6.67 (m, 2H), 6.49 – 6.32 (m, 2H), 5.35 (d, J = 12.7 Hz, 3H), 4.05 (s, 3H), 3.97 – 3.54 (m, 7H), 3.45 – 3.24 (m, 3H), 2.00 (s, 1H), 1.69 (ddd, J = 13.8, 8.9, 4.8 Hz, 1H).

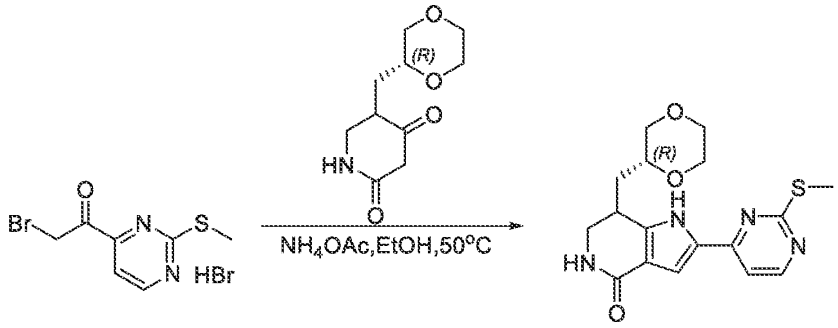
Example 103. (7S)-7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 529)**



To a stirred mixture of 1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone (20 g, 118.899 mmol,

1 equiv.) and HBr (20.00 mL, 684.858 mmol, 5.76 equiv.) in AcOH (60 mL) was added Br2 (24.70 g, 154.569 mmol, 1.3 equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 60 °C. Desired product could be detected by LCMS. The precipitated solids were collected by filtration and washed with ethyl acetate (3x20 mL). This resulted in 2-bromo-1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone hydrobromide (28 g, 71.79%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 246.95.



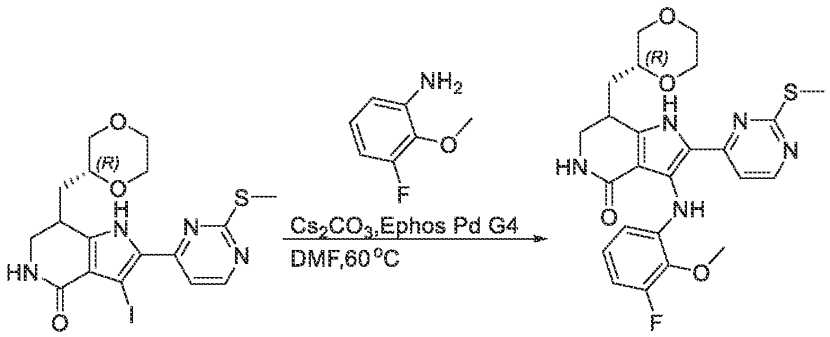
To a stirred solution of 5-[(2R)-1,4-dioxan-2-ylmethyl]piperidine-2,4-dione (3.2 g, 15.007 mmol, 1 equiv.) in EtOH (30 mL) were added 2-bromo-1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone hydrobromide (5.91 g, 18.008 mmol, 1.2 equiv.) and NH_4OAc (11.57 g, 150.070 mmol, 10 equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 60 °C. Desired product could be detected by LCMS. The aqueous layer was extracted with CH_2Cl_2 (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (25:1) to afford 7-[(2R)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (2 g, 36.98%) as a brown solid.

LC-MS: $(M+H)^+$ found: 361.30.



To a stirred solution of 7-[(2R)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (2 g, 5.549 mmol, 1 equiv.) in DMF (20 mL) was added NIS (1.50 g, 6.659 mmol, 1.2 equiv.) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature. Desired product could be detected by LCMS. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was washed with 2x50 mL of water. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (30:1) to afford 7-[(2R)-1,4-dioxan-2-ylmethyl]-3-iodo-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.65 g, 61.14%) as a light yellow solid.

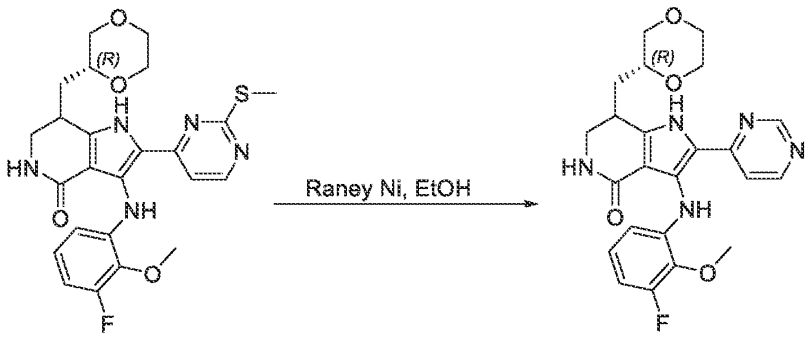
LC-MS: $(M+H)^+$ found: 487.15.



To a stirred mixture of 7-[(2R)-1,4-dioxan-2-ylmethyl]-3-iodo-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.1 g, 2.262 mmol, 1 equiv.) and 3-fluoro-2-methoxyaniline (0.96 g, 6.786 mmol, 3 equiv.) in DMF (15 mL) were added Cs2CO3 (2.21 g, 6.786 mmol, 3 equiv.) and Ephos Pd G4 (0.21 g, 0.226 mmol, 0.1 equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at 50 °C. Desired product could be detected by LCMS. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel;

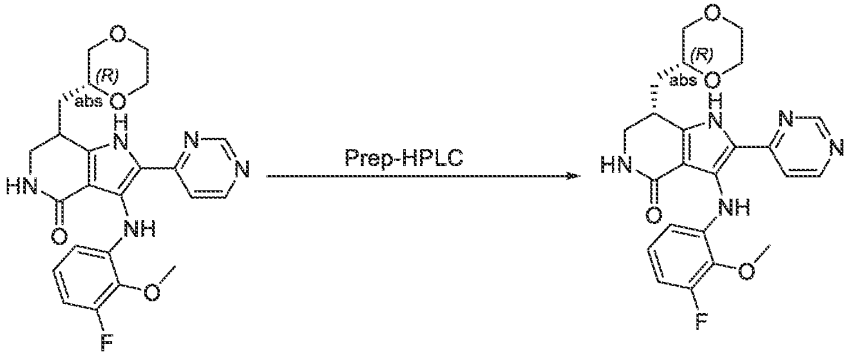
mobile phase, MeCN in water, 45% to 70% gradient in 10 min; detector, UV 254 nm. This resulted in 7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (810 mg, 71.69%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 500.10.



To a stirred solution of (7S)-7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one, 1 equiv.) in EtOH (30 mL) was added Raney-Ni (2.78 g, 32.420 mmol, 20 equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 24 h at 90°C. Desired product could be detected by LCMS. The resulting mixture was filtered, the filter cake was washed with EtOH (3x30 mL). The filtrate was concentrated under reduced pressure. This resulted in 7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (600 mg, 81.59%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 454.15.

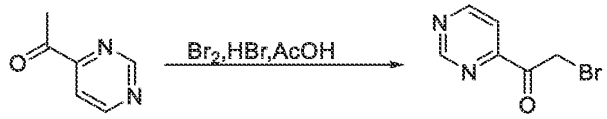


The crude product (600mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 37% B in 10 min, 37% B; Wave Length: 254/220 nm; RT1(min): 7 10) to afford (7S)-7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (92.4 mg, 15.37%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 454.10.

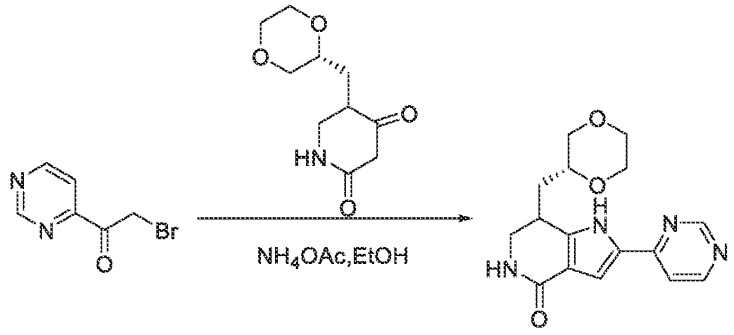
^{1}H NMR (300 MHz, Chloroform-d) δ 10.35 (s, 1H), 8.75 (d, J = 177.8 Hz, 2H), 7.53 (s, 1H), 7.02 (s, 1H), 6.71 (d, J = 7.1 Hz, 1H), 6.61 – 6.45 (m, 1H), 6.19 (d, J = 7.7 Hz, 1H), 5.52 (s, 1H), 4.10 (d, J = 1.3 Hz, 3H), 4.03 (d, J = 11.2 Hz, 1H), 3.74 (ddt, J = 44.3, 34.9, 10.1 Hz, 6H), 3.49 – 3.14 (m, 3H), 1.98 (t, J = 12.0 Hz, 1H), 1.74 – 1.64 (m, 1H).

Example 104. (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 528)**



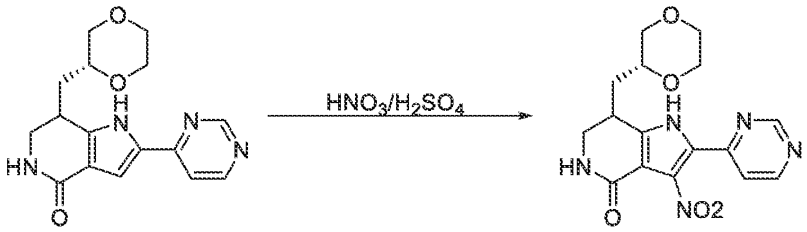
To a stirred solution of 1-(pyrimidin-4-yl)ethanone (1 g, 8.188 mmol, 1.00 equiv) and HBr (1.45 mL, 49.640 mmol, 6.06 equiv) in AcOH (3 mL) was added Br2 (1 g, 6.258 mmol, 0.76 equiv) dropwise at room temperature .Then the mixture was stirred at 60 degree for 3h. After the reaction was completed ,the mixture was diluted with ethyl acetate. The solution was stirred for overnight. The solid was filtrated and dried to get 2-bromo-1-(pyrimidin-4-yl)ethanone (1.3 g, 78.98%) brown solid as product.

LC-MS: $(M+H)^+$ found: 200.95.



A solution of 2-bromo-1-(pyrimidin-4-yl)ethanone hydrobromide (3 g, 10.641 mmol, 1 equiv) in EtOH (50 mL) was treated with 5-[(2R)-1,4-dioxan-2-ylmethyl]piperidine-2,4-dione (2.27 g, 10.641 mmol, 1 equiv) for 2 min at room temperature under nitrogen atmosphere followed by the addition of NH4OAc (8.20 g, 106.410 mmol, 10 equiv) in portions at room temperature. The resulting mixture was stirred for 2 h at 60°C under nitrogen atmosphere. The resulting mixture was extracted with EtOAc (8 x 100 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (10:1) to afford 7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.5 g, 44.84%) as a yellow solid.

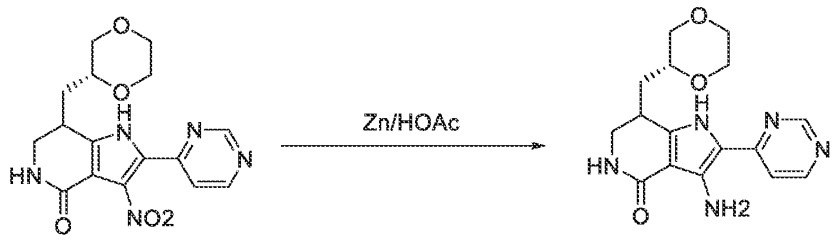
LC-MS: $(M+H)^+$ found: 315.10.



A solution of 7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (700 mg, 2.227 mmol, 1 equiv) in H2SO4 (10 mL) was treated with Nitric acid fuming (140.32 mg, 2.227 mmol, 1 equiv) for 2 min at -5°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere. The resulting mixture was diluted with water (40 mL). The mixture was basified to pH 9 with NaOH(aq.). The resulting mixture was extracted with CH2Cl2 (5 x 50 mL). The

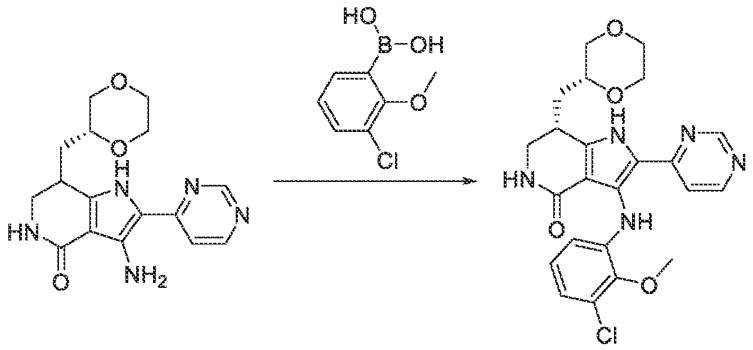
combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 7-[(2R)-1,4-dioxan-2-ylmethyl]-3-nitro-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (800 mg, 99.97%) as a Brown yellow solid.

LC-MS: $(M+H)^+$ found: 360.25.



A solution of 7-[(2R)-1,4-dioxan-2-ylmethyl]-3-nitro-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (800 mg, 2.226 mmol, 1 equiv) in HOAc (10 mL) was treated with Zn (728.10 mg, 11.130 mmol, 5 equiv) for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water (30 mL). The mixture was basified to pH 8 with NaOH(aq.). The resulting mixture was extracted with CH2Cl2 (5 x 300 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 3-amino-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (500 mg, 68.19%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 330.30.



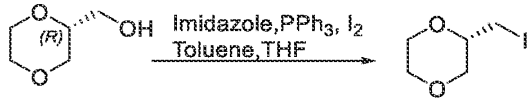
A solution of 3-amino-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-

pyrrolo[3,2-c]pyridin-4-one (500 mg, 1.518 mmol, 1 equiv) and 3-chloro-2-methoxyphenylboronic acid (565.95 mg, 3.036 mmol, 2 equiv) in DCM (10 mL) was treated with Pyridine (240.16 mg, 3.036 mmol, 2 equiv) and TEA (307.23 mg, 3.036 mmol, 2 equiv) for 2 min at 0 °C under nitrogen atmosphere followed by the addition of Cu(OAc)2 (275.74 mg, 1.518 mmol, 1 equiv) in portions at room temperature. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The resulting mixture was extracted with CH2Cl2 (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions:Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 50% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5. This resulted in (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (7.6 mg) as a yellow solid.

LC-MS: $(M+H)^+$ found: 470.35.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.00 (s, 1H), 9.05 (d, J = 1.4 Hz, 1H), 8.56 (d, J = 5.6 Hz, 1H), 7.96 (s, 1H), 7.20 (m, 2H), 6.86 – 6.76 (m, 2H), 6.31 (dd, J = 6.8, 2.8 Hz, 1H), 3.93 (s, 3H), 3.83 – 3.39 (m, 8H), 3.19 (dd, J = 11.3, 9.7 Hz, 1H), 3.09 (dd, J = 8.8, 4.6 Hz, 1H), 1.78 (dt, J = 14.1, 4.7 Hz, 1H), 1.67 – 1.55 (m, 1H).

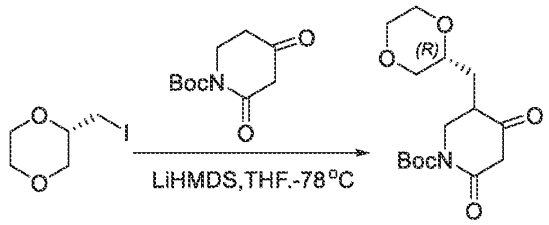
Example 105. (7S)-7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 526)**



To a suspension of (R)-(1,4-dioxan-2-yl)methanol (100.00 g, 0.847 mol, 1.00 equiv) in Tolune (1000 mL) and THF (500 mL) was added imidazole(115.2 g, 1.69 mol, 2.00 equiv), PPh3(214.4 g, 0.847 mol, 1.00 equiv) at room temperature ,I2(214.4 g, 0.847 mol, 1.00 equiv) was added at 0 degrees. The mixture was stirred for 3 h at room temperature under

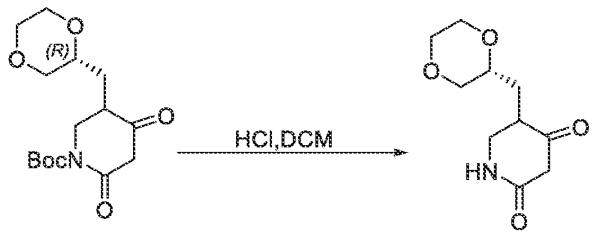
nitrogen atmosphere. The reaction was monitored by GCMS, Desired product could be detected by GCMS. The resulting solution was quenching with 500 ml of Na2S2O3 saturated solution. The aqueous layer was extracted with EtOAc (3 x 250 mL), dried (Na2SO4) and concentrated. The resulting residue was purified on silica (EtOAc/PE=1:6) to provide 130 g (67%) of the title compound as a white oil.

LC-MS: $(M+H)^+$ found: 229.



To a suspension of (S)-2-(iodomethyl)-1,4-dioxane (104.00 g, 0.457 mol, 1.40 equiv) and tert-butyl 2,4-dioxopiperidine-1-carboxylate (70.00 g, 0.327 mol, 1.00 equiv) in THF (1000 mL) was added LiHMDS (1.37 L, 1.37 mol, 3.00 equiv) at -60 degrees dropwise. The mixture was stirred for 1 h at 0 degrees under nitrogen atmosphere. The reaction was monitored by LCMS, Desired product could be detected by LCMS. The resulting solution was quenching with 500 ml of HCl (5%) at 0 degrees. The aqueous layer was extracted with EtOAc (3 x 250 mL), dried (Na2SO4) and concentrated. The resulting residue was purified on silica (0-80% PE /EtOAc) to provide 45 g (46%) of the title compound as a little brown oil.

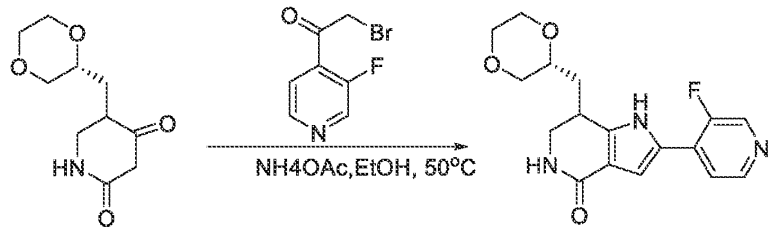
LC-MS: $(M+H)^+$ found: 314.



To a stirred mixture of tert-butyl 5-(((R)-1,4-dioxan-2-yl)methyl)-2,4-dioxopiperidine-1-carboxylate (45.00 g) in DCM (300 mL) was added HCl (150 mL) dropwise at 0 degrees C under nitrogen atmosphere. The mixture was stirred at 0 degrees C for 1 h. The resulting

mixture was concentrated under reduced pressure to afford 30g crude product, which was used to the next step without further purification.

LC-MS: $(M+H)^+$ found: 214.



To a stirred mixture of 5-[(2R)-1,4-dioxan-2-ylmethyl]piperidine-2,4-dione (1.5 g, 7.035 mmol, 1.00 equiv) and 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (1.69 g, 7.739 mmol, 1.1 equiv) in EtOH (40 mL) were added NH4OAc (5.42 g, 70.350 mmol, 10.00 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 50 degrees C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The aqueous layer was extracted with EtOAc (5x30 mL).The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (20:1) to afford 7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.02 g, 43.76%) as a white solid.

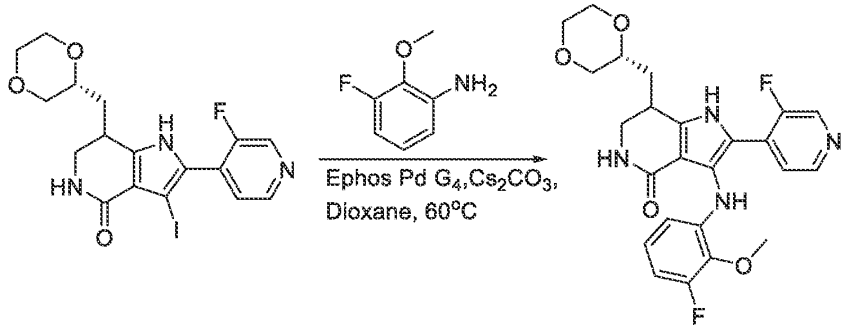
LCMS: $[M+H]^+$ found: 332.



To a stirred mixture of 7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (970 mg, 2.927 mmol, 1.00 equiv) and in DMF (20 mL) were added NIS (790.36 mg, 3.512 mmol, 1.2 equiv) in portions at room temperature under nitrogen atmosphere.The resulting mixture was stirred for 4 h at room temperature under nitrogen atmosphere. The aqueous layer was extracted with EtOAc (5x30 mL).This resulted in 7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-

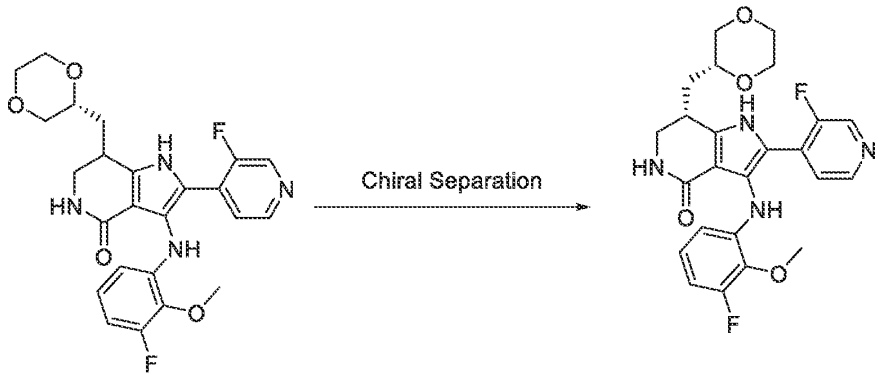
pyrrolo[3,2-c]pyridin-4-one (1 g, 74.71%) as a yellow oil.The crude product was used in the next step directly without further purification.

LCMS: $[M+H]^+$ found: 458.



To a stirred mixture of 7-(1,4-dioxan-2-ylmethyl)-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.17 g, 2.559 mmol, 1.00 equiv) and 3-fluoro-2-methoxyaniline (1.08 g, 7.677 mmol, 3 equiv) in DMF (15 mL) were added Cs2CO3 (1.67 g, 5.118 mmol, 2 equiv) and Ephos Pd G4 (0.47 g, 0.512 mmol, 0.2 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 60 degrees C under nitrogen atmosphere. The aqueous layer was extracted with EtOAc (5x50 mL).The residue was purified by silica gel column chromatography, eluted with PE / EA (0:1) to afford 7-(1,4-dioxan-2-ylmethyl)-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.07 g, 88.88%) as a yellow solid.This resulted in 7-(1,4-dioxan-2-ylmethyl)-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.07 g, 88.88%) as a yellow solid.

LCMS: $[M+H]^+$ found: 471.

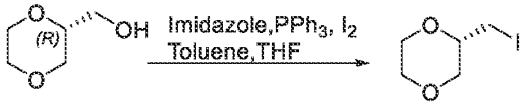


The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford (7S)-7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (137.6 mg, NaN) as a white solid.

LCMS: $[M+H]^+$ found: 471.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 10.41 (s, 1H), 8.46 (d, *J* = 4.9 Hz, 1H), 8.12 (d, *J* = 5.8 Hz, 1H), 7.87 (s, 1H), 7.47 – 7.35 (m, 1H), 6.76 – 6.49 (m, 2H), 6.06 (d, *J* = 7.8 Hz, 1H), 5.29 (s, 1H), 4.12 – 3.97 (m, 3H), 3.95 – 3.44 (m, 8H), 3.35 (d, *J* = 8.4 Hz, 2H), 2.13 – 2.01 (m, 1H), 1.74 – 1.66 (m, 1H).

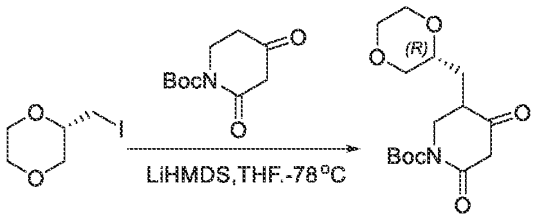
Example 106. (7*S*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2*R*)-1,4-dioxan-2-ylmethyl]-2-(2-methylpyrimidin-4-yl)-1*H*,5*H*,6*H*,7*H*-pyrrolo[3,2-c]pyridin-4-one **(compound 552)**



To a suspension of (R)-(1,4-dioxan-2-yl)methanol (100.00 g, 0.847 mol, 1.00 equiv) in Tolune (1000 mL) and THF (500 mL) was added imidazole(115.2 g, 1.69 mol, 2.00 equiv), PPh_3(214.4 g, 0.847 mol, 1.00 equiv) at room temperature ,I_2(214.4 g, 0.847 mol, 1.00 equiv) was added at 0 degrees C. The mixture was stirred for 3 h at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting solution was quenching with

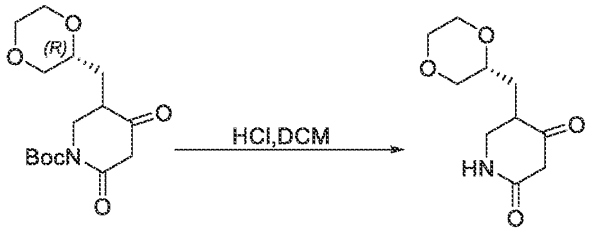
500 ml of $Na_2S_2O_3$ saturated solution. The aqueous layer was extracted with EtOAc (3 x 250 mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified on silica (EtOAc/PE=1:6) to provide 130 g (67%) of the title compound as a colorless oil.

LC-MS: $(M+H)^+$ 229.



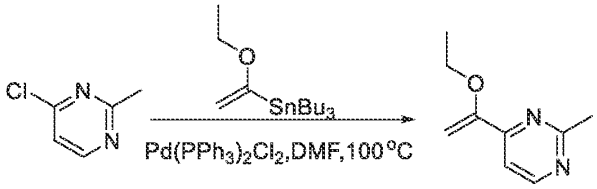
To a suspension of (S)-2-(iodomethyl)-1,4-dioxane (104.00 g, 0.457 mol, 1.40 equiv) and tert-butyl 2,4-dioxopiperidine-1-carboxylate (70.00 g, 0.327 mol, 1.00 equiv) in THF (1000 mL) was dropwise added LiHMDS (1.37 L, 1.37 mol, 3.00 equiv) at -60°C. The mixture was stirred for 1 h at 0 degrees under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting solution was quenching with 500 ml of HCl (5%) at 0 degrees. The aqueous layer was extracted with EtOAc (3 x 250 mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column (PE /EtOAc, 1:1) to provide 45 g (46%) of the title compound as a light brown oil.

LC-MS: $(M+H)^+$ found: 314.



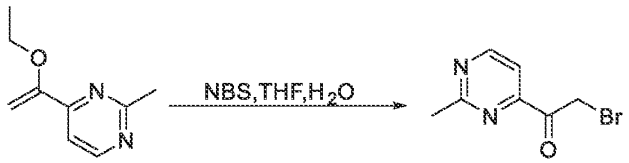
To a stirred mixture of tert-butyl 5-(((R)-1,4-dioxan-2-yl)methyl)-2,4-dioxopiperidine-1-carboxylate (45.00 g) in DCM (300 mL) was added HCl (150 mL) dropwise at 0 degrees C under nitrogen atmosphere. The mixture was stirred at 0 degrees C for 1 h. The resulting mixture was concentrated under reduced pressure to afford 30g crude product, which was used to the next step without further purification.

LC-MS: $(M+H)^+$ found: 214.



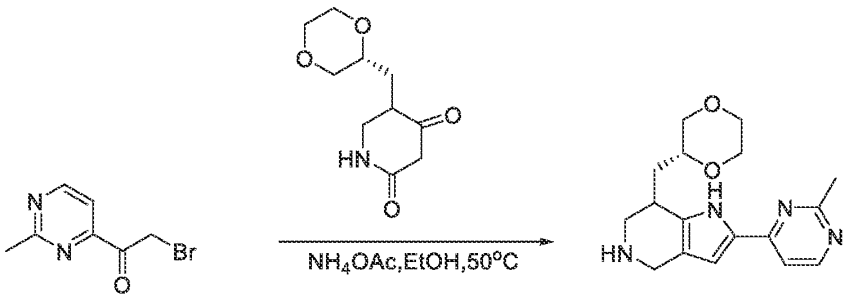
A mixture of 4-chloro-2-methylpyrimidine (20.00 g, 156.2 mmol, 1.00 equiv), tributyl(1-ethoxyvinyl)stannane (45.82 g, 468 mmol, 3.00 equiv) and $Pd(PPh_3)_2Cl_2$ (8.86 g, 15.6 mmol, 0.10 equiv) in DMF (200.00 mL) was stirred for 12 h at 100 degrees C. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford 4-(1-ethoxyvinyl)-2-methylpyrimidine 17 g (66%) as a yellow oil.

LC-MS: M+H found: 165.0.



A mixture of 4-(1-ethoxyvinyl)-2-methylpyrimidine (17.00 g, 103.0 mmol, 1.00 equiv), NBS (30.13 g, 133.9 mmol, 1.30 equiv) and H_2O (15 mL) in THF (150 mL) was stirred for 1 h at room temperature. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 2-bromo-1-(2-methylpyrimidin-4-yl) ethan-1-one 18 g crude as a brown oil.

LC-MS: $(M+H)^+$ found 215.



A mixture of 5-(((*R*)-1,4-dioxan-2-yl)methyl)piperidine-2,4-dione (14g, 83 mmol, 1.0 equiv), 2-bromo-1-(2-methylpyrimidin-4-yl)ethan-1-one (18g,107mmol, 1.3 equiv),and NH_4OAc (50.3g, 830 mmol, 10 equiv) in EtOH (150.0 mL) was stirred at 50 degrees C for 3 h. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH (10:1)) to afford 7-(((*R*)-1,4-dioxan-2-yl)methyl)-2-(2-methylpyrimidin-4-yl)-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-c]pyridine (9g, 57%) as a yellow solid.

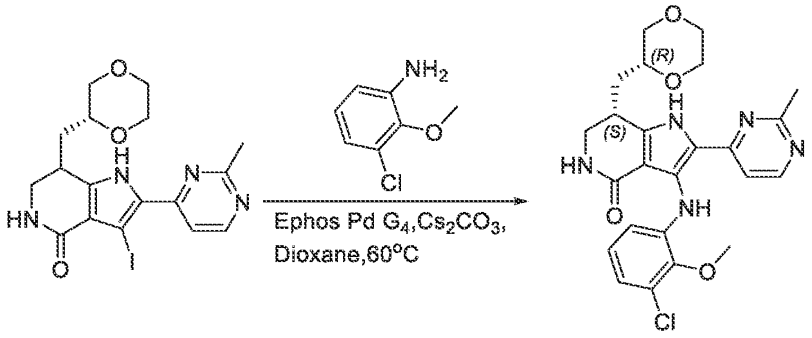
LC-MS: $(M+H)^+$ found: 329.



To a stirred mixture of 7-(((*R*)-1,4-dioxan-2-yl)methyl)-2-(2-methylpyrimidin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-c]pyridin-4-one (17g, 51.6 mmol, 1.00 equiv) in DMF (150 mL) was added NIS (15.1 g, 67.8 mmol, 1.3 equiv) at 0 degrees C. The mixture was stirred at room temperature for 2 h.
The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH (20:1))

to afford 7-(((*R*)-1,4-dioxan-2-yl)methyl)-3-iodo-2-(2-methylpyrimidin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-c]pyridin-4-one (16 g, 53%) as yellow solid.

LC-MS: $(M+H)^+$ found: 455.

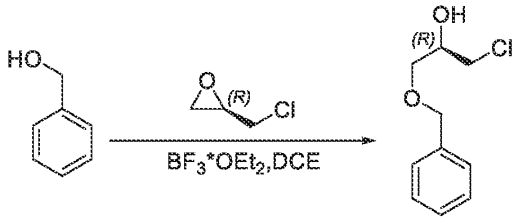


A mixture of 7-[(2*R*)-1,4-dioxan-2-ylmethyl]-3-iodo-2-(2-methylpyrimidin-4-yl)-1*H*,5*H*,6*H*,7*H*-pyrrolo[3,2-c]pyridin-4-one (35 g, 77.047 mmol, 1 equiv),Cs_2CO_3 (50.21 g, 154 mmol, 2 equiv) ,3-chloro-2-methoxyaniline (14.57 g, 92.456 mmol, 1.2 equiv) and EPhos Pd G4 (10.62 g, 11.557 mmol, 0.15 equiv) in DMF was stirred for 3 h at 60 °C under nitrogen atmosphere. The reaction was quenched with Water at room temperature.The resulting mixture was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with water (2x200 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (5 g) was purified by Prep-SFC with the following conditions (Column: CHIRALPAK IB N-3, 4.6*100mm, 3μm; Mobile Phase B: MeOH (0.1%DEA; Flow rate: 2 mL/min; Gradient: isocratic 10% B; Wave Length: 220 nm) to afford (7*S*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2*R*)-1,4-dioxan-2-ylmethyl]-2-(2-methylpyrimidin-4-yl)-1*H*,5*H*,6*H*,7*H*-pyrrolo[3,2-c]pyridin-4-one (3.3716 g, 9.04%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 484.

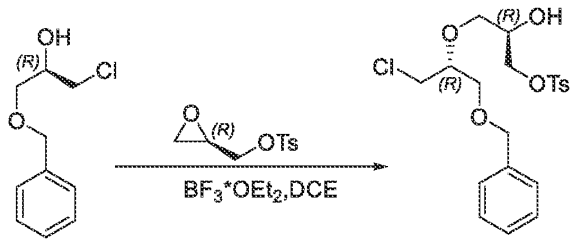
^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.30 – 11.26 (m, 1H), 8.40 – 8.29 (m, 1H), 760 – 7.55 (m, 1H), 6.85 – 6.68 (m, 3H), 6.50 – 6.29 (m, 1H), 5.70 – 5.52 (m, 1H), 4.25 – 4.14 (m, 1H), 4.13 – 4.05 (m, 3H), 4.05 – 3.73 (m, 5H), 3.41 – 3.35 (m, 4H), 2.81 – 2.66 (m, 3H), 1.91 – 1.77 (m, 1H), 1.66 – 1.52 (m, 1H).

Example 107. (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2S,5R)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (2.7 mg, 6.75%). This resulted in (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2S,5R)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 565)**



To a stirred solution/mixture of benzyl alcohol (1 g, 9.247 mmol, 1 equiv) and (-)-epichlorohydrin (0.94 g, 10.172 mmol, 1.1 equiv) in DCE (20 mL, 252.653 mmol, 27.32 equiv) was added BF3*Et2O (0.13 g, 0.925 mmol, 0.1 equiv) dropwise at 0°C under nitrogen atmosphere. Themixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of Water (20 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase flash with the following conditions (ACN/H2O=3/7) to afford (2R)-1-(benzyloxy)-3-chloropropan-2-ol (800 mg, 43.11%) as a white solid.

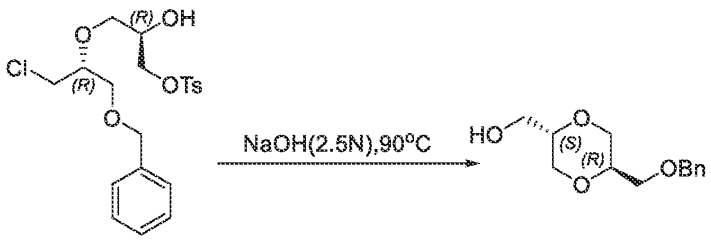
LC-MS: $(M+H)^+$ found: 201.



To a stirred solution of (2R)-1-(benzyloxy)-3-chloropropan-2-ol (72 g, 358.816 mmol, 1 equiv) and (2R)-oxiran-2-ylmethyl 4-methylbenzenesulfonate (24.57 g, 107.645 mmol, 0.3

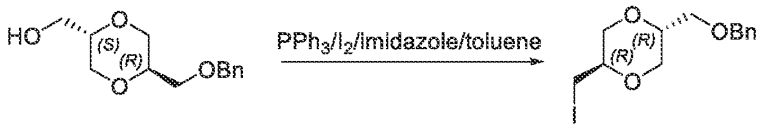
equiv) in DCE (1.5 L) was added BF3*Et2O (4.55 mL, 35.882 mmol, 0.1 equiv) dropwise at 0 °C under nitrogen atmosphere.The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS. The residue was washed with saturated sodium bicarbonate solution(2x1 L). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 40% to 50% gradient in 10 min; detector, UV 254 nm.This resulted in (2R)-1-{[(2R)-1-(benzyloxy)-3-chloropropan-2-yl]oxy}-3-[(4-methylbenzenesulfonyl)oxy]propan-2-ol (34 g, 22.09%) as a colorless oil.

LC-MS: $(M+H)^+$ found: 429.



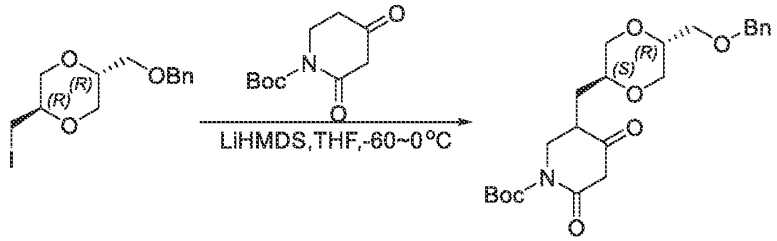
A solution of (2R)-1-{[(2R)-1-(benzyloxy)-3-chloropropan-2-yl]oxy}-3-[(4-methylbenzenesulfonyl)oxy]propan-2-ol (34 g, 79.269 mmol, 1 equiv) in NaOH (130 mL, 1.5N) was stirred for overnight at room temperature under nitrogen atmosphere.Then it was heated to 90 °C stirred for 4 h under nitrogen atmosphere. After that the reaction was cooled to room temperature and stirred for overnight. The mixture was then re-heated to 90 °C for about 2 h and finally cooled to room temperature. The mixture was acidified to pH 6 with 1N HCl (aq.).The resulting mixture was extracted with EtOAc (3 x mL). The combined organic layers were washed with brine (2x2 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 50% to 60% gradient in 10 min; detector, UV 254 nm.This resulted in [(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methanol (6.1 g, 32.29%) as a colorless oil.

LC-MS: $(M+H)^+$ found: 239.



To a stirred solution of [(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methanol (1 g, 4.197 mmol, 1 equiv) and Imidazole (0.57 g, 8.394 mmol, 2 equiv) in Toluene (8 mL) were added PPh3 (1.10 g, 4.197 mmol, 1 equiv) and iodine (1.07 g, 4.197 mmol, 1 equiv) in portions at room temperature under nitrogen atmosphere.The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere.To the above mixture was added THF (4 mL) dropwise at room temperature. The resulting mixture was stirred for additional 1 h at room temperature.The reaction was monitored by LCMS. The reaction was quenched by the addition of sat. sodium hyposulfite (aq.) (5 mL) at room temperature.The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2x2 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford (2R,5R)-2-[(benzyloxy)methyl]-5-(iodomethyl)-1,4-dioxane (1.3 g, 88.97%) as a colorless oil.

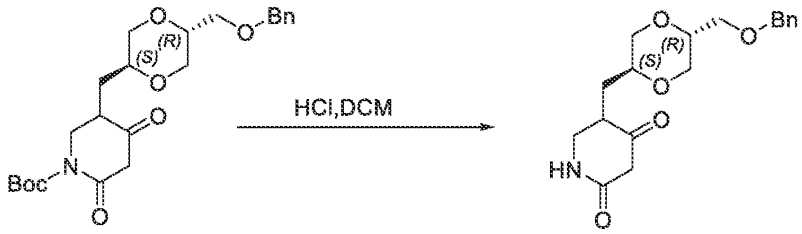
LC-MS: $(M+H)^+$ found: 349.



To a stirred mixture of (2R,5R)-2-[(benzyloxy)methyl]-5-(iodomethyl)-1,4-dioxane (1 g, 2.872 mmol, 1 equiv) and tert-butyl 2,4-dioxopiperidine-1-carboxylate (0.73 g, 3.446 mmol, 1.2 equiv) in THF (20 mL) was added LiHMDS (1.44 g, 8.616 mmol, 3 equiv) dropwise at -20°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at -20°C. Desired product could be detected by LCMS. The mixture was acidified to pH 5 with HCl (aq.). The resulting mixture was extracted with EtOAc (2 x 40mL). The combined organic layers were washed with brine (2x100 mL), dried over anhydrous Na2SO4. After

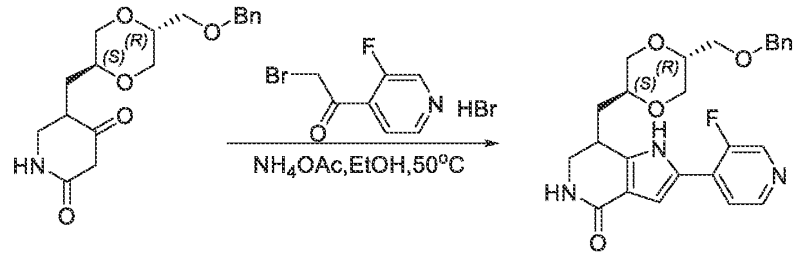
filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (4:1) to afford tert-butyl 5-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2,4-dioxopiperidine-1-carboxylate (350 mg, 28.11%) as a light green oil.

LC-MS: $(M+H)^+$ found: 434.



Into a 100 mL round-bottom flask were added tert-butyl 5-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2,4-dioxopiperidine-1-carboxylate (1 g, 2.307 mmol, 1 equiv), HCl(gas)in 1,4-dioxane (10 mL) and DCM (20 mL) at room temperature. The mixture was stirred 1 h at room temperature under nitrogen atmosphere. After the reaction, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:2) to afford 5-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}piperidine-2,4-dione (650 mg, 84.52%) as a yellow solid.

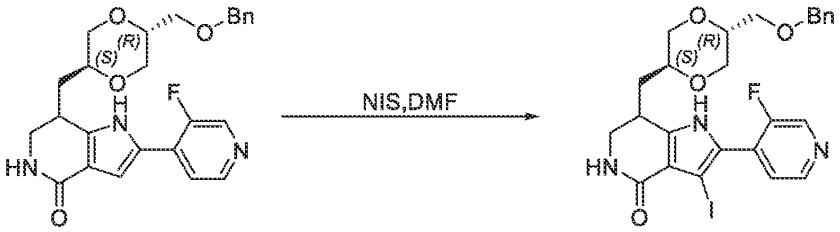
LC-MS: $(M+H)^+$ found: 334.



Into a 100 mL round-bottom flask were added 5-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}piperidine-2,4-dione (500 mg, 1.500 mmol, 1 equiv), 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (490.48 mg, 2.250 mmol, 1.5 equiv), NH4OAc (1156.07 mg, 15.000 mmol, 10 equiv) and EtOH (10 mL) at room temperature. The mixture was stirred

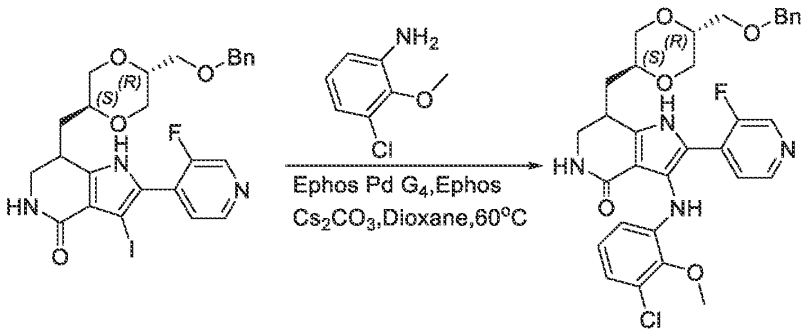
for 5 h at 50 degrees C under nitrogen atmosphere. After the reaction, The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 59.07%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 452.



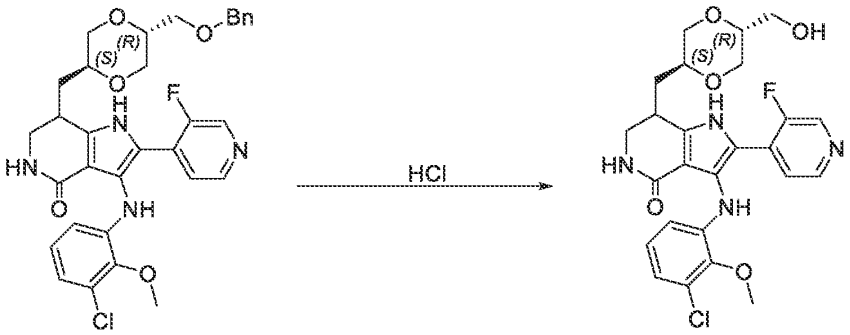
To a stirred solution of 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (500 mg, 1.107 mmol, 1 equiv) in DMF (10 mL) was added NIS (298.98 mg, 1.328 mmol, 1.2 equiv) in portions at -35°C under nitrogen atmosphere. The reaction solution was stirred at room temperature for 1h, The resulting mixture was extracted with EtOAc (4 x 40mL). The combined organic layers were washed with brine (1x20 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 1:1) to afford 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (420 mg, 65.68%) as a white solid.

LC-MS: $(M+H)^+$ found: 578.



To a solution of 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 0.693 mmol, 1 equiv) and Cs2CO3 (451.43 mg, 1.386 mmol, 2 equiv) in DMF (10 mL) were added EPhos Pd G4 (63.64 mg, 0.069 mmol, 0.1 equiv) and 3-chloro-2-methoxyaniline (131.02 mg, 0.832 mmol, 1.2 equiv) at room temperature under argon atmosphere. The resulting mixture was stirred for 4 h at 50 degrees C under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (30:1) to afford 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (320 mg, 76.09%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 607.



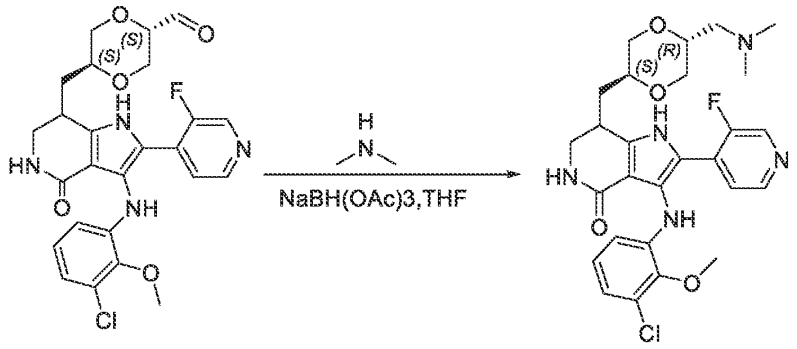
Into a 100 mL round-bottom flask were added 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.165 mmol, 1 equiv) and HCl(gas)in 1,4-dioxane (10 mL) at room temperature. The mixture was stirred 1 h at room temperature under nitrogen atmosphere. After the reaction, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:4) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-{[(2S,5R)-5-(hydroxymethyl)-1,4-dioxan-2-yl]methyl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 93.95%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 517.



Into a 50 mL round-bottom flask were added 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-{[(2S,5R)-5-(hydroxymethyl)-1,4-dioxan-2-yl]methyl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.193 mmol, 1 equiv), Dess-Martin (90.25 mg, 0.212 mmol, 1.1 equiv) and DCM (10 mL) at room temperature. The mixture was stirred 1 h at room temperature under nitrogen atmosphere. After the reaction, the mixture was concentrated under reduced pressure to afford (2S,5S)-5-({3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-7-yl}methyl)-1,4-dioxane-2-carbaldehyde (95 mg, 95.37%) as a yellow solid.

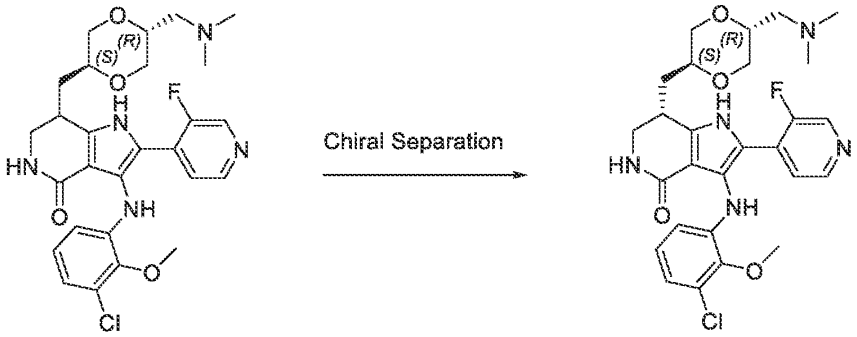
LC-MS: $(M+H)^+$ found 515.



To a stirred mixture of (2S,5S)-5-({3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-7-yl}methyl)-1,4-dioxane-2-carbaldehyde (50 mg, 0.097 mmol, 1 equiv) and dimethylamine (5.25 mg, 0.116 mmol, 1.2 equiv) in THF (5 mL) was added NaBH(OAc)3 (20.58 mg, 0.097 mmol, 1 equiv) dropwise at -20°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at -20°C. Desired product could be detected by LCMS. The resulting mixture was extracted

with EtOAc (2 x 40mL). The combined organic layers were washed with brine (2x100 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:3) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2S,5R)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (30 mg, 56.79%) as a light yellow oil.

LC-MS: $(M+H)^+$ found: 544.

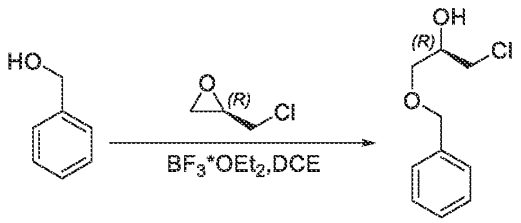


3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2S,5R)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (40 mg, 0.074 mmol, 1 equiv) was used for chiral separation(Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 19 min; Wave Length: 220/254 nm; RT1(min): 7.92; RT2(min): 9.81; Sample Solvent: ETOH: DCM=1: 1; Injection Volume: 0.8 mL; Number Of Runs: 4), and 2 peak was splitted from the material, the prepeak is the product (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2S,5R)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (2.7 mg, 6.75%). This resulted in (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2S,5R)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (2.7 mg, 6.75%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 544.

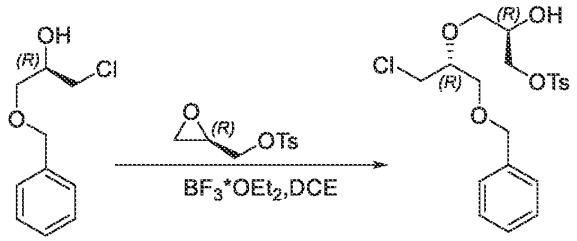
^{1}H NMR (400 MHz, Methanol-d4) δ 8.43 (d, J = 3.5 Hz, 1H), 8.18 (d, J = 5.3 Hz, 1H), 7.52 (dd, J = 6.9, 5.3 Hz, 1H), 6.74 – 6.61 (m, 2H), 6.23 (dd, J = 8.0, 1.6 Hz, 1H), 3.98 (s, 3H), 3.92 (dd, J = 11.6, 2.6 Hz, 1H), 3.83 – 3.72 (m, 3H), 3.71 (d, J = 5.1 Hz, 1H), 3.68 – 3.56 (m, 1H), 3.49 – 3.37 (m, 2H), 3.26 (td, J = 7.2, 3.5 Hz, 1H), 2.59 – 2.50 (m, 1H), 2.50 – 2.43 (m, 1H), 2.41 (s, 6H), 1.87 (ddd, J = 14.3, 7.6, 3.5 Hz, 1H), 1.75 (ddd, J = 14.6, 8.5, 6.7 Hz, 1H).

Example 108. (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2S,5R)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (5 mg, 12.50%). This resulted in (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2S,5R)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 564)**



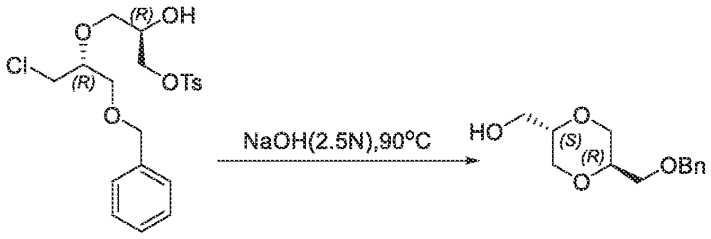
To a stirred solution/mixture of benzyl alcohol (1 g, 9.247 mmol, 1 equiv) and (-)-epichlorohydrin (0.94 g, 10.172 mmol, 1.1 equiv) in DCE (20 mL, 252.653 mmol, 27.32 equiv) was added BF3*Et2O (0.13 g, 0.925 mmol, 0.1 equiv) dropwise at 0°C under nitrogen atmosphere. Themixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of Water (20 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase flash with the following conditions (ACN/H2O=3/7) to afford (2R)-1-(benzyloxy)-3-chloropropan-2-ol (800 mg, 43.11%) as a white solid.

LC-MS: $(M+H)^+$ found: 201.



To a stirred solution of (2R)-1-(benzyloxy)-3-chloropropan-2-ol (72 g, 358.816 mmol, 1 equiv) and (2R)-oxiran-2-ylmethyl 4-methylbenzenesulfonate (24.57 g, 107.645 mmol, 0.3 equiv) in DCE (1.5 L) was added BF3*Et2O (4.55 mL, 35.882 mmol, 0.1 equiv) dropwise at 0 °C under nitrogen atmosphere.The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS. The residue was washed with saturated sodium bicarbonate solution(2x1 L). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 40% to 50% gradient in 10 min; detector, UV 254 nm.This resulted in (2R)-1-{[(2R)-1-(benzyloxy)-3-chloropropan-2-yl]oxy}-3-[(4-methylbenzenesulfonyl)oxy]propan-2-ol (34 g, 22.09%) as a colorless oil.

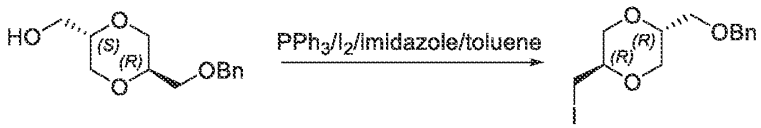
LC-MS: $(M+H)^+$ found: 429.



A solution of (2R)-1-{[(2R)-1-(benzyloxy)-3-chloropropan-2-yl]oxy}-3-[(4-methylbenzenesulfonyl)oxy]propan-2-ol (34 g, 79.269 mmol, 1 equiv) in NaOH (130 mL, 1.5N) was stirred for overnight at room temperature under nitrogen atmosphere.Then it was heated to 90 °C stirred for 4 h under nitrogen atmosphere. After that the reaction was cooled to room temperature and stirred for overnight. The mixture was then re-heated to 90 °C for about 2 h and finally cooled to room temperature. The mixture was acidified to

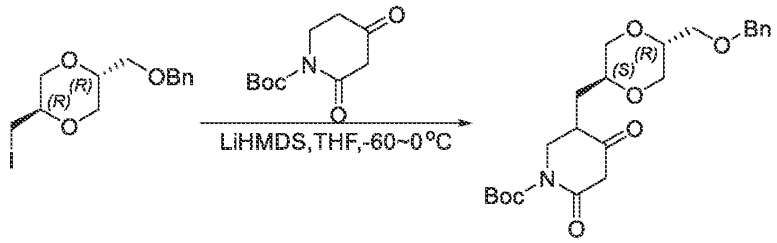
pH 6 with 1N HCl (aq.).The resulting mixture was extracted with EtOAc (3 x mL). The combined organic layers were washed with brine (2x2 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 50% to 60% gradient in 10 min; detector, UV 254 nm.This resulted in [(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methanol (6.1 g, 32.29%) as a colorless oil.

LC-MS: $(M+H)^+$ found: 239.



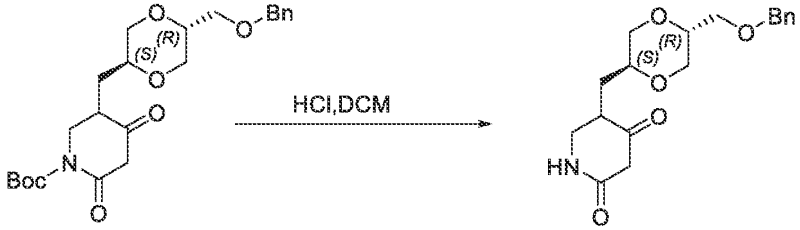
To a stirred solution of [(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methanol (1 g, 4.197 mmol, 1 equiv) and Imidazole (0.57 g, 8.394 mmol, 2 equiv) in Toluene (8 mL) were added PPh3 (1.10 g, 4.197 mmol, 1 equiv) and iodine (1.07 g, 4.197 mmol, 1 equiv) in portions at room temperature under nitrogen atmosphere.The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere.To the above mixture was added THF (4 mL) dropwise at room temperature. The resulting mixture was stirred for additional 1 h at room temperature.The reaction was monitored by LCMS. The reaction was quenched by the addition of sat. sodium hyposulfite (aq.) (5 mL) at room temperature.The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2x2 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford (2R,5R)-2-[(benzyloxy)methyl]-5-(iodomethyl)-1,4-dioxane (1.3 g, 88.97%) as a colorless oil.

LC-MS: $(M+H)^+$ found: 349.



To a stirred mixture of (2R,5R)-2-[(benzyloxy)methyl]-5-(iodomethyl)-1,4-dioxane (1 g, 2.872 mmol, 1 equiv) and tert-butyl 2,4-dioxopiperidine-1-carboxylate (0.73 g, 3.446 mmol, 1.2 equiv) in THF (20 mL) was added LiHMDS (1.44 g, 8.616 mmol, 3 equiv) dropwise at -20°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at -20°C. Desired product could be detected by LCMS. The mixture was acidified to pH 5 with HCl (aq.). The resulting mixture was extracted with EtOAc (2 x 40mL). The combined organic layers were washed with brine (2x100 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (4:1) to afford tert-butyl 5-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2,4-dioxopiperidine-1-carboxylate (350 mg, 28.11%) as a light green oil.

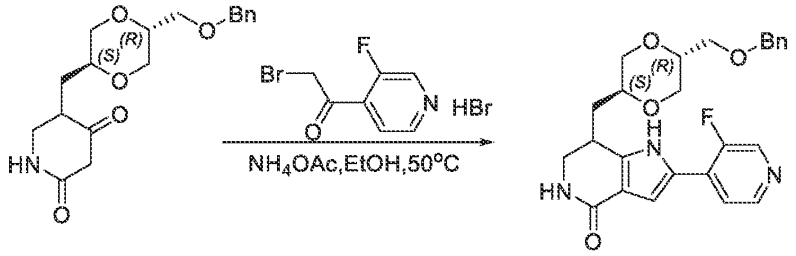
LC-MS: $(M+H)^+$ found: 434.



Into a 100 mL round-bottom flask were added tert-butyl 5-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2,4-dioxopiperidine-1-carboxylate (1 g, 2.307 mmol, 1 equiv), HCl(gas)in 1,4-dioxane (10 mL) and DCM (20 mL) at room temperature. The mixture was stirred 1 h at room temperature under nitrogen atmosphere. After the reaction, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:2) to afford 5-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}piperidine-2,4-dione (650 mg,

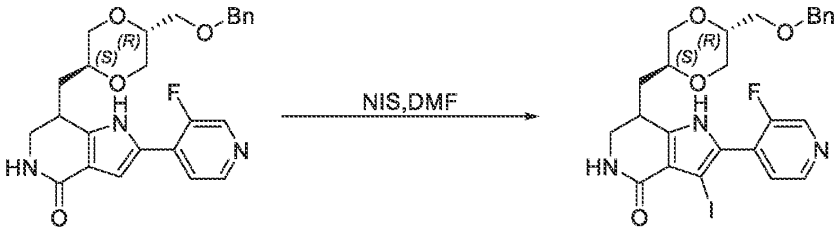
84.52%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 334.



Into a 100 mL round-bottom flask were added 5-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}piperidine-2,4-dione (500 mg, 1.500 mmol, 1 equiv), 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (490.48 mg, 2.250 mmol, 1.5 equiv), NH4OAc (1156.07 mg, 15.000 mmol, 10 equiv) and EtOH (10 mL) at room temperature. The mixture was stirred for 5 h at 50 degrees C under nitrogen atmosphere. After the reaction, The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 59.07%) as a yellow solid.

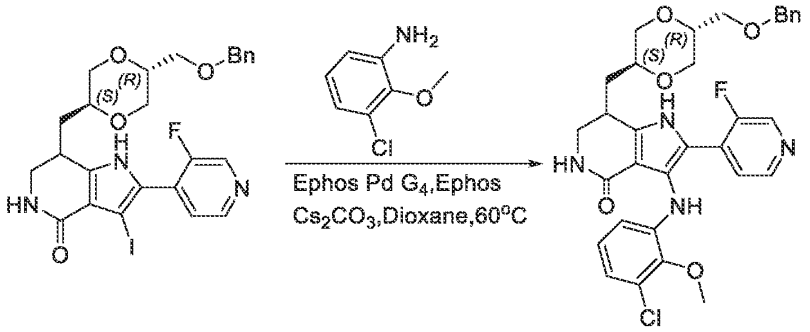
LC-MS: $(M+H)^+$ found: 452.



To a stirred solution of 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (500 mg, 1.107 mmol, 1 equiv) in DMF (10 mL) was added NIS (298.98 mg, 1.328 mmol, 1.2 equiv) in portions at -35°C under nitrogen atmosphere. The reaction solution was stirred at room temperature for 1h, The resulting mixture was extracted with EtOAc (4 x 40mL). The combined organic layers were washed with brine (1x20 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-

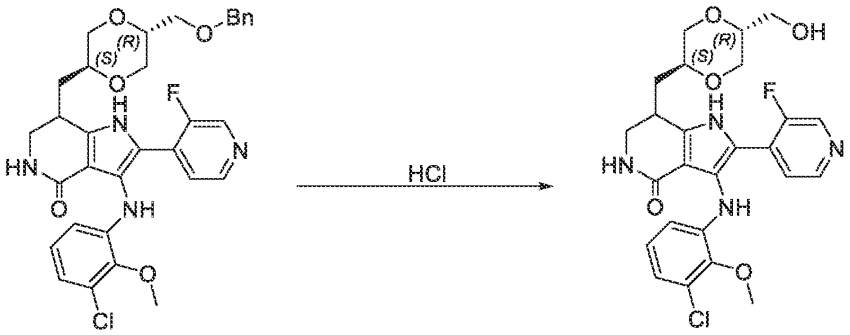
TLC (PE/EtOAc 1:1) to afford 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (420 mg, 65.68%) as a white solid.

LC-MS: $(M+H)^+$ found: 578.



To a solution of 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 0.693 mmol, 1 equiv) and Cs2CO3 (451.43 mg, 1.386 mmol, 2 equiv) in DMF (10 mL) were added EPhos Pd G4 (63.64 mg, 0.069 mmol, 0.1 equiv) and 3-chloro-2-methoxyaniline (131.02 mg, 0.832 mmol, 1.2 equiv) at room temperature under argon atmosphere. The resulting mixture was stirred for 4 h at 50 degrees C under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (30:1) to afford 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (320 mg, 76.09%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 607.



Into a 100 mL round-bottom flask were added 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.165 mmol, 1 equiv) and HCl(gas)in 1,4-dioxane (10 mL) at room temperature. The mixture was stirred 1 h at room temperature under nitrogen atmosphere. After the reaction, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:4) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-{[(2S,5R)-5-(hydroxymethyl)-1,4-dioxan-2-yl]methyl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 93.95%) as a yellow solid.

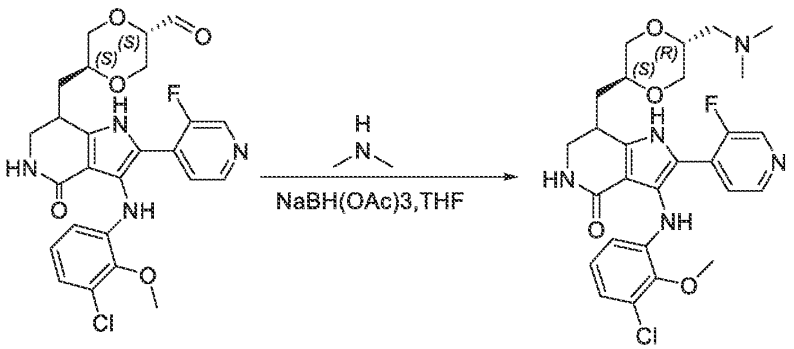
LC-MS: $(M+H)^+$ found: 517.



Into a 50 mL round-bottom flask were added 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-{[(2S,5R)-5-(hydroxymethyl)-1,4-dioxan-2-yl]methyl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.193 mmol, 1 equiv), Dess-Martin (90.25 mg, 0.212 mmol, 1.1 equiv) and DCM (10 mL) at room temperature. The mixture was stirred 1 h at room temperature under nitrogen atmosphere. After the reaction, the

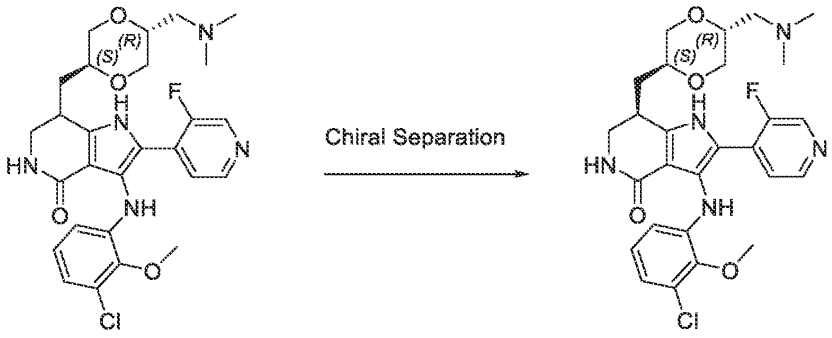
mixture was concentrated under reduced pressure to afford (2S,5S)-5-({3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-7-yl}methyl)-1,4-dioxane-2-carbaldehyde (95 mg, 95.37%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 515.



To a stirred mixture of (2S,5S)-5-({3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-7-yl}methyl)-1,4-dioxane-2-carbaldehyde (50 mg, 0.097 mmol, 1 equiv) and dimethylamine (5.25 mg, 0.116 mmol, 1.2 equiv) in THF (5 mL) was added NaBH(OAc)3 (20.58 mg, 0.097 mmol, 1 equiv) dropwise at -20°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at -20°C. Desired product could be detected by LCMS. The resulting mixture was extracted with EtOAc (2 x 40mL). The combined organic layers were washed with brine (2x100 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:3) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2S,5R)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (30 mg, 56.79%) as a light yellow oil.

LC-MS: $(M+H)^+$ found: 544.



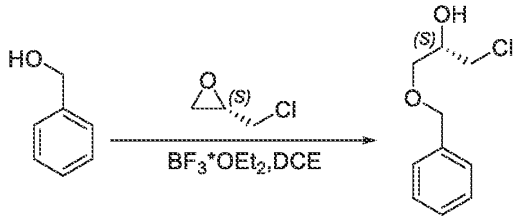
3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2S,5R)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (40 mg, 0.074 mmol, 1 equiv) was used for chiral separation(Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 19 min; Wave Length: 220/254 nm; RT1(min): 7.92; RT2(min): 9.81; Sample Solvent: ETOH: DCM=1: 1; Injection Volume: 0.8 mL; Number Of Runs: 4), and 2 peak was splitted from the material, the postpeak is the product (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2S,5R)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (5 mg, 12.50%). This resulted in (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2S,5R)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (5 mg, 12.50%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 544.

1H NMR (400 MHz, Methanol-d4) δ 8.44 (d, J = 3.8 Hz, 1H), 8.16 (d, J = 5.4 Hz, 1H), 7.52 (dd, J = 7.0, 5.3 Hz, 1H), 6.73 (dd, J = 8.1, 1.6 Hz, 1H), 6.67 (t, J = 8.1 Hz, 1H), 6.23 (dd, J = 8.0, 1.6 Hz, 1H), 4.04 – 3.96 (m, 1H), 3.99 (s, 3H), 3.86 (dd, J = 11.5, 2.5 Hz, 1H), 3.79 (td, J = 8.5, 7.0, 4.3 Hz, 2H), 3.62 – 3.54 (m, 1H), 3.52 – 3.44 (m, 2H), 3.46 – 3.34 (m, 2H), 2.48 – 2.34 (m, 2H), 2.32 (s, 6H), 1.83 – 1.67 (m, 2H).

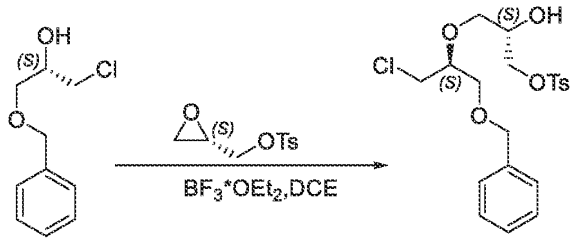
Example 109. (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2R,5S)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (9.2 mg, 4.35%). This resulted in (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2R,5S)-5-[(dimethylamino)methyl]-1,4-dioxan-2-

yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 563)**



To a stirred solution/mixture of benzyl alcohol (1 g, 9.247 mmol, 1 equiv) and (-)-epichlorohydrin (0.94 g, 10.172 mmol, 1.1 equiv) in DCE (20 mL, 252.653 mmol, 27.32 equiv) was added BF3*Et2O (0.13 g, 0.925 mmol, 0.1 equiv) dropwise at 0°C under nitrogen atmosphere. Themixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of Water (20 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase flash with the following conditions (ACN/H2O=3/7) to afford (2R)-1-(benzyloxy)-3-chloropropan-2-ol (800 mg, 43.11%) as a white solid.

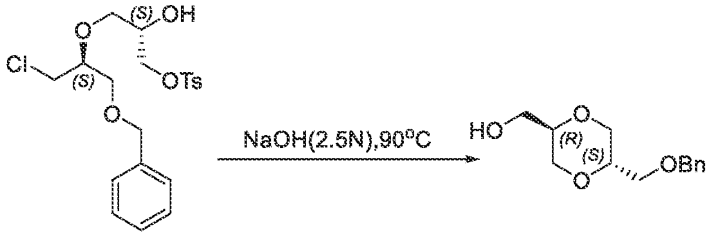
LC-MS: $(M+H)^+$ found: 201.



To a stirred solution of (2R)-1-(benzyloxy)-3-chloropropan-2-ol (72 g, 358.816 mmol, 1 equiv) and (2R)-oxiran-2-ylmethyl 4-methylbenzenesulfonate (24.57 g, 107.645 mmol, 0.3 equiv) in DCE (1.5 L) was added BF3*Et2O (4.55 mL, 35.882 mmol, 0.1 equiv) dropwise at 0 °C under nitrogen atmosphere.The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS. The residue was washed with saturated sodium bicarbonate solution(2x1 L). The combined organic

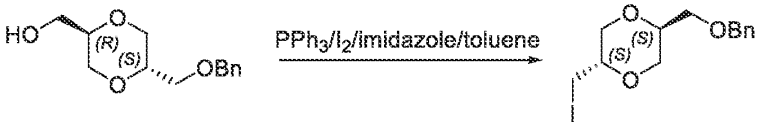
layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 40% to 50% gradient in 10 min; detector, UV 254 nm.This resulted in (2R)-1-{[(2R)-1-(benzyloxy)-3-chloropropan-2-yl]oxy}-3-[(4-methylbenzenesulfonyl)oxy]propan-2-ol (34 g, 22.09%) as a colorless oil.

LC-MS: $(M+H)^+$ found: 429.



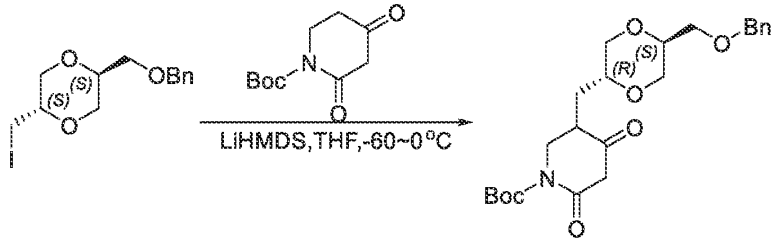
A solution of (2R)-1-{[(2R)-1-(benzyloxy)-3-chloropropan-2-yl]oxy}-3-[(4-methylbenzenesulfonyl)oxy]propan-2-ol (34 g, 79.269 mmol, 1 equiv) in NaOH (130 mL, 1.5N) was stirred for overnight at room temperature under nitrogen atmosphere.Then it was heated to 90 °C stirred for 4 h under nitrogen atmosphere. After that the reaction was cooled to room temperature and stirred for overnight. The mixture was then re-heated to 90 °C for about 2 h and finally cooled to room temperature. The mixture was acidified to pH 6 with 1N HCl (aq.).The resulting mixture was extracted with EtOAc (3 x mL). The combined organic layers were washed with brine (2x2 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 50% to 60% gradient in 10 min; detector, UV 254 nm.This resulted in [(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methanol (6.1 g, 32.29%) as a colorless oil.

LC-MS: $(M+H)^+$ found: 239.



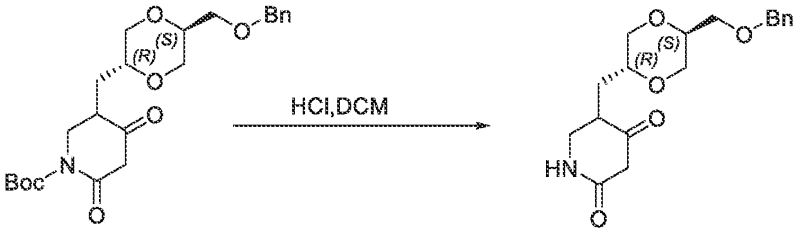
To a stirred solution of [(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methanol (1 g, 4.197 mmol, 1 equiv) and Imidazole (0.57 g, 8.394 mmol, 2 equiv) in Toluene (8 mL) were added PPh3 (1.10 g, 4.197 mmol, 1 equiv) and iodine (1.07 g, 4.197 mmol, 1 equiv) in portions at room temperature under nitrogen atmosphere.The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere.To the above mixture was added THF (4 mL) dropwise at room temperature. The resulting mixture was stirred for additional 1 h at room temperature.The reaction was monitored by LCMS. The reaction was quenched by the addition of sat. sodium hyposulfite (aq.) (5 mL) at room temperature.The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2x2 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford (2R,5R)-2-[(benzyloxy)methyl]-5-(iodomethyl)-1,4-dioxane (1.3 g, 88.97%) as a colorless oil.

LC-MS: $(M+H)^+$ found: 349.



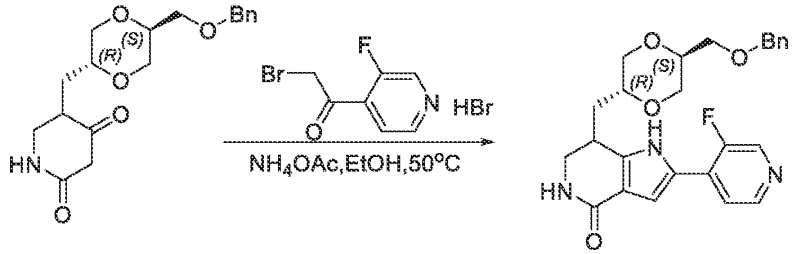
To a stirred mixture of (2R,5R)-2-[(benzyloxy)methyl]-5-(iodomethyl)-1,4-dioxane (1 g, 2.872 mmol, 1 equiv) and tert-butyl 2,4-dioxopiperidine-1-carboxylate (0.73 g, 3.446 mmol, 1.2 equiv) in THF (20 mL) was added LiHMDS (1.44 g, 8.616 mmol, 3 equiv) dropwise at -20°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at -20°C. Desired product could be detected by LCMS. The mixture was acidified to pH 5 with HCl (aq.). The resulting mixture was extracted with EtOAc (2 x 40mL). The combined organic layers were washed with brine (2x100 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (4:1) to afford tert-butyl 5-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2,4-dioxopiperidine-1-carboxylate (350 mg, 28.11%) as a light green oil.

LC-MS: $(M+H)^+$ found: 434.



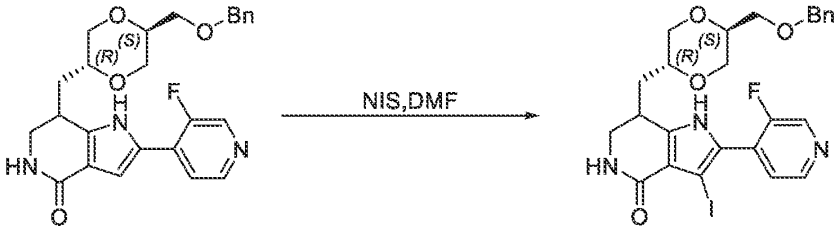
Into a 100 mL round-bottom flask were added tert-butyl 5-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2,4-dioxopiperidine-1-carboxylate (1 g, 2.307 mmol, 1 equiv), HCl(gas)in 1,4-dioxane (10 mL) and DCM (20 mL) at room temperature. The mixture was stirred 1 h at room temperature under nitrogen atmosphere. After the reaction, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:2) to afford 5-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}piperidine-2,4-dione (650 mg, 84.52%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 334.



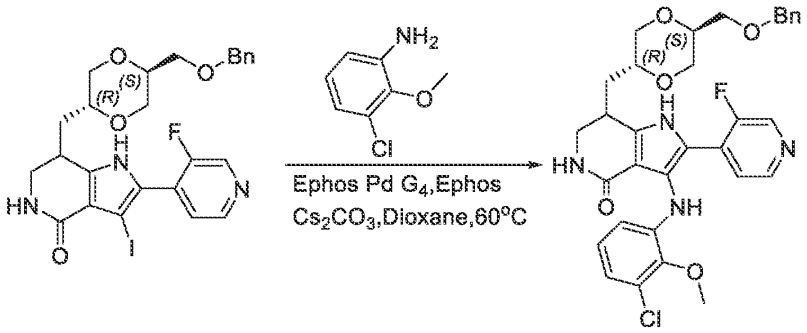
Into a 100 mL round-bottom flask were added 5-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}piperidine-2,4-dione (500 mg, 1.500 mmol, 1 equiv), 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (490.48 mg, 2.250 mmol, 1.5 equiv), NH4OAc (1156.07 mg, 15.000 mmol, 10 equiv) and EtOH (10 mL) at room temperature. The mixture was stirred for 5 h at 50 degrees C under nitrogen atmosphere. After the reaction, The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 59.07%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 452.



To a stirred solution of 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (500 mg, 1.107 mmol, 1 equiv) in DMF (10 mL) was added NIS (298.98 mg, 1.328 mmol, 1.2 equiv) in portions at -35°C under nitrogen atmosphere. The reaction solution was stirred at room temperature for 1h, The resulting mixture was extracted with EtOAc (4 x 40mL). The combined organic layers were washed with brine (1x20 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 1:1) to afford 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (420 mg, 65.68%) as a white solid.

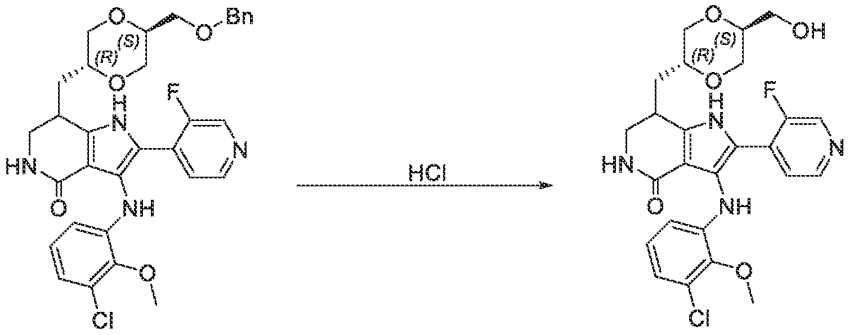
LC-MS: $(M+H)^+$ found: 578.



To a solution of 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 0.693 mmol, 1 equiv) and Cs2CO3 (451.43 mg, 1.386 mmol, 2 equiv) in DMF (10 mL) were added EPhos Pd G4 (63.64 mg, 0.069 mmol, 0.1 equiv) and 3-chloro-2-methoxyaniline (131.02 mg, 0.832 mmol, 1.2 equiv) at room temperature under argon atmosphere. The

resulting mixture was stirred for 4 h at 50 degrees C under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (30:1) to afford 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (320 mg, 76.09%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 607.



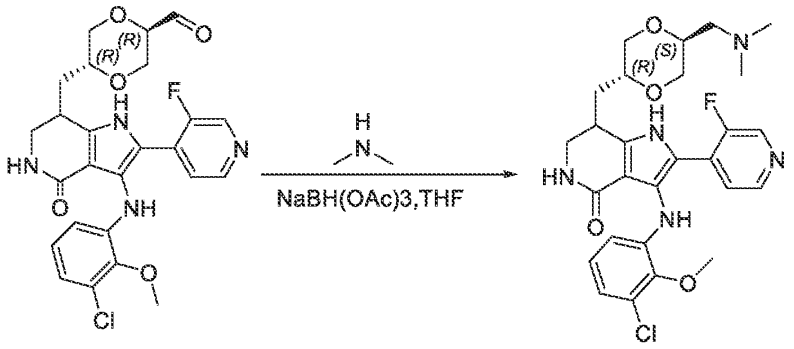
Into a 100 mL round-bottom flask were added 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.165 mmol, 1 equiv) and HCl(gas)in 1,4-dioxane (10 mL) at room temperature. The mixture was stirred 1 h at room temperature under nitrogen atmosphere. After the reaction, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:4) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-{[(2S,5R)-5-(hydroxymethyl)-1,4-dioxan-2-yl]methyl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 93.95%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 517.



Into a 50 mL round-bottom flask were added 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-{[(2S,5R)-5-(hydroxymethyl)-1,4-dioxan-2-yl]methyl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.193 mmol, 1 equiv), Dess-Martin (90.25 mg, 0.212 mmol, 1.1 equiv) and DCM (10 mL) at room temperature. The mixture was stirred 1 h at room temperature under nitrogen atmosphere. After the reaction, the mixture was concentrated under reduced pressure to afford (2S,5S)-5-({3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-7-yl}methyl)-1,4-dioxane-2-carbaldehyde (95 mg, 95.37%) as a yellow solid.

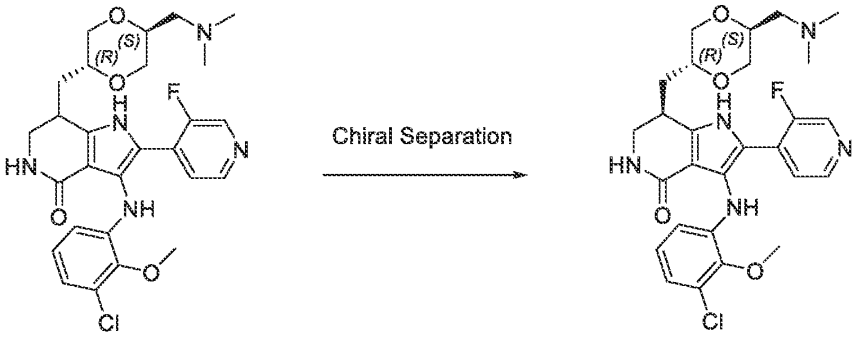
LC-MS: $(M+H)^+$ found: 515.



To a stirred mixture of (2S,5S)-5-({3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-7-yl}methyl)-1,4-dioxane-2-carbaldehyde (50 mg, 0.097 mmol, 1 equiv) and dimethylamine (5.25 mg, 0.116 mmol, 1.2 equiv) in THF (5 mL) was added NaBH(OAc)3 (20.58 mg, 0.097 mmol, 1 equiv) dropwise at -20°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at -20°C. Desired product could be detected by LCMS. The resulting mixture was extracted

with EtOAc (2 x 40mL). The combined organic layers were washed with brine (2x100 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:3) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2S,5R)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (30 mg, 56.79%) as a light yellow oil.

LC-MS: $(M+H)^+$ found: 544.

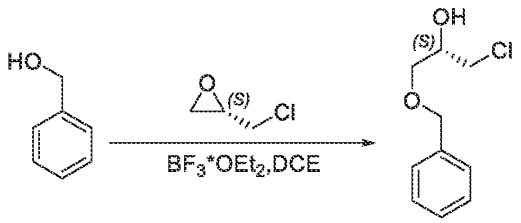


(2R,5R)-5-({3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-7-yl}methyl)-1,4-dioxane-2-carbaldehyde (200 mg, 0.388 mmol, 1 equiv) was used for chiral separation(Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 19 min; Wave Length: 220/254 nm; RT1(min): 7.92; RT2(min): 9.81; Sample Solvent: ETOH: DCM=1: 1; Injection Volume: 0.8 mL; Number Of Runs: 4), and 2 peak was splitted from the material, the prepeak is the product (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2R,5S)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (9.2 mg, 4.35%). This resulted in (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2R,5S)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (9.2 mg, 4.35%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 544.

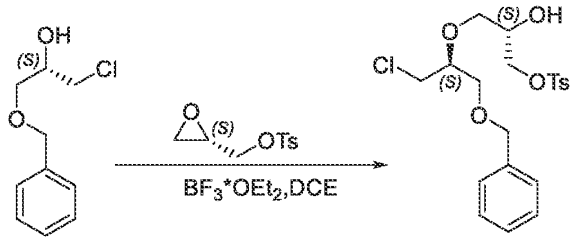
^{1}H NMR (400 MHz, Methanol-d4) δ 8.43 (d, J = 3.5 Hz, 1H), 8.18 (dd, J = 5.2, 1.0 Hz, 1H), 7.52 (dd, J = 6.9, 5.2 Hz, 1H), 6.71 (dd, J = 8.0, 1.6 Hz, 1H), 6.65 (t, J = 8.0 Hz, 1H), 6.23 (dd, J = 8.0, 1.6 Hz, 1H), 3.98 (s, 3H), 3.91 (dd, J = 11.5, 2.6 Hz, 1H), 3.82 – 3.68 (m, 3H), 3.61 (t, J = 9.2 Hz, 1H), 3.49 – 3.37 (m, 3H), 3.30 – 3.21 (m, 1H), 2.43 (dd, J = 13.1, 7.6 Hz, 1H), 2.35 (d, J = 3.7 Hz, 1H), 2.32 (s, 6H), 1.87 (ddd, J = 14.3, 7.6, 3.6 Hz, 1H), 1.75 (ddd, J = 14.6, 8.4, 6.7 Hz, 1H).

Example 110. (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2R,5S)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (14.9 mg, 7.05%). This resulted in (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2R,5S)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 562)**



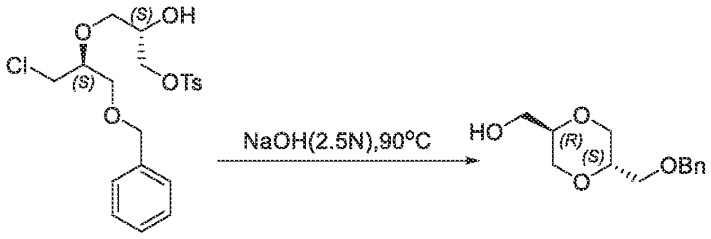
To a stirred solution/mixture of benzyl alcohol (1 g, 9.247 mmol, 1 equiv) and (-)-epichlorohydrin (0.94 g, 10.172 mmol, 1.1 equiv) in DCE (20 mL, 252.653 mmol, 27.32 equiv) was added BF3*Et2O (0.13 g, 0.925 mmol, 0.1 equiv) dropwise at 0°C under nitrogen atmosphere. Themixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of Water (20 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase flash with the following conditions (ACN/H2O=3/7) to afford (2R)-1-(benzyloxy)-3-chloropropan-2-ol (800 mg, 43.11%) as a white solid.

LC-MS: $(M+H)^+$ found: 201.



To a stirred solution of (2R)-1-(benzyloxy)-3-chloropropan-2-ol (72 g, 358.816 mmol, 1 equiv) and (2R)-oxiran-2-ylmethyl 4-methylbenzenesulfonate (24.57 g, 107.645 mmol, 0.3 equiv) in DCE (1.5 L) was added BF3*Et2O (4.55 mL, 35.882 mmol, 0.1 equiv) dropwise at 0 °C under nitrogen atmosphere.The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS. The residue was washed with saturated sodium bicarbonate solution(2x1 L). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 40% to 50% gradient in 10 min; detector, UV 254 nm.This resulted in (2R)-1-{[(2R)-1-(benzyloxy)-3-chloropropan-2-yl]oxy}-3-[(4-methylbenzenesulfonyl)oxy]propan-2-ol (34 g, 22.09%) as a colorless oil.

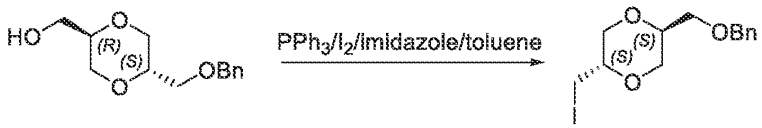
LC-MS: $(M+H)^+$ found: 429.



A solution of (2R)-1-{[(2R)-1-(benzyloxy)-3-chloropropan-2-yl]oxy}-3-[(4-methylbenzenesulfonyl)oxy]propan-2-ol (34 g, 79.269 mmol, 1 equiv) in NaOH (130 mL, 1.5N) was stirred for overnight at room temperature under nitrogen atmosphere.Then it was heated to 90 °C stirred for 4 h under nitrogen atmosphere. After that the reaction was cooled to room temperature and stirred for overnight. The mixture was then re-heated to 90 °C for about 2 h and finally cooled to room temperature. The mixture was acidified to

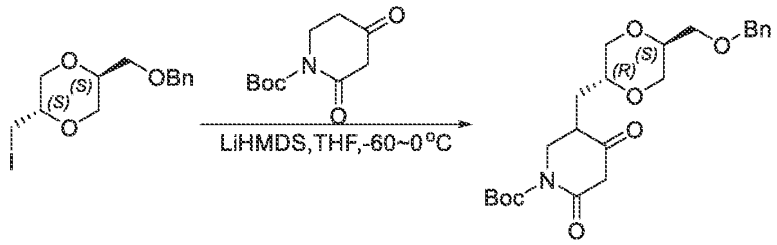
pH 6 with 1N HCl (aq.).The resulting mixture was extracted with EtOAc (3 x mL). The combined organic layers were washed with brine (2x2 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 50% to 60% gradient in 10 min; detector, UV 254 nm.This resulted in [(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methanol (6.1 g, 32.29%) as a colorless oil.

LC-MS: $(M+H)^+$ found: 239.



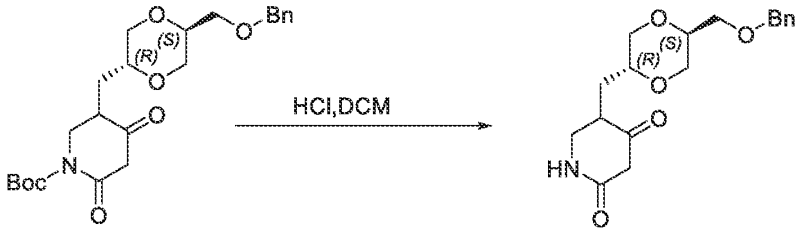
To a stirred solution of [(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methanol (1 g, 4.197 mmol, 1 equiv) and Imidazole (0.57 g, 8.394 mmol, 2 equiv) in Toluene (8 mL) were added PPh3 (1.10 g, 4.197 mmol, 1 equiv) and iodine (1.07 g, 4.197 mmol, 1 equiv) in portions at room temperature under nitrogen atmosphere.The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere.To the above mixture was added THF (4 mL) dropwise at room temperature. The resulting mixture was stirred for additional 1 h at room temperature.The reaction was monitored by LCMS. The reaction was quenched by the addition of sat. sodium hyposulfite (aq.) (5 mL) at room temperature.The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2x2 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford (2R,5R)-2-[(benzyloxy)methyl]-5-(iodomethyl)-1,4-dioxane (1.3 g, 88.97%) as a colorless oil.

LC-MS: $(M+H)^+$ found: 349.



To a stirred mixture of (2R,5R)-2-[(benzyloxy)methyl]-5-(iodomethyl)-1,4-dioxane (1 g, 2.872 mmol, 1 equiv) and tert-butyl 2,4-dioxopiperidine-1-carboxylate (0.73 g, 3.446 mmol, 1.2 equiv) in THF (20 mL) was added LiHMDS (1.44 g, 8.616 mmol, 3 equiv) dropwise at -20°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at -20°C. Desired product could be detected by LCMS. The mixture was acidified to pH 5 with HCl (aq.). The resulting mixture was extracted with EtOAc (2 x 40mL). The combined organic layers were washed with brine (2x100 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (4:1) to afford tert-butyl 5-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2,4-dioxopiperidine-1-carboxylate (350 mg, 28.11%) as a light green oil.

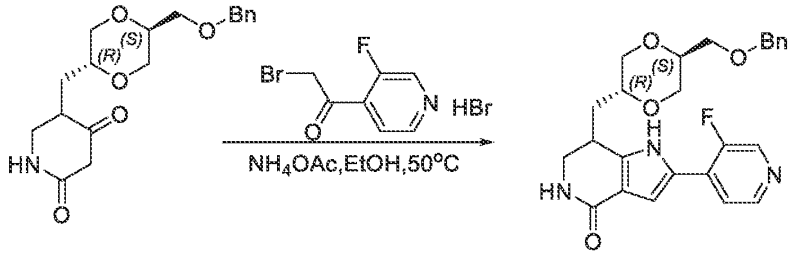
LC-MS: $(M+H)^+$ found: 434.



Into a 100 mL round-bottom flask were added tert-butyl 5-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2,4-dioxopiperidine-1-carboxylate (1 g, 2.307 mmol, 1 equiv), HCl(gas)in 1,4-dioxane (10 mL) and DCM (20 mL) at room temperature. The mixture was stirred 1 h at room temperature under nitrogen atmosphere. After the reaction, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:2) to afford 5-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}piperidine-2,4-dione (650 mg,

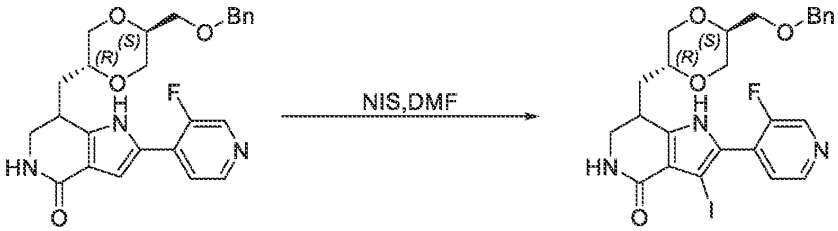
84.52%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 334.



Into a 100 mL round-bottom flask were added 5-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}piperidine-2,4-dione (500 mg, 1.500 mmol, 1 equiv), 2-bromo-1-(3-fluoropyridin-4-yl)ethanone (490.48 mg, 2.250 mmol, 1.5 equiv), NH4OAc (1156.07 mg, 15.000 mmol, 10 equiv) and EtOH (10 mL) at room temperature. The mixture was stirred for 5 h at 50 degrees C under nitrogen atmosphere. After the reaction, The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 59.07%) as a yellow solid.

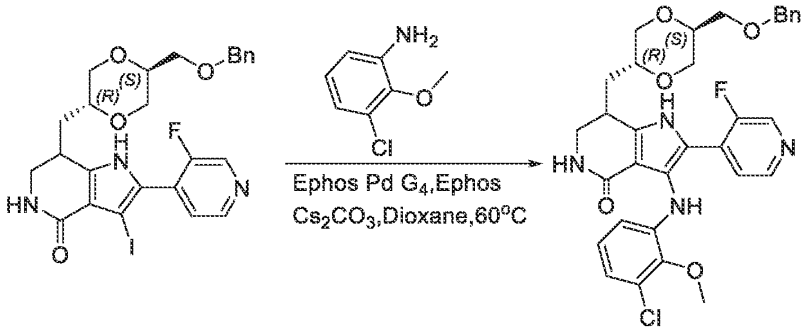
LC-MS: $(M+H)^+$ found: 452.



To a stirred solution of 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (500 mg, 1.107 mmol, 1 equiv) in DMF (10 mL) was added NIS (298.98 mg, 1.328 mmol, 1.2 equiv) in portions at -35°C under nitrogen atmosphere. The reaction solution was stirred at room temperature for 1h, The resulting mixture was extracted with EtOAc (4 x 40mL). The combined organic layers were washed with brine (1x20 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-

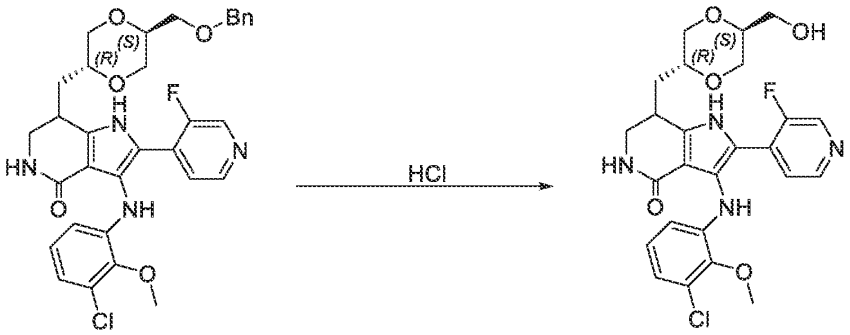
TLC (PE/EtOAc 1:1) to afford 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (420 mg, 65.68%) as a white solid.

LC-MS: $(M+H)^+$ found: 578.



To a solution of 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 0.693 mmol, 1 equiv) and Cs2CO3 (451.43 mg, 1.386 mmol, 2 equiv) in DMF (10 mL) were added EPhos Pd G4 (63.64 mg, 0.069 mmol, 0.1 equiv) and 3-chloro-2-methoxyaniline (131.02 mg, 0.832 mmol, 1.2 equiv) at room temperature under argon atmosphere. The resulting mixture was stirred for 4 h at 50 degrees C under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (30:1) to afford 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (320 mg, 76.09%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 607.



Into a 100 mL round-bottom flask were added 7-{[(2S,5R)-5-[(benzyloxy)methyl]-1,4-dioxan-2-yl]methyl}-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.165 mmol, 1 equiv) and HCl(gas)in 1,4-dioxane (10 mL) at room temperature. The mixture was stirred 1 h at room temperature under nitrogen atmosphere. After the reaction, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:4) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-{[(2S,5R)-5-(hydroxymethyl)-1,4-dioxan-2-yl]methyl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 93.95%) as a yellow solid.

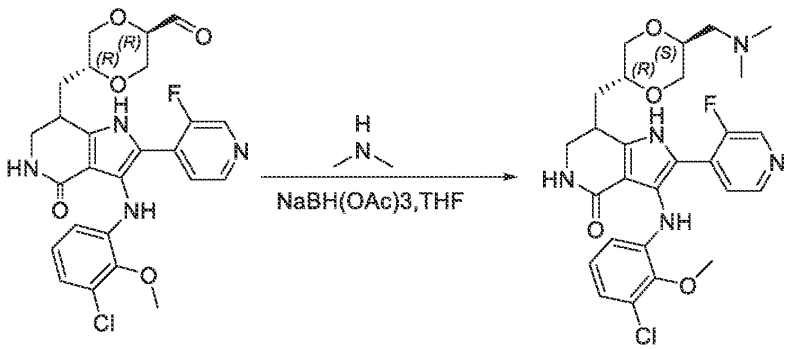
LC-MS: $(M+H)^+$ found: 517.



Into a 50 mL round-bottom flask were added 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-{[(2S,5R)-5-(hydroxymethyl)-1,4-dioxan-2-yl]methyl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.193 mmol, 1 equiv), Dess-Martin (90.25 mg, 0.212 mmol, 1.1 equiv) and DCM (10 mL) at room temperature. The mixture was stirred 1 h at room temperature under nitrogen atmosphere. After the reaction, the

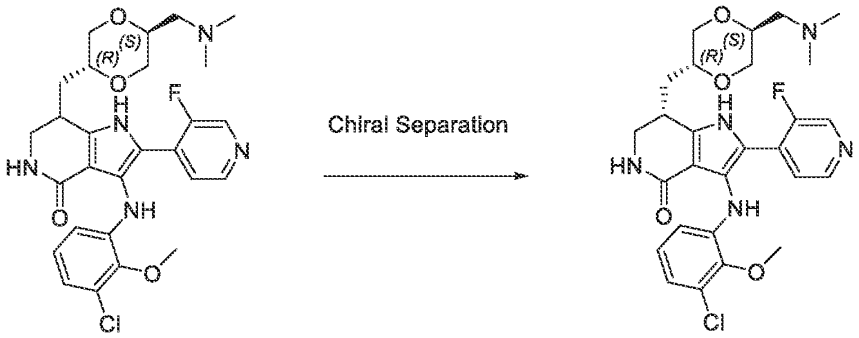
mixture was concentrated under reduced pressure to afford (2S,5S)-5-({3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-7-yl}methyl)-1,4-dioxane-2-carbaldehyde (95 mg, 95.37%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 515.



To a stirred mixture of (2S,5S)-5-({3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-7-yl}methyl)-1,4-dioxane-2-carbaldehyde (50 mg, 0.097 mmol, 1 equiv) and dimethylamine (5.25 mg, 0.116 mmol, 1.2 equiv) in THF (5 mL) was added NaBH(OAc)3 (20.58 mg, 0.097 mmol, 1 equiv) dropwise at -20°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at -20°C. Desired product could be detected by LCMS. The resulting mixture was extracted with EtOAc (2 x 40mL). The combined organic layers were washed with brine (2x100 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:3) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2S,5R)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (30 mg, 56.79%) as a light yellow oil.

LC-MS: $(M+H)^+$ found: 544.

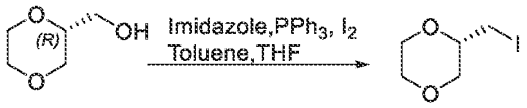


(2R,5R)-5-({3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-7-yl}methyl)-1,4-dioxane-2-carbaldehyde (200 mg, 0.388 mmol, 1 equiv) was used for chiral separation(Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 19 min; Wave Length: 220/254 nm; RT1(min): 7.92; RT2(min): 9.81; Sample Solvent: ETOH: DCM=1: 1; Injection Volume: 0.8 mL; Number Of Runs: 4), and 2 peak was splitted from the material, the postpeak is the product (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2R,5S)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (14.9 mg, 7.05%). This resulted in (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2R,5S)-5-[(dimethylamino)methyl]-1,4-dioxan-2-yl]methyl}-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (14.9 mg, 7.05%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 544.

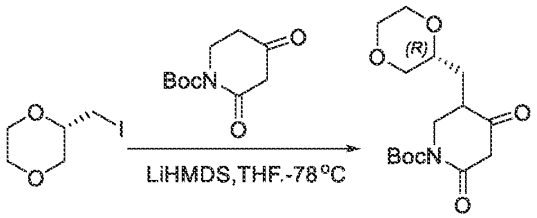
^{1}H NMR (400 MHz, Methanol-d4) δ 8.44 (d, J = 3.9 Hz, 1H), 8.16 (dd, J = 5.3, 1.1 Hz, 1H), 7.52 (dd, J = 7.1, 5.3 Hz, 1H), 6.73 (dd, J = 8.1, 1.6 Hz, 1H), 6.67 (t, J = 8.0 Hz, 1H), 6.23 (dd, J = 8.0, 1.6 Hz, 1H), 4.04 – 3.96 (m, 1H), 3.99 (s, 3H), 3.90 – 3.75 (m, 2H), 3.80 (s, 1H), 3.64 – 3.54 (m, 1H), 3.52 – 3.33 (m, 3H), 3.31 (s, 1H), 2.47 (dd, J = 13.1, 7.6 Hz, 1H), 2.43 – 2.36 (m, 1H), 2.35 (s, 6H), 1.75 (s, 1H), 1.76 – 1.67 (m, 1H).

Example 111. (7*R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2*R*)-1,4-dioxan-2-ylmethyl]-2-(2-methylpyrimidin-4-yl)-1*H*,5*H*,6*H*,7*H*-pyrrolo[3,2-c]pyridin-4-one **(compound 570)**



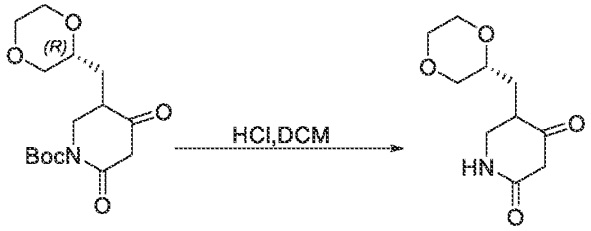
To a suspension of (R)-(1,4-dioxan-2-yl)methanol (100.00 g, 0.847 mol, 1.00 equiv) in Tolune (1000 mL) and THF (500 mL) was added imidazole(115.2 g, 1.69 mol, 2.00 equiv), PPh_3(214.4 g, 0.847 mol, 1.00 equiv) at room temperature ,I_2(214.4 g, 0.847 mol, 1.00 equiv) was added at 0 degrees C. The mixture was stirred for 3 h at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting solution was quenching with 500 ml of $Na_2S_2O_3$ saturated solution. The aqueous layer was extracted with EtOAc (3 x 250 mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified on silica (EtOAc/PE=1:6) to provide 130 g (67%) of the title compound as a colorless oil.

LC-MS: $(M+H)^+$ found: 229.



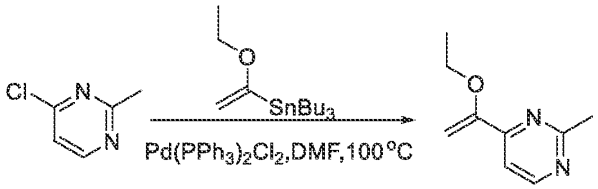
To a suspension of (S)-2-(iodomethyl)-1,4-dioxane (104.00 g, 0.457 mol, 1.40 equiv) and tert-butyl 2,4-dioxopiperidine-1-carboxylate (70.00 g, 0.327 mol, 1.00 equiv) in THF (1000 mL) was dropwise added LiHMDS (1.37 L, 1.37 mol, 3.00 equiv) at -60°C. The mixture was stirred for 1 h at 0 degrees under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting solution was quenching with 500 ml of HCl (5%) at 0 degrees. The aqueous layer was extracted with EtOAc (3 x 250 mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column (PE /EtOAc, 1:1) to provide 45 g (46%) of the title compound as a light brown oil.

LC-MS: $(M+H)^+$ found: 314.



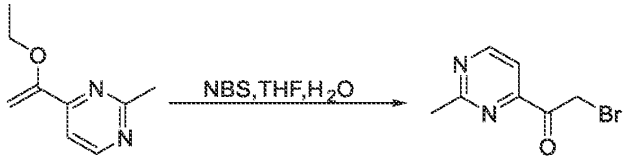
To a stirred mixture of tert-butyl 5-(((R)-1,4-dioxan-2-yl)methyl)-2,4-dioxopiperidine-1-carboxylate (45.00 g) in DCM (300 mL) was added HCl (150 mL) dropwise at 0 degrees C under nitrogen atmosphere. The mixture was stirred at 0 degrees C for 1 h. The resulting mixture was concentrated under reduced pressure to afford 30g crude product, which was used to the next step without further purification.

LC-MS: $(M+H)^+$ found: 214.



A mixture of 4-chloro-2-methylpyrimidine (20.00 g, 156.2 mmol, 1.00 equiv), tributyl(1-ethoxyvinyl)stannane (45.82 g, 468 mmol, 3.00 equiv) and $Pd(PPh_3)_2Cl_2$ (8.86 g, 15.6 mmol, 0.10 equiv) in DMF (200.00 mL) was stirred for 12 h at 100 degrees C. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford 4-(1-ethoxyvinyl)-2-methylpyrimidine 17 g (66%) as a yellow oil.

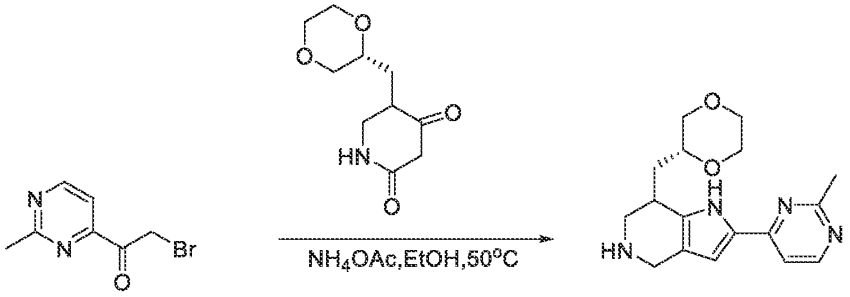
LC-MS: M+H found: 165.0.



A mixture of 4-(1-ethoxyvinyl)-2-methylpyrimidine (17.00 g, 103.0 mmol, 1.00 equiv), NBS (30.13 g, 133.9 mmol, 1.30 equiv) and H_2O (15 mL) in THF (150 mL) was stirred for 1 h at room temperature. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 2-bromo-1-(2-

methylpyrimidin-4-yl) ethan-1-one 18 g crude as a brown oil.

LC-MS: $(M+H)^+$ found: 215.



A mixture of 5-(((*R*)-1,4-dioxan-2-yl)methyl)piperidine-2,4-dione (14g, 83 mmol, 1.0 equiv), 2-bromo-1-(2-methylpyrimidin-4-yl)ethan-1-one (18g,107mmol, 1.3 equiv),and NH_4OAc (50.3g, 830 mmol, 10 equiv) in EtOH (150.0 mL) was stirred at 50 degrees C for 3 h. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH (10:1)) to afford 7-(((*R*)-1,4-dioxan-2-yl)methyl)-2-(2-methylpyrimidin-4-yl)-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-c]pyridine (9g, 57%) as a yellow solid.

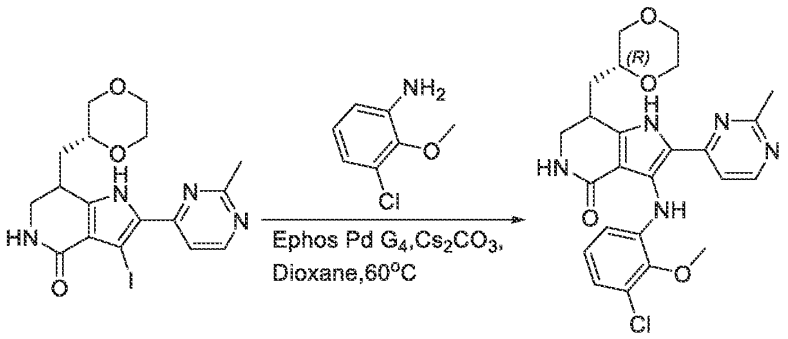
LC-MS: $(M+H)^+$ found 329.



To a stirred mixture of 7-(((*R*)-1,4-dioxan-2-yl)methyl)-2-(2-methylpyrimidin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-c]pyridin-4-one (17g, 51.6 mmol, 1.00 equiv) in DMF (150 mL) was added NIS (15.1 g, 67.8 mmol, 1.3 equiv) at 0 degrees C. The mixture was stirred at room temperature for 2 h. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine

(3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH (20:1)) to afford 7-(((*R*)-1,4-dioxan-2-yl)methyl)-3-iodo-2-(2-methylpyrimidin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-c]pyridin-4-one (16 g, 53%) as yellow solid.

LC-MS: $(M+H)^+$ found: 455.



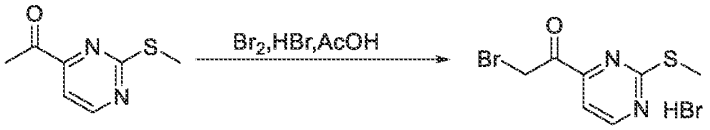
A mixture of 7-[(2*R*)-1,4-dioxan-2-ylmethyl]-3-iodo-2-(2-methylpyrimidin-4-yl)-1*H*,5*H*,6*H*,7*H*-pyrrolo[3,2-c]pyridin-4-one (7 g, 15.409 mmol, 1 equiv)Cs_2CO_3 (10.04 g, 30.818 mmol, 2 equiv) ,3-chloro-2-methoxyaniline (3.16 g, 20.032 mmol, 1.3 equiv) and EPhos Pd G4 (2.12 g, 2.311 mmol, 0.15 equiv) in DMF was stirred for 3 h at 60 °C under nitrogen atmosphere. The reaction was quenched with Water at room temperature.The resulting mixture was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with water (2x200 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (5 g) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: MeOH----Preparative; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5;) to afford (7*R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2*R*)-1,4-dioxan-2-ylmethyl]-2-(2-methylpyrimidin-4-yl)-1*H*,5*H*,6*H*,7*H*-pyrrolo[3,2-c]pyridin-4-one (peak2, 1.5814 g, 21.21%) as an orange solid

LC-MS: $(M+H)^+$ found: 484.

^1H NMR (400 MHz, Chloroform-*d*) δ 11.41 – 11.26 (m, 1H), 8.40 – 8.29 (m, 1H), 7.62 – 7.55 (m, 1H), 6.85 – 6.68 (m, 3H), 6.37 – 6.29 (m, 1H), 5.61 – 5.52 (m, 1H), 4.25 – 4.14

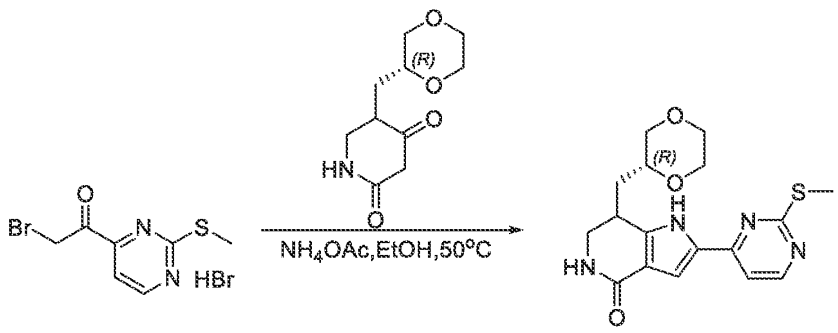
(m, 1H), 4.12 – 4.05 (m, 3H), 4.05 – 3.73 (m, 5H), 3.50 – 3.35 (m, 4H), 2.78 – 2.66 (m, 3H), 1.90 – 1.77 (m, 1H), 1.63 – 1.52 (m, 1H).

Example 112. (7R)-7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 569)**



To a stirred mixture of 1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone (20 g, 118.899 mmol, 1 equiv.) and HBr (20.00 mL, 684.858 mmol, 5.76 equiv.) in AcOH (60 mL) was added Br2 (24.70 g, 154.569 mmol, 1.3 equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 60 °C. Desired product could be detected by LCMS. The precipitated solids were collected by filtration and washed with ethyl acetate (3x20 mL). This resulted in 2-bromo-1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone hydrobromide (28 g, 71.79%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 246.95.



To a stirred solution of 5-[(2R)-1,4-dioxan-2-ylmethyl]piperidine-2,4-dione (3.2 g, 15.007 mmol, 1 equiv.) in EtOH (30 mL) were added 2-bromo-1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone hydrobromide (5.91 g, 18.008 mmol, 1.2 equiv.) and NH_4OAc (11.57 g, 150.070 mmol, 10 equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 60 °C. Desired product could be detected by LCMS. The aqueous layer was extracted with CH_2Cl_2 (3x100 mL). The resulting mixture was

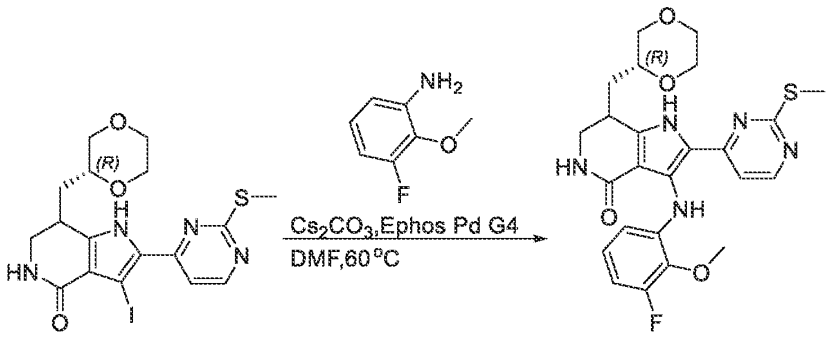
concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (25:1) to afford 7-[(2R)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (2 g, 36.98%) as a brown solid.

LC-MS: $(M+H)^+$ found: 361.30.



To a stirred solution of 7-[(2R)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (2 g, 5.549 mmol, 1 equiv.) in DMF (20 mL) was added NIS (1.50 g, 6.659 mmol, 1.2 equiv.) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature. Desired product could be detected by LCMS. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was washed with 2x50 mL of water. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (30:1) to afford 7-[(2R)-1,4-dioxan-2-ylmethyl]-3-iodo-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.65 g, 61.14%) as a light yellow solid.

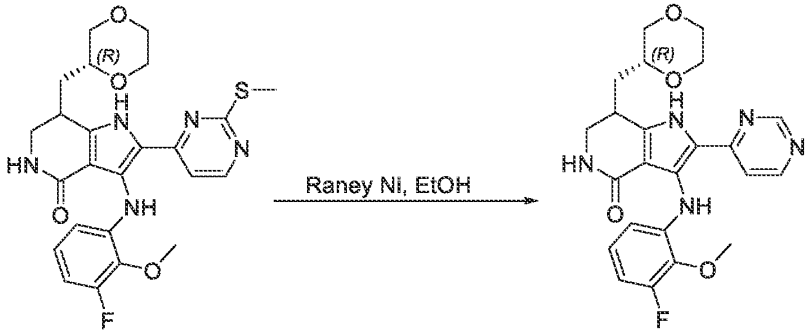
LC-MS: $(M+H)^+$ found: 487.15.



To a stirred mixture of 7-[(2R)-1,4-dioxan-2-ylmethyl]-3-iodo-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.1 g, 2.262

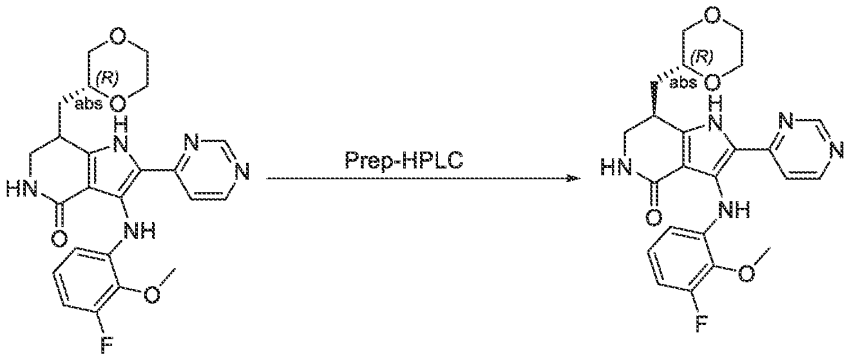
mmol, 1 equiv.) and 3-fluoro-2-methoxyaniline (0.96 g, 6.786 mmol, 3 equiv.) in DMF (15 mL) were added Cs2CO3 (2.21 g, 6.786 mmol, 3 equiv.) and Ephos Pd G4 (0.21 g, 0.226 mmol, 0.1 equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at 50 °C. Desired product could be detected by LCMS. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 45% to 70% gradient in 10 min; detector, UV 254 nm. This resulted in 7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (810 mg, 71.69%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 500.10



To a stirred solution of (7S)-7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one, 1 equiv.) in EtOH (30 mL) was added Raney-Ni (2.78 g, 32.420 mmol, 20 equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 24 h at 90°C. Desired product could be detected by LCMS. The resulting mixture was filtered, the filter cake was washed with EtOH (3x30 mL). The filtrate was concentrated under reduced pressure. This resulted in 7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (600 mg, 81.59%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 454.15.

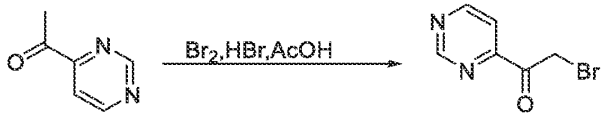


The crude product (600 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 37% B in 10 min, 37% B; Wave Length: 254/220 nm; RT1(min): 7 10) to afford (7R)-7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (169.8 mg, 26.29%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 454.10.

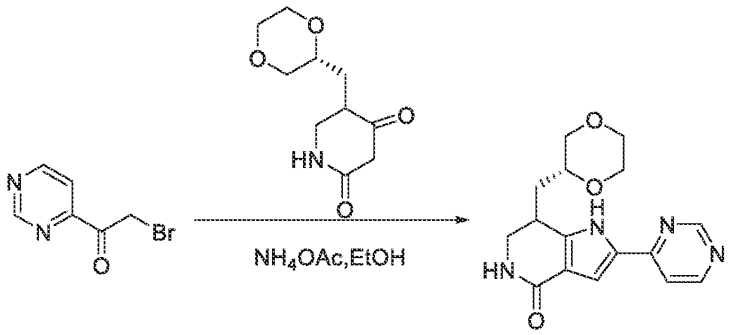
^{1}H NMR (300 MHz, Chloroform-*d*) δ 11.29 (s, 1H), 8.72 (d, *J* = 179.0 Hz, 2H), 7.51 (s, 1H), 7.14 – 6.92 (m, 1H), 6.68 (q, *J* = 7.5 Hz, 1H), 6.61 – 6.43 (m, 1H), 6.17 (d, *J* = 8.0 Hz, 1H), 5.58 (s, 1H), 4.12 (d, *J* = 12.4 Hz, 4H), 4.01 – 3.73 (m, 5H), 3.50 – 3.25 (m, 4H), 1.83 – 1.77 (m, 1H), 1.54 (d, *J* = 14.7 Hz, 1H).

Example 113. (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 568)**



To a stirred solution of 1-(pyrimidin-4-yl)ethanone (1 g, 8.188 mmol, 1.00 equiv) and HBr (1.45 mL, 49.640 mmol, 6.06 equiv) in AcOH (3 mL) was added Br2 (1 g, 6.258 mmol, 0.76 equiv) dropwise at room temperature .Then the mixture was stirred at 60 degree for 3h. After the reaction was completed ,the mixture was diluted with ethyl acetate. The solution was stirred for overnight. The solid was filtrated and dried to get 2-bromo-1-(pyrimidin-4-yl)ethanone (1.3 g, 78.98%) brown solid as product.

LC-MS: $(M+H)^+$ found: 200.95.



A solution of 2-bromo-1-(pyrimidin-4-yl)ethanone hydrobromide (3 g, 10.641 mmol, 1 equiv) in EtOH (50 mL) was treated with 5-[(2R)-1,4-dioxan-2-ylmethyl]piperidine-2,4-dione (2.27 g, 10.641 mmol, 1 equiv) for 2 min at room temperature under nitrogen atmosphere followed by the addition of NH4OAc (8.20 g, 106.410 mmol, 10 equiv) in portions at room temperature. The resulting mixture was stirred for 2 h at 60°C under nitrogen atmosphere. The resulting mixture was extracted with EtOAc (8 x 100 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (10:1) to afford 7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.5 g, 44.84%) as a yellow solid.

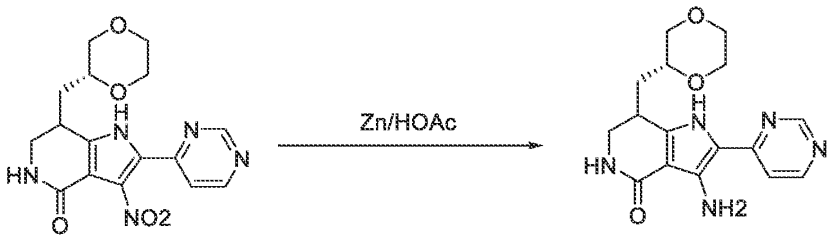
LC-MS: $(M+H)^+$ found: 315.10.



A solution of 7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (700 mg, 2.227 mmol, 1 equiv) in H2SO4 (10 mL) was treated with Nitric acid fuming (140.32 mg, 2.227 mmol, 1 equiv) for 2 min at -5°C under nitrogen

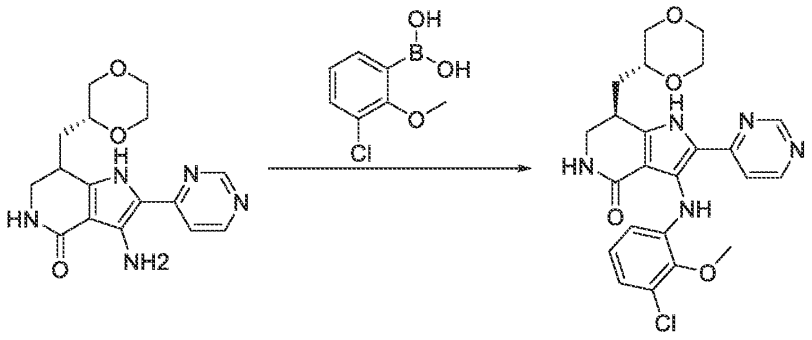
atmosphere. The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere. The resulting mixture was diluted with water (40 mL). The mixture was basified to pH 9 with NaOH(aq.). The resulting mixture was extracted with CH2Cl2 (5 x 50 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 7-[(2R)-1,4-dioxan-2-ylmethyl]-3-nitro-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (800 mg, 99.97%) as a Brown yellow solid.

LC-MS: $(M+H)^+$ found: 360.25.



A solution of 7-[(2R)-1,4-dioxan-2-ylmethyl]-3-nitro-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (800 mg, 2.226 mmol, 1 equiv) in HOAc (10 mL) was treated with Zn (728.10 mg, 11.130 mmol, 5 equiv) for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water (30 mL). The mixture was basified to pH 8 with NaOH(aq.). The resulting mixture was extracted with CH2Cl2 (5 x 300 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 3-amino-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (500 mg, 68.19%) as a yellow solid.

LC-MS: (M+H)+ found: 330.30.



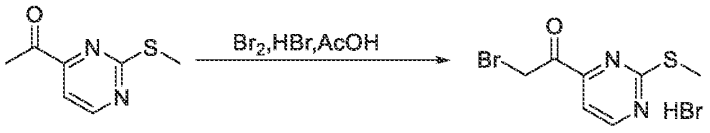
A solution of 3-amino-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (500 mg, 1.518 mmol, 1 equiv) and 3-chloro-2-methoxyphenylboronic acid (565.95 mg, 3.036 mmol, 2 equiv) in DCM (10 mL) was treated with Pyridine (240.16 mg, 3.036 mmol, 2 equiv) and TEA (307.23 mg, 3.036 mmol, 2 equiv) for 2 min at 0 °C under nitrogen atmosphere followed by the addition of Cu(OAc)2 (275.74 mg, 1.518 mmol, 1 equiv) in portions at room temperature. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The resulting mixture was extracted with CH2Cl2 (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions:Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 50% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5. This resulted in (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (8.8 mg) as a yellow solid.

LC-MS: $(M+H)^+$ found: 470.35.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.04 (s, 1H), 9.04 (d, J = 1.4 Hz, 1H), 8.56 (d, J = 5.6 Hz, 1H), 8.06 (s, 1H), 7.26 – 7.16 (m, 2H), 6.87 – 6.76 (m, 2H), 6.34 (dd, J = 7.0, 2.7 Hz, 1H), 3.93 (s, 3H), 3.86 – 3.56 (m, 5H), 3.50 (td, J = 10.6, 10.1, 3.6 Hz, 2H), 3.29 – 3.14 (m, 3H), 1.84 (ddd, J = 14.3, 9.2, 5.3 Hz, 1H), 1.65 – 1.54 (m, 1H).

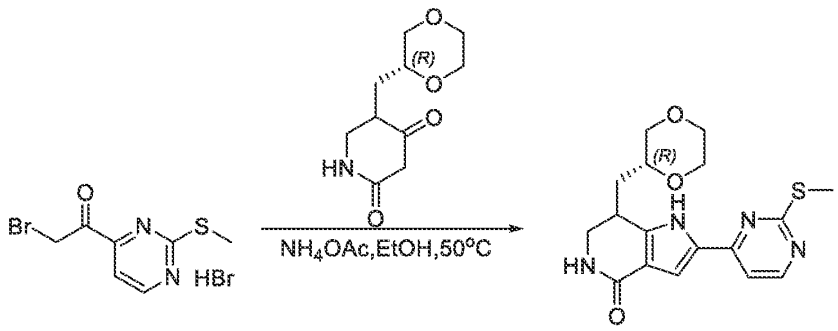
Example 114. (7R)-2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound**

567)



To a stirred mixture of 1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone (20 g, 118.899 mmol, 1 equiv.) and HBr (20.00 mL, 684.858 mmol, 5.76 equiv.) in AcOH (60 mL) was added Br2 (24.70 g, 154.569 mmol, 1.3 equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 60 °C. Desired product could be detected by LCMS. The precipitated solids were collected by filtration and washed with ethyl acetate (3x20 mL). This resulted in 2-bromo-1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone hydrobromide (28 g, 71.79%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 246.95.



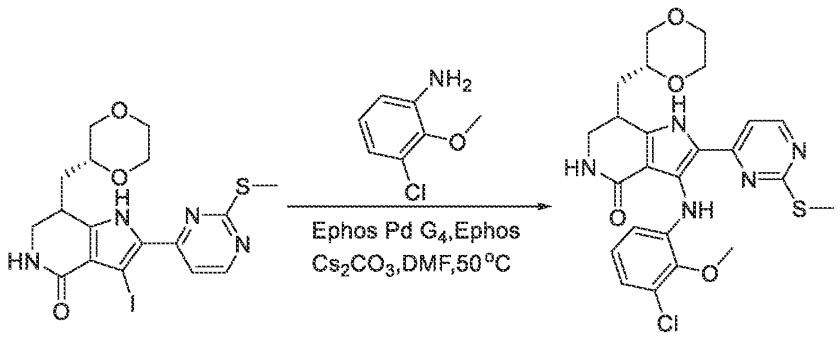
To a stirred solution of 5-[(2R)-1,4-dioxan-2-ylmethyl]piperidine-2,4-dione (3.2 g, 15.007 mmol, 1 equiv.) in EtOH (30 mL) were added 2-bromo-1-[2-(methylsulfanyl)pyrimidin-4-yl]ethanone hydrobromide (5.91 g, 18.008 mmol, 1.2 equiv.) and NH_4OAc (11.57 g, 150.070 mmol, 10 equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 60 °C. Desired product could be detected by LCMS. The aqueous layer was extracted with CH_2Cl_2 (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (25:1) to afford 7-[(2R)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (2 g, 36.98%) as a brown solid.

LC-MS: $(M+H)^+$ found: 361.30.



To a stirred solution of 7-[(2R)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (2 g, 5.549 mmol, 1 equiv.) in DMF (20 mL) was added NIS (1.50 g, 6.659 mmol, 1.2 equiv.) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature. Desired product could be detected by LCMS. The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was washed with 2x50 mL of water. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (30:1) to afford 7-[(2R)-1,4-dioxan-2-ylmethyl]-3-iodo-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.65 g, 61.14%) as a light yellow solid.

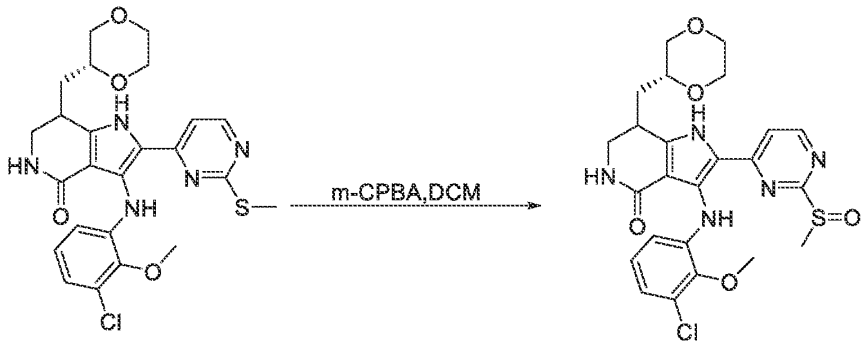
LC-MS: $(M+H)^+$ found: 487.15.



To a stirred mixture of 7-[(2R)-1,4-dioxan-2-ylmethyl]-3-iodo-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.5 g, 3.084 mmol, 1 equiv.) and 3-chloro-2-methoxyaniline (1.46 g, 9.252 mmol, 3 equiv.) in DMF (20 mL) were added Cs_2CO_3 (3.01 g, 9.252 mmol, 3 equiv.) and Ephos Pd G4 (0.28 g, 0.308 mmol, 0.1 equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 50 °C. Desired product could be detected by LCMS. The

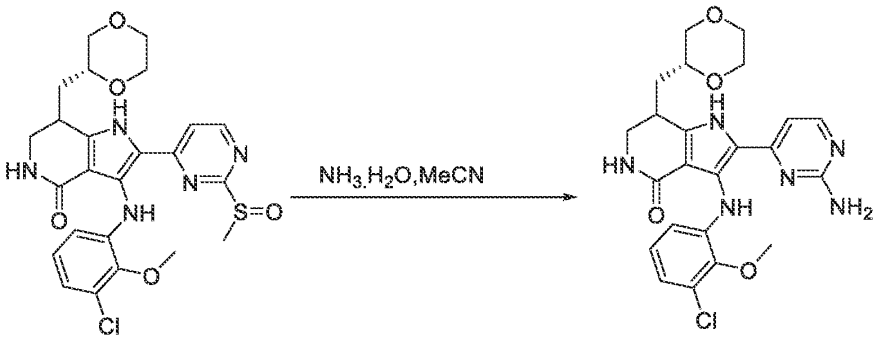
residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 40% to 60% gradient in 10 min; detector, UV 254 nm. This resulted in 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1 g, 62.83%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 516.30.



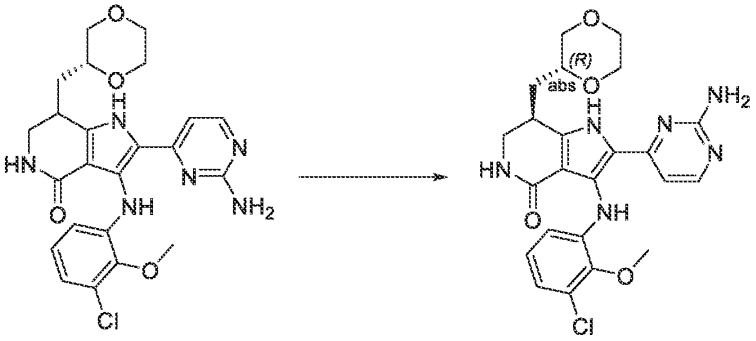
To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (350 mg, 0.678 mmol, 1 equiv.) in DCM (5 mL) was added m-CPBA (234.10 mg, 1.356 mmol, 2 equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 10 min at room temperature. Desired product could be detected by LCMS. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was washed with 3x10 mL of sat.$NaHCO_3$. The resulting mixture was concentrated under reduced pressure. This resulted in 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (370 mg, 92.28%) as a reddish solid.

LC-MS: $(M+H)^+$ found: 532.45.



To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (370 mg, 0.626 mmol, 1 equiv, 90%) in ACN (4 mL) was added NH3.H2O (2 mL, 15.408 mmol, 24.62 equiv, 30%) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80 °C. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. This resulted in 150 mg crude product.

LC-MS: $(M+H)^+$ found: 485.2.

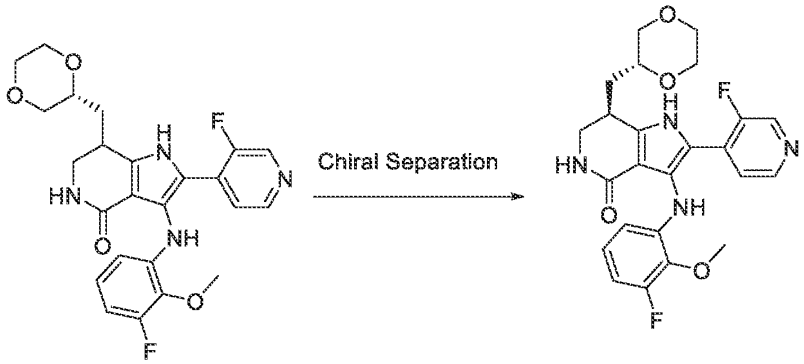


The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 35% B in 10 min, 35% B; Wave Length: 254/220 nm; RT1(min): 9.92) to afford (7R)-2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (27.9 mg, 18.40%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 485.2

^{1}H NMR (300 MHz, Chloroform-d) δ 10.97 (s, 1H), 7.95 – 7.77 (m, 2H), 6.87 – 6.68 (m, 2H), 6.40 (t, J = 6.3 Hz, 2H), 5.77 (s, 2H), 5.33 (s, 1H), 4.05 (s, 3H), 4.03 – 3.67 (m, 6H), 3.42 (dt, J = 20.4, 8.6 Hz, 4H), 1.57 (d, J = 14.7 Hz, 1H), 1.26 (s, 1H).

Example 115. (7R)-7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 566)**

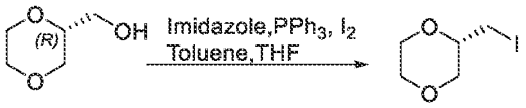


The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford (7R)-7-[(2R)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (257.2 mg) as a white solid.

LCMS: $[M+H]^+$ found: 471.

^{1}H NMR (300 MHz, Chloroform-d) δ 11.06 (s, 1H), 8.44 (d, J = 4.7 Hz, 1H), 8.12 (d, J = 5.6 Hz, 1H), 7.74 (s, 1H), 7.48 – 7.37 (m, 1H), 6.69 – 6.48 (m, 2H), 6.11 – 6.03 (m, 1H), 5.30 (s, 1H), 4.11 (d, J = 1.5 Hz, 4H), 3.95 – 3.69 (m, 5H), 3.51 – 3.21 (m, 4H), 1.83 – 1.72 (m, 1H), 1.52 (d, J = 14.8 Hz, 1H).

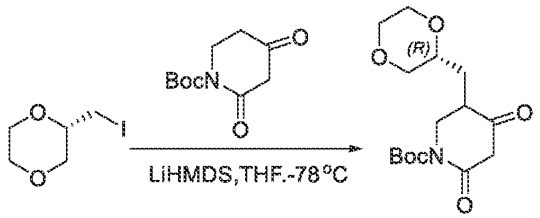
Example 116. (*R*)-7-(((*R*)-1,4-dioxan-2-yl)methyl)-3-((3-fluoro-2-methoxyphenyl)amino)-2-(2-methylpyrimidin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-c]pyridin-4-one **(compound 605)**



To a suspension of (R)-(1,4-dioxan-2-yl)methanol (100.00 g, 0.847 mol, 1.00 equiv) in Tolune (1000 mL) and THF (500 mL) was added imidazole(115.2 g, 1.69 mol, 2.00 equiv), PPh_3(214.4 g, 0.847 mol, 1.00 equiv) at room temperature ,I_2(214.4 g, 0.847 mol, 1.00 equiv) was added at 0 degrees C. The mixture was stirred for 3 h at room temperature under nitrogen atmosphere.

Desired product could be detected by LCMS. The resulting solution was quenching with 500 ml of $Na_2S_2O_3$ saturated solution. The aqueous layer was extracted with EtOAc (3 x 250 mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified on silica (EtOAc/PE=1:6) to provide 130 g (67%) of the title compound as a colorless oil.

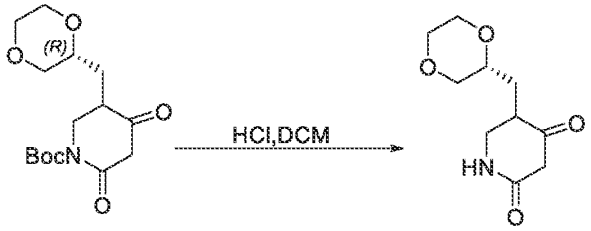
LC-MS: $(M+H)^+$ found: 229.



To a suspension of (S)-2-(iodomethyl)-1,4-dioxane (104.00 g, 0.457 mol, 1.40 equiv) and tert-butyl 2,4-dioxopiperidine-1-carboxylate (70.00 g, 0.327 mol, 1.00 equiv) in THF (1000 mL) was dropwise added LiHMDS (1.37 L, 1.37 mol, 3.00 equiv) at -60°C. The mixture was stirred for 1 h at 0 degrees under nitrogen atmosphere.

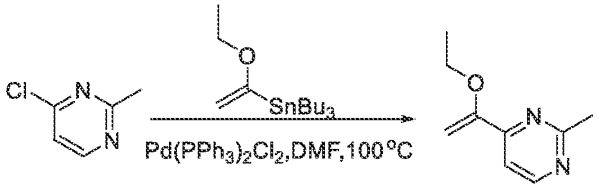
Desired product could be detected by LCMS. The resulting solution was quenching with 500 ml of HCl (5%) at 0 degrees. The aqueous layer was extracted with EtOAc (3 x 250 mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column (PE /EtOAc, 1:1) to provide 45 g (46%) of the title compound as a light brown oil.

LC-MS: $(M+H)^+$ found: 314.



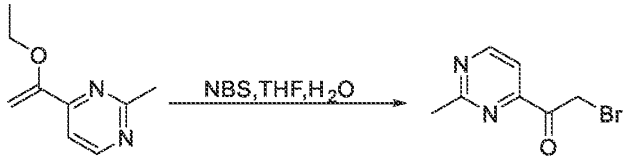
To a stirred mixture of tert-butyl 5-(((R)-1,4-dioxan-2-yl)methyl)-2,4-dioxopiperidine-1-carboxylate (45.00 g) in DCM (300 mL) was added HCl (150 mL) dropwise at 0 degrees C under nitrogen atmosphere. The mixture was stirred at 0 degrees C for 1 h. The resulting mixture was concentrated under reduced pressure to afford 30g crude product, which was used to the next step without further purification.

LC-MS: $(M+H)^+$ found: 214.



A mixture of 4-chloro-2-methylpyrimidine (20.00 g, 156.2 mmol, 1.00 equiv), tributyl(1-ethoxyvinyl)stannane (45.82 g, 468 mmol, 3.00 equiv) and $Pd(PPh_3)_2Cl_2$ (8.86 g, 15.6 mmol, 0.10 equiv) in DMF (200.00 mL) was stirred for 12 h at 100 degrees C. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford 4-(1-ethoxyvinyl)-2-methylpyrimidine 17 g (66%) as a yellow oil.

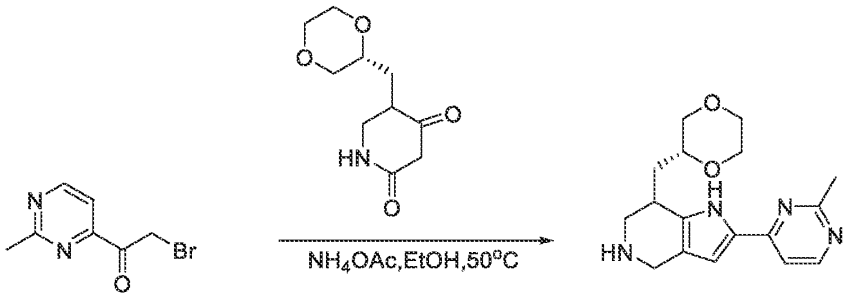
LC-MS: M+H found: 165.0.



A mixture of 4-(1-ethoxyvinyl)-2-methylpyrimidine (17.00 g, 103.0 mmol, 1.00 equiv), NBS (30.13 g, 133.9 mmol, 1.30 equiv) and H_2O (15 mL) in THF (150 mL) was stirred for 1 h at room temperature. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the

filtrate was concentrated under reduced pressure. This resulted in 2-bromo-1-(2-methylpyrimidin-4-yl) ethan-1-one 18 g crude as a brown oil.

LC-MS: $(M+H)^+$ found: 215.



A mixture of 5-(((*R*)-1,4-dioxan-2-yl)methyl)piperidine-2,4-dione (14g, 83 mmol, 1.0 equiv), 2-bromo-1-(2-methylpyrimidin-4-yl)ethan-1-one (18g,107mmol, 1.3 equiv),and NH_4OAc (50.3g, 830 mmol, 10 equiv) in EtOH (150.0 mL) was stirred at 50 degrees C for 3 h. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH (10:1)) to afford 7-(((*R*)-1,4-dioxan-2-yl)methyl)-2-(2-methylpyrimidin-4-yl)-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-c]pyridine (9g, 57%) as a yellow solid.

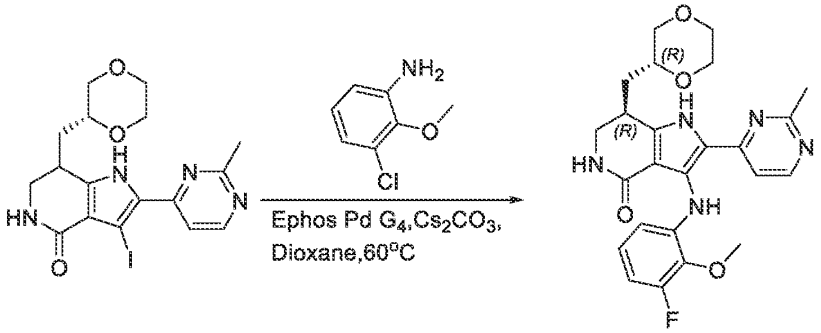
LC-MS: $(M+H)^+$ found: 329.



To a stirred mixture of 7-(((*R*)-1,4-dioxan-2-yl)methyl)-2-(2-methylpyrimidin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-c]pyridin-4-one (17g, 51.6 mmol, 1.00 equiv) in DMF (150 mL) was added NIS (15.1 g, 67.8 mmol, 1.3 equiv) at 0 degrees C. The mixture was stirred at room temperature for 2 h. The reaction was quenched with Water at room temperature. The resulting mixture was

extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH (20:1)) to afford 7-(((*R*)-1,4-dioxan-2-yl)methyl)-3-iodo-2-(2-methylpyrimidin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-c]pyridin-4-one (16 g, 53%) as yellow solid.

LC-MS: $(M+H)^+$ found: 455.

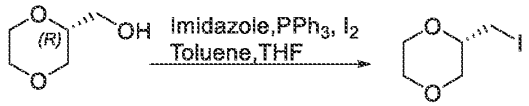


A mixture of 7-[(2*R*)-1,4-dioxan-2-ylmethyl]-3-iodo-2-(2-methylpyrimidin-4-yl)-1*H*,5*H*,6*H*,7*H*-pyrrolo[3,2-c]pyridin-4-one (10 g, 22.013 mmol, 1 equiv),Cs_2CO_3 (10.04 g, 30.818 mmol, 2 equiv) ,3-fluoro-2-methoxyaniline (4.04 g, 28.617 mmol, 1.3 equiv) and EPhos Pd G4 (2.02 g, 2.201 mmol, 0.1 equiv) in DMF was stirred for overnight at 60 °C under nitrogen atmosphere. The reaction was quenched with Water at room temperature.The resulting mixture was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with water (2x200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.The crude product (9 g) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 53% B in 8 min, 53% B; Wave Length: 220/254 nm; RT1(min): 8.02) to afford (*R*)-7-(((*R*)-1,4-dioxan-2-yl)methyl)-3-((3-fluoro-2-methoxyphenyl)amino)-2-(2-methylpyrimidin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-c]pyridin-4-one (1.2586 g, 11.86%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 468.

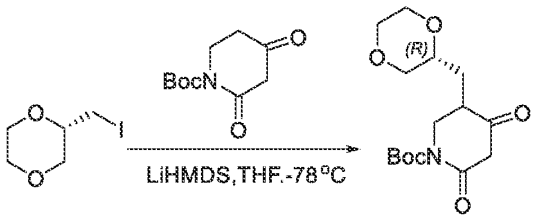
^{1}H NMR (400 MHz, Chloroform-d) δ 11.42 – 11.20 (m, 1H), 8.43 – 8.25 (m, 1H), 7.69 – 7.56 (m, 1H), 6.93 – 6.81 (m, 1H), 6.78 – 6.68 (m, 1H), 6.61 – 6.54 (m, 1H), 6.26 – 6.16 (m, 1H), 5.51 – 5.37 (m, 1H), 4.22 – 3.78 (m, 9H), 3.50 – 3.34 (m, 4H), 2.78 – 2.68 (m, 3H), 1.89 – 1.78 (m, 1H), 1.63 – 1.53 (m, 1H).

Example 117. (7*S*)-7-[(2*R*)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(2-methylpyrimidin-4-yl)-1*H*,5*H*,6*H*,7*H*-pyrrolo[3,2-c]pyridin-4-one **(compound 604)**



To a suspension of (R)-(1,4-dioxan-2-yl)methanol (100.00 g, 0.847 mol, 1.00 equiv) in Tolune (1000 mL) and THF (500 mL) was added imidazole(115.2 g, 1.69 mol, 2.00 equiv), PPh_3(214.4 g, 0.847 mol, 1.00 equiv) at room temperature ,I_2(214.4 g, 0.847 mol, 1.00 equiv) was added at 0 degrees C. The mixture was stirred for 3 h at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting solution was quenching with 500 ml of $Na_2S_2O_3$ saturated solution. The aqueous layer was extracted with EtOAc (3 x 250 mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified on silica (EtOAc/PE=1:6) to provide 130 g (67%) of the title compound as a colorless oil.

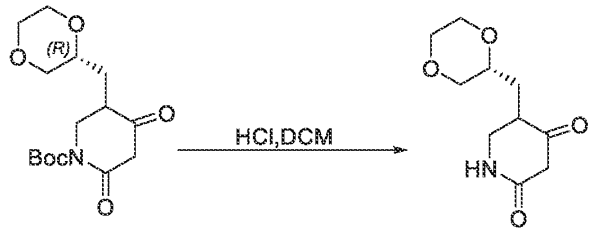
LC-MS: $(M+H)^+$ found: 229.



To a suspension of (S)-2-(iodomethyl)-1,4-dioxane (104.00 g, 0.457 mol, 1.40 equiv) and tert-butyl 2,4-dioxopiperidine-1-carboxylate (70.00 g, 0.327 mol, 1.00 equiv) in THF (1000 mL) was dropwise added LiHMDS (1.37 L, 1.37 mol, 3.00 equiv) at -60°C. The mixture was stirred for 1 h at 0 degrees under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting solution was quenching with 500 ml of HCl (5%) at 0 degrees. The aqueous layer was extracted with EtOAc (3 x 250

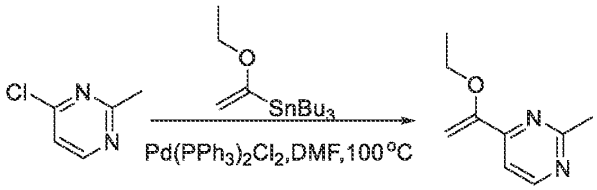
mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column (PE /EtOAc, 1:1) to provide 45 g (46%) of the title compound as a light brown oil.

LC-MS: $(M+H)^+$ found: 314.



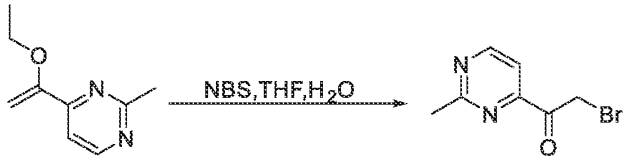
To a stirred mixture of tert-butyl 5-(((R)-1,4-dioxan-2-yl)methyl)-2,4-dioxopiperidine-1-carboxylate (45.00 g) in DCM (300 mL) was added HCl (150 mL) dropwise at 0 degrees C under nitrogen atmosphere. The mixture was stirred at 0 degrees C for 1 h. The resulting mixture was concentrated under reduced pressure to afford 30g crude product, which was used to the next step without further purification.

LC-MS: $(M+H)^+$ found: 214.



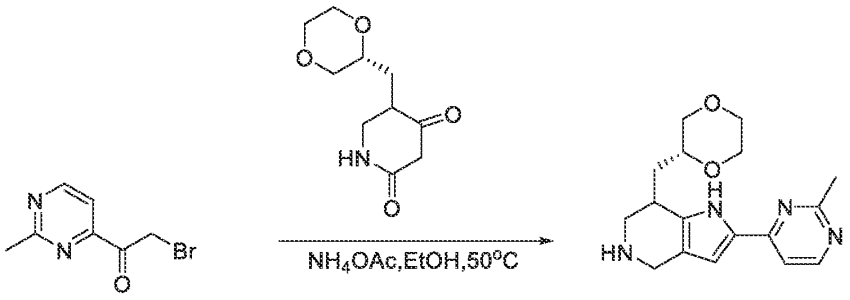
A mixture of 4-chloro-2-methylpyrimidine (20.00 g, 156.2 mmol, 1.00 equiv), tributyl(1-ethoxyvinyl)stannane (45.82 g, 468 mmol, 3.00 equiv) and $Pd(PPh_3)_2Cl_2$ (8.86 g, 15.6 mmol, 0.10 equiv) in DMF (200.00 mL) was stirred for 12 h at 100 degrees C. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford 4-(1-ethoxyvinyl)-2-methylpyrimidine 17 g (66%) as a yellow oil.

LC-MS: M+H found: 165.0.



A mixture of 4-(1-ethoxyvinyl)-2-methylpyrimidine (17.00 g, 103.0 mmol, 1.00 equiv), NBS (30.13 g, 133.9 mmol, 1.30 equiv) and H_2O (15 mL) in THF (150 mL) was stirred for 1 h at room temperature. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 2-bromo-1-(2-methylpyrimidin-4-yl) ethan-1-one 18 g crude as a brown oil.

LC-MS: $(M+H)^+$ found: 215.



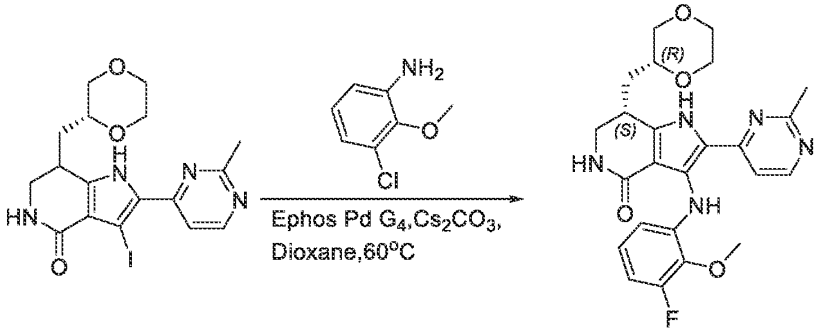
A mixture of 5-(((R)-1,4-dioxan-2-yl)methyl)piperidine-2,4-dione (14g, 83 mmol, 1.0 equiv), 2-bromo-1-(2-methylpyrimidin-4-yl)ethan-1-one (18g,107mmol, 1.3 equiv), and NH_4OAc (50.3g, 830 mmol, 10 equiv) in EtOH (150.0 mL) was stirred at 50 degrees C for 3 h. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH (10:1)) to afford 7-(((*R*)-1,4-dioxan-2-yl)methyl)-2-(2-methylpyrimidin-4-yl)-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-c]pyridine (9g, 57%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 329.



To a stirred mixture of 7-(((*R*)-1,4-dioxan-2-yl)methyl)-2-(2-methylpyrimidin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-c]pyridin-4-one (17g, 51.6 mmol, 1.00 equiv) in DMF (150 mL) was added NIS (15.1 g, 67.8 mmol, 1.3 equiv) at 0 degrees C. The mixture was stirred at room temperature for 2 h. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH (20:1)) to afford 7-(((*R*)-1,4-dioxan-2-yl)methyl)-3-iodo-2-(2-methylpyrimidin-4-yl)-1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-c]pyridin-4-one (16 g, 53%) as yellow solid.

LC-MS: $(M+H)^+$ found: 455.



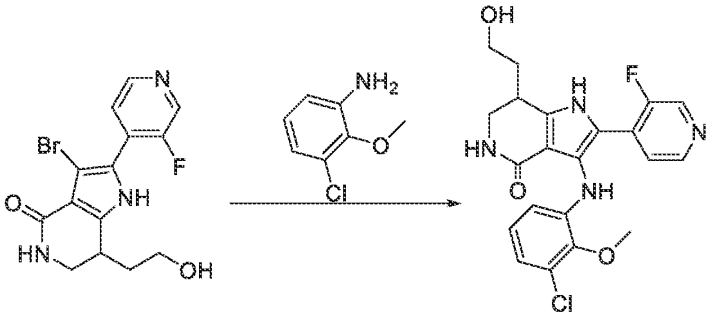
A mixture of 7-[(2*R*)-1,4-dioxan-2-ylmethyl]-3-iodo-2-(2-methylpyrimidin-4-yl)-1*H*,5*H*,6*H*,7*H*-pyrrolo[3,2-c]pyridin-4-one (10 g, 22.013 mmol, 1 equiv),Cs_2CO_3 (10.04 g, 30.818 mmol, 2 equiv) ,3-fluoro-2-methoxyaniline (4.04 g, 28.617 mmol, 1.3 equiv) and EPhos Pd G4 (2.02 g, 2.201 mmol, 0.1 equiv) in DMF was stirred for overnight at 60 °C under nitrogen atmosphere. The reaction was quenched with Water at room temperature.The resulting mixture was extracted with EtOAc (2 x 200 mL). The combined

organic layers were washed with water (2x200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.The crude product (9 g) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 53% B in 8 min, 53% B; Wave Length: 220/254 nm; RT1(min): 8.02) to afford (7*S*)-7-[(2*R*)-1,4-dioxan-2-ylmethyl]-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(2-methylpyrimidin-4-yl)-1*H*,5*H*,6*H*,7*H*-pyrrolo[3,2-c]pyridin-4-one (1.5675 g, 15.00%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 468.

^{1}H NMR (400 MHz, Chloroform-d) δ 11.42 – 11.20 (m, 1H), 8.43 – 8.25 (m, 1H), 7.69 – 7.56 (m, 1H), 6.93 – 6.81 (m, 1H), 6.78 – 6.68 (m, 1H), 6.61 – 6.54 (m, 1H), 6.26 – 6.16 (m, 1H), 5.51 – 5.37 (m, 1H), 4.22 – 3.78 (m, 9H), 3.50 – 3.34 (m, 4H), 2.78 – 2.68 (m, 3H), 1.89 – 1.78 (m, 1H), 1.63 – 1.53 (m, 1H).

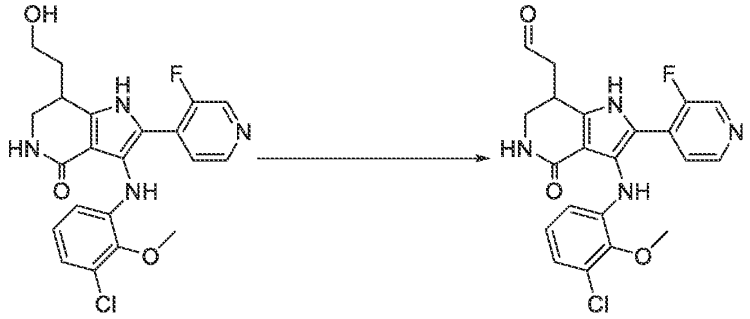
Example 118. (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-hydroxy-2-methylpropyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 496)**



A solution of 3-bromo-2-(3-fluoropyridin-4-yl)-7-(2-hydroxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (460 mg, 1.299 mmol, 1.00 equiv) in DMF (10 mL) was treated with 3-chloro-2-methoxyaniline (225.16 mg, 1.429 mmol, 1.1 equiv) and Cs2CO3 (1269.50 mg, 3.897 mmol, 3 equiv) for 2 min at room temperature under nitrogen atmosphere followed by the addition of EPhos (104.19 mg, 0.195 mmol, 0.15 equiv) and EPhos Pd G4 (178.95 mg, 0.195 mmol, 0.15 equiv) in portions at room temperature. The resulting mixture was stirred for 2 h at 120 degrees C under nitrogen atmosphere. The resulting mixture was extracted with CH2Cl2 (3 x 50 mL). The combined organic layers

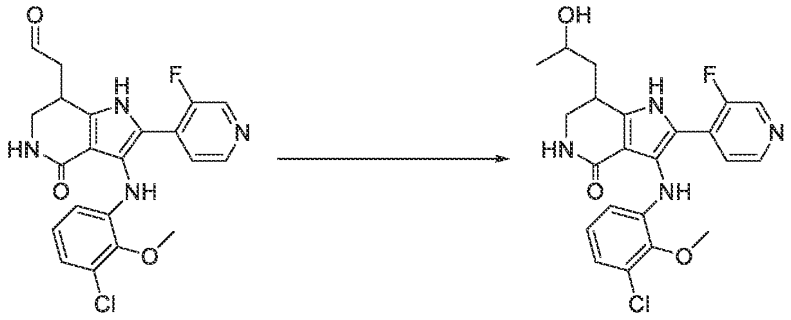
were washed with brine (2 x 30 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-hydroxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (170 mg, 30.38%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 431.30.



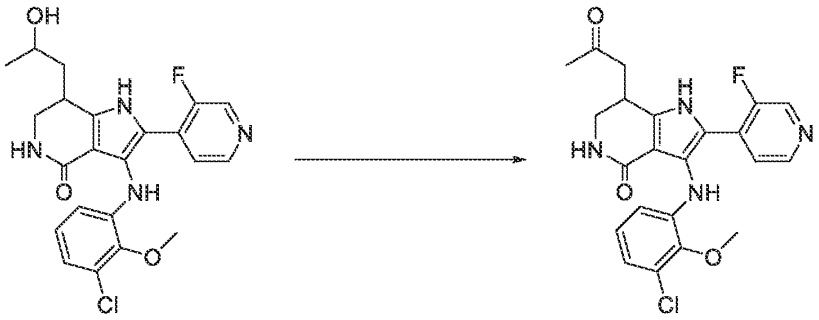
A solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-hydroxyethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (700 mg, 1.625 mmol, 1 equiv) in DCM (10 mL) was treated with Dess-Martin (826.90 mg, 1.950 mmol, 1.2 equiv) for 2 min at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The resulting mixture was extracted with CH2Cl2 (3 x 50 mL). The combined organic layers were washed with NaHCO3 (aq.). (2 x 10 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (10:1) to afford 2-{3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-7-yl}acetaldehyde (400 mg, 57.41%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 429.00.



A solution of 2-{3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-7-yl}acetaldehyde (400 mg, 0.933 mmol, 1 equiv) in THF (10 mL) was treated with MeMgBr (222.44 mg, 1.866 mmol, 2 equiv) for 2 h at -5 °C under nitrogen atmosphere. The resulting mixture was diluted with EtOAc (10 mL). The reaction was quenched by the addition of sat. NH4Cl (aq.) (20 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / PE (1:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-hydroxypropyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (170 mg, 40.97%) as a yellow solid.

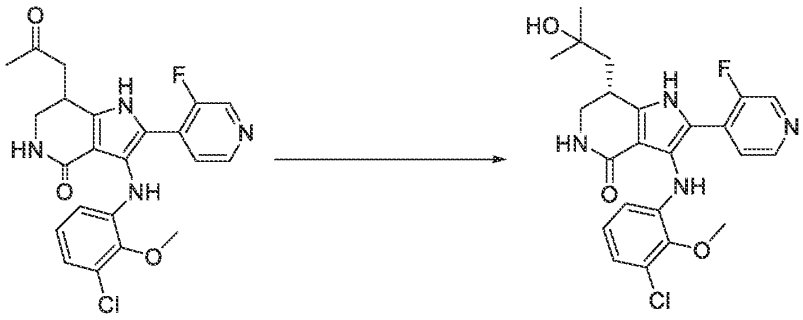
LC-MS: $(M+H)^+$ found: 444.95.



A solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-hydroxypropyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (160 mg, 0.360 mmol, 1 equiv) in DCM (4 mL) was treated with Dess-Martin (51.46 mg, 0.432 mmol, 1.2 equiv) for 10 min at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at

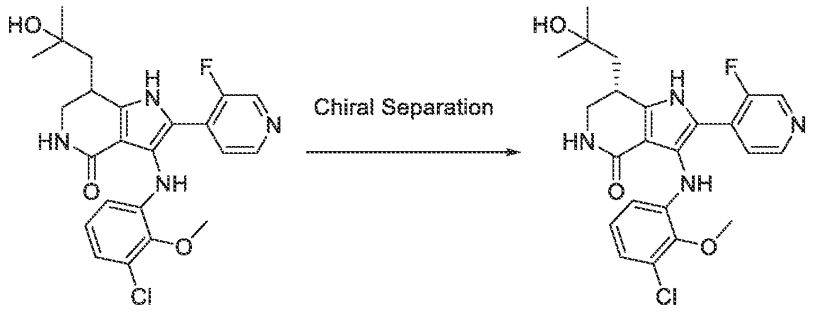
room temperature under nitrogen atmosphere. The resulting mixture was diluted with DCM (10 mL). The reaction was quenched with sat. NaHCO3 (aq.) at 0 °C. The resulting mixture was extracted with CH2Cl2 (3 x 30 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

LC-MS: $(M+H)^+$ found: 442.95.



A solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-oxopropyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (140 mg, 0.316 mmol, 1 equiv) in THF (5 mL) was treated with MeMgBr (75.39 mg, 0.632 mmol, 2 equiv) for 2 h at -5 °C under nitrogen atmosphere. The resulting mixture was diluted with EtOAc (10 mL). The reaction was quenched by the addition of sat. NH4Cl (aq.) (20 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (100 mg) was purified by Prep-HPLC with the following conditions () to afford (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-hydroxy-2-methylpropyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (30 mg, 19.65%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 459.05.

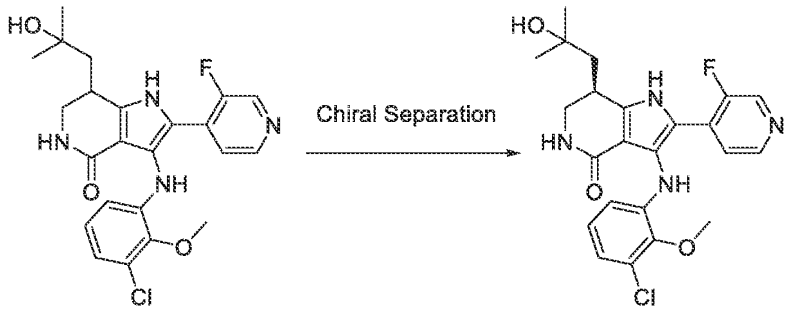


The crude product (30 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IG-3, 4.6*50mm, 3μm; Mobile Phase A: Hex: DCM=3: 1)(0.1%DEA): IPA=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-hydroxy-2-methylpropyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (10.3 mg) as a white solid.

LC-MS: $(M+H)^+$ found: 459.00.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.85 (s, 1H), 8.52 (d, J = 3.3 Hz, 1H), 8.25 (d, J = 5.1 Hz, 1H), 7.65 (s, 1H), 7.40 (dd, J = 7.0, 5.2 Hz, 1H), 7.28 (d, J = 3.4 Hz, 1H), 6.77 – 6.60 (m, 2H), 6.16 (dd, J = 6.7, 2.9 Hz, 1H), 5.42 (s, 1H), 3.89 (s, 3H), 3.44 – 3.34 (m, 1H), 3.24 (d, J = 6.3 Hz, 2H), 1.81 (dd, J = 14.3, 6.0 Hz, 1H), 1.68 – 1.56 (m, 1H), 1.26 (d, J = 9.7 Hz, 6H).

Example 119. (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-hydroxy-2-methylpropyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 495)**



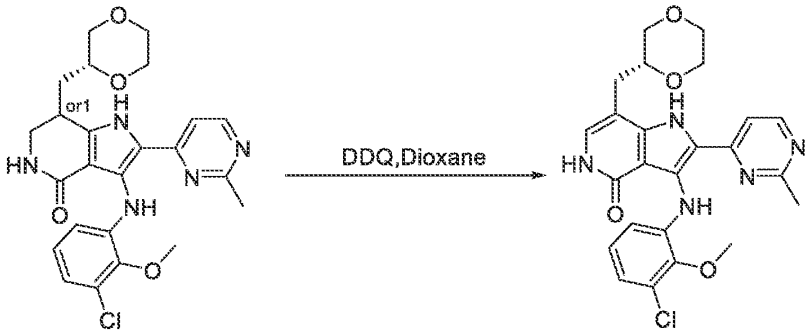
The crude product (30 mg) was purified by Prep-HPLC with the following conditions (Column: CHIRALPAK IG-3, 4.6*50mm, 3μm; Mobile Phase A: Hex: DCM=3: 1)(

0.1%DEA): IPA=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(2-hydroxy-2-methylpropyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (10.7 mg) as a yellow solid.

LC-MS: $(M+H)^+$ found: 459.00.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.90 (s, 1H), 8.61 – 8.54 (m, 1H), 8.27 (d, J = 5.3 Hz, 1H), 7.71 (s, 1H), 7.42 (dd, J = 7.0, 5.2 Hz, 1H), 7.34 – 7.22 (m, 1H), 6.78 – 6.64 (m, 2H), 6.17 (dd, J = 7.2, 2.5 Hz, 1H), 5.42 (s, 1H), 3.89 (s, 3H), 3.39 (s, 1H), 3.24 (d, J = 6.6 Hz, 2H), 1.81 (dd, J = 14.4, 6.1 Hz, 1H), 1.69 – 1.57 (m, 1H), 1.26 (d, J = 9.7 Hz, 6H).

Example 120. 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(2-methylpyrimidin-4-yl)-1H,5H-pyrrolo[3,2-c]pyridin-4-one **(compound 655)**



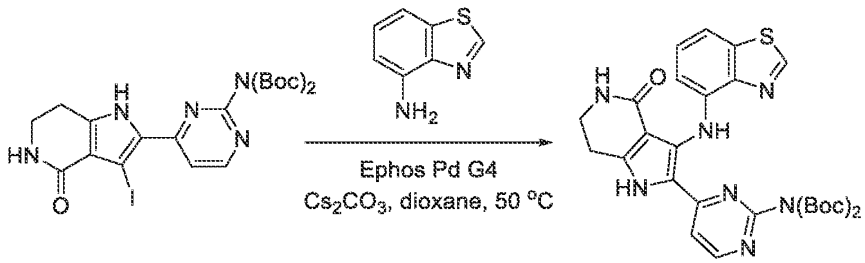
To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-ylmethyl]-2-(2-methylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (150 mg, 0.310 mmol, 1 equiv) in dioxane (3.75 mL, 0.084 mmol, 0.27 equiv) was added DDQ (105.54 mg, 0.465 mmol, 1.5 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 100 °C under nitrogen atmosphere. The resulting mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 47% B in 10 min, 47% B; Wave Length: 254/220 nm; RT1(min): 8.17) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-7-[(2R)-1,4-dioxan-2-

ylmethyl]-2-(2-methylpyrimidin-4-yl)-1H,5H-pyrrolo[3,2-c]pyridin-4-one (31.8 mg, 20.80%) as a yellow solid.

LCMS: $[M+H]^+$ found: 482.

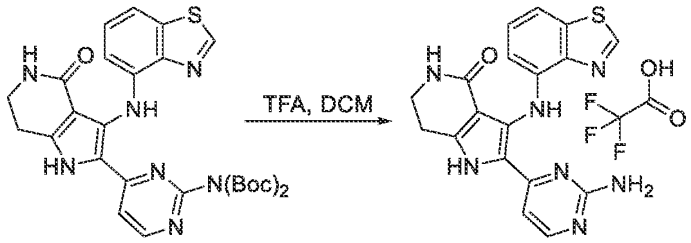
^{1}H NMR (300 MHz, Chloroform-*d*) δ 11.17 (s, 1H), 10.05 (s, 1H), 8.36 (d, J = 5.8 Hz, 1H), 7.87 (s, 1H), 7.02 – 6.83 (m, 3H), 6.84 – 6.71 (m, 1H), 6.39 – 6.32 (m, 1H), 4.10 (s, 4H), 3.94 – 3.73 (m, 5H), 3.49 – 3.40 (m, 1H), 2.81 (s, 4H), 2.67 (d, J = 15.6 Hz, 1H).

Example 121. 2-(2-aminopyrimidin-4-yl)-3-(1,3-benzothiazol-4-ylamino)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid **(compound 718)**



To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (100.00 mg, 0.18 mmol, 1.00 equiv) in dioxane (2.00 mL) was added Cs_2CO_3 (117.00 mg, 0.36 mmol, 2.00 equiv) and EPhos Pd G4 (33.00 mg, 0.03 mmol, 0.20 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added 1,3-benzothiazol-4-amine (32.00 mg, 0.21 mmol, 1.20 equiv) in portions at room temperature. The resulting mixture was stirred for additional 3h at 50 ℃. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC ($CHCl_3$ / MeOH 10:1) to afford tert-butyl N-[4-[3-(1,3-benzothiazol-4-ylamino)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl]-N-(tert-butoxycarbonyl)carbamate (90.00 mg, 86.53%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 578.3.

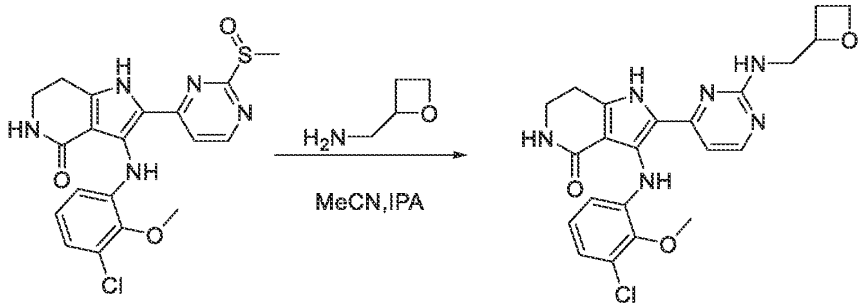


To a stirred solution of tert-butyl N-[4-[3-(1,3-benzothiazol-4-ylamino)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl]-N-(tert-butoxycarbonyl)carbamate (90.00 mg, 0.15 mmol, 1.00 equiv) in DCM (1 mL) was added TFA (1 mL) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product (60.00 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 19*250mm, 10 um; Mobile Phase A: Water (0.05%TFA), Mobile Phase B: MeOH------Preparative; Flow rate: 25 mL/min; Gradient: 37% B to 49% B in 7 min, 49% B; Wave Length: 254 nm; RT1(min): 5.93) to afford 2-(2-aminopyrimidin-4-yl)-3-(1,3-benzothiazol-4-ylamino)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid (48.5mg,63.34%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 378.0.

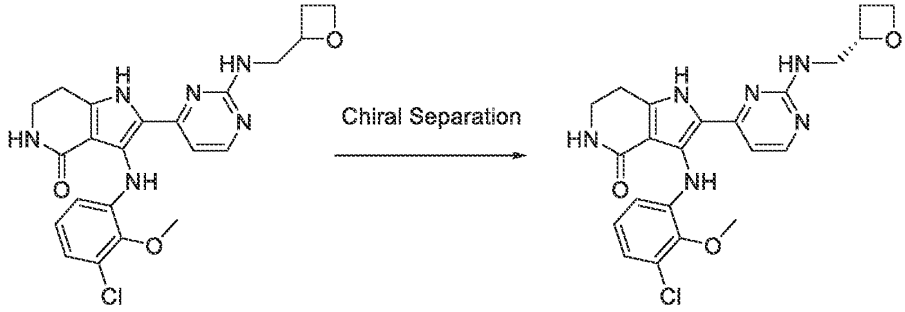
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H), 9.62 (s, 1H), 9.35 (s, 1H), 8.02 (d, J = 6.7 Hz, 1H), 7.56 - 7.36 (m, 4H), 7.23 (t, J = 8.0 Hz, 1H), 6.69-6.62 (m, 2H), 3.45-3.41 (m, 2H), 2.92 (t, J = 8.0 Hz, 2H).

Example 122. (S)-((3-chloro-2-methoxyphenyl)amino)-2-(2-((oxetan-2-ylmethyl)amino) pyrimidin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(compound 719)**



To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (270.00 mg, 0.63 mmol, 1.00 equiv) in IPA (1.50 mL) and MeCN (1.50 mL) was added 1-(oxetan-2-yl)methanamine (796.00 mg, 9.16 mmol, 15.00 equiv). The resulting mixture was stirred for additional 1 h at 80 ℃. The reaction was monitored by TLC and LCMS. The precipitated solid was collected by filtration and purified by Prep-HPLC with the following conditions (Column: Column Size: 4.6*50 mm,3 um, mobile Phase: (Hex: DCM = 3:1) (0.1% DEA): IPA=70 :30 Flow: 1 mL/min Temperature: 25 degree: Wavelength1: 254nm) to afford (R)-((3-chloro-2-methoxyphenyl)amino)-2-(2-((oxetan-2-ylmethyl)amino)pyrimidin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (51.70 mg, 18.20%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 455.1.

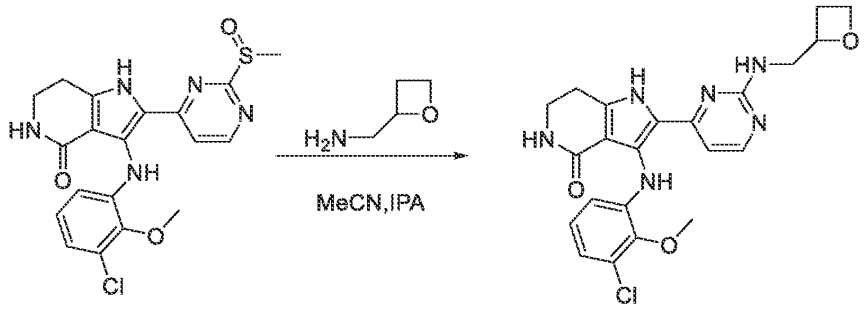


The crude product (51.70 mg) was purified by CHIRAL_HPLC with the following conditions (Column: CHIRALPAK ID - 3, 4.6*50 mm,3 um; Mobile Phase A: (Hex: DCM=3:1)(0.1%DEA):IPA=70:30， Flow rate: 1.0/min; 254m; 20 nm) to (S)-((3-chloro-2-methoxyphenyl)amino)-2-(2-((oxetan-2-ylmethyl)amino) pyrimidin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (11.10 mg, 4.10%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 455.1.

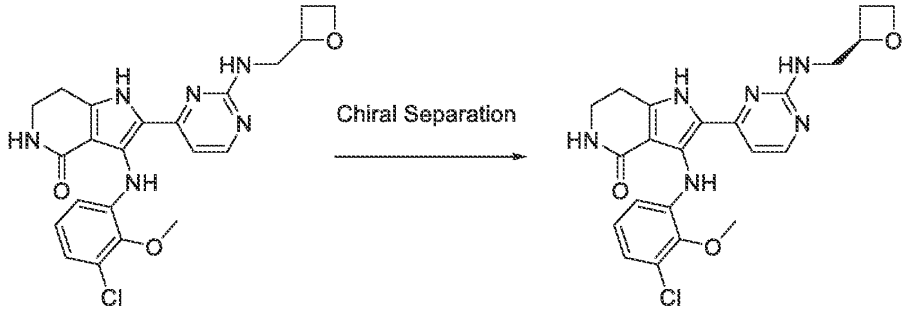
^{1}H NMR (300 MHz, DMSO-d_6) δ 11.49 (s, 1H), 7.95 (d, J = 5.3 Hz, 1H), 7.79 (s, 1H), 7.01 (s, 1H), 6.78 - 6.57 (m, 3H), 6.38 (d, J = 5.3 Hz, 1H), 6.26 (dd, J =7.6, 2.0 Hz, 1H), 4.70 (m, 1H), 4.34 (m, 2H), 3.76 (s, 3H), 3.60 - 3.49 (m, 1H), 3.47 - 3.35 (m, 1H), 3.29 (td, J = 6.7, 2.5 Hz, 2H), 2.75 (t, J = 6.0 Hz, 2H), 2.52 - 2.44 (m, 1H), 2.29 - 2.24 (m, 1H).

Example 123. (R)-((3-chloro-2-methoxyphenyl)amino)-2-(2-((oxetan-2-ylmethyl)amino)pyrimidin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(compound 720)**



To a stirred solution of 3-[(3-chloro-2-methoxyphenyl) amino]-2-(2-methanesulfinylpyrimidin-4-yl) -1H,5H,6H,7H - pyrrolo[3,2-c]pyridin-4-one (270.00 mg, 0.63 mmol, 1.00 equiv) in IPA (1.50 mL) and MeCN (1.50 mL) was added 1-(oxetan-2-yl)methanamine (796.00 mg, 9.16 mmol, 15.00 equiv). The resulting mixture was stirred for additional 1 h at 80 ℃. The reaction was monitored by TLC and LCMS. The precipitated solids were collected by filtration and purified by Prep-HPLC with the following conditions (Column: Column Size: 4.6*50 mm,3 um, mobile Phase: (Hex: DCM=3:1) (0.1%DEA) : IPA=70:30 Flow: 1 mL/min Temperature: 25 degree: Wavelength1 : 254nm) to afford (R)-((3-chloro-2-methoxyphenyl)amino)-2-(2-((oxetan-2-ylmethyl)amino)pyrimidin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (51.70 mg, 18.20%) as a yellow solid.

LC-MS: M+H found: 455.1.



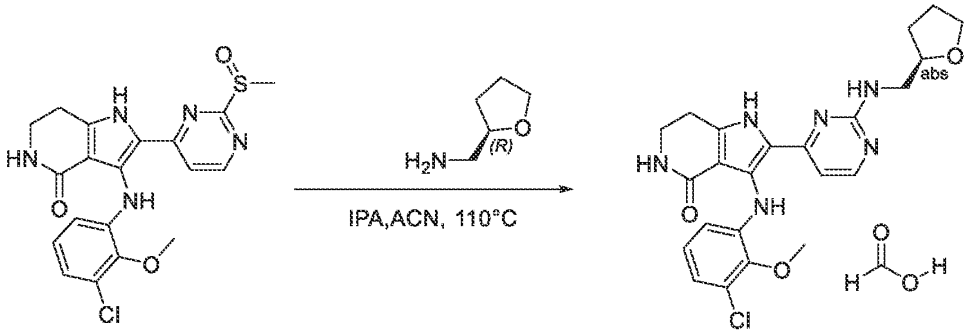
The crude product (51.70 mg) was purified by CHIRAL_HPLC with the following

conditions (Column: CHIRALPAK ID - 3, 4.6*50 mm,3 um; Mobile Phase A: (Hex : DCM=3:1)(0.1%DEA):IPA=70:30， Flow rate:1.0/min; 254m; 20 nm) to (R)-((3-chloro-2-methoxyphenyl)amino)-2-(2-((oxetan-2-ylmethyl)amino)pyrimidin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (9.40 mg, 3.50%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 455.1.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.61 (s, 1H), 8.07 (t, J = 4.6 Hz, 1H), 7.91 (s, 1H), 7.13 (s, 1H), 6.75 - 6.85 (m, 3H), 6.50 (t, J = 4.7 Hz, 1H), 6.36 - 6.39 (m, 1H), 4.87 - 4.76 (m, 1H), 4.40 - 4.51 (m, 2H), 3.88 (s, 3H), 3.64 - 3.70 (m, 1H), 3.51 - 3.56 (m, 1H), 3.07 - 3.41 (m, 2H), 2.87 (m, 2H), 2.64 - 2.57 (m, 1H), 2.43 - 2.34 (m, 1H).

Example 124. (R)-3-((3-chloro-2-methoxyphenyl)amino)-2-(2-(((tetrahydrofuran-2-yl)methyl)amino)pyrimidin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(compound 721)**

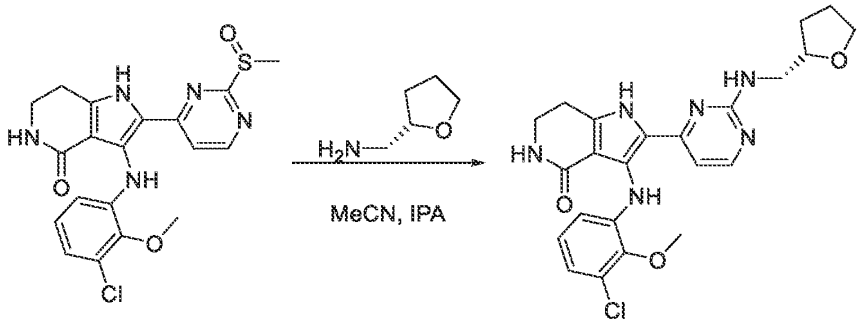


To a stirred mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6-H,7H-pyrrolo[3,2-c]pyridin-4-one (80.00 mg, 0.19 mmol, 1.00 equiv), 1-[(2R)-oxolan-2-yl]methanamine (234.00 mg, 2.32 mmol, 10.0 equiv) in MeOH/ACN (1:1, 2 mL) in portions under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 110 ℃ under nitrogen atmosphere. Desired product could be detected by LCMS. The crude product was purified by Prep-HPLC with the following conditions (Column: Atlantis HILIC OBD Column, 19*150mm*5μm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 11% B to 35% B in 7 min, 35% B; Wave Length: 254 nm; RT1(min): 6.32) to afford (R)-3-((3-chloro-2-methoxyphenyl)amino)-2-(2-(((tetrahydrofuran-2-yl)methyl)amino)pyrimidin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (30.00 mg, 34.00 %) as a yellow solid.

LC-MS: $(M+H)^+$ found: 469.3.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.63 (s, 1H), 8.08 (d, J = 5.3 Hz, 1H), 7.96 (s, 1H), 7.15 (s, 1H), 6.87 - 6.72 (m, 3H), 6.51 (d, J = 5.3 Hz, 1H), 6.42 - 6.35 (m, 1H), 3.96 (t, J = 6.3 Hz, 1H), 3.88 (s, 3H), 3.82 - 3.72 (m, 1H), 3.66 - 3.58 (m, 1H), 3.45 - 3.38 (m, 4H), 2.88 (t, J = 6.7 Hz, 2H), 1.95 - 1.73 (m, 3H), 1.45 - 1.63 (m, 1H).

Example 125. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-[[(2S)-oxolan-2-ylmethyl]amino]pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 722)**



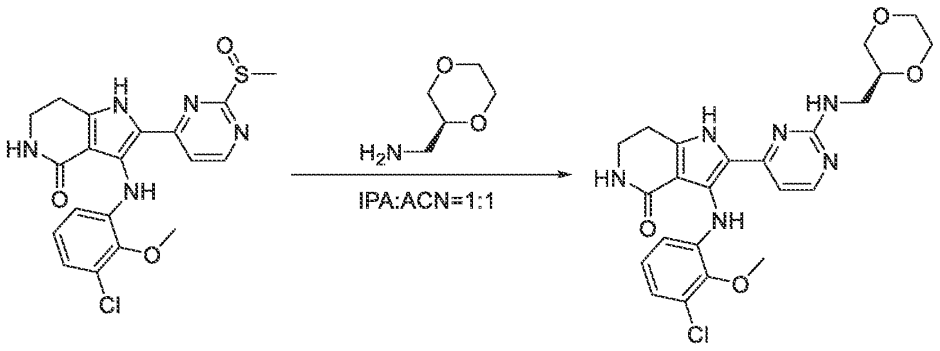
To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (130.00 mg, 0.30 mmol, 1.00 equiv) in IPA (1.00 mL) and MeCN (1.00 mL) was added 1-[(2S)-oxolan-2-yl]methanamine (456.00 mg, 4.52 mmol, 15.00 equiv). The resulting mixture was stirred for overnight at 80 ℃. The mixture was allowed to cool down to room temperature. The reaction was directly purified by Prep-HPLC with the following conditions ((2#SHIMADZU (HPLC-01)): Column, Xselect CSH OBD Column 30*150mm 5um, 254 nm; mobile phase, Water (0.1%FA) and ACN (11% ACN up to 35% in 8 min) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-[[(2S)-oxolan-2-ylmethyl]amino]pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (32.80 mg, 23.00%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 469.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.63 (s, 1H), 8.19 (s, 1H), 8.14 - 7.87 (m, 2H), 7.16 (t, J = 2.6 Hz, 1H), 7.05 - 6.61 (m, 3H), 6.51 (d, J = 5.3 Hz, 1H), 6.38 (dd, J = 7.9, 1.8 Hz,

1H), 4.01 - 3.94 (m, 1H), 3.88 (s, 3H), 3.81 - 3.73 (m, 1H), 3.67 - 3.58 (m, 1H), 3.49 - 3.30 (m, 4H), 2.87 (t, *J* =6.7 Hz, 2H), 1.96 - 1.71 (m, 3H), 1.63 - 1.50 (m, 1H).

Example 126. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-[[(2S)-1,4-dioxan-2-ylmethyl]amino]pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 723)**



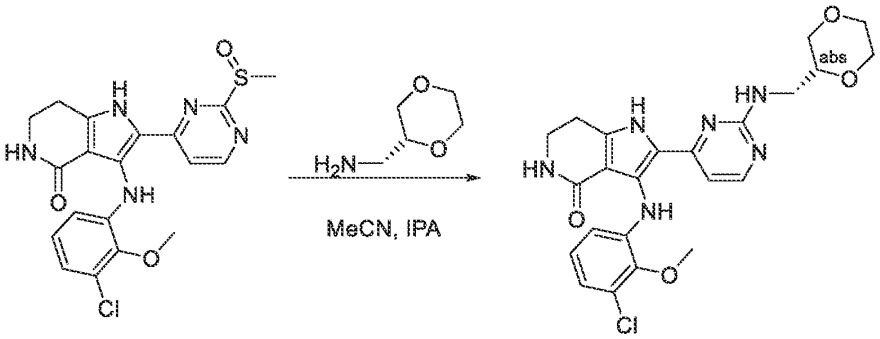
Into an 8 mL pressure tank reactor were added 3-[(3-chloro-2-methoxyphenyl) amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo [3,2-c] pyridin-4-one (100.00 mg, 0.23 mmol, 1.00 equiv), 1-[(2S)-1,4-dioxan-2-yl] methanamine (406.86 mg, 3.47 mmol, 15.00 equiv) and IPA (1 mL), ACN (1 mL) at room temperature under air atmosphere. The resulting mixture was stirred for 30 h at 110 ℃ under air atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under vacuum. The crude product (100.00 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 32% B in 8 min, 32% B; Wave Length: 254/220 nm; RT1(min): 7.72) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-[[(2S)-1,4-dioxan-2-ylmethyl]amino]pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (15.70 mg, 13.98%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 485.3.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.61 (s, 1H), 8.19 - 8.04 (m, 1H), 7.89 (s, 1H), 7.16 (d, *J* = 2.7 Hz, 1H), 6.88 - 6.72 (m, 2H), 6.50 (d, *J* = 5.3 Hz, 1H), 6.37 (dd, *J* = 7.6, 2.0 Hz, 1H), 3.89 (s, 3H), 3.79 - 3.55 (m, 4H), 3.54 - 3.35 (m, 5H), 3.26 (dd, *J* = 11.4, 9.7 Hz,

2H), 2.88 (t, *J* = 6.8 Hz, 2H).

Example 127. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-[(1,4-dioxan-2-ylmethyl)amino]pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 724)**

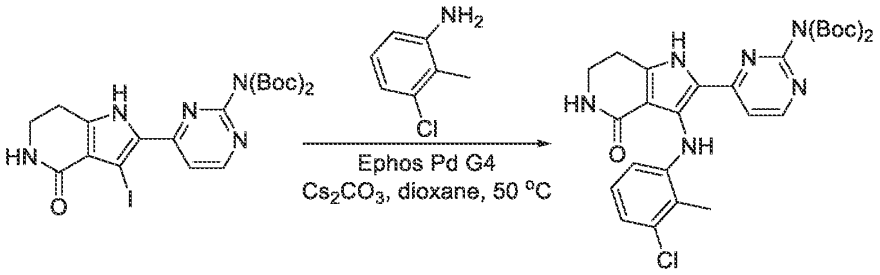


To a stirred solution of 3-[(3-chloro-2-methoxyphenyl) amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (100.00 mg, 0.23 mmol, 1.00 equiv) in IPA (1.00 mL) and MeCN (1.00 mL) was added 1-[(2R)-1,4-dioxan-2-yl] methanamine (271.00 mg, 2.31 mmol, 10.00 equiv) in portions. The resulting mixture was stirred for overnight at 80 ℃. The mixture was allowed to cool down to room temperature. The reaction was directly purified Chiral-Prep-HPLC with the following conditions (2#SHIMADZU (HPLC-01)): Column, Xselect CSH F-Phenyl OBD column, 19*250 mm, 5μm; mobile phase, Water (0.1% FA) and ACN (13% ACN up to 29% in 7 min) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-[(1,4-dioxan-2-ylmethyl)amino]pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (11.80 mg, 9.60%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 485.0.

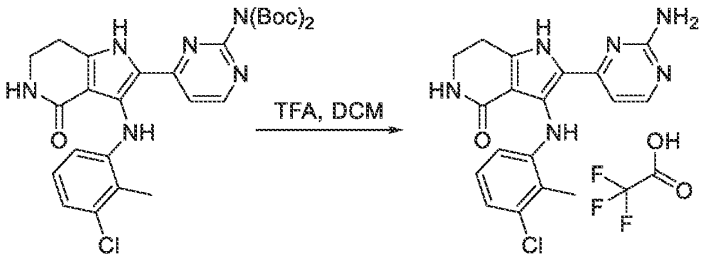
^{1}H NMR (300 MHz, DMSO-d_6) δ 11.59 (s, 1H), 8.05 (d, *J* = 5.3 Hz, 1H), 7.87 (s, 1H), 7.13 (t, *J* = 2.5 Hz, 1H), 6.85 - 6.71 (m, 3H), 6.48 (d, *J* = 5.3 Hz, 1H), 6.34 (m, 1H), 3.86 (s, 3H), 3.76 - 3.67 (m, 2H), 3.66 - 3.56 (m, 2H), 3.55 - 3.45 (m, 2H), 3.44 - 3.41 (m, 1H), 3.38 - 3.30 (m, 2H), 3.28 - 3.17 (m, 2H), 2.86 (t, *J* = 6.7 Hz, 2H).

Example 128. 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methylphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid **(compound 725)**



To a stirred mixture of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (100.00 mg, 0.18 mmol, 1.00 equiv) and 2-methyl-3-chloroaniline (25.00 mg, 0.18 mmol, 1.00 equiv) in dioxane (2.00 mL) was added EPhos Pd G4 (33.00 mg, 0.03 mmol, 0.20 equiv) and Cs_2CO_3 (117.00 mg, 0.36 mmol, 2.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 50 °C under argon atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-chloro-2-methylphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (50.00 mg, 48.80%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 569.1.



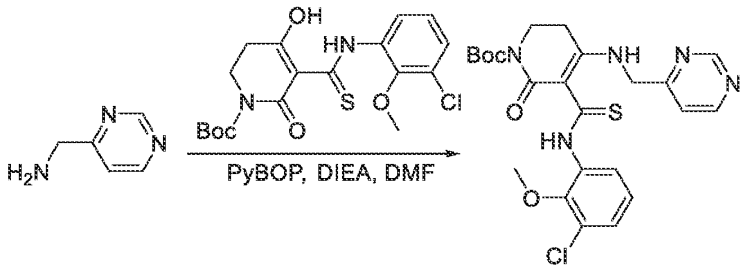
To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-chloro-2-methylphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (50.00 mg, 0.08 mmol, 1.00 equiv) in DCM (1.00 mL) was added TFA (1.00 mL) dropwise at 0 ℃ under nitrogen atmosphere. The resulting mixture was stirred for additional 2 h at 50 ℃. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The

crude product (30.00 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water (0.05%TFA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 35% B in 8 min, 35% B; Wave Length: 254/220 nm; RT1(min): 7.63) to afford 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-methylphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid (13.20 mg, 31.11%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 369.1.

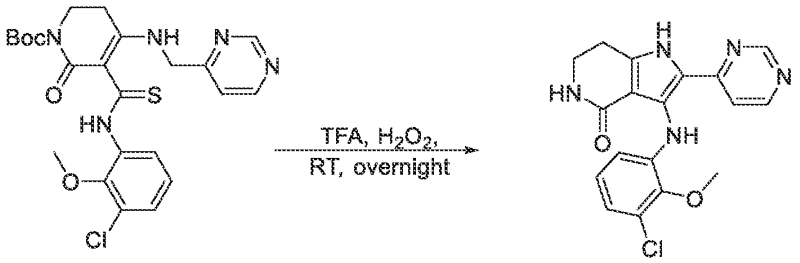
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.97 (s, 1H), 8.90 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.67 (s, 2H), 7.11 (s, 1H), 7.00 - 6.98 (m, 2H), 6.77 (s, 2H), 3.38-3.35 (m, 2H), 2.85 (t, J = 8.0 Hz, 2H), 2.36 (s, 3H).

Example 129. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 675)**



To a stirred mixture of 1-(pyrimidin-4-yl)methanamine (1.20 g, 11.00 mmol, 1.00 equiv) and tert-butyl 3-[(3-chloro-2-methoxyphenyl)carbamothioyl]-4-hydroxy-2-oxo-5,6-dihydropyridine-1-carboxylate (4.54 g, 11.00 mmol, 1.00 equiv) and PyBOP (8.58 g, 16.49 mmol, 1.50 equiv) and DIEA (4.26 g, 33.00 mmol, 3.00 equiv) in DMF (40 mL) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The residue was purified by reverse flash chromatography with the following conditions (column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm) to afford tert-butyl 3-[(3-chloro-2-methoxyphenyl)carbamothioyl]-2-oxo-4-[(pyrimidin-4-ylmethyl)amino]-5,6-dihydropyridine-1-carboxylate (830.00 mg, 14.98%) as a red oil.

LC-MS: $(M+H)^+$ found: 504.0.

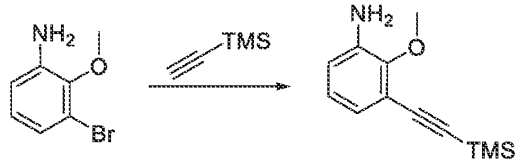


To a stirred mixture of tert-butyl 3-[(3-chloro-2-methoxyphenyl)carbamothioyl]-2-oxo-4-[(pyrimidin-4-ylmethyl)amino]-5,6-dihydropyridine-1-carboxylate (410.00 mg, 0.81 mmol, 1.00 equiv) and TFA (139.10 mg, 1.22 mmol, 1.50 equiv) and H_2O_2 (55.30 mg, 1.63 mmol, 2.00 equiv) in MeOH (8 mL) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80 ℃ under nitrogen atmosphere. Desired product could be detected by LCMS. The crude product (70.00 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150mm, 5um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 18% B to 40% B in 10 min, 40% B; Wave Length: 220/254 nm; RT1(min): 10.72) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (31.60 mg, 10.28%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 370.0.

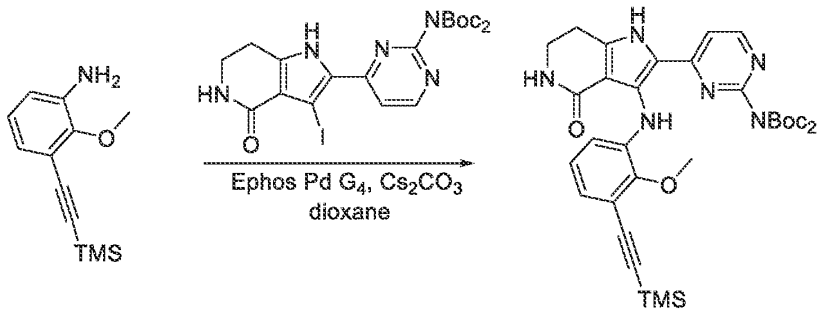
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (s, 1H), 9.04 (d, J = 1.4 Hz, 1H), 8.55 (d, J = 5.6 Hz, 1H), 7.93 (s, 1H), 7.34 - 7.11 (m, 2H), 6.94 - 6.74 (m, 2H), 6.33 (dd, J = 7.0, 2.6 Hz, 1H), 3.93 (s, 3H), 3.41 (td, J = 6.8, 2.6 Hz, 2H), 2.87 (t, J = 6.8 Hz, 2H).

Example 130. 3-[(3-acetyl-2-methoxyphenyl)amino]-2-(2-aminopyri midin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 728)**



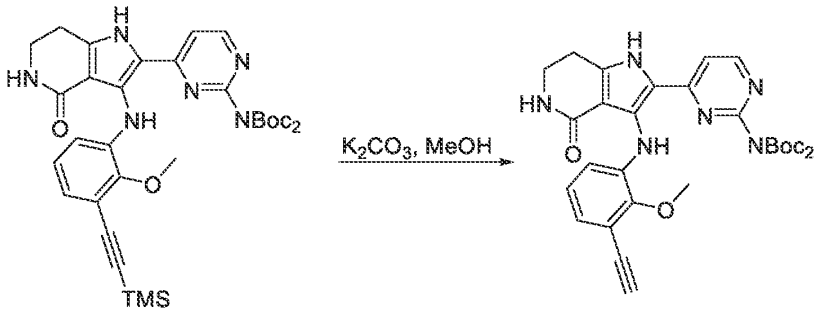
A solution of 3-bromo-2-methoxyaniline (1.00 g, 4.95 mmol, 1.00 equiv), $Pd(PPh_3)_2Cl_2$ (347.39 mg, 0.50 mmol, 0.10 equiv) and CuI (377.03 mg, 1.98 mmol, 0.40 equiv) was bubbled under N_2 for over 10 minutes. Then trimethylsilylacetylene (2430.57 mg, 24.75 mmol, 5.00 equiv) and DIPA (1.54 mL) was added, and the reaction was stirred at 105 °C overnight. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The mixture was diluted with EA (10 mL) and washed with NH_4OH/NH_4Cl (1:1, 10ml), NH_4Cl (10ml), and brine (20ml). The organic phase was concentrated. The residue was purified by silica gel column chromatography, eluted with hexane/EtOAc (20:1) to afford 2-methoxy-3-[2-(trimethylsilyl)ethynyl]aniline (930.00 mg, 85.66%) as a brown oil.

LC-MS: $(M+H)^+$ found: 220.2.



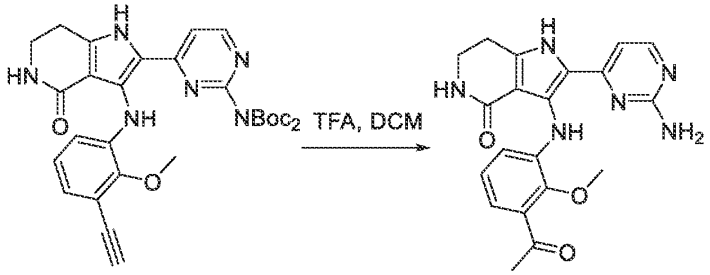
To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-2-yl]pyrimidin-2-yl)carbamate (200.00 mg, 0.36 mmol, 1.00 equiv) and 2-methoxy-3-[2-(trimethylsilyl)ethynyl]aniline (118.49 mg, 0.54 mmol, 1.50 equiv) in 1,4-dioxane was added Cs_2CO_3 (234.67 mg, 0.72 mmol, 2.00 equiv) and Ephos Pd G4 (66.16 mg, 0.07 mmol, 0.20 equiv) in one portion at room temperature under argon atmosphere. The resulting mixture was stirred for 2.5 h at 50 °C under argon atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH: 20:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-[4-[3-([2-methoxy-3-[2-(trimethylsilyl)ethynyl]phenyl]amino)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl]carbamate (118.00 mg, 50.66%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 647.1.



To a solution of tert-butyl N-(tert-butoxycarbonyl)-N-[4-[3-([2-methoxy-3-[2-(trimethylsilyl) ethynyl]phenyl]amino)-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl]carbamate （108.00 mg, 0.17 mol, 1.00 equiv） in MeOH (10 mL) was added K_2CO_3 (69.23 mg, 0.50 mmol, 3.00 equiv) at rt under Nitrogen atmosphere. Desired product could be detected by LC-MS after 1 h. The reaction was worked up with last batch (E10346-076). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TTLC (CH_2Cl_2 / MeOH: 20:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-ethynyl-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (99.00 mg, 103.18%) as orange solid.

LC-MS: $(M+H)^+$ found: 575.1.



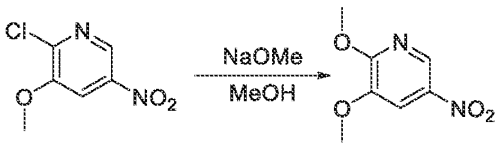
To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-ethynyl-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (113.00 mg, 1.00 equiv) in DCM was added TFA (4.00 mL) dropwise at rt. The mixture was stirred for 2 h at rt. After start material was consumed, the resulting mixture was concentrated under vacuum. The crude product (80.00 mg) was purified by Prep-HPLC with the following conditions (NH_4HCO_3) to afford 3-[(3-acetyl-2-

methoxyphenyl)amino]-2-(2-aminopyri midin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (7.70 mg) as a yellow solid.

LC-MS: $(M+H)^+$ found: 393.1.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.65 (s, 1H), 8.05 (t, 2H), 7.15 (s, 1H), 6.96 - 6.88(m, 2H), 6.61 - 6.59 (m, 1H), 6.46 (d, 1H), 6.19 (s, 2H), 3.90 (s, 3H), 3.41 (t, 2H), 2.85 (t, 2H), 2.57 (s, 3H).

Example 131. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6,7-dimethoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 730)**



To a stirred solution 2-chloro-3-methoxy-5-nitropyridine (5.00 g, 26.52 mmol, 1.00 equiv) in methanol (80 mL) was added sodium methoxide (2.29 g, 42.42 mmol, 1.60 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 1 h at room temperature. Desired product could be detected by LCMS. The resulting mixture was filtered, the filter cake was washed with MeOH (1x20 mL). This resulted in 2,3-dimethoxy-5-nitropyridine (4.63 g, 94.82%) as a yellow solid.

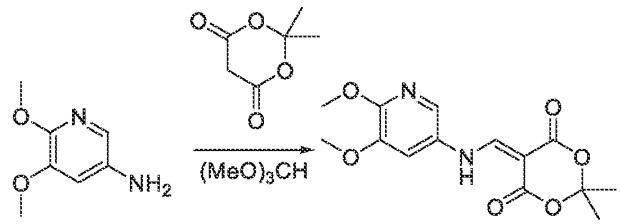
LC-MS: $(M+H)^+$ found: 184.9.



To a stirred mixture of 2,3-dimethoxy-5-nitropyridine (400.00 mg, 2.17 mmol, 1.00 equiv), Pd/C (231.16 mg, 0.22 mmol, 0.10 equiv, 10%) in EA (5 mL) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under hydrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH (3x30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (1:1) to 5,6-dimethoxypyridin-3-amine (318.00 mg, 94.96%) as a

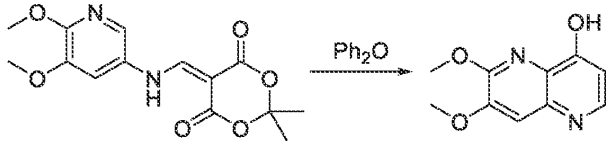
brown solid.

LC-MS: $(M+H)^+$ found: 155.2.



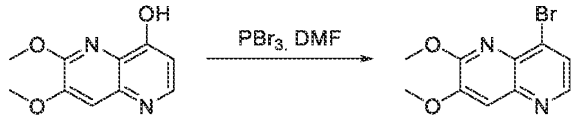
A mixture of 5,6-dimethoxypyridin-3-amine (300.00 mg, 1.95 mmol, 1.00 equiv) and meldrum's acid (280.46 mg, 1.95 mmol, 1.00 equiv) in trimethyl orthoformate (3 mL) was stirred for 2 h at 110 °C under air atmosphere. Desired product could be detected by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure to afford 5-[[(5,6-dimethoxypyridin-3-yl)amino]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (495.00 mg, 82.51%) as a brown solid.

LC-MS: $(M+H)^+$ found: 309.1.



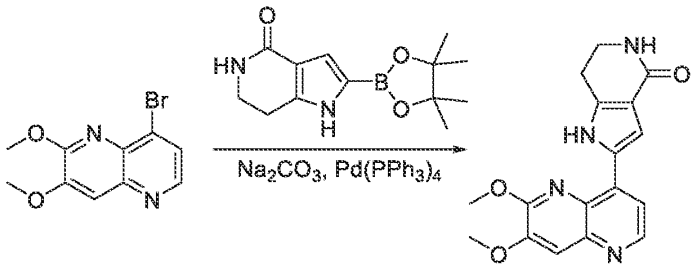
A solution of 5-{[(5,6-dimethoxypyridin-3-yl)amino]methylidene}-2,2-dimethyl-1,3-dioxane-4,6-dione (200.00 mg, 0.65 mmol, 1.00 equiv) in diphenyl-ether (5 mL) was stirred for 1h at 250 ℃ under argon atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with Et_2O (50 mL). The precipitated solids were collected by filtration and washed with Et_2O (2x100 mL). This resulted in 6,7-dimethoxy-1,5-naphthyridin-4-ol (80.00 mg, 59.80%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 207.1.



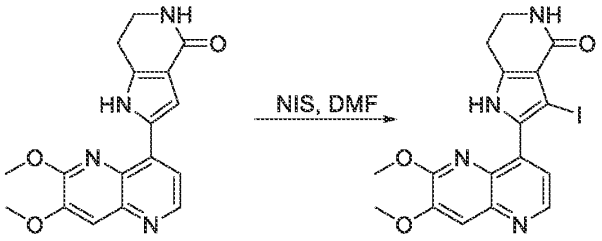
To a stirred solution/mixture of 6,7-dimethoxy-1,5-naphthyridin-4-ol (80.00 mg, 0.39 mmol, 1.00 equiv) in DMF (1 mL) was added PBr_3 (136.52 mg, 0.50 mmol, 1.30 equiv) in portions at 0 ℃ under nitrogen atmosphere. The resulting mixture was stirred for additional 2 h at room temperature. Desired product could be detected by LCMS. The mixture was allowed to cool down to 0 ℃. The reaction was quenched with Ice/Salt at 0 ℃. The aqueous layer was extracted with EtOAc (3x200 mL). The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 8-bromo-2,3-dimethoxy-1,5-naphthyridine (60.00 mg, 57.47%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 269.0.



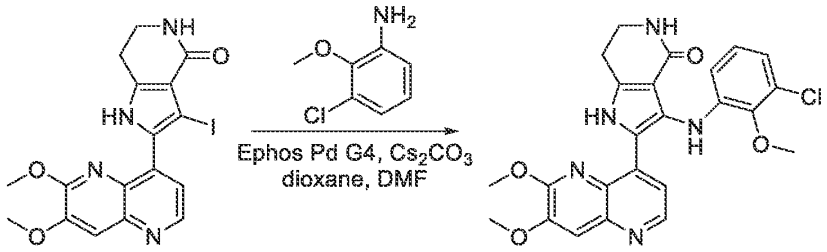
To a stirred mixture of 8-bromo-2,3-dimethoxy-1,5-naphthyridine (630.00 mg, 2.34 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1227.33 mg, 4.68 mmol, 2.00 equiv) in 1,4-dioxane (20 mL) and H_2O (4 mL) were added Na_2CO_3 (744.41 mg, 7.02 mmol, 3.00 equiv) and $Pd(PPh_3)_4$ (270.53 mg, 0.23 mmol, 0.10 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for 2 h at 50 °C under argon atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 2-(6,7-dimethoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (570.00 mg, 75.07%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 325.1.



A mixture of 2-(6,7-dimethoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (200.00 mg, 0.62 mmol, 1.00 equiv) and NIS (208.10 mg, 0.35 mmol, 1.50 equiv) in DMF (2 mL) was stirred for 2 h at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (12:1) to afford 2-(6,7-dimethoxy-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (190.00 mg, 68.44%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 450.9.



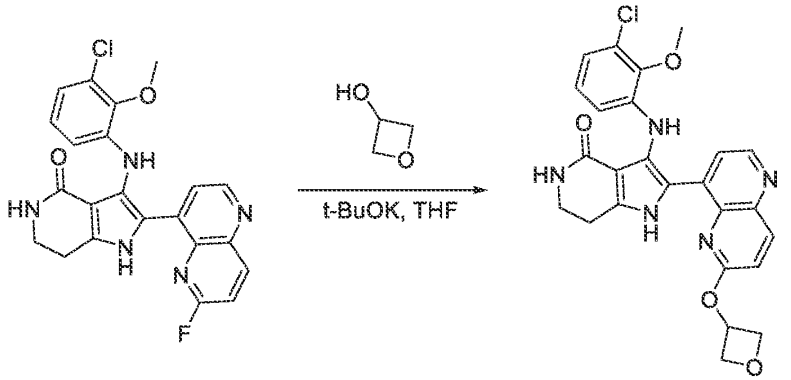
To a stirred mixture of 2-(6,7-dimethoxy-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (160.00 mg, 0.36 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (168.02 mg, 1.07 mmol, 3.00 equiv) in dioxane (2 mL) and DMF (2 mL) were added Cs_2CO_3 (231.57 mg, 0.71 mmol, 2.00 equiv) and Ephos Pd G4 (65.28 mg, 0.07 mmol, 0.20 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for overnight at 50 °C under argon atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to

39% B in 8 min, 39% B; Wave Length: 254/220 nm; RT1(min): 7.9) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6,7-dimethoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (9.80 mg, 5.71%) as an orange solid.

LC-MS: $(M+H)^+$ found: 480.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.47 (d, J = 4.8 Hz, 1H), 7.65 (s, 1H), 7.58 (s, 1H), 7.32 (d, J = 5.2 Hz, 1H), 7.11 (s, 1H), 6.64 - 6.55 (m, 2H), 6.14 - 6.09 (m, 1H), 4.12 (s, 3H), 3.95 (s, 3H), 3.84 (s, 3H), 3.43 (s, 2H), 2.94 (t, J = 6.8 Hz, 2H).

Example 132. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(oxetan-3-yloxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 732)**



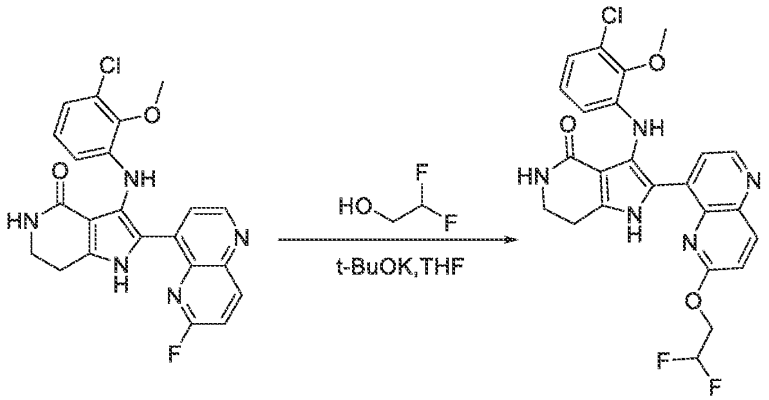
To a solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70.00 mg, 0.16 mmol, 1.00 equiv) and oxetan-3-ol (59.21 mg, 0.80 mmol, 5.00 equiv) in THF (1.60 mL) were added t-BuOK (53.80 mg, 0.48 mmol, 3.00 equiv) at 0 ℃ and stirred for 0.5 h. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 29% B to 59% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(oxetan-3-yloxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (27.20 mg, 34.38%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 492.0.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.71 (s, 1H), 8.61 (d, J = 4.8 Hz, 1H), 8.66 (d, J =

9.1 Hz, 1H), 7.65 (s, 1H), 7.52 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 9.0 Hz, 1H), 7.19 (t, J = 2.6 Hz, 1H), 6.72 - 6.55 (m, 2H), 6.13 (dd, J = 7.8, 1.9 Hz, 1H), 6.09 - 5.95 (m, 1H), 5.03 - 4.86 (m, 2H), 4.72 (dd, J = 7.6, 5.1 Hz, 2H), 3.85 (s, 3H), 3.50 (td, J = 6.9, 2.6 Hz, 2H), 2.99 (t, J = 6.8 Hz, 2H).

Example 133. 3-[(3-chloro-2-methoxyphenyl) amino]-2-[6-(2,2-difluoroethoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 733)**



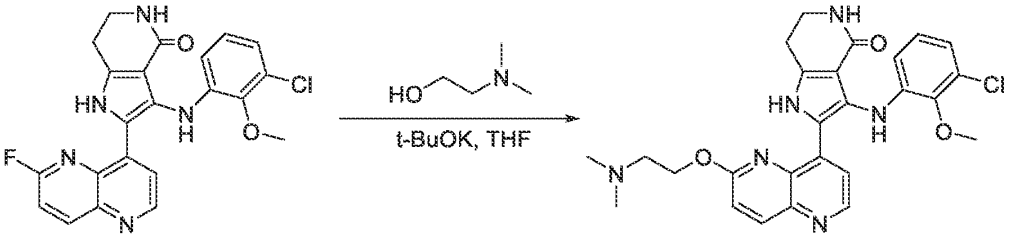
A solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50.00 mg, 0.11 mmol, 1.00 equiv) in THF (1.00 mL) was added 2,2-difluoroethanol (47.00 mg, 0.57 mmol, 5.00 equiv) and t-BuOK (38.00 mg, 0.34 mmol, 3.00 equiv) dropwise at 0 ℃. The resulting mixture was stirred for 1 h at room temperature. The reaction was monitored by LCMS. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 36% B to 66% B in 7 min, 66% B; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl) amino]-2-[6-(2,2-difluoroethoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (29.60 mg, 59.36%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 500.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1H), 8.62 (d, J = 4.8 Hz, 1H), 8.36 (d, J = 9.2 Hz, 1H), 7.76 (s, 1H), 7.52 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.20 (s, 1H), 6.69 - 6.55 (m, 3H), 6.17 - 6.15 (m, 1H), 4.94 - 4.86 (m,2H), 3.88 (s, 3H), 3.48 - 3.46 (m, 2H),

2.93 (t, J = 6.8 Hz, 2H).

Example 134. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[2-(dimethylamino)ethoxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one; formic acid **(compound 736)**

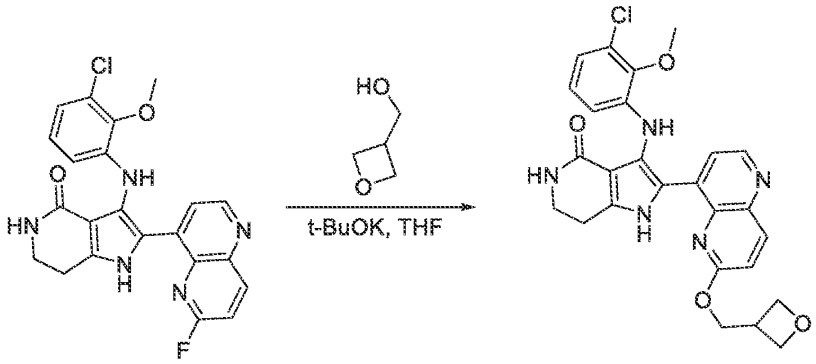


To a stirred solution of 3-[(3-chloro-2-methoxyphenyl) amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (80.00 mg, 0.18 mmol, 1.00 equiv) and dimethylaminoethanol (81.00 mg, 0.91 mmol, 5.00 equiv) in THF (4 mL) was added t-BuOK (62.00 mg, 0.55 mmol, 3.00 equiv) in portions at 0 ℃ under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The reaction was quenched by the addition of Water (1mL) at 0 ℃. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 11% B to 24% B in 8 min, 24% B; Wave Length: 254/220 nm; RT1(min): 7.18) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[2-(dimethylamino)ethoxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one; formic acid (24.80 mg, 24.05%) as an orange solid.

LC-MS: $(M+H)^+$ found: 507.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 8.58 (d, J = 4.8 Hz, 1H), 8.29 (d, J = 9.0 Hz, 1H), 7.74 (s, 1H), 7.52 (d, J = 4.9 Hz, 1H), 7.34 (d, J = 9.1 Hz, 1H), 7.21 (t, J = 2.6 Hz, 1H), 6.72 - 6.61 (m, 2H), 6.21 - 6.15 (m, 1H), 4.67 (t, J = 6.0 Hz, 2H), 3.86 (s, 3H), 3.50 - 3.44 (m, 2H), 2.93 (t, J = 6.8 Hz, 2H), 2.77 (t, J = 6.0 Hz, 2H), 2.27 (s, 6H).

Example 135. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(oxetan-3-ylmethoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one **(compound 737)**

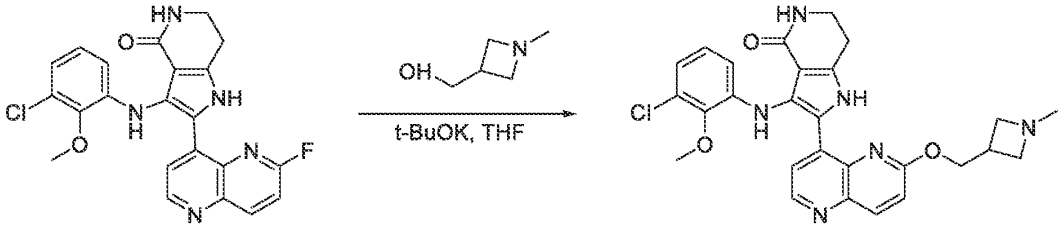


To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100.00 mg, 0.23 mmol, 1.00 equiv) in THF (3.00 mL) were added oxetan-3-ylmethanol (100.61 mg, 1.14 mmol, 5.00 equiv) and t-BuOK (76.88 mg, 0.69 mmol, 3.00 equiv) in portions at degrees 0 ℃ under argon atmosphere. The resulting mixture was stirred for 1 h at room temperature under argon atmosphere. The crude product (100.00 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 19*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 48% B in 10 min, 48% B; Wave Length: 254/220 nm; RT1(min): 9.28) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(oxetan-3-ylmethoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (29.70 mg, 25.19%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 506.0.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.07 (s, 1H), 8.59 (d, J = 4.8 Hz, 1H), 8.30 (d, J = 9.1 Hz, 1H), 7.77 (s, 1H), 7.52 (d, J = 4.8 Hz, 1H), 7.36 (d, J = 9.1 Hz, 1H), 7.22 (s, 1H), 6.75 - 6.60 (m, 2H), 6.15 - 6.13 (m, 1H), 4.87 - 4.73 (m, 4H), 4.53 (t, J = 6.0 Hz, 2H), 3.89 (s, 3H), 3.62 - 3.43 (m, 3H), 2.96 (t, J = 6.7 Hz, 2H).

Example 136. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(1-methylazetidin-3-yl)methoxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 738)**

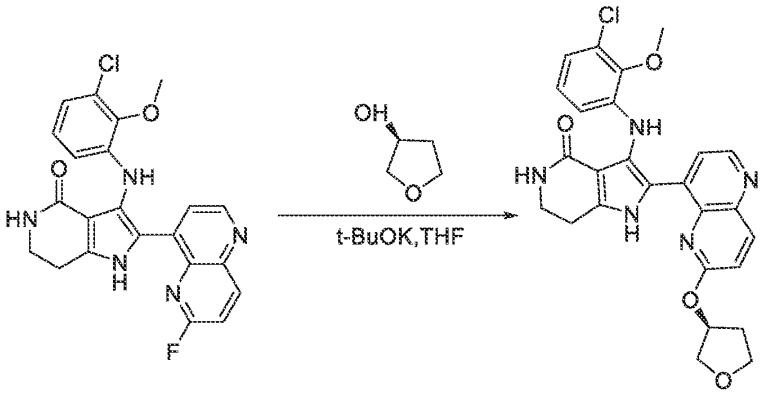


To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (40.00 mg, 0.09 mmol, 1.00 equiv) and (1-methylazetidin-3-yl)methanol (92.00 mg, 0.91 mmol, 10.00 equiv) in THF (1.00 mL) were added t-BuOK (31.00 mg, 0.27 mmol, 3.00 equiv) in portions at 0 ℃ under N_2 atmosphere. The resulting mixture was stirred for 1 h at rt under N_2 atmosphere. The resulting mixture was concentrated under reduced pressure. The resulting mixture was concentrated under vacuum and dissolved in DMF. The crude product (100.00 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 11% B to 25% B in 8 min, 25% B; Wave Length: 254/220 nm; RT1(min): 7.37) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(1-methylazetidin-3-yl)methoxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (15.90 mg, 33.54%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 519.1.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.08 (s, 1H), 8.58 (d, J = 4.8 Hz, 1H), 8.35 - 8.18 (m, 1H), 7.74 (s, 1H), 7.52 (d, J = 4.9 Hz, 1H), 7.34 (d, J = 9.1 Hz, 1H), 7.19 (d, J = 2.7 Hz, 1H), 6.75 - 6.54 (m, 2H), 6.17 (m, J = 7.7, 2.0 Hz, 1H), 4.73 (d, J = 7.0 Hz, 2H), 3.83 (s, 3H), 3.48 (m, J = 6.4, 3.3 Hz, 2H), 3.35 (s, 2H), 3.09 (t, J = 6.5 Hz, 2H), 2.92 (m, J = 12.4, 6.7 Hz, 3H), 2.26 (s, 3H).

Example 137. 3-[(3-chloro-2-methoxyphenyl) amino]-2-[6-[(3S)-oxolan-3-yloxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 739)**

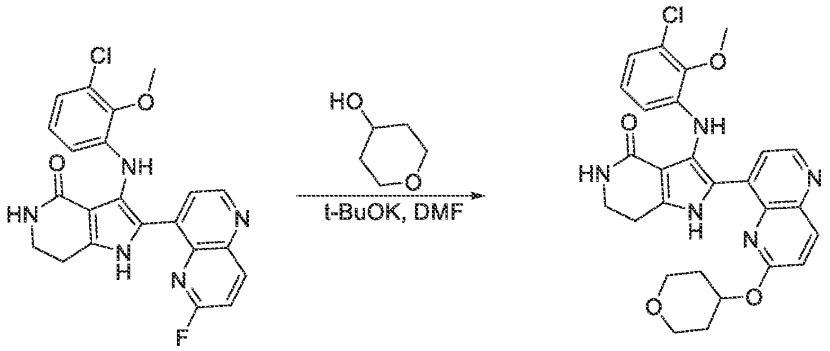


A solution of 3-[(3-chloro-2-methoxyphenyl) amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (60.00 mg, 0.18 mmol, 1.00 equiv) in THF (1.50 mL) was added (3S)-oxolan-3-ol (60.00 mg, 0.90 mmol, 5.00 equiv) and t-BuOK (46.00 mg, 0.41 mmol, 3.00 equiv) dropwise at 0 ℃. The resulting mixture was stirred for 1 h at room temperature. The reaction was monitored by LCMS. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 63% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl) amino]-2-[6-[(3S)-oxolan-3-yloxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (15.40 mg, 22.06%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 447.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.96 (s, 1H), 8.58 (d, J = 4.8 Hz, 1H), 8.30 (d, J = 8.8 Hz, 1H), 7.70 (s, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.33 (d, J = 9.2 Hz, 1H), 7.20 (s, 1H), 6.69 - 6.61 (m, 2H), 6.17 - 6.14 (m, 1H), 5.84 - 5.83 (m, 1H), 4.04 - 3.93 (m, 3H), 3.91 (s, 3H) ,3.88 - 3.81 (m, 1H), 3.48 - 3.45 (m, 2H), 2.95 (t, J = 6.8 Hz, 2H), 2.44 - 2.29 (m, 1H), 2.28 - 2.17(m,1H).

Example 138. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(oxan-4-yloxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 740)**

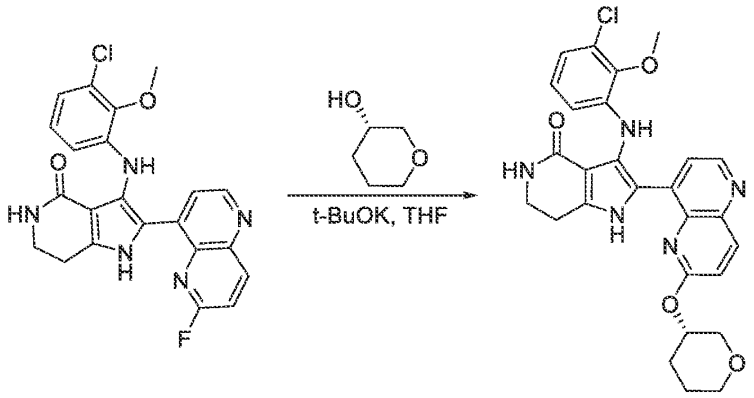


To a solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100.00 mg, 0.23 mmol, 1.00 equiv) and oxan-4-ol (116.63 mg, 1.14 mmol, 5.00 equiv) in DMF (2.00 mL) were added t-BuOK (28.19 mg, 0.25 mmol, 1.10 equiv) dropwise at 0 ℃ under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. The mixture was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 45% B in 8 min, 45% B; Wave Length: 254/220 nm; RT1(min): 7.58) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(oxan-4-yloxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (18.40 mg, 14.72%) as a red solid.

LC-MS: $(M+H)^+$ found: 520.1.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.90 (s, 1H), 8.57 (d, J = 4.8 Hz, 1H), 8.29 (d, J = 9.0 Hz, 1H), 7.72 (s, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.32 (d, J = 9.1 Hz, 1H), 7.25 - 7.17 (m, 1H), 6.75 - 6.56 (m, 2H), 6.13 (dd, J = 8.0, 1.7 Hz, 1H), 5.60 - 5.44 (m, 1H), 4.01 - 3.92 (m, 2H), 3.90 (s, 3H), 3.62 - 3.43 (m, 4H), 3.02 - 2.91 (m, 2H), 2.24 - 2.13 (m, 2H), 1.87 - 1.69 (m, 2H).

Example 139. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(3S)-oxan-3-yloxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; formic acid **(compound 741)**

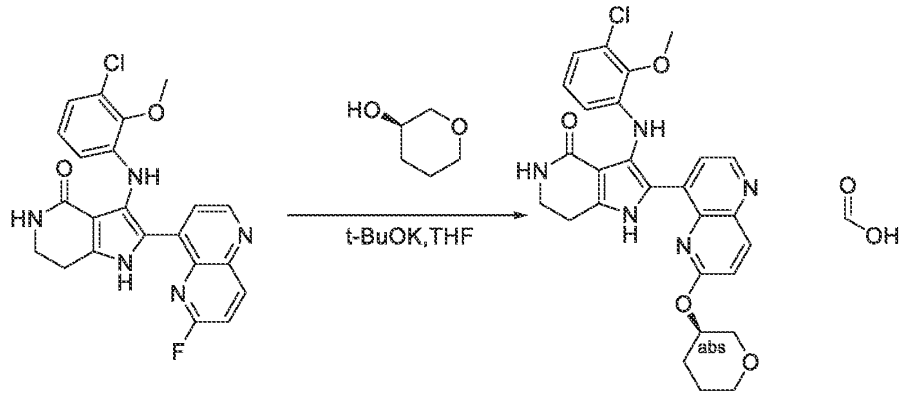


To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70.00 mg, 0.16 mmol, 1.00 equiv) in THF (2.00 mL) were added t-BuOK (35.88 mg, 0.32 mmol, 2.00 equiv) in portions at 0 ℃ under nitrogen atmosphere for 0.5 h. The crude product (100.00 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 18% B to 48% B in 10 min, 48% B; Wave Length: 220/254 nm; RT1(min): 9.35) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(3S)-oxan-3-yloxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; formic acid (13.50 mg, 14.17%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 520.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.97 (s, 1H), 8.57 (d, J = 4.8 Hz, 1H), 8.30 (d, J = 9.1 Hz, 1H), 8.21 (s, 1H), 7.69 (s, 1H), 7.50 (d, J = 4.8 Hz, 1H), 7.33 (d, J = 9.1 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 6.72 - 6.61 (m, 2H), 6.15 (dd, J = 7.9, 1.8 Hz, 1H), 5.31 (tt, J = 7.1, 3.6 Hz, 1H), 4.07 - 3.99 (m, 1H), 3.89 (s, 3H), 3.69 (ddd, J = 14.5, 11.1, 5.1 Hz, 2H), 3.59 (ddd, J = 11.0, 7.5, 3.3 Hz, 1H), 3.47 (td, J = 6.9, 2.5 Hz, 1H), 2.95 (t, J = 6.8 Hz, 2H), 2.21 (td, J = 8.1, 2.6 Hz, 1H), 1.98 – 1.81 (m, 2H), 1.64 - 1.60 (m, 1H).

Example 140. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(3R)-oxan-3-yloxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; formic acid **(compound 742)**

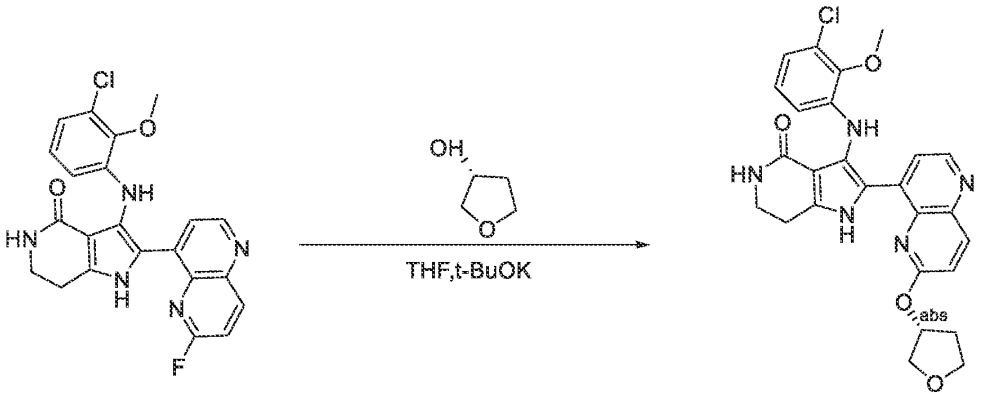


A solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50.00 mg, 0.11 mmol, 1.00 equiv) in THF (2.00 mL) was added (3R)-oxan-3-ol (58.00 mg, 0.55 mmol, 5.00 equiv) and t-BuOK (38.00 mg, 0.33 mmol, 3.00 equiv) dropwise at 0 ℃. The resulting mixture was stirred for 1 h at RT. The reaction was monitored by LCMS. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 46% B in 8 min, 46% B; Wave Length: 254/220 nm; RT1(min): 7.8) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(3R)-oxan-3-yloxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; formic acid (10.00 mg, 15.22%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 566.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.97 (s, 1H), 8.57 (d, J = 4.8 Hz, 1H), 8.30 - 8.25 (m, 2H), 7.69 (s, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.32 (d, J = 9.2 Hz, 1H), 7.21 (s, 1H), 6.70 - 6.62 (m, 2H), 6.16 - 6.13 (m, 1H), 5.31 - 5.30 (m, 1H), 4.04 - 4.00 (m, 1H), 3.89 (s, 3H), 3.69 - 3.60 (m, 2H), 3.59 - 3.57 (m, 1H), 3.48 - 3.45 (m, 2H), 2.94 (t, J = 6.8 Hz, 2H), 2.21 - 2.18 (m, 1H), 2.08 (s, 1H), 1.93 - 1.85 (m, 2H), 1.67 - 1.56 (m, 1H).

Example 141. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(3R)-oxolan-3-yloxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 743)**

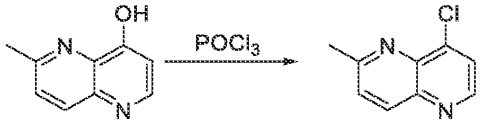


To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100.00 mg, 0.23 mmol, 1.00 equiv) and (3R)-oxolan-3-ol (20.12 mg, 0.23 mmol, 1.00 equiv) in THF (3 mL) was added t-BuOK (76.88 mg, 0.69 mmol, 3.00 equiv) dropwise at 0 ℃ under nitrogen atmosphere. The solution was stirred for 3 h at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure and dissolved in DMF. The residue was purified by silica gel column with the following conditions (column, silica gel; mobile phase, DCM in MeOH, 0% to 10% gradient in 10 min; detector, UV 254 nm) to afford crude product (100.00 mg). Then the crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 56% B in 7 min, 56% B; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(3R)-oxolan-3-yloxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (4.80 mg, 4.10%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 506.2.

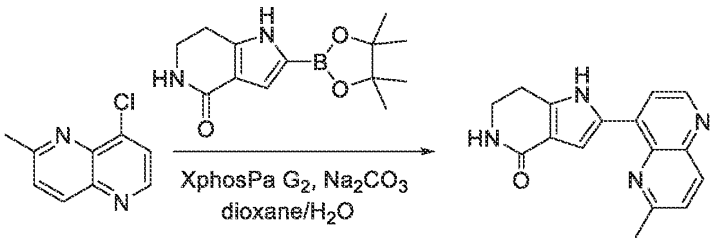
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.96 (s, 1H), 8.59 (d, J = 4.9 Hz, 1H), 8.29 (s, 1H), 7.70 (s, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.33 (d, J = 9.1 Hz, 1H), 7.20 (s, 1H), 6.72 - 6.49 (m, 2H), 6.29 - 6.08 (m, 1H), 5.85 (s, 1H), 4.00 - 3.83 (m, 7H), 3.47 (q, J = 6.2, 5.6 Hz, 2H), 2.96 (t, J = 6.8 Hz, 2H), 2.39 - 2.07 (m, 2H).

Example 142. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 749)**



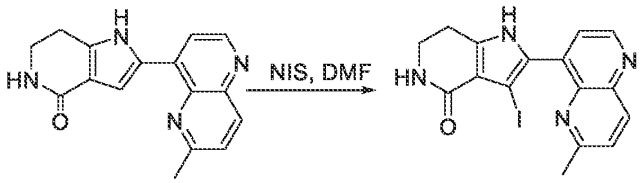
A stirred solution of 6-methyl-1,5-naphthyridin-4-ol (300.00 mg, 1.00 equiv) in $POCl_3$ (5.00 mL) was stirred for 1 h to reflux under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under vacuum and basified with saturated $NaHCO_3$ (aq.) to give 8-chloro-2-methyl-1,5-naphthyridine (170.00 mg) as off-white solid.

LC-MS: $(M+H)^+$ found: 179.0.



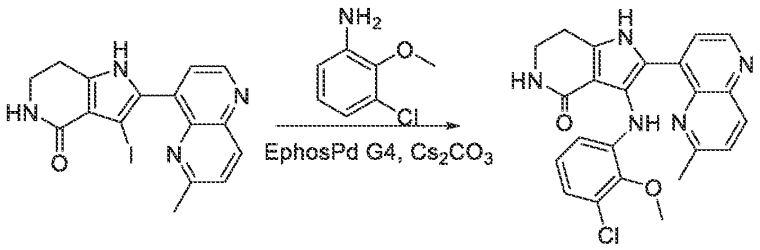
To a stirred solution/mixture of 8-chloro-2-methyl-1,5-naphthyridine (170.00 mg, 1.68 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (660.36 mg, 2.52 mmol, 1.50 equiv) in dioxane (0.50 mL) and H_2O (0.10 mg) was added Na_2CO_3 (356.02 mg, 3.36 mmol, 2.00 equiv) and XPhos-PdCl-2nd G (255.21 mg, 0.34 mmol, 0.20 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for 3 h at 60 ℃ under argon atmosphere. The resulting mixture was concentrated under vacuum. The resulting mixture was diluted with water (5mL) and stirred for 20 min. The precipitated solids were collected by filtration and washed with water (2x3 mL). The solid was washed with DCM (10 mL) and filtered to give 2-(6-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (130.00 mg, 68.46%) as brown solid which was used directly in next step.

LC-MS: $(M+H)^+$ found: 279.0.



To a stirred solution of 2-(6-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (130.00 g, 0.47 mmol, 1.00 equiv) in DMF was added NIS (126.00 mg, 0.56 mmol, 1.20 equiv) in 2 portions at room temperature under air. The resulting mixture was stirred for 2 h at room temperature under air. Desired product could be detected in LC-MS. The reaction was quenched with Na_2SO_3 (aq.) at room temperature. The resulting mixture was filtered, the filter cake was washed with water (3x10 mL) and DCM (5 mL). The filtrate was concentrated under reduced pressure to give 3-iodo-2-(6-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (140.00 mg, 74.05%).

LC-MS: $(M+H)^+$ found: 405.0.



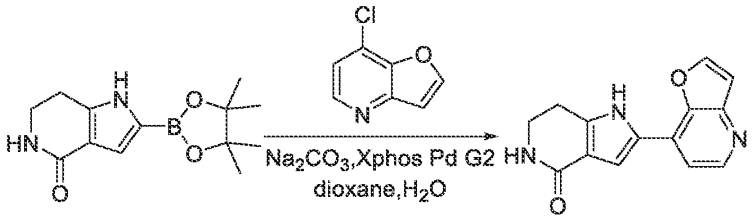
To a stirred solution of 3-iodo-2-(6-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100.00 mg, 0.25 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (58.48 mg, 0.37 mmol, 1.50 equiv) in 1,4-dioxane were added EPhos Pd G4 (45.45 mg, 0.05 mmol, 0.20 equiv) and Cs_2CO_3 (161.21 mg, 0.50 mmol, 2.00 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for 4 h at 50 ℃ under argon atmosphere. Desired product could be detected by LC-MS. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) and HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 34% B to 64% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-methyl-

1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (13.20 mg, 14.35%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 434.0.

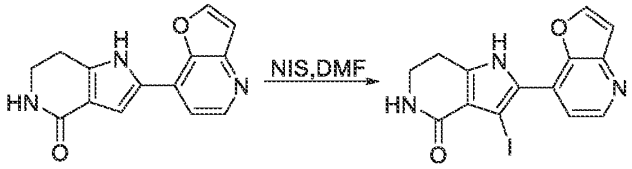
^{1}H NMR (300 MHz, CD_3OD) δ 8.54 (d, 1H), 8.26 (d, 1H), 7.71 (d, 1H), 7.61 (d, 1H), 6.71 (d, 1H), 6.65 (d, 1H), 6.23 (m, 1H), 4.01 (s, 3H), 3.34 (t, 2H), 3.29 (t, 2H), 2.90 (s, 3H).

Example 143. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[furo[3,2-b]pyridin-7-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 750)**



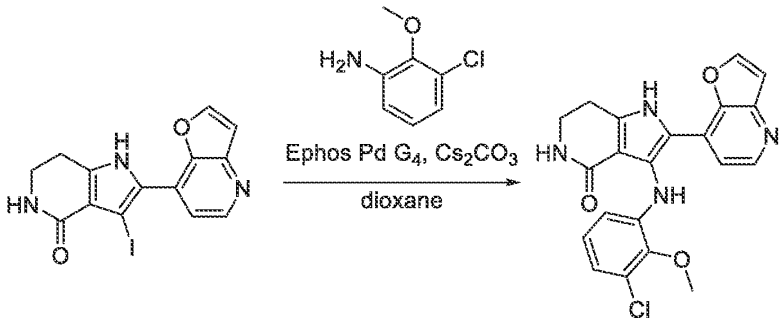
A mixture of 7-chlorofuro[3,2-b]pyridine (400.00 mg, 2.60 mmol, 1.00 equiv), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.02 g, 3.91 mmol, 1.50 equiv) and Na_2CO_3 (323.00 mg, 3.05 mmol, 2.00 equiv) in dioxane (15 mL) and water (3 mL) at room temperature under nitrogen atmosphere. To the above mixture was added 2nd Generation XPhos precatalyst (232.00 mg, 0.31 mmol, 0.20 equiv) under nitrogen atmosphere. The resulting mixture was stirred for additional overnight at 50 ℃. The resulting mixture was extracted with CH_2Cl_2 (3 x 300mL). The combined organic layers were washed with water (3x50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 2-[furo[3,2-b]pyridin-7-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (430.00 mg, 76.66%) as a brown solid.

LC-MS: $(M+H)^+$ found: 254.0.



To a stirred mixture of 2-[furo[3,2-b]pyridin-7-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (150.00 mg, 0.59 mmol, 1.00 equiv) in DMF (6.00 mL) was added NIS (160.00 mg, 0.71 mmol, 1.20 equiv) in three portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 1 h at room temperature. The resulting mixture was filtered, the filter cake was washed with water (3x5 mL). The filtrate was concentrated under reduced pressure. This resulted in 2-[furo[3,2-b]pyridin-7-yl]-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (220.00 mg, 91.31%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 380.0.

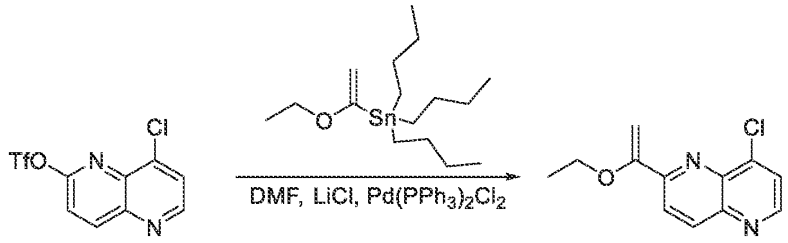


A mixture of 2-[furo[3,2-b]pyridin-7-yl]-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100.00 mg, 0.26 mmol, 1.00 equiv) in dioxane (3 mL) under argon atmosphere. To the above mixture was added 3-chloro-2-methoxyaniline (42.00 mg, 0.26 mmol, 1.00 equiv), Ephos Pd G4 (48.00 mg, 0.05 mmol, 0.20 equiv) and Cs_2CO_3 (172.00 mg, 0.53 mmol, 2.00 equiv) under argon atmosphere. The resulting mixture was stirred for additional overnight at 50 ℃. The resulting mixture was washed with 3x50mL of CH_2Cl_2/MeOH=10/1. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford product. The crude product (80.00 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 35% B in 12 min, 35% B; Wave Length: 254/220 nm; RT1(min): 11.65) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[furo[3,2-b]pyridin-7-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50.60 mg, 46.69%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 409.0.

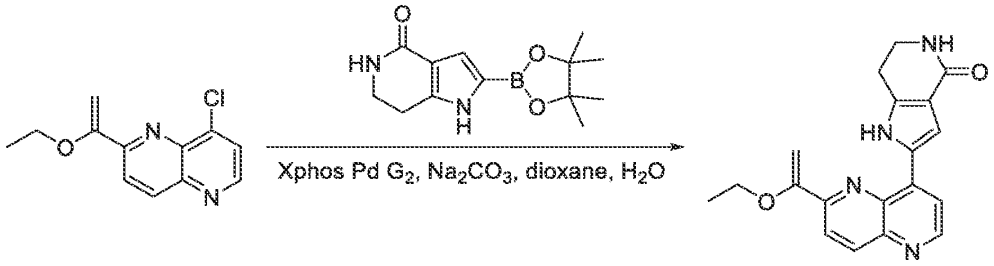
^{1}H NMR (300 MHz, DMSO-d_6) δ 11.64 (s, 1H), 8.39 - 8.27 (m, 2H), 7.58 (s, 1H), 7.30 - 7.18 (m, 2H), 7.12 (d, J = 2.3 Hz, 1H), 6.70 - 6.57 (m, 2H), 6.14 (dd, J = 7.8, 1.9 Hz, 1H), 3.91 (s, 3H), 3.44 (td, J = 6.8, 2.4 Hz, 2H), 2.93 (t, J = 6.8 Hz, 2H).

Example 144. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(1S)-1-ethoxyethyl]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid **(compound 754)**



Into a 40-mL vial, was placed 8-chloro-1,5-naphthyridin-2-yl trifluoromethanesulfonate (1.10 g, 3.52 mmol, 1.00 equiv), DMF (11.00 mL), LiCl (462.00 mg, 10.91 mmol, 3.10 equiv), $Pd(PPh_3)_2Cl_2$ (247.00 mg, 0.35 mmol, 0.10 equiv), tributyl(1-ethoxyethenyl)stannane (1.14 g, 3.17 mmol, 0.90 equiv). The resulting solution was stirred overnight at 60 ℃. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The reaction was quenched with sat. KF (aq.) at room temperature. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford 8-chloro-2-(1-ethoxyethenyl)-1,5-naphthyridine (600.00 mg, 71.21%) as a yellow solid.

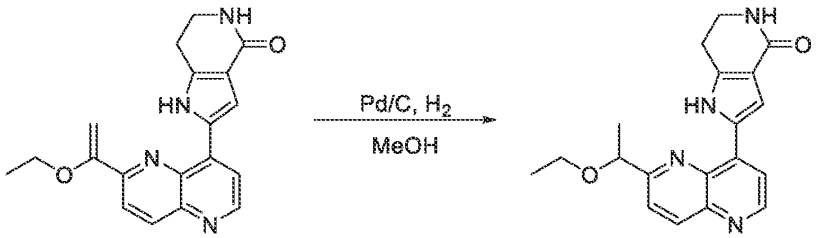
LC-MS: $(M+H)^+$ found: 235.0.



Into a 40-mL vial, was placed 8-chloro-2-(1-ethoxyethenyl)-1,5-naphthyridine (600.00

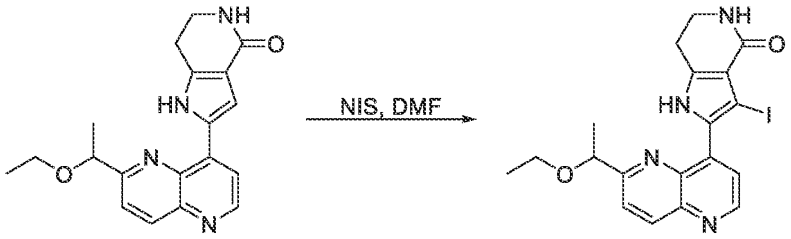
mg, 2.56 mmol, 1.00 equiv), dioxane (10 mL), H_2O (2 mL), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.01 g, 3.84 mmol, 1.50 equiv), Na_2CO_3 (542.00 mg, 5.11 mmol, 2.00 equiv), XPhos palladium(II) biphenyl-2-amine chloride (402.00 mg, 0.51 mmol, 0.20 equiv). The resulting solution was stirred for 2 h at 60 ℃. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The precipitated solids were collected by filtration and washed with water (3x10 mL) to afford 2-[6-(1-ethoxyethenyl)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (550.00 mg, 55.97%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 335.0.



To a stirred mixture of 2-[6-(1-ethoxyethenyl)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (300.00 mg, 0.90 mmol, 1.00 equiv) in MeOH (5.00 mL) was added Pd/C (477.39 mg, 0.45 mmol, 0.50 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under hydrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was filtered, the filter cake was washed with MeOH (3x50 mL). The filtrate was concentrated under reduced pressure to afford 2-[6-(1-ethoxyethyl)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (220.00 mg, 62.69%) as a yellow solid.

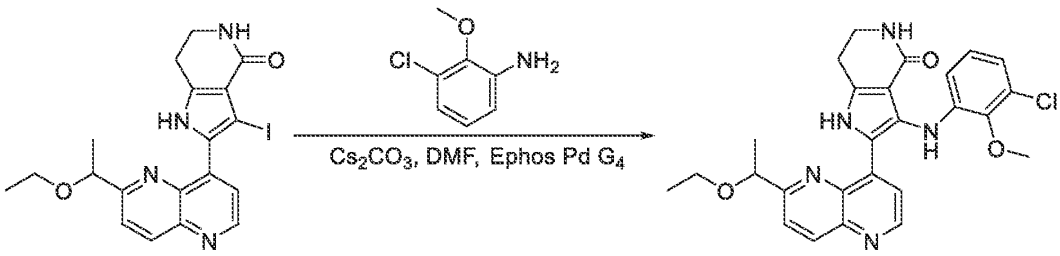
LC-MS: $(M+H)^+$ found: 337.0.



Into a 40-mL vial, was placed 2-[6-(1-ethoxyethyl)-1,5-naphthyridin-4-yl]-

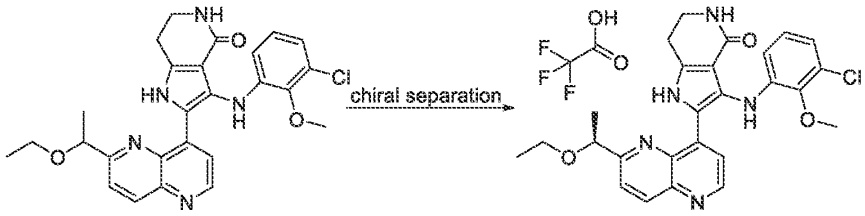
1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (360.00 mg, 1.07 mmol, 1.00 equiv), DMF (10 mL), NIS (289.00 mg, 1.28 mmol, 1.20 equiv). The resulting solution was stirred for 1 h at room temperature. The reaction was monitored by LCMS. The reaction was quenched by the addition of sat. Na_2SO_3 (aq.) (15 mL) at 0 ℃. The precipitated solids were collected by filtration and washed with water (3x50 mL) to afford 2-[6-(1-ethoxyethyl)-1,5-naphthyridin-4-yl]-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400.00 mg, 78.43%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 463.0.



Into a 40-mL vial, was placed 2-[6-(1-ethoxyethyl)-1,5-naphthyridin-4-yl]-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400.00 mg, 0.87 mmol, 1.00 equiv), DMF (9 mL), 3-chloro-2-methoxyaniline (136.00 mg, 0.87 mmol, 1.00 equiv), Ephos Pd G4 (79.00 mg, 0.09 mmol, 0.10 equiv), Cs_2CO_3 (564.00 mg, 1.73 mmol, 2.00 equiv). The resulting solution was stirred for 3 h at 50 ℃. The reaction was monitored by LCMS. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(1-ethoxyethyl)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (300.00 mg) as a red solid. The crude product (300.00 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (0.05%TFA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 21% B to 51% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(1-ethoxyethyl)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (120.00 mg, 27.91%) as a red solid.

LC-MS: $(M+H)^+$ found: 492.0.

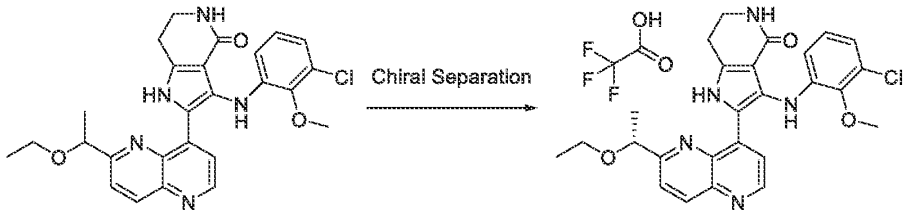


The crude product (120.00 mg) was purified by Prep-CHIRAL-HPLC with the following conditions (Column: CHIRALPAK IH, 3*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 19.5 min; Wave Length: 220/254 nm; RT1(min): 20.524; RT2(min): 24.81; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 17) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(1S)-1-ethoxyethyl]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid (37.80 mg, 25.29%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 492.0.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.84 (s, 1H), 8.73 (d, J = 4.9 Hz, 1H), 8.46 (d, J = 8.8 Hz, 1H), 7.90 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 4.8 Hz, 1H), 7.28 (t, J = 2.5 Hz, 1H), 6.81 - 6.66 (m, 2H), 6.20 (dd, J = 7.7, 1.9 Hz, 1H), 4.96 (q, J = 6.5 Hz, 1H), 3.92 (s, 3H), 3.60 (dq, J = 9.2, 7.0 Hz, 1H), 3.53 - 3.36 (m, 3H), 3.01 (t, J = 6.8 Hz, 2H), 1.54 (d, J = 6.5 Hz, 3H), 1.21 (t, J = 7.0 Hz, 3H).

Example 145. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(1R)-1-ethoxyethyl]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid **(compound 753)**



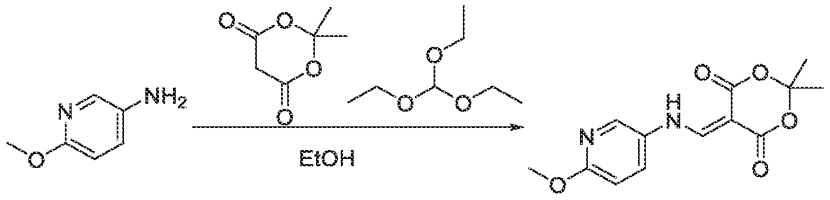
The crude product (120.00 mg) was purified by Prep-CHIRAL-HPLC with the following conditions (Column: CHIRALPAK IH, 3*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M

NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 19.5 min; Wave Length: 220/254 nm; RT1(min): 20.524; RT2(min): 24.81; Sample Solvent: EtOH--HPLC; Injection Volume: 1.5 mL; Number Of Runs: 17) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(1R)-1-ethoxyethyl]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid (41.70 mg, 28.04%) as a red solid.

LC-MS: $(M+H)^+$ found: 492.0.

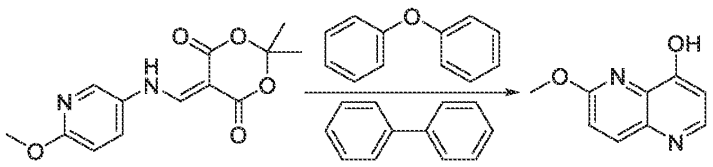
^{1}H NMR (300 MHz, DMSO-d_6) δ 12.85 (s, 1H), 8.75 (d, J = 5.0 Hz, 1H), 8.47 (d, J = 8.8 Hz, 1H), 8.01 (s, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 5.0 Hz, 1H), 7.29 (d, J = 16.8 Hz, 1H), 6.79 (dd, J = 8.1, 1.8 Hz, 1H), 6.73 (t, J = 8.0 Hz, 1H), 6.21 (dd, J = 7.9, 1.7 Hz, 1H), 4.97 (q, J = 6.5 Hz, 1H), 3.92 (s, 3H), 3.61 (dq, J = 9.1, 6.9 Hz, 1H), 3.47 (dtd, J = 13.7, 6.9, 2.3 Hz, 3H), 3.02 (t, J = 6.8 Hz, 2H), 1.54 (d, J = 6.5 Hz, 3H), 1.21 (t, J = 7.0 Hz, 3H).

Example 146. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-cyclopropyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 752)**



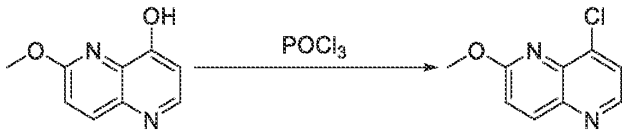
Into a 500-mL round-bottom flask, was placed 5-amino-2-methoxypyridine (10.00 g, 80.55 mmol, 1.00 equiv), ethyl alcohol (100 mL), meldrum (11.61 g, 80.55 mmol, 1.00 equiv), triethyl orthoformate (11.94 g, 80.55 mmol, 1.00 equiv). The resulting solution was stirred for 4 h at 85 ℃. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The precipitated solids were collected by filtration and washed with EtOH (3x30 mL) to afford 5-[[(6-methoxypyridin-3-yl)amino]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (19.00 g, 84.77%) as an off-white solid.

LC-MS: $(M+H)^+$ found: 279.0.



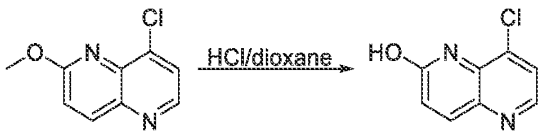
Into a 500-mL 3-necked round-bottom flask, was placed diphenyl-ether (110.25 mL), diphenyl (39.75 mL). This was followed by the addition of 5-[[(6-methoxypyridin-3-yl)amino]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (12.00 g, 43.13 mmol, 1.00 equiv) at 250 ℃. The resulting solution was stirred for 15 min at 250 ℃. Desired product could be detected by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with diethyl ether (100 mL). The precipitated solids were collected by filtration and washed with hexane (2x100 mL) to afford 6-methoxy-1,5-naphthyridin-4-ol (6.00 g, 72.66%) as a Brown yellow solid.

LC-MS: $(M+H)^+$ found: 177.0.



Into a 40-mL vial, was placed 6-methoxy-1,5-naphthyridin-4-ol (5.00 g, 28.38 mmol, 1.00 equiv), phosphorus oxychloride (50 mL). The resulting solution was stirred for 1 h at 100 ℃. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The mixture was neutralized to pH 7 with NaOH. The precipitated solids were collected by filtration and washed with water (2x50 mL) to afford 8-chloro-2-methoxy-1,5-naphthyridine (5.00 g, 84.19%) as an off-white solid.

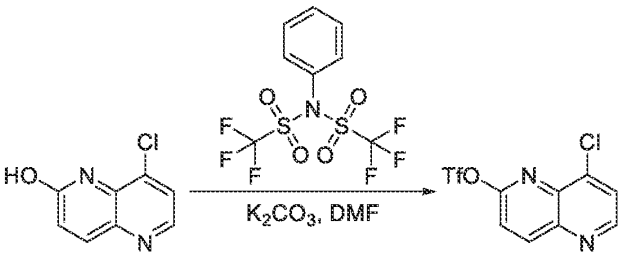
LC-MS: $(M+H)^+$ found: 195.0.



Into a 100-mL round-bottom flask, was placed 8-chloro-2-methoxy-1,5-naphthyridine (2.00 g, 10.28 mmol, 1.00 equiv), HCl(gas) in 1,4-dioxane (25 mL). The resulting solution

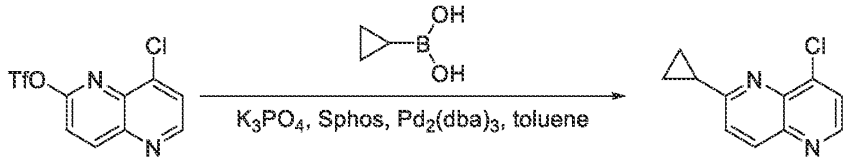
was stirred for 24 h at 100 ℃. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The precipitated solids were collected by filtration and washed with DCM (2x3 mL) to afford 8-chloro-1,5-naphthyridin-2-ol (1.40 g, 73.93%) as a Brown yellow solid.

LC-MS: $(M+H)^+$ found: 181.0.



Into a 50-mL round-bottom flask, was placed 8-chloro-1,5-naphthyridin-2-ol (1.40 g, 7.75 mmol, 1.00 equiv), DMF (20 mL), K_2CO_3 (3.75 g, 27.13 mmol, 3.50 equiv), 1,1,1-trifluoro-N-phenyl-N-trifluoro methanesulfonylmethanesulfonamide (2.91 g, 8.14 mmol, 1.05 equiv). The resulting solution was stirred for 4 h at room temperature. The reaction was monitored by LCMS. The resulting mixture was filtered, the filter cake was washed with DMF (2x3 mL). The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOEt (3x50 mL). The resulting mixture was concentrated under reduced pressure to afford 8-chloro-1,5-naphthyridin-2-yl trifluoromethanesulfonate (1.60 g, 63.37%) as a Brown yellow solid.

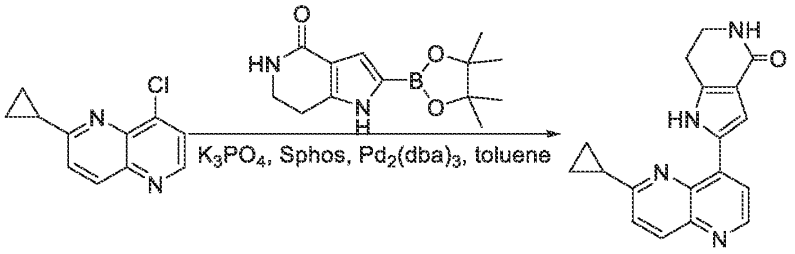
LC-MS: $(M+H)^+$ found: 313.0.



Into a 40-mL vial, was placed 8-chloro-1,5-naphthyridin-2-yl trifluoromethanesulfonate (500.00 mg, 1.60 mmol, 1.00 equiv), toluene (10 mL), cyclopropylboronic acid (144.00 mg, 1.68 mmol, 1.05 equiv), K_3PO_4 (1.02 g, 4.80 mmol, 3.00 equiv), Sphos (328.00 mg, 0.80 mmol, 0.50 equiv), $Pd_2(dba)_3$ (293.00 mg, 0.32 mmol, 0.20 equiv). The resulting solution was stirred overnight at 40 ℃. The reaction was monitored by LCMS. The

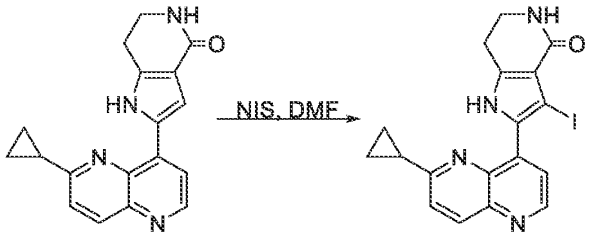
resulting mixture was concentrated under reduced pressure to afford 8-chloro-2-cyclopropyl-1,5-naphthyridine (300.00 mg, 49.50%) as a yellow solid. The residue was used in the next step directly without further purification.

LC-MS: $(M+H)^+$ found: 205.0.



Into a 40-mL vial, was placed 8-chloro-2-cyclopropyl-1,5-naphthyridine (300.00 mg, 1.47 mmol, 1.00 equiv), toluene (10 mL), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridine-4-one (576.00 mg, 2.20 mmol, 1.50 equiv), K_3PO_4 (933.00 mg, 4.40 mmol, 3.00 equiv), Sphos (301.00 mg, 0.73 mmol, 0.50 equiv), $Pd_2(dba)_3$ (268.00 mg, 0.29 mmol, 0.20 equiv). The resulting solution was stirred for 5 h at 60 ℃. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with MeOH (3 mL). The residue was purified by reverse flash chromatography with the following conditions (column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 10 min; detector, UV 254 nm) to afford 2-(6-cyclopropyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (130.00 mg, 25.35%) as a yellow solid.

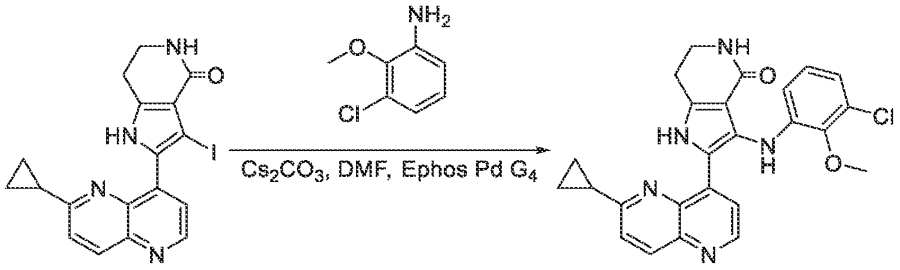
LC-MS: $(M+H)^+$ found: 305.0.



Into a 20-mL vial, was placed 2-(6-cyclopropyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (120.00 mg, 0.39 mmol, 1.00 equiv), DMF (5 mL), NIS

(106.00 mg, 0.47 mmol, 1.20 equiv). The resulting solution was stirred for 3 h at room temperature. The reaction was monitored by LCMS. The reaction was quenched with sat. Na_2SO_3 (aq.) at 0 ℃. The precipitated solids were collected by filtration and washed with water (3x6 mL) to afford 2-(6-cyclopropyl-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (90.00 mg, 36.61%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 431.0.

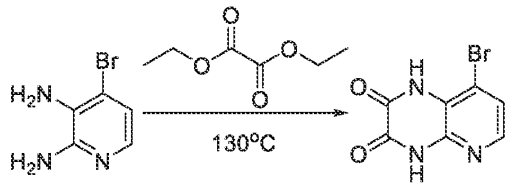


Into a 20-mL vial, was placed 2-(6-cyclopropyl-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (90.00 mg, 0.21 mmol, 1.00 equiv), DMF (4 mL), 3-chloro-2-methoxyaniline (33.00 mg, 0.21 mmol, 1.00 equiv), Ephos Pd G4 (38.00 mg, 0.04 mmol, 0.20 equiv), Cs_2CO_3 (136.00 mg, 0.42 mmol, 2.00 equiv). The resulting solution was stirred for 3 h at 50 ℃. The reaction was monitored by LCMS. The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 15:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-cyclopropyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (45.00 mg) as a yellow solid. The crude product (45.00 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 36% B to 66% B in 7 min, 66% B; Wave Length: 254/220 nm; RT1(min): 6.32) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-cyclopropyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (20.80 mg, 21.55%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 460.0.

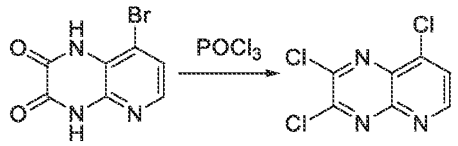
^{1}H NMR (300 MHz, DMSO-d_6) δ 12.62 (s, 1H), 8.64 (d, J = 4.8 Hz, 1H), 8.29 (d, J = 8.8 Hz, 1H), 7.84 (s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.24 (d, J = 2.6 Hz, 1H), 6.78 - 6.64 (m, 2H), 6.19 (dd, J = 7.3, 2.3 Hz, 1H), 3.88 (s, 3H), 3.47 (td, J = 6.7, 2.5 Hz, 2H), 2.98 (t, J = 6.7 Hz, 2H), 2.64 - 2.52 (m, 1H), 1.32 - 1.13 (m, 4H).

Example 147. 8-(3-((3-chloro-2-methoxyphenyl)amino)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)-2-methoxypyrido[2,3-b]pyrazin-3(4H)-one **(compound 729)**



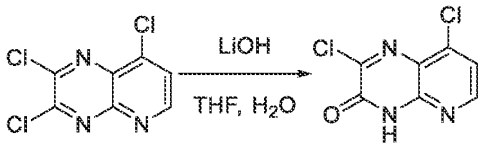
4-bromopyridine-2,3-diamine (3.00 g, 16.04 mmol, 1.00 equiv) was dissolved in diethyl oxalate (10 mL). The resulting mixture was stirred for 16 h at 130 ℃. The reaction was monitored by TLC and LCMS. The precipitated solids were collected by filtration and washed with petroleum ether (3x20 mL). This resulted in 8-bromo-1,4-dihydropyrido[2,3-b]pyrazine-2,3-dione (3.80 g, 77.69%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 242.0.



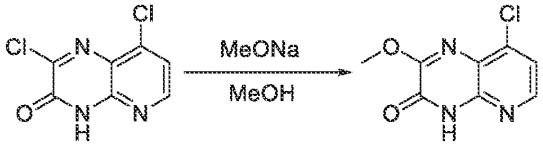
8-bromo-1,4-dihydropyrido[2,3-b]pyrazine-2,3-dione (3.00 g, 0.20 mmol, 1.00 equiv) was dissolved in $POCl_3$ (20.0 mL). The resulting mixture was stirred for overnight at 130 ℃ and cooled to room temperature. The mixture was poured into the ice water (100 mL). The precipitated solids were collected by filtration and washed with petroleum ether (3x20 mL) to afford 2,3,8-trichloropyrido[2,3-b]pyrazine (1.50 g, 51.72%) as a brown solid.

LC-MS: $(M+H)^+$ found: 234.0.



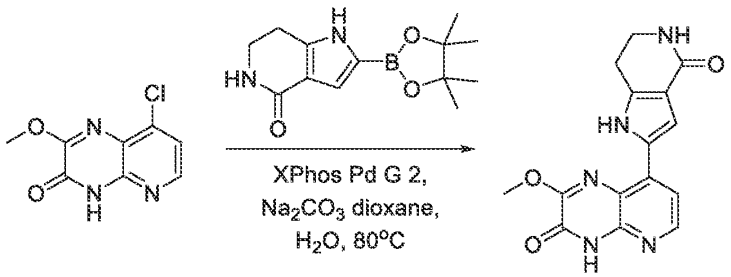
2,3,8-trichloropyrido[2,3-b]pyrazine (1.50 g, 6.44 mmol, 1.00 equiv) was dissolved in THF (20.0 mL) and H_2O (8 mL). Then LiOH (309.00 mg, 12.88 mmol, 2.00 equiv) was added. The resulting mixture was stirred for 3 h at 50 ℃. The precipitated solids were collected by filtration and washed with petroleum ether (3x20 mL) to afford 2,8-dichloropyrido[2,3-b]pyrazin-3(4H)-one (1.10 g, 79.71%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 216.0.



2,8-dichloropyrido[2,3-b]pyrazin-3(4H)-one (1.00 g, 4.65 mmol, 1.00 equiv) was dissolved in MeOH (10.0 mL). Then NaOMe (502.20 mg, 9.30 mmol, 2.00 equiv) was added. The resulting mixture was stirred for overnight at 50 ℃ and cooled to room temperature. The mixture was poured into NH_4Cl aq. (30 mL). The precipitated solids were collected by filtration and washed with petroleum ether (3x10 mL). This resulted in 8-chloro-2-methoxypyrido[2,3-b]pyrazin-3(4H)-one (500.00 mg, 51.0%) as a brown solid.

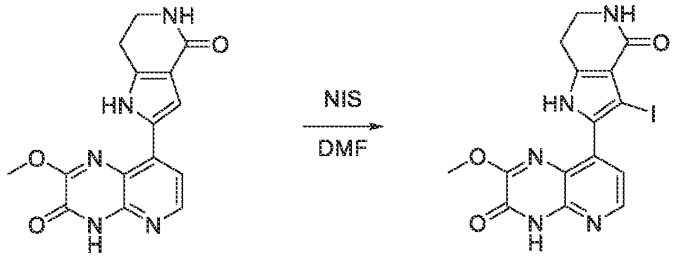
LC-MS: $(M+H)^+$ found: 212.0.



8-chloro-2-methoxypyrido[2,3-b]pyrazin-3(4H)-one (250.00 mg, 1.18 mmol, 1.00 equiv) was dissolved in dioxane (5.0 mL) and H_2O (0.2 mL). Then 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (463.70 mg, 1.77

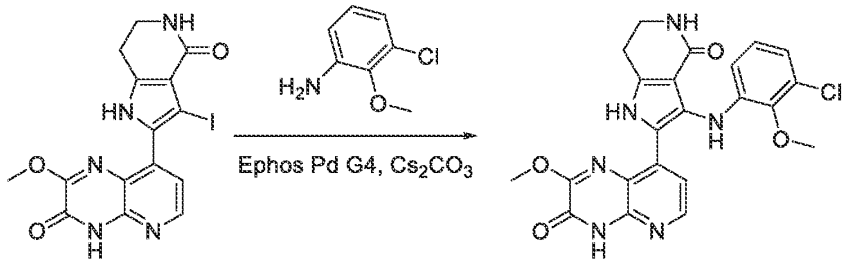
mmol, 1.50 equiv), XPhos Pd G 2 (94.30 mg, 0.12 mmol, 0.10 equiv) and Na_2CO_3 (375.20 mg, 3.54 mmol, 3.00 equiv) were added. The resulting mixture was stirred for 2 h at 80 ℃ under N_2 and cooled to room temperature. The precipitated solids were collected by filtration and washed with dioxane (3x5 mL) to afford 2-methoxy-8-(4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)pyrido[2,3-b]pyrazin-3(4H)-one (260.00 mg, 70.7%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 312.0.



2-methoxy-8-(4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)pyrido[2,3-b]pyrazin-3(4H)-one (260.00 mg, 0.84 mmol, 1.00 equiv) was dissolved in DMF (3.0 mL). Then NIS (378.00 mg, 1.68 mmol, 2.00 equiv) was added. The resulting mixture was stirred for overnight at RT. The mixture was poured into Na_2SO_3 aq. (0.5 mL). The precipitated solids were collected by filtration and washed with petroleum ether (3x3 mL) to afford 8-(3-iodo-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)-2-methoxypyrido [2,3-b]pyrazin-3(4H)-one (160.00 mg, 43.8%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 438.0.



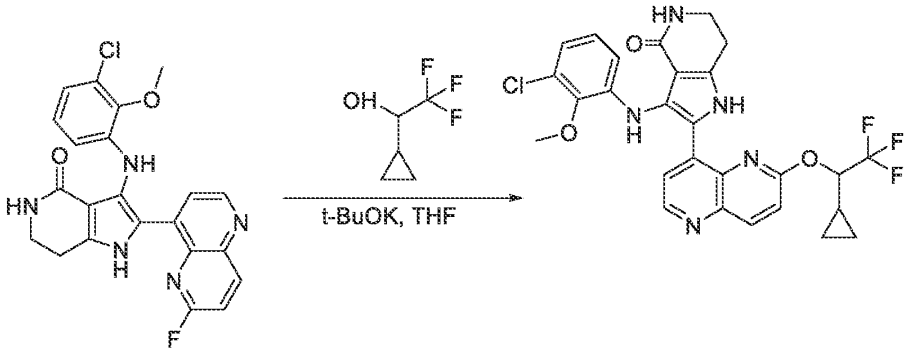
8-(3-iodo-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)-2-methoxypyrido[2,3-b]pyrazin-3(4H)-one (100.00 mg, 0.23 mmol, 1.00 equiv) was dissolved in DMF (2 mL). Then 3-chloro-2-methoxyaniline (35.90 mg, 0.23 mmol, 1.00

equiv), EPhos Pd G 4 (21.01 mg, 0.02 mmol, 0.10 equiv) and Cs_2CO_3 (149.05 mg, 0.46 mmol, 2.00 equiv) were added. The resulting mixture was stirred for 3 h at 50 ℃ under N_2 and cooled to room temperature. The crude product was purified by Prep-HPLC with the following conditions ((2# SHIMADZU HPLC-01): Column, XBridge Prep OBD C18 Column, 30*150 mm, 5μm; mobile phase, Water (10 mmol/L NH_4HCO_3) and CAN (18% Phase B up to 48% in 7 min); Detector, UV 254/210 nm) to afford 8-(3-((3-chloro-2-methoxyphenyl)amino)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)-2-methoxypyrido[2,3-b]pyrazin-3(4H)-one (24.00 mg, 22.47%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 467.0.

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.44 (s, 1H), 11.62 (s, 1H), 8.12 (d, J = 5.1 Hz, 1H), 7.68 (s, 1H), 7.21 (d, J = 5.1 Hz, 1H), 7.16 (s, 1H), 6.69 - 6.64 (m, 2H), 6.20 (dd, J = 5.7, 3.9 Hz, 1H), 4.13 (s, 3H), 3.87 (s, 3H), 3.45 - 3.43 (m, 2H), 2.94 - 2.90 (m, 2H).

Example 148. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-[[1-(trifluoromethyl)cyclopropyl]methoxy]-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 758)**



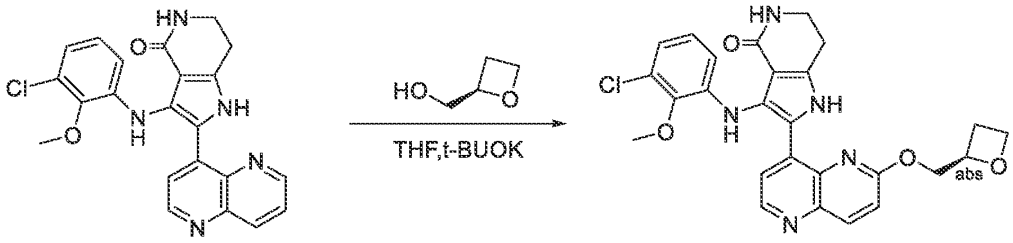
To a stirred solution of 3-[(3-chloro-2-methoxyphenyl) amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (45.00 mg, 0.10 mmol, 1.00 equiv) and [1-(trifluoromethyl) cyclopropyl]methanol (72.00 mg, 0.51 mmol, 5.00 equiv) in THF (1 mL) was added t-BuOK (35.00 mg, 0.31 mmol, 3.00 equiv) dropwise at 0 ℃. The resulting mixture was stirred for 1 h at room temperature. The reaction was monitored by LCMS. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A:

Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 41% B to 63% B in 8 min, 63% B; Wave Length: 254/220 nm; RT1(min): 8) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-[[1-(trifluoromethyl)cyclopropyl]methoxy]-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (14.70 mg, 25.15%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 558.0.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.58 (d, J = 4.8 Hz, 1H), 8.31 (d, J = 9.0 Hz, 1H), 7.75 (s, 1H), 7.52 (d, J = 4.8 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 7.21 (s, 1H), 6.69 - 6.58 (m, 2H), 6.15 - 6.12 (m, 1H), 4.78 (s, 2H) 3.88 (s, 3H), 3.48 - 3.46 (m, 2H), 2.92 (t, J = 6.9 Hz, 2H), 1.17 - 1.10 (m, 4H).

Example 149. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(2R)-oxetan-2-ylmethoxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 734)**



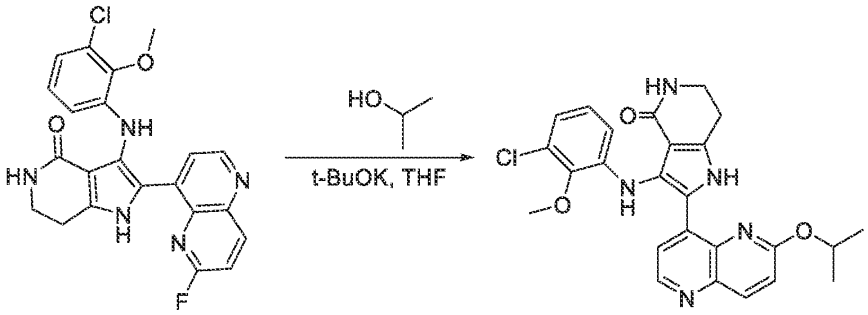
To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (45.00 mg, 0.11 mmol, 1.00 equiv) and (2R)-oxetan-2-ylmethanol (9.44 mg, 0.11 mmol, 1.00 equiv) in THF (3 mL) was added t-BuOK (36.08 mg, 0.32 mmol, 3.00 equiv) in portions at rt under Ar atmosphere. The resulting mixture was stirred for 1 h at 50 ℃ under Ar atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure and dissolved in DMF. The residue was purified by silica gel column with the following conditions (column, silica gel; mobile phase, DCM in MeOH, 0% to 10% gradient in 10 min; detector, UV 254 nm) to afford crude product (45.00 mg). The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 56% B in 7 min, 56% B; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-

[(2R)-oxetan-2-ylmethoxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (9.20 mg, 16.73%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 506.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 (s, 1H), 8.58 (d, J = 4.8 Hz, 1H), 8.32 (d, J = 9.1 Hz, 1H), 7.78 (s, 1H), 7.51 (d, J = 4.9 Hz, 1H), 7.41 (d, J = 9.1 Hz, 1H), 7.20 (t, J = 2.4 Hz, 1H), 6.73 - 6.62 (m, 2H), 6.18 (dd, J = 7.9, 1.8 Hz, 1H), 5.20 (q, J = 6.6, 5.3 Hz, 1H), 4.94 - 4.25 (m, 4H), 3.90 (s, 3H), 3.32 (s, 2H), 2.95 (d, J = 1.7 Hz, 2H), 2.51 (p, J = 1.9 Hz, 2H).

Example 150. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-isopropoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 762)**

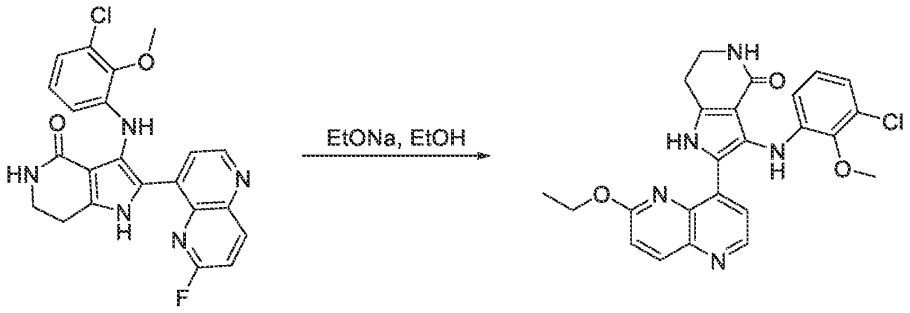


To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (40.00 mg, 0.09 mmol, 1.00 equiv) and Cs_2CO_3 (89.29 mg, 0.27 mmol, 3.00 equiv) in isopropyl alcohol (0.50 mL) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The crude product (60.00 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 47% B to 72% B in 9 min, 72% B; Wave Length: 254/220 nm; RT1(min): 8.85) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-isopropoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (10.10 mg, 23.13%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 478.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H), 8.56 (d, J = 4.9 Hz, 1H), 8.27 (d, J = 9.1 Hz, 1H), 7.71 (s, 1H), 7.50 (d, J = 4.9 Hz, 1H), 7.28-7.23 (m, 2H), 6.71-6.67 (t, J = 7.9 Hz, 2H), 6.18 (dd, J = 7.7, 1.9 Hz, 1H), 5.45-5.51 (m, J = 6.2 Hz, 1H), 3.89 (s, 3H), 3.47 (td, J = 6.9, 2.5 Hz, 2H), 2.95 (t, J = 6.8 Hz, 2H), 1.47 (d, J = 6.2 Hz, 6H).

Example 151. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-ethoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 761)**



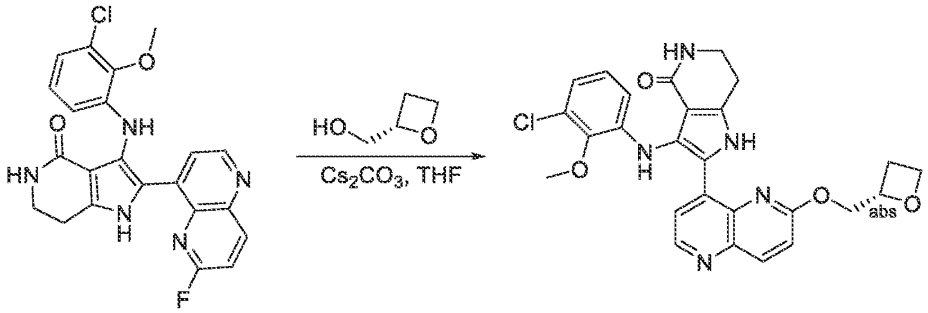
A mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50.00 mg, 0.11 mmol, 1.00 equiv) in EtOH (1.10 mL) was added EtONa (23.31 mg, 0.33 mmol, 3.00 equiv) at 0 ℃ and stirred for 1 h. The resulting mixture was concentrated under reduced pressure and purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 43% B to 60% B in 8 min, 60% B; Wave Length: 254/220 nm; RT1(min): 7.5) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-ethoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (14.00 mg, 26.14%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 464.1.

^{1}H NMR (400 MHz, DMSO-$d6$): δ 12.13 (s, 1H), 8.58 (d, J = 4.8 Hz, 1H), 8.29 (d, J = 9.1 Hz, 1H), 7.76 (s, 1H), 7.50 (d, J = 4.9 Hz, 1H), 7.33 (d, J = 9.1 Hz, 1H), 7.24 - 7.17 (m, 1H), 6.79 - 6.58 (m, 2H), 6.19 (dd, J = 7.0, 2.6 Hz, 1H), 4.62 (q, J = 7.0 Hz, 2H), 3.86 (s, 3H), 3.47 (td, J = 6.8, 2.4 Hz, 2H), 2.95 (t, J = 6.8 Hz, 2H), 1.48 (t, J = 7.0 Hz, 3H).

Example 152. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(2S)-oxetan-2-ylmethoxy]-

1,5-naphthyridin-4-yl]-1H,5H,6H, 7H-pyrrolo[3,2-c]pyridin-4-one **(compound 735)**

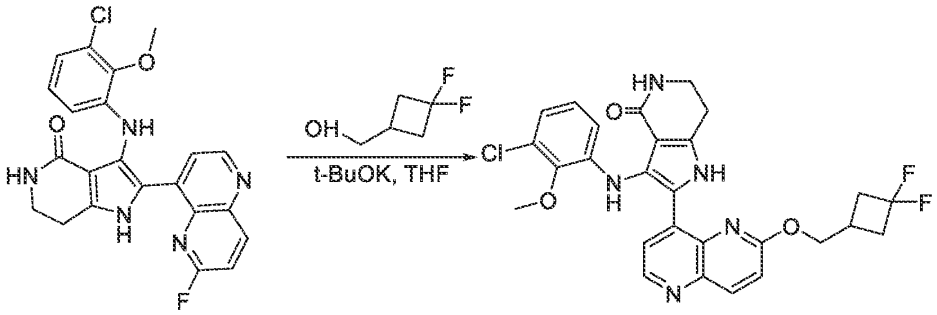


To a solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (65.00 mg, 0.15 mmol, 1.00 equiv) and (2S)-oxetan-2-ylmethanol (65.40 mg, 0.75 mmol, 5.00 equiv) in THF (1.50 mL) were added Cs_2CO_3 (145.10 mg, 0.44 mmol, 3.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 63% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(2S)-oxetan-2-ylmethoxy]-1,5-naphthyridin-4-yl]-1H,5H,6H, 7H-pyrrolo[3,2-c]pyridin-4-one (17.40 mg) as a brown solid.

LC-MS: $(M+H)^+$ found: 506.1.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (s, 1H), 8.58 (d, J = 4.9 Hz, 1H), 8.32 (d, J = 9.1 Hz, 1H), 7.78 (s, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.20 (t, J = 2.6 Hz, 1H), 6.83 - 6.55 (m, 2H), 6.18 (dd, J = 7.8, 1.8 Hz, 1H), 5.26 - 5.13 (m, 1H), 4.90 - 4.40 (m, 4H), 3.89 (s, 3H), 3.50 (td, J = 6.9, 2.5 Hz, 2H), 3.06 - 2.88 (m, 2H), 2.84 - 2.59 (m, 2H).

Example 153. 3-[(3-chloro-2-methoxyphenyl) amino]-2-[6-[(3,3-difluorocyclobutyl)methoxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 757)**

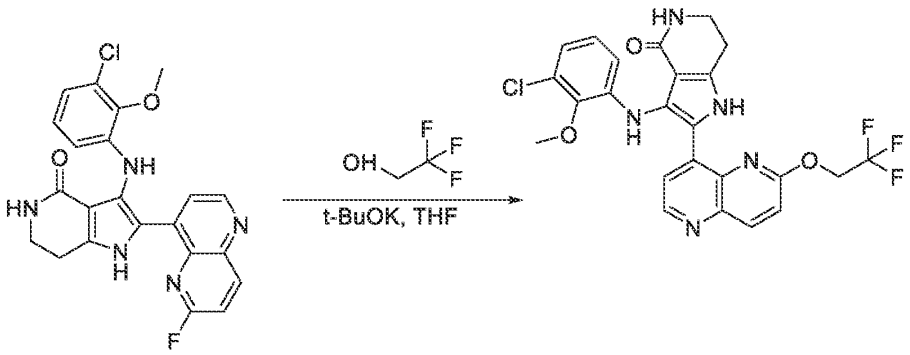


To a stirred solution of 3-[(3-chloro-2-methoxyphenyl) amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (50.00 mg, 0.11 mmol, 1.00 equiv) and (3,3-difluorocyclobutyl) methanol (69.72 mg, 0.57 mmol, 5.00 equiv) in THF (1 mL) were added t-BuOK (38.44 mg, 0.34 mmol, 3.00 equiv) in portions at 0 ℃ under nitrogen atmosphere. The resulting solid was dried in an oven under reduced pressure. The crude product (50.00 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5 μ m, n; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 41% B to 54% B in 7 min, 54% B; Wave Length: 254/220 nm; RT1(min): 6.37) to afford 3-[(3-chloro-2-methoxyphenyl) amino]-2-[6-[(3,3-difluorocyclobutyl)methoxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (12.90 mg,19.98%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 416.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 8.58 (d, J = 4.8 Hz, 1H), 8.30 (d, J = 9.0 Hz, 1H), 8.17 (s, 1H), 7.77 (s, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.35 (d, J = 9.1 Hz, 1H), 7.22 (d, J = 2.6 Hz, 1H), 6.77 - 6.62 (m, 2H), 6.17 - 6.15 (m, 1H), 4.66 (d, J = 5.9 Hz, 2H), 3.88 (s, 3H), 3.47 (td, J = 6.9, 2.5 Hz, 2H), 2.94 (t, J = 6.8 Hz, 2H), 2.79 - 2.77 (m, 3H), 2.64 - 2.49 (m, 1H).

Example 154. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(2,2,2-trifluoroethoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 763)**

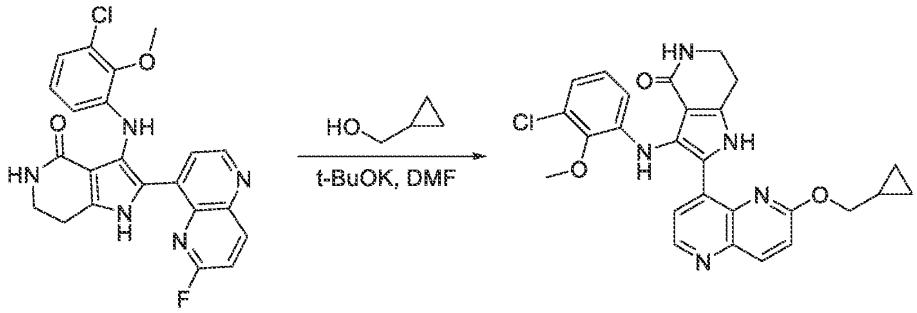


A solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (44.00 mg, 0.10 mmol, 1.00 equiv) in THF (2 mL) was added trifluoroethanol (50.00 mg, 0.50 mmol, 5.00 equiv) and t-BuOK (34.00 mg, 0.30 mmol, 3.00 equiv) dropwise at 0 ℃. The resulting mixture was stirred for 1 h at room temperature. The reaction was monitored by LCMS. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 70% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(2,2,2-trifluoroethoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (14.70 mg) as a yellow solid.

LC-MS: $(M+H)^+$ found: 518.0.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.76 (s, 1H), 8.63 (d, J = 4.8 Hz, 1H), 8.39 (d, J = 6.3 Hz, 1H), 7.82 (s, 1H), 7.55 - 7.47 (m, 2H), 7.23 (s, 1H), 6.69 - 6.57 (m, 2H), 6.13 (d, J = 6.9 Hz, 1H), 5.37 - 6.28 (m, 2H), 3.90 (s, 3H), 3.49 - 3.45 (m, 2H), 2.93 (t, J = 6.6 Hz, 2H).

Example 155. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(cyclopropylmethoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 755)**

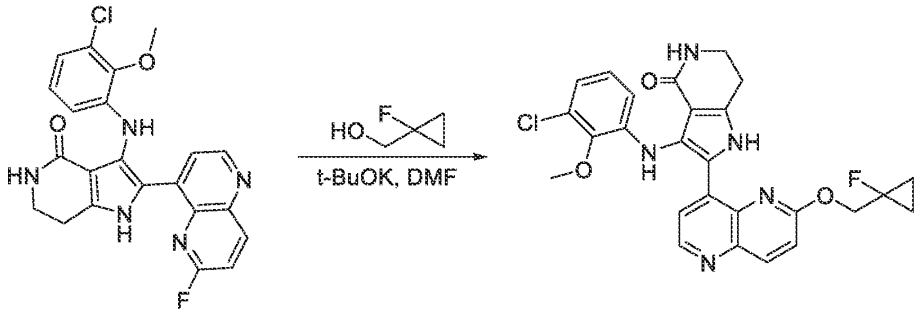


To a solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (60.00 mg, 0.14 mmol, 1.00 equiv) and cyclopropylmethanol (49.40 mg, 0.69 mmol, 5.00 equiv) in DMF (1.50 mL) were added t-BuOK (16.91 mg, 0.15 mmol, 1.10 equiv) dropwise at 0 ℃ under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0 ℃ under nitrogen atmosphere. The mixture was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 43% B to 68% B in 7 min, 68% B; Wave Length: 254/220 nm; RT1(min): 6.32) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(cyclopropylmethoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (16.30 mg, 24.04%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 490.0.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.14 (s, 1H), 8.57 (d, J = 4.9 Hz, 1H), 8.29 (d, J = 9.1 Hz, 1H), 7.74 (s, 1H), 7.50 (d, J = 4.8 Hz, 1H), 7.37 (d, J = 9.1 Hz, 1H), 7.23 - 7.18 (m, 1H), 6.84 - 6.56 (m, 2H), 6.16 (dd, J = 7.8, 1.9 Hz, 1H), 4.43 (d, J = 7.1 Hz, 2H), 3.88 (s, 3H), 3.47 (td, J = 6.9, 2.5 Hz, 2H), 2.92 (t, J = 6.8 Hz, 2H), 1.48 - 1.30 (m, 1H), 0.73 - 0.56 (m, 2H), 0.49 - 0.33 (m, 2H).

Example 156. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(1-fluorocyclopropyl)methoxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 759)**

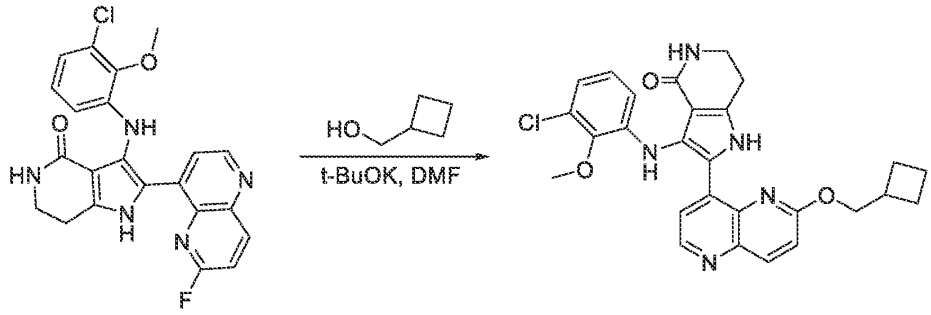


To a solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70.00 mg, 0.16 mmol, 1.00 equiv) and (1-fluorocyclopropyl)methanol (72.02 mg, 0.80 mmol, 5.00 equiv) in DMF (2 mL) were added t-BuOK (19.73 mg, 0.18 mmol, 1.10 equiv) dropwise at 0 ℃ under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0 ℃ under nitrogen atmosphere. The mixture was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 37% B to 57% B in 10 min, 57% B; Wave Length: 254/220 nm; RT1(min): 8.85) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(1-fluorocyclopropyl)methoxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (16.70 mg, 20.50%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 508.0.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.94 (s, 1H), 8.59 (d, J = 4.8 Hz, 1H), 8.33 (d, J = 9.1 Hz, 1H), 7.77 (s, 1H), 7.52 (d, J = 4.9 Hz, 1H), 7.44 (d, J = 9.1 Hz, 1H), 7.25 - 7.17 (m, 1H), 6.80 - 6.51 (m, 2H), 6.15 (dd, J = 7.9, 1.7 Hz, 1H), 4.93 (d, J = 23.3 Hz, 2H), 3.88 (s, 3H), 3.47 (td, J = 6.9, 2.5 Hz, 2H), 2.93 (t, J = 6.8 Hz, 2H), 1.29 - 1.11 (m, 2H), 1.03 - 0.88 (m, 2H).

Example 157 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(cyclobutylmethoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 756)**

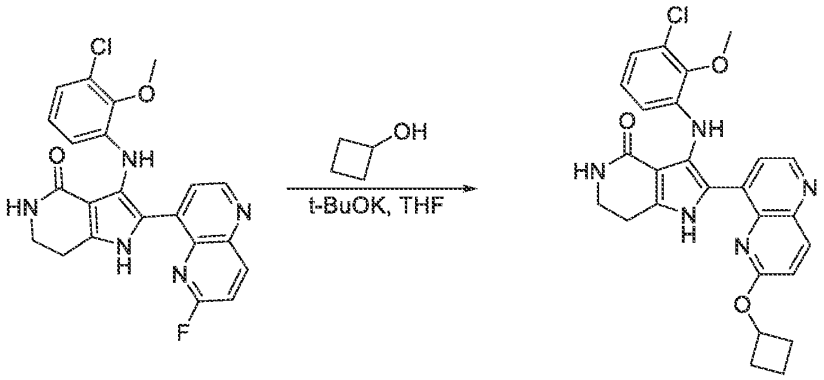


To a solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80.00 mg, 0.18 mmol, 1.00 equiv) and cyclobutylmethanol (78.69 mg, 0.91 mmol, 5.00 equiv) in DMF (1.80 mL) were added t-BuOK (22.55 mg, 0.20 mmol, 1.10 equiv) dropwise at 0 ℃ under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0 ℃ under nitrogen atmosphere. The mixture was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 60% B in 10 min, 60% B; Wave Length: 254/220 nm; RT1(min): 10.38) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(cyclobutylmethoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (19.20 mg, 19.95%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 504.1.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.18 (s, 1H), 8.57 (d, J = 4.9 Hz, 1H), 8.28 (d, J = 9.1 Hz, 1H), 7.75 (s, 1H), 7.51 (d, J = 4.9 Hz, 1H), 7.34 (d, J = 9.1 Hz, 1H), 7.23 - 7.19 (m, 1H), 6.77 - 6.58 (m, 2H), 6.17 (dd, J = 7.8, 1.9 Hz, 1H), 4.57 (d, J = 6.9 Hz, 2H), 3.88 (s, 3H), 3.48 (td, J = 6.9, 2.5 Hz, 2H), 3.04 - 2.78 (m, 3H), 2.23 - 2.07 (m, 2H), 2.02 - 1.81 (m, 4H).

Example 158. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-cyclobutoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one **(compound 768)**

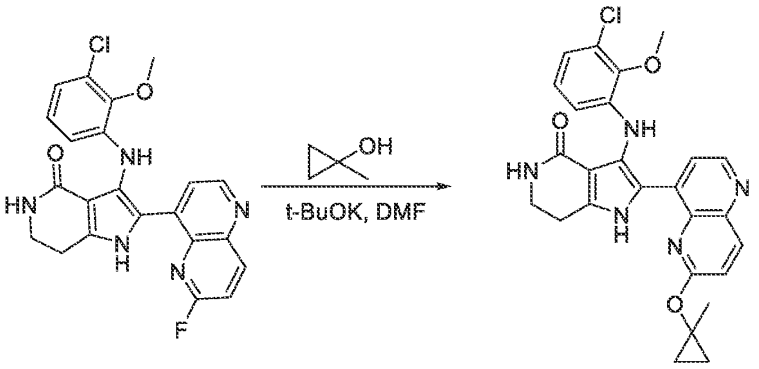


To a stirred solution of 3-[(3-chloro-2-methoxyphenyl) amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (10.00 mg, 0.02 mmol, 1.00 equiv) and cyclobutanol (8.23 mg, 0.11 mmol, 5.00 equiv) in DMF (0.50 mL) were added t-BuOK (2.82 mg, 0.03 mmol, 1.10 equiv) in portions at degrees 0 ℃ under nitrogen atmosphere. The crude product (60.00 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 46% B to 76% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-cyclobutoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (9.90 mg, 17.59%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 490.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H), 8.58 (d, J = 4.9 Hz, 1H), 8.30 (d, J = 9.1 Hz, 1H), 7.70 (s, 1H), 7.51 (d, J = 4.9 Hz, 1H), 7.33 (d, J = 9.0 Hz, 1H), 7.24 (s, 1H), 6.75 - 6.65 (m, 2H), 6.17 - 6.15 (m, 1H), 5.53 (p, J = 7.2 Hz, 1H),3.90 (s, 3H), 3.54 - 3.42 (m, 2H), 3.00 (t, J = 6.8 Hz, 2H), 2.51 (p, J = 1.8 Hz, 2H), 2.35 - 2.13 (m, 2H), 1.99 - 1.68 (m, 2H).

Example 159. 3-[(3-chloro-2-methoxyphenyl) amino]-2-[6-(1-methylcyclopropoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 767)**

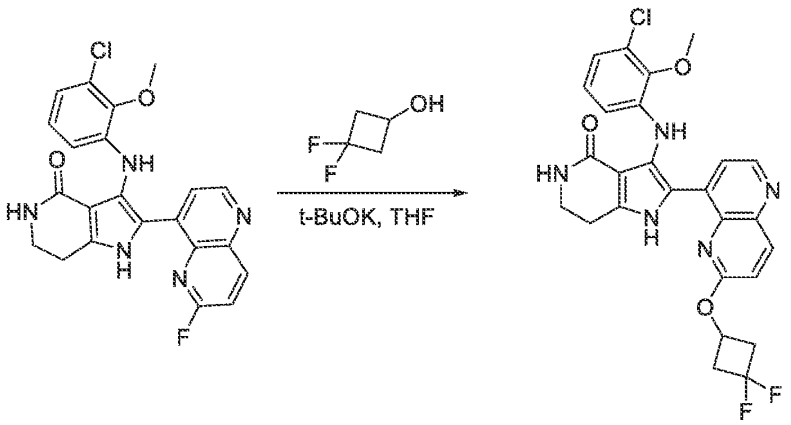


To a stirred solution of 3-[(3-chloro-2-methoxyphenyl) amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (80.00 mg, 0.18 mmol, 1.00 equiv) and 1-methylcyclopropan-1-ol (131.74 mg, 1.83 mmol, 10.00 equiv) in DMF (1.2 mL) were added t-BuOK (24.60 mg, 0.22 mmol, 1.20 equiv) in portions at 0 ℃ under nitrogen atmosphere. The resulting mixture was stirred for additional 3 h at 50 ℃. The crude product (80.00 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45% B to 75% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl) amino]-2-[6-(1-methylcyclopropoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (15.00 mg, 16.54%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 490.0.

^{1}H NMR (400 MHz, DMSO-*d*6) δ 12.95 (s, 1H), 8.57 (d, J = 4.9 Hz, 1H), 8.31 (d, J = 9.1 Hz, 1H), 7.78 (s, 1H), 7.51 (d, J = 4.9 Hz, 1H), 7.33 - 7.26 (m, 2H), 6.87 - 6.63 (m, 2H), 6.21 - 6.19 (m, 1H), 3.97 (s, 3H), 3.48 (td, J = 6.7, 2.4 Hz, 2H), 3.01 (t, J = 6.8 Hz, 2H), 1.80 (s, 3H), 1.26 - 1.15 (m, 2H), 1.07 - 0.95 (m, 2H).

Example 160. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(3,3-difluorocyclobutoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3, 2 -c] pyridin-4-one **(compound 766)**

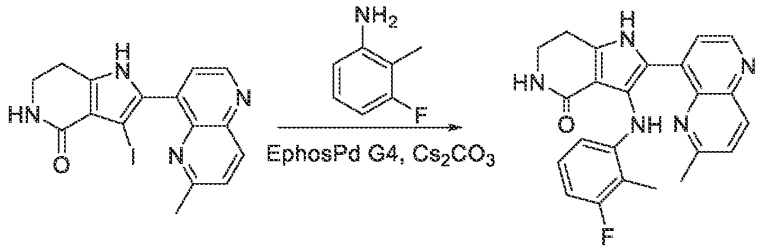


To a stirred solution of 3-[(3-chloro-2-methoxyphenyl) amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (80.00 mg, 0.18 mmol, 1.00 equiv) and 3,3-difluorocyclobutan-1-ol (197.48 mg, 1.83 mmol, 10.00 equiv) in DMF (1.20 mL) were added t-BuOK (22.55 mg, 0.20 mmol, 1.10 equiv) in portions at 0 ℃ under nitrogen atmosphere. The crude product (80.00 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 37% B to 57% B in 8 min, 57% B; Wave Length: 254/220 nm; RT1(min): 8) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(3,3-difluorocyclobutoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3, 2 -c] pyridin-4-one (13.60 mg, 13.62%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 526.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.62 (d, J = 4.9 Hz, 1H), 8.35 (d, J = 9.1 Hz, 1H), 7.65 (s, 1H), 7.53 (d, J = 4.8 Hz, 1H), 7.39 (d, J = 9.1 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 6.72 - 6.59 (m, 2H), 6.14 - 6.12 (m, 1H), 5.58 (d, J = 6.4 Hz, 1H), 3.88 (s, 3H), 3.49 (td, J = 6.9, 2.6 Hz, 2H), 3.22 - 3.04 (m, 2H), 3.01 - 2.80 (m, 4H).

Example 161. 3-[(3-fluoro-2-methylphenyl)amino]-2-(6-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 810)**

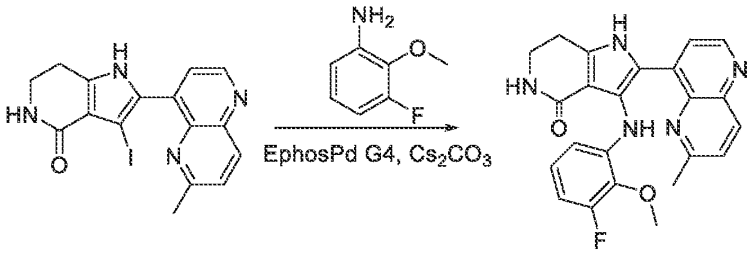


To a stirred solution of 3-iodo-2-(6-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) and 3-fluoro-2-methyl-aniline (29 mg, 0.23 mmol, 1.2 equiv) in DMF was added Cs_2CO_3 (128.97 mg, 0.396 mmol, 2 equiv) and EPhos Pd G4 (36 mg, 0.04 mmol, 0.2 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for 3h at 50°C under argon atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (DCM / MeOH 10:1) to give the crude product. Then the crude product was The crude product (40mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 50% B in 9 min, 50% B; Wave Length: 254/220 nm; RT1(min): 8.85) to afford 3-[(3-fluoro-2-methylphenyl)amino]-2-(6-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (28.4 mg, 35.24%) as an orange solid.

LC-MS: $(M+H)^+$ found: 402.30.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.62 (d, 1H), 8.61 (d, 1H), 8.30 (d, 1H), 7.72 (t, 2H), 7.44 (d, 1H), 7.27 (s, 1H), 6.76 (m, 1H), 6.51 (t, 1H), 6.11 (d, 1H),3.48 (t, 2H), 3.00 (t, 2H), 2.86 (s, 3H), 2.23 (s, 3H).

Example 162. 3-[(3-fluoro-2-methoxyphenyl)amino]-2-(6-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 809)**

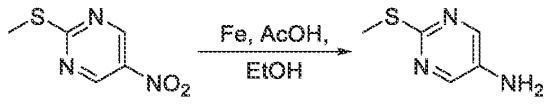


To a stirred solution/mixture of 3-iodo-2-(6-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) and 3-fluoro-2-methoxyaniline (33 mg, 0.23 mmol, 1.2 equiv) in DMF was added Cs_2CO_3 (128 mg, 0.39 mmol, 2 equiv) and EPhos Pd G4 (36 mg, 0.04 mmol, 0.2 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for 3 h at 50 degrees C under argon atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) and HPLC(Column: XBridge Prep C18 OBD Column, 30*100 mm, 5 μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 50% B in 10 min, 50% B; Wave Length: 254/220 nm; RT1(min): 9.28) to afford 3-[(3-fluoro-2-methoxyphenyl)amino]-2-(6-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (37.0 mg, 44.16%) as an orange solid.

LC-MS: $(M+H)^+$ found: 418.00.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.48 (d, 1H), 8.68 (d, 1H), 8.32 (d, 1H), 8.05 (s, 1H), 7.75 (d, 1H), 7.53 (s, 1H), 7.21 (s, 1H), 6.65 (m, 1H), 6.52 (m, 1H), 6.08 (d, 1H), 3.85 (s, 3H), 3.46 (t, 2H), 2.99 (t, 2H), 2.67 (s, 3H).

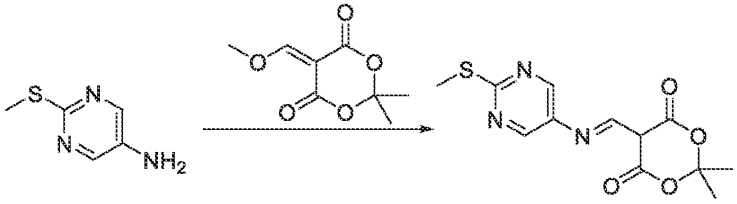
Example 163. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-cyclopropoxypyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 771)**



To a stirred solution of 2-(methylsulfanyl)-5-nitropyrimidine (5 g, 29.21 mmol, 1.00 equiv) in EtOH (200 mL) was added AcOH (120 mL) and Fe (17 g, 292.11 mmol, 10 equiv) in portions at rt under N_2 atmosphere. The resulting mixture was stirred for 2 h at 80 degrees

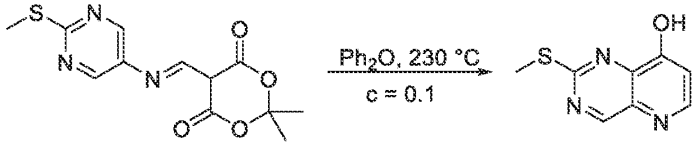
C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 142. The resulting mixture was concentrated under reduced pressure. The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with Saturated NaCl (3x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2-(methylsulfanyl)pyrimidin-5-amine (3.5 g, 84.86%) as a yellow solid.

LC-MS: M+H found: 142.0.



To a stirred solution of 2-(methylsulfanyl)pyrimidin-5-amine (3.2 g, 22.66 mmol, 1.00 equiv) and 5-(methoxymethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (5.06 g, 27.18 mmol, 1.20 equiv) in DMF (80.00 mL) at rt under N_2 atmosphere. The resulting mixture was stirred for 1 h at 80 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. The resulting mixture was added MeOH(50 mL). The resulting mixture was filtered, the filter cake was washed with MeOH (3 x20 mL). The filter cake was concentrated under reduced pressure to afford 2,2-dimethyl-5-[(1E)-[[2-(methylsulfanyl)pyrimidin-5-yl]imino]methyl]-1,3-dioxane-4,6-dione (5.4 g, 80.68%) as a yellow solid.

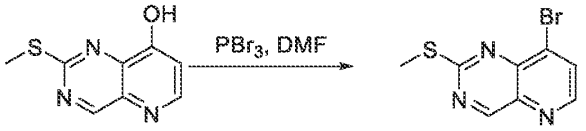
LC-MS: $(M+H)^+$ found: 296.0.



To a stirred solution of 2,2-dimethyl-5-[(1E)-{[2-(methylsulfanyl)pyrimidin-5-yl]imino}methyl]-1,3-dioxane-4,6-dione (5.3 g, 17.95 mmol, 1.00 equiv) in phenoxybenzene (360 mL) at rt under N_2 atmosphere. The resulting mixture was stirred at 230 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 194. The reaction was addition of Hexane (700 ml) at rt. The resulting mixture

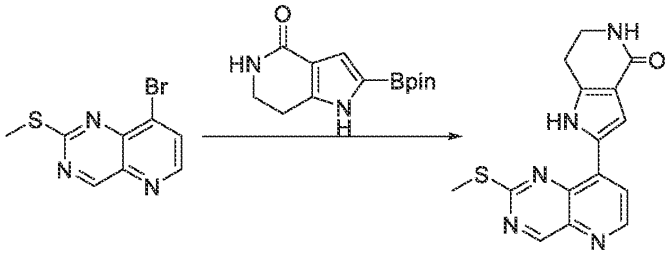
was filtered; the filter cake was washed with Hexane (3x200 ml). The filtrate was concentrated under reduced pressure.

LC-MS: $(M+H)^+$ found: 194.0.



To a stirred solution of 2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-ol (2.8 g, 14.49 mmol, 1.00 equiv) in DMF (80 mL) was added PBr_3 (4.3 g, 15.94 mmol, 1.1 equiv) dropwise at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 1 h at rt under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 256. The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with aq. NaCl (3 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE:EA (4:1) to afford 8-bromo-2-(methylsulfanyl)pyrido[3,2-d]pyrimidine (1.6 g, 43.11%) as a white solid.

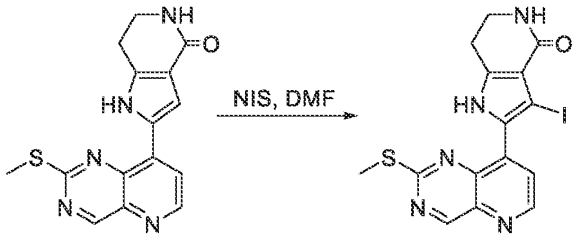
LC-MS: $(M+H)^+$ found: 256.0.



To a stirred solution of 8-bromo-2-(methylsulfanyl)pyrido[3,2-d]pyrimidine (700 mg, 2.73 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1075 mg, 4.10 mmol, 1.50 equiv) in dioxane (10 mL) and H_2O (1 mL) were added Na_2CO_3 (869 mg, 8.19 mmol, 3.00 equiv) and XPhos Pd G2 (215 mg, 0.27 mmol, 0.10 equiv) dropwise/ in portions at rt under N_2 atmosphere. The resulting mixture was stirred for 2 h at 80 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH=24:1 to

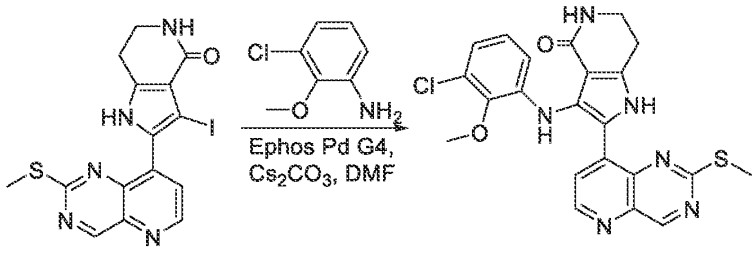
afford 2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (700 mg, 82.26%) as a yellow solid.

LC-MS: $(M+H)^+$ found 312.0.



To a stirred solution of 2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (600 mg, 1.93 mmol, 1.00 equiv) and NIS (650 mg, 2.89 mmol, 1.50 equiv) in DMF (10 mL) at rt under N_2 atmosphere. The resulting mixture was stirred for overnight at 30 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 438.The reaction was quenched by the addition of Saturated aq. Na_2SO_3 (20 mL) at 0 degrees C. The precipitated solids were collected by filtration and washed with H_2O (20 mLx3). The residue was purified by silica gel column chromatography, eluted with DCM:MeOH=10:1 to afford 3-iodo-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (650 mg, 77.14%) as a yellow solid.

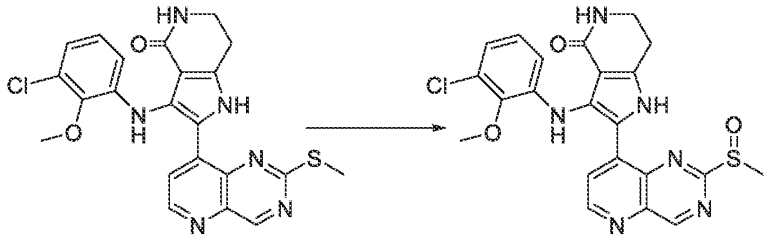
LC-MS: $(M+H)^+$ found: 438.0.



To a stirred solution of 3-iodo-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (370 mg, 0.85 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (134 mg, 0.85 mmol, 1 equiv) in DMF (4 mL) were added EPhos Pd G4 (78 mg, 0.08 mmol, 0.1 equiv) and Cs_2CO_3 (827 mg, 2.54 mmol, 3 equiv) in portions at rt under Ar atmosphere. The resulting mixture was stirred for 1.5 h at 50 degrees C under Ar

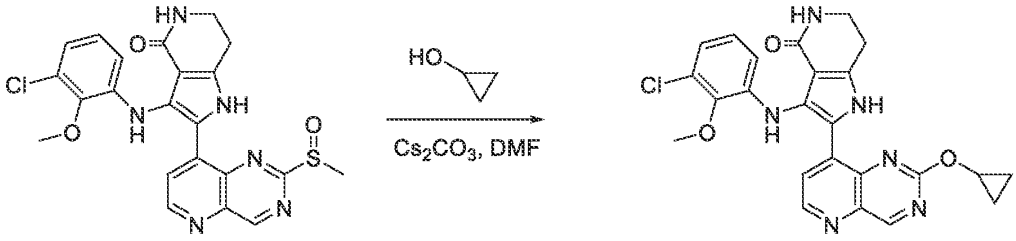
atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM:MeOH (10:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (220 mg, 55.68%) as an orange solid.

LC-MS: $(M+H)^+$ found: 467.0.



To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50 mg, 0.11 mmol, 1.00 equiv) in DCM (2 mL, 31.46 mmol, 293.80 equiv) were added MCPBA (29 mg, 0.12 mmol, 1.1 equiv) dropwise/ in portions at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 1 h at 0 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 483. The resulting mixture was extracted with DCM (3 x 4 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

LC-MS: $(M+H)^+$ found: 483.0.



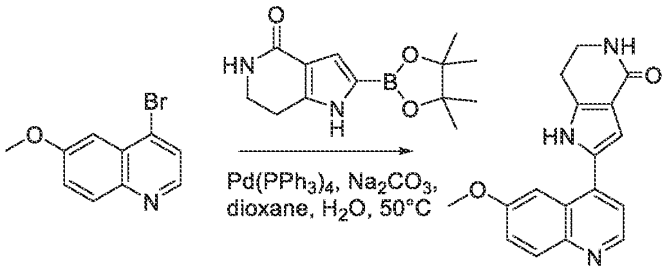
To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-methanesulfinylpyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.20 mmol, 1.00 equiv) and Cs_2CO_3 (162 mg, 0.49 mmol, 2.4 equiv) in DMF (2

mL) were added cyclopropanol (14 mg, 0.25 mmol, 1.2 equiv) dropwise at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 1 h at rt under N_2 atmosphere. The resulting mixture was extracted with DCM:MeOH=10:1 (3 x 5 mL). The combined organic layers were washed with aq. NaCl (3x10 ml), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and dissolved in DMF. The crude product (50 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 42% B to 47% B in 10 min, 47% B; Wave Length: 220/254 nm; RT1(min): 9.13) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-cyclopropoxypyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (8.6 mg, 8.71%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 477.25.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 9.51 (s, 1H), 8.71 (d, J = 4.8 Hz, 1H), 7.91 (s, 1H), 7.54 (d, J = 4.9 Hz, 1H), 7.33 (d, J = 2.6 Hz, 1H), 6.79 (m, J = 8.1, 1.7 Hz, 1H), 6.75 (t, J = 8.0 Hz, 1H), 6.17 (m, J = 7.9, 1.8 Hz, 1H), 4.69 – 4.60 (m, 1H), 3.95 (s, 3H), 3.54 – 3.42 (m, 2H), 2.99 (t, J = 6.8 Hz, 2H), 1.00 – 0.94 (m, 4H).

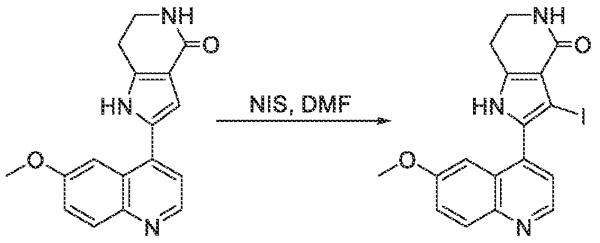
Example 164. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-methoxyquinolin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 773)**



To a stirred mixture of 4-bromo-6-methoxyquinoline (250 mg, 1.05 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (412 mg, 1.57mmol, 1.50 equiv) in dioxane was added Na_2CO_3 (333 mg, 3.15 mmol, 3.00 equiv) and $Pd(PPh_3)_4$ (121 mg, 0.10 mmol, 0.10 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added H_2O (1.5 mL, 83.26 mmol, 79.29 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 2h at room temperature. The reaction was monitored by LCMS. LCMS

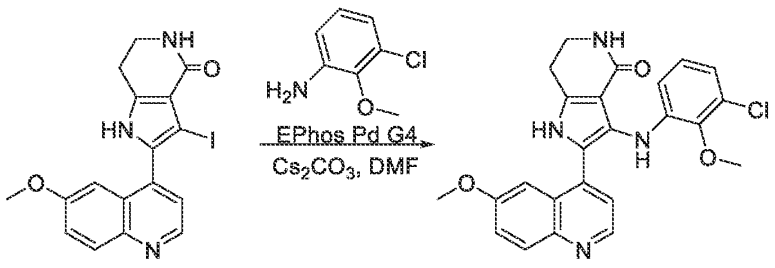
showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 2-(6-methoxyquinolin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (250 mg, 81.17%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 294.1.



To a stirred solution of 2-(6-methoxyquinolin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (250 mg, 0.85 mmol, 1.00 equiv) in DMF (10.00 mL) was added N-iodosuccinimide (210 mg, 0.93 mmol, 1.10 equiv) in portions at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 3-iodo-2-(6-methoxyquinolin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (220 mg, 61.57%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 419.95.



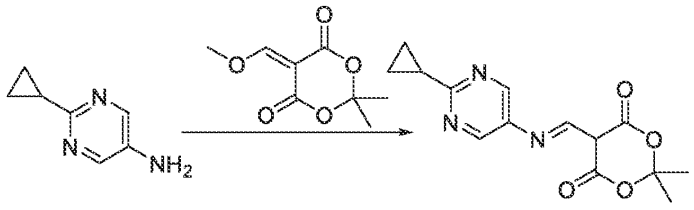
To a stirred solution of 3-iodo-2-(6-methoxyquinolin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.23 mmol, 1.00 equiv) in DMF (2.00 mL) was added Cs_2CO_3 (155 mg, 0.47 mmol, 2.00 equiv) and EPhos Pd G4 (43 mg, 0.04 mmol, 0.20 equiv) at

room temperature under nitrogen atmosphere. To the above mixture was added 3-chloro-2-methoxyaniline (37 mg, 0.23 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred for additional 2 h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed.The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford Product 60 mg (crude).The crude product (60mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*250 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 24% B to 44% B in 10 min, 44% B; Wave Length: 254/220 nm; RT1(min): 10.85) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-methoxyquinolin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (39.7 mg, 37.07%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 449.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.73 (s, 1H), 8.70 (d, *J* = 4.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.66 (s, 1H), 7.45 (d, *J* = 4.0 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.19 (s,1H), 6.48-6.45 (m, 1H), 6.35 (t, *J* = 8.0 Hz, 1H), 6.07-6.07 (m, 1H), 3.76 (s, 6H), 3.49-3.45 (m, 2H), 2.88 (t, *J* = 8 Hz, 2H).

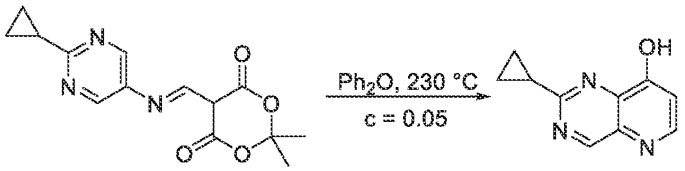
Example 165. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-cyclopropylpyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 776)**



To a stirred solution of 2-cyclopropylpyrimidin-5-amine (1.5 g, 11.09 mmol, 1.00 equiv) in DMF (10.00 mL) was added 5-(methoxymethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.27 g, 12.20 mmol, 1.10 equiv) dropwise at room temperature under argon atmosphere. The resulting mixture was stirred for 2h at 80°C under air atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with MeOH (20 mL). The precipitated solids were collected by filtration and washed with

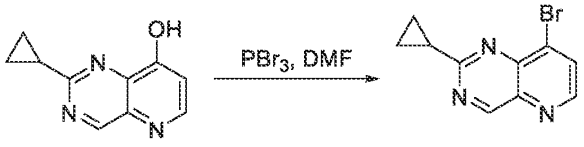
MeOH (3x 10 mL). The resulting mixture was concentrated under reduced pressure to obtain 5-[(1E)-[(2-cyclopropylpyrimidin-5-yl)imino]methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (3 g, 93.45%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 289.90



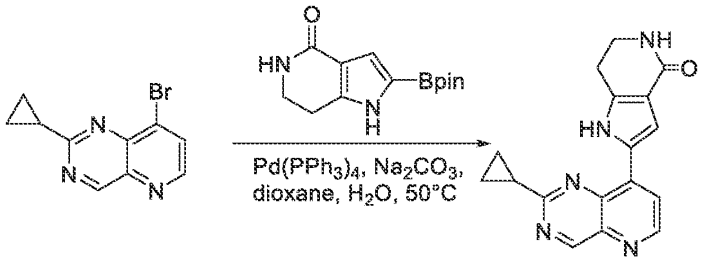
A solution of diphenyl-ether (50 mL) was stirred at 220 °C under argon atmosphere. To the above solution was added 5-[(1E)-[(2-cyclopropylpyrimidin-5-yl)imino]methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (3 g, 10.37 mmol, 1.00 equiv) dropwise over 10 min at 220°C. The resulting mixture was stirred for additional 5 min at 220°C. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with hexane (200 mL) at 0°C. The precipitated solids were collected by filtration and washed with hexane (3x20 mL). The resulting mixture was concentrated under reduced pressure to obtain 2-cyclopropylpyrido[3,2-d]pyrimidin-8-ol (1.7 g, crude) as a brown solid.

LC-MS: $(M+H)^+$ found: 290.00.



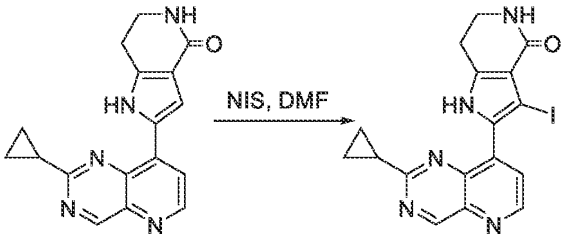
To a stirred solution of 2-cyclopropylpyrido[3,2-d]pyrimidin-8-ol (800 mg, 4.27 mmol, 1.00 equiv) in DMF (5.00 mL) was added PBr_3 (1.73 g, 6.41 mmol, 1.50 equiv) dropwise at 0°C under argon atmosphere. The resulting mixture was stirred for 1 h at 0°C under argon atmosphere. The reaction was quenched with sat. $NaHCO_3$ (aq.) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (5/1) to afford 8-bromo-2-cyclopropylpyrido[3,2-d]pyrimidine (650 mg, 60.82%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 252.0



To a stirred mixture of 8-bromo-2-cyclopropylpyrido[3,2-d]pyrimidine (300 mg, 1.20 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (377 mg, 1.44 mmol, 1.20 equiv) in 1,4-dioxane (2.00 mL) and H_2O (0.20 mL) were added $Pd(PPh_3)_4$ (277 mg, 0.24 mmol, 0.20 equiv) and Na_2CO_3 (381 mg, 3.60 mmol, 3.00 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for overnight at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2 x 10 mL). The filtrate was concentrated under reduced pressure that was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 2-{2-cyclopropylpyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (110 mg, 30.03%) as a yellow solid.

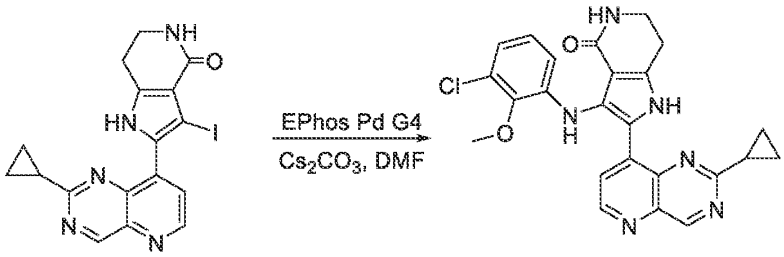
LC-MS: $(M+H)^+$ found: 306.



To a stirred solution of 2-{2-cyclopropylpyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (110 mg, 0.36 mmol, 1.00 equiv) in DMF (1.00 mL) was added NIS (97 mg, 0.43 mmol, 1.20 equiv) dropwise at 0°C under argon atmosphere. The resulting mixture was stirred for 2h at 0°C under argon atmosphere. The reaction was quenched by the addition of sat. Na_2SO_3 (aq.) (2.00 mL) at 0°C. The resulting mixture was

extracted with CH_2Cl_2/MeOH (3 x 10 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography to obtain 2-{2-cyclopropylpyrido[3,2-d]pyrimidin-8-yl}-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50 mg, 32.18%) as a light-yellow solid.

LC-MS: $(M+H)^+$ found: 431.85.

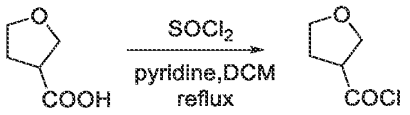


To a stirred mixture of 2-{2-cyclopropylpyrido[3,2-d]pyrimidin-8-yl}-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.23 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (36 mg, 0.23 mmol, 1.00 equiv) in DMF (1.00 mL) were added EPhos Pd G4 (21 mg, 0.023 mmol, 0.10 equiv) and Cs_2CO_3 (226.66 mg, 0.69 mmol, 3.00 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 2h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2 x 10 mL). The filtrate was concentrated under reduced pressure that was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-cyclopropylpyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (16.3 mg, 14.49%) as a yellow solid.

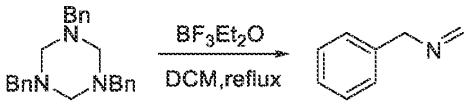
LC-MS: $(M+H)^+$ found: 461.25.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 (s, 1H), 9.47 (d, 1H), 8.74 (d, 1H), 7.99 (s, 1H), 7.56 (d, 1H), 7.27 (s, 1H), 6.78-6.66 (m, 2H), 6.20-6.16 (m, 1H), 4.00 (s, 3H), 3.51-3.42 (m, 2H), 3.02 (t, 2H), 2.79-2.69 (m, 1H), 1.25 (d, 4H).

Example 166. (3R)-3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[oxolane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 782)**

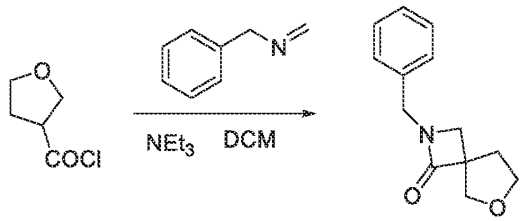


A solution of oxolane-3-carbonyl chloride (10 g, 74.32 mmol, 1.00 equiv) and $SOCl_2$ (9.28 g, 78.03 mmol, 1.05 equiv) and pyridine (118 mg, 1.48 mmol, 0.02 equiv) in DCM (100 mL) was stirred for 3h at 45 degrees C under nitrogen atmosphere. The mixture was monitored by TLC The resulting mixture was concentrated under vacuum.This resulted in oxolane-3-carbonyl chloride (11.5 g, 115.00%) as a yellow oil. The reaction is confirmed by TLC.



A solution of 1,3,5-tribenzyl-1,3,5-triazinane (10.3 g, 28.81 mmol, 1.00 equiv) and BF3.Et2O (12.27 g, 86.43 mmol, 3.00 equiv) in DCM (100 mL) was stirred for 3h at 45 degrees C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. This resulted in benzyl(methylidene)amine (11.5 g, 334.95%) as a yellow oil.

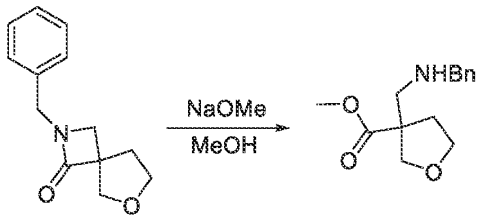
LC-MS: $(M+H)^+$ found: 119.



To a stirred solution of oxolane-3-carbonyl chloride (11.5 g, 85.46 mmol, 1.00 equiv) in DCM (100 mL) were added NEt3 (34.59 g, 341.86 mmol, 4.00 equiv) dropwise at -78 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 30min at -78 degrees C under nitrogen atmosphere. To the above mixture was added benzyl(methylidene)amine (11.20 g, 94.01 mmol, 1.1 equiv) in DCM (20ml) dropwise over 20min at -55 degrees C. The resulting mixture was stirred for additional 1h at -45degrees C. To the above mixture was added H_2O (40ml) at -45 degrees C. The resulting mixture was stirred for overnight at room temperature. The reaction was quenched with sat. NH4Cl (aq.) at 0 degrees C. The resulting mixture was extracted with CH2Cl2 (2 x 30 mL). The combined organic layers were washed with brine (1x100ml), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue

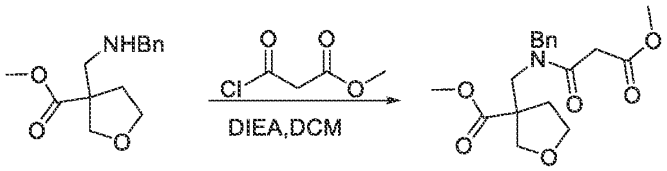
was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water(NH4HCO3,5%), 20% to 60% gradient in 30 min; detector, UV 220 nm. This resulted in 2-benzyl-6-oxa-2-azaspiro[3.4]octan-1-one (14.7 g, 79.17%) as a yellow oil.

LC-MS: $(M+H)^+$ found: 218.



A solution of 2-benzyl-6-oxa-2-azaspiro[3.4]octan-1-one (14.7 g, 67.66 mmol, 1.00 equiv) and MeONa (4.02 g, 74.42 mmol, 1.10 equiv) in MeOH (150 mL) was stirred for overnight at 45 degrees C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature.The reaction was quenched by the addition of sat. NH4Cl (aq.) (100 mL) at room temperature.The resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were washed with brine (1x100mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeOH in water (NH_4HCO_3,5%), 20% to 80% gradient in 30 min; detector, UV 254 nm.This resulted in methyl 3-[(benzylamino)methyl]oxolane-3-carboxylate (12.7 g, 75.29%) as a yellow oil.

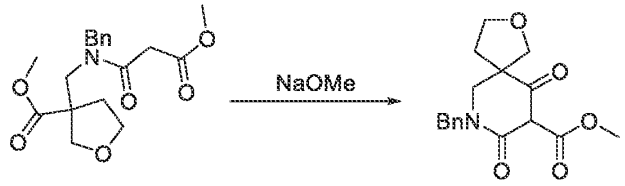
LC-MS: $(M+H)^+$ found: 250.



To a stirred solution of methyl 3-[(benzylamino)methyl]oxolane-3-carboxylate (14.7 g, 58.96 mmol, 1.00 equiv) in DCM (150 mL)were added DIEA (8.00 g, 61.91 mmol, 1.05 equiv) at 0 degrees C under nitrogen atmosphere.The resulting mixture was stirred for 30 min at 0 degrees C under nitrogen atmosphere.To the above mixture was added methyl 3-chloro-3-oxopropanoate (8.05 g, 58.96 mmol, 1 equiv) dropwise over 30 min at 0 degrees C. The resulting mixture was stirred for additional 1h at 0 degrees C. The reaction was

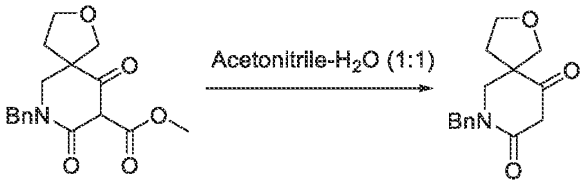
quenched by the addition of Water/Ice (100mL) at 0 degrees C.The resulting mixture was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with brine (1x100ml), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeOH in water(NH_4HCO_3,5%), 20% to 80% gradient in 30 min; detector, UV 210 nm. This resulted in methyl 3-[(N-benzyl-3-methoxy-3-oxopropanamido)methyl]oxolane-3-carboxylate (18.2 g, 88.35%) as a yellow oil.

LC-MS: $(M+H)^+$ found: 350.



A solution/mixture of methyl 3-[(N-benzyl-3-methoxy-3-oxopropanamido)methyl]oxolane-3-carboxylate (16.7 g, 47.80 mmol, 1.00 equiv) and sodium methoxide (3.87 g, 71.70 mmol, 1.50 equiv) in toluene (160 mL) and MeOH (25 mL) was stirred for 6h at 85degrees C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature.The reaction was quenched by the addition of Water/Ice (100mL) at 0 degrees C.The resulting mixture was extracted with EtOAc (3 x200 mL). The combined organic layers were washed with brine (1x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.This resulted in methyl 7-benzyl-8,10-dioxo-2-oxa-7-azaspiro[4.5]decane-9-carboxylate (16.5 g, 108.78%) as a yellow oil.

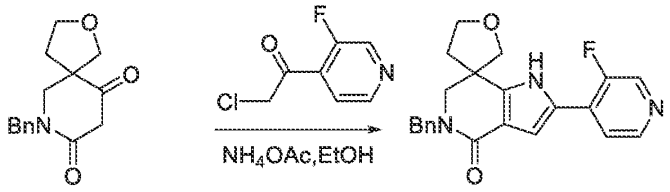
LC-MS: $(M+H)^+$ found: 318.



A solution of methyl 7-benzyl-8,10-dioxo-2-oxa-7-azaspiro[4.5]decane-9-carboxylate (16.5 g, 52.00 mmol, 1.00 equiv) in MeCN (100 mL) and H_2O (100 mL) was stirred for 2h at 85 degrees C under nitrogen atmosphere. The mixture was allowed to cool down to

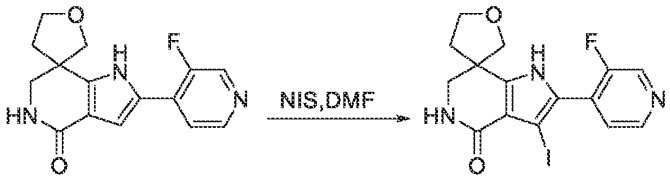
room temperature.The resulting mixture was extracted with EtOAc (2 x 200mL). The combined organic layers were washed with brine (1x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was re-crystallized from diethyl ether (50 mL) to afford 7-benzyl-2-oxa-7-azaspiro[4.5]decane-8,10-dione (10.5 g, 77.88%) as a white solid.

LC-MS: $(M+H)^+$ found: 260.



A solution of 7-benzyl-2-oxa-7-azaspiro[4.5]decane-8,10-dione (1.5g, 5.79 mmol, 1 equiv) and 2-chloro-1-(3-fluoropyridin-4-yl)ethan-1-one (1.503g,.8.59 mmol, 1.50 equiv)and NH_4OAc (2.67g, 34.75 mmol, 6.00 equiv) in EtOH (5 mL) was stirred for overnight at 50 degrees C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature.The resulting mixture was extracted with EtOAc (2 x 200mL). The combined organic layers were washed with brine (1x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water(NH_4HCO_3,5%), 20% to 70% gradient in 30 min; detector, UV 220 nm to afford 5'-benzyl-2'-(3-fluoropyridin-4-yl)-4,5,5',6'-tetrahydro-2H-spiro[furan-3,7'-pyrrolo[3,2-c]pyridin]-4'(1'H)-one(1 g) as a brown solid.

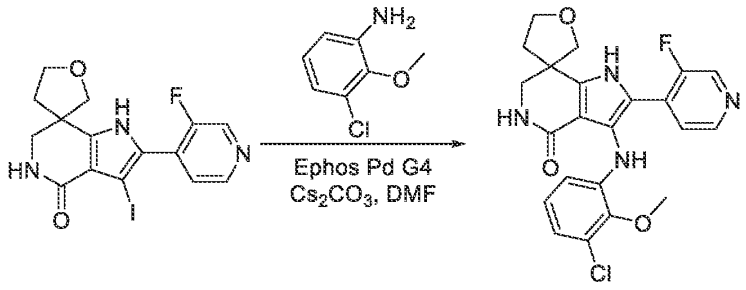
LC-MS: $(M+H)^+$ found: 378.



A solution of 2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[oxolane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (110 mg, 0.38 mmol, 1.00 equiv) and NIS (86 mg, 0.38 mmol, 1 equiv) in DMF (4 mL) was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The residue

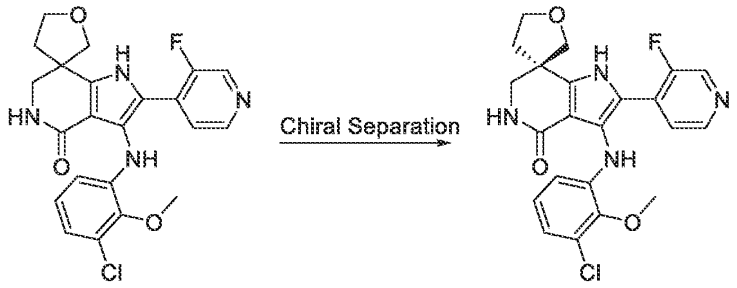
was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford 2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[oxolane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (130 mg, 82.17%) as a yellow solid.

LC-MS: $(M+H)^+$ found 414.



To a stirred mixture of 2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[oxolane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (110 mg, 0.26 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (42 mg, 0.26 mmol, 1.00 equiv) in DMF (2.5 mL) were added Ephos Pd G4 (24 mg, 0.03 mmol, 0.1 equiv) and Cs_2CO_3 (173 mg, 0.53 mmol, 2.00 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 2h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure that was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[oxolane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (95 mg, 80.57%) as a yellow solid.

LC-MS: M+H found: 443.0.

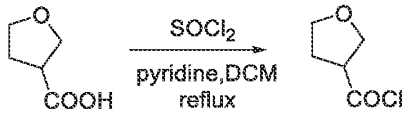


The product (95 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG-3, 4.6*50mm, 3um; Mobile Phase A: Hex: DCM=3: 1)(0.1%DEA): IPA=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (3R)-3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[oxolane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (28.8 mg, 30.10%) as a yellow solid.

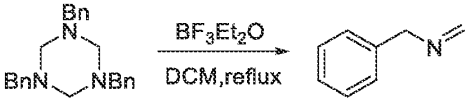
^{1}H NMR (400 MHz, DMSO-d$_6$) δ 11.62 (s, 1H), 8.50 (d, *J* = 2.5 Hz, 1H), 8.35 (m, 1H), 7.63 (s, 1H), 7.49 (m, 1H), 7.37 (m, 1H), 6.70 – 6.55 (m, 2H), 6.11 (m, 1H), 3.95 (m, 2H), 3.85 (d, *J* = 7.0 Hz, 4H), 3.60 (d, *J* = 8.6 Hz, 1H), 3.32 (s, 1H), 3.27 (m, 1H), 2.49 (m, 1H), 2.04 – 1.91 (m, 1H).

LC-MS: $(M+H)^+$ found: 443.

Example 167. (3R)-3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[oxolane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one **(compound 781)**

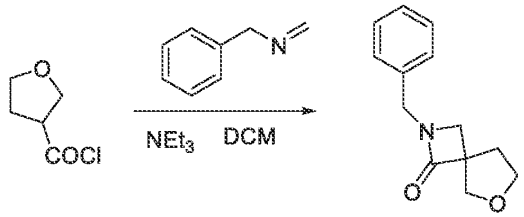


A solution of oxolane-3-carbonyl chloride (10 g, 74.32 mmol, 1.00 equiv) and $SOCl_2$ (9.28 g, 78.03 mmol, 1.05 equiv) and pyridine (118 mg, 1.48 mmol, 0.02 equiv) in DCM (100 mL) was stirred for 3h at 45 degrees C under nitrogen atmosphere. The mixture was monitored by TLC The resulting mixture was concentrated under vacuum.This resulted in oxolane-3-carbonyl chloride (11.5 g, 115.00%) as a yellow oil. The reaction is confirmed by TLC.



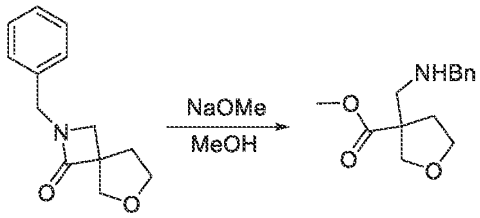
A solution of 1,3,5-tribenzyl-1,3,5-triazinane (10.3 g, 28.81 mmol, 1.00 equiv) and $BF_3.Et_2O$ (12.27 g, 86.43 mmol, 3.00 equiv) in DCM (100 mL) was stirred for 3h at 45 degrees C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum.This resulted in benzyl(methylidene)amine (11.5 g, 334.95%) as a yellow oil.

LC-MS: $(M+H)^+$ found: 119.



To a stirred solution of oxolane-3-carbonyl chloride (11.5 g, 85.46 mmol, 1.00 equiv) in DCM (100 mL) were added NEt_3 (34.59 g, 341.86 mmol, 4.00 equiv) dropwise at -78 degrees C under nitrogen atmosphere.The resulting mixture was stirred for 30min at -78 degrees C under nitrogen atmosphere.To the above mixture was added benzyl(methylidene)amine (11.20 g, 94.01 mmol, 1.1 equiv) in DCM(20ml) dropwise over 20min at -55 degrees C. The resulting mixture was stirred for additional 1h at -45degrees C.To the above mixture was added H_2O(40ml) at -45 degrees C. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with sat. NH_4Cl (aq.) at 0 degrees C.The resulting mixture was extracted with CH_2Cl_2 (2 x 3mL). The combined organic layers were washed with brine (1x100ml), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water(NH_4HCO_3,5%), 20% to 60% gradient in 30 min; detector, UV 220 nm. This resulted in 2-benzyl-6-oxa-2-azaspiro[3.4]octan-1-one (14.7 g, 79.17%) as a yellow oil.

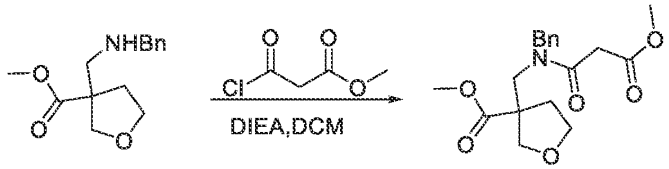
LC-MS: $(M+H)^+$ found: 218.



A solution of 2-benzyl-6-oxa-2-azaspiro[3.4]octan-1-one (14.7 g, 67.66 mmol, 1.00 equiv)

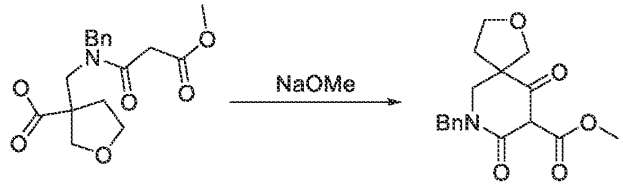
and MeONa (4.02 g, 74.42 mmol, 1.10 equiv) in MeOH (150 mL) was stirred for overnight at 45 degrees C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature.The reaction was quenched by the addition of sat. NH_4Cl (aq.) (100mL) at room temperature.The resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were washed with brine (1x100mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeOH in water(NH_4HCO_3,5%), 20% to 80% gradient in 30 min; detector, UV 254 nm.This resulted in methyl 3-[(benzylamino)methyl]oxolane-3-carboxylate (12.7 g, 75.29%) as a yellow oil.

LC-MS: $(M+H)^+$ found: 250.



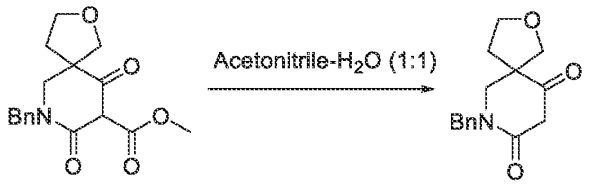
To a stirred solution of methyl 3-[(benzylamino)methyl]oxolane-3-carboxylate (14.7 g, 58.96 mmol, 1.00 equiv) in DCM (150 mL)were added DIEA (8.00 g, 61.91 mmol, 1.05 equiv) at 0 degrees C under nitrogen atmosphere.The resulting mixture was stirred for 30 min at 0 degrees C under nitrogen atmosphere.To the above mixture was added methyl 3-chloro-3-oxopropanoate (8.05 g, 58.96 mmol, 1 equiv) dropwise over 30 min at 0 degrees C. The resulting mixture was stirred for additional 1h at 0 degrees C. The reaction was quenched by the addition of Water/Ice (100mL) at 0 degrees C.The resulting mixture was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with brine (1x100ml), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeOH in water(NH_4HCO_3,5%), 20% to 80% gradient in 30 min; detector, UV 210 nm. This resulted in methyl 3-[(N-benzyl-3-methoxy-3-oxopropanamido)methyl]oxolane-3-carboxylate (18.2 g, 88.35%) as a yellow oil.

LC-MS: $(M+H)^+$ found: 350.



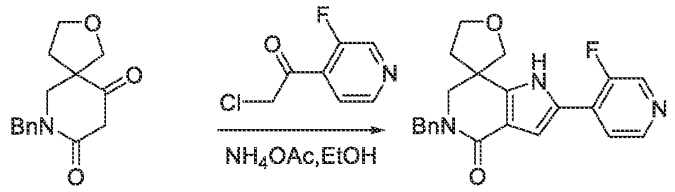
A solution/mixture of methyl 3-[(N-benzyl-3-methoxy-3-oxopropanamido)methyl]oxolane-3-carboxylate (16.7 g, 47.80 mmol, 1.00 equiv) and sodium methoxide (3.87 g, 71.70 mmol, 1.50 equiv) in toluene (160 mL) and MeOH (25 mL) was stirred for 6h at 85degrees C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of Water/Ice (100mL) at 0 degrees C.The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.This resulted in methyl 7-benzyl-8,10-dioxo-2-oxa-7-azaspiro[4.5]decane-9-carboxylate (16.5 g, 108.78%) as a yellow oil.

LC-MS: $(M+H)^+$ found: 318.



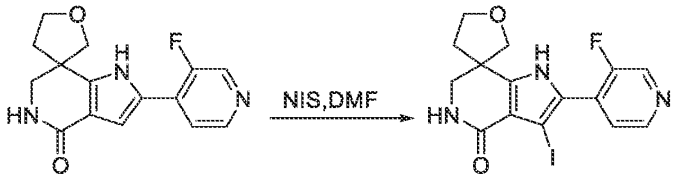
A solution of methyl 7-benzyl-8,10-dioxo-2-oxa-7-azaspiro[4.5]decane-9-carboxylate (16.5 g, 52.00 mmol, 1.00 equiv) in MeCN (100 mL) and H_2O (100 mL) was stirred for 2h at 85 degrees C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature.The resulting mixture was extracted with EtOAc (2 x 200mL). The combined organic layers were washed with brine (1x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was re-crystallized from diethyl ether (50 mL) to afford 7-benzyl-2-oxa-7-azaspiro[4.5]decane-8,10-dione (10.5 g, 77.88%) as a white solid.

LC-MS: $(M+H)^+$ found: 260.



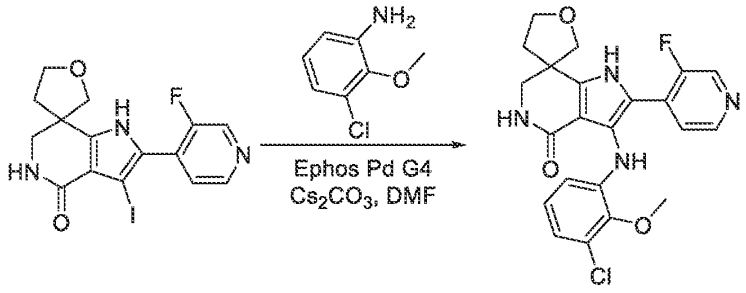
A solution of 7-benzyl-2-oxa-7-azaspiro[4.5]decane-8,10-dione (1.5g, 5.79 mmol, 1 equiv) and 2-chloro-1-(3-fluoropyridin-4-yl)ethan-1-one (1.50 g,.8.59 mmol, 1.50 equiv)and NH_4OAc (2.67 g, 34.75 mmol, 6.00 equiv) in EtOH (5 mL) was stirred for overnight at 50 degrees C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature.The resulting mixture was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine (1x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water(NH_4HCO_3,5%), 20% to 70% gradient in 30 min; detector, UV 220 nm to afford 5'-benzyl-2'-(3-fluoropyridin-4-yl)-4,5,5',6'-tetrahydro-2H-spiro[furan-3,7'-pyrrolo[3,2-c]pyridin]-4'(1'H)-one(1 g) as a brown solid.

LC-MS: $(M+H)^+$ found: 378.



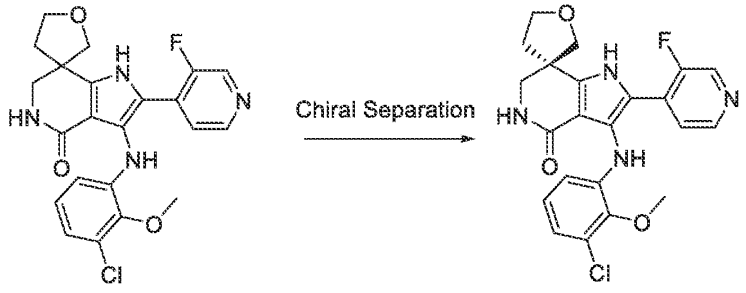
A solution of 2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[oxolane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (110 mg, 0.38 mmol, 1.00 equiv) and NIS (86 mg, 0.38 mmol, 1 equiv) in DMF (4 mL) was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford 2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[oxolane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (130 mg, 82.17%) as a yellow solid.

LC-MS: $(M+H)^+$ found 414.



To a stirred mixture of 2'-(3-fluoropyridin-4-yl)-3'-iodo-5',6'-dihydro-1'H-spiro[oxolane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (110 mg, 0.26 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (42 mg, 0.26 mmol, 1.00 equiv) in DMF (2.5 mL) were added Ephos Pd G4 (24 mg, 0.03 mmol, 0.1 equiv) and Cs_2CO_3 (173 mg, 0.53 mmol, 2.00 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 2h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure that was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford 3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[oxolane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (95 mg, 80.57%) as a yellow solid.

LC-MS: M+H found: 443.0.



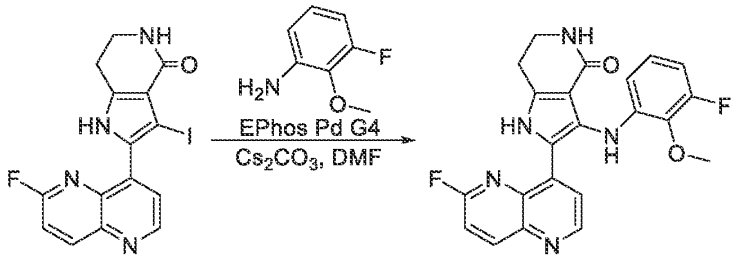
The product (95 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG-3, 4.6*50mm, 3um; Mobile Phase A: Hex: DCM=3: 1)(0.1%DEA): IPA=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection

Volume: 5ul mL) to afford (3R)-3'-[(3-chloro-2-methoxyphenyl)amino]-2'-(3-fluoropyridin-4-yl)-5',6'-dihydro-1'H-spiro[oxolane-3,7'-pyrrolo[3,2-c]pyridin]-4'-one (29.5 mg, 30.87%) as a white solid.

LC-MS: $(M+H)^+$ found: 443.

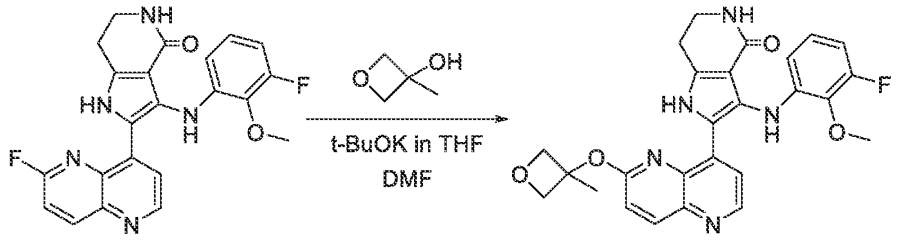
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (s, 1H), 8.50 (d, J = 2.5 Hz, 1H), 8.35 (m, 1H), 7.63 (s, 1H), 7.49 (m, 1H), 7.37 (m, 1H), 6.70 - 6.55 (m, 2H), 6.11 (m, 1H), 3.95 (m, 2H), 3.85 (d, J = 7.0 Hz, 4H), 3.60 (d, J = 8.6 Hz, 1H), 3.32 (s, 1H), 3.27 (m, 1H), 2.49 (m, 1H), 2.04 - 1.91 (m, 1H).

Example 168. 3-[(3-fluoro-2-methoxyphenyl)amino]-2-[6-[(3-methyloxetan-3-yl)oxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 788)**



To a stirred solution of 2-(6-fluoro-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (530 mg, 1.29 mmol, 1.00 equiv) in DMF (13.00 mL, 171.15mmol, 131.86 equiv)was added Cs_2CO_3 (846 mg, 2.59 mmol, 2.00 equiv) and EPhos Pd G4 (119 mg, 0.13 mmol, 0.10 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added 3-fluoro-2-methoxyaniline (201 mg, 1.42 mmol, 1.10 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 2h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 2-(6-fluoro-1,5-naphthyridin-4-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (320 mg, 58.48%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 422.1.

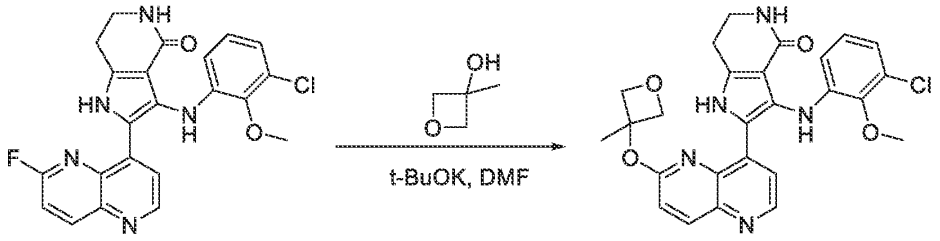


To a stirred solution of 2-(6-fluoro-1,5-naphthyridin-4-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (120 mg, 0.28 mmol, 1.00 equiv) in DMF (3.00 mL) were added 3-methyloxetan-3-ol (75 mg, 0.85 mmol, 3.00 equiv) dropwise at room temperature under nitrogen atmosphere. To the above mixture was added t-BuOK (35 mg, 0.31 mmol, 1.10 equiv) dropwise at 0 degrees C. The resulting mixture was stirred for additional 24 h at room temperature. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was filtered, The filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min, Gradient: 24% B to 42% B in 8 min, 42% B; Wave Length: 254/220 nm; RT1(min): 7.33) to afford 3-[(3-fluoro-2-methoxyphenyl)amino]-2-[6-[(3-methyloxetan-3-yl)oxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (16.1 mg, 11.55%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 490.3.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.45 (s, 1H), 8.61 (d, J = 4.0 Hz, 1H), 8.33 (d, J = 8.0 Hz, 1H), 8.17 (s, 1H), 7.53 (d, J = 4.0 Hz, 1H), 7.36 – 7.32 (m, 2H), 7.15 (s, 1H), 6.53 – 6.36 (m, 2H), 5.98(d, J = 8.0 Hz ,1H), 4.95 (d, J = 8.0 Hz, 2H), 4.48 (d, J =4.0 Hz, 2H), 3.87 (s, 3H), 3.46-3.45 (m, 2H), 2.89 (t, J = 8.0 Hz, 2H), 1.86 (s, 3H).

Example 169. 3-[(3-chloro-2-methoxyphenyl) amino]-2-[6-[(3-methyloxetan-3-yl) oxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one **(compound 787)**

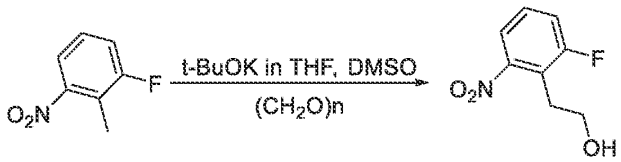


To a stirred solution of 3-[(3-chloro-2-methoxyphenyl) amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (80 mg, 0.18 mmol, 1.00 equiv) and 3-methyloxetan-3-ol (80 mg, 0.91 mmol, 5.00 equiv) in DMF (1.00 mL) was added t-BuOK (1M in THF) (0.20 mL, 0.20 mmol, 1.10 equiv) dropwise at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for overnight at 50 degrees C under nitrogen atmosphere. Desired product could be detected by LCMS. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 47% B in 8 min, 47% B; Wave Length: 254/220 nm; RT1(min): 7.43) to afford 3-[(3-chloro-2-methoxyphenyl) amino]-2-[6-[(3-methyloxetan-3-yl) oxy]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (13.0 mg,12.66%) as an orange solid.

LC-MS: $(M+H)^+$ found: 506.00.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H), 8.64 (d, J = 4.6 Hz, 1H), 8.34 (d, J = 9.1 Hz, 1H), 7.56 (d, J = 4.6 Hz, 1H), 7.46 - 7.30 (m, 2H), 7.17 (t, J = 2.6 Hz, 1H), 6.65 - 6.48 (m, 2H), 6.18 - 6.09 (m, 1H), 4.96 (d, J = 7.0 Hz, 2H), 4.50 (d, J = 7.0 Hz, 2H), 3.86 (s, 3H), 3.52 - 3.42 (m, 2H), 2.90 (t, J = 6.8 Hz, 2H), 1.87 (s, 3H).

Example 170. 3-{[2-(2,2-difluoroethyl)-3-fluorophenyl]amino}-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 795)**



To a stirred mixture of 1-fluoro-2-methyl-3-nitrobenzene (10.00 g, 64.463 mmol, 1.00 equiv) and DMSO (100.00 mL) were added t-BuOK (1.16 g, 10.314 mmol, 0.16 equiv) and methoxymethanol amine (2.84 g, 64.463 mmol, 1.00 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 70 degrees C under nitrogen atmosphere. The reaction was monitored by TLC. The mixture was allowed to cool down to room temperature. The mixture was acidified to pH 7 with HCl (aq.). The resulting mixture was diluted with water (200 mL). The aqueous layer was extracted with EtOAc (3x200 mL). The resulting mixture was washed with 3x200 mL of brine. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 2-(2-fluoro-6-nitrophenyl)ethanol (8.3 g, 69.54%) as a yellow oil. H-NMR analysis indicated it was the desired product.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 (dt, J = 7.8, 1.4 Hz, 1H), 7.45 - 7.25 (m, 2H), 3.94 (t, J = 6.6 Hz, 2H), 3.22 (td, J = 6.6, 2.2 Hz, 2H).



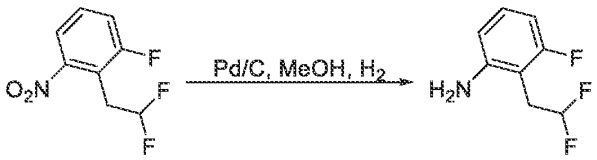
To a stirred mixture of 2-(2-fluoro-6-nitrophenyl)ethanol (8.30 g, 44.828 mmol, 1.00 equiv) in DCM (88.00 mL) was added Dess-Martin (19.96 g, 47.069 mmol, 1.05 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was monitored by TLC. The reaction was quenched with Na2CO3 (aq.) at 0 degrees C. The aqueous layer was extracted with CH2Cl2 (3x100 mL). The resulting mixture was washed with 3x100 mL of brine. The resulting mixture was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 2-(2-fluoro-6-nitrophenyl)acetaldehyde (5.10 g, 62.12%) as a yellow oil. H-NMR analysis indicated it was the desired product.

1H NMR (300 MHz, DMSO-d6) δ 9.75 (d, J = 1.1 Hz, 1H), 7.97 (dt, J = 8.0, 1.3 Hz, 1H), 7.81 - 7.47 (m, 2H), 4.20 (d, J = 1.5 Hz, 2H).



To a stirred mixture of 2-(2-fluoro-6-nitrophenyl)acetaldehyde (3.00 g, 16.381 mmol, 1.00 equiv) and DCM (40.00 mL) was added DAST (6.60 g, 40.953 mmol, 2.50 equiv) in portions at -30 degrees C under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was monitored by TLC. The mixture was allowed to cool down to -30 degrees C.The reaction was quenched by the addition of MeOH (30 mL). The mixture was neutralized to pH 8 with saturated Na2CO3 (aq.).The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with EtOAc (3x200 mL)). The combined organic layers were washed with brine (3x200 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 2-(2,2-difluoroethyl)-1-fluoro-3-nitrobenzene (300 mg, 8.93%) as a yellow oil. H-NMR analysis indicated it was the desired product.

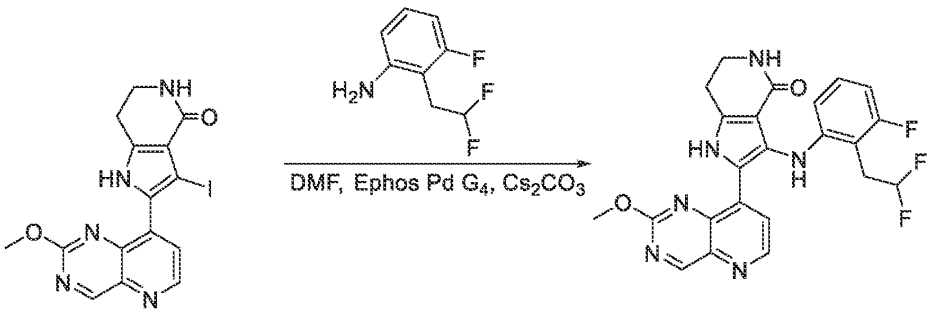
1H NMR (300 MHz, DMSO-d6) δ 7.95 (dt, J = 7.9, 1.4 Hz, 1H), 7.80 - 7.58 (m, 2H), 6.65 - 6.05 (m, 1H), 3.56 (tdd, J = 17.7, 4.0, 2.0 Hz, 2H).



To a stirred mixture of 2-(2,2-difluoroethyl)-1-fluoro-3-nitrobenzene (300.00 mg, 1.462 mmol, 1.00 equiv) in MeOH (20.00 mL) were added Pd/C (311.27 mg, 0.292 mmol, 0.20 equiv, 10%) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 5 h at room temperature under hydrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was filtered, the filter cake was washed with MeOH (3x50 mL). The filtrate was concentrated under reduced pressure to afford 2-(2,2-difluoroethyl)-3-fluoroaniline (180.00 mg, 59.59%) as a yellow oil. The crude product was used in the next step directly

without further purification.

LC-MS: M+H found: 176.0.

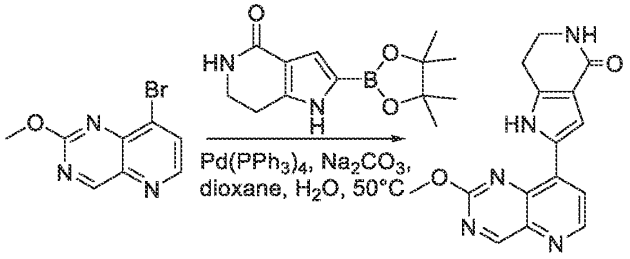


To a stirred mixture of 3-iodo-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80.00 mg, 0.190 mmol, 1.00 equiv) and 2-(2,2-difluoroethyl)-3-fluoroaniline (49.90 mg, 0.285 mmol, 1.50 equiv) in DMF (2.00 ml) were added EPhos Pd G4 (34.89 mg, 0.038 mmol, 0.20 equiv) and Cs_2CO_3 (123.77 mg, 0.380 mmol, 2.00 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for 3 h at 50 degrees C under argon atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 3-{[2-(2,2-difluoroethyl)-3-fluorophenyl]amino}-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg) as a yellow solid. The crude product (80 mg) was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Fluoro Phenyl, 30*150 mm, 5μm; Mobile Phase A: Water(0.05%TFA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 49% B in 8 min, 49% B; Wave Length: 254/220 nm; RT1(min): 7.85) to afford 3-{[2-(2,2-difluoroethyl)-3-fluorophenyl]amino}-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (12.4 mg, 13.74%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 469.0.

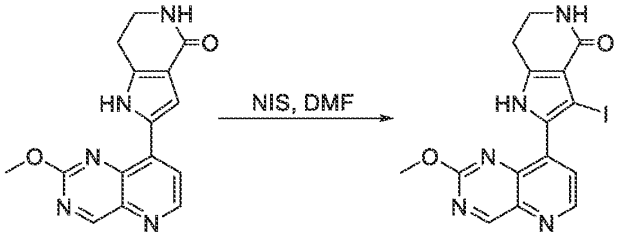
^{1}H NMR (300 MHz, DMSO-d_6) δ 12.05 (s, 1H), 9.49 (s, 1H), 8.65 (d, J = 4.7 Hz, 1H), 7.69 (d, J = 4.7 Hz, 2H), 7.23 (d, J = 2.5 Hz, 1H), 6.89 (q, J = 7.8 Hz, 1H), 6.76 - 6.38 (m, 2H), 6.18 (d, J = 8.2 Hz, 1H), 4.21 (s, 3H), 3.52 - 3.40 (m, 4H), 2.98 (t, J = 6.8 Hz, 2H).

Example 171. 3-[(3-fluoro-2-methylphenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 794)**



To a stirred mixture of 8-bromo-2-methoxypyrido[3,2-d]pyrimidine (500 mg, 2.08 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (655 mg, 2.50 mmol, 1.20 equiv) in dioxane (15.00 mL, 177.06 mmol, 85.01 equiv) was added Na_2CO_3 (662 mg, 6.24mmol, 3.00 equiv) and $Pd(PPh_3)_4$ (240 mg, 0.20 mmol, 0.10 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added H_2O (3.00 mL) at room temperature. The resulting mixture was stirred for additional overnight at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (410 mg, 66.66%) as a yellow solid.

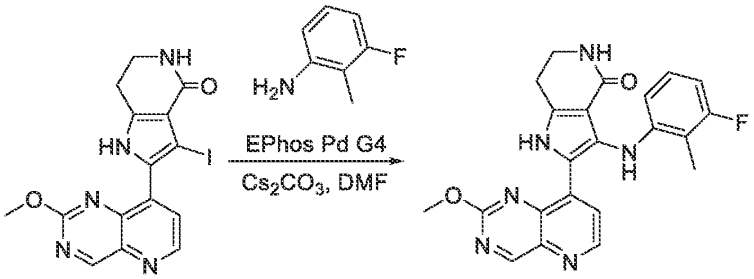
LC-MS: $(M+H)^+$ found: 295.95.



To a stirred solution of 2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one(720 mg, 2.43 mmol, 1.00 equiv) in DMF(25.00 mL) was added N-iodosuccinimide(603 mg, 2.68 mmol, 1.10 equiv) in portions at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature

under nitrogen atmosphere. The reaction was monitored by LCMS. LCMS showed the reaction was completed.The reaction was quenched by the addition of sat. Na_2SO_3 (aq.) (10mL) at 0 degrees C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2C_2 / MeOH (10:1) to afford 3-iodo-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one(1 g, 97.38%) as a yellow solid.

LC-MS: $(M+H)^+$ found 421.95.

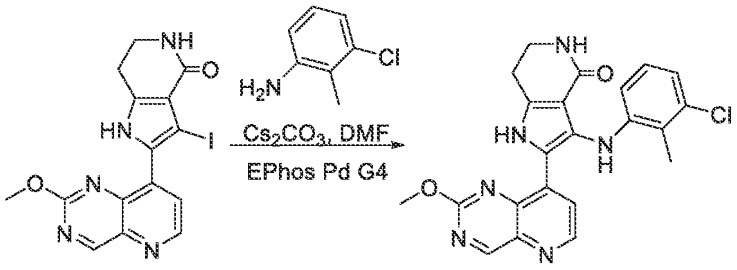


To a stirred solution of 3-iodo-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) in DMF (2.00 mL) was added Cs_2CO_3 (123 mg, 0.38 mmol, 2.00 equiv) and EPhos Pd G4 (174 mg, 0.19 mmol, 0.10 equiv) at room temperature under nitrogen atmosphere. To the above mixture was added 3-fluoro-2-methyl-aniline (71 mg, 0.57 mmol, 3.00 equiv) at room temperature. The resulting mixture was stirred for additional 2h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 50% B in 9 min, 50% B; Wave Length: 254/220 nm; RT1(min): 8.85) to afford 3-[(3-fluoro-2-methylphenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (18.5 mg, 22.11%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 419.25.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.01 (s, 1H), 9.47 (s, 1H), 8.62 (d, *J* =8.0 Hz, 1H), 7.66 (s, 1H), 7.45 (d, *J* = 4.0Hz, 1H), 7.30 (s, 1H), 6.76-6.74 (m, 1H), 6.51 (t, *J* = 8.0 Hz, 1H), 6.07 (d, *J* = 8.0 Hz, 1H), 4.21 (s, 3H), 3.48-3.44 (m, 2H), 2.97 (t, *J* = 8.0 Hz, 2H), 2.23 (s, 3H).

Example 172. 3-[(3-chloro-2-methylphenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 793)**



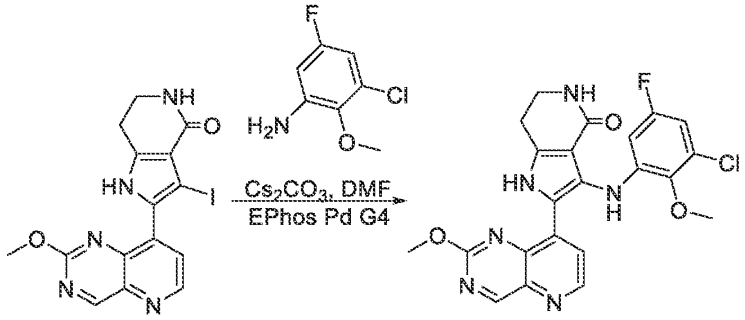
To a stirred solution of 3-iodo-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) in DMF (2.00 mL) was added Cs_2CO_3 (123 mg, 0.38 mmol, 2.00 equiv) and EPhos Pd G4 (17 mg, 0.01 mmol, 0.10 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added 2-methyl-3-chloroaniline (26 mg, 0.19 mmol, 1.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 2h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31% B to 56% B in 9 min, 56% B; Wave Length: 254/220 nm; RT1(min): 7.53) to afford 3-[(3-chloro-2-methylphenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (3.3mg,3.98%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 434.95.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.01 (s, 1H), 9.47 (s, 1H), 8.63 (d, *J* = 8.0 Hz, 1H), 7.69 (s, 1H), 7.46 (d, *J* = 4.0 Hz, 1H), 7.29 (s, 1H), 6.79 – 6.73 (m, 2H), 6.22-6.20 (m, 1H),

4.21 (s, 3H), 3.46 (s, 2H), 2.98 (t, *J* = 6.8 Hz, 2H), 2.40-2.32 (m, 3H).

Example 173. 3-[(3-chloro-5-fluoro-2-methoxyphenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 792)**

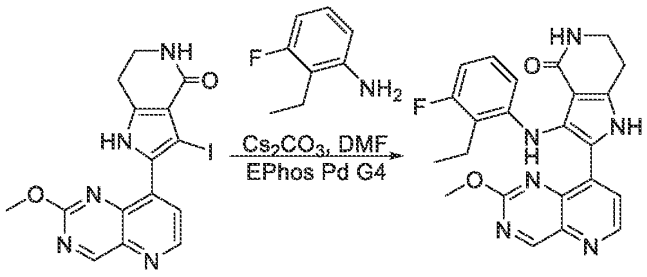


To a stirred solution of 3-iodo-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) in DMF (2.00 mL) was added Cs_2CO_3 (123 mg, 0.38 mmol, 2.00 equiv) and EPhos Pd G4 (17mg, 0.01 mmol, 0.10 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added 3-chloro-5-fluoro-2-methoxyaniline (33 mg, 0.19 mmol, 1.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 2h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31% B to 61% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-5-fluoro-2-methoxyphenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (16.7mg,18.75%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 468.95.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.03 (s, 1H), 9.52 (s, 1H), 8.78 (d, *J* = 4.0 Hz, 1H), 7.99 (s, 1H), 7.7 (d, *J* = 4.0 Hz, 1H), 7.21 (s, 1H), 6.60-6.57 (m, 1H), 5.93-5.89 (m, 1H), 4.19 (s, 3H), 3.80 (s, 3H), 3.48-3.44 (m, 2H), 2.96 (t, J = 8.0 Hz, 2H).

Example 174. 3-[(2-ethyl-3-fluorophenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 791)**

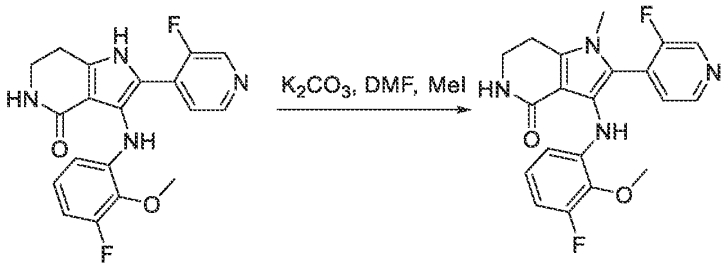


To a stirred solution of 3-iodo-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) in DMF (2.00 mL) was added Cs_2CO_3 (123 mg, 0.38 mmol, 2.00 equiv) and EPhos Pd G4 (17 mg, 0.01 mmol, 0.10 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added 2-ethyl-3-fluoroaniline (79 mg, 0.57 mmol, 3.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 2h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 62% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(2-ethyl-3-fluorophenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (8.7 mg, 10.59%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 433.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.02 (s, 1H), 9.47 (s, 1H), 8.60 (d, J = 8.0 Hz, 1H), 7.76 (s, 1H), 7.41 (d, J = 4.0 Hz, 1H), 7.29 (s, 1H), 6.77-6.72 (1H), 6.54-6.49 (m,1H), 6.11 (d, J = 8.0 Hz, 1H), 4.22 (s, 3H), 3.49-3.45 (m, 2H), 2.97 (t, J = 8.0 Hz, 2H), 2.75 – 2.67 (m, 2H), 1.26 (s, 3H).

Example 175. 3-[(3-chloro-2-ethylphenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 789)**

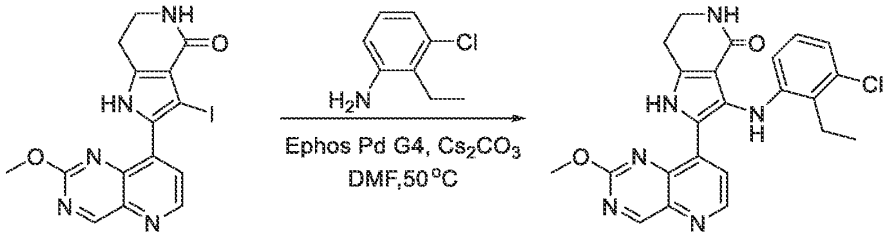


To a stirred solution of 3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50 mg, 0.13 mmol, 1.00 equiv) and MeI (19 mg, 0.13 mmol, 1 equiv) in DMF (2 mL) was added K_2CO_3 (37 mg, 0.27 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The resulting mixture was diluted with hexane (20 mL).The aqueous layer was extracted with EtOAc (3 x 10 mL).The crude product (30.00 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 38% B in 9.4 min, 38% B; Wave Length: 220/254 nm; RT1(min): 9.40;) to afford 3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-1-methyl-5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (10.3 mg, 19.72%) as a white solid

LC-MS: $(M+H)^+$ found: 385.00.

^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.59 (d, J = 1.9 Hz, 1H), 8.40 (dd, J = 4.9, 1.2 Hz, 1H), 7.47 (dd, J = 6.5, 4.9 Hz, 1H), 7.13 (d, J = 2.5 Hz, 2H), 6.55 (td, J = 8.3, 6.1 Hz, 1H), 6.39 (ddd, J = 10.8, 8.3, 1.5 Hz, 1H), 5.96 (dt, J = 8.3, 1.3 Hz, 1H), 3.80 (d, J = 0.7 Hz, 3H), 3.46 (dd, J = 6.5, 2.1 Hz, 5H), 2.90 (t, J = 6.8 Hz, 2H).

Example 176. 3-[(3-chloro-2-ethylphenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 800)**

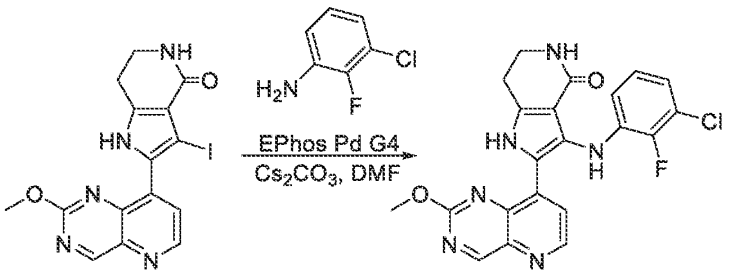


To a stirred mixture of 3-iodo-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.190 mmol, 1.00 equiv) and 3-chloro-2-ethylaniline (29 mg, 0.19 mmol, 1.00 equiv) and EPhos Pd G4 (17 mg, 0.019 mmol, 0.1 equiv) and Cs2CO3 (123 mg, 0.38 mmol, 2 equiv) in DMF (1.90 mL) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for 2 h at 50 degrees C under argon atmosphere. Desired product could be detected by LCMS. The crude product (80 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5[Im; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 36% B to 55% B in 10 min, 55% B; Wave Length: 254/220 nm; RT1(min): 8.85) to afford 3-[(3-chloro-2-ethylphenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (9.2 mg, 10.67%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 449.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.03 (s, 1H), 9.48 (s, 1H), 8.62 (d, J = 4.8 Hz, 1H), 7.79 (s, 1H), 7.41 (d, J = 4.8 Hz, 1H), 7.31 (d, J = 2.6 Hz, 1H), 6.89 – 6.63 (m, 2H), 6.25 (dd, J = 7.6, 1.7 Hz, 1H), 4.22 (s, 3H), 3.48 (td, J = 6.9, 2.5 Hz, 2H), 2.99 (t, J = 6.8 Hz, 2H), 2.91 (q, J = 7.4 Hz, 2H), 1.27 (t, J = 7.5 Hz, 3H).

Example 177. 3-[(3-chloro-2-fluorophenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 799)**

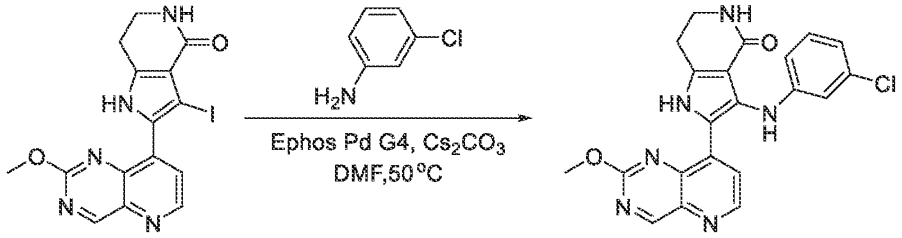


To a stirred solution of 3-iodo-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) in DMF (2.00 mL) was added Cs_2CO_3 (123 mg, 0.38 mmol, 2.00 equiv) and EPhos Pd G4 (17 mg, 0.01 mmol, 0.10 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added 3-chloro-2-fluoroaniline (27 mg, 0.19 mmol, 1.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 2h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed.The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 36% B to 37% B in 10 min, 37% B; Wave Length: 254/220 nm; RT1(min): 10) to afford 3-[(3-chloro-2-fluorophenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (14.8 mg, 17.45%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 438.95.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.02 (s, 1H), 9.50 (s, 1H), 8.74 (d, J = 8.0 Hz, 1H), 7.97 (s, 1H), 7.71 (d, J = 4.0 Hz, 1H), 7.25 (s, 1H), 6.78 – 6.76 (m, 2H), 6.32 – 6.27 (m, 1H), 4.19 (s, 3H), 3.45 (t, J = 8.0 Hz, 2H), 2.96 (t, J = 8.0 Hz, 2H).

Example 178. 3-[(3-chlorophenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 798)**



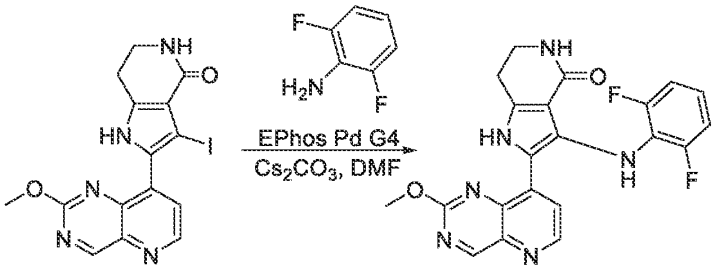
To a stirred mixture of 3-iodo-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) and 3-chloroaniline (24 mg, 0.19 mmol, 1.00 equiv) and Ephos Pd g4 (17 mg, 0.019 mmol, 0.1 equiv) and Cs2CO3 (123 mg, 0.38 mmol, 2 equiv) in DMF (1.90 mL) in portions at room temperature under

argon atmosphere. The resulting mixture was stirred for 2 h at 50 degrees C under argon atmosphere. Desired product could be detected by LCMS. The crude product (80 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 14% B to 44% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chlorophenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (11.8 mg, 14.72%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 421.

^{1}H NMR (300 MHz, DMSO-d6) δ 12.05 (s, 1H), 9.49 (s, 1H), 8.71 (d, J = 4.8 Hz, 1H), 7.99 (s, 1H), 7.72 (d, J = 4.8 Hz, 1H), 7.21 (t, J = 2.6 Hz, 1H), 7.02 (t, J = 8.3 Hz, 1H), 6.68 – 6.58 (m, 2H), 6.56 – 6.51 (m, 1H), 4.20 (s, 3H), 3.46 (td, J = 6.8, 2.5 Hz, 2H), 2.97 (t, J = 6.8 Hz, 2H)

Example 179. 3-[(2,6-difluorophenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 806)**



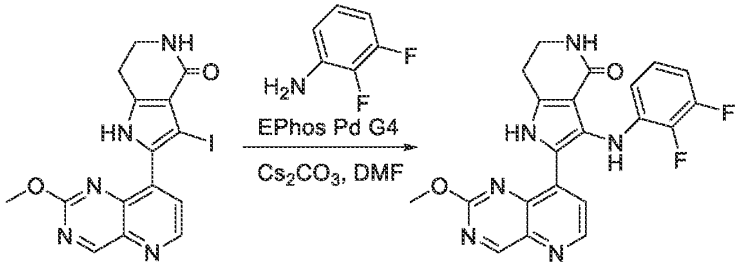
To a stirred solution of 3-iodo-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) in DMF (2.00 mL)was added Cs_2CO_3 (123 mg, 0.38 mmol, 2.00 equiv) and EPhos Pd G4 (17 mg, 0.01 mmol, 0.10 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added 2,6-difluoroaniline (73 mg, 0.57 mmol, 3.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 2h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture

was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 14% B to 38% B in 10 min, 38% B; Wave Length: 254/220 nm; RT1(min): 9.67) to afford 3-[(2,6-difluorophenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (10.4 mg, 12.79%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 422.95.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.63 (s, 1H), 9.43 (s, 1H), 8.63 (d, *J* = 4.0 Hz, 1H), 7.68 (d, *J* =8.0 Hz, 1H), 7.54 (s, 1H), 7.06 (s, 1H), 6.80 – 6.75 (m, 2H), 6.69 – 6.67 (m, 1H), 4.14 (s, 3H), 3.44-3.32 (m, 2H), 2.91 (t, *J* = 4.0 Hz, 2H).

Example 180. 3-[(2,3-difluorophenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 805)**



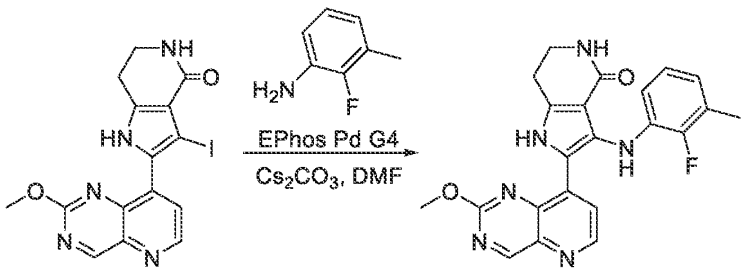
To a stirred solution of 3-iodo-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) in DMF (2.00 mL) was added Cs_2CO_3 (123 mg, 0.38 mmol, 2.00 equiv) and EPhos Pd G4 (17 mg, 0.01 mmol, 0.10 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added 2,3-difluoroaniline (73 mg, 0.57 mmol, 3.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 2h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep

C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 47% B in 9 min, 47% B; Wave Length: 254/220 nm; RT1(min): 8.85) to afford 3-[(2,3-difluorophenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (11.8 mg, 14.52%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 423.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.98 (s, 1H), 9.49 (s, 1H), 8.73 (d, J = 8.0 Hz, 1H), 7.94 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.24 (s, 1H), 6.71 – 6.63 (m, 2H), 6.20 – 6.14 (m, 1H), 4.18 (s, 3H), 3.47-3.43 (m, 2H), 2.95 (t, J = 8.0 Hz, 2H).

Example 181. 3-[(2-fluoro-3-methylphenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 804)**



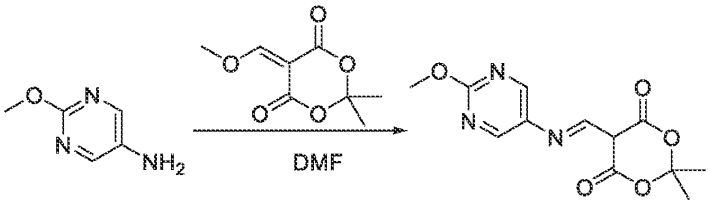
To a stirred solution of 3-iodo-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) in DMF (2.00 mL) was added Cs_2CO_3 (123 mg, 0.38 mmol, 2.00 equiv) and EPhos Pd G4 (17 mg, 0.01 mmol, 0.10 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added 2-fluoro-3-methylaniline (71 mg, 0.57 mmol, 3.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 2h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 58% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(2-fluoro-3-

methylphenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (10.9mg,13.55%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 419.

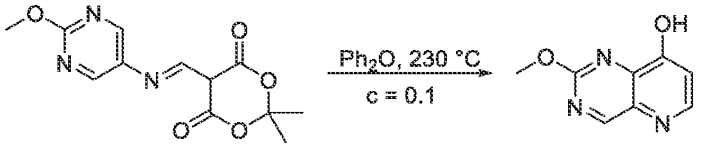
^{1}H NMR (400 MHz, DMSO-d6) δ 11.97 (s, 1H), 9.48 (s, 1H), 8.66 (d, *J* = 4.0 Hz, 1H), 7.80 (d, *J* = 4.0 Hz, 1H), 7.53 (d, *J* = 4.0 Hz, 1H), 7.30 (s, 1H), 6.59 – 6.54 (m, 2H), 6.14-6.12 (m, 1H), 4.20 (s, 3H), 3.48-3.44 (m, 2H), 2.96 (t, *J* = 4.0 Hz, 2H), 2.22 (d, *J* = 4.0 Hz, 3H).

Example 182. 3-[(2,3-dichlorophenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 803)**



To a stirred solution of 2-methoxypyrimidin-5-amine (2.00 g, 15.983 mmol, 1.00 equiv) in DMF (16.00 mL) was added 5-(methoxymethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (3.27 g, 17.582 mmol, 1.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 80 degrees C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with MeOH (50 ml). The precipitated solids were collected by filtration and washed with MeOH (3x50 mL). This resulted in 5-[(1E)-[(2-methoxypyrimidin-5-yl)imino]methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (3.9 g, 87.38%) as a light yellow solid.

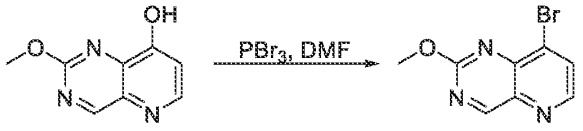
LC-MS: M+H found: 280.



A solution of 5-[(1E)-[(2-methoxypyrimidin-5-yl)imino]methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione(2.00 g, 7.162 mmol, 1.00 equiv) in diphenyl-ether(70.00 mL) was stirred for 1 h at 230 degrees C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with hexane (50 mL). The precipitated solids

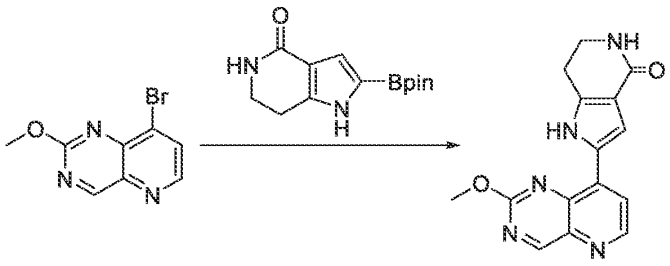
were collected by filtration and washed with hexane (3x20 mL). The crude product (1.26 g) was used in the next step directly without further purification.

LC-MS: M+H found: 178.



To a stirred solution of 2-methoxypyrido[3,2-d]pyrimidin-8-ol (1.26 g, 7.112 mmol, 1.00 equiv) in DMF (18.00 mL) was added phosphorus tribromide (2.31 g, 8.535 mmol, 1.20 equiv) dropwise at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. LCMS showed the reaction was completed.The mixture was basified to pH 7 with saturated Na2CO3 (aq.).The resulting mixture was extracted with EtOAc (3 x 150mL). The combined organic layers were washed with brine (2x250 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 1:1) to afford 8-bromo-2-methoxypyrido[3,2-d]pyrimidine (40 mg, 2.34%) as a off-white solid.

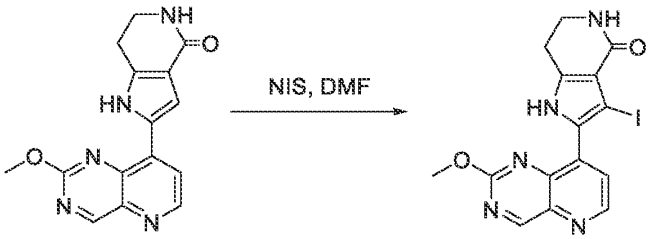
LC-MS: M+H found: 240.



To a stirred solution of 8-bromo-2-methoxypyrido[3,2-d]pyrimidine (110 mg, 0.45 mmol, 1.00 equiv) in dioxane (3.50 mL) was added 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (240 mg, 0.91 mmol, 2.00 equiv) and Na_2CO_3 (145 mg, 1.37 mmol, 3.00 equiv) and Pd(PPh3)4 (52 mg, 0.046 mmol, 0.10 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added H2O (0.70 mL) dropwise at room temperature. The resulting mixture was stirred for additional overnight at 50 degrees C. The reaction was monitored by LCMS. LCMS

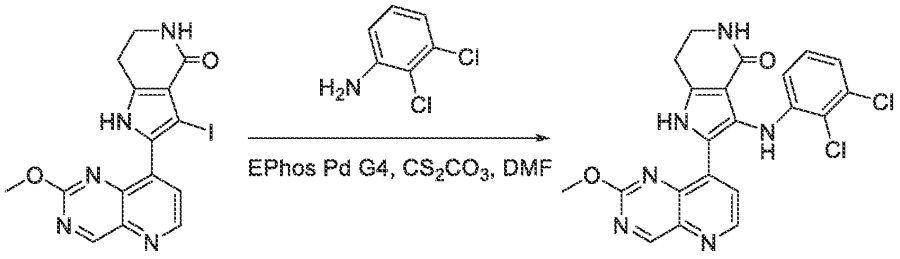
showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (10:1) to afford 2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (120 mg, 88.68%) as a yellow solid.

LC-MS: M+H found: 296.



To a stirred solution of 2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (120 mg, 0.40 mmol, 1.00 equiv) in DMF (6.00 mL) was added N-iodosuccinimide (109 mg, 0.48 mmol, 1.20 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 24h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The reaction was quenched by the addition of sat. Na2SO3 (aq.) (5mL) at room temperature. The mixture was stirred for 10 min at room temperature under nitrogen atmosphere. The mixture was basified to pH 7 with saturated Na2CO3 (aq.). The resulting mixture was extracted with CH2Cl2: MeOH (10:1) 3 x 50 mL). The combined organic layers were washed with brine (2x20 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 0% to 100% gradient in 40 min; detector, UV 254 nm. The resulting mixture was concentrated under vacuum to afford 3-iodo-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 58.42%) as an orange solid.

LC-MS: M+H found: 422.

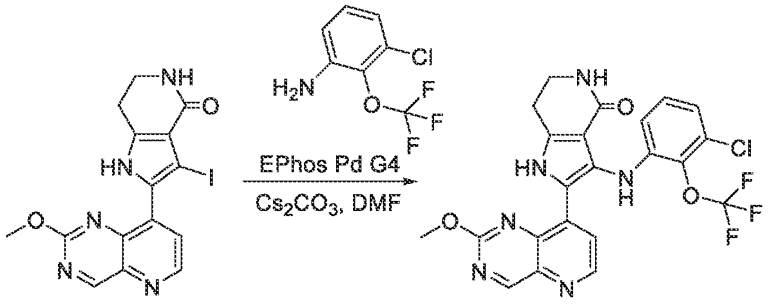


To a stirred solution of 3-iodo-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) and 2,3-dichloroaniline (30 mg, 0.19 mmol, 1.00 equiv) in DMF (2.00 mL) were added EPhos Pd G4 (17 mg, 0.019 mmol, 0.10 equiv) and Cs_2CO_3 (123 mg, 0.38 mmol, 2.00 equiv) under Ar atmosphere. The resulting mixture was stirred for 2hrs at 50degrees C under Ar atmosphere. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 50% B in 9 min, 50% B; Wave Length: 254/220 nm; RT1(min): 9.67) to afford 3-[(2,3-dichlorophenyl)amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (8.3 mg, 9.30%) as an orange solid.

LC-MS: M+H found: 454.95.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.03 (s, 1H), 9.50 (s, 1H), 8.73 (d, J = 4.8 Hz, 1H), 8.04 (s, 1H), 7.59 (d, J = 4.8 Hz, 1H), 7.25 (s, 1H), 6.93 – 6.83 (m, 2H), 6.32 (t, J = 4.8 Hz, 1H), 4.20 (s, 3H), 3.52 – 3.43 (m, 2H), 2.97 (t, J = 6.8 Hz, 2H).

Example 183. 3-[[3-chloro-2-(trifluoromethoxy)phenyl]amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 802)**

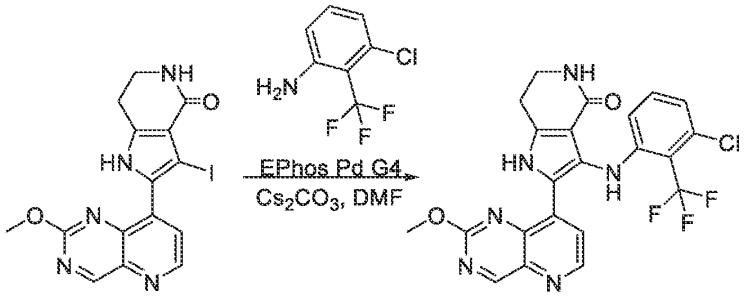


To a stirred solution of 3-iodo-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) in DMF (2.00 mL) was added Cs_2CO_3 (123 mg, 0.38 mmol, 2.00 equiv) and EPhos Pd G4 (17 mg, 0.01 mmol, 0.10 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added 3-chloro-2-(trifluoromethoxy)aniline (40 mg, 0.19 mmol, 1.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 2h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 55% B in 9 min, 55% B; Wave Length: 254/220 nm; RT1(min): 8.85) to afford 3-[[3-chloro-2-(trifluoromethoxy)phenyl]amino]-2-[2-methoxypyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (2.4 mg, 2.48%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 504.95.

^{1}H NMR (400 MHz, Methanol-d4) δ 9.40 (s, 1H), 8.64 – 8.50 (m, 1H), 7.68 (s, 1H), 6.84 (d, J = 4.0 Hz, 2H), 6.52 – 6.40 (m, 1H), 4.27 (s, 3H), 3.62-3.59 (m, 3H), 3.12-3.06 (m, 2H), 1.18 (t, J = 8.0 Hz, 2H).

Example 184. 3-{[3-chloro-2-(trifluoromethyl)phenyl]amino}-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 801)**

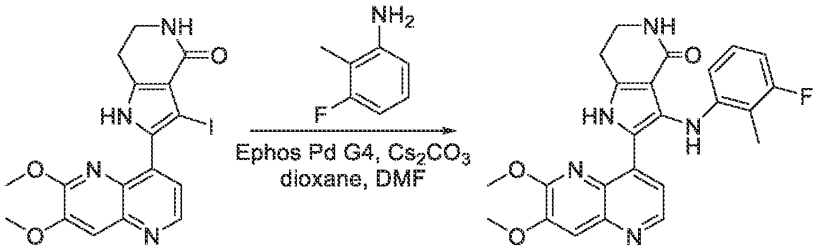


To a stirred solution of 3-iodo-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (60 mg, 0.14 mmol, 1.00 equiv) in 2ml DMF was added Cs_2CO_3 (92 mg, 0.28 mmol, 2.00 equiv) and EPhos Pd G4 (13 mg, 0.01 mmol, 0.10 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added 3-chloro-2-(trifluoromethyl)aniline (27 mg, 0.14 mmol, 1.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 2h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford crude product. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 52% B in 8 min, 52% B; Wave Length: 220/254 nm; RT1(min): 7.97) to afford 3-{[3-chloro-2-(trifluoromethyl)phenyl]amino}-2-{2-methoxypyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (2.3 mg, 3.27%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 488.9.

^{1}H NMR (300 MHz, DMSO-d6) δ 12.02 (s, 1H), 9.50 (s, 1H), 8.72 (d, *J* = 8.0 Hz, 1H), 8.08 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.23 (s, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.55 (d, J = 8.0 Hz, 1H), 4.18 (s, 3H), 3.47 (d, *J* = 8.0Hz, 2H), 2.97 (t, *J* = 8.0 Hz, 2H).

Example 185. 2-(6,7-dimethoxy-1,5-naphthyridin-4-yl)-3-[(3-fluoro-2-methylphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 808)**

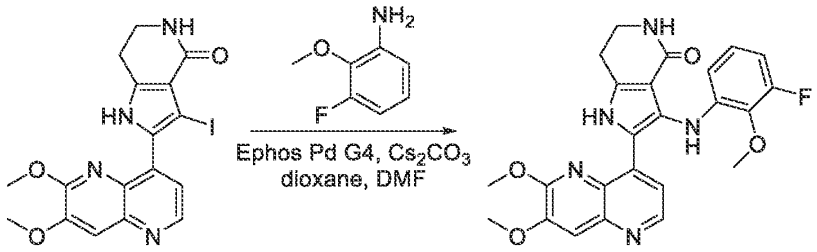


To a stirred mixture of 2-(6,7-dimethoxy-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (90 mg, 0.20 mmol, 1.00 equiv) and 3-fluoro-2-methyl-aniline (125 mg, 1.0 mmol, 5 equiv) in DMF (2.00 mL) were added Ephos Pd G4 (18 mg, 0.02 mmol, 0.1 equiv) and Cs_2CO_3 (130 mg, 0.40 mmol, 2 equiv) in portions at 50 degrees C under argon atmosphere. The resulting mixture was stirred for overnight at 50 degrees C under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/ MeOH 10:1) to afford crude product as a light yellow solid. The crude product (50 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 50% B in 9 min, 50% B; Wave Length: 254/220 nm; RT1(min): 8.98) to afford 2-(6,7-dimethoxy-1,5-naphthyridin-4-yl)-3-[(3-fluoro-2-methylphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (23.3 mg, 25.50%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 448.25.

^{1}H NMR (300 MHz, DMSO-d6) δ 12.04 (s, 1H), 8.44 (d, J = 5.0 Hz, 1H), 7.65 (s, 1H), 7.50 (s, 1H), 7.34 (d, J = 5.0 Hz, 1H), 7.23 (d, J = 2.5 Hz, 1H), 6.74 (q, J = 7.9 Hz, 1H), 6.48 (t, J = 8.8 Hz, 1H), 6.10 (d, J = 8.2 Hz, 1H), 4.21 (s, 3H), 3.99 (s, 3H), 3.46 (d, J = 2.5 Hz, 2H), 2.95 (t, J = 6.8 Hz, 2H), 2.23 (d, J = 1.7 Hz, 3H).

Example 186. 2-(6,7-dimethoxy-1,5-naphthyridin-4-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 807)**

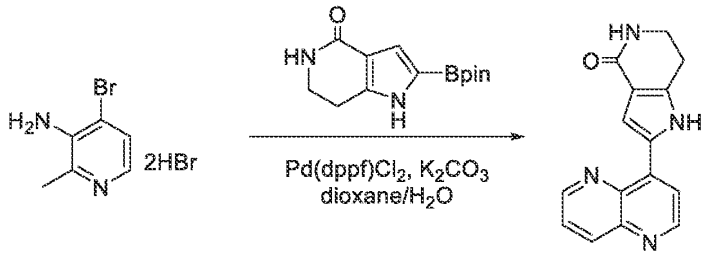


To a stirred mixture of 2-(6,7-dimethoxy-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.22 mmol, 1.00 equiv) and 3-fluoro-2-methoxyaniline (157 mg, 1.1 mmol, 5.00 equiv) in DMF (2.00 mL) were added Ephos Pd G4 (20 mg, 0.02 mmol, 0.10 equiv) and Cs_2CO_3 (145 mg, 0.44 mmol, 2.00 equiv) in portions at 50 degrees C under argon atmosphere. The resulting mixture was stirred for overnight at 50 degrees C under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford crude product as a light yellow solid. The crude product (50 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 45% B in 10 min, 45% B; Wave Length: 254/220 nm; RT1(min): 9.67) to afford 2-(6,7-dimethoxy-1,5-naphthyridin-4-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (19.4 mg, 18.68%) as a light yellow solid.

LC-MS: $(M+H)^+$ found 464.25.

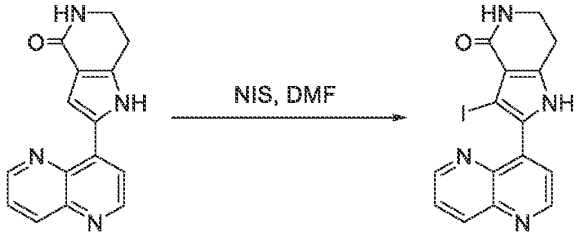
^{1}H NMR (300 MHz, DMSO-d6) δ 11.98 (s, 1H), 8.51 (d, J = 4.9 Hz, 1H), 7.76 (s, 1H), 7.67 (s, 1H), 7.41 (d, J = 4.9 Hz, 1H), 7.18 (d, J = 2.5 Hz, 1H), 6.61 (m, J = 6.1 Hz, 1H), 6.48 (m, J = 1.5 Hz, 1H), 6.05 (m, J = 1.4 Hz, 1H), 4.20 (s, 3H), 4.00 (s, 3H), 3.86 (d, J = 1.0 Hz, 3H), 3.46 (m, J =4.0 Hz, 2H), 2.94 (t, J = 6.8 Hz,2H).

Example 187. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 683)**



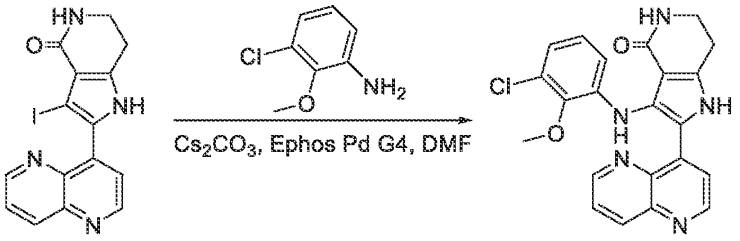
To a stirred solution of 4-bromo-1,5-naphthyridine (500 mg,1.22 mmol, 1.00 equiv) and K_2CO_3 (956 mg, 6.80 mmol, 5.00 equiv) in 1,4 - dioxane (5.00 mL) was added 2-(dihydroxymethyl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c] pyridin-4-one (426 mg, 1.58 mmol, 1.20 equiv) in portions at room temperature under Ar atmosphere. The resulting mixture was stirred for 4 h at 80 degrees C under Ar atmosphere. The reaction was monitored by TLC and LCMS. The mixture was allowed to cool down to room temperature. The residue was purified by Prep-TLC (DCM/MeOH = 10/1) to afford 2-(1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (250 mg, 69.0%) as a yellow solid.

LC-MS: M+H found: 265.05.



To a stirred solution of 2-(1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (200 mg, 0.75 mmol, 1.00 equiv) in DMF (6.00 mL) was added NIS (170 mg, 0.75 mmol, 1.00 equiv) in portions at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 2 h at room temperature. The precipitated solids were collected by filtration and washed with CH_2Cl_2 (2 x 8 mL). The crude product (450 mg) was purified by silica gel column chromatography with the following conditions (DCM/MeOH = 10/1) to afford 3-iodo-2-(1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (180 mg, 61.0%) as a white solid.

LC-MS: M+H found: 390.90.

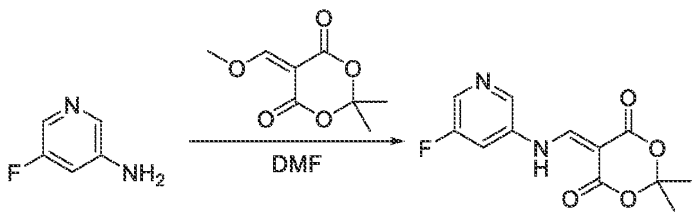


To a stirred solution of 3-iodo-2-(1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.03 mmol, 1.00 equiv) and3-chloro-2-methoxyaniline (40 mg, 0.03 mmol, 1.00 equiv) in DMF (3.00 mL) was added Cs_2CO_3 (45 mg, 3.00 equiv) and Ephos Pd G4 (9 mg, 0.15 equiv) under Ar atmosphere. The resulting mixture was stirred for 2 h at 80 degrees C. The precipitated solids were collected by filtration and washed with MeOH. The crude product (80 mg) was purified by Prep-HPLC with the following conditions ((2#SHIMADZU (HPLC-01): Column, XBridge Prep OBD C18 Column, 30*150 mm, 5μm; mobile phase, Water (10 mmol/L NH_4HCO_3) and ACN (30% ACN up to 60% in 7 min), Mobile Phase B: ACN; Flow rate:60 mL/min; Gradient:40 B to 55 B in 8 min; 220 nm; RT: 6) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (7.0 mg, 6.5%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 420.20.

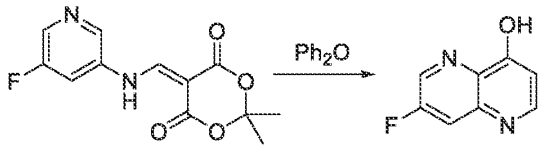
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.61 (s, 1H), 9.11 (dd, J = 4.2, 1.8 Hz, 1H), 8.76 (d, J = 4.9 Hz, 1H), 8.46 (dd, J = 8.6, 1.8 Hz, 1H), 8.11 (s, 1H), 7.89 (dd, J = 8.5, 4.2 Hz, 1H), 7.56 (d, J = 4.7 Hz, 1H), 7.25 (s, 1H), 6.77 – 6.67 (m, 2H), 6.22 (dd, J = 7.8, 1.9 Hz, 1H), 3.93 (s, 3H), 3.46 (td, J = 6.8, 2.8 Hz, 2H), 3.01 (t, J = 6.7 Hz, 2H).

Example 188. 2-(7-fluoro-1,5-naphthyridin-4-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 825)**



Into a dimethylformamide (80 mL) were added 5-fluoropyridin-3-amine (10 g, 89.2 mmol, 1.00 equiv) and 5-(methoxymethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (19.9 g, 107.04 mmol, 1.20 equiv) at room temperature. The resulting mixture was stirred for 1 h at 80 degrees C under N2 atmosphere. The reaction was monitored by TLC. The resulting mixture was washed with MeOH (160.00mL). The resulting mixture was filtered, the filter cake was washed with MeOH(10.00 mL). The filter cake was concentrated under reduced pressure to give 5-{[(5-fluoropyridin-3-yl)amino]methylidene}-2,2-dimethyl-1,3-dioxane-4,6-dione (23 g, 87.17%) as a white solid.

LC-MS: $(M+H)^+$ found: 266.90.



Into a diphenyl-ether (200 mL) were added 5-{[(5-fluoropyridin-3-yl)amino]methylidene}-2,2-dimethyl-1,3-dioxane-4,6-dione (5 g, 18.78 mmol, 1.00 equiv) at 230 degrees C. The resulting mixture was stirred for 10 min at 230 degrees C. The reaction was monitored by LCMS. The mixture was allowed to cool down to 50 degrees C. The resulting mixture was diluted with n-hexane (400 mL). The precipitated solids were collected by filtration and washed with n-hexane (10 mL) to give 7-fluoro-1,5-naphthyridin-4-ol (3 g, 87.59%) as a white solid.

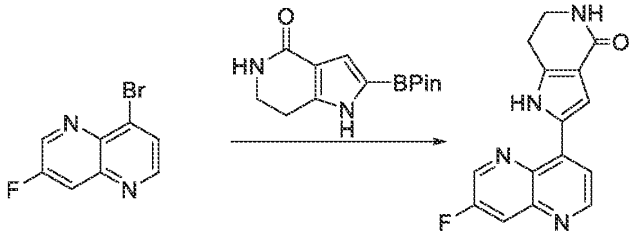
LC-MS: $(M+H)^+$ found: 165.



Into a DMF (36.00 mL) were added 7-fluoro-1,5-naphthyridin-4-ol (3.6 g, 21.93 mmol, 1.00 equiv) and PBr_3 (6.53 g, 24.13 mmol, 1.10 equiv) at 0 degrees C. The resulting mixture was stirred for 1 h at room temperature under N2 atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The reaction was quenched with $NaHCO_3$ solution (50.00 mL) at 0 degrees C. The resulting mixture was extracted with EA (3 x 100.00 mL). The combined organic layers were washed with

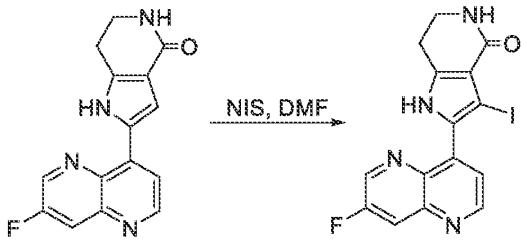
NaCl solution (3 x 150 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (0 to 100%) to afford 8-bromo-3-fluoro-1,5-naphthyridine (3.5 g, 63.26%) as a white solid.

LC-MS: $(M+H)^+$ found: 165.



To a stirred solution of 8-bromo-3-fluoro-1,5-naphthyridine (1 g, 4.40 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.73 g, 6.60 mmol, 1.5 equiv) in dioxane (20.00 mL) and H_2O (4.00 mL) were added $Pd(PPh_3)_4$ (0.51 g, 0.44 mmol, 0.10 equiv) and Na2CO3 (1.40 g, 13.21 mmol, 3.00 equiv) dropwise at RT under N2 atmosphere. The resulting mixture was stirred for 1 h at 50 degrees C under N2 atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0 to10%) to afford 2-(7-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (300 mg, 22.92%) as a as a yellow solid .

LC-MS: $(M+H)^+$ found: 283.

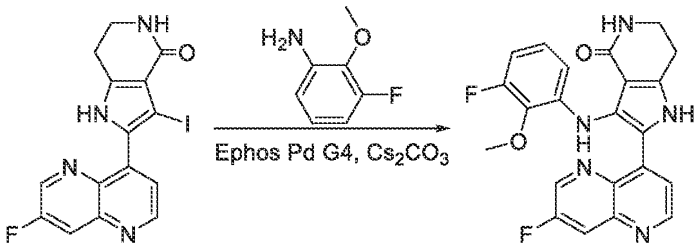


Into a DMF (3.00 mL) were 2-(7-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (150 mg, 0.53 mmol, 1.00 equiv) and NIS (119 mg, 0.53 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred for 1 h at room

temperature. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (3%) to afford 2-(7-fluoro-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (160 mg, 70.08%) as a yellow solid.

LC-MS: MH (C15H10FIN4O) = 408; should be 408.

LC-MS: $(M+H)^+$ found: 283.



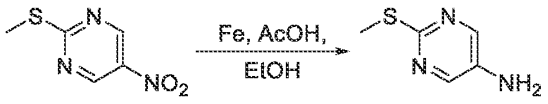
To a stirred solution of 2-(7-fluoro-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) and 3-fluoro-2-methoxyaniline (83 mg, 0.59 mmol, 3.00 equiv) in DMF (1.00 mL) was added Ephos Pd G4 (18 mg, 0.02 mmol, 0.10 equiv) dropwise at RT under Ar atmosphere. The resulting mixture was stirred for 1 h at 50 degrees C under Ar atmosphere. The reaction was monitored by LCMS. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 46% B in 8 min, 46% B; Wave Length: 254/220 nm; RT1(min): 7.8) to afford 2-(7-fluoro-1,5-naphthyridin-4-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (43.7 mg, 52.22%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 422.20.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.36 (s, 1H), 9.12 (d, J = 2.4 Hz, 1H), 8.76 (d, J = 4.0 Hz, 1H), 8.33– 8.31 (m, 1H), 8.04 (s, 1H), 7.56 (d, J = 4.8 Hz, 1H), 7.25 (s, 1H), 6.66 – 6.10 (m, 1H), 6.56 (t, J = 8.8 Hz, 1H),6.05 (d, J = 8.0 Hz, 1H), 3.94 (s, 3H), 3.50 – 3.42 (m, 2H), 2.98 (t, J = 6.4 Hz, 2H).

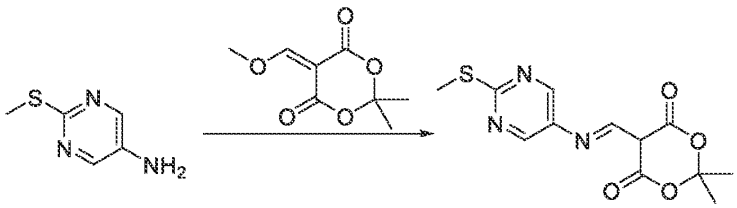
Example 189. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-ethoxypyrido[3,2-

d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 827)**



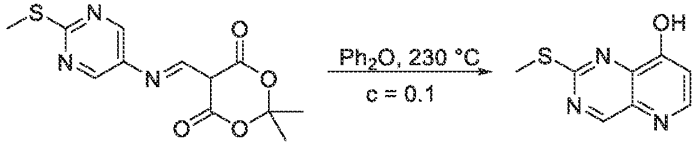
To a stirred solution of 2-(methylsulfanyl)-5-nitropyrimidine (5 g, 29.211 mmol, 1.00 equiv) in EtOH (200 mL) was added AcOH (120 mL) and Fe (17 g, 292.11 mmol, 10 equiv) in portions at rt under N_2 atmosphere. The resulting mixture was stirred for 2 h at 80 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 142. The resulting mixture was concentrated under reduced pressure. The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with Saturated NaCl (3x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2-(methylsulfanyl)pyrimidin-5-amine (3.5 g, 84.86%) as a yellow solid.

LC-MS: M+H found: 142.0.



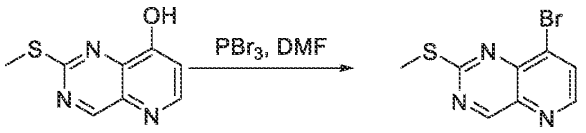
To a stirred solution of 2-(methylsulfanyl)pyrimidin-5-amine (3.2 g, 22.66 mmol, 1.00 equiv) and 5-(methoxymethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (5.06 g, 27.18 mmol, 1.20 equiv) in DMF (80.00 mL) at rt under N_2 atmosphere. The resulting mixture was stirred for 1 h at 80 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 296.The resulting mixture was added MeOH(50 mL). The resulting mixture was filtered, the filter cake was washed with MeOH (3 x20 mL). The filter cake was concentrated under reduced pressure to afford 2,2-dimethyl-5-[(1E)-[[2-(methylsulfanyl)pyrimidin-5-yl]imino]methyl]-1,3-dioxane-4,6-dione (5.4 g, 80.68%) as a yellow solid.

LC-MS: $(M+H)^+$ found 296.0.



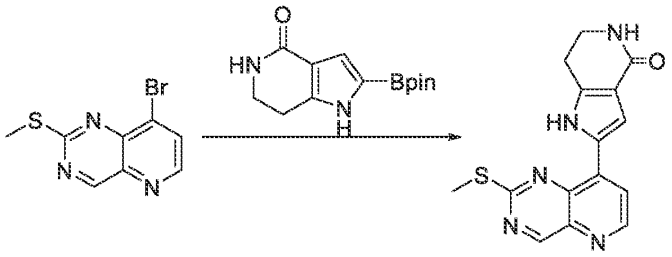
To a stirred solution of 2,2-dimethyl-5-[(1E)-{[2-(methylsulfanyl)pyrimidin-5-yl]imino}methyl]-1,3-dioxane-4,6-dione (5.3 g, 17.95 mmol, 1.00 equiv) in phenoxybenzene (360 mL) at rt under N_2 atmosphere. The resulting mixture was stirred at 230 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 194. The reaction was addition of Hexane (700 ml) at rt. The resulting mixture was filtered; the filter cake was washed with Hexane (3x200 ml). The filtrate was concentrated under reduced pressure.

LC-MS: $(M+H)^+$ found: 194.0.



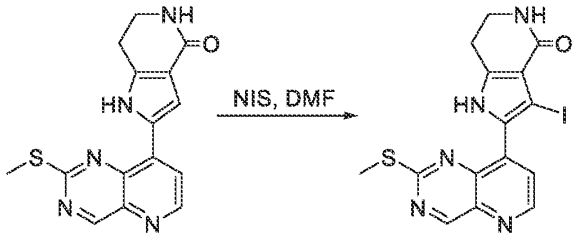
To a stirred solution of 2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-ol (2.8 g, 14.49 mmol, 1.00 equiv) in DMF (80 mL) was added PBr_3 (4.31 g, 15.94 mmol, 1.1 equiv) dropwise at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 1 h at rt under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 256. The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with aq. NaCl (3x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE:EA (4:1) to afford 8-bromo-2-(methylsulfanyl)pyrido[3,2-d]pyrimidine (1.6 g, 43.11%) as a white solid.

LC-MS: $(M+H)^+$ found: 256.0.



To a stirred solution of 8-bromo-2-(methylsulfanyl)pyrido[3,2-d]pyrimidine (700 mg, 2.73 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1075 mg, 4.10 mmol, 1.50 equiv) in dioxane (10 mL) and H_2O (1 mL) were added Na_2CO_3 (869.03 mg, 8.199 mmol, 3.00 equiv) and XPhos Pd G2 (215 mg, 0.27 mmol, 0.10 equiv) dropwise/ in portions at rt under N_2 atmosphere. The resulting mixture was stirred for 2 h at 80 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 312. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH=24:1 to afford 2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (700 mg, 82.26%) as a yellow solid.

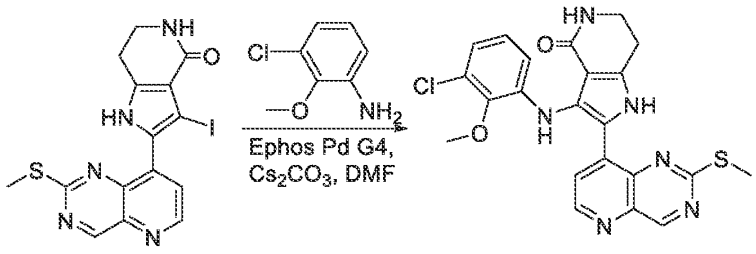
LC-MS: $(M+H)^+$ found: 312.0.



To a stirred solution of 2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (600 mg, 1.93 mmol, 1.00 equiv) and NIS (650 mg, 2.89 mmol, 1.50 equiv) in DMF (10 mL) at rt under N_2 atmosphere. The resulting mixture was stirred for overnight at 30 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 438.The reaction was quenched by the addition of Saturated aq. Na_2SO_3 (20 mL) at 0 degrees C. The precipitated solids were collected by filtration and washed with H_2O (20 mLx3). The residue was purified by silica gel column chromatography, eluted with DCM:MeOH=10:1 to afford 3-iodo-2-[2-

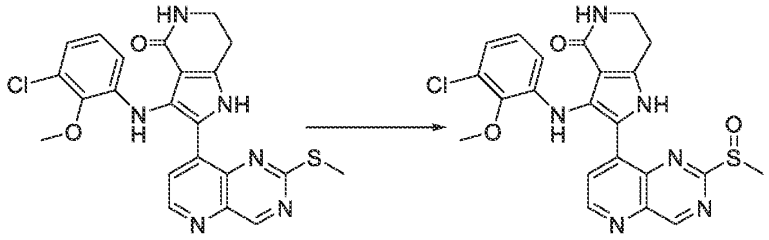
(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (650 mg, 77.14%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 438.0.



To a stirred solution of 3-iodo-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (370 mg, 0.85 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (134 mg, 0.85 mmol, 1 equiv) in DMF (4 mL) were added EPhos Pd G4 (78 mg, 0.08 mmol, 0.1 equiv) and Cs_2CO_3 (827 mg, 2.54 mmol, 3 equiv) in portions at rt under Ar atmosphere. The resulting mixture was stirred for 1.5 h at 50 degrees C under Ar atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 467. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM:MeOH (10:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (220 mg, 55.68%) as a orange solid.

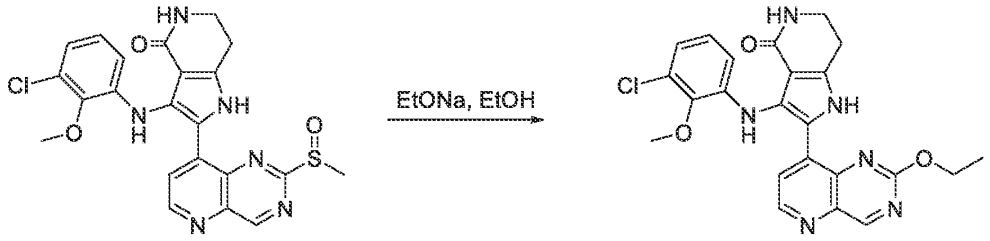
LC-MS: $(M+H)^+$ found: 467.0.



To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50 mg, 0.11 mmol, 1.00 equiv) in DCM (2 mL, 31.46 mmol, 293.80 equiv) were added MCPBA (29 mg, 0.12 mmol, 1.1 equiv) dropwise/ in portions at 0 degrees C under N_2

atmosphere. The resulting mixture was stirred for 1 h at 0 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 483. The resulting mixture was extracted with DCM (3 x 4 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

LC-MS: $(M+H)^+$ found: 483.0.



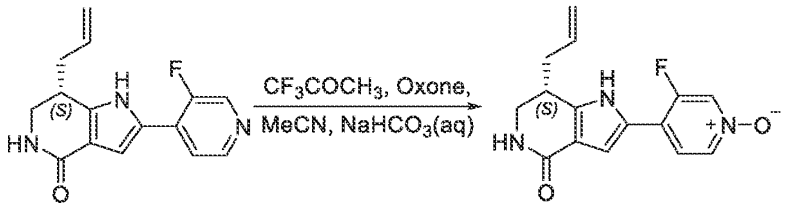
To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-methanesulfinylpyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (90 mg, 0.19 mmol, 1.00 equiv) in CH_3CH_2OH (2.00 mL) were added EtONa (211.36 mg, 0.558 mmol, 3 equiv) dropwise at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 1 h at 0 degrees C under N_2 atmosphere. The resulting mixture was concentrated under vacuum and dissolved in DMF. The crude product (50 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 63% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-ethoxypyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (14.7 mg) as a yellow solid.

LC-MS: $(M+H)^+$ found: 465.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H), 9.50 (s, 1H), 8.70 (d, J = 4.8 Hz, 1H), 7.89 (s, 1H), 7.57 (d, J = 4.8 Hz, 1H), 7.26 (d, J = 2.7 Hz, 1H), 6.73 (m, J = 8.1, 1.8 Hz, 1H), 6.68 (t, J = 8.0 Hz, 1H), 6.17 (m, J = 7.8, 1.8 Hz, 1H), 4.65 (m, J = 7.0 Hz, 2H), 3.89 (s, 3H), 3.47 (m, J = 6.8, 2.5 Hz, 2H), 2.97 (t, J = 6.8 Hz, 2H), 1.49 (t, J = 7.1 Hz, 3H).

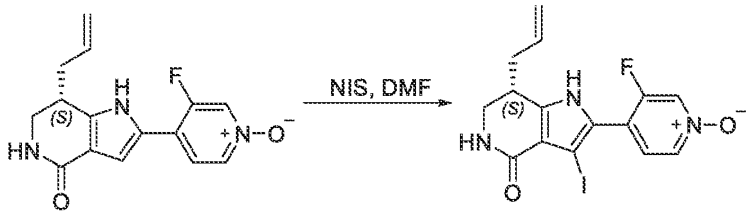
Example 190. (S)-4-(7-allyl-3-((3-chloro-2-methoxyphenyl)amino)-4-oxo-4,5,6,7-

tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)-3-fluoropyridine 1-oxide **(compound 828)**



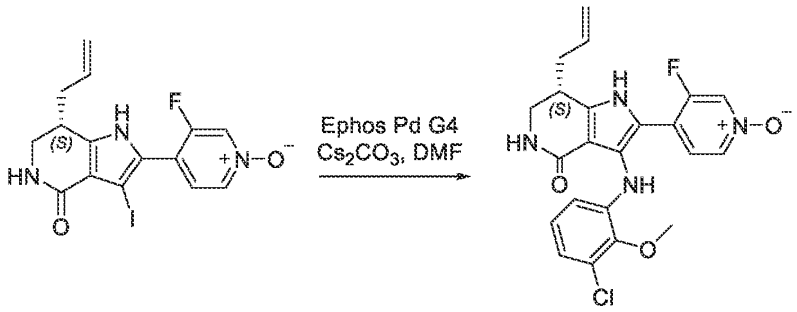
To a stirred solution/mixture of (7S)-2-(3-fluoropyridin-4-yl)-7-(prop-2-en-1-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (300 mg, 1.11 mmol, 1.00 equiv) in H_2O (10 mL) were added $NaHCO_3$ (743 mg, 8.85 mmol, 8 equiv) and oxone (680 mg, 1.11 mmol, 1.00 equiv) in portions at 0 degrees C under nitrogen atmosphere. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (20:1) to afford (S)-4-(7-allyl-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)-3-fluoropyridine 1-oxide (28 mg, 8.81%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 287.95.



To a stirred mixture of (S)-4-(7-allyl-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)-3-fluoropyridine 1-oxide (28 mg, 0.097 mmol, 1.00 equiv) in DMF (1.00 mL) was added NIS (24 mg, 0.11 mmol, 1.10 equiv) in portions at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (20:1) to afford (S)-4-(7-allyl-3-iodo-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)-3-fluoropyridine 1-oxide (26 mg, 64.56%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 413.85.

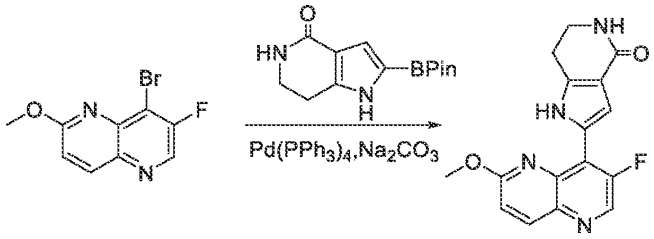


To a stirred mixture of (S)-4-(7-allyl-3-iodo-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)-3-fluoropyridine 1-oxide (40 mg, 0.10 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (15 mg, 0.097 mmol, 1.00 equiv) in DMF (1 mL) were added EPhos Pd G4 (44 mg, 0.05 mmol, 0.50 equiv) and Cs2CO3 (65 mg, 0.19 mmol, 2.00 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 2h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure that was purified by silica gel column chromatography, eluted with DCM / MeOH (20:1) to afford (S)-4-(7-allyl-3-((3-chloro-2-methoxyphenyl)amino)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)-3-fluoropyridine 1-oxide (6.1 mg, 14.23%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 443.00

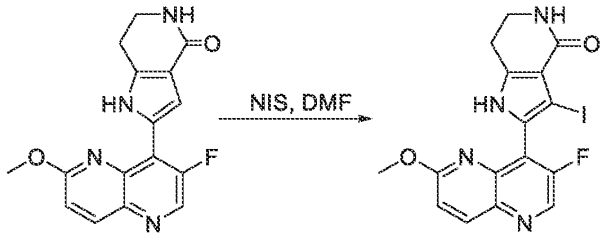
^{1}H NMR (400 MHz, DMSO-*d*6) δ 11.77 (s, 1H), 8.50 - 8.18 (m, 2H), 7.51 - 7.30 (m, 2H), 7.16 (t, J = 2.6 Hz, 1H), 6.92 - 6.62 (m, 2H), 6.27 - 6.09 (m, 1H), 5.97 - 5.78 (m, 1H), 5.23 - 4.96 (m, 2H), 3.90 (s, 3H), 3.52 - 3.41 (m, 1H), 3.24 - 3.14 (m, 1H), 3.11 - 3.01 (m, 1H), 2.65 - 2.55 (m, 1H), 2.40 - 2.26 (m, 1H).

Example 191. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 829)**



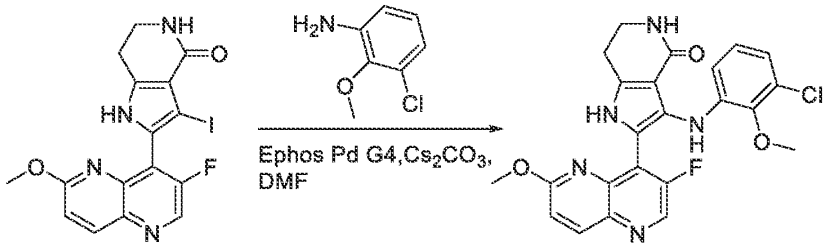
To a stirred solution of 8-bromo-7-fluoro-2-methoxy-1,5-naphthyridine (200 mg, 0.78 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (306 mg, 1.167 mmol, 1.5 equiv) in dioxane (5 mL) and H_2O (0.5 mL) were added 2nd Generation XPhos Precatalyst/X-Phos aminobiphenyl palladium chloride precatalyst (62 mg, 0.08 mmol, 0.1 equiv) and Na_2CO_3 (247 mg, 2.33 mmol, 3 equiv) dropwise/ in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80 degrees C under nitrogen atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 313. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 41.16%) as a yellow solid.

LC-MS: M+H found: 313.0.



To a stirred solution of 2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (90 mg, 0.29 mmol, 1.00 equiv) in DMF (4.5 mL) was added NIS (130 mg, 0.58 mmol, 2 equiv) in portions at 50 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 439. The resulting mixture was extracted with DCM:MeOH=10:1 (3 x 20 ml). The combined organic layers were washed with NaCl (3 x 100ml), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM:MeOH=40:1 to afford 2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70 mg, 55.43%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 438.85.



To a stirred solution of 2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (60 mg, 0.14 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (22 mg, 0.14 mmol, 1 equiv) in DMF (1 mL) were added EPhos Pd G4 (12 mg, 0.014 mmol, 0.1 equiv) and Cs_2CO_3 (133 mg, 0.41 mmol, 3 equiv) in portions at rt under Ar atmosphere. The resulting mixture was stirred for 2 h at 50 degrees C under Ar atmosphere. The resulting mixture was concentrated under reduced pressure. The resulting mixture was concentrated under vacuum and dissolved in DMF. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 62% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoro-6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (19.4 mg, 30.28%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 438.85.

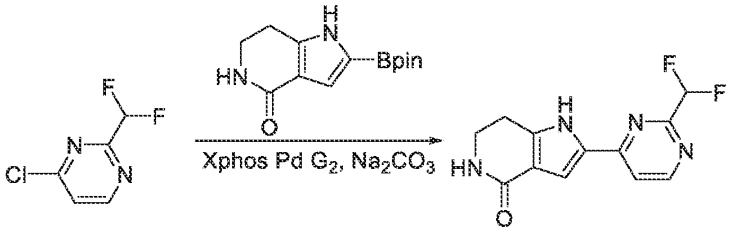
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (s, 1H), 8.73 (d, J = 1.6 Hz, 1H), 8.34 (d, J = 9.1 Hz, 1H), 7.78 (s, 1H), 7.32 (d, J = 9.0 Hz, 1H), 7.14 (d, J = 2.7 Hz, 1H), 6.55 (dd, J = 8.0, 1.5 Hz, 1H), 6.46 (t, J = 8.1 Hz, 1H), 6.14 (dd, J = 8.2, 1.5 Hz, 1H), 4.08 (s, 3H), 3.67 (s, 3H), 3.48 (td, J = 6.9, 2.5 Hz, 2H), 2.91 (t, J = 6.8 Hz, 2H).

Example 192. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(difluoromethyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 472)**



A mixture of 4-chloropyrimidine-2-carbaldehyde (100 mg, 0.702 mmol, 1 equiv) and

DAST (226.17 mg, 1.404 mmol, 2 equiv) in DCM (7 mL) was stirred for 2h at -78°C under nitrogen atmosphere.Desired product could be detected by TLC.The resulting mixture was concentrated under vacuum.The residue was purified by silica gel column chromatography, eluted with PE / EA (8:1) to afford 4-chloro-2-(difluoromethyl)pyrimidine (110 mg, 95.29%) as a yellow oil.



To a stirred mixture of 4-chloro-2-(difluoromethyl)pyrimidine (500 mg, 3.039 mmol, 1 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (955.83 mg, 3.647 mmol, 1.2 equiv) in 1,4-dioxane (15 mL) and water (3 mL) were added Na2CO3 (644.15 mg, 6.078 mmol, 2 equiv) and XPhos palladium(II) biphenyl-2-amine chloride (239.09 mg, 0.304 mmol, 0.1 equiv) in portions at room temperature under argon atmosphere.The resulting mixture was stirred for overnight at 50°C under argon atmosphere.Desired product could be detected by LCMS.The resulting mixture was concentrated under vacuum.The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (20:1) to afford 2-[2-(difluoromethyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (550 mg, 68.50%) as a yellow solid.

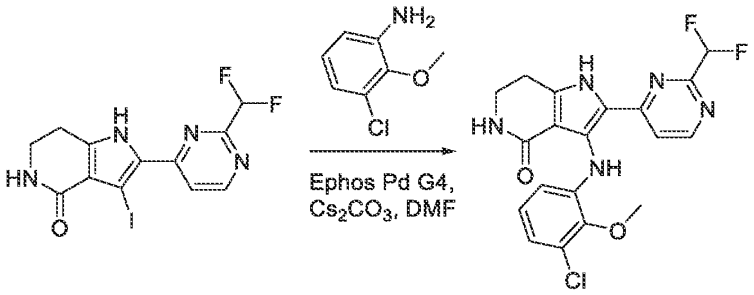
LC-MS: $[M+H]^+$ found: 264.95.



A mixture of 2-[2-(difluoromethyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (133 mg, 0.50 mmol, 1 equiv) and NIS (135 mg, 0.60 mmol, 1.2 equiv) in DMF (2 mL) was stirred for 1h at room temperature under air atmosphere. Desired product could

be detected by LCMS. The reaction was quenched by the addition of sat. sodium sulfite (aq.) (0.5mL) at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (15:1) to afford 2-[2-(difluoromethyl)pyrimidin-4-yl]-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (90 mg, 45.83%) as a yellow solid.

LC-MS: $[M+H]^+$ found: 390.85.



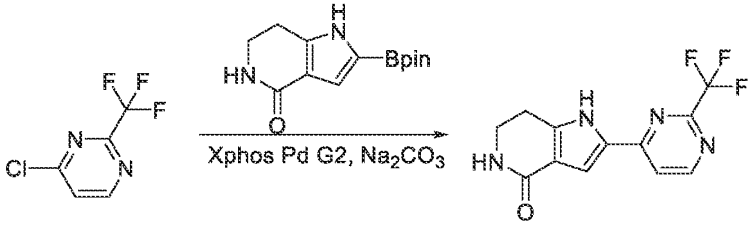
To a stirred mixture of 2-[2-(difluoromethyl)pyrimidin-4-yl]-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.20 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (29 mg, 0.184 mmol, 0.9 equiv) in DMF (2 mL) were added EPhos Pd G4 (18 mg, 0.021 mmol, 0.1 equiv) and Cs_2CO_3 (133 mg, 0.410 mmol, 2.0 equiv)in portions at room temperature under argon atmosphere.The resulting mixture was stirred for 2 h at 50 °C under argon atmosphere.The resulting mixture was concentrated under reduced pressure.The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 38% B to 54% B in 8 min, 54% B; Wave Length: 254/220 nm; RT1(min): 7) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(difluoromethyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (24.4 mg, 27.63%) as a yellow solid.

LC-MS: $[M+H]^+$ found: 420.00.

^1H NMR (300 MHz, DMSO-d6) δ 12.07 (s, 1H), 8.67 (d, J = 5.4 Hz, 1H), 8.02 (s, 1H), 7.25 (t, J = 7.8 Hz, 2H), 6.82 (t, J = 3.6 Hz, 3H), 6.34 (t, J = 4.8 Hz, 1H), 3.92 (s, 3H), 3.44 – 3.40 (m, 2H), 2.91 (t, J = 6.6 Hz, 2H).

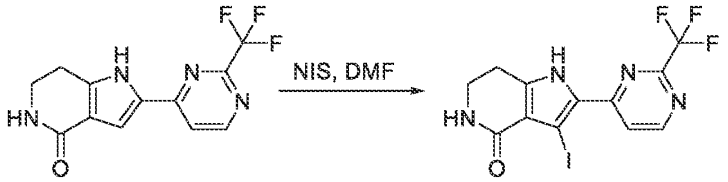
Example 193. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(trifluoromethyl)pyrimidin-4-

yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 476)**



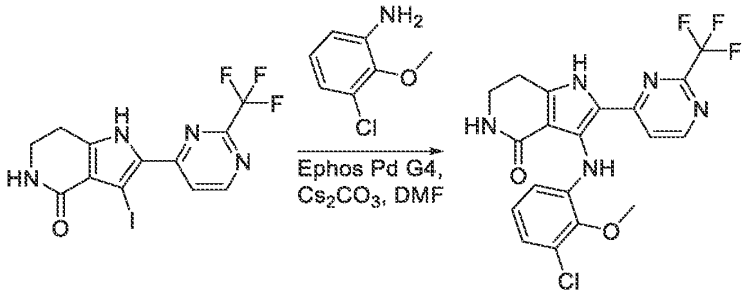
To a stirred mixture of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (345 mg, 1.31 mmol, 2.00 equiv) and 4-chloro-2-(trifluoromethyl)pyrimidine (120 mg, 0.66 mmol, 1.00 equiv) in dioxane (3.60 mL) and H_2O (0.36 mL) was added XPhos Pd G2 (52 mg, 0.07 mmol, 0.10 equiv) dropwise at room temperature. The resulting mixture was stirred for 2 h at 50 degrees C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (20:1) to afford 2-[2-(trifluoromethyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (160 mg, 86.23%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 282.90.



To a stirred mixture of 2-[2-(trifluoromethyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (170 mg, 0.60 mmol, 1.00 equiv) in DMF (3 mL) was added NIS (271 mg, 1.2 mmol, 2.00 equiv) dropwise at 0 degrees C .The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched with sat. Na_2SO_3 (aq.) at 0 degrees C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (20:1) to afford 3-iodo-2-[2-(trifluoromethyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (200 mg, 81.36%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 408.85.

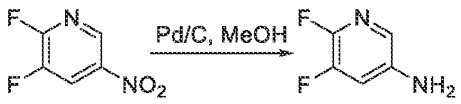


To a stirred mixture of 3-iodo-2-[2-(trifluoromethyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.25 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (39 mg, 0.25 mmol, 1.00 equiv) in DMF (5 mL) were added EPhos Pd G4 (45 mg, 0.05 mmol, 0.20 equiv) and Cs2CO3 (160 mg, 0.49 mmol, 2.00 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 2h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure that was purified by silica gel column chromatography, eluted with DCM / MeOH (20:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(trifluoromethyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (64.8 mg, 60.41%) as a white solid.

LC-MS: $(M+H)^+$ found: 438.20.

^{1}H NMR (400 MHz, DMSO-*d*6) δ 12.09 (s, 1H), 8.73 (d, *J* = 5.6 Hz, 1H), 8.03 (s, 1H), 7.34 (d, *J* = 5.9 Hz, 2H), 6.88 - 6.78 (m, 2H), 6.35 (m, 1H), 3.91 (s, 3H), 3.44 (m, 2H), 2.92 (t, *J* = 6.7 Hz, 2H).

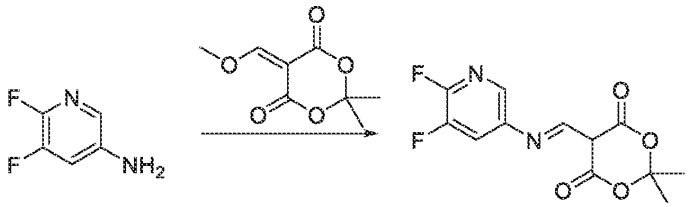
Example 194. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(7-fluoro-6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 477)**



To a solution of 2,3-difluoro-5-nitropyridine (2.5 g, 15.62 mmol, 1.00 equiv) in MeOH (160 mL) was added Pd/C (10%, 300 mg) under nitrogen atmosphere. The mixture was hydrogenated at room temperature for 2.5 h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. Desired

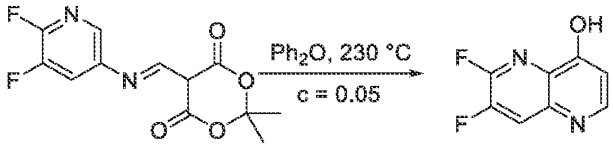
product could be detected by LCMS. LC-MS: M+H found: 131. The resulting mixture was filtered, the filter cake was washed with MeOH (3x50 ml). The filtrate was concentrated under reduced pressure to afford 5,6-difluoropyridin-3-amine (2 g, 98.44%) as a brown solid.

LC-MS: M+H found: 131.0.



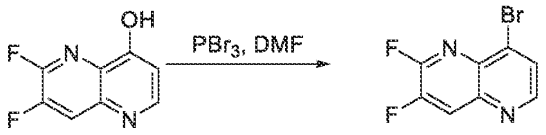
To a stirred solution of 5,6-difluoropyridin-3-amine (1.93 g, 14.84 mmol, 1.00 equiv) and 5-(methoxymethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (3.31 g, 17.80 mmol, 1.2 equiv) in DMF (40 mL) at rt under N_2 atmosphere. The resulting mixture was stirred for 1 h at 80 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M-H found: 283. The precipitated solids were collected by filtration and washed with MeOH (3x100 ml) to afford 5-[(1E)-[(5,6-difluoropyridin-3-yl)imino]methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (3.3 g, 78.27%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 283.0.



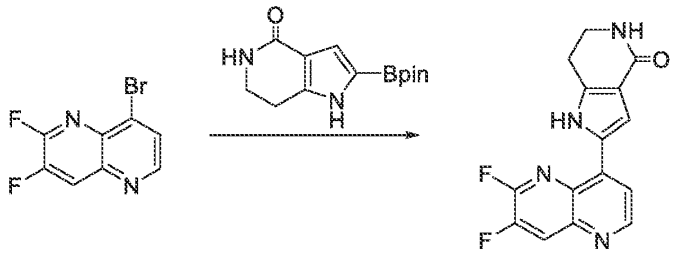
To a stirred phenoxybenzene (210 mL) at rt to 230 degrees C under N_2 atmosphere. To the above solution was added 5-[(1E)-[(5,6-difluoropyridin-3-yl)imino]methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (3 g, 10.55 mmol, 1.00 equiv) in portions at 230 degrees C. The resulting mixture was stirred for additional 5 min at 230 degrees C. Desired product could be detected by LCMS. LC-MS: M+H found: 183. The above mixture was added to 15 ml n-Hexane dropwise, The precipitated solids were collected by filtration and washed with n-Hexane (3x100 ml) to afford 6,7-difluoro-1,5-naphthyridin-4-ol (1.6 g, 83.23%) as a white solid.

LC-MS: $(M+H)^+$ found: 183.0.



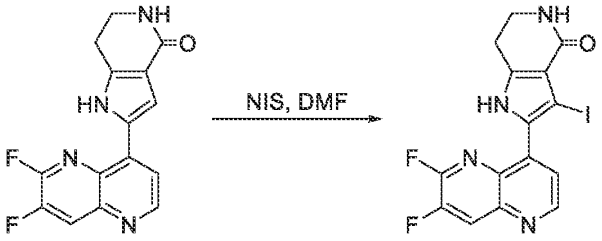
To a stirred solution of 6,7-difluoro-1,5-naphthyridin-4-ol (1.66 g, 9.11 mmol, 1.00 equiv) in DMF (30 mL) was added PBr_3 (3.70 g, 13.67 mmol, 1.5 equiv) dropwise at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 1 h at rt under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 245. The resulting mixture was diluted with Na_2CO_3 aq (30 ml). The resulting mixture was extracted with EA (3 x 80 mL). The combined organic layers were washed with NaCl (3x100 ml), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE:EA (3:2) to afford 8-bromo-2,3-difluoro-1,5-naphthyridine (2.1 g, 94.03%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 245.0.



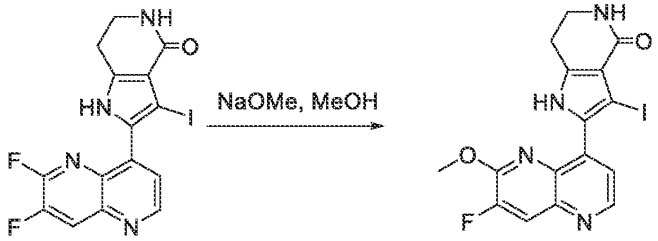
To a stirred solution of 8-bromo-2,3-difluoro-1,5-naphthyridine (500 mg, 2.04 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (641.86 mg, 2.449 mmol, 1.2 equiv) in dioxane (10 mL) and H_2O (1 mL) were added 2nd Generation XPhos Precatalyst (161 mg, 0.20 mmol, 0.1 equiv) and Na_2CO_3 (649 mg, 6.12 mmol, 3 equiv) dropwise/ in portions at rt under N_2 atmosphere. The resulting mixture was stirred for 1.5 h at 80 degrees C under N2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 301. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM:MeOH (95:5) to afford 2-(6,7-difluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (180 mg, 29.38%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 301.0.



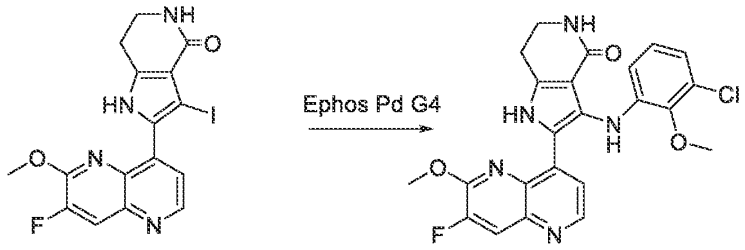
To a stirred solution/mixture of 2-(6,7-difluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (180 mg, 0.60 mmol, 1.00 equiv) and NIS (202 mg, 0.90 mmol, 1.5 equiv) in DMF (3 mL) at RT under N2 atmosphere. The resulting mixture was stirred for 3 H at RT under N2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 427. The resulting mixture was concentrated under vacuum.The residue was purified by silica gel column chromatography, eluted with DCM:MeOH (10:1) to afford 2-(6,7-difluoro-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (180 mg, 70.46%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 427.0.



To a stirred solution of 2-(6,7-difluoro-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (110 mg, 0.258 mmol, 1.00 equiv) in MeOH (2.5 mL, 61.747 mmol) was added NaOMe (27.89 mg, 0.516 mmol, 2 equiv) dropwise at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 2 h at rt under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 439.The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM:MeOH (10:1) to afford 2-(7-fluoro-6-methoxy-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70 mg, 61.89%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 439.0.

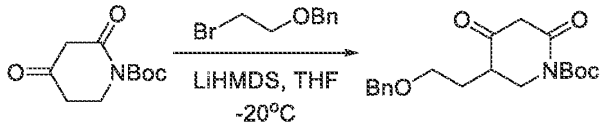


To a stirred solution of 2-(7-fluoro-6-methoxy-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (65 mg, 0.15 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (24 mg, 0.15 mmol, 1 equiv) in DMF (1.5 mL) were added Ephos Pd G4 (14 mg, 0.01 mmol, 0.1 equiv) and Cs_2CO_3 (145 mg, 0.44 mmol, 3 equiv) in portions at rt under Ar atmosphere. The resulting mixture was stirred for 1.5 h at 50 degrees C under Ar atmosphere. The resulting mixture was concentrated under reduced pressure. The resulting mixture was concentrated under vacuum and dissolved in DMF. The crude product (60 mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 44% B to 53% B in 10 min, 53% B; Wave Length: 220/254 nm; RT1(min): 8.23) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(7-fluoro-6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (14.4 mg, 20.75%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 468.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.61 (d, J = 4.8 Hz, 1H), 8.24 (d, J = 10.9 Hz, 1H), 7.79 (s, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.23 (d, J = 2.6 Hz, 1H), 6.69 (dd, J = 8.1, 1.7 Hz, 1H), 6.64 (t, J = 8.0 Hz, 1H), 6.16 (m, J = 7.9, 1.8 Hz, 1H), 4.27 (s, 3H), 3.87 (s, 3H), 3.47 (m, J = 6.8, 2.5 Hz, 2H), 2.95 (t, J = 6.8 Hz, 2H).

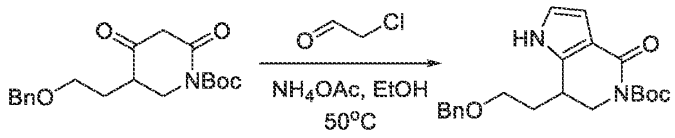
Example 195. (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[2-(dimethylamino)ethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 486)**



To a stirred mixture of tert-butyl 2,4-dioxopiperidine-1-carboxylate (20 g, 93.794 mmol,

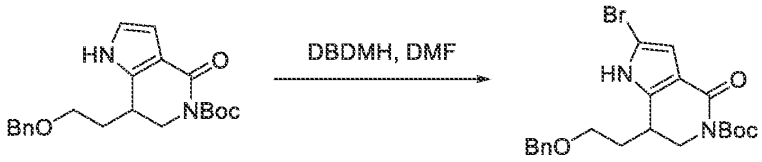
1.00 equiv) and [(2-bromoethoxy)methyl]benzene (80.70 g, 375.192 mmol, 4.00 equiv) in THF (600 mL) was added LiHMDS (235.00 mL, 235.000 mmol, 2.51 equiv) dropwise at -20 degrees C under argon atmosphere. The resulting mixture was stirred for 1 h at -20 degrees C under argon atmosphere. The reaction was quenched with Water at -20 degrees C. The mixture was acidified to pH= 5 with 5% KHSO4 solution. The resulting mixture was extracted with CH2Cl2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2:1) to afford tert-butyl 5-[2-(benzyloxy)ethyl]-2,4-dioxopiperidine-1-carboxylate (17 g, 52.17%) as a green oil.

LC-MS: M+H found: 348.



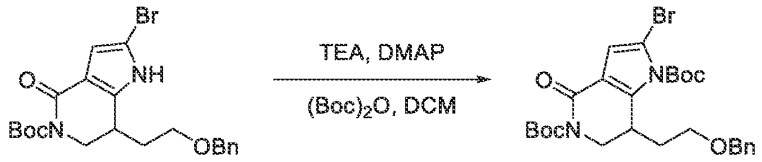
Into a round-bottom flask were added tert-butyl 5-[2-(benzyloxy)ethyl]-2,4-dioxopiperidine-1-carboxylate (10 g, 28.78 mmol, 1.00 equiv) , Ammonia, 7.0 M Solution In Methanol, SpcSeal (10 mL), NH_4OAc (11.09 g, 143.92 mmol, 5.0 equiv), EtOH (100 mL) and chloroacetaldehyde (2.71 g, 34.54 mmol, 1.2 equiv) at room temperature. The resulting mixture was stirred for 1 h at 50 degrees C under nitrogen atmosphere. The solvents were concentrated under reduced pressure. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (1x300 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford tert-butyl 7-[2-(benzyloxy)ethyl]-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (1.45 g, 13.60%) as a white solid.

LC-MS: M+H found: 371.



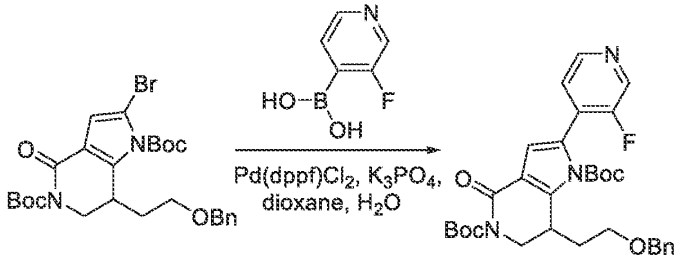
To a stirred solution of tert-butyl 7-[2-(benzyloxy)ethyl]-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (1.05 g, 2.83 mmol, 1.00 equiv) in DMF (10 mL) was added dbdmh (0.39 g, 1.36 mmol, 0.48 equiv) in portions at -50 degrees C under nitrogen atmosphere. The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was diluted with water (10 mL).The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford tert-butyl 7-[2-(benzyloxy)ethyl]-2-bromo-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (1200 mg, 83.86%) as a white oil.

LC-MS: M+H found: 449.0.



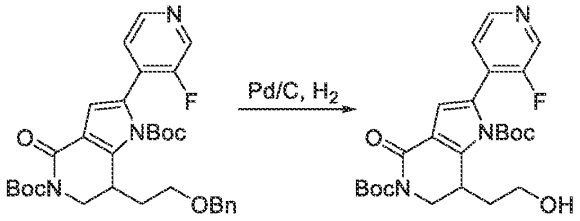
A solution of tert-butyl 7-[2-(benzyloxy)ethyl]-2-bromo-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (500 mg, 1.11 mmol, 1.00 equiv) and $(Boc)_2O$ (267 mg, 1.224 mmol, 1.1 equiv) and TEA (135 mg, 1.34 mmol, 1.2 equiv)in DCM (5.00 mL) was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was concentrated under reduced pressure.The residue was purified by Prep-TLC (PE / EA 5:1) to afford 1,5-di-tert-butyl 7-[2-(benzyloxy)ethyl]-2-bromo-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (590 mg, 92.64%) as a white oil.

LC-MS: M+H found: 549.0.



A solution of 1,5-di-tert-butyl 7-[2-(benzyloxy)ethyl]-2-bromo-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (6.5 g, 11.83 mmol, 1.00 equiv) and 3-fluoropyridin-4-ylboronic acid (2.50 g, 17.74 mmol, 1.5 equiv) and $Pd(dppf)Cl_2.CH_2Cl_2$ (964 mg, 1.18 mmol, 0.1 equiv)and K_3PO_4 (7.53 g, 35.49 mmol, 3 equiv) in dioxane (100 mL)and H2O (20 mL) was stirred for 1 h at 50 degrees C under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was concentrated under vacuum.The aqueous layer was extracted with EtOAc (4 x 50 mL).The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 1,5-di-tert-butyl 7-[2-(benzyloxy)ethyl]-2-(3-fluoropyridin-4-yl)-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (5.6 g, 82.02%) as a yellow oil.

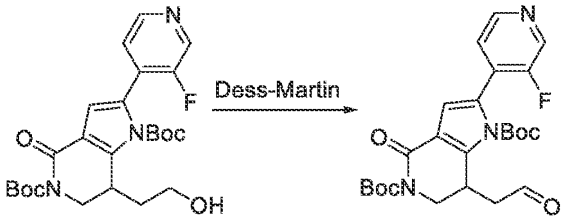
LC-MS: M+H found: 566.0.



To a solution of 1,5-di-tert-butyl 7-[2-(benzyloxy)ethyl]-2-(3-fluoropyridin-4-yl)-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (4 g, 7.072 mmol, 1.00 equiv) in 140 mL MeOH was added dry Pd/C (10%, 1.6 g) under nitrogen atmosphere in a 500 mL round-bottom flask. The mixture was hydrogenated at room temperature for 2 days under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was filtered, the filter cake was washed with MeOH (3x50 mL). The filtrate was concentrated under reduced pressure to

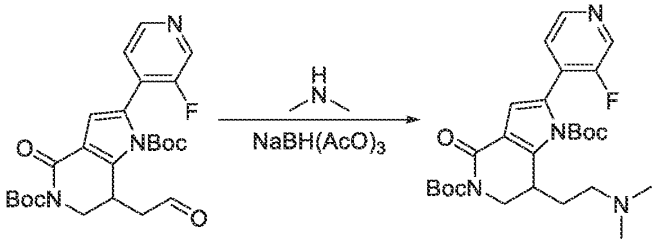
afford 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-7-(2-hydroxyethyl)-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (2.27 g, 57.38%) as a white oil.

LC-MS: M+H found: 476.0.



To a stirred solution of 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-7-(2-hydroxyethyl)-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (500 mg, 1.05 mmol, 1.00 equiv) in DCM (10 mL) were added Dess-Martin (535 mg, 1.26 mmol, 1.20 equiv)in portions at 0 degrees C under nitrogen atmosphere.The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was concentrated under vacuum.The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-4-oxo-7-(2-oxoethyl)-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (235 mg, 37.29%) as a yellow solid.

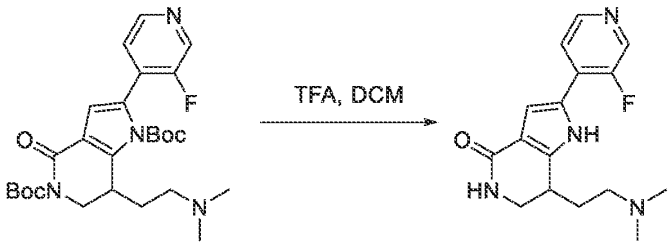
LC-MS: M+H found: 474.0.



A solution of 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-4-oxo-7-(2-oxoethyl)-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (170 mg, 0.36 mmol, 1.00 equiv) in DCM (4 mL) was treated with diacetyl peroxide; sodioboranyl acetate (91 mg, 0.43 mmol, 1.20 equiv) for 30 min at room temperature under nitrogen atmosphere followed by the addition of dimethylamine (19 mg, 0.43 mmol, 1.20 equiv) dropwise at room temperature. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The

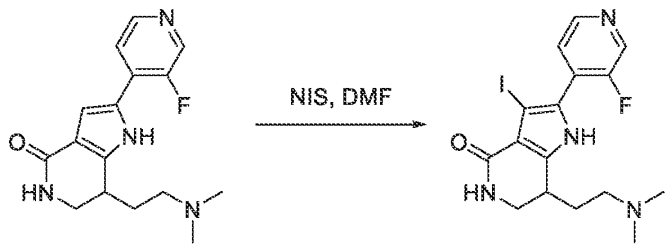
reaction was monitored by LCMS .Desired product could be detected by LCMS. The resulting mixture was diluted with water (10 mL).The aqueous layer was extracted with CH_2Cl_2 (2x10 mL).The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

LC-MS: M+H found: 503.0.



To a stirred mixture of 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-7-[2-(morpholin-4-yl)ethyl]-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (170 mg, 0.34 mmol, 1.00 equiv) in DCM (6 mL) was added TFA (2 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h and concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford 7-[2-(dimethylamino)ethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 97.78%) as a yellow solid.

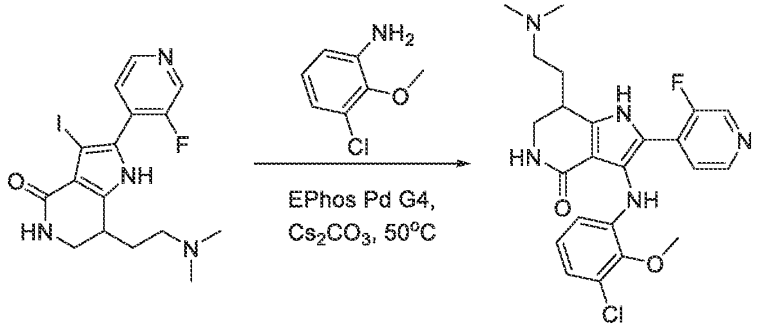
LC-MS: $(M+H)^+$ found: 303.



A solution of 7-[2-(dimethylamino)ethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (130 mg, 0.430 mmol, 1.00 equiv) and NIS (96.73 mg, 0.430 mmol, 1 equiv) in DMF (4 mL) was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by

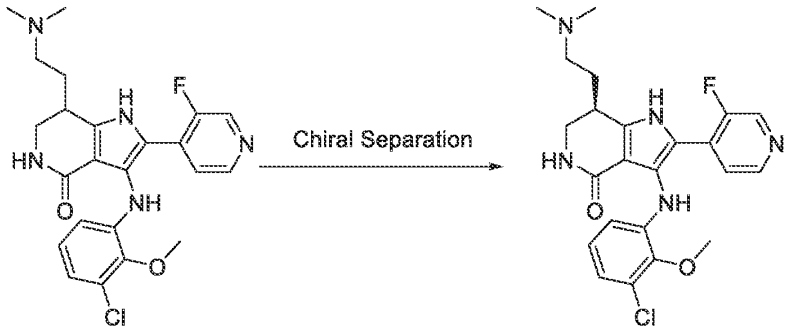
LCMS.The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford 7-[2-(dimethylamino)ethyl]-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (130 mg, 70.60%) as a yellow solid.

LC-MS: M+H found: 429.0.



To a stirred mixture of 7-[2-(dimethylamino)ethyl]-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (110 mg, 0.26 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (40 mg, 0.26 mmol, 1.00 equiv) in DMF (2.5 mL) were added EPhos Pd G4 (24 mg, 0.026 mmol, 0.1 equiv) and Cs_2CO_3 (167 mg, 0.51 mmol, 2.00 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 2h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure that was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford 3-[(3-chloro-2-methoxyphenyl)amino]-7-[2-(dimethylamino)ethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70 mg, 59.51%) as a yellow solid.

LC-MS: M+H found: 458.0.

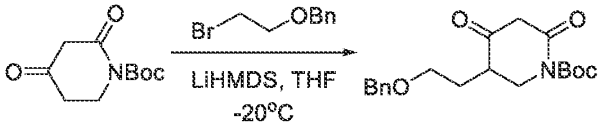


The crude product (80 mg) was purified by Prep-CHIRAL-HPLC with the following conditions (Column: CHIRALPAK IG-3, 4.6*50 mm, 3 um; Mobile Phase A: Hex (0.1% DEA): EtOH=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[2-(dimethylamino)ethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (18.5 mg, 22.22%) as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.10 (s, 1H), 8.59 (t, J = 1.9 Hz, 1H), 8.33 (d, J = 2.7 Hz, 1H), 7.72 (m, 1H), 7.38 (s, 1H), 7.13 (t, J = 2.7 Hz, 1H), 6.80 – 6.63 (m, 2H), 6.16 (m, 1H), 3.89 (s, 3H), 3.48 (m, 1H), 3.20 (m, 1H), 3.09 – 2.96 (m, 1H), 2.48 – 2.38 (m, 1H), 2.32 (m, 1H), 2.23 (s, 6H), 1.97 (m, 1H), 1.73 – 1.55 (m, 1H).

LCMS found 458.

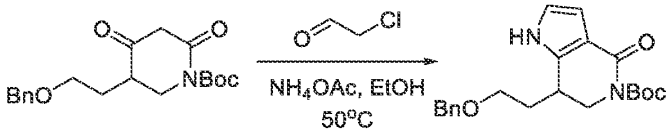
Example 196. (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[2-(morpholin-4-yl)ethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 485)**



To a stirred mixture of tert-butyl 2,4-dioxopiperidine-1-carboxylate (20 g, 93.794 mmol, 1.00 equiv) and [(2-bromoethoxy)methyl]benzene (80.70 g, 375.192 mmol, 4.00 equiv) in THF (600 mL) was added LiHMDS (235.00 mL, 235.000 mmol, 2.51 equiv) dropwise at -20 degrees C under argon atmosphere. The resulting mixture was stirred for 1 h at -20 degrees C under argon atmosphere. The reaction was quenched with Water at -20 degrees C. The mixture was acidified to pH= 5 with 5% KHSO4 solution. The resulting mixture

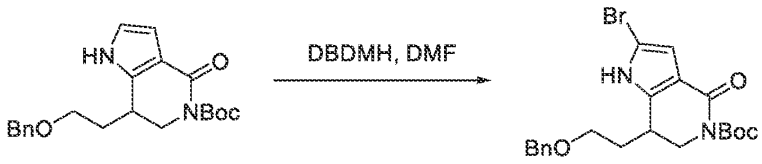
was extracted with CH2Cl2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2:1) to afford tert-butyl 5-[2-(benzyloxy)ethyl]-2,4-dioxopiperidine-1-carboxylate (17 g, 52.17%) as a green oil.

LC-MS: M+H found: 348.



Into a round-bottom flask were added tert-butyl 5-[2-(benzyloxy)ethyl]-2,4-dioxopiperidine-1-carboxylate (10 g, 28.78 mmol, 1.00 equiv) , Ammonia, 7.0 M Solution In Methanol, SpcSeal (10 mL), NH_4OAc (11.09 g, 143.92 mmol, 5.0 equiv), EtOH (100 mL) and chloroacetaldehyde (2.71 g, 34.54 mmol, 1.2 equiv) at room temperature. The resulting mixture was stirred for 1 h at 50 degrees C under nitrogen atmosphere. The solvents were concentrated under reduced pressure. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (1x300 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford tert-butyl 7-[2-(benzyloxy)ethyl]-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (1.45 g, 13.60%) as a white solid.

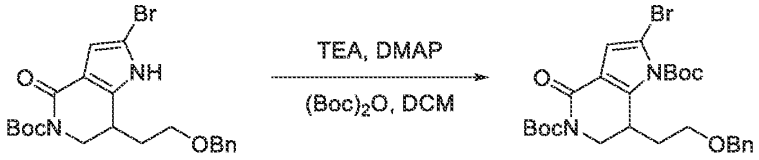
LC-MS: M+H found: 371.



To a stirred solution of tert-butyl 7-[2-(benzyloxy)ethyl]-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (1.05 g, 2.83 mmol, 1.00 equiv) in DMF (10 mL) was added dbdmh (0.39 g, 1.36 mmol, 0.48 equiv) in portions at -50 degrees C under nitrogen

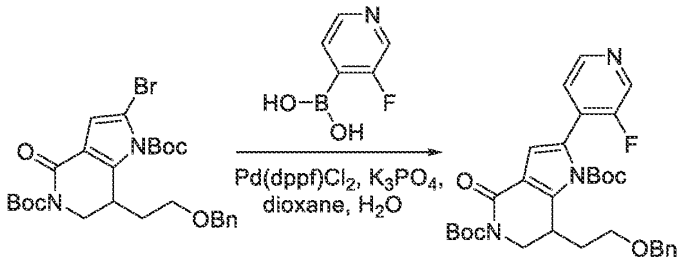
atmosphere. The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was diluted with water (10 mL).The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford tert-butyl 7-[2-(benzyloxy)ethyl]-2-bromo-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (1200 mg, 83.86%) as a white oil.

LC-MS: M+H found: 449.0.



A solution of tert-butyl 7-[2-(benzyloxy)ethyl]-2-bromo-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (500 mg, 1.11 mmol, 1.00 equiv) and $(Boc)_2O$ (267 mg, 1.224 mmol, 1.1 equiv) and TEA (135 mg, 1.34 mmol, 1.2 equiv)in DCM (5.00 mL) was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was concentrated under reduced pressure.The residue was purified by Prep-TLC (PE / EA 5:1) to afford 1,5-di-tert-butyl 7-[2-(benzyloxy)ethyl]-2-bromo-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (590 mg, 92.64%) as a white oil.

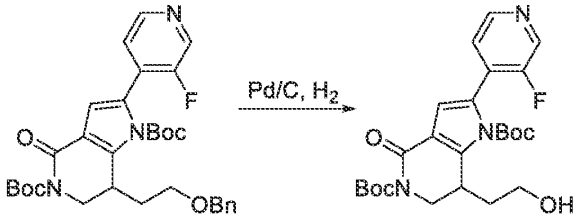
LC-MS: M+H found: 549.0.



A solution of 1,5-di-tert-butyl 7-[2-(benzyloxy)ethyl]-2-bromo-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (6.5 g, 11.83 mmol, 1.00 equiv) and 3-fluoropyridin-4-ylboronic acid (2.50 g, 17.74 mmol, 1.5 equiv) and $Pd(dppf)Cl_2.CH_2Cl_2$ (964 mg, 1.18

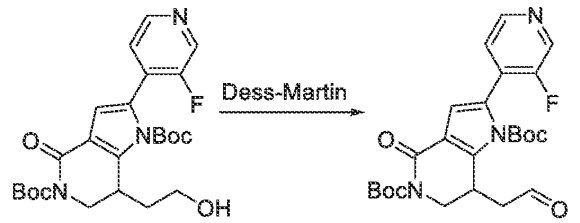
mmol, 0.1 equiv)and K_3PO_4 (7.53 g, 35.49 mmol, 3 equiv) in dioxane (100 mL)and H2O (20 mL) was stirred for 1 h at 50 degrees C under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was concentrated under vacuum.The aqueous layer was extracted with EtOAc (4 x 50 mL).The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 1,5-di-tert-butyl 7-[2-(benzyloxy)ethyl]-2-(3-fluoropyridin-4-yl)-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (5.6 g, 82.02%) as a yellow oil.

LC-MS: M+H found: 566.0.



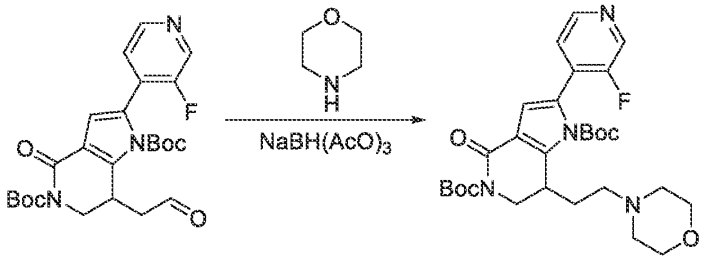
To a solution of 1,5-di-tert-butyl 7-[2-(benzyloxy)ethyl]-2-(3-fluoropyridin-4-yl)-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (4 g, 7.072 mmol, 1.00 equiv) in 140 mL MeOH was added dry Pd/C (10%, 1.6 g) under nitrogen atmosphere in a 500 mL round-bottom flask. The mixture was hydrogenated at room temperature for 2 days under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was filtered, the filter cake was washed with MeOH (3x50 mL). The filtrate was concentrated under reduced pressure to afford 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-7-(2-hydroxyethyl)-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (2.27 g, 57.38%) as a white oil.

LC-MS: M+H found: 476.0.



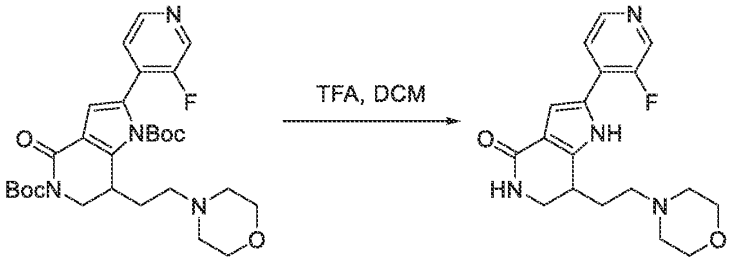
To a stirred solution of 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-7-(2-hydroxyethyl)-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (500 mg, 1.05 mmol, 1.00 equiv) in DCM (10 mL) were added Dess-Martin (535 mg, 1.26 mmol, 1.20 equiv)in portions at 0 degrees C under nitrogen atmosphere.The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was concentrated under vacuum.The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-4-oxo-7-(2-oxoethyl)-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (235 mg, 37.29%) as a yellow solid.

LC-MS: M+H found: 474.0.



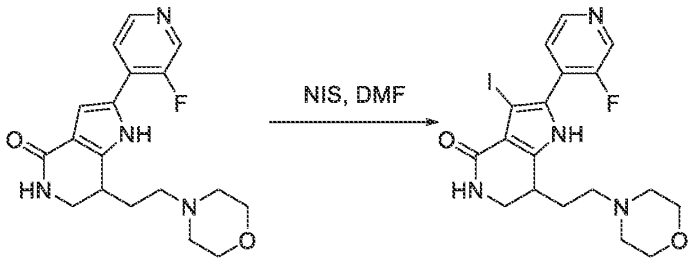
A solution of 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-4-oxo-7-(2-oxoethyl)-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (280 mg, 0.59 mmol, 1.00 equiv) in DCM (7.00 mL) was treated with diacetyl peroxide; sodioboranyl acetate (150 mg, 0.71 mmol, 1.20 equiv) for 30 min at room temperature under nitrogen atmosphere followed by the addition of morpholine (62 mg, 0.71 mmol, 1.20 equiv) dropwise at room temperature.The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The reaction was quenched with Water at 0 degrees C.The resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (2x5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.The crude product was used in the next step directly without further purification.

LC-MS: M+H found: 545.0.



To a stirred mixture of 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-7-[2-(morpholin-4-yl)ethyl]-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (280 mg, 0.514 mmol, 1.00 equiv) in DCM (7.5 mL) was added TFA (2.5 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h and concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford 2-(3-fluoropyridin-4-yl)-7-[2-(morpholin-4-yl)ethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (140 mg, 77.49%) as a light yellow solid.

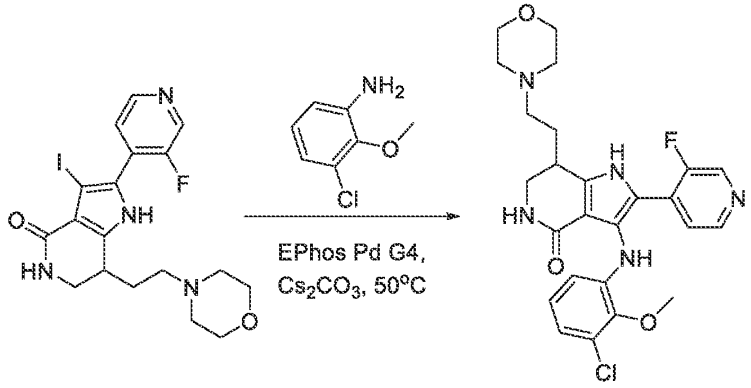
LC-MS: $(M+H)^+$ found: 345.



To a stirred solution of 2-(3-fluoropyridin-4-yl)-7-[2-(morpholin-4-yl)ethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (130 mg, 0.38 mmol, 1.00 equiv) in DMF (7 mL) was added NIS (85 mg, 0.38 mmol, 1 equiv) in portions at room temperature under nitrogen atmosphere.The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nmto afford 2-(3-fluoropyridin-4-yl)-3-iodo-7-[2-(morpholin-4-yl)ethyl]-1H,5H,6H,7H-pyrrolo[3,2-

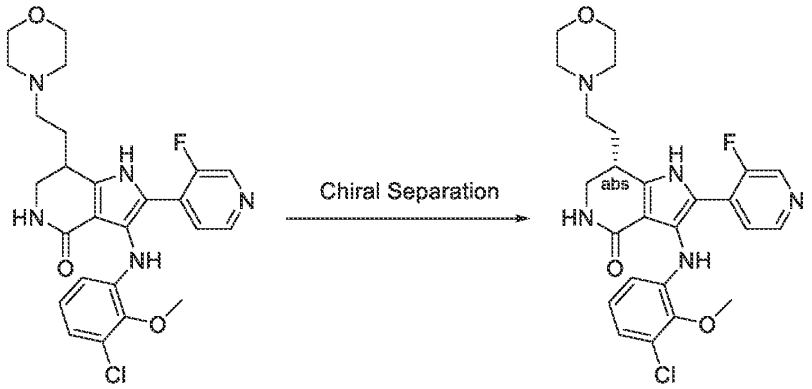
c]pyridin-4-one (167 mg, 94.07%) as a yellow solid. Desired product could be detected by LCMS.

LC-MS: M+H found: 471.0.



To a stirred mixture of 2-(3-fluoropyridin-4-yl)-3-iodo-7-[2-(morpholin-4-yl)ethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.17 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (26.81 mg, 0.17 mmol, 1 equiv) in DMF (2 mL) were added EPhos Pd G4 (16 mg, 0.017 mmol, 0.1 equiv) and Cs_2CO_3 (110mg, 0.34 mmol, 2 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 2h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure that was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[2-(morpholin-4-yl)ethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (42 mg, 49.38%) as a yellow solid.

LC-MS: M+H found: 500.0.

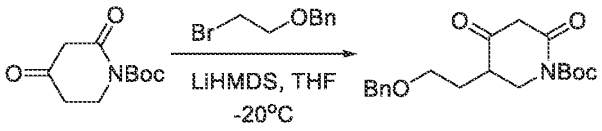


The product (42 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG-3, 4.6*50mm, 3μm; Mobile Phase A: (Hex: DCM=3: 1)(0.1%DEA): EtOH=90: 10; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[2-(morpholin-4-yl)ethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (16.2 mg, 37.34%) as a yellow solid.

LC-MS: $(M+H)^+$ found 500.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (s, 1H), 8.62 (t, J = 1.9 Hz, 1H), 8.33 (d, J = 2.7 Hz, 1H), 7.77 (m, 1H), 7.38 (s, 1H), 7.14 (t, J = 2.6 Hz, 1H), 6.81 – 6.65 (m, 2H), 6.15 (m, 1H), 3.89 (s, 3H), 3.59 (t, J = 4.8 Hz, 4H), 3.51 (m, 1H), 3.22 (m, 1H), 3.03 (dq, J = 10.4, 5.4 Hz, 1H), 2.40 (m, 6H), 2.13 – 2.00 (m, 1H), 1.67 (m, 1H).

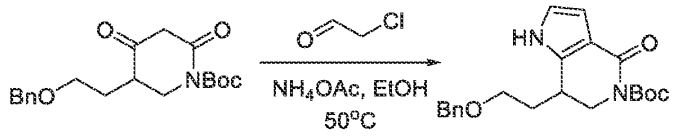
Example 197. (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[2-(morpholin-4-yl)ethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 484)**



To a stirred mixture of tert-butyl 2,4-dioxopiperidine-1-carboxylate (20 g, 93.794 mmol, 1.00 equiv) and [(2-bromoethoxy)methyl]benzene (80.70 g, 375.192 mmol, 4.00 equiv) in THF (600 mL) was added LiHMDS (235.00 mL, 235.000 mmol, 2.51 equiv) dropwise at -20 degrees C under argon atmosphere. The resulting mixture was stirred for 1 h at -20 degrees C under argon atmosphere. The reaction was quenched with Water at -20 degrees C. The mixture was acidified to pH= 5 with 5% KHSO4 solution. The resulting mixture

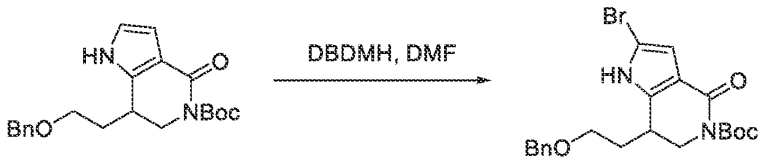
was extracted with CH2Cl2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2:1) to afford tert-butyl 5-[2-(benzyloxy)ethyl]-2,4-dioxopiperidine-1-carboxylate (17 g, 52.17%) as a green oil.

LC-MS: M+H found: 348.



Into a round-bottom flask were added tert-butyl 5-[2-(benzyloxy)ethyl]-2,4-dioxopiperidine-1-carboxylate (10 g, 28.78 mmol, 1.00 equiv), Ammonia, 7.0 M Solution In Methanol, SpcSeal (10 mL), NH_4OAc (11.09 g, 143.92 mmol, 5.0 equiv), EtOH (100 mL) and chloroacetaldehyde (2.71 g, 34.54 mmol, 1.2 equiv) at room temperature. The resulting mixture was stirred for 1 h at 50 degrees C under nitrogen atmosphere. The solvents were concentrated under reduced pressure. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (1x300 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford tert-butyl 7-[2-(benzyloxy)ethyl]-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (1.45 g, 13.60%) as a white solid.

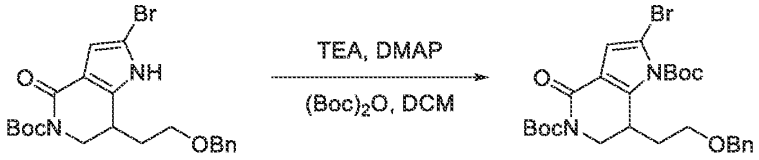
LC-MS: M+H found: 371.



To a stirred solution of tert-butyl 7-[2-(benzyloxy)ethyl]-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (1.05 g, 2.83 mmol, 1.00 equiv) in DMF (10 mL) was added dbdmh (0.39 g, 1.36 mmol, 0.48 equiv) in portions at -50 degrees C under nitrogen

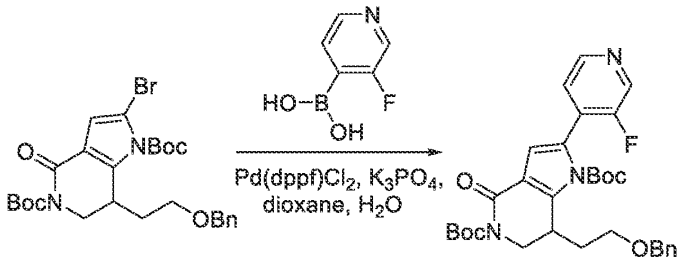
atmosphere. The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was diluted with water (10 mL).The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford tert-butyl 7-[2-(benzyloxy)ethyl]-2-bromo-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (1200 mg, 83.86%) as a white oil.

LC-MS: M+H found: 449.0.



A solution of tert-butyl 7-[2-(benzyloxy)ethyl]-2-bromo-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (500 mg, 1.11 mmol, 1.00 equiv) and $(Boc)_2O$ (267 mg, 1.224 mmol, 1.1 equiv) and TEA (135 mg, 1.34 mmol, 1.2 equiv)in DCM (5.00 mL) was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was concentrated under reduced pressure.The residue was purified by Prep-TLC (PE / EA 5:1) to afford 1,5-di-tert-butyl 7-[2-(benzyloxy)ethyl]-2-bromo-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (590 mg, 92.64%) as a white oil.

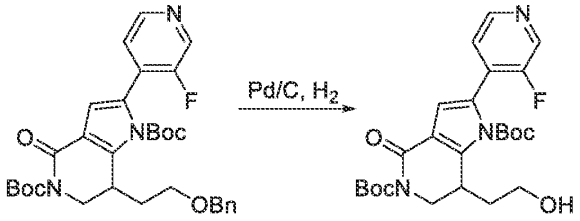
LC-MS: M+H found: 549.0.



A solution of 1,5-di-tert-butyl 7-[2-(benzyloxy)ethyl]-2-bromo-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (6.5 g, 11.83 mmol, 1.00 equiv) and 3-fluoropyridin-4-ylboronic acid (2.50 g, 17.74 mmol, 1.5 equiv) and $Pd(dppf)Cl_2.CH_2Cl_2$ (964 mg, 1.18

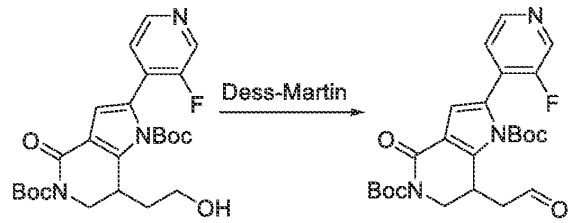
mmol, 0.1 equiv)and K_3PO_4 (7.53 g, 35.49 mmol, 3 equiv) in dioxane (100 mL)and H_2O (20 mL) was stirred for 1 h at 50 degrees C under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was concentrated under vacuum.The aqueous layer was extracted with EtOAc (4 x 50 mL).The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 1,5-di-tert-butyl 7-[2-(benzyloxy)ethyl]-2-(3-fluoropyridin-4-yl)-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (5.6 g, 82.02%) as a yellow oil.

LC-MS: M+H found: 566.0.



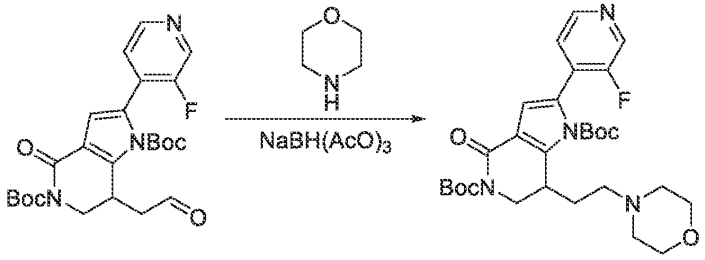
To a solution of 1,5-di-tert-butyl 7-[2-(benzyloxy)ethyl]-2-(3-fluoropyridin-4-yl)-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (4 g, 7.072 mmol, 1.00 equiv) in 140 mL MeOH was added dry Pd/C (10%, 1.6 g) under nitrogen atmosphere in a 500 mL round-bottom flask. The mixture was hydrogenated at room temperature for 2 days under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was filtered, the filter cake was washed with MeOH (3x50 mL). The filtrate was concentrated under reduced pressure to afford 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-7-(2-hydroxyethyl)-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (2.27 g, 57.38%) as a white oil.

LC-MS: M+H found: 476.0.



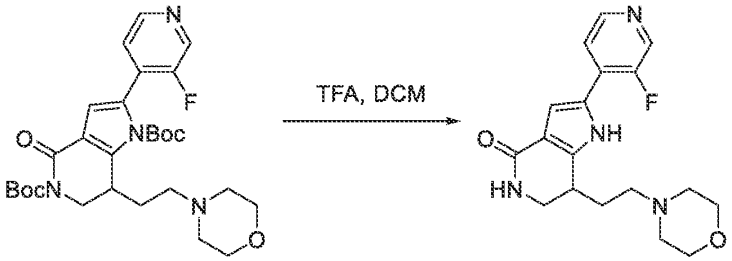
To a stirred solution of 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-7-(2-hydroxyethyl)-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (500 mg, 1.05 mmol, 1.00 equiv) in DCM (10 mL) were added Dess-Martin (535 mg, 1.26 mmol, 1.20 equiv)in portions at 0 degrees C under nitrogen atmosphere.The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was concentrated under vacuum.The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-4-oxo-7-(2-oxoethyl)-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (235 mg, 37.29%) as a yellow solid.

LC-MS: M+H found: 474.0.



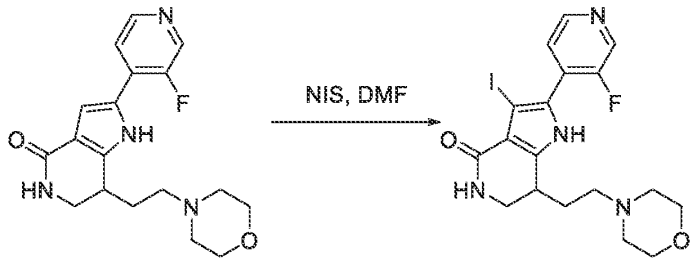
A solution of 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-4-oxo-7-(2-oxoethyl)-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (280 mg, 0.59 mmol, 1.00 equiv) in DCM (7.00 mL) was treated with diacetyl peroxide; sodioboranyl acetate (150 mg, 0.71 mmol, 1.20 equiv) for 30 min at room temperature under nitrogen atmosphere followed by the addition of morpholine (62 mg, 0.71 mmol, 1.20 equiv) dropwise at room temperature.The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The reaction was quenched with Water at 0 degrees C.The resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (2x5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.The crude product was used in the next step directly without further purification.

LC-MS: M+H found: 545.0.



To a stirred mixture of 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-7-[2-(morpholin-4-yl)ethyl]-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (280 mg, 0.514 mmol, 1.00 equiv) in DCM (7.5 mL) was added TFA (2.5 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h and concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford 2-(3-fluoropyridin-4-yl)-7-[2-(morpholin-4-yl)ethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (140 mg, 77.49%) as a light yellow solid.

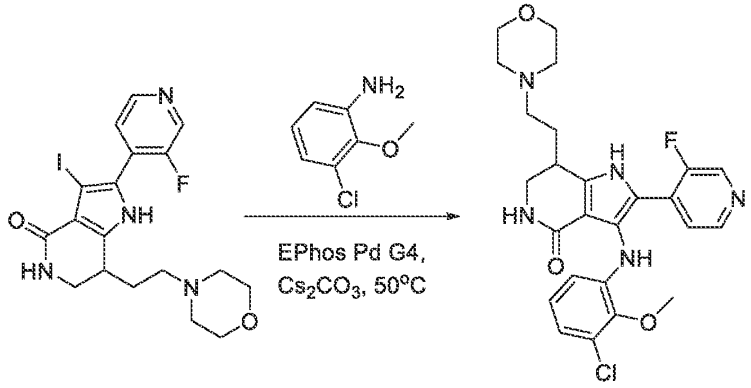
LC-MS: $(M+H)^+$ found: 345.



To a stirred solution of 2-(3-fluoropyridin-4-yl)-7-[2-(morpholin-4-yl)ethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (130 mg, 0.38 mmol, 1.00 equiv) in DMF (7 mL) was added NIS (85 mg, 0.38 mmol, 1 equiv) in portions at room temperature under nitrogen atmosphere.The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nmto afford 2-(3-fluoropyridin-4-yl)-3-iodo-7-[2-(morpholin-4-yl)ethyl]-1H,5H,6H,7H-pyrrolo[3,2-

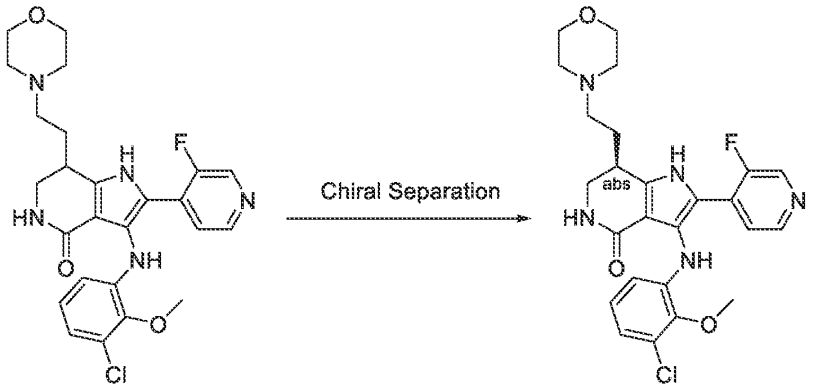
c]pyridin-4-one (167 mg, 94.07%) as a yellow solid. Desired product could be detected by LCMS.

LC-MS: M+H found: 471.0.



To a stirred mixture of 2-(3-fluoropyridin-4-yl)-3-iodo-7-[2-(morpholin-4-yl)ethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.17 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (26.81 mg, 0.17 mmol, 1 equiv) in DMF (2 mL) were added EPhos Pd G4 (16 mg, 0.017 mmol, 0.1 equiv) and Cs_2CO_3 (110mg, 0.34 mmol, 2 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 2h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure that was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[2-(morpholin-4-yl)ethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (42 mg, 49.38%) as a yellow solid.

LC-MS: M+H found: 500.0.

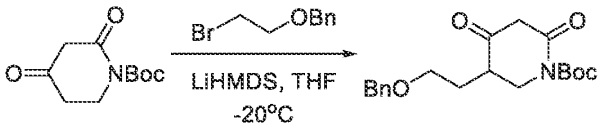


The product (42 mg) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG-3, 4.6*50mm, 3μm; Mobile Phase A: (Hex: DCM=3: 1)(0.1%DEA): EtOH=90: 10; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[2-(morpholin-4-yl)ethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (13.6 mg, 32.19%) as a white solid.

LC-MS: $(M+H)^+$ found: 500.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.64 (s, 1H), 8.62 (t, J = 1.9 Hz, 1H), 8.33 (d, J = 2.7 Hz, 1H), 7.77 (m, 1H), 7.38 (s, 1H), 7.14 (d, J = 2.6 Hz, 1H), 6.77 – 6.64 (m, 2H), 6.15 (m, 1H), 3.89 (s, 3H), 3.59 (t, J = 4.8 Hz, 4H), 3.51 m, 1H), 3.22 m, 1H), 3.03 (d, J = 4.9 Hz, 1H), 2.48 – 2.26 (m, 6H), 2.14 – 1.99 (m, 1H), 1.67 (m, 1H).

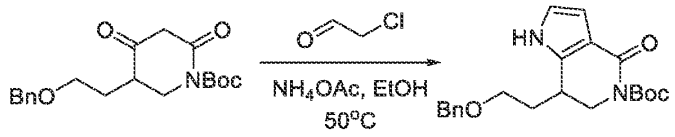
Example 198. (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[2-(dimethylamino)ethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 475)**



To a stirred mixture of tert-butyl 2,4-dioxopiperidine-1-carboxylate (20 g, 93.794 mmol, 1.00 equiv) and [(2-bromoethoxy)methyl]benzene (80.70 g, 375.192 mmol, 4.00 equiv) in THF (600 mL) was added LiHMDS (235.00 mL, 235.000 mmol, 2.51 equiv) dropwise at -20 degrees C under argon atmosphere. The resulting mixture was stirred for 1 h at -20 degrees C under argon atmosphere. The reaction was quenched with Water at -20 degrees C. The mixture was acidified to pH= 5 with 5% KHSO4 solution. The resulting mixture

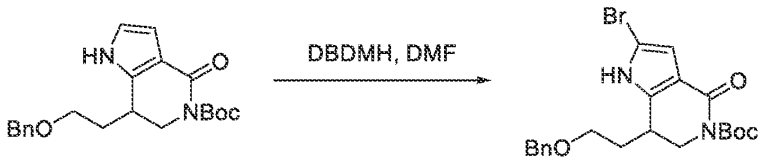
was extracted with CH2Cl2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2:1) to afford tert-butyl 5-[2-(benzyloxy)ethyl]-2,4-dioxopiperidine-1-carboxylate (17 g, 52.17%) as a green oil.

LC-MS: M+H found: 348.



Into a round-bottom flask were added tert-butyl 5-[2-(benzyloxy)ethyl]-2,4-dioxopiperidine-1-carboxylate (10 g, 28.78 mmol, 1.00 equiv), Ammonia, 7.0 M Solution In Methanol, SpcSeal (10 mL), NH_4OAc (11.09 g, 143.92 mmol, 5.0 equiv), EtOH (100 mL) and chloroacetaldehyde (2.71 g, 34.54 mmol, 1.2 equiv) at room temperature. The resulting mixture was stirred for 1 h at 50 degrees C under nitrogen atmosphere. The solvents were concentrated under reduced pressure. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (1x300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford tert-butyl 7-[2-(benzyloxy)ethyl]-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (1.45 g, 13.60%) as a white solid.

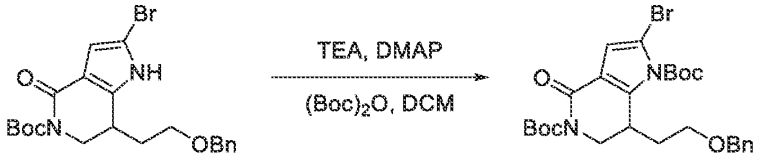
LC-MS: M+H found: 371.



To a stirred solution of tert-butyl 7-[2-(benzyloxy)ethyl]-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (1.05 g, 2.83 mmol, 1.00 equiv) in DMF (10 mL) was added dbdmh (0.39 g, 1.36 mmol, 0.48 equiv) in portions at -50 degrees C under nitrogen

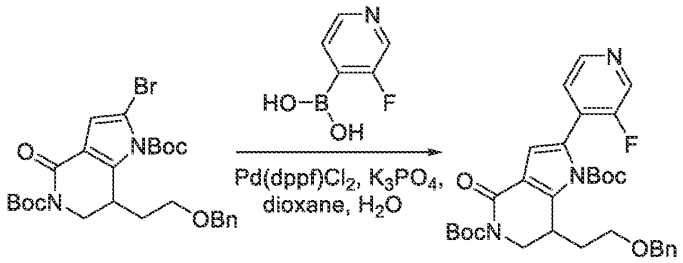
atmosphere. The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was diluted with water (10 mL).The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford tert-butyl 7-[2-(benzyloxy)ethyl]-2-bromo-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (1200 mg, 83.86%) as a white oil.

LC-MS: M+H found: 449.0.



A solution of tert-butyl 7-[2-(benzyloxy)ethyl]-2-bromo-4-oxo-1H,6H,7H-pyrrolo[3,2-c]pyridine-5-carboxylate (500 mg, 1.11 mmol, 1.00 equiv) and $(Boc)_2O$ (267 mg, 1.224 mmol, 1.1 equiv) and TEA (135 mg, 1.34 mmol, 1.2 equiv)in DCM (5.00 mL) was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was concentrated under reduced pressure.The residue was purified by Prep-TLC (PE / EA 5:1) to afford 1,5-di-tert-butyl 7-[2-(benzyloxy)ethyl]-2-bromo-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (590 mg, 92.64%) as a white oil.

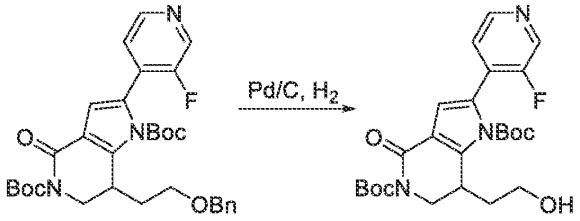
LC-MS: M+H found: 549.0.



A solution of 1,5-di-tert-butyl 7-[2-(benzyloxy)ethyl]-2-bromo-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (6.5 g, 11.83 mmol, 1.00 equiv) and 3-fluoropyridin-4-ylboronic acid (2.50 g, 17.74 mmol, 1.5 equiv) and $Pd(dppf)Cl_2.CH_2Cl_2$ (964 mg, 1.18

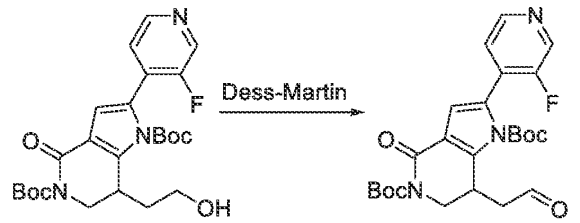
mmol, 0.1 equiv)and K_3PO_4 (7.53 g, 35.49 mmol, 3 equiv) in dioxane (100 mL)and H2O (20 mL) was stirred for 1 h at 50 degrees C under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was concentrated under vacuum.The aqueous layer was extracted with EtOAc (4 x 50 mL).The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 1,5-di-tert-butyl 7-[2-(benzyloxy)ethyl]-2-(3-fluoropyridin-4-yl)-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (5.6 g, 82.02%) as a yellow oil.

LC-MS: M+H found: 566.0.



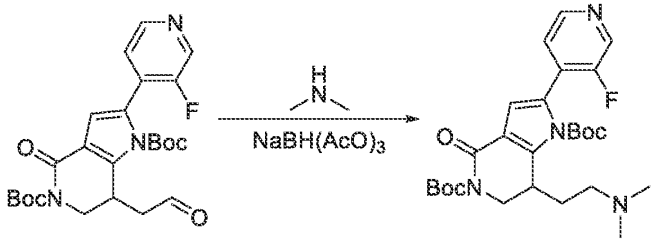
To a solution of 1,5-di-tert-butyl 7-[2-(benzyloxy)ethyl]-2-(3-fluoropyridin-4-yl)-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (4 g, 7.072 mmol, 1.00 equiv) in 140 mL MeOH was added dry Pd/C (10%, 1.6 g) under nitrogen atmosphere in a 500 mL round-bottom flask. The mixture was hydrogenated at room temperature for 2 days under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was filtered, the filter cake was washed with MeOH (3x50 mL). The filtrate was concentrated under reduced pressure to afford 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-7-(2-hydroxyethyl)-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (2.27 g, 57.38%) as a white oil.

LC-MS: M+H found: 476.0.



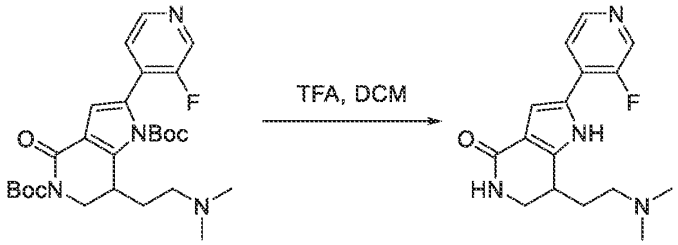
To a stirred solution of 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-7-(2-hydroxyethyl)-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (500 mg, 1.05 mmol, 1.00 equiv) in DCM (10 mL) were added Dess-Martin (535 mg, 1.26 mmol, 1.20 equiv)in portions at 0 degrees C under nitrogen atmosphere.The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was concentrated under vacuum.The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-4-oxo-7-(2-oxoethyl)-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (235 mg, 37.29%) as a yellow solid.

LC-MS: M+H found: 474.0.



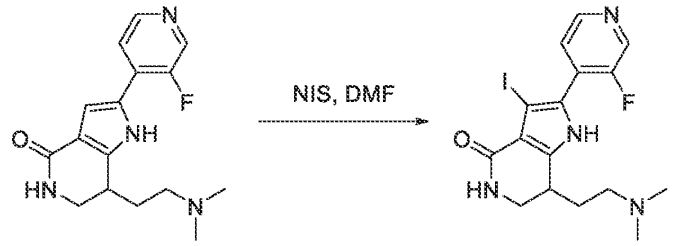
A solution of 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-4-oxo-7-(2-oxoethyl)-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (170 mg, 0.36 mmol, 1.00 equiv) in DCM (4 mL) was treated with diacetyl peroxide; sodioboranyl acetate (91 mg, 0.43 mmol, 1.20 equiv) for 30 min at room temperature under nitrogen atmosphere followed by the addition of dimethylamine (19 mg, 0.43 mmol, 1.20 equiv) dropwise at room temperature.The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The resulting mixture was diluted with water (10 mL).The aqueous layer was extracted with CH_2Cl_2 (2x10 mL).The resulting mixture was concentrated under reduced pressure.The crude product was used in the next step directly without further purification.

LC-MS: M+H found: 503.0.



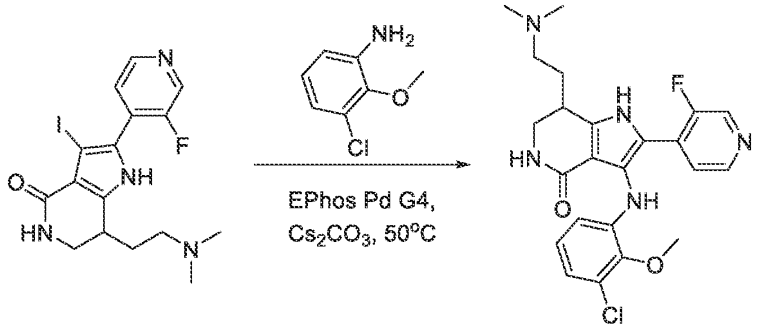
To a stirred mixture of 1,5-di-tert-butyl 2-(3-fluoropyridin-4-yl)-7-[2-(morpholin-4-yl)ethyl]-4-oxo-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (170 mg, 0.34 mmol, 1.00 equiv) in DCM (6 mL) was added TFA (2 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h and concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford 7-[2-(dimethylamino)ethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 97.78%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 303.



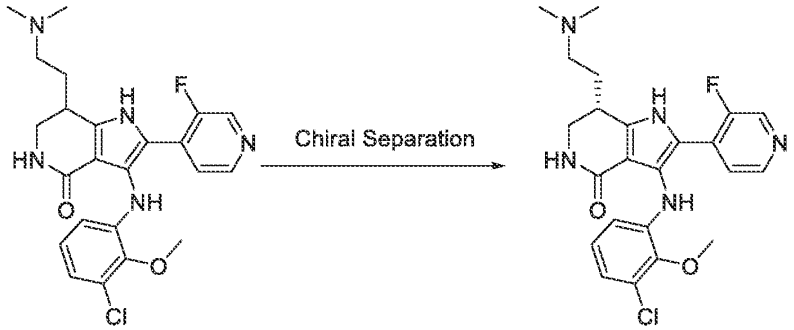
A solution of 7-[2-(dimethylamino)ethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (130 mg, 0.430 mmol, 1.00 equiv) and NIS (96.73 mg, 0.430 mmol, 1 equiv) in DMF (4 mL) was stirred for 2 h at room temperature under nitrogen atmosphere.The reaction was monitored by LCMS.Desired product could be detected by LCMS.The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford 7-[2-(dimethylamino)ethyl]-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (130 mg, 70.60%) as a yellow solid.

LC-MS: M+H found: 429.0.



To a stirred mixture of 7-[2-(dimethylamino)ethyl]-2-(3-fluoropyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (110 mg, 0.26 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (40 mg, 0.26 mmol, 1.00 equiv) in DMF (2.5 mL) were added EPhos Pd G4 (24 mg, 0.026 mmol, 0.1 equiv) and Cs_2CO_3 (167 mg, 0.51 mmol, 2.00 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 2h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure that was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford 3-[(3-chloro-2-methoxyphenyl)amino]-7-[2-(dimethylamino)ethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70 mg, 59.51%) as a yellow solid.

LC-MS: M+H found: 458.0.



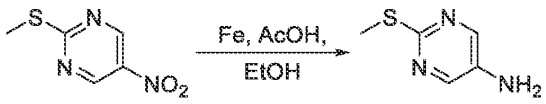
The crude product (80 mg) was purified by Prep-CHIRAL-HPLC with the following conditions (Column: CHIRALPAK IG-3, 4.6*50 mm, 3 um; Mobile Phase A: Hex (0.1%

DEA): EtOH=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (7S)-3-[(3-chloro-2-methoxyphenyl)amino]-7-[2-(dimethylamino)ethyl]-2-(3-fluoropyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (18.6 mg, 22.39%) as a white solid.

LCMS $(M+H)^+$ found: 458.

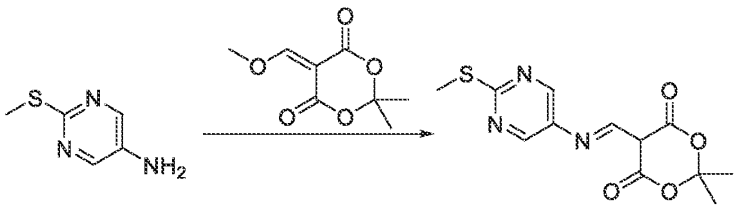
^{1}H NMR (400 MHz, DMSO-d6) δ 12.10 (s, 1H), 8.59 (t, J = 1.9 Hz, 1H), 8.33 (d, J = 2.7 Hz, 1H), 7.72 (m, 1H), 7.38 (s, 1H), 7.13 (t, J = 2.7 Hz, 1H), 6.80 – 6.63 (m, 2H), 6.16 (m, 1H), 3.89 (s, 3H), 3.48 (m, 1H), 3.20 (m, 1H), 3.09 – 2.96 (m, 1H), 2.48 – 2.38 (m, 1H), 2.32 (m, 1H), 2.23 (s, 6H), 1.97 (m, 1H), 1.73 – 1.55 (m, 1H).

Example 199. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[2-(dimethylamino)ethoxy]pyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 502)**



To a stirred solution of 2-(methylsulfanyl)-5-nitropyrimidine (5 g, 29.211 mmol, 1.00 equiv) in EtOH (200 mL) was added AcOH (120 mL) and Fe (17 g, 292.11 mmol, 10 equiv) in portions at rt under N_2 atmosphere. The resulting mixture was stirred for 2 h at 80 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 142. The resulting mixture was concentrated under reduced pressure. The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with Saturated NaCl (3x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2-(methylsulfanyl)pyrimidin-5-amine (3.5 g, 84.86%) as a yellow solid.

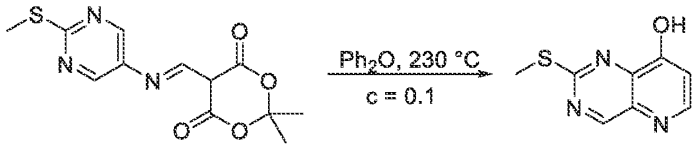
LC-MS: M+H found: 142.0.



To a stirred solution of 2-(methylsulfanyl)pyrimidin-5-amine (3.2 g, 22.66 mmol, 1.00

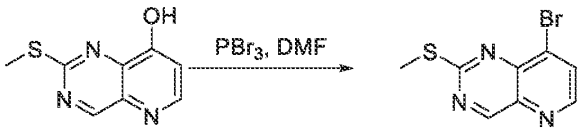
equiv) and 5-(methoxymethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (5.06 g, 27.18 mmol, 1.20 equiv) in DMF (80.00 mL) at rt under N_2 atmosphere. The resulting mixture was stirred for 1 h at 80 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 296.The resulting mixture was added MeOH(50 mL). The resulting mixture was filtered, the filter cake was washed with MeOH (3 x20 mL). The filter cake was concentrated under reduced pressure to afford 2,2-dimethyl-5-[(1E)-[[2-(methylsulfanyl)pyrimidin-5-yl]imino]methyl]-1,3-dioxane-4,6-dione (5.4 g, 80.68%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 296.0.



To a stirred solution of 2,2-dimethyl-5-[(1E)-{[2-(methylsulfanyl)pyrimidin-5-yl]imino}methyl]-1,3-dioxane-4,6-dione (5.3 g, 17.95 mmol, 1.00 equiv) in phenoxybenzene (360 mL) at rt under N_2 atmosphere. The resulting mixture was stirred at 230 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 194. The reaction was addition of Hexane (700 ml) at rt. The resulting mixture was filtered; the filter cake was washed with Hexane (3x200 ml). The filtrate was concentrated under reduced pressure.

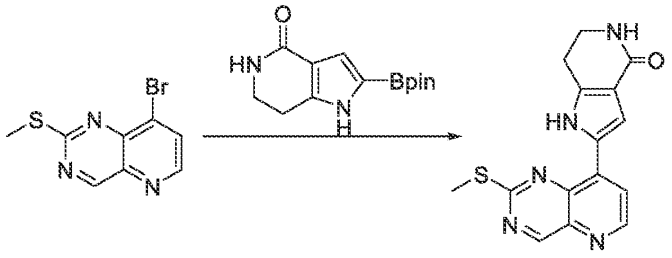
LC-MS: $(M+H)^+$ found: 194.0.



To a stirred solution of 2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-ol (2.8 g, 14.49 mmol, 1.00 equiv) in DMF (80 mL) was added PBr_3 (4.31 g, 15.94 mmol, 1.1 equiv) dropwise at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 1 h at rt under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 256. The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with aq. NaCl (3x100 mL), dried over anhydrous Na_2SO_4. After filtration, the

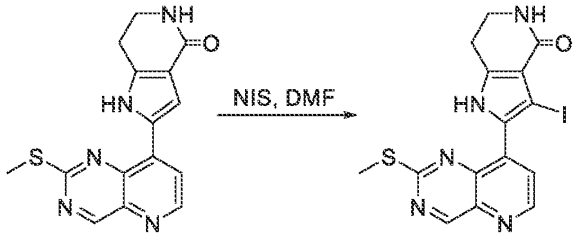
filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE:EA (4:1) to afford 8-bromo-2-(methylsulfanyl)pyrido[3,2-d]pyrimidine (1.6 g, 43.11%) as a white solid.

LC-MS: $(M+H)^+$ found: 256.0.



To a stirred solution of 8-bromo-2-(methylsulfanyl)pyrido[3,2-d]pyrimidine (700 mg, 2.73 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1075 mg, 4.10 mmol, 1.50 equiv) in dioxane (10 mL) and H_2O (1 mL) were added Na_2CO_3 (869.03 mg, 8.199 mmol, 3.00 equiv) and XPhos Pd G2 (215 mg, 0.27 mmol, 0.10 equiv) dropwise/ in portions at rt under N_2 atmosphere. The resulting mixture was stirred for 2 h at 80 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 312. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH=24:1 to afford 2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (700 mg, 82.26%) as a yellow solid.

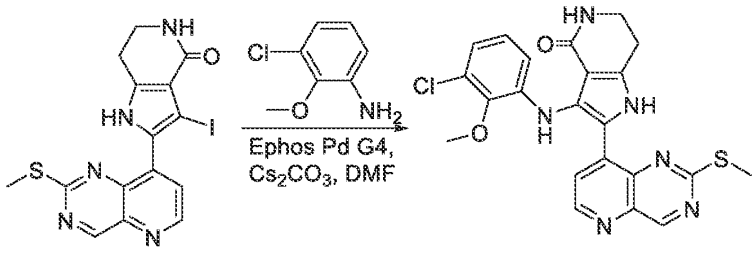
LC-MS: $(M+H)^+$ found: 312.0.



To a stirred solution of 2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (600 mg, 1.93 mmol, 1.00 equiv) and NIS (650.33 mg, 2.891 mmol, 1.50 equiv) in DMF (10 mL) at rt under N_2 atmosphere. The resulting mixture was

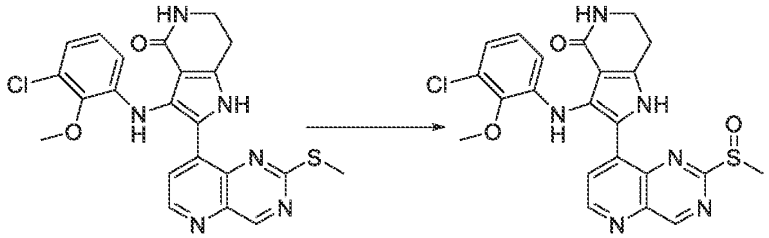
stirred for overnight at 30 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 438.The reaction was quenched by the addition of Saturated aq. Na_2SO_3 (20 mL) at 0 degrees C. The precipitated solids were collected by filtration and washed with H_2O (20 mLx3). The residue was purified by silica gel column chromatography, eluted with DCM:MeOH=10:1 to afford 3-iodo-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (650 mg, 77.14%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 438.0.



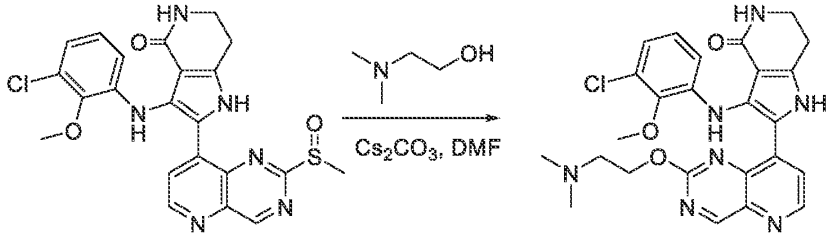
To a stirred solution of 3-iodo-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (370 mg, 0.85 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (134 mg, 0.85 mmol, 1 equiv) in DMF (4 mL) were added EPhos Pd G4 (78 mg, 0.08 mmol, 0.1 equiv) and Cs_2CO_3 (827 mg, 2.54 mmol, 3 equiv) in portions at rt under Ar atmosphere. The resulting mixture was stirred for 1.5 h at 50 degrees C under Ar atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 467. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM:MeOH (10:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (220 mg, 55.68%) as a orange solid.

LC-MS: $(M+H)^+$ found: 467.0.



To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50 mg, 0.11 mmol, 1.00 equiv) in DCM (2 mL, 31.46 mmol, 293.80 equiv) were added MCPBA (29 mg, 0.12 mmol, 1.1 equiv) dropwise/ in portions at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 1 h at 0 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 483. The resulting mixture was extracted with DCM (3 x 4 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

LC-MS: $(M+H)^+$ found: 483.0.

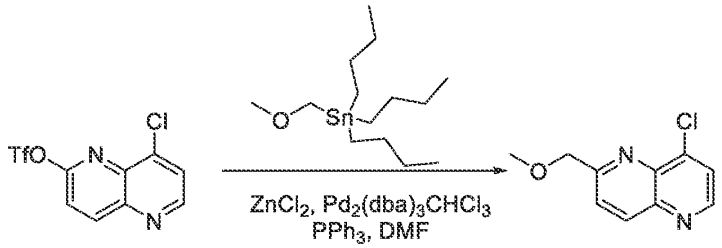


To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-methanesulfinylpyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (145 mg, 0.30 mmol, 1.00 equiv) and Cs_2CO_3 (235 mg, 0.72 mmol, 2.4 equiv) in DMF (2 mL) were added dimethylaminoethanol (33 mg, 0.36 mmol, 1.2 equiv) dropwise at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 1 h at RT under N_2 atmosphere. The resulting mixture was concentrated under vacuum.The resulting mixture was concentrated under vacuum and dissolved in DMF. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 42% B in 11 min, 42% B; Wave Length: 254/220 nm; RT1(min): 9.67) to 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[2-(dimethylamino)ethoxy]pyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (6.1 mg, 4.00%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 508.30.

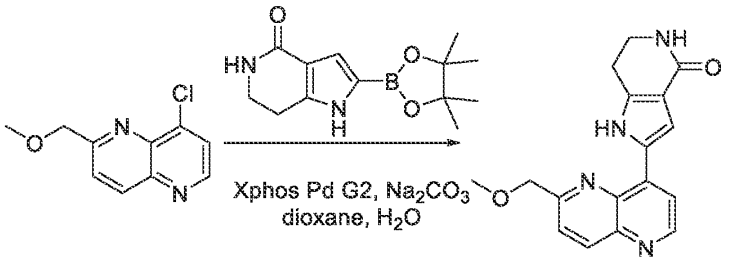
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 9.50 (s, 1H), 8.70 (d, J = 4.8 Hz, 1H), 7.87 (s, 1H), 7.58 (d, J = 4.8 Hz, 1H), 7.27 (d, J = 2.6 Hz, 1H), 6.72 (m, J = 8.0, 1.7 Hz, 1H), 6.66 (t, J = 8.0 Hz, 1H), 6.16 (m, J = 8.0, 1.7 Hz, 1H), 4.70 (t, J = 5.9 Hz, 2H), 3.89 (s, 3H), 3.43–3.51 (m, 2H), 2.95 (t, J = 6.8 Hz, 2H), 2.80 (s, 2H), 2.29 (s, 6H).

Example 200. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(methoxymethyl)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 679)**



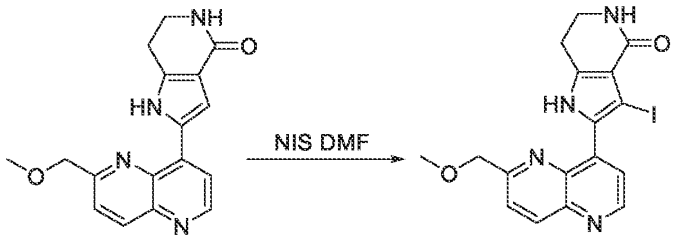
To a stirred mixture of 8-chloro-1,5-naphthyridin-2-yl trifluoromethanesulfonate (100 mg, 0.32 mmol, 1.00 equiv) and tributyl(methoxymethyl)stannane (108 mg, 0.32 mmol, 1 equiv) in DMF (3 mL) were added ZnCl2 (44 mg, 0.32 mmol, 1 equiv) and Pd2(dba)3CHCl3 (33 mg, 0.03 mmol, 0.1 equiv)and PPh3 (8 mg, 0.03 mmol, 0.1 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for overnight at 90degrees C under argon atmosphere. The reaction was quenched by the addition of sat.KF (aq.) (5mL) at 0 degrees C. The resulting mixture was extracted with EtOAc (3 x 10mL). The combined organic layers were washed with brine (1x5 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 3:1) to afford 8-chloro-2-(methoxymethyl)-1,5-naphthyridine (40 mg, 59.94%) as a yellow solid.

LC-MS: M+H found: 209.



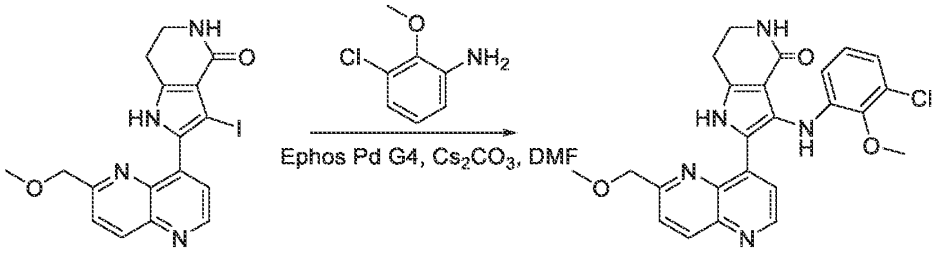
To a stirred mixture of 8-chloro-2-(methoxymethyl)-1,5-naphthyridine (30 mg, 0.144 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (45 mg, 0.17 mmol, 1.2 equiv) in dioxane (1 mL) and H_2O (0.2 mL) were added XPhos Pd G2 (23 mg, 0.02 mmol, 0.2 equiv) and Na_2CO_3 (30 mg, 0.29 mmol, 2 equiv) in portions at 60 degrees C under argon atmosphere. The resulting mixture was extracted with EtOAc (3 x 10mL). The combined organic layers were washed with brine (1x10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 2-[6-(methoxymethyl)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (40 mg, 90.22%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 309.



A mixture of 2-[6-(methoxymethyl)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (30 mg, 0.10 mmol, 1.00 equiv) and NIS (26 mg, 0.12 mmol, 1.2 equiv) in DMF (1 mL) was stirred for 1h at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was extracted with EtOAc (3 x 10mL). The combined organic layers were washed with brine (1x5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 3-iodo-2-[6-(methoxymethyl)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (40 mg, 94.68%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 435.

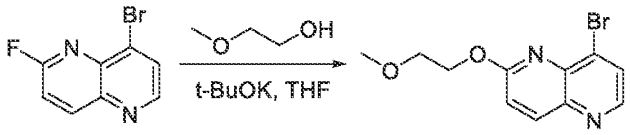


To a stirred mixture of 3-iodo-2-[6-(methoxymethyl)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (30 mg, 0.07 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (12 mg, 0.08 mmol, 1.10 equiv) in DMF (1.00 mL) were added Ephos Pd G4 (6 mg, 0.01 mmol, 0.1 equiv) and Cs2CO3 (45 mg, 0.14 mmol, 2 equiv) in portions at 50 degrees C under argon atmosphere. The resulting mixture was stirred for 2h at 50 degrees C under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 10:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(methoxymethyl)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (30 mg) as a light yellow solid. The crude product (30 mg) was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 55% B to 57% B in 9 min, 57% B; Wave Length: 254 nm; RT1(min): 6.00) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(methoxymethyl)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (10.6 mg, 33.07%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 464.05.

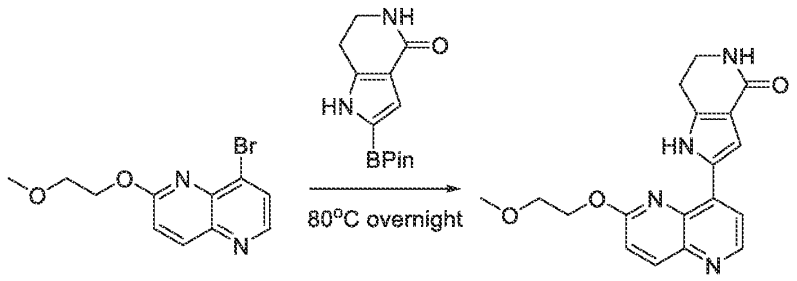
1H NMR (400 MHz, DMSO-d6) δ 12.68 (s, 1H), 8.72 (d, J = 4.9 Hz, 1H), 8.44 (d, J = 8.7 Hz, 1H), 7.93 (s, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.52 (d, J = 4.9 Hz, 1H), 7.23 (d, J = 2.8 Hz, 1H), 6.73 (m, J = 1.8 Hz, 1H), 6.69 (t, J = 8.0 Hz, 1H), 6.20 (m, J = 1.8 Hz, 1H), 4.91 (s, 2H), 3.89 (s, 3H), 3.55 – 3.43 (m, 5H), 2.99 (t, J = 6.8 Hz, 2H).

Example 201. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 678)**



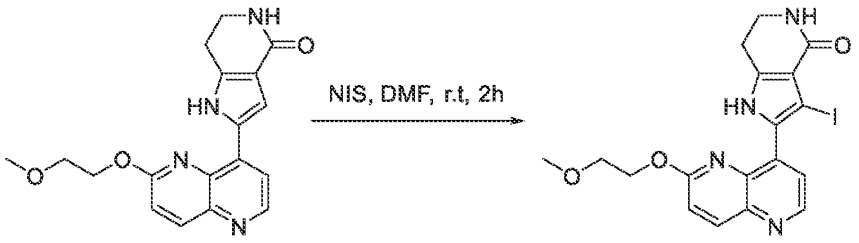
To a solution of 8-bromo-2-fluoro-1,5-naphthyridine (500 mg, 2.202 mmol, 1 equiv) and 2-methoxyethanol (837.92 mg, 11.010 mmol, 5 equiv) in THF (22 mL) was added t-BuOK (741.38 mg, 6.606 mmol, 3 equiv) in portions at 0°C, then the reaction was stirred at 0°C for 1 hrs. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (100:1) to afford 8-bromo-2-(2-methoxyethoxy)-1,5-naphthyridine (640 mg, 98.54%) as a off-white solid.

LC-MS: $(M+H)^+$ found: 283.0.



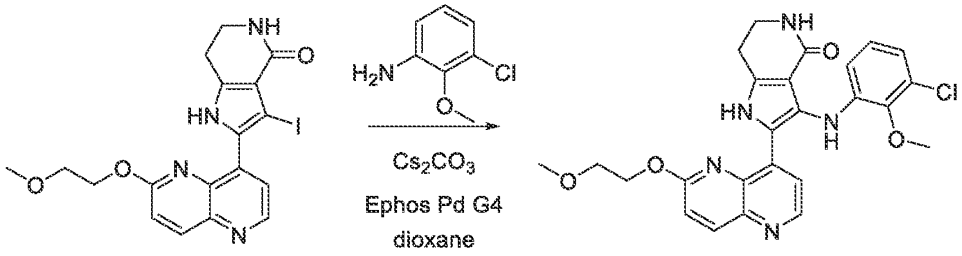
To a stirred mixture of 8-bromo-2-(2-methoxyethoxy)-1,5-naphthyridine (600 mg, 2.119 mmol, 1 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (833.23 mg, 3.179 mmol, 1.5 equiv) in DME (20 mL) H_2O (0.5 mL, 27.755 mmol, 13.10 equiv) was added Pd(dppf)Cl2 (155.06 mg, 0.212 mmol, 0.1 equiv) , TEA (536.12 mg, 5.298 mmol, 2.5 equiv) at room temperature under argon atmosphere. The resulting mixture was stirred for overnight at 80°C under argon atmosphere. The reaction was monitored by LCMS. The resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were washed with water (1x50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 2-[6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (620 mg, 83.00%) as a off-white solid.

LC-MS: $(M+H)^+$ found: 339.0.



To a stirred mixture of 2-[6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (350 mg, 1.034 mmol, 1 equiv) in DMF (10 mL) was added NIS (279.26 mg, 1.241 mmol, 1.2 equiv) in portions at room temperature under argon atmosphere. The reaction was monitored by LCMS. The resulting mixture was stirred for 2h at room temperature under argon atmosphere. The reaction was quenched by the addition of sat. sodium sulfite (aq.) (50mL) at room temperature. The precipitated solids were collected by filtration and washed with water (3x50 mL) to afford 3-iodo-2-[6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 78.71%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 464.85.



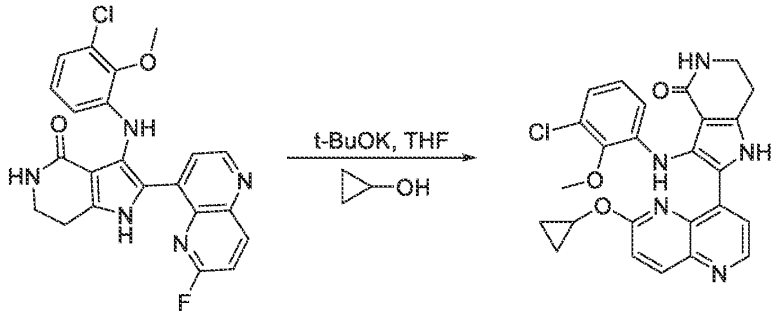
To a stirred mixture of 3-iodo-2-[6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (200.00 mg, 0.430 mmol, 1.00 equiv) in dioxane (4.30 mL) was added 3-chloro-2-methoxyaniline (68.00 mg, 0.430 mmol, 1.00 equiv) , Ephos Pd G4 (79.00 mg, 0.086 mmol, 0.20 equiv) and caesio methaneperoxoate caesium (281.00 mg, 0.859 mmol, 2.00 equiv) at room temperature under argon atmosphere. The resulting mixture was stirred for overnight at 50 degrees C under argon atmosphere. Desired product could be detected by LCMS. The residue was dissolved in ethyl acetate (50mL).The resulting mixture was washed with 3x10 mL of water. The crude

product (mg) was purified by Prep-HPLC with the following conditions ((Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10MMOL/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 34% B to 64% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5;) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (33 mg) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 494.05.

1H NMR (300 MHz, DMSO-d6) δ 12.09 (s, 1H), 8.57 (d, J = 4.8 Hz, 1H), 8.30 (d, J = 9.1 Hz, 1H), 7.79 (s, 1H), 7.50 (d, J = 4.9 Hz, 1H), 7.36 (d, J = 9.1 Hz, 1H), 7.23 (t, J = 2.5 Hz, 1H), 6.79 – 6.57 (m, 2H), 6.18 (dd, J = 7.5, 2.2 Hz, 1H), 4.82 – 4.66 (m, 2H), 3.88 (s, 3H), 3.84 – 3.75 (m, 2H), 3.47 (td, J = 6.8, 2.4 Hz, 2H), 3.35 (s, 3H), 2.95 (t, J = 6.8 Hz, 2H).

Example 202. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-cyclopropoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 677)**

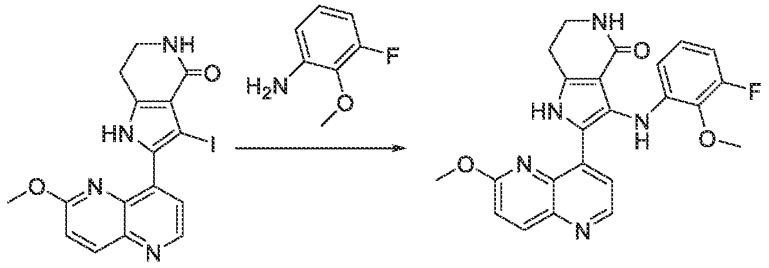


To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (200.00 mg, 0.457 mmol, 1.00 equiv) and cyclopropanol (132.65 mg, 2.284 mmol, 5.00 equiv) in THF (5.00 mL) was added t-BuOK (56.38 mg, 0.502 mmol, 1.1 0equiv) dropwise at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 70% gradient in 30min; detector, UV 254 nm. This resulted in 3-[(3-chloro-2-methoxyphenyl)amino]-2-(6-cyclopropoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (44.1 mg, 19.44%) as a yellow solid.

LC-MS: $(M+H)^+$ found 476.25.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.73 (s, 1H), 8.51-8.50 (d, J = 5.0 Hz, 1H), 8.26-8.23 (d, J = 9.1 Hz, 1H), 7.74 (s, 1H), 7.44-7.43 (d, J = 4.9 Hz, 1H), 7.28-7.26 (d, J = 9.1 Hz, 1H), 7.20 (s, 1H), 6.71 – 6.64 (m, 2H), 6.12-6.10 (dd, J = 7.7, 2.0 Hz, 1H), 4.52-4.50 (dt, J = 6.0, 3.0 Hz, 1H), 3.87 (s, 3H), 3.73-3.40 (dt, J = 7.0, 3.6 Hz, 2H), 2.81-2.97 (t, J = 6.8 Hz, 2H), 0.82-0.90 (ddd, J = 15.2, 6.0, 3.8 Hz, 4H).

Example 203. 3-[(3-fluoro-2-methoxyphenyl)amino]-2-(6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 681)**

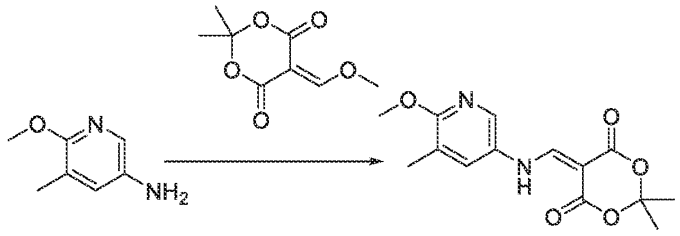


To a stirred mixture of 3-iodo-2-(6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (60 mg, 0.14 mmol, 1.00 equiv) and 3-fluoro-2-methoxyaniline (25 mg, 0.17 mmol, 1.20 equiv) in dioxane (2.5 mL) were added Cs_2CO_3 (93 mg, 0.28 mmol, 2.00 equiv), EPhos (8 mg, 0.01 mmol, 0.10 equiv) and EPhos Pd G4 (53 mg, 0.06 mmol, 0.40 equiv)under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for overnight at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). After filtration, the filtrate was concentrated under reduced pressure. 1.The residue was dissolved in DMF(0.5 mL). The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 35% B to 60% B in 7 min, 60% B; Wave Length: 254 nm; RT1(min): 6.2) to afford 3-[(3-fluoro-2-methoxyphenyl)amino]-2-(6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (5.1 mg, 8.24%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 434.05.

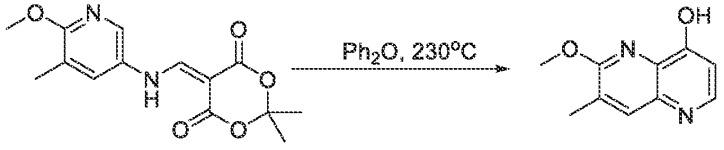
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 1H), 8.59 (d, J = 4.9 Hz, 1H), 8.30 (d, J = 9.0 Hz, 1H), 7.81 (s, 1H), 7.52 (d, J = 4.9 Hz, 1H), 7.36 (d, J = 9.1 Hz, 1H), 7.19 (t, J = 2.4 Hz, 1H), 6.62 (m, J = 8.3, 6.0 Hz, 1H), 6.50 (m, J = 11.0, 8.3, 1.5 Hz, 1H), 6.06 (m, J = 8.2, 1.3 Hz, 1H), 4.18 (s, 3H), 3.87 (d, J = 0.9 Hz, 3H), 3.46 (m, J = 6.9, 2.5 Hz, 2H), 2.95 (t, J = 6.8 Hz, 2H).

Example 204. 3-[(3-fluoro-2-methoxyphenyl)amino]-2-(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 682)**



To a stirred solution of 6-methoxy-5-methylpyridin-3-amine (1.00 g, 7.237 mmol, 1.00 equiv) and 5-(methoxymethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione(1.62 g, 8.685 mmol, 1.20 equiv) in DMF(20.00 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at 80 degrees C under nitrogen atmosphere. The residue was purified by trituration with MeOH (10 mL). This resulted in 5-[[(6-methoxy-5-methylpyridin-3-yl)amino]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione(1.50 g,70.91%) as a yellow solid.

LC-MS: M+H found: 293.10.



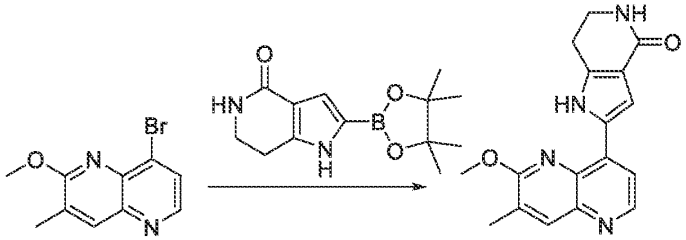
To a stirred solution of 5-[[(6-methoxy-5-methyl-2,3-dihydropyridin-3-yl)amino]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione(1.00 g) in diphenyl-ether(15.00 mL) at 240 degrees C under air atmosphere. The resulting mixture was stirred for 1h at 240 degrees C under air atmosphere. The residue was purified by trituration with hexane (10 mL). The precipitated solids were collected by filtration This resulted in 6-methoxy-7-methyl-1,5-naphthyridin-4-ol (800.00 mg) as a brown solid.

LC-MS: M+H found: 191.20.



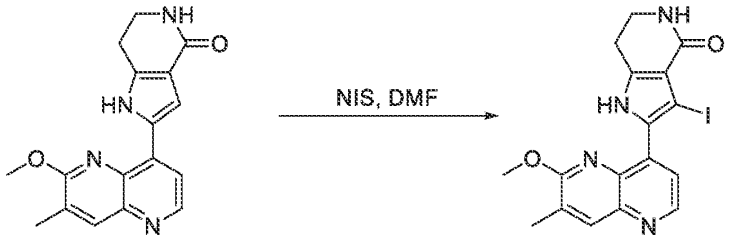
To a stirred solution of 6-methoxy-7-methyl-1,5-naphthyridin-4-ol (800.00 mg, 4.206 mmol, 1.00 equiv) in DMF (10.00 mL) was added PBr3 (1366.22 mg, 0.000 mmol, 1.20 equiv) dropwise at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 2h at room temperature under nitrogen atmosphere. The resulting mixture was diluted with ice water (15 mL). The mixture was basified to pH 8 with saturated Na2CO3 (aq.). The precipitated solids were collected by filtration. This resulted in 8-bromo-2-methoxy-3-methyl-1,5-naphthyridine (750.00 mg) as a brown solid.

LC-MS: M+H found: 253.00.



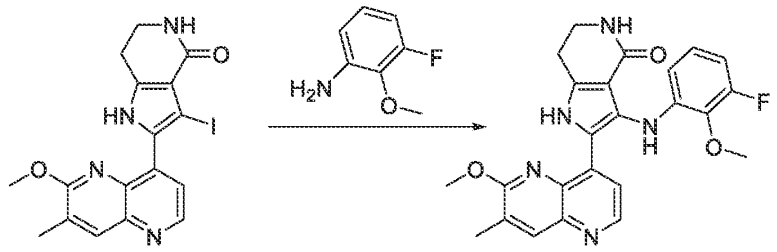
To a stirred solution of 8-bromo-2-methoxy-3-methyl-1,5-naphthyridine (500.00 mg, 1.976 mmol, 1.00 equiv), Cs2CO3 (1930.98 mg, 5.928 mmol, 3.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (569.60 mg, 0.000 mmol, 1.10 equiv) in dioxane (4.00 mL) and H2O (1.00 mL) was added Pd(dppf)Cl2 (144.55 mg, 0.198 mmol, 0.10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 12h at 95 degrees C under nitrogen atmosphere. The resulting mixture was diluted with water (20 mL). The aqueous layer was extracted with EtOAc (3x30 mL). The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 20:1) to afford 2-(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (200.00 mg, 32.83%) as a yellow solid.

LC-MS: M+H found: 309.10.



To a stirred solution of 2-(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (200.00 mg, 1.297 mmol, 1.00 equiv) in DMF (3 mL) was added NIS (291.86 mg, 1.297 mmol, 1.00 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature under nitrogen atmosphere. The reaction was quenched with sat. Na2O3S(aq.) 3mL at 0 degrees C. The product was precipitated by the addition of water. The precipitated solids were collected by filtration This resulted in 3-iodo-2-(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (90 mg, 29.81%) as a brown solid.

LC-MS: M+H found: 435.0.



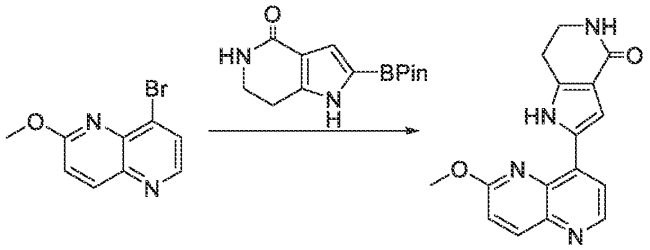
To a stirred solution of 3-iodo-2-(6-methoxy-7-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80.00 mg, 0.184 mmol, 1.00 equiv), Cs_2CO_3 (120.05 mg, 0.368 mmol, 2.00 equiv) and 3-fluoro-2-methoxyaniline (28.60 mg, 0.000 mmol, 1.10 equiv) in dioxane (2.00 mL) was added BrettPhos Pd G3 (33.40 mg, 0.037 mmol, 0.20 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 70 degrees C under nitrogen atmosphere. The crude product (40 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10MMOL/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 60% B in 8 min; Wave Length: 254 nm; RT1(min): 6;) to afford 3-[(3-fluoro-2-methoxyphenyl)amino]-2-(6-

methoxy-7-methyl-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.40 mg) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 448.10.

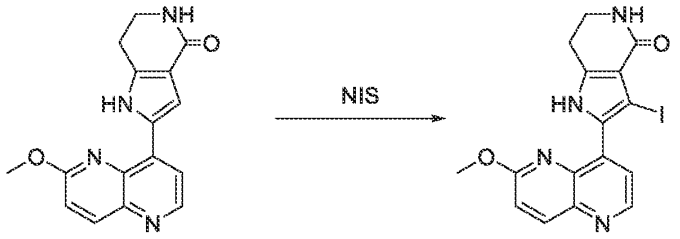
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (s, 1H), 8.54 (d, J = 4.9 Hz, 1H), 8.15 (d, J = 1.2 Hz, 1H), 7.78 (s, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.18 (s, 1H), 6.62 – 6.60 (m, 1H), 6.51 – 6.49 (m, 1H), 6.06 (d, J = 8.1 Hz, 1H), 4.21 (s, 3H),3.85 (s, 3H) 3.44-3.48 (m, 2H), 2.94 (t, J = 6.8 Hz, 2H), 2.39 (d, J = 1.1 Hz, 3H).

Example 205. 3-[(3-fluoro-2-methylphenyl)amino]-2-(6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 684)**



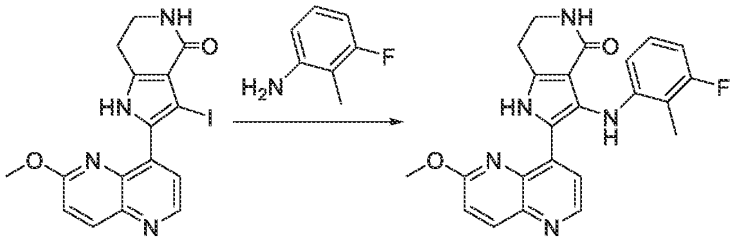
To a stirred solution of 8-bromo-2-methoxy-1,5-naphthyridine (273 mg, 1.14 mmol, 1.00 equiv) and 2-(3,3,4,4-tetramethylborolan-1-yl)-octahydro-1H-pyrrolo[3,2-c]pyridin-4-ol (302 mg, 1.14 mmol, 1.00 equiv) in dioxan (2.5 mL) and H_2O (0.5 mL) were added Na_2CO_3 (363 mg, 3.43 mmol, 3.00 equiv) and $Pd(PPh_3)_4$ (264 mg, 0.23 mmol, 0.20 equiv) in portions at room temperature under N_2 atmosphere. The resulting mixture was stirred for overnight at 50 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. The resulting mixture was extracted with EA (3 x 10 ml). The combined organic layers were washed with Saturated aq. NaCl (3x20 ml), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH=10:1 to afford 2-(6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70 mg, 20.83%) as a yellow solid.

LC-MS: M+H found: 295.05.



To a stirred solution of 2-(6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (60 mg, 0.20 mmol, 1.00 equiv) and NIS (46 mg, 0.21 mmol, 1.00 equiv) in DMF (2 mL) at rt under N_2 atmosphere. Desired product could be detected by LCMS. By added water, the precipitated solids were collected by filtration and washed with H_2O (3x20 mL) to afford 3-iodo-2-(6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50 mg, 58.37%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 420.9.



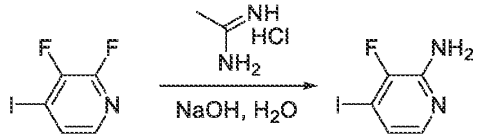
To a stirred mixture of 3-iodo-2-(6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (60 mg, 0.14 mmol, 1.00 equiv) and 3-fluoro-2-methyl-aniline (21 mg, 0.17 mmol, 1.20 equiv) in dioxane (2.5 mL) were added Cs_2CO_3 (93 mg, 0.28 mmol, 2.00 equiv), EPhos (8 mg, 0.01 mmol, 0.10 equiv) and EPhos Pd G4 (53 mg, 0.06 mmol, 0.40 equiv)under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for overnight at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). After filtration, the filtrate was concentrated under reduced pressure. 1.The residue was dissolved in DMF(0.5 mL). The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10mmoL/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient:

40% B to 60% B in 7 min, 60% B; Wave Length: 254 nm; RT1(min): 5.82) to afford 3-[(3-fluoro-2-methylphenyl)amino]-2-(6-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (5.8 mg, 9.73%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 418.05.

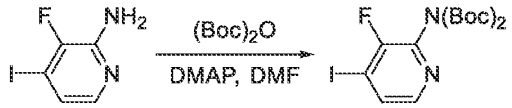
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (s, 1H), 8.51 (d, J = 4.9 Hz, 1H), 8.29 (d, J = 9.1 Hz, 1H), 7.55 (s, 1H), 7.44 (d, J = 4.9 Hz, 1H), 7.34 (d, J = 9.1 Hz, 1H), 7.24 (s, 1H), 6.75 (q, J = 7.8 Hz, 1H), 6.49 (t, J = 8.8 Hz, 1H), 6.10 (d, J = 8.2 Hz, 1H), 4.18 (s, 3H), 3.47 (d, J = 2.5 Hz, 2H), 2.96 (t, J = 6.8 Hz, 2H), 2.24 (d, J = 1.7 Hz, 3H).

Example 206. 2-(2-amino-3-fluoropyridin-4-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 687)**



To a stirred solution of 2,3-difluoro-4-iodopyridine(4.60 g, 19.08 mmol, 1.00 equiv) in DMSO(45.00 mL) was added acetamidine(2.19 g, 22.90 mmol, 1.20 equiv) and NaOH (1.91 g, 47.722 mmol, 2.50 equiv) dropwise at room temperature under nitrogen atmosphere. To the above mixture was added H_2O(1.72 g, 95.47 mmol, 5.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional overnight at 130 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed.The resulting mixture was extracted with EtOAc (3 x150 mL). The combined organic layers were washed with brine (3x200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford 3-fluoro-4-iodopyridin-2-amine(1.725g,37.97%) as an off-white solid.

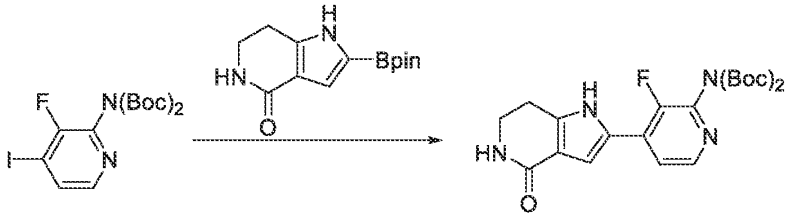
LC-MS: $(M+H)^+$ found: 238.85.



To a stirred solution of 3-fluoro-4-iodopyridin-2-amine(1.70 g, 7.14 mmol, 1.00 equiv) in DMF(35.00 mL) was added DMAP(0.13 g, 1.07 mmol, 0.15 equiv) dropwise at room

temperature under nitrogen atmosphere. To the above mixture was added di-tert-butyl dicarbonate(4.68 g, 21.42 mmol, 3.00 equiv) in portions at room temperature. The resulting mixture was stirred for additional 3h at room temperature. The reaction was monitored by LCMS. LCMS showed the reaction was completed.The resulting mixture was extracted with EtOAc (3 x 150mL). The combined organic layers were washed with brine (2x200mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 3:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(3-fluoro-4-iodopyridin-2-yl)carbamate(2.38g,76.03%) as an off-white solid.

LC-MS: $(M+H)^+$ found: 438.95.



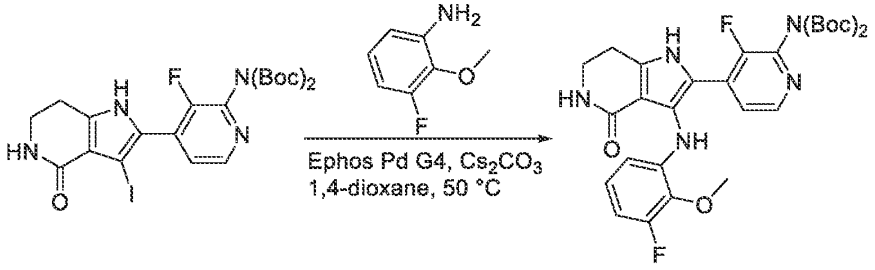
To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(3-fluoro-4-iodopyridin-2-yl)carbamate (1.00 g, 2.28 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.20 g, 4.57 mmol, 2.00 equiv) in dioxane (20.00 mL) was added Na_2CO_3 (725 mg, 6.84 mmol, 3.00 equiv) and $Pd(PPh_3)_4$ (264 mg, 0.22 mmol, 0.10 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added H_2O (4.00 mL) dropwise at 50 degrees C. The resulting mixture was stirred for additional overnight at 50 degrees C. The precipitated solids were collected by filtration and washed with EtOAc (3x100 mL). To afford tert-butyl N-(tert-butoxycarbonyl)-N-(3-fluoro-4-[4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyridin-2-yl)carbamate (600 mg) as a grey solid.

LC-MS: $(M+H)^+$ found: 447.



To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(3-fluoro-4-[4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyridin-2-yl)carbamate (690 mg, 1.54 mmol, 1.00 equiv) in DMF (15.00 mL) was added N-iodosuccinimide (382 mg, 1.70 mmol, 1.10 equiv) dropwise at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The reaction was quenched by the addition of Na_2SO_3 (10mL) at room temperature. The mixture was neutralized to pH 7 with saturated NaHCO3 (aq.). The resulting mixture was extracted with CH_2Cl_2:MeOH (3 x 100mL). The combined organic layers were washed with brine (2x300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(3-fluoro-4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyridin-2-yl)carbamate (317 mg, 35.84%) as an off-white solid.

LC-MS: $(M+H)^+$ found: 573.1.

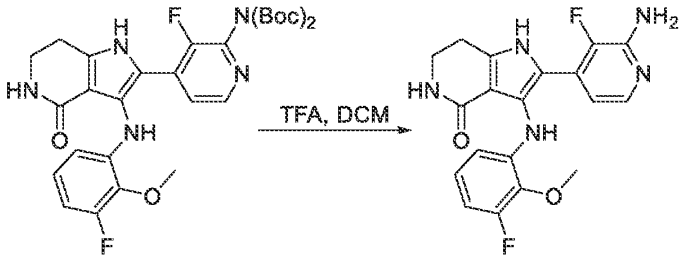


To a stirred mixture of tert-butyl N-(tert-butoxycarbonyl)-N-(3-fluoro-4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyridin-2-yl)carbamate (270.00 mg, 0.472 mmol, 1.00 equiv) and 3-fluoro-2-methoxyaniline (199.74 mg, 1.416 mmol, 3.00 equiv) in dioxane (2 mL, 0.047 mmol, 0.10 equiv) was added EPhos Pd G4 (86.66 mg, 0.094 mmol, 0.20 equiv) and Cs2CO3 (307.39 mg, 0.944 mmol, 2.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 3h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed.

The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (10:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(3-fluoro-4-[3-[(3-fluoro-2-methoxyphenyl)amino]-4-

oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyridin-2-yl)carbamate (260 mg, 94.12%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 486.15.

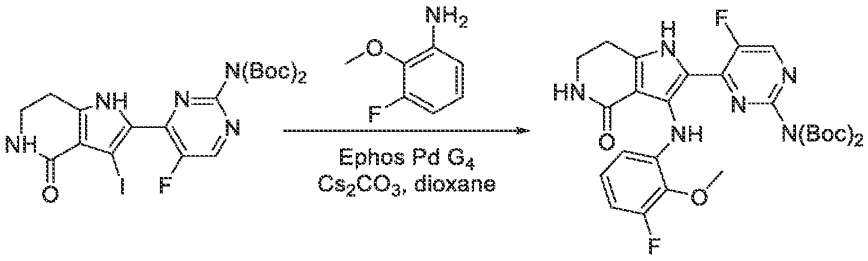


To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(3-fluoro-4-[3-[(3-fluoro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyridin-2-yl)carbamate (240 mg, 0.41 mmol, 1.00 equiv) in DCM (2.00 mL) was added TEA (2.00 mL) dropwise at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was monitored by LCMS. LCMS showed the reaction was completed.The resulting mixture was concentrated under vacuum. The crude product (150mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5um; Mobile Phase A: Water(10MMOL/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 45% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5;) to afford 2-(2-amino-3-fluoropyridin-4-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (96.5mg,61.10%) as a white solid.

LC-MS: $(M+H)^+$ found: 386.05.

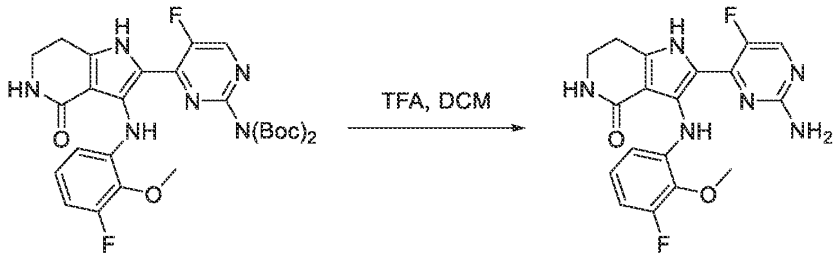
^{1}H NMR (400 MHz, DMSO-d6) δ 11.39 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.39 (s, 1H), 7.09 (s, 1H), 6.65 – 6.58 (m, 2H), 6.48-6.45 (m, 1H), 6.09 – 6.03 (m, 3H), 3.88 (s, 3H), 3.42-3.38 (m, 2H), 2.83 (t, J = 8.0 Hz, 2H).

Example 207. 2-(2-amino-5-fluoropyrimidin-4-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 688)**



To a stirred mixture of tert-butyl N-(tert-butoxycarbonyl)-N-(5-fluoro-4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (200 mg, 0.35 mmol, 1.00 equiv) and 3-fluoro-2-methoxyaniline (74 mg, 0.52 mmol, 1.50 equiv) in dioxane (3 mL) were added Ephos Pd G4 (64 mg, 0.07 mmol, 0.2 equiv)and Cs_2CO_3 (227 mg, 0.70 mmol, 2.00 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 2h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure that was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(5-fluoro-4-[3-[(3-fluoro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (87 mg, 42.52%) as a light yellow oil.

LC-MS: M+H found: 587.0.



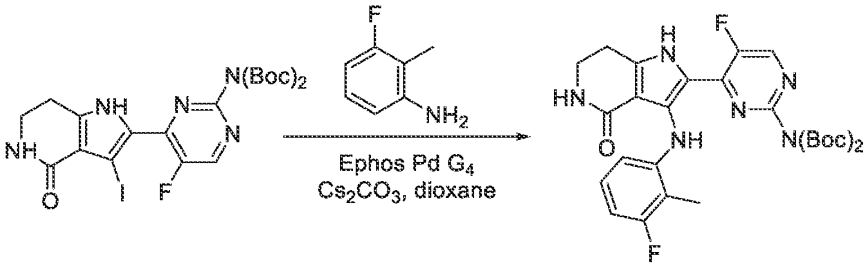
To a stirred mixture of tert-butyl N-(tert-butoxycarbonyl)-N-(5-fluoro-4-[3-[(3-fluoro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (87 mg, 0.15 mmol, 1.00 equiv) in DCM (1.2 mL) and TFA (0.4 mL) was stirred for 1 h at room temperature under nitrogen atmosphere.The resulting mixture was concentrated under reduced pressure.The crude product was purified by Prep-HPLC with

the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 19% B to 30% B in 8 min, 30% B; Wave Length: 254/220 nm; RT1(min): 7.07) to afford 2-(2-amino-5-fluoropyrimidin-4-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (13.7 mg, 23.67%) as a yellow solid.

LC-MS: M+H found: 387.0.

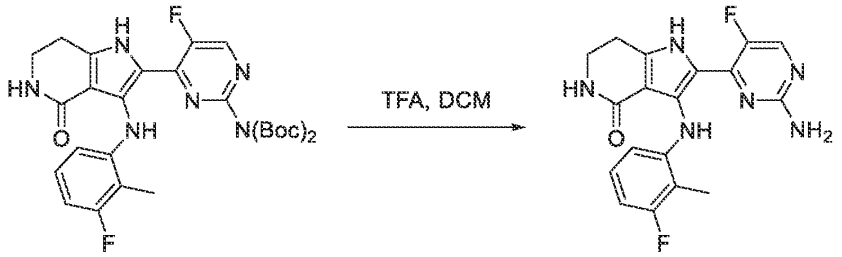
^{1}H NMR (400 MHz, DMSO-d6) δ 11.45 (s, 1H), 8.57 (s, 1H), 8.13 (d, J = 3.4 Hz, 1H), 7.17 (d, J = 3.3 Hz, 1H), 6.74 (m, 1H), 6.54 (m, 1H), 6.38 – 6.21 (m, 3H), 3.90 (s, 3H), 3.42 (m, 2H), 2.85 (t, J = 6.7 Hz, 2H).

Example 208. 2-(2-amino-5-fluoropyrimidin-4-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 689)**



To a stirred mixture of tert-butyl N-(tert-butoxycarbonyl)-N-(5-fluoro-4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (200 mg, 0.35 mmol, 1.00 equiv) and 3-fluoro-2-methyl-aniline (65 mg, 0.52 mmol, 1.50 equiv) in dioxane (3 mL) were added Ephos Pd G4 (64 mg, 0.07 mmol, 0.20 equiv) and Cs_2CO_3 (227.3 mg, 0.70 mmol, 2.00 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 2h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure that was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to affordtert-butyl N-(tert-butoxycarbonyl)-N-(5-fluoro-4-[3-[(3-fluoro-2-methylphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (95 mg, 47.73%) as a yellow oil.

LC-MS: M+H found: 571.0.

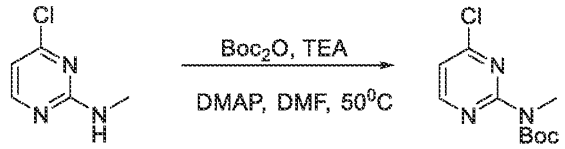


To a stirred mixture of tert-butyl N-(tert-butoxycarbonyl)-N-(5-fluoro-4-[3-[(3-fluoro-2-methylphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (95 mg, 1.00 equiv) in DCM (1.2 mL) and TFA (0.4 mL)was stirred for 1 h at room temperature under nitrogen atmosphere.The resulting mixture was concentrated under reduced pressure.The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 19% B to 30% B in 8 min, 30% B; Wave Length: 254/220 nm; RT1(min): 7.13) to afford 2-(2-amino-5-fluoropyrimidin-4-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (13.7 mg, 23.67%)2-(2-amino-5-fluoropyrimidin-4-yl)-3-[(3-fluoro-2-methylphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (17.8 mg, 28.52%) as a orange solid.

LC-MS: M+H found: 371.0.

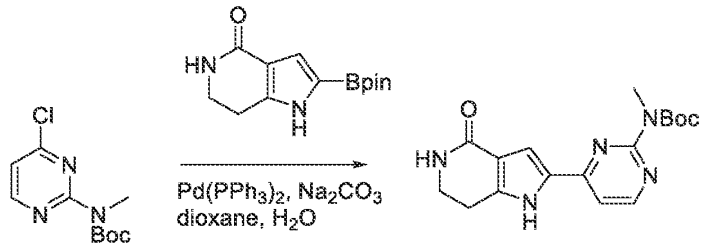
^{1}H NMR (400 MHz, DMSO-d6) δ 11.35 (s, 1H), 8.45 (s, 1H), 8.13 (d, J = 3.7 Hz, 1H), 7.09 (d, J = 2.9 Hz, 1H), 6.87 (q, J = 7.8 Hz, 1H), 6.54 (t, J = 8.8 Hz, 1H), 6.47 (d, J = 8.2 Hz, 1H), 6.37 (s, 2H), 3.40 (d, J = 2.7 Hz, 2H), 2.85 (t, J = 6.7 Hz, 2H), 2.20 (d, J = 1.8 Hz, 3H).

Example 209. 3-[(3-fluoro-2-methylphenyl)amino]-2-[2-(methylamino)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 690)**



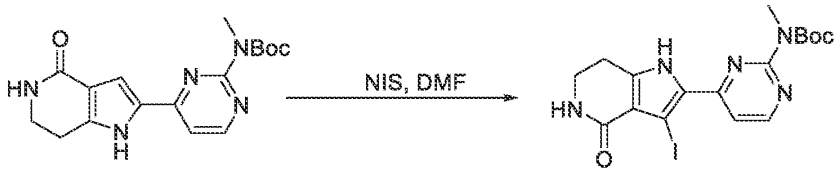
To a stirred mixture of 4-chloro-N-methylpyrimidin-2-amine(2.00 g, 13.93 mmol, 1.00 equiv) and Boc2O(7.60 g, 34.83 mmol, 2.5 equiv) in DMF (40.00 mL) were added TEA(3.52 g, 34.83 mmol, 2.50 equiv) and DMAP(0.51 g, 4.18 mmol, 0.3 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at 50 degrees C under nitrogen atmosphere. The resulting mixture was extracted with EtOAc (3 x 30mL). The combined organic layers were washed with brine (1x20 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford tert-butyl N-(4-chloropyrimidin-2-yl)-N-methylcarbamate(3g,88.37%) as a yellow oil.

LC-MS: M+H found: 244.



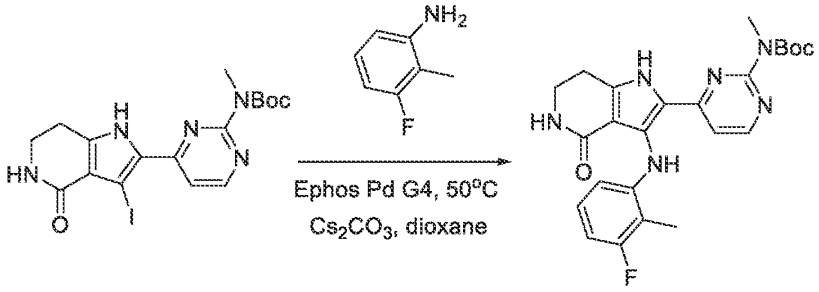
To a stirred mixture of tert-butyl N-(4-chloropyrimidin-2-yl)-N-methylcarbamate (2.80 g, 11.49 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (6.02 g, 22.98 mmol, 2.00 equiv) in dioxane (100.00 mL) and H_2O (20.00 mL) were added $Pd(PPh_3)_4$ (1.33 g, 1.15 mmol, 0.1 equiv) and Na_2CO_3 (2.44 g, 23.0 mmol, 2 equiv) in portions at room temperature under argon atmosphere.The resulting mixture was stirred for overnight at 60 degrees C under argon atmosphere. The resulting mixture was extracted with EtOAc (3 x 50mL). The combined organic layers were washed with brine (1x20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford tert-butyl N-methyl-N-(4-[4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (4.5 g, 96.95%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 344.



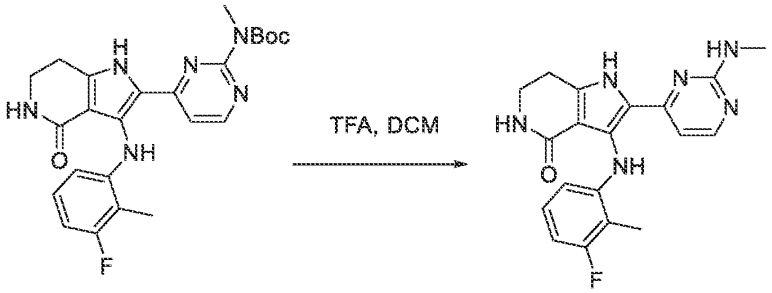
A mixture of tert-butyl N-methyl-N-(4-[4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (2.00 g, 5.82 mmol, 1.00 equiv) and NIS (1.57 g, 6.98 mmol, 1.20 equiv) in DMF (20.00 mL) was stirred for 2h at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of sat. Na_2SO_3 (aq.) (10mL) at 0 degrees C. The resulting mixture was diluted with water (10mL). The precipitated solids were collected by filtration and washed with water (1x5 mL) to afford tert-butyl N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)-N-methylcarbamate (2 g, 73.17%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 470.



To a stirred mixture of tert-butyl N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)-N-methylcarbamate (300 mg, 0.64 mmol, 1.00 equiv) and 3-fluoro-2-methyl-aniline (240 mg, 1.92 mmol, 3 equiv) in dioxane (6.00 mL) were added Ephos Pd G4 (117 mg, 0.13 mmol, 0.2 equiv) and Cs_2CO_3 (417 mg, 1.28 mmol, 2 equiv) in portions at 50 degrees C under argon atmosphere. The resulting mixture was stirred for overnight at 50 degrees C under nitrogen atmosphere.The resulting mixture was filtered, the filter cake was washed with EtOAc (2x10 mL). The filtrate was concentrated under reduced pressure.The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford tert-butyl N-(4-[3-[(3-fluoro-2-methylphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)-N-methylcarbamate (150 mg, 50.30%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 467.

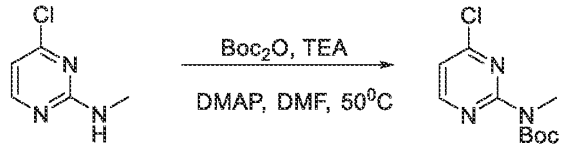


A mixture of tert-butyl N-(4-[3-[(3-fluoro-2-methylphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)-N-methylcarbamate (140 mg, 0.30 mmol, 1.00 equiv) in TFA (2.00 mL) and DCM (2.00 mL) was stirred for 3 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product (140mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30*150 mm, 5μm; Mobile Phase A: Water(10MMOL/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 57% B in 8 min; Wave Length: 254/220 nm; RT1(min): 7.68;) to afford 3-[(3-fluoro-2-methylphenyl)amino]-2-[2-(methylamino)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (53.7 mg, 47.81%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 367.05.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.54 (s, 1H), 8.03 (d, J = 5.3 Hz, 1H), 7.60 (s, 1H), 7.10 (d, J = 2.7 Hz, 1H), 6.88 (m, J = 7.8 Hz, 1H), 6.69 (s, 1H), 6.54 (d, J = 8.3 Hz, 1H), 6.42 (d, J = 5.0 Hz, 1H), 6.29 (d, J = 8.2 Hz, 1H), 3.40 (d, J = 2.6 Hz, 2H), 2.85 (d, J = 5.8 Hz, 5H), 2.20 (d, J = 1.7 Hz, 3H).

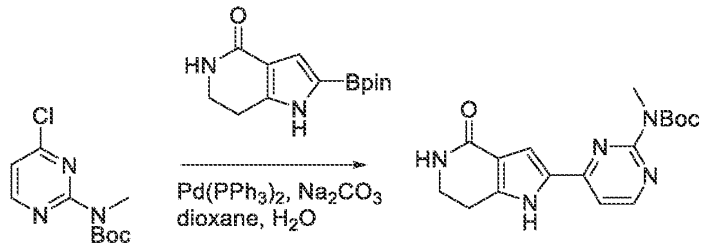
Example 210. 3-[(3-fluoro-2-methoxyphenyl)amino]-2-[2-(methylamino)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 691)**



To a stirred mixture of 4-chloro-N-methylpyrimidin-2-amine(2.00 g, 13.93 mmol, 1.00 equiv) and Boc_2O (7.60 g, 34.83 mmol, 2.5 equiv) in DMF (40.00 mL) were added TEA(3.52 g, 34.83 mmol, 2.50 equiv) and DMAP (0.51 g, 4.18 mmol, 0.3 equiv) in

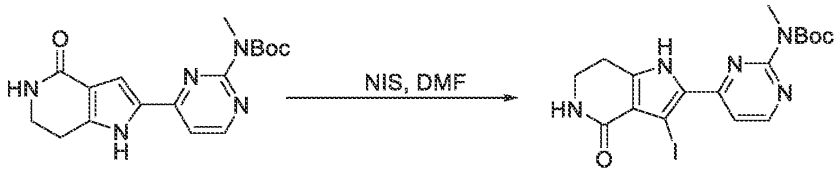
portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at 50 degrees C under nitrogen atmosphere. The resulting mixture was extracted with EtOAc (3 x 30mL). The combined organic layers were washed with brine (1x20 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford tert-butyl N-(4-chloropyrimidin-2-yl)-N-methylcarbamate (3g, 88.37%) as a yellow oil.

LC-MS: M+H found: 244.



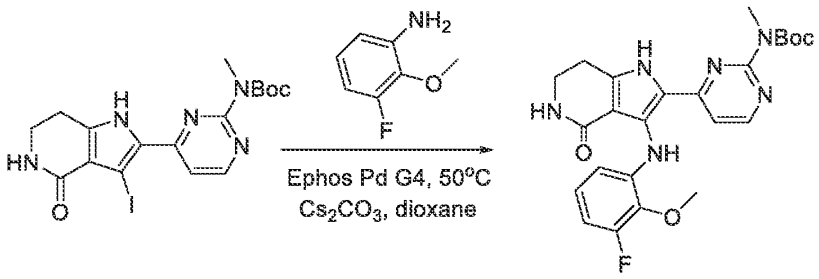
To a stirred mixture of tert-butyl N-(4-chloropyrimidin-2-yl)-N-methylcarbamate (2.80 g, 11.490 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (6.02 g, 22.98 mmol, 2.00 equiv) in dioxane (100.00 mL) and H_2O (20.00 mL) were added $Pd(PPh_3)_4$ (1.33 g, 1.15 mmol, 0.1 equiv) and Na_2CO_3 (2.44 g, 22.98 mmol, 2 equiv) in portions at room temperature under argon atmosphere.The resulting mixture was stirred for overnight at 60 degrees C under argon atmosphere. The resulting mixture was extracted with EtOAc (3 x 50mL). The combined organic layers were washed with brine (1x20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford tert-butyl N-methyl-N-(4-[4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (4.5 g, 96.95%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 344.



A mixture of tert-butyl N-methyl-N-(4-[4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (2.00 g, 5.82 mmol, 1.00 equiv) and NIS (1.57 g, 6.98 mmol, 1.20 equiv) in DMF (20.00 mL) was stirred for 2h at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of sat. Na_2SO_3 (aq.) (10mL) at 0 degrees C. The resulting mixture was diluted with water (10mL). The precipitated solids were collected by filtration and washed with water (1x5 mL) to afford tert-butyl N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)-N-methylcarbamate (2 g, 73.17%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 470.



To a stirred mixture of tert-butyl N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)-N-methylcarbamate (300 mg, 0.64 mmol, 1.00 equiv) and 3-fluoro-2-methoxyaniline (271 mg, 1.98 mmol, 3.00 equiv) in dioxane (6.00 mL) were added Ephos Pd G4 (117 mg, 0.13 mmol, 0.20 equiv) and Cs_2CO_3 (417 mg, 1.28 mmol, 2.00 equiv) in portions at 50 degrees C under argon atmosphere. The resulting mixture was stirred for overnight at 50 degrees C under argon atmosphere. The resulting mixture was filtered, the filter cake was washed with EtOAc (2x10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford tert-butyl N-(4-[3-[(3-fluoro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)-N-methylcarbamate (170 mg, 55.11%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 483.

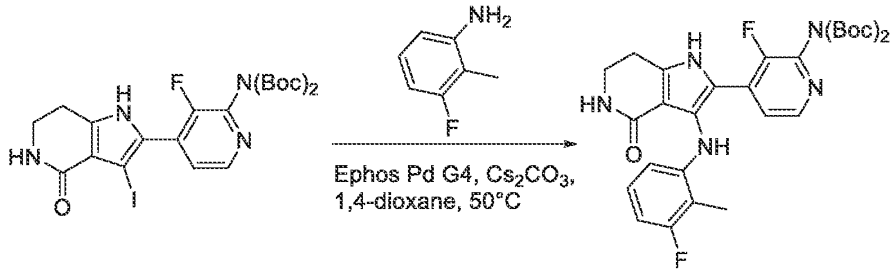


A mixture of tert-butyl N-(4-[3-[(3-fluoro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)-N-methylcarbamate (160 mg, 0.33 mmol, 1.00 equiv) in TFA (2.00 mL) and DCM (2.00 mL) was stirred for 2 h at room temperature under nitrogen atmosphere.The resulting mixture was concentrated under reduced pressure. The crude product (170mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(10MMOL/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 40% B in 8 min; Wave Length: 254; 220 nm; RT1(min): 6.35) to afford 3-[(3-fluoro-2-methoxyphenyl)amino]-2-[2-(methylamino)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50.1 mg, 39.35%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 383.15.

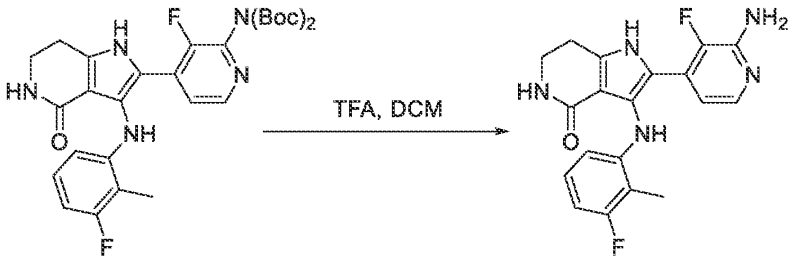
^{1}H NMR (400 MHz, DMSO-d6) δ 11.57 (s, 1H), 8.06 (d, J = 5.3 Hz, 1H), 7.89 (s, 1H), 7.13 (t, J = 2.7 Hz, 1H), 6.76 (m, J = 6.0 Hz, 1H), 6.68 (s, 1H), 6.57 (m, J = 1.5 Hz, 1H), 6.47 (d, J = 5.3 Hz, 1H), 6.24 (m, J = 1.3 Hz, 1H), 3.90 (s, 3H), 3.40 (d, J = 2.6 Hz, 2H), 2.86 (d, J = 5.7 Hz, 5H).

Example 211. 2-(2-amino-3-fluoropyridin-4-yl)-3-[(3-fluoro-2-methylphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 692)**



To a stirred mixture of tert-butyl N-(tert-butoxycarbonyl)-N-(3-fluoro-4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyridin-2-yl)carbamate (270 mg, 0.472 mmol, 1.00 equiv) and 3-fluoro-2-methyl-aniline (177 mg, 1.42 mmol, 3.00 equiv) in 1,4-dioxane (5.00 mL) were added EPhos Pd G4 (87 mg, 0.09 mmol, 0.20 equiv) and Cs_2CO_3 (308 mg, 0.94 mmol, 2.00 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 2h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure that was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(3-fluoro-4-[3-[(3-fluoro-2-methylphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyridin-2-yl)carbamate (250 mg, 92.94%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 570.35.



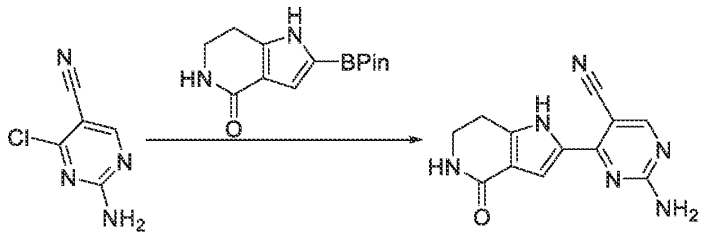
To a stirred mixture of tert-butyl N-(tert-butoxycarbonyl)-N-(3-fluoro-4-[3-[(3-fluoro-2-methylphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyridin-2-yl)carbamate (220 mg, 0.39 mmol, 1.00 equiv) in DCM (2 mL) was added TFA (1 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h and concentrated under reduced pressure. The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150

mm, 5μm; Mobile Phase A: Water(10MMOL/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 47% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 2-(2-amino-3-fluoropyridin-4-yl)-3-[(3-fluoro-2-methylphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (69.4 mg, 48.21%) as a white solid.

LC-MS: $(M+H)^+$ found: 570.35.

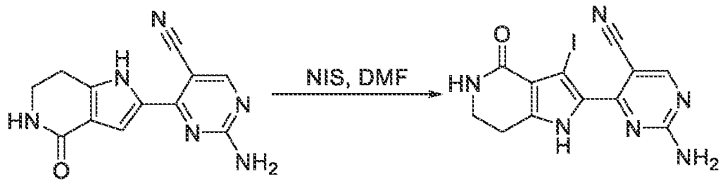
^{1}H NMR (300 MHz, DMSO-d6): δ 11.37 (s, 1H), 7.53 (d, *J* = 5.4 Hz, 1H), 7.17 (d, *J* =20.1 Hz, 2H), 6.81 – 6.73 (m, 1H), 6.55 (t, *J* = 5.1 Hz, 1H), 6.43 (t, *J* = 9.0 Hz, 1H), 6.10 (d, *J* = 9.6 Hz, 3H), 3.42 – 3.38 (m, 2H), 2.83 (t, *J* = 6.9 Hz, 2H), 2.15 (s, 3H).

Example 212. 2-amino-4-[3-[(3-chloro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidine-5-carbonitrile **(compound 693)**



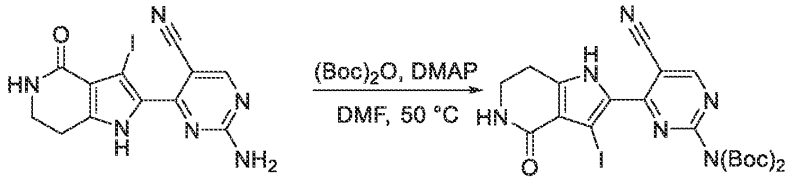
To a stirred solution of 2-amino-4-chloropyrimidine-5-carbonitrile(500 mg, 3.23 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one(1.69 g, 6.47 mmol, 2.00 equiv) in 1,4-dioxane(10.00 mL) and H_2O(2.00 mL) were added K_2CO_3(894 mg, 6.47 mmol, 2.00 equiv) and $Pd(PPh_3)_4$(747 mg, 0.64 mmol, 0.20 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80 °C under nitrogen atmosphere. Desired product could be detected by LCMS. The precipitated solids were collected by filtration and washed with CH_2Cl_2/MeOH = 10/1 (3 x 10 mL). The resulting solid was dried under vacuum to give 2-amino-4-(4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)pyrimidine-5-carbonitrile (600 mg, crude) as a yellow solid.

LC-MS: $(M+H)^+$ found: 255.20.



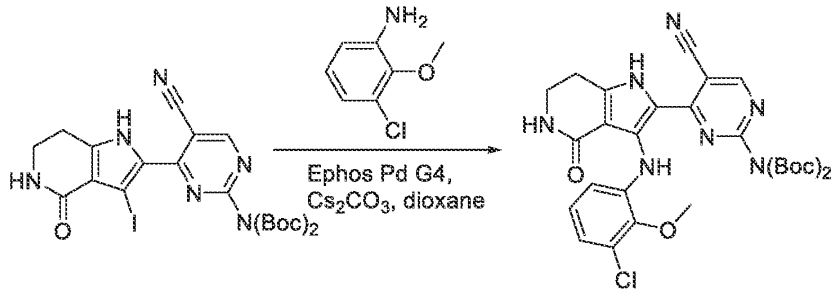
To a stirred solution of 2-amino-4-{4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}pyrimidine-5-carbonitrile (500 mg, 1.96 mmol, 1.00 equiv) in DMF (5.00 mL) was added NIS (663 mg, 2.95 mmol, 1.5 equiv) dropwise at 0°C under argon atmosphere. The resulting mixture was stirred for 2h at 0°C under nitrogen atmosphere. The reaction was quenched by the addition of sat. Na_2SO_3 (aq.) (2 mL) at 0°C. The resulting mixture was filtered, the filter cake was washed with ethyl acetate (3x10 mL). The resulting solid was dried under vacuum to give 2-amino-4-{3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}pyrimidine-5-carbonitrile (230 mg, crude) as a yellow solid.

LC-MS: $(M+H)^+$ found: 380.10.



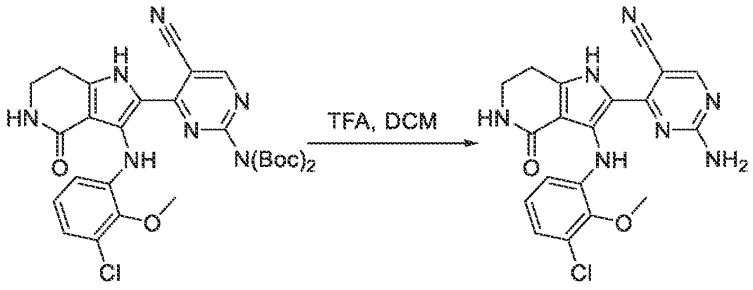
To a stirred solution of 2-amino-4-{3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}pyrimidine-5-carbonitrile (220 mg, 0.57 mmol, 1.00 equiv) in DMF (10 mL) was added $(Boc)_2O$ (315 mg, 1.45 mmol, 2.5 equiv) dropwise at room temperature under argon atmosphere. The resulting mixture was stirred for overnight at 50°C under argon atmosphere. The resulting mixture was extracted with CH_2Cl_2/MeOH (10/1) (3 x 30 mL). The combined organic layers were washed with saturated salt water (3 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 20:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(5-cyano-4-{3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}pyrimidin-2-yl)carbamate (220 mg, 65.50%) as a light yellow oil.

LC-MS: $(M+H)^+$ found: 581.00.



To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(5-cyano-4-{3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}pyrimidin-2-yl)carbamate (200 mg, 0.34 mmol, 1.00 equiv) in DMF (2.00 mL) was added Cs_2CO_3 (336 mg, 1.03 mmol, 3.00 equiv), Cs_2CO_3 (336 mg, 1.03 mmol, 3.00 equiv) dropwise at room temperature under argon atmosphere. The resulting mixture was stirred for 2h at 50°C under argon atmosphere. The resulting mixture was extracted with CH_2Cl_2/MeOH(10:1) (3 x 10mL). The combined organic layers were washed with saturated salt water (1 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(4-{3-[(3-chloro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-5-cyanopyrimidin-2-yl)carbamate (90 mg, 42.81%) as a light yellow oil.

LC-MS: $(M+H)^+$ found: 610.10.



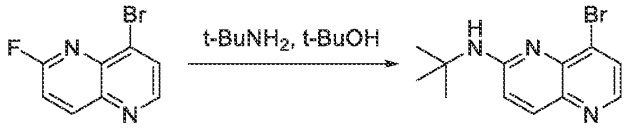
To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-chloro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]-5-cyanopyrimidin-2-yl)carbamate (90 mg, 0.14 mmol, 1.00 equiv) in DCM (2.00 mL) was added TFA (1.00 mL) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred

for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 19*250 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH------Preparative; Flow rate: 25 mL/min; Gradient: 25% B to 38% B in 10 min, 38% B; Wave Length: 254 nm; RT1(min): 8.67) to afford 2-amino-4-[3-[(3-chloro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidine-5-carbonitrile (7.2 mg, 11.31%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 410.00.

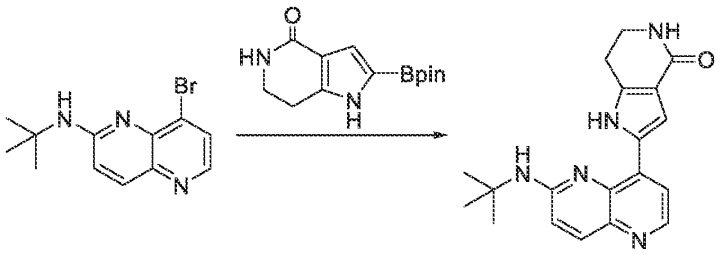
^{1}H NMR (400 MHz, CD_3OD-d_4) δ 9.17 (s, 9H), 7.65-7.56 (m, 1H), 7.31-7.19 (m, 2H), 3.72 (s, 3H), 3.47-3.38 (m, 2H), 2.98-2.88 (m, 2H).

Example 213. 2-[6-(tert-butylamino)-1,5-naphthyridin-4-yl]-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 694)**



To a stirred solution of 8-bromo-2-fluoro-1,5-naphthyridine (500.00 mg, 2.202 mmol, 1.00 equiv) and t-BuOH(4897.13 mg, 66.069 mmol, 30.00 equiv) in tert-butylamine borane(5.00 mL) in portions at degrees 100 C under nitrogen atmosphere. The resulting solid was dried under vacuum to afford 8-bromo-N-tert-butyl-1,5-naphthyridin-2-amine (650 mg,94.81%) as a white solid.

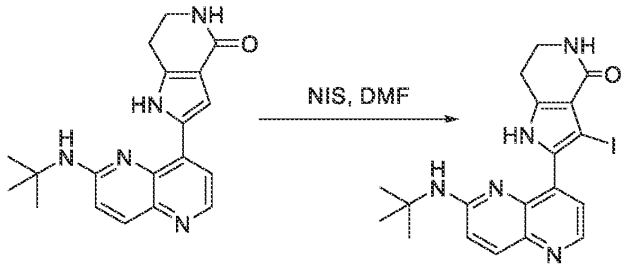
LC-MS: M+H found: 280.0.



To a stirred solution 8-bromo-N-tert-butyl-1,5-naphthyridin-2-amine (600.00 mg, 2.142

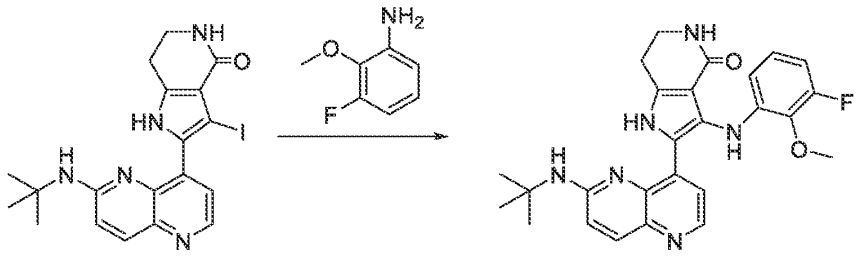
mmol, 1.00 equiv) and TEA (541.76 mg, 5.354 mmol, 2.50 equiv) in DME (14.30 mL) and H2O (0.70 mL) were added Pd(dppf)Cl2(156.70 mg, 0.214 mmol, 0.10 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (842.02 mg, 3.212 mmol, 1.50 equiv) in portions at degrees 80 C under nitrogen atmosphere. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 10:1) to afford 2-[6-(tert-butylamino)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (230 mg, 27.54%) as a yellow solid.

LC-MS: M+H found: 336.0.



A solution of 2-[6-(isopropylamino)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (120.00 mg, 0.373 mmol, 1.00 equiv) and NIS (168.01 mg, 0.747 mmol, 2.00 equiv) in DMF (2.50 mL) was stirred for 2 h at room temperature under nitrogen atmosphere. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 2-[6-(tert-butylamino)-1,5-naphthyridin-4-yl]-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (60 mg, 37.62%) as a brown solid.

LC-MS: M+H found: 462.0.



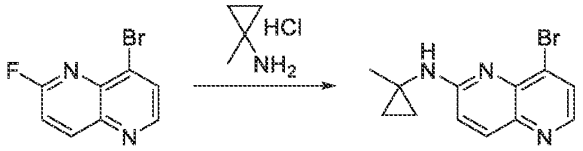
To a stirred solution 2-[6-(tert-butylamino)-1,5-naphthyridin-4-yl]-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c] pyridine -4-one (50.00 mg, 0.108 mmol, 1.00 equiv) and Cs2CO3(70.63 mg, 0.217 mmol, 2.00 equiv) in dioxane(1.00 mL) were added EPhos Pd G4(19.91 mg, 0.022

mmol, 0.20 equiv) and 3-fluoro-2-methoxyaniline(19.89 mg, 0.141 mmol, 1.30 equiv) in portions at degrees 50 C under nitrogen atmosphere. The resulting mixture was stirred for overnight at degrees 50 C under nitrogen atmosphere. The residue was purified by Prep-TLC (CH2Cl2 / MeOH 10:1) to afford 2-[6-(tert-butylamino)-1,5-naphthyridin-4-yl]-3-[(3-fluoro-2-methoxyphenyl) amino]-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (50 mg, 68.05%) as a yellow solid.The crude product (mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10MMOL/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 45% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 2-[6-(tert-butylamino)-1,5-naphthyridin-4-yl]-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50 mg, 68.05%) as a yellow solid.

LC-MS: M+H found: 475.1.

^{1}H NMR (400 MHz, DMSO-d6) δ 13.39 (s, 1H), 8.40 (d, J = 5.9 Hz, 1H), 8.15 – 7.75 (m, 3H), 7.39 (dd, J = 19.5, 12.4 Hz, 3H), 6.81 – 6.51 (m, 2H), 6.09 (d, J = 8.0 Hz, 1H), 4.00 (s, 3H), 3.49 (d, J = 8.4 Hz, 2H), 3.01 (t, J = 6.8 Hz, 2H), 1.58 (s, 9H).

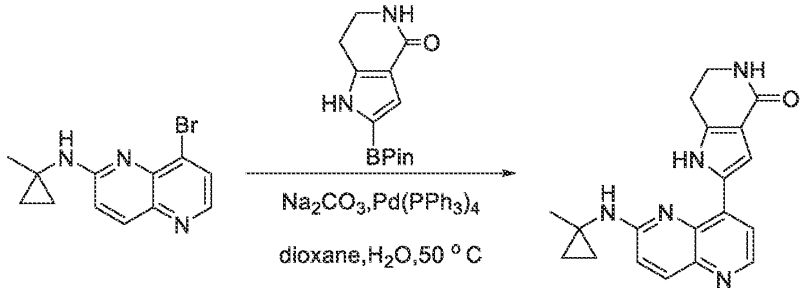
Example 214. 3-[(3-fluoro-2-methoxyphenyl)amino]-2-[6-[(1-methylcyclopropyl)amino]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; formic acid **(compound 695)**



To a stirred solution of 8-bromo-2-fluoro-1,5-naphthyridine (400 mg, 1.762 mmol, 1.00 equiv) and 1-methylcyclopropan-1-amine (626.53 mg, 8.810 mmol, 5 equiv) in t-BuOH (5 mL) were added K2CO3 (1217.48 mg, 8.810 mmol, 5 equiv) at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 5 h at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was diluted with water (15 mL).The aqueous layer was extracted with EtOAc (3x15 mL).The resulting mixture was concentrated under reduced pressure. This resulted in 8-bromo-N-

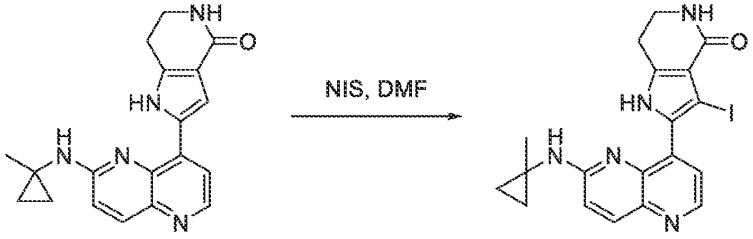
(1-methylcyclopropyl)-1,5-naphthyridin-2-amine (500 mg, 102.03%) as a white solid.

LC-MS: $[M-H]^-$ found: 278.05.



To a solution of 8-bromo-N-(1-methylcyclopropyl)-1,5-naphthyridin-2-amine (300 mg, 1.079 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (424.06 mg, 1.619 mmol, 1.5 equiv) in dioxane (3 mL) and water (0.6 mL) were added Na2CO3 (228.63 mg, 2.158 mmol, 2 equiv) and Pd(PPh3)4 (124.63 mg, 0.108 mmol, 0.1 equiv) . After stirring for overnight at 50 degrees C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (15:1) to afford 2-[6-[(1-methylcyclopropyl)amino]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (420 mg, 116.80%) as a light brown solid.

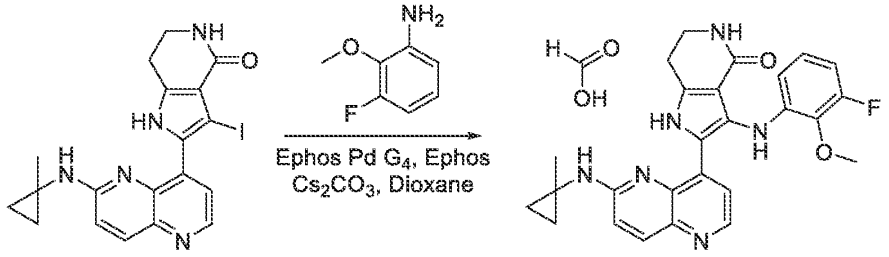
LC-MS: $[M-H]^-$ found: 334.00.



A solution of 2-{6-[(1-methylcyclopropyl)amino]-1,5-naphthyridin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (300 mg, 0.900 mmol, 1.00 equiv) and nis (222.69 mg, 0.990 mmol, 1.1 equiv) in DMF (3 mL) was stirred for overnight at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS.The resulting solution was purified by reverse phase flash with the following conditions (10mmol/L NH4HCO3, 40%ACN to 65%ACN in 20 min) to afford 3-iodo-2-{6-[(1-methylcyclopropyl)amino]-

1,5-naphthyridin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (350 mg, 84.69%) as a light brown solid.

LC-MS: $[M-H]^-$ found: 459.95.

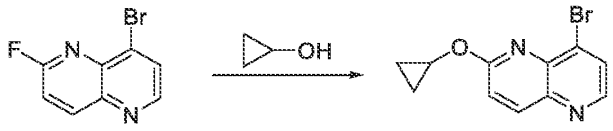


A mixture of 3-iodo-2-[6-[(1-methylcyclopropyl)amino]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (110.00 mg, 0.239 mmol, 1.00 equiv), 3-fluoro-2-methoxyaniline (101.41 mg, 0.718 mmol, 3.00 equiv), Ephos Pd G4 (44.00 mg, 0.048 mmol, 0.20 equiv), Ephos (25.62 mg, 0.048 mmol, 0.20 equiv) and Cs2CO3 (156.07 mg, 0.479 mmol, 2.00 equiv) in 1,4-dioxane (1.00 mL) and DMF (1.00 mL) was stirred for overnight at 50 °C under argon atmosphere.Desired product could be detected by LCMS.The resulting mixture was concentrated under reduced pressure.The crude product (mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 33% B in 9 min, 33% B; Wave Length: 254/220 nm; RT1(min): 7.48) to afford 3-[(3-fluoro-2-methoxyphenyl)amino]-2-[6-[(1-methylcyclopropyl)amino]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; formic acid (30.8 mg, 24.48%) as a orange solid.

LC-MS: $[M+H]^+$ found: 473.10.

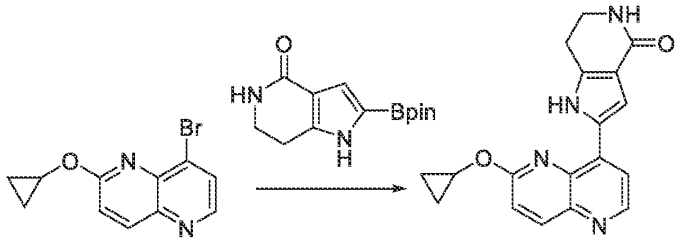
^{1}H NMR (300 MHz, DMSO-d6) δ 14.07 (s, 1H), 8.27 (d, J = 5.1 Hz, 1H), 8.13 (d, J = 15.3 Hz, 2H), 7.99 (d, J = 15.0 Hz, 1H), 7.67 (s, 1H), 7.41 (d, J = 5.1 Hz, 1H), 7.23 (s, 1H), 7.02 (s, 1H), 6.72-6.69 (m, 1H), 6.62-6.56 (m, 1H), 6.05 (d, J = 8.4 Hz, 1H), 3.98 (s, 3H), 3.47-3.44 (m, 2H), 3.00-2.92 (m, 2H), 1.62 (s, 3H), 0.89 (s, 4H).

Example 215. 2-(6-cyclopropoxy-1,5-naphthyridin-4-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid **(compound 696)**



To a stirred solution of 8-bromo-2-fluoro-1,5-naphthyridine (300 mg, 1.32 mmol, 1 equiv) and cyclopropanol (383.73 mg, 6.60 mmol, 5 equiv) in THF (13 mL) was added t-BuOK (444.83 mg, 3.96 mmol, 3 equiv) in portions at 0°C under argon atmosphere. The resulting mixture was stirred for 1h at room temperature under argon atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (100:1) to afford 8-bromo-2-cyclopropoxy-1,5-naphthyridine (360 mg, 99.89%) as an off-white solid.

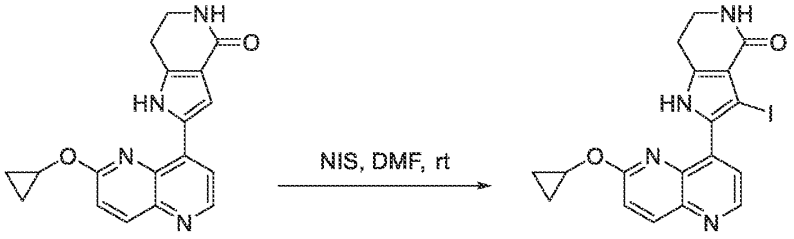
LC-MS: $(M+H)^+$ found: 266.8.



To a stirred mixture of 8-bromo-2-cyclopropoxy-1,5-naphthyridine (670 mg, 2.527 mmol, 1 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (794.93 mg, 3.032 mmol, 1.2 equiv) in DME (4 mL) H_2O (0.1 mL) was added $Pd(dppf)Cl_2.CH_2Cl_2$ (205.88 mg, 0.253 mmol, 0.1 equiv) and TEA (639.35 mg, 6.318 mmol, 2.5 equiv) at room temperature under argon atmosphere. The resulting mixture was stirred for overnight at 50°C under argon atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was extracted with EtOAc (3 x 50mL). The combined organic layers were washed with water (3x10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 2-(6-cyclopropoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (700 mg, 77.86%) as a off-

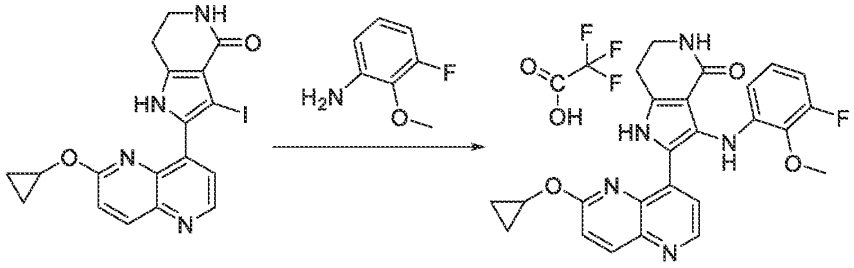
white solid.

LC-MS: $(M+H)^+$ found: 321.1.



To a stirred mixture of 2-(6-cyclopropoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 1.12 mmol, 1 equiv) in DMF (11 mL, 142.14 mmol, 126.48 equiv) was added NIS (303.40 mg, 1.35 mmol, 1.2 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for 2h at room temperature under argon atmosphere. The reaction was monitored by LCMS. The reaction was quenched with sat. sodium sulfite (aq.) at room temperature. The precipitated solids were collected by filtration and washed with water (3x10 mL).

LC-MS: $(M+H)^+$ found: 446.85.



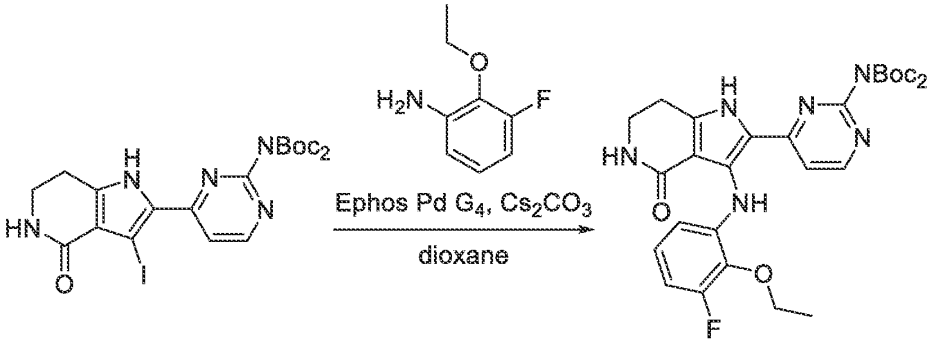
To a stirred mixture of 2-(6-cyclopropoxy-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (200 mg, 0.45 mmol, 1.00 equiv) and 3-fluoro-2-methoxyaniline (75.91 mg, 0.54 mmol, 1.2 equiv) in dioxane (5.00 mL) was added EPhos Pd G4 (41.17 mg, 0.045 mmol, 0.10 equiv) and Cs_2CO_3 (438.08 mg, 1.34 mmol, 3.00 equiv) at room temperature under argon atmosphere. The resulting mixture was stirred for overnight at 50°C under argon atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The crude product (300 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column

30*150mm 5μm, n; Mobile Phase A: Water(0.05%TFA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 40% B in 8 min, 40% B; Wave Length: 254/220 nm; RT1(min): 7.2) to afford 2-(6-cyclopropoxy-1,5-naphthyridin-4-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid (56.3 mg, 21.68%) as an orange solid.

LC-MS: $(M+H)^+$ found: 460.05.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.82 (s, 1H), 8.65 (d, J = 5.5 Hz, 1H), 8.36 (d, J = 9.2 Hz, 1H), 8.05 (s, 1H), 7.52 – 7.43 (m, 2H), 7.40 (s, 1H), 6.73 (td, J = 8.3, 6.1 Hz, 1H), 6.65 (ddd, J = 10.1, 8.4, 1.5 Hz, 1H), 6.07 (dt, J = 8.0, 1.3 Hz, 1H), 4.70 – 4.58 (m, 1H), 3.98 (s, 3H), 3.48 (td, J = 6.8, 2.3 Hz, 2H), 3.01 (t, J = 6.8 Hz, 2H), 0.99 (td, J = 5.2, 4.4, 2.5 Hz, 2H), 0.93 (dq, J = 7.8, 3.5 Hz, 2H).

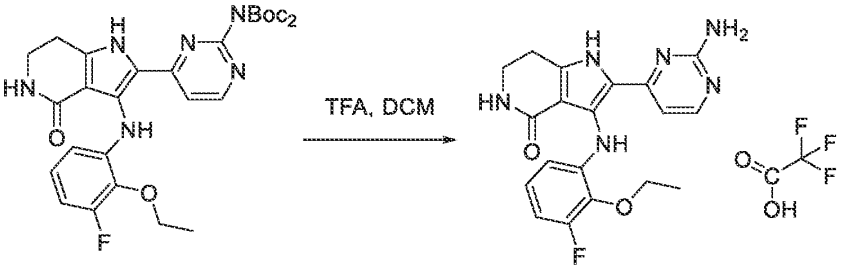
Example 216. 2-(2-aminopyrimidin-4-yl)-3-[(2-ethoxy-3-fluorophenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid **(compound 699)**



To a stirred mixture of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (100.00 mg, 0.180 mmol, 1.00 equiv) and 2-ethoxy-3-fluoroaniline (33.53 mg, 0.216 mmol, 1.20 equiv) in dioxane (1.80 mL) were added Ephos Pd G4 (33.08 mg, 0.036 mmol, 0.20 equiv) and Cs2CO3 (117.33 mg, 0.360 mmol, 2.00 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 50 degrees C under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was filtered, the filter cake was washed with MeOH (3x5 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column

chromatography, eluted with CH2Cl2 / MeOH (50:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(2-ethoxy-3-fluorophenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (66 mg) as a light yellow solid.

LC-MS: M+H found: 583.15.



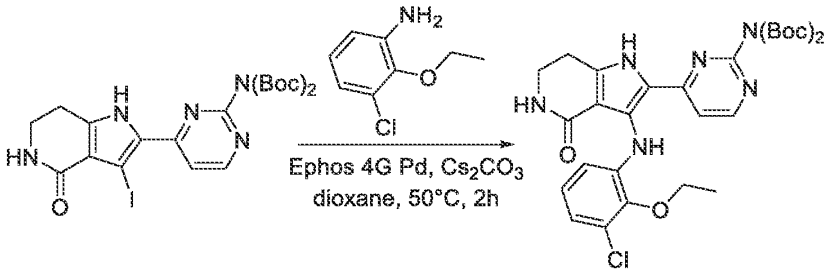
To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(2-ethoxy-3-fluorophenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (66.00 mg, 0.113 mmol, 1.00 equiv) in DCM (1.13 mL) was added TFA (1.13 mL) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water(0.05%TFA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 12% B to 30% B in 8 min, 30% B; Wave Length: 254/220 nm; RT1(min): 8) to afford 2-(2-aminopyrimidin-4-yl)-3-[(2-ethoxy-3-fluorophenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid (34.8mg,61.88%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 383.05.

^{1}H NMR (300 MHz, DMSO-*d*6) δ 12.01 (s, 1H), 8.04 (d, *J* = 6.7 Hz, 1H), 7.62 (s, 2H), 7.31 (s, 1H), 7.00 - 6.05 (m, 4H), 4.13 (q, *J* = 7.0 Hz, 2H), 3.41 (td, *J* = 6.7, 2.5 Hz, 2H), 2.89 (t, *J* = 6.6 Hz, 2H), 1.35 (t, *J* = 7.0 Hz, 3H).

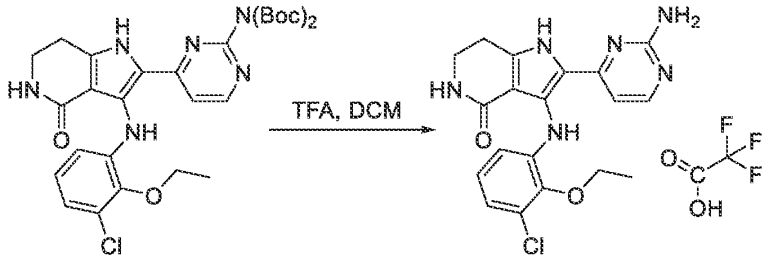
^{19}F NMR (282 MHz, DMSO) δ -73.98, -131.81.

Example 217. 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-ethoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid **(compound 700)**



To a stirred mixture of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (100.00 mg, 0.180 mmol, 1.00 equiv) and 3-chloro-2-ethoxyaniline (30.90 mg, 0.180 mmol, 1 equiv) in 1,4-dioxane (1.80 mL) was added EPhos Pd G4 (33.08 mg, 0.036 mmol, 0.2 equiv) and Cs_2CO_3 (234.67 mg, 0.720 mmol, 4 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 2h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure that was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-chloro-2-ethoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (70 mg, 64.89%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 599.15.



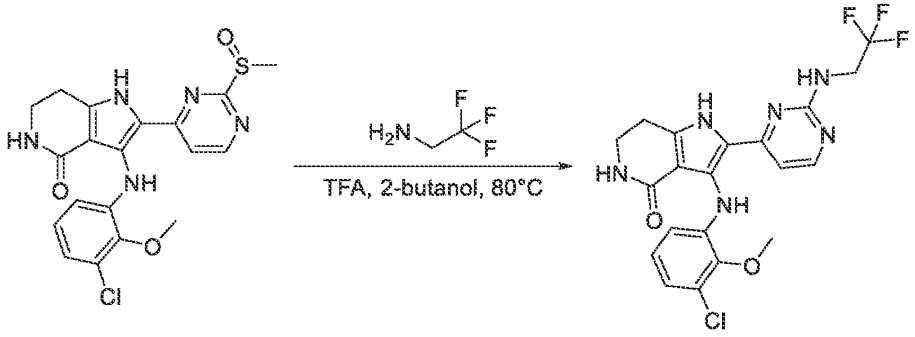
To a stirred mixture of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-chloro-2-ethoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (53.00 mg, 0.088 mmol, 1.00 equiv) in DCM (2 mL) was added TFA (1 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h and concentrated under reduced pressure. The crude product (40 mg) was purified by Prep-

HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm; Mobile Phase A: Water(0.05%TFA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 34% B in 8 min; Wave Length: 254/220 nm; RT1(min): 7.5;) to afford 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-ethoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid (25.2 mg, 55.15%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 399.30.

^{1}H NMR (400 MHz, DMSO-d6): δ 11.94 (s, 1H), 8.46 (s, 1H), 8.03 (d, J = 6.4 Hz, 1H), 7.30 (s, 2H), 7.26 (s, 1H), 6.91 – 6.84 (m, 2H), 6.62 – 6.53 (m, 2H), 6.11 – 6.06 (m, 2H), 3.42 – 3.39 (m, 2H), 2.87 (t, J = 6.6 Hz, 2H), 1.38 (t, J = 3.5 Hz, 3H).

Example 218. **3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-[(2,2,2-trifluoroethyl)amino]pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one** (compound 701)



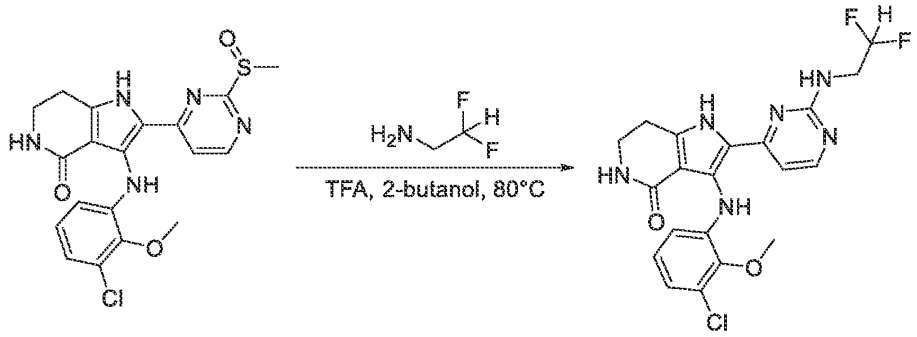
Into a 8-mL sealed tube, was placed 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (130.00 mg, 0.301 mmol, 1.00 equiv), 2-butanol (3.00 mL), 2,2,2-trifluoroethylamine (178.89 mg, 1.806 mmol, 6.00 equiv), TFA (68.64 mg, 0.602 mmol, 2.00 equiv). The resulting solution was stirred overnight at 80 degrees C. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product (130 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH F-Phenyl OBD column, 19*250 mm, 5μm; Mobile Phase A: Water(0.05%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min;

Gradient: 25% B to 35% B in 10 min, 35% B; Wave Length: 254 nm; RT1(min): 8.83) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-[(2,2,2-trifluoroethyl)amino]pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (55.6 mg, 38.62%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 467.05.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.89 (s, 1H), 8.14 (d, J = 5.8 Hz, 1H), 7.94 (s, 1H), 7.28 (s, 1H), 6.91 - 6.78 (m, 2H), 6.62 (d, J = 5.8 Hz, 1H), 6.37 (dd, J = 6.5, 3.1 Hz, 1H), 4.36 - 4.24 (m, 2H), 3.89 (s, 3H), 3.43 (dt, J = 6.3, 3.8 Hz, 2H), 2.93 (t, J = 6.8 Hz, 2H).

Example 219. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-[(2,2-difluoroethyl)amino]pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 702)**



Into a 8-mL sealed tube, was placed 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (150.00 mg, 0.347 mmol, 1.00 equiv), 2-butanol (3.50 mL), 2,2-difluoroethanamine (281.54 mg, 0.000 mmol, 10.00 equiv), TFA (118.80 mg, 1.041 mmol, 3.00 equiv). The resulting solution was stirred overnight at 80 degrees C. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 33% B in 8 min; Wave Length: 254/220 nm; RT1(min): 7.9;) to afford 3-[(3-chloro-2-

methoxyphenyl)amino]-2-[2-[(2,2-difluoroethyl)amino]pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (23.9 mg, 14.89%) as a yellow solid.

LC-MS: $(M+H)^+$ found 449.05.

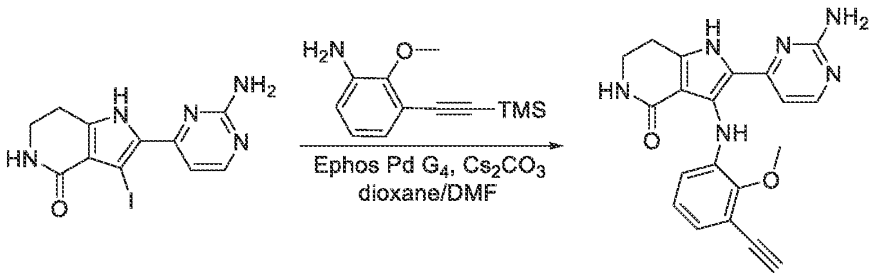
^{1}H NMR (300 MHz, DMSO-d6) δ 11.66 (s, 1H), 8.17 - 8.07 (m, 1H), 7.76 (s, 1H), 7.18 (d, J = 2.7 Hz, 2H), 6.88 - 6.73 (m, 2H), 6.53 (d, J = 5.3 Hz, 1H), 6.37 - 6.22 (m, 1H), 6.07 (t, J = 4.3 Hz, 1H), 3.89 (s, 3H), 3.76 (dq, J = 15.2, 5.0 Hz, 2H), 3.42 (td, J = 6.8, 2.5 Hz, 2H), 2.89 (t, J = 6.7 Hz, 2H).

Example 220. 2-(2-aminopyrimidin-4-yl)-3-[(3-ethynyl-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 703)**



To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (200.00 mg,) in DCM （3mL） was added TFA (1.5 mL) dropwise at room temperature under air. The resulting mixture was stirred for 1h at room temperature . Desired product could be detected by LCMS. The resulting mixture was concentrated under vacuum. The residue was basified with saturated NaHCO3 (aq.). The resulting mixture was extracted with CH2Cl2:MeOH (3 x 20mL) to give 2-(2-aminopyrimidin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (69 mg) as brown solid.

LC-MS: $(M+H)^+$ found: 356.05.



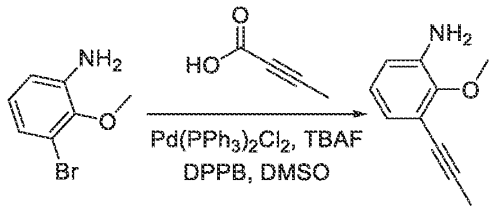
To a solution of 2-(2-aminopyrimidin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-

4-one (60.00 mg, 0.113 mmol, 1.00 equiv) in dioxane (1.00 mL) and DMF (1.00 mL) was added 2-methoxy-3-[2-(trimethylsilyl)ethynyl]aniline (37.06 mg, 0.169 mmol, 1.5 equiv), Ephos Pd G4 (31.04 mg, 0.034 mmol, 0.30 equiv), Cs_2CO_3 (73.40 mg, 0.225 mmol, 2 equiv) in sequence. Desired product could be detected by LC-MS after 3 hours. The reaction mixture was concentrated under vacuum and purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1). The crude product (40mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 45% B in 7 min, 45% B; Wave Length: 254 nm; RT1(min): 6.5) to afford 2-(2-aminopyrimidin-4-yl)-3-[(3-ethynyl-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (3.2 mg, 7.21%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 375.10.

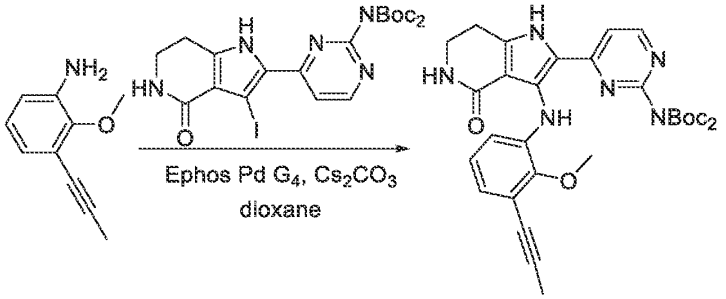
^{1}H NMR (400 MHz, CD3OD) δ 7.95 (d, 1H), 6.81 (m, 2H), 6.51 (m, 2H), 4.10(s, 3H), 3.55 (t, 2H), 2.97 (t, 2H).

Example 221. 2-(2-aminopyrimidin-4-yl)-3-[[2-methoxy-3-(prop-1-yn-1-yl)phenyl]amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 704)**



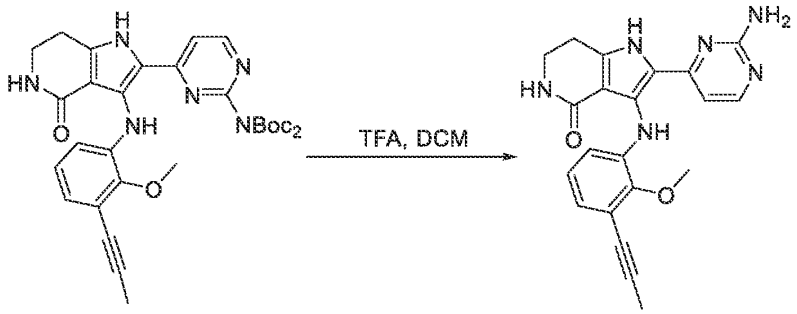
Into a 8-mL vial purged and maintained with an inert atmosphere of argon, was placed 3-bromo-2-methoxyaniline (250.00 mg, 1.237 mmol, 1.00 equiv), DMSO (2.50 mL), $Pd(PPh_3)_2Cl_2$ (86.85 mg, 0.124 mmol, 0.1 equiv), DPPB (121.37 mg, 0.285 mmol, 0.23 equiv), 2-butynoic acid (104.03 mg, 1.237 mmol, 1 equiv), TBAF (647.02 mg, 2.475 mmol, 2 equiv). The resulting solution was stirred for 2 hours at 110 degrees C. Desired product could be detected by LCMS. The resulting mixture was diluted with EtOAc (50 mL). The resulting mixture was washed with 50 mL of sat. NH_4Cl (aq.). The resulting mixture was washed with 50 mL of water. The residue was purified by Prep-TLC (PE/EtOAc 4:1) to afford 2-methoxy-3-(prop-1-yn-1-yl)aniline (170 mg, 68.18%) as a light yellow oil.

LC-MS: $(M+H)^+$ found: 162.



Into a 8-mL vial purged and maintained with an inert atmosphere of argon, was placed tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (100.00 mg, 0.180 mmol, 1.00 equiv), dioxane (1.50 mL), 2-methoxy-3-(prop-1-yn-1-yl)aniline (43.54 mg, 0.270 mmol, 1.5 equiv), Ephos Pd G4 (33.08 mg, 0.036 mmol, 0.20 equiv), Cs_2CO_3 (117.33 mg, 0.360 mmol, 2.00 equiv). The resulting solution was stirred for 4 hours at 50 degrees C. Desired product could be detected by LCMS. The resulting mixture was filtered, the filter cake was washed with MeOH (2x10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 30:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-[4-(3-[[2-methoxy-3-(prop-1-yn-1-yl)phenyl]amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl)pyrimidin-2-yl]carbamate (70 mg, 62.74%) as a red oil.

LC-MS $(M+H)^+$ found: 589.



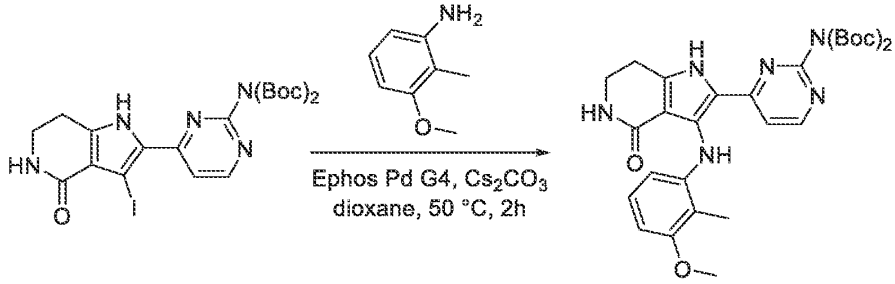
Into a 50-mL round-bottom flask, was placed tert-butyl N-(tert-butoxycarbonyl)-N-[4-(3-[[2-methoxy-3-(prop-1-yn-1-yl)phenyl]amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl)pyrimidin-2-yl]carbamate (70.00 mg, 0.119 mmol, 1.00 equiv), DCM (2.50 mL), TFA (2.50 mL). The resulting solution was stirred for 2 hours at room

temperature.Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10MMOL/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 18% B to 48% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5;) to afford 2-(2-aminopyrimidin-4-yl)-3-[[2-methoxy-3-(prop-1-yn-1-yl)phenyl]amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (26.6 mg, 55.86%) as a white solid.

LC-MS $(M+H)^+$ found: 389.

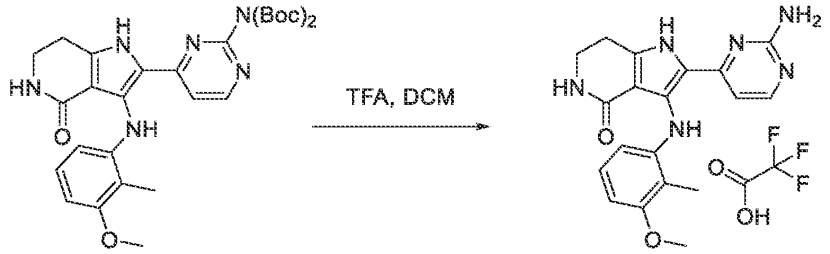
^{1}H NMR (300 MHz, DMSO-d6) 11.61 (s, 1H), 8.05-8.03 (m, 1H), 7.94 (s, 1H), 7.15 (s, 1H), 7.29 (s, 1H), 6.78-6.69 (d, 2H), 6.44-6.36 (d, 2H), 6.18 (s, 2H), 3.95 (s, 3H), 3.39-3.37 (d, 2H), 2.86-2.82 (t, 2H), 2.09 (s, 3H).

Example 222. 2-(2-aminopyrimidin-4-yl)-3-[(3-methoxy-2-methylphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 705)**



To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (100 mg, 0.18 mmol, 1.00 equiv) in dioxane (2.00 mL) were added Cs_2CO_3 (117 mg, 0.36 mmol, 2 equiv), Ephos Pd G4 (33 mg, 0.036 mmol, 0.2 equiv) and 3-methoxy-2-methylaniline (30 mg, 0.22 mmol, 1.20 equiv). The mixture was stirred for 2 h at 50 degrees C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH 15:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-methoxy-2-methylphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (59 mg, 58.03%) as a yellow oil.

LC-MS: $(M+H)^+$ found: 565.20.

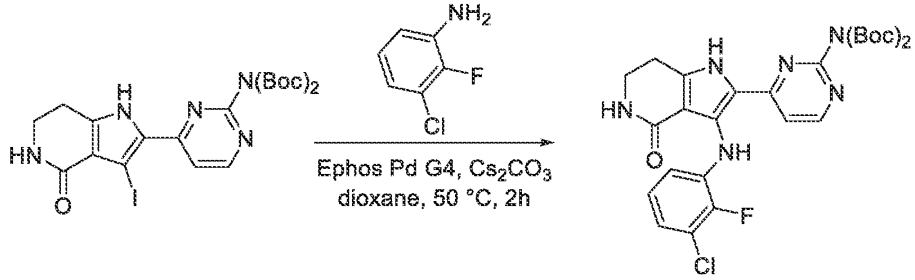


To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-methoxy-2-methylphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate) in DCM (2.00 mL) was added TFA (1.00 mL) in portions. The mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The crude product (mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm; Mobile Phase A: Water(0.05%TFA), Mobile Phase B: MeOH; Flow rate: 60 mL/min; Gradient: 23% B to 49% B in 8 min; Wave Length: 254/220 nm; RT1(min): 8;) to afford 2-(2-aminopyrimidin-4-yl)-3-[(3-methoxy-2-methylphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid (31.5mg, 60.68%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 365.10.

^{1}H NMR (300 MHz, Methanol-d4): δ 7.68 (d, J = 7.2 Hz, 1H), 6.94 (t, J = 8.4 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 8.1 Hz, 2H), 3.82 (s, 3H), 3.60 – 3.54 (m, 2H), 3.01 – 2.97 (m, 2H), 2.23 (s, 3H).

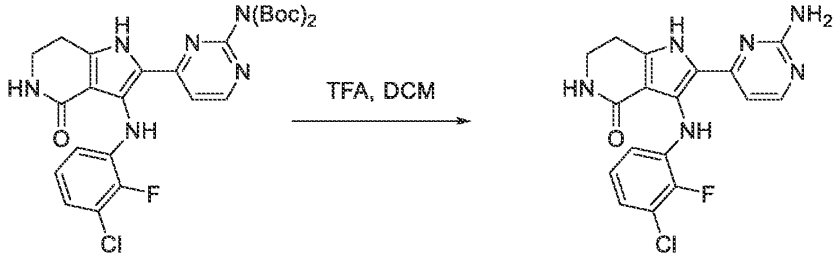
Example 223. 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-fluorophenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 706)**



To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-iodo-4-oxo-

1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (100 mg, 0.18 mmol, 1.00 equiv) in Dioxane (2.00 mL) was added Cs_2CO_3 (118 mg, 0.36 mmol, 2.00 equiv), Ephos Pd G4 (33 mg, 0.04 mmol, 0.20 equiv) and 3-chloro-2-fluoroaniline (26 mg, 0.18 mmol, 1.00 equiv). The mixture was stirred for 2 h at 50 degrees C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH 15:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-chloro-2-fluorophenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (65 mg, 63.00%) as a yellow oil.

LC-MS: $(M+H)^+$ found: 573.15.



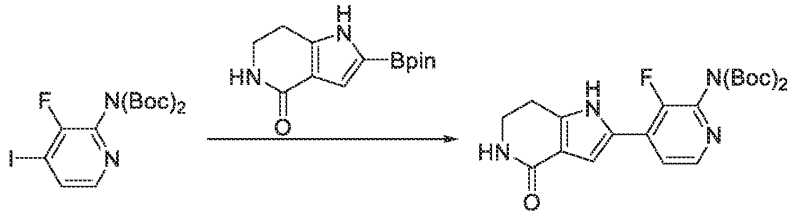
To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-chloro-2-fluorophenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (65 mg, 0.11 mmol, 1.00 equiv) in DCM (2.00 mL) was added TFA (1.00 mL) in portions. The mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product (40 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH F-Phenyl OBD column, 19*250 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH--Preparative; Flow rate: 25 mL/min; Gradient: 56% B to 68% B in 7 min, 68% B; Wave Length: 254 nm; RT1(min): 6.42) to afford 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-fluorophenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (7.9 mg, 17.75%) as a white solid.

LC-MS: $(M+H)^+$ found: 373.00.

^1H NMR (400 MHz, DMSO-d6): δ 11.71 (s, 1H), 8.25 (s, 1H), 8.10 (d, J = 5.4 Hz, 1H),

7.11 (s, 1H), 6.89 – 6.82 (m, 2H), 6.63 (d, J = 5.4 Hz, 1H), 6.57 – 6.52 (m, 1H), 6.29 (s, 2H), 3.41 – 3.34 (m, 2H), 2.84 (t, J = 6.7 Hz, 2H).

Example 224. 2-(2-amino-3-fluoropyridin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid **(compound 686)**



To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(3-fluoro-4-iodopyridin-2-yl)carbamate (1.00 g, 2.28 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.20 g, 4.56 mmol, 2.00 equiv) in dioxane (20.00 mL) were added Na_2CO_3 (725 mg, 6.84 mmol, 3.00 equiv) and $Pd(PPh_3)_4$ (263 mg, 0.22 mmol, 0.10 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added H_2O (4.00 mL) dropwise at room temperature. The resulting mixture was stirred for additional overnight at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(3-fluoro-4-[4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyridin-2-yl)carbamate (890 mg, 87.36%) as a grey solid.

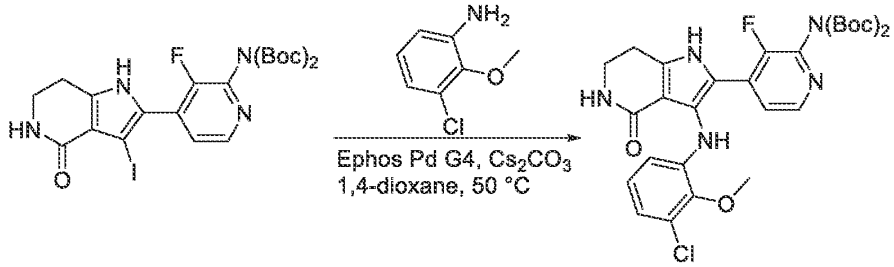
LC-MS: $(M+H)^+$ found: 477.20.



To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(3-fluoro-4-[4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyridin-2-yl)carbamate (690 mg, 1.54 mmol, 1.00 equiv) in DMF (15.00 mL) was added N-iodosuccinimide (382 mg, 1.70 mmol, 1.10 equiv) dropwise at room temperature under nitrogen atmosphere. The reaction was

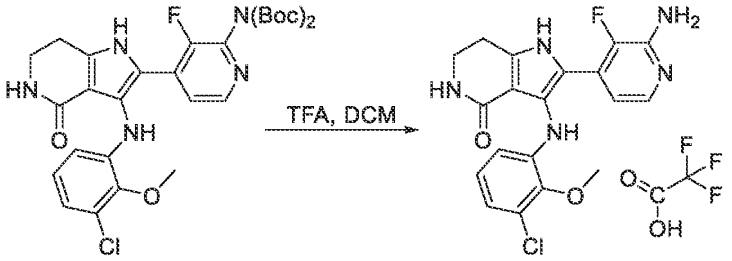
monitored by LCMS. LCMS showed the reaction was completed. The reaction was quenched by the addition of Na_2SO_3 (10mL) at room temperature. The mixture was neutralized to pH 7 with saturated Na2CO3 (aq.). The resulting mixture was extracted with CH_2Cl_2:MeOH (3 x 100mL). The combined organic layers were washed with brine (2x300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (10:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(3-fluoro-4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyridin-2-yl)carbamate (317 mg, 35.84%) as an off-white solid.

LC-MS: $(M+H)^+$ found: 573.1.



To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(3-fluoro-4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyridin-2-yl)carbamate (100 mg, 0.17 mmol, 1.00 equiv) in dioxane (1.80 mL) was added Cs_2CO_3 (113 mg, 0.34 mmol, 2.00 equiv) and EPhos Pd G4 (32 mg, 0.03 mmol, 0.20 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added 3-chloro-2-methoxyaniline (27 mg, 0.17 mmol, 1.00 equiv) in portions at room temperature. The resulting mixture was stirred for additional 3h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-chloro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]-3-fluoropyridin-2-yl)carbamate (50 mg, 47.53%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 602.05.

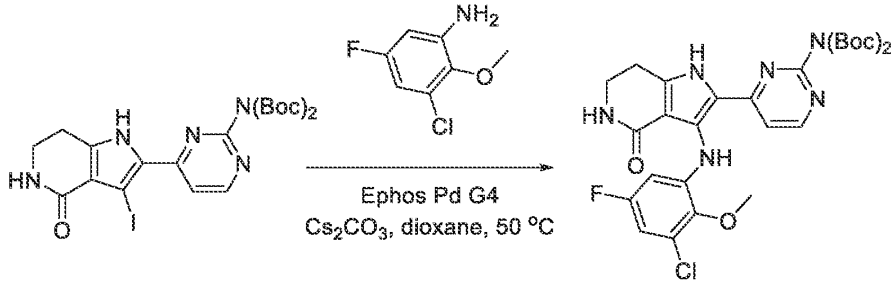


To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-chloro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]-3-fluoropyridin-2-yl)carbamate (50 mg, 0.08 mmol, 1.00 equiv) in DCM (1.00 mL) was added TFA (1.00 mL) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The crude product (33mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm; Mobile Phase A: Water(0.05%TFA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 13% B to 30% B in 8 min; Wave Length: 254/220 nm; RT1(min): 7.42;) to afford 2-(2-amino-3-fluoropyridin-4-yl)-3-[(3-chloro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid (14.8mg,34.55%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 402.

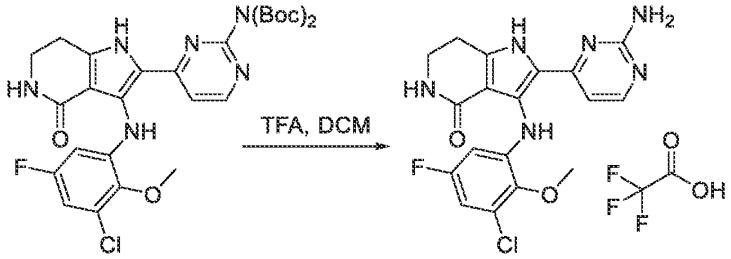
^{1}H NMR (400 MHz, DMSO-d6) δ 11.67 (s, 1H), 7.71 – 7.62 (m, 4H), 7.26 (s, 1H), 6.79 – 6.72 (m, 3H), 6.23-6.20 (m, 1H), 3.87 (s, 3H), 3.43-3.39 (m, 2H), 2.87 (t, J = 8.0 Hz, 2H).

Example 225. 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-5-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid **(compound 714)**



To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (100 mg, 0.18 mmol, 1.00 equiv) in dioxane (2.00 mL) was added EPhos Pd G4 (33 mg, 0.03 mmol, 0.20 equiv) and Cs_2CO_3 (117 mg, 0.36 mmol, 2.00 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added 3-chloro-5-fluoro-2-methoxyaniline (31 mg, 0.18 mmol, 1.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 2h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH 10:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-chloro-5-fluoro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (96 mg, 88.41%) as a brown solid.

LC-MS: $(M+H)^+$ found: 603.05.



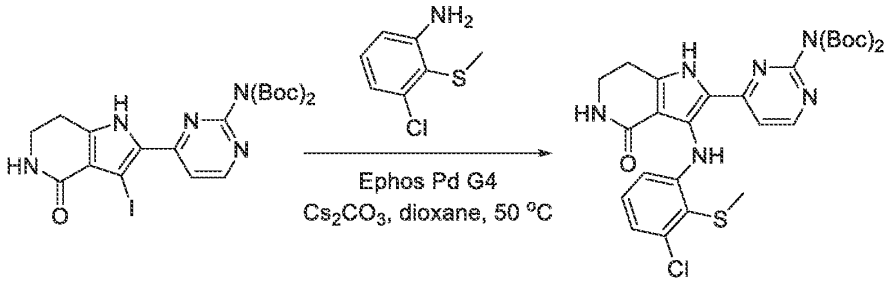
To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-chloro-5-fluoro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (60 mg, 0.09 mmol, 1.00 equiv) in DCM (1.00 mL) was added TFA (1.00 mL) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 2h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The crude product (55 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water(0.05%TFA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 30% B in 8 min, 30% B; Wave Length: 254/220 nm; RT1(min): 7.43) to afford 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-5-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-

pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid (37.7 mg, 73.31%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 403.

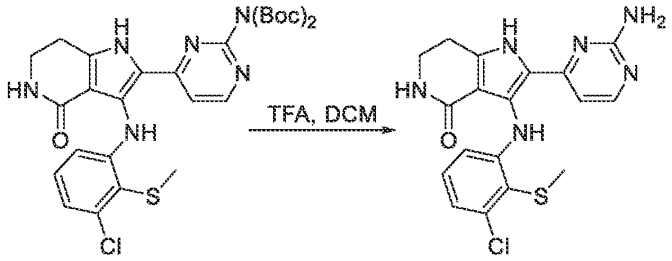
^{1}H NMR (400 MHz, DMSO-d6) δ 12.07 (s, 1H), 8.54 (s, 1H), 8.10 (d, *J* = 4 Hz, 1H), 7.43 – 7.27 (m, 3H), 6.81 – 6.78 (m, 2H), 6.30-6.26 (m, 1H), 3.83 (s, 3H), 3.43-3.39 (m, 2H), 2.89 (t, *J* = 4 Hz, 2H).

Example 226. 2-(2-aminopyrimidin-4-yl)-3-[[3-chloro-2-(methylsulfanyl)phenyl]amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 715)**



To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (100 mg, 0.18 mmol, 1.00 equiv) in dioxane (2.00 mL) was added EPhos Pd G4 (33 mg, 0.03 mmol, 0.20 equiv) and Cs_2CO_3 (117 mg, 0.36 mmol, 2.00 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added 3-chloro-2-(methylsulfanyl)aniline (31 mg, 0.18 mmol, 1.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 2h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-[4-(3-[[3-chloro-2-(methylsulfanyl)phenyl]amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl)pyrimidin-2-yl]carbamate (42 mg, 38.80%) as a brown solid.

LC-MS: $(M+H)^+$ found: 601.05.

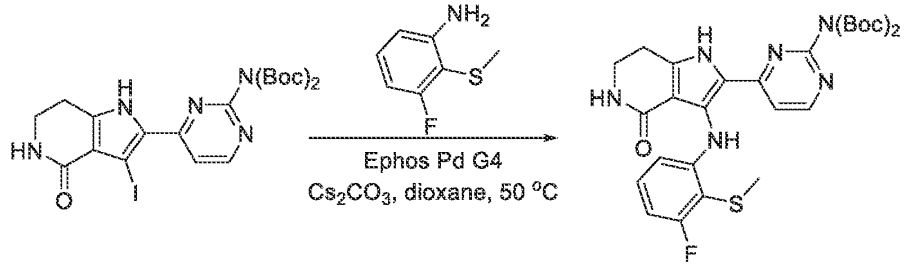


To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-[4-(3-[[3-chloro-2-(methylsulfanyl)phenyl]amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl)pyrimidin-2-yl]carbamate (42 mg, 0.07 mmol, 1.00 equiv) in DCM (1.00 mL) was added TFA (1.00 mL) dropwise at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for additional 1h at room temperature. The reaction was monitored by LCMS. LCMS showed the reaction was completed.The resulting mixture was concentrated under reduced pressure. The crude product (24mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30¡Á150mm 5um; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 52% B in 7 min, 52% B; Wave Length: 254 nm; RT1(min): 6.5) to afford 2-(2-aminopyrimidin-4-yl)-3-[[3-chloro-2-(methylsulfanyl)phenyl]amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.4 mg, 5.00%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 401.

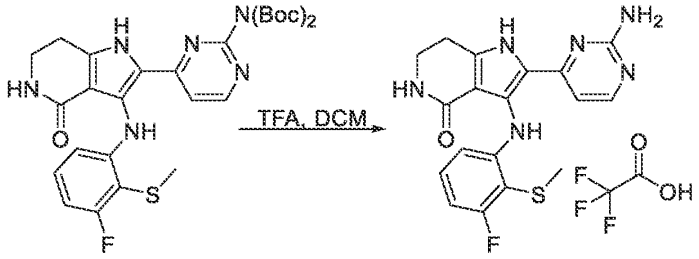
^{1}H NMR (400 MHz, DMSO-d6) δ 11.71 (s, 1H), 8.60 (s, 1H), 8.06 (d, *J* = 4.0 Hz, 1H), 7.13 (s, 1H), 7.05 (t, *J* = 8.0 Hz, 1H), 6.87-6.85 (m, 1H), 6.48 (d, *J* = 4.0Hz, 1H), 6.43-6.40 (m, 1H), 6.20 (s, 2H), 3.40 – 3.33(m, 2H), 2.84 (t, *J* = 8.0 Hz, 2H), 2.39 (s, 3H).

Example 227. 2-(2-aminopyrimidin-4-yl)-3-[[3-fluoro-2-(methylsulfanyl)phenyl]amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid **(compound 716)**



To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (100 mg, 0.18 mmol, 1.00 equiv) in dioxane (1.80 mL) was added EPhos Pd G4 (33 mg, 0.03 mmol, 0.20 equiv) and Cs_2CO_3 (117 mg, 0.36 mmol, 2.00 equiv) in portions at room temperature under nitrogen atmosphere. To the above mixture was added 3-fluoro-2-(methylsulfanyl)aniline (84mg, 0.54 mmol, 3.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 3h at 50 degrees C. The reaction was monitored by LCMS. LCMS showed the reaction was completed. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-[4-(3-[[3-fluoro-2-(methylsulfanyl)phenyl]amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl)pyrimidin-2-yl]carbamate (90 mg, 85.49%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 585.



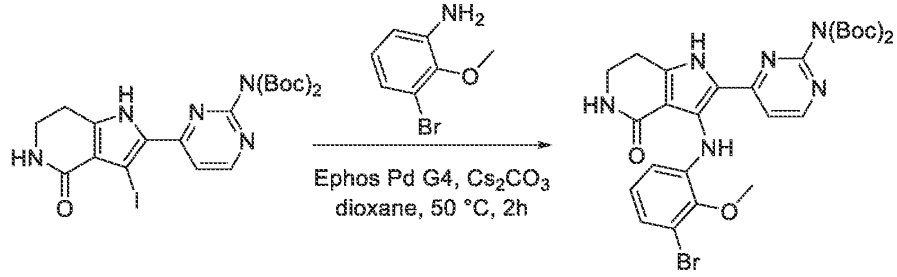
To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-[4-(3-[[3-fluoro-2-(methylsulfanyl)phenyl]amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl)pyrimidin-2-yl]carbamate (90 mg, 0.15mmol, 1.00 equiv) in DCM (1.00 mL) was added TFA (1.00 mL) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. LCMS showed the reaction was completed.The resulting mixture was concentrated under vacuum. The crude product (60mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water(0.05%TFA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 12% B to 30% B in 8 min, 30% B; Wave Length: 254/220 nm; RT1(min): 7.7) to afford 2-(2-aminopyrimidin-4-yl)-3-[[3-fluoro-2-

(methylsulfanyl)phenyl]amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid (45.5 mg, 59.30%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 385.

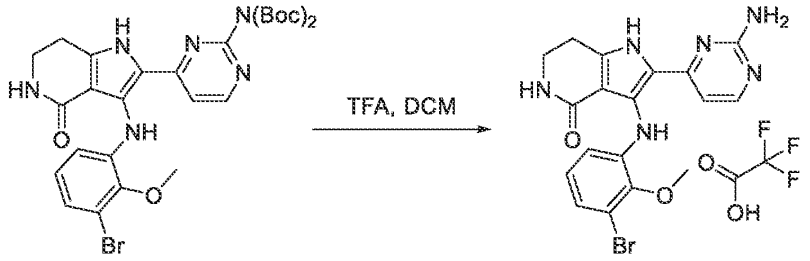
^{1}H NMR (400 MHz, DMSO-d6) δ 12.06 (s, 1H), 8.95 (s, 1H), 8.06 (d, *J* = 4 Hz, 1H), 7.43 (s, 2H), 7.27 (s, 1H), 7.15-7.09 (m, 1H), 6.72 – 6.67 (m, 2H), 6.46 (d, *J* = 8.0 Hz, 1H), 3.43-3.41 (m, 2H), 2.90 (t, *J* = 8.0 Hz, 2H), 2.38 (s, 3H).

Example 228. 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-fluorophenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 717)**



To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (100 mg, 0.18 mmol, 1.00 equiv) in Dioxane (2.00 mL) was added Cs_2CO_3 (118 mg, 0.36 mmol, 2.00 equiv), Ephos Pd G4 (33 mg, 0.04 mmol, 0.20 equiv) and 3-chloro-2-fluoroaniline (26 mg, 0.18 mmol, 1.00 equiv). The mixture was stirred for 2 h at 50 degrees C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH 15:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-chloro-2-fluorophenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (65 mg, 63.00%) as a yellow oil.

LC-MS: $(M+H)^+$ found: 573.15.

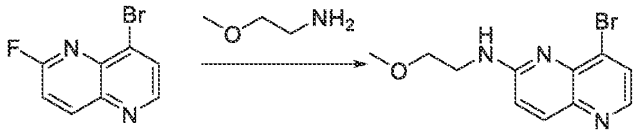


To a stirred solution of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-chloro-2-fluorophenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (65 mg, 0.11 mmol, 1.00 equiv) in DCM (2.00 mL) was added TFA (1.00 mL) in portions. The mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product (40 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH F-Phenyl OBD column, 19*250 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH-----Preparative; Flow rate: 25 mL/min; Gradient: 56% B to 68% B in 7 min, 68% B; Wave Length: 254 nm; RT1(min): 6.42) to afford 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-2-fluorophenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (7.9 mg, 17.75%) as a white solid.

LC-MS: $(M+H)^+$ found: 373.00.

^{1}H NMR (400 MHz, DMSO-d6): δ 11.71 (s, 1H), 8.25 (s, 1H), 8.10 (d, J = 5.4 Hz, 1H), 7.11 (s, 1H), 6.89 – 6.82 (m, 2H), 6.63 (d, J = 5.4 Hz, 1H), 6.57 – 6.52 (m, 1H), 6.29 (s, 2H), 3.41 – 3.34 (m, 2H), 2.84 (t, J = 6.7 Hz, 2H).

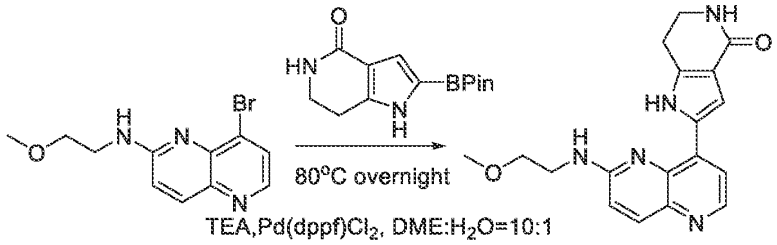
Example 229. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(2-methoxyethyl)amino]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; formic acid **(compound 680)**



A solution of 8-bromo-2-fluoro-1,5-naphthyridine (100.00 mg, 0.440 mmol, 1.00 equiv) in

tert-butanol (4.00 mL) was treated with ethanamine, 2-methoxy- (264.67 mg, 3.528 mmol, 8.00 equiv) under Argon atmosphere. The resulting mixture was stirred for 1.5 hours at 100 degrees C under Argon atmosphere. Tert-BuOH was removed under reduced pressure and the residue was purified by silica gel column chromatography, eluted with DCM:CH_3OH = 98:2 to afford 8-bromo-N-(2-methoxyethyl)-1,5-naphthyridin-2-amine (110 mg, 88.52%) as a white solid.

LC-MS: $(M+H)^+$ found: 282 and 284.



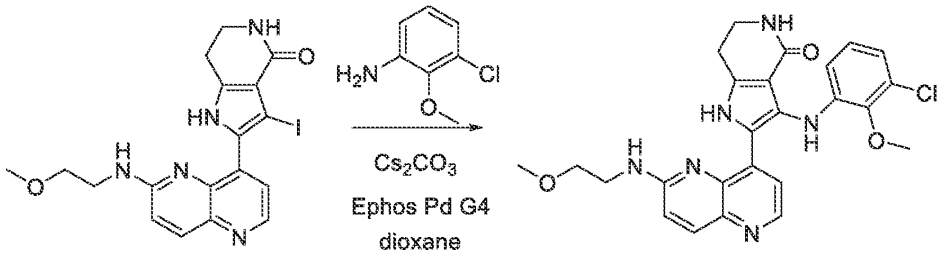
To a solution of 8- bromo-N-(2-methoxyethyl)-1,5-naphthyridin-2-amine (200.00 mg, 0.710 mmol, 1.00 equiv), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (460.00 mg, 1.770 mmol, 2.50 equiv) and triethylamine (180.00 mg, 1.770 mmol, 2.50 equiv) in DME:H_2O=10:1 was added Pd(dppf)Cl_2 CH_2Cl_2 (58.00 mg, 0.070 mmol, 0.10 equiv) inone portion under Argon atmosphere. The resulting mixture was stirred for 10 hours at 80 degrees C under Argon atmosphere. The mixture was evaporated to remove DME and resolved with CH_3OH:DCM=1:1. The residue was purified by Prep-TLC (DCM:CH_3OH=10:1) to afford 2-[6-[(2-methoxyethyl)amino]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one(210.00 mg, 0.623 mmol, 87.7%) as a brown solid.

LC-MS: $(M+H)^+$ found: 338.



To a stirred solution of 2-[6-[(2-methoxyethyl)amino]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100.00 mg, 0.297 mmol, 1.00 equiv) in DMF (3.00 mL) was added NIS (80.00 mg, 0.356 mmol, 1.20 equiv) dropwise by two times at 0 degrees C under Argon atmosphere. The resulting mixture was stirred for 2 hours at room temperature under Argon atmosphere. The reaction mixture was then quenched by NaHSO3(aq) until no more precipitate formed. The precipitate was collected by filtration, washed with excess amount of water and dried under vacuum to afford 3-iodo-2-[6-[(2-methoxyethyl)amino]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (120 mg, 87.39%) as a brown solid.

LC-MS: LC-MS: $(M+H)^+$ found: 464.



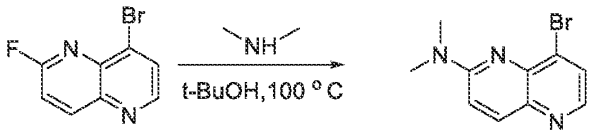
To a solution of 33-iodo-2-[6-[(2-methoxyethyl)amino]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (200.00 mg, 0.432 mmol, 1.00 equiv), 3-chloro-2-methoxyaniline (68.04 mg, 0.432 mmol, 1.00 equiv) and Ephos Pd G4 (79.31 mg, 0.086 mmol, 0.20 equiv) in dioxane (4.00 mL) was added cesium carbonate (281.32 mg, 0.864 mmol, 2.00 equiv) in one portion under Argon atmosphere. The resulting mixture was stirred for 10 hours at 50 degrees C under Argon atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC DCM:CH3OH=10:1. The crude product was purified by Prep-HPLC(Column: Xselect CSH C18 OBD Column 30*150mm 5μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 30% B in 9 min; Wave Length: 254/220 nm; RT1(min): 8.07;) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[6-[(2-methoxyethyl)amino]-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; formic acid (16 mg, 6.88%) as a orange solid.

LC-MS: LC-MS: $(M+H)^+$ found: 540.

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 8.41 – 8.16 (m, 2H), 7.94 (d, J = 9.2 Hz,

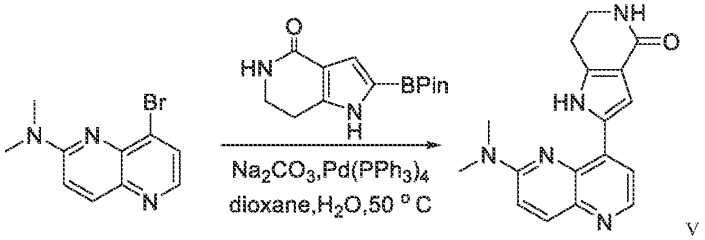
1H), 7.87 – 7.78 (m, 1H), 7.74 (s, 1H), 7.38 (d, J = 5.0 Hz, 1H), 7.23 – 7.03 (m, 2H), 6.31 – 6.02 (m, 1H), 3.90 (s, 3H), 3.66 (d, J = 11.8 Hz, 3H), 3.46 (td, J = 6.8, 2.5 Hz, 2H), 3.33 (s, 3H), 2.94 (t, J = 6.8 Hz, 2H).

Example 230. 2-[6-(dimethylamino)-1,5-naphthyridin-4-yl]-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 697)**



A mixture of 8-bromo-2-fluoro-1,5-naphthyridine (500 mg, 2.20 mmol, 1.00 equiv) and dimethylamine (794 mg, 17.6 mmol, 8.00 equiv) in tert-butanol (20.0 mL) was stirred for 1 h at 100 degrees C under nitrogen atmosphere. The aqueous layer was extracted with CH_2Cl_2 (3x70mL). The resulting mixture was concentrated under reduced pressure. This resulted in 8-bromo-N,N-dimethyl-1,5-naphthyridin-2-amine (570 mg, 101.63%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 252.0.

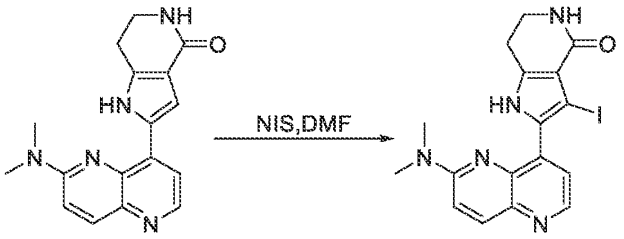


V

A mixture of 8-bromo-N,N-dimethyl-1,5-naphthyridin-2-amine (520 mg, 2.06 mmol, 1.00 equiv) ,2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (810 mg, 3.00 mmol, 1.50 equiv) ,Na_2CO_3 (655 mg, 6.18 mmol, 3.00 equiv) and $Pd(PPh_3)_4$ (476 mg, 0.41 mmol, 0.20 equiv) in dioxane (20.0 mL) and H_2O (4.00 mL) under nitrogen atmosphere. The resulting mixture was stirred for overnight at 50 degrees C under nitrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH (2x3 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 10 min; detector,

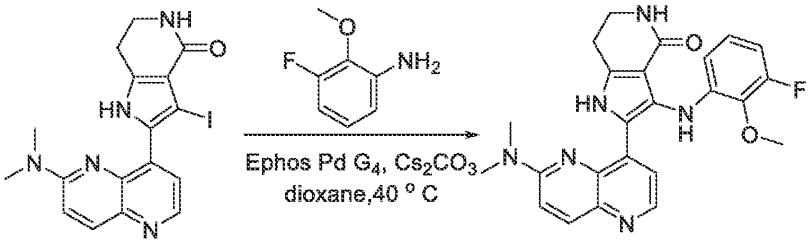
UV 254 nm. This resulted in 2-[6-(dimethylamino)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (500 mg, 74.93%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 308.10.



A mixture of 2-[6-(dimethylamino)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (200 mg, 0.65 mmol, 1.00 equiv) in DMF (20.00 mL) was added NIS (175 mg, 0.78 mmol, 1.20 equiv) in three portions at room temperature under nitrogen atmosphere. The mixture was stirred for 2h at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched with sat. Na_2SO_3 (aq.) at 0 degrees C. The aqueous layer was extracted with CH_2Cl_2 (3x100 mL). The residue was purified by Prep-TLC (PE/EtOAc 1:1) to afford 2-[6-(dimethylamino)-1,5-naphthyridin-4-yl]-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (118 mg, 35.12%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 433.95.



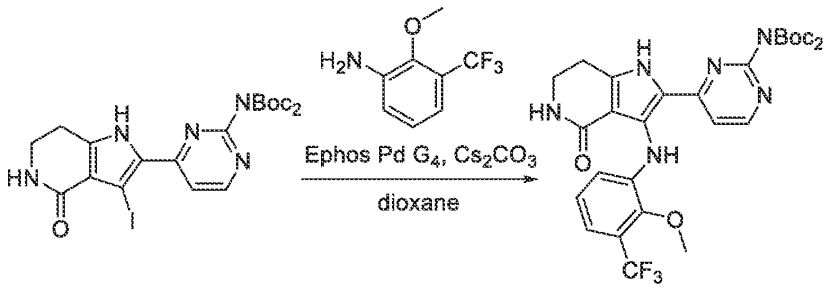
A mixture of 2-[6-(dimethylamino)-1,5-naphthyridin-4-yl]-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.23 mmol, 1.00 equiv) in dioxane (3.00 mL) under argon atmosphere. To the above mixture was added 3-fluoro-2-methoxyaniline (97 mg, 0.69 mmol, 3.00 equiv), EPhos Pd G4 (42 mg, 0.04 mmol, 0.20 equiv) and Cs_2CO_3 (150 mg, 0.46 mmol, 2.00 equiv) under argon atmosphere. The resulting mixture was stirred for additional overnight at 40 degrees C. The aqueous layer was extracted with CH_2Cl_2 (3x30

mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford crude products. The crude product (60mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH-----Preparative; Flow rate: 25 mL/min; Gradient: 71% B to 87% B in 9 min, 87% B; Wave Length: 254 nm; RT1(min): 7.97) to afford 2-[6-(dimethylamino)-1,5-naphthyridin-4-yl]-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (29.0 mg, 26.85%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 447.10.

^{1}H NMR (300 MHz, DMSO-*d6*) δ 12.95 (s, 1H), 8.35 (d, *J* = 4.9 Hz, 1H), 8.08 (d, *J* = 9.4 Hz, 1H), 7.76 (s, 1H), 7.47 – 7.36 (m, 2H), 7.17 (t, *J* = 2.5 Hz, 1H), 6.68 (td, *J* = 8.3, 6.1 Hz, 1H), 6.52 (ddd, *J* = 10.0, 8.4, 1.5 Hz, 1H), 6.18 – 6.03 (m, 1H), 3.86 (s, 3H), 3.45 (td, *J* = 6.9, 2.4 Hz, 2H), 2.91 (t, *J* = 6.8 Hz, 2H).

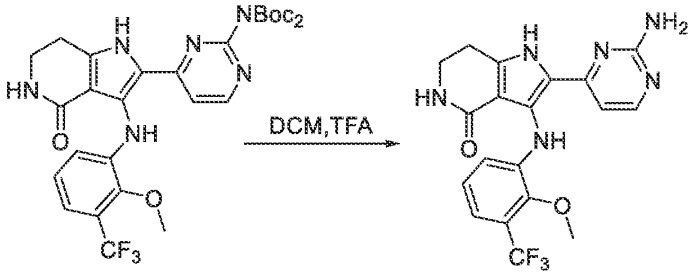
Example 231. 2-(2-aminopyrimidin-4-yl)-3-[[2-methoxy-3-(trifluoromethyl)phenyl]amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 698)**



A mixture of tert-butyl tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (120 mg, 0.21 mmol, 1.00 equiv) in dioxane (2.00 mL) under argon atmosphere. To the above mixture was added 2-methoxy-3-(trifluoromethyl) aniline (124 mg, 0.65 mmol, 3.00 equiv), Ephos Pd G4 (40 mg, 0.04 mmol, 0.20 equiv) and Cs_2CO_3 (140 mg, 0.43 mmol, 2.00 equiv) under argon atmosphere. The resulting mixture was stirred for additional overnight at 40 degrees C. The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was

concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 1:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-[4-(3-[[2-methoxy-3-(trifluoromethyl)phenyl]amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl)pyrimidin-2-yl]carbamate (63 mg, 16.03%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 619.05.



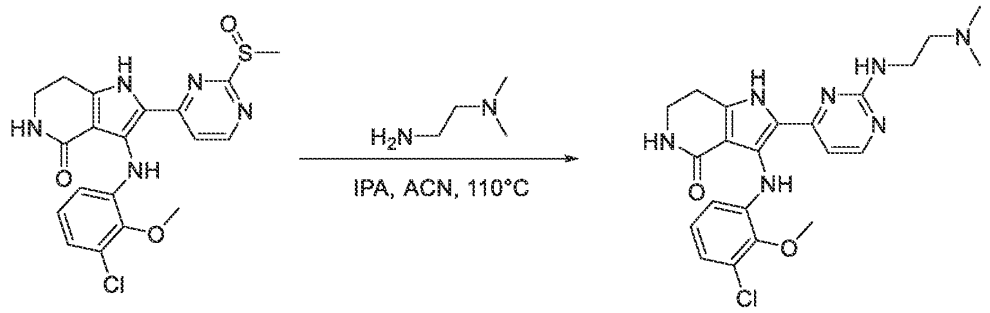
A mixture of tert-butyl tert-butyl N-(tert-butoxycarbonyl)-N-[4-(3-[[2-methoxy-3-(trifluoromethyl)phenyl]amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl)pyrimidin-2-yl]carbamate (62 mg, 0.10 mmol, 1.00 equiv) in DCM (1.00 mL).To the above mixture was added TFA (1.00 mL) at 0 degrees C. The resulting mixture was stirred for additional 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. The crude product (60 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water(10MMOL/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: MeOH-Preparative; Flow rate: 25 mL/min; Gradient: 56% B to 63% B in 10 min, 63% B; Wave Length: 254 nm; RT1(min): 9.5) to afford 2-(2-aminopyrimidin-4-yl)-3-[[2-methoxy-3-(trifluoromethyl)phenyl]amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (38.3 mg, 89.88%) as a white solid.

LC-MS: $(M+H)^+$ found: 419.0.

^{1}H NMR (300 MHz, DMSO-*d*6) δ 11.70 (s, 1H), 8.18 (s, 1H), 8.08 (d, *J* = 5.4 Hz, 1H), 7.15 (d, *J* = 2.7 Hz, 1H), 7.05 – 6.89 (m, 2H), 6.75 (dd, *J* = 7.5, 2.3 Hz, 1H), 6.52 (d, *J* = 5.3 Hz, 1H), 6.19 (s, 2H), 3.92 (s, 3H), 3.40 (td, *J* = 6.7, 2.5 Hz, 2H), 2.86 (t, *J* = 6.7 Hz, 2H).

Example 232. 3-((3-chloro-2-methoxyphenyl)amino)-2-(2-((2-

(dimethylamino)ethyl)amino)pyrimidin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one **(compound 707)**

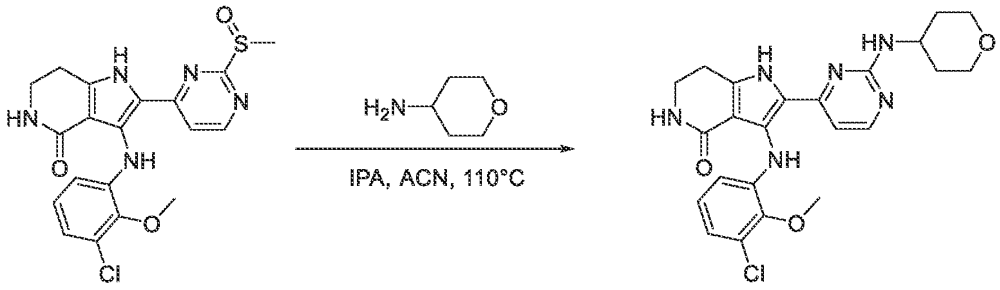


To a stirred mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6-H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.186 mmol, 1.0 equiv) , (2-aminoethyl)dimethylamine (164 mg, 1.86 mmol, 10.0 equiv) in MeOH/ACN (1:1, 2 mL) in portions under nitrogen atmosphere. The resulting mixture was stirred for 2 hours at 110 degrees C under nitrogen atmosphere. Desired product could be detected by LCMS. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 8% B to 20% B in 8 min, 20% B; Wave Length: 254/220 nm; RT1(min): 7) to afford 3-((3-chloro-2-methoxyphenyl)amino)-2-(2-((2-(dimethylamino)ethyl)amino)pyrimidin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (5.9 mg, 7.0%) as a yellow solid.

LC-MS: M+H found: 456.10.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 8.08 (d, J = 5.2 Hz, 1H), 7.91 (s, 1H), 7.16 (d, J = 3.0 Hz, 1H), 6.89 - 6.71 (m, 2H), 6.61 - 6.32 (m, 3H), 3.89 (s, 3H), 3.57 - 3.32 (m, 6H), 2.87 (t, J = 6.8 Hz, 2H), 2.25 (s, 6H).

Example 233. 3-((3-chloro-2-methoxyphenyl)amino)-2-(2-((tetrahydro-*2H*-pyran-4-yl)amino)pyrimidin-4-yl)-1,5,6,7-tetrahydro-*4H*-pyrrolo[3,2-c]pyridin-4-one **(compound 708)**

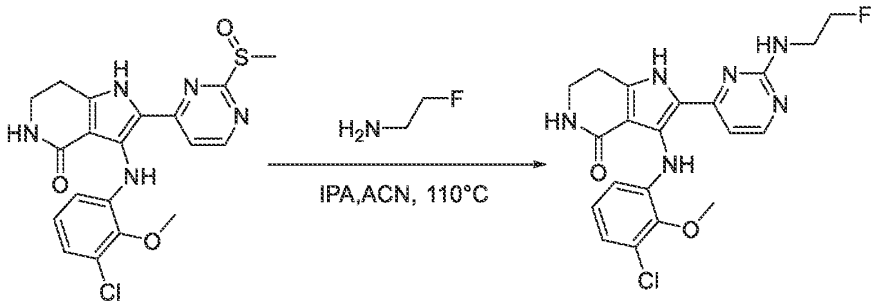


To a stirred mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6-H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.186 mmol, 1.0 equiv) , oxan-4-amine (188 mg, 1.86 mmol, 10.0 equiv) in MeOH/ACN (1:1, 2 mL) in portions under nitrogen atmosphere. The resulting mixture was stirred for 2 hours at 110 degrees C under nitrogen atmosphere. Desired product could be detected by LCMS. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge BEH C18 OBD Prep Column, 19*250 mm, 5μm; Mobile Phase A: Water(0.05%FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 22% B to 39% B in 11 min, 39% B; Wave Length: 254/220 nm; RT1(min): 7) to afford 3-((3-chloro-2-methoxyphenyl)amino)-2-(2-((tetrahydro-*2H*-pyran-4-yl)amino)pyrimidin-4-yl)-1,5,6,7-tetrahydro-*4H*-pyrrolo[3,2-c]pyridin-4-one (7.3 mg, 8.3 %) as a yellow solid.

LC-MS: M+H found: 469.05.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 8.08 (d, J = 5.3 Hz, 1H), 7.89 (s, 1H), 7.14 (s, 1H), 6.88 - 6.71 (m, 3H), 6.52 (d, J = 5.3 Hz, 1H), 6.38 (dd, J = 7.8, 1.8 Hz, 1H), 4.06 - 3.94 (m, 1H), 3.89 (s, 3H), 3.81 (s, 2H), 3.49 - 3.33 (m, 4H), 2.89 (d, J = 6.4 Hz, 2H), 1.74 (d, J = 12.6 Hz, 2H), 1.55 - 1.37 (m, 2H).

Example 234. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-[(2-fluoroethyl)amino]pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 710)**

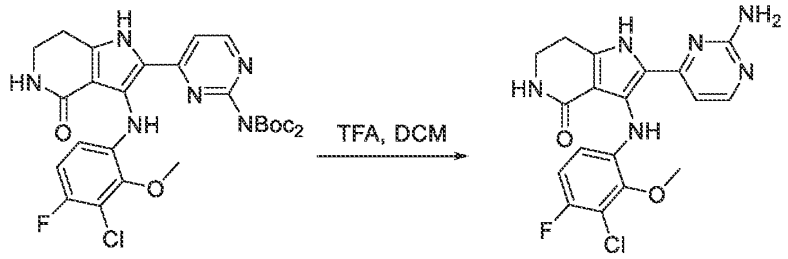


A solution of 3-[(3-chloro-2-methoxyphenyl) amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.18 mmol, 1.00 equiv) and 2-fluoroethanamine (116 mg, 1.85 mmol, 10.00 equiv) in ACN (1.00 mL) and IPA (1.00 mL) was stirred for 3 h at 110 degrees C under nitrogen atmosphere. The aqueous layer was extracted with CH_2Cl_2 (2x20 mL). The resulting mixture was concentrated under reduced pressure. The crude product (80 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 13% B to 29% B in 8 min, 29% B; Wave Length: 254 nm; RT1(min): 7.9) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-[(2-fluoroethyl)amino]pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (8.1 mg, 10.00%) as a light yellow solid

LC-MS: M+H found: 431.30.

^{1}H NMR (300 MHz, DMSO-*d*6) δ 8.24 – 7.94 (m, 1H), 6.87 – 6.70 (m, 2H), 6.48 (d, *J* = 5.4 Hz, 1H), 6.32 (dd, *J* = 7.3, 2.4 Hz, 1H), 4.48 (dt, *J* = 47.7, 5.0 Hz, 2H), 3.62 (dt, *J* = 26.7, 5.0 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 2.86 (t, *J* = 6.8 Hz, 2H).

Example 235. 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-4-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 713)**

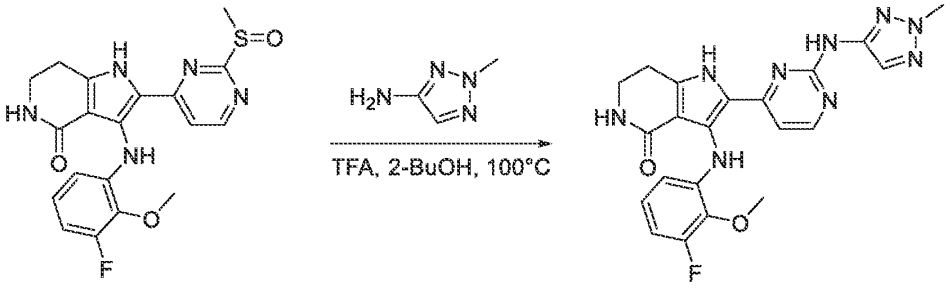


To a stirred mixture of tert-butyl N-(tert-butoxycarbonyl)-N-(4-[3-[(3-chloro-4-fluoro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl]pyrimidin-2-yl)carbamate (99.00 mg, 0.164 mmol, 1.00 equiv) in TFA (1.50 mL) and DCM (1.00 mL) in portions at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 11% B to 27% B in 8 min, 27% B; Wave Length: 254/220 nm; RT1(min): 7.23) to afford 2-(2-aminopyrimidin-4-yl)-3-[(3-chloro-4-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (18.1mg,26.63%) as a yellow solid.

LC-MS: M+H found: 403.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.78 (s, 1H), 8.23 (s, 1H), 8.17 – 8.00 (m, 1H), 7.13 (d, J = 2.8 Hz, 1H), 6.94 (t, J = 9.0 Hz, 1H), 6.83 – 6.58 (m, 3H), 6.51 (dd, J = 9.2, 5.6 Hz, 1H), 3.91 (s, 3H), 3.40 (dd, J = 6.6, 2.6 Hz, 2H), 2.86 (d, J = 13.4 Hz, 2H).

Example 236. 3-[(3-fluoro-2-methoxyphenyl)amino]-2-{2-[(2-methyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 593)**



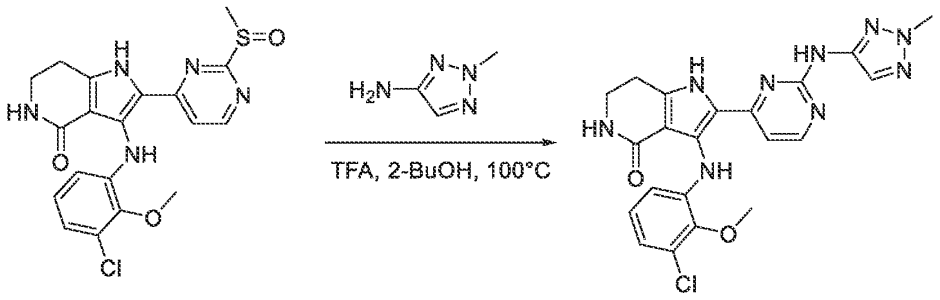
To a stirred solution/mixture of 3-[(3-fluoro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.241 mmol, 1 equiv) and 2-methyl-1,2,3-triazol-4-amine (47.23 mg, 0.482 mmol, 2 equiv) in 2-methyl-2-butanol (1 mL) was added TFA (54.89 mg, 0.482 mmol, 2 equiv) dropwise at r.t.The solution was stirred at 100 °C for overnight.LCMS showed ok.The resulting mixture was concentrated under reduced pressure.The mixture/residue

was neutralized to pH =10 with saturate NaHCO3.The precipitated solids were collected by filtration and washed with water (3x3 mL) amd purified with Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 9.67 to give 3-[(3-fluoro-2-methoxyphenyl)amino]-2-{2-[(2-methyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (10.9 mg, 10.08%) as light-yellow solid.

LC-MS: $(M+H)^+$ found: 450.05.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.45 (s, 1H), 9.80 (s, 1H), 8.25 (d, J = 5.3 Hz, 1H), 8.11 (s, 1H), 7.78 (s, 1H), 7.21 (t, J = 2.6 Hz, 1H), 6.78 – 6.73 (m, 1H), 6.71 (d, J = 5.4 Hz, 1H), 6.60-6.54 (m, 1H), 6.16 (d, J = 8.3 Hz, 1H), 4.05 (s, 3H), 3.93 (d, J = 0.9 Hz, 3H), 3.41 (d, J = 2.5 Hz, 2H), 2.91 (t, J = 6.8 Hz, 2H).

Example 237. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(2-methyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 592)**



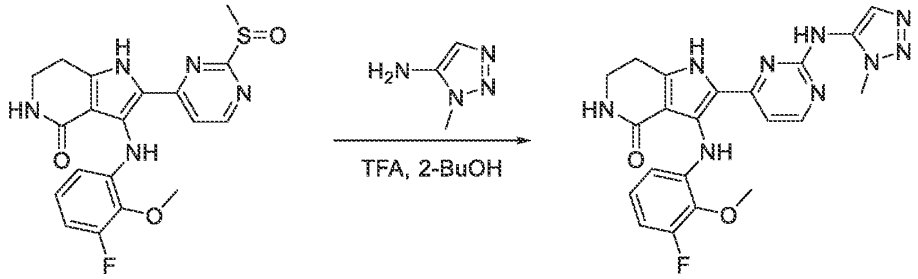
To a stirred solution/mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.232 mmol, 1 equiv) and 2-methyl-1,2,3-triazol-4-amine (45.43 mg, 0.464 mmol, 2 equiv) in 2-methyl-2-butanol (1 mL) was added TFA (52.80 mg, 0.464 mmol, 2 equiv) dropwise at r.t.The solution was stirred at 100 °C for overnight.LCMS showed ok.The resulting mixture was concentrated under reduced pressure.The mixture/residue was neutralized to pH =10 with saturate NaHCO3.The precipitated solids were collected by filtration and washed with water (3x3 mL) amd purified with Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.05%TFA), Mobile

Phase B: ACN; Flow rate: 60 mL/min; Gradient: 24% B to 42% B in 8 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8 to give 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(2-methyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (42.6 mg, 39.49%) as yellow solid.

LC-MS: $(M+H)^+$ found: 466.05.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 10.01 (s, 1H), 8.24 (d, J = 5.5 Hz, 1H), 8.08 (s, 1H), 7.90 (s, 1H), 7.23 (d, J = 5.3 Hz, 1H), 6.81-6.78 (m, 2H), 6.73 (d, J = 5.6 Hz, 1H), 6.37-6.33 (m, 1H), 4.05 (s, 3H), 3.88 (s, 3H), 3.42 (t, J = 6.9 Hz, 2H), 2.92 (t, J = 6.7 Hz, 2H).

Example 238. 3-[(3-fluoro-2-methoxyphenyl)amino]-2-{2-[(3-methyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 591)**



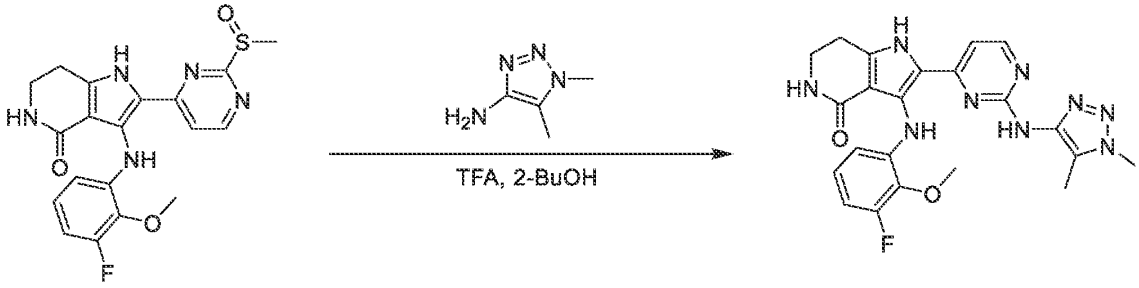
To a stirred solution/mixture of 3-[(3-fluoro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.241 mmol, 1 equiv) and 3-methyl-1,2,3-triazol-4-amine (47.23 mg, 0.482 mmol, 2 equiv) in 2-methyl-2-butanol (1 mL) was added TFA (54.89 mg, 0.482 mmol, 2 equiv) dropwise at r.t.The solution was stirred at 100 °C for overnight.LCMS showed ok.The resulting mixture was concentrated under reduced pressure.The mixture/residue was neutralized to pH =10 with saturate NaHCO3.The precipitated solids were collected by filtration and washed with water (3x3 mL) amd purified with Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 44% B in 9 min, 44% B; Wave Length: 254/220 nm; RT1(min): 8.85 to give 3-[(3-fluoro-2-methoxyphenyl)amino]-2-{2-[(3-methyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-

1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (21.2 mg, 19.03%) as light-yellow solid.

LC-MS: $(M+H)^+$ found: 450.05.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 1H), 9.80 (s, 1H), 8.25 (d, J = 5.3 Hz, 1H), 8.11 (s, 1H), 7.77 (s, 1H), 7.20 (t, J = 2.6 Hz, 1H), 6.79 – 6.66 (m, 2H), 6.63 – 6.53 (m, 1H), 4.05 (s, 3H), 3.98 – 3.84 (m, 3H), 3.43-3.39 (m, 2H), 2.91 (t, J = 6.8 Hz, 2H).

Example 239. 2-{2-[(1,5-dimethyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 608)**

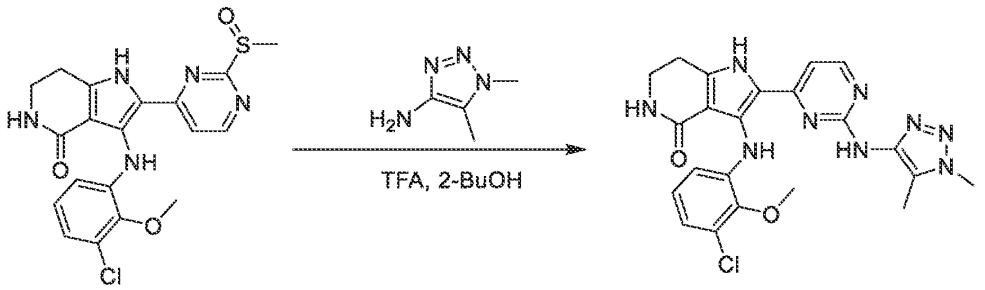


To a stirred solution/mixture of 3-[(3-fluoro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.241 mmol, 1 equiv) and dimethyl-1,2,3-triazol-4-amine (53.98 mg, 0.482 mmol, 2 equiv) in 2-methyl-2-butanol (1 mL) was added TFA (54.89 mg, 0.482 mmol, 2 equiv) dropwise at r.t.The solution was stirred at 100 °C for overnight.LCMS showed ok.The resulting mixture was concentrated under reduced pressure.The mixture/residue was neutralized to pH =10 with saturate NaHCO3.The precipitated solids were collected by filtration and washed with water (3x3 mL) amd purified with Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 18% B to 35% B in 10 min, 35% B; Wave Length: 254/220 nm; RT1(min): 8.85 to give 2-{2-[(1,5-dimethyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (51.6 mg, 46.25%) as light-yellow solid.

LC-MS: $(M+H)^+$ found: 464.10.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.46 (s, 1H), 8.67 (s, 1H), 8.11 (d, J = 5.4 Hz, 1H), 7.71 (s, 1H), 7.14 (d, J = 2.6 Hz, 1H), 6.81-6.751 (m, 1H), 6.66 – 6.50 (m, 2H), 6.22-6.19 (m, 1H), 3.90 (d, J = 10.0 Hz, 6H), 3.51 (s, 2H), 2.85 (t, J = 6.7 Hz, 2H), 2.09 (s, 3H).

Example 240. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(1,5-dimethyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 607)**

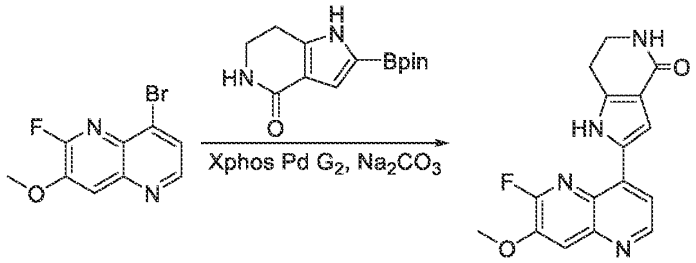


To a stirred solution/mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.232 mmol, 1 equiv) and dimethyl-1,2,3-triazol-4-amine (51.93 mg, 0.464 mmol, 2 equiv) in 2-methyl-2-butanol (1 mL) was added TFA (52.80 mg, 0.464 mmol, 2 equiv) dropwise at r.t.The solution was stirred at 100 °C for overnight. The resulting mixture was concentrated under reduced pressure.The mixture/residue was neutralized to pH =10 with saturated $NaHCO_3$.The precipitated solids were collected by filtration and washed with water (3x3 mL) amd purified with Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 14% B to 32% B in 8 min, 32% B; Wave Length: 254/220 nm; RT1(min): 8 to give 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(1,5-dimethyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (34.6 mg, 31.14%) as yellow solid.

LC-MS: $(M+H)^+$ found: 480.10

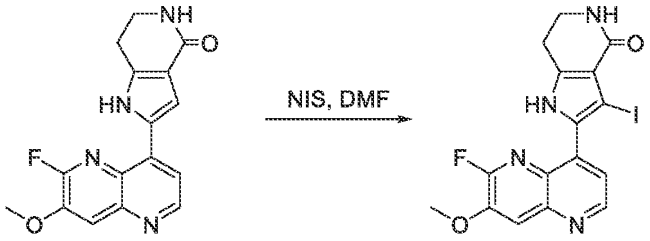
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 1H), 8.67 (s, 1H), 8.13 (d, J = 5.4 Hz, 1H), 7.73 (s, 1H), 7.12 (t, J = 2.6 Hz, 1H), 6.92 – 6.72 (m, 2H), 6.63 (d, J = 5.4 Hz, 1H), 6.38-6.30 (m, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.43 – 3.38 (m, 2H), 2.85 (t, J = 6.7 Hz, 2H), 2.09 (s, 3H).

Example 241. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{6-[2-(dimethylamino)ethoxy]-7-methoxy-1,5-naphthyridin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 501)**



To a stirred mixture of 8-bromo-2-fluoro-3-methoxy-1,5-naphthyridine (300 mg, 1.167 mmol, 1 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (367.08 mg, 1.400 mmol, 1.2 equiv) in 1,4-dioxane (12 mL) and water (3 mL) were added Na2CO3 (247.38 mg, 2.334 mmol, 2 equiv) and XPhos palladium(II) biphenyl-2-amine chloride (91.82 mg, 0.117 mmol, 0.1 equiv) in portions at room temperature under argon atmosphere.The resulting mixture was stirred for overnight at 50°C under argon atmosphere.Desired product could be detected by LCMS.The resulting mixture was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (20:1) to afford 2-(6-fluoro-7-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (267 mg, 73.26%) as a yellow solid.

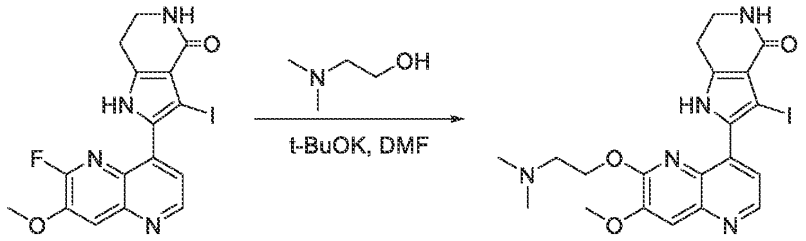
LC-MS: $[M-H]^-$ found: 313.00.



A mixture of 2-(6-fluoro-7-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (185 mg, 0.592 mmol, 1 equiv) and NIS (199.91 mg, 0.888 mmol, 1.5 equiv) in DMF (6.5 mL) was stirred for overnight at room temperature under air atmosphere.Desired product could be detected by LCMS.The reaction was quenched by

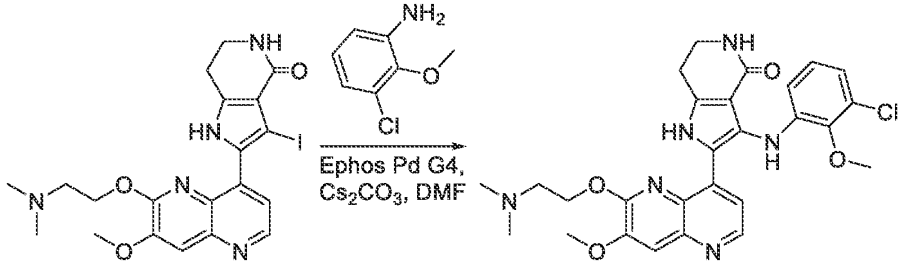
the addition of sat. sodium sulfite (aq.) (1mL) at room temperature.The resulting mixture was concentrated under vacuum.The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (20:1) to afford 2-(6-fluoro-7-methoxy-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (230 mg, 88.61%) as a yellow solid.

LC-MS: $[M-H]^-$ found: 438.85.



To a stirred mixture of 2-(6-fluoro-7-methoxy-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (60 mg, 0.137 mmol, 1 equiv) and dimethylaminoethanol (36.62 mg, 0.411 mmol, 3 equiv) in DMF (1 mL) was added Potassium tert-butoxide in THF (1 M) (0.16 mL, 0.164 mmol, 1.2 equiv) in portions at 0°C under argon atmosphere.The resulting mixture was stirred for 1h at 0°C under argon atmosphere.Desired product could be detected by LCMS.The reaction was quenched by the addition of Water (1mL) at 0° C.The resulting mixture was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (20:1) to afford 2-{6-[2-(dimethylamino)ethoxy]-7-methoxy-1,5-naphthyridin-4-yl}-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (65 mg, 93.57%) as a yellow solid.

LC-MS: $[M+H]^+$ found: 508.10.

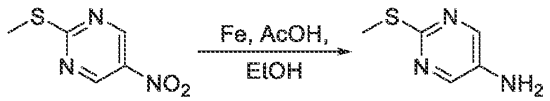


To a stirred mixture of 2-{6-[2-(dimethylamino)ethoxy]-7-methoxy-1,5-naphthyridin-4-yl}-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70 mg, 0.138 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (19.57 mg, 0.124 mmol, 0.9 equiv) in DMF (2 mL) were added Cs2CO3 (89.91 mg, 0.276 mmol, 2 equiv) and EPhos Pd G4 (12.67 mg, 0.014 mmol, 0.1 equiv)in portions at room temperature under argon atmosphere.The resulting mixture was stirred for 2 h at 50 °C under argon atmosphere.The resulting mixture was concentrated under reduced pressure.The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 38% B to 54% B in 8 min, 54% B; Wave Length: 254/220 nm; RT1(min): 7) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-{6-[2-(dimethylamino)ethoxy]-7-methoxy-1,5-naphthyridin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (5.7 mg, 7.32%) as a yellow solid.

LC-MS: $[M+H]^+$ found: 537.00.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.90 (s, 1H), 8.49 (d, J = 5.1 Hz, 1H), 7.66 (d, J = 3.0 Hz, 2H), 7.40 (d, J = 4.8 Hz, 1H), 7.17 (s, 1H), 6.65-6.62 (m, 2H), 6.18-6.15 (m, 1H), 4.68 (t, J = 6.3 Hz, 2H), 3.99 (s, 3H), 3.85 (s, 3H), 2.92 (t, J = 6.8 Hz, 2H), 2.76 (s, 0H), 2.24 (s, 6H).

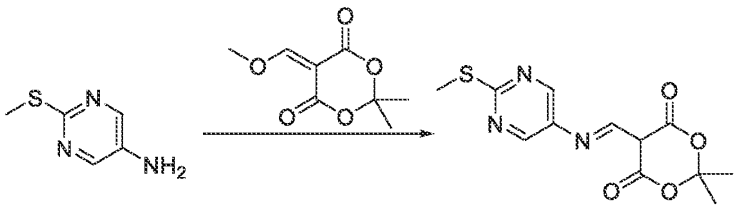
Example 242. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[2-(morpholin-4-yl)ethoxy]pyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 506)**



To a stirred solution of 2-(methylsulfanyl)-5-nitropyrimidine (5 g, 29.211 mmol, 1.00 equiv) in EtOH (200 mL) was added AcOH (120 mL) and Fe (17 g, 292.11 mmol, 10 equiv) in portions at rt under N_2 atmosphere. The resulting mixture was stirred for 2 h at 80 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 142. The resulting mixture was concentrated under reduced pressure. The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with

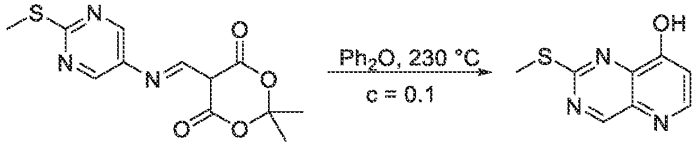
Saturated NaCl (3x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2-(methylsulfanyl)pyrimidin-5-amine (3.5 g, 84.86%) as a yellow solid.

LC-MS: M+H found: 142.0.



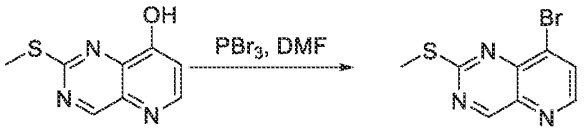
To a stirred solution of 2-(methylsulfanyl)pyrimidin-5-amine (3.2 g, 22.66 mmol, 1.00 equiv) and 5-(methoxymethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (5.06 g, 27.18 mmol, 1.20 equiv) in DMF (80.00 mL) at rt under N_2 atmosphere. The resulting mixture was stirred for 1 h at 80 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 296.The resulting mixture was added MeOH(50 mL). The resulting mixture was filtered, the filter cake was washed with MeOH (3 x20 mL). The filter cake was concentrated under reduced pressure to afford 2,2-dimethyl-5-[(1E)-[[2-(methylsulfanyl)pyrimidin-5-yl]imino]methyl]-1,3-dioxane-4,6-dione (5.4 g, 80.68%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 296.0.



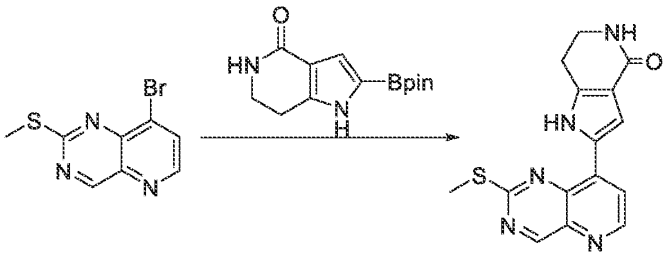
To a stirred solution of 2,2-dimethyl-5-[(1E)-{[2-(methylsulfanyl)pyrimidin-5-yl]imino}methyl]-1,3-dioxane-4,6-dione (5.3 g, 17.95 mmol, 1.00 equiv) in phenoxybenzene (360 mL) at rt under N_2 atmosphere. The resulting mixture was stirred at 230 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 194. The reaction was addition of Hexane (700 ml) at rt. The resulting mixture was filtered; the filter cake was washed with Hexane (3x200 ml). The filtrate was concentrated under reduced pressure.

LC-MS: $(M+H)^+$ found: 194.0.



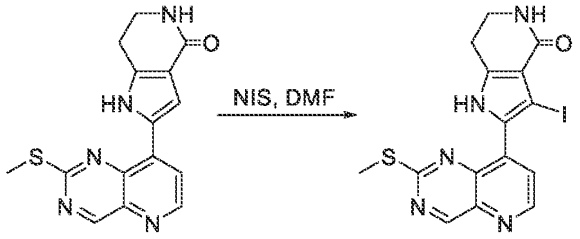
To a stirred solution of 2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-ol (2.8 g, 14.49 mmol, 1.00 equiv) in DMF (80 mL) was added PBr_3 (4.31 g, 15.94 mmol, 1.1 equiv) dropwise at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 1 h at rt under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 256. The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with aq. NaCl (3x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE:EA (4:1) to afford 8-bromo-2-(methylsulfanyl)pyrido[3,2-d]pyrimidine (1.6 g, 43.11%) as a white solid.

LC-MS: $(M+H)^+$ found: 256.0.



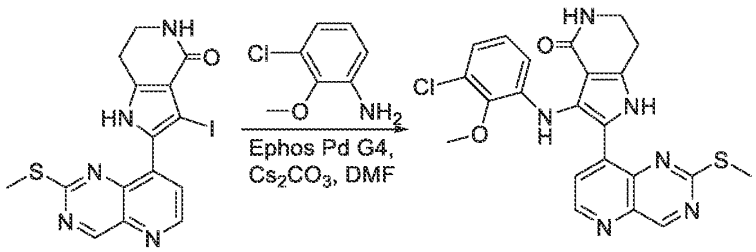
To a stirred solution of 8-bromo-2-(methylsulfanyl)pyrido[3,2-d]pyrimidine (700 mg, 2.73 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1075 mg, 4.10 mmol, 1.50 equiv) in dioxane (10 mL) and H_2O (1 mL) were added Na_2CO_3 (869.03 mg, 8.199 mmol, 3.00 equiv) and XPhos Pd G2 (215 mg, 0.27 mmol, 0.10 equiv) dropwise/ in portions at rt under N_2 atmosphere. The resulting mixture was stirred for 2 h at 80 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 312. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH=24:1 to afford 2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (700 mg, 82.26%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 312.0.



To a stirred solution of 2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (600 mg, 1.93 mmol, 1.00 equiv) and NIS (650.33 mg, 2.891 mmol, 1.50 equiv) in DMF (10 mL) at rt under N_2 atmosphere. The resulting mixture was stirred for overnight at 30 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 438.The reaction was quenched by the addition of Saturated aq. Na_2SO_3 (20 mL) at 0 degrees C. The precipitated solids were collected by filtration and washed with H_2O (20 mLx3). The residue was purified by silica gel column chromatography, eluted with DCM:MeOH=10:1 to afford 3-iodo-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (650 mg, 77.14%) as a yellow solid.

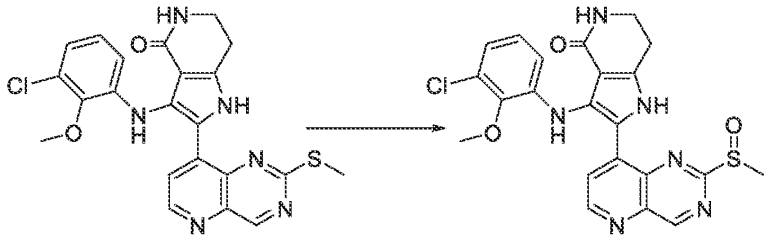
LC-MS: $(M+H)^+$ found: 438.0.



To a stirred solution of 3-iodo-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (370 mg, 0.85 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (134 mg, 0.85 mmol, 1 equiv) in DMF (4 mL) were added EPhos Pd G4 (78 mg, 0.08 mmol, 0.1 equiv) and Cs_2CO_3 (827 mg, 2.54 mmol, 3 equiv) in portions at rt under Ar atmosphere. The resulting mixture was stirred for 1.5 h at 50 degrees C under Ar atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 467. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM:MeOH (10:1) to afford 3-[(3-chloro-2-

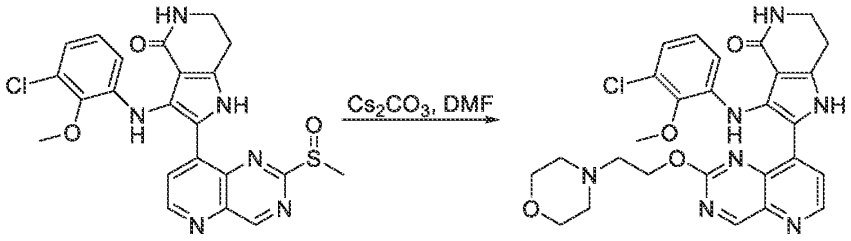
methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (220 mg, 55.68%) as a orange solid.

LC-MS: $(M+H)^+$ found: 467.0.



To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50 mg, 0.11 mmol, 1.00 equiv) in DCM (2 mL, 31.46 mmol, 293.80 equiv) were added MCPBA (29 mg, 0.12 mmol, 1.1 equiv) dropwise/ in portions at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 1 h at 0 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 483. The resulting mixture was extracted with DCM (3 x 4 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

LC-MS: $(M+H)^+$ found: 483.0.



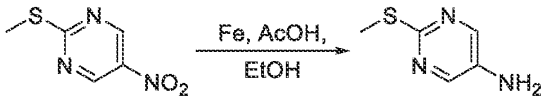
To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-methanesulfinylpyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (145 mg, 0.300 mmol, 1.00 equiv) and Cs_2CO_3 (234.78 mg, 0.72 mmol, 2.4 equiv) in DMF (5 mL) were added 4-morpholineethanol (47 mg, 0.36 mmol, 1.2 equiv) dropwise at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 1 h at 0 degrees C under N_2 atmosphere. The resulting mixture was concentrated under vacuum. The

resulting mixture was concentrated under vacuum and dissolved in DMF. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 43% B in 9 min, 43% B; Wave Length: 254/220 nm; RT1(min): 8.85) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[2-(morpholin-4-yl)ethoxy]pyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (7.5 mg, 4.54%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 550.0.

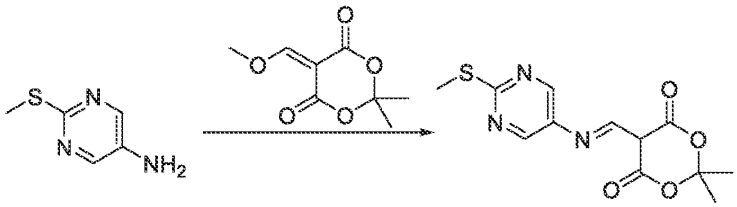
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 9.50 (s, 1H), 8.71 (d, J = 4.8 Hz, 1H), 7.89 (s, 1H), 7.59 (d, J = 4.8 Hz, 1H), 7.26 (d, J = 2.9 Hz, 1H), 6.71 (dd, J = 8.1, 1.7 Hz, 1H), 6.66 (t, J = 8.0 Hz, 1H), 6.16 (m, J = 8.0, 1.7 Hz, 1H), 4.72 (t, J = 5.7 Hz, 2H), 3.87 (s, 3H), 3.58 (t, J = 4.6 Hz, 4H), 3.51 – 3.43 (m, 2H), 2.95 (t, J = 6.8 Hz, 2H), 2.82 (t, J = 5.7 Hz, 2H),2.49-2.50(m,4H).

Example 243. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[3-(morpholin-4-yl)propoxy]pyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 505)**



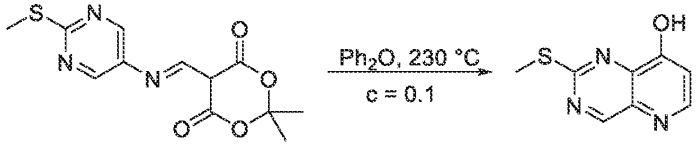
To a stirred solution of 2-(methylsulfanyl)-5-nitropyrimidine (5 g, 29.211 mmol, 1.00 equiv) in EtOH (200 mL) was added AcOH (120 mL) and Fe (17 g, 292.11 mmol, 10 equiv) in portions at rt under N_2 atmosphere. The resulting mixture was stirred for 2 h at 80 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 142. The resulting mixture was concentrated under reduced pressure. The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with Saturated NaCl (3x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2-(methylsulfanyl)pyrimidin-5-amine (3.5 g, 84.86%) as a yellow solid.

LC-MS: M+H found: 142.0.

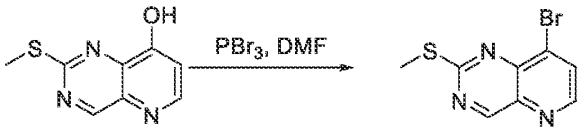


To a stirred solution of 2-(methylsulfanyl)pyrimidin-5-amine (3.2 g, 22.66 mmol, 1.00 equiv) and 5-(methoxymethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (5.06 g, 27.18 mmol, 1.20 equiv) in DMF (80.00 mL) at rt under N_2 atmosphere. The resulting mixture was stirred for 1 h at 80 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 296.The resulting mixture was added MeOH(50 mL). The resulting mixture was filtered, the filter cake was washed with MeOH (3 x20 mL). The filter cake was concentrated under reduced pressure to afford 2,2-dimethyl-5-[(1E)-[[2-(methylsulfanyl)pyrimidin-5-yl]imino]methyl]-1,3-dioxane-4,6-dione (5.4 g, 80.68%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 296.0.



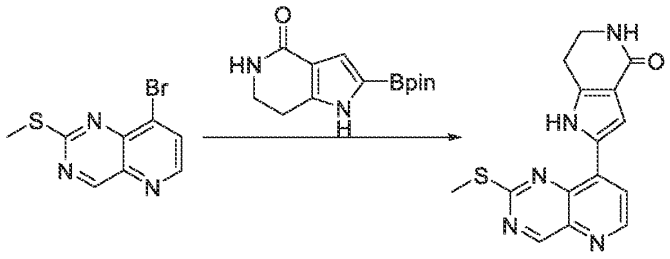
To a stirred solution of 2,2-dimethyl-5-[(1E)-{[2-(methylsulfanyl)pyrimidin-5-yl]imino}methyl]-1,3-dioxane-4,6-dione (5.3 g, 17.95 mmol, 1.00 equiv) in phenoxybenzene (360 mL) at rt under N_2 atmosphere. The resulting mixture was stirred at 230 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 194. The reaction was addition of Hexane (700 ml) at rt. The resulting mixture was filtered; the filter cake was washed with Hexane (3x200 ml). The filtrate was concentrated under reduced pressure.



To a stirred solution of 2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-ol (2.8 g, 14.49 mmol,

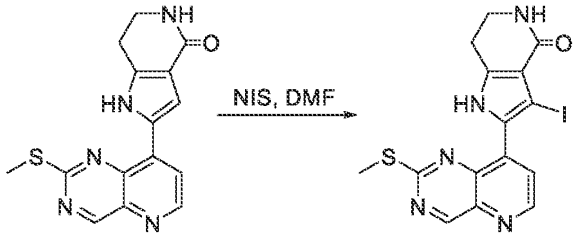
1.00 equiv) in DMF (80 mL) was added PBr_3 (4.31 g, 15.94 mmol, 1.1 equiv) dropwise at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 1 h at rt under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 256. The resulting mixture was extracted with EA (3 x 100 mL). The combined organic layers were washed with aq. NaCl (3x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE:EA (4:1) to afford 8-bromo-2-(methylsulfanyl)pyrido[3,2-d]pyrimidine (1.6 g, 43.11%) as a white solid.

LC-MS: $(M+H)^+$ found 256.0.



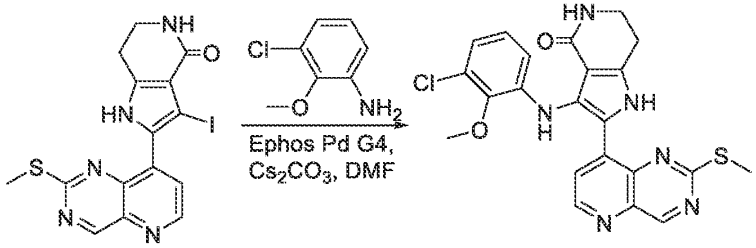
To a stirred solution of 8-bromo-2-(methylsulfanyl)pyrido[3,2-d]pyrimidine (700 mg, 2.73 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1075 mg, 4.10 mmol, 1.50 equiv) in dioxane (10 mL) and H_2O (1 mL) were added Na_2CO_3 (869.03 mg, 8.199 mmol, 3.00 equiv) and XPhos Pd G2 (215 mg, 0.27 mmol, 0.10 equiv) dropwise/ in portions at rt under N_2 atmosphere. The resulting mixture was stirred for 2 h at 80 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 312. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH=24:1 to afford 2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (700 mg, 82.26%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 312.0.



To a stirred solution of 2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (600 mg, 1.93 mmol, 1.00 equiv) and NIS (650.33 mg, 2.891 mmol, 1.50 equiv) in DMF (10 mL) at rt under N_2 atmosphere. The resulting mixture was stirred for overnight at 30 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 438.The reaction was quenched by the addition of Saturated aq. Na_2SO_3 (20 mL) at 0 degrees C. The precipitated solids were collected by filtration and washed with H_2O (20 mLx3). The residue was purified by silica gel column chromatography, eluted with DCM:MeOH=10:1 to afford 3-iodo-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (650 mg, 77.14%) as a yellow solid.

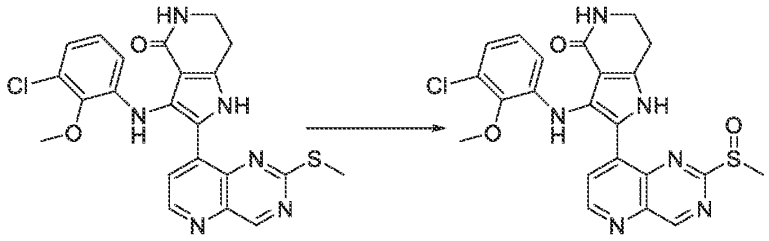
LC-MS: $(M+H)^+$ found: 438.0.



To a stirred solution of 3-iodo-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (370 mg, 0.85 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (134 mg, 0.85 mmol, 1 equiv) in DMF (4 mL) were added EPhos Pd G4 (78 mg, 0.08 mmol, 0.1 equiv) and Cs_2CO_3 (827 mg, 2.54 mmol, 3 equiv) in portions at rt under Ar atmosphere. The resulting mixture was stirred for 1.5 h at 50 degrees C under Ar atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 467. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM:MeOH (10:1) to afford 3-[(3-chloro-2-

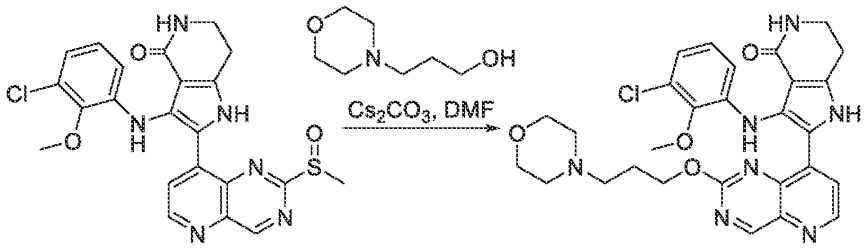
methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (220 mg, 55.68%) as a orange solid.

LC-MS: $(M+H)^+$ found: 467.0.



To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50 mg, 0.11 mmol, 1.00 equiv) in DCM (2 mL, 31.46 mmol, 293.80 equiv) were added MCPBA (29 mg, 0.12 mmol, 1.1 equiv) dropwise/ in portions at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 1 h at 0 degrees C under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS: M+H found: 483. The resulting mixture was extracted with DCM (3 x 4 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

LC-MS: $(M+H)^+$ found: 483.0.



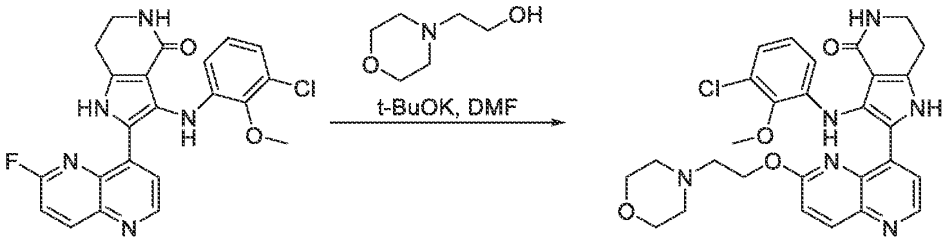
To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-methanesulfinylpyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (135 mg, 0.280 mmol, 1.00 equiv) and Cs2CO3 (218.59 mg, 0.672 mmol, 2.4 equiv) inDMF (2 mL) were added 3-(morpholin-4-yl)propan-1-ol (48.71 mg, 0.336 mmol, 1.2 equiv) dropwise at 0 degrees C under N_2 atmosphere. The resulting mixture was stirred for 1 h at RT under N_2 atmosphere. Desired product could be detected by LCMS. LC-MS:

M+H found: 564. The resulting mixture was concentrated under vacuum.The resulting mixture was concentrated under vacuum and dissolved in DMF. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 45% B in 10 min, 45% B; Wave Length: 254/220 nm; RT1(min): 9.67) to 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[3-(morpholin-4-yl)propoxy]pyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (10.3 mg, 6.53%) as a orange solid.

LC-MS: $(M+H)^+$ found: 564.30.

^{1}H NMR (400 MHz, DMSO-d_6) δ12.00 (s, 1H), 9.49 (s, 1H), 8.70 (d, J = 4.8 Hz, 1H), 7.88 (s, 1H), 7.57 (d, J = 4.8 Hz, 1H), 7.26 (d, J = 2.7 Hz, 1H), 6.61–6.75 (m, 2H), 6.16 (m, J = 7.9, 1.8 Hz, 1H),) 4.63 (t, J = 6.6 Hz, 2H), 3.87 (s, 3H), 3.57 (t, J = 4.6 Hz, 4H), 3.48 (s, 4H), 2.96 (t, J = 6.8 Hz, 2H), 2.39 (s, 4H), 2.03 (m, J = 6.9 Hz, 2H).

Example 244. 3-[(3-chloro-2-methoxyphenyl) amino]-2-{6-[2-(morpholin-4-yl) ethoxy]-1,5-naphthyridin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one **(compound 504)**



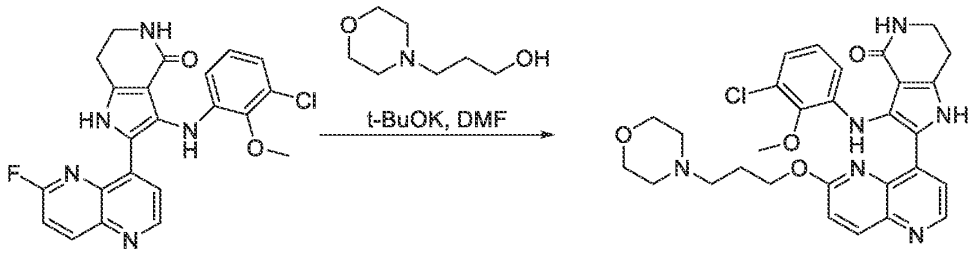
To a stirred solution of 3-[(3-chloro-2-methoxyphenyl) amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (80 mg, 0.183 mmol, 1.00 equiv) in DMF (1.5 mL) was added 4-morpholineethanol (119.83 mg, 0.915 mmol, 5 equiv) in portions at degrees 0 C under nitrogen atmosphere. To the above mixture was added t-BuOK (22.55 mg, 0.201 mmol, 1.1 equiv) in portions over 30 min at room temperature. The crude product (80 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 58% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl) amino]-2-{6-[2-(morpholin-4-yl) ethoxy]-1,5-naphthyridin-4-yl}-

1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one as a yellow solid.

LC-MS: M+H found: 549.0.

^{1}H NMR (400 MHz, DMSO-d6) δ 12.02 (s, 1H), 8.59 (d, J = 4.8 Hz, 1H), 8.29 (d, J = 9.1 Hz, 1H), 7.74 (s, 1H), 7.52 (d, J = 4.8 Hz, 1H), 7.35 (d, J = 9.1 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 6.72 – 6.53 (m, 2H), 6.19 (dd, J = 7.7, 1.9 Hz, 1H), 4.70 (t, J = 5.9 Hz, 2H), 3.84 (s, 3H), 3.57 (t, J = 4.6 Hz, 4H), 3.47 (td, J = 6.9, 2.5 Hz, 2H), 2.92 (t, J = 6.8 Hz, 2H), 2.80 (t, J = 5.9 Hz, 2H), 2.52 (s, 4H).

Example 245. 3-[(3-chloro-2-methoxyphenyl) amino]-2-{6-[3-(morpholin-4-yl) propoxy]-1,5-naphthyridin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one **(compound 503)**

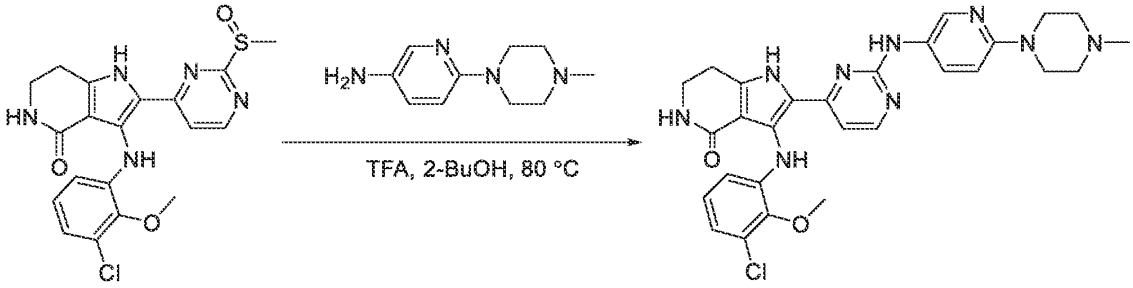


To a stirred solution of 3-[(3-chloro-2-methoxyphenyl) amino]-2-(6-fluoro-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (80 mg, 0.183 mmol, 1.00 equiv) in DMF (1.5 mL, 19.383 mmol, 106.09 equiv) was added 3-(morpholin-4-yl) propan-1-ol (132.65 mg, 0.915 mmol, 5 equiv) in portions at degrees 0 C under nitrogen atmosphere. To the above mixture was added t-BuOK (22.55 mg, 0.201 mmol, 1.1 equiv) in portions over 30 min at room temperature. The crude product (80 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 62% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl) amino]-2-{6-[3-(morpholin-4-yl) propoxy]-1,5-naphthyridin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (26.7 mg, 25.54%) as a yellow solid.

LC-MS: M+H found: 563.0.

^{1}H NMR (300 MHz, DMSO-d6) δ 12.14 (s, 1H), 8.59 (d, J = 4.8 Hz, 1H), 8.31 (d, J = 9.1 Hz, 1H), 7.77 (s, 1H), 7.52 (d, J = 4.8 Hz, 1H), 7.40 – 7.14 (m, 2H), 6.79 – 6.58 (m, 2H), 6.19 – 6.17 (m, 1H), 4.61 (d, J = 7.2 Hz, 2H), 3.85 (s, 3H), 3.74 – 3.38 (m, 6H), 2.96 (t, J = 6.7 Hz, 2H), 2.53 (s, 4H), 2.39 (s, 2H), 2.05 (s, 2H).

Example 246. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-{[6-(4-methylpiperazin-1-yl)pyridin-3-yl]amino}pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 518)**



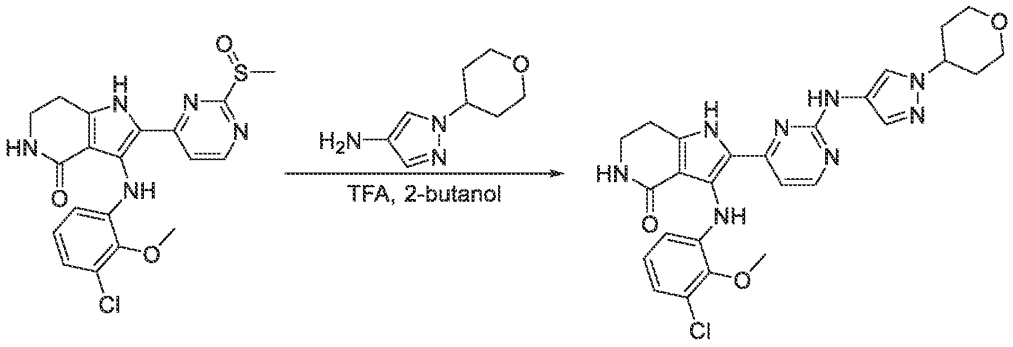
To a stirred mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.185 mmol, 1.00 equiv) and 6-(4-methylpiperazin-1-yl)pyridin-3-amine (356.13 mg, 1.850 mmol, 10 equiv) in butan-2-ol (1.8 mL) was added TFA (42.24 mg, 0.370 mmol, 2 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 days at 80 degrees C under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-{[6-(4-methylpiperazin-1-yl)pyridin-3-yl]amino}pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (17.3 mg, 15.86%) as a red solid.

LC-MS: $(M+H)^+$ found: 560.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.53 (s, 1H), 9.00 (s, 1H), 8.43 (d, J = 2.7 Hz, 1H), 8.21 (d, J = 5.3 Hz, 1H), 7.95 (dd, J = 9.1, 2.8 Hz, 1H), 7.76 (s, 1H), 7.19 (d, J = 2.8 Hz, 1H), 6.87 – 6.73 (m, 3H), 6.65 (d, J = 5.4 Hz, 1H), 6.34 (dd, J = 7.8, 1.9 Hz, 1H), 3.89 (s,

3H), 3.41 (td, *J* = 6.9, 2.5 Hz, 4H), 2.89 (t, *J* = 6.8 Hz, 2H), 2.76 (s, 3H), 2.55 (s, 6H).

Example 247. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-{[1-(oxan-4-yl)pyrazol-4-yl]amino}pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 517)**



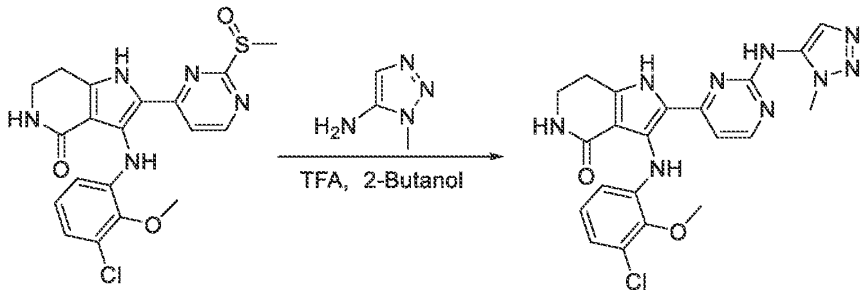
To a stirred mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.23 mmol, 1.00 equiv) and 1-(oxan-4-yl)pyrazol-4-amine (194 mg, 1.15 mmol, 5.00 equiv) in butan-2-ol (2.00 mL) was added TFA (53 mg, 0.46 mmol, 2.00 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80 degrees C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 55% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-{[1-(oxan-4-yl)pyrazol-4-yl]amino}pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (78.8 mg, 61.39%) as a off-white solid.

LC-MS: $(M+H)^+$ found: 534.95.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.50 (s, 1H), 9.08 (s, 1H), 8.20 (d, *J* = 5.3 Hz, 1H), 7.99 (s, 1H), 7.73 (s, 1H), 7.61 (s, 1H), 7.21 (d, *J* = 2.6 Hz, 1H), 6.86 - 6.75 (m, 1H), 6.75 (dd, *J* = 8.0, 2.1 Hz, 1H), 6.59 (d, *J* = 5.3 Hz, 1H), 6.32 (dd, *J* = 7.5, 2.1 Hz, 1H), 4.33 (p, *J* = 8.2 Hz, 1H), 3.97 (dt, *J* = 11.7, 3.5 Hz, 2H), 3.91 (s, 3H), 3.52 - 3.37 (m, 4H), 2.90 (t,

J = 6.7 Hz, 2H), 1.96 (td, *J* = 7.2, 5.3, 2.9 Hz, 4H).

Example 248. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(3-methyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 512)**

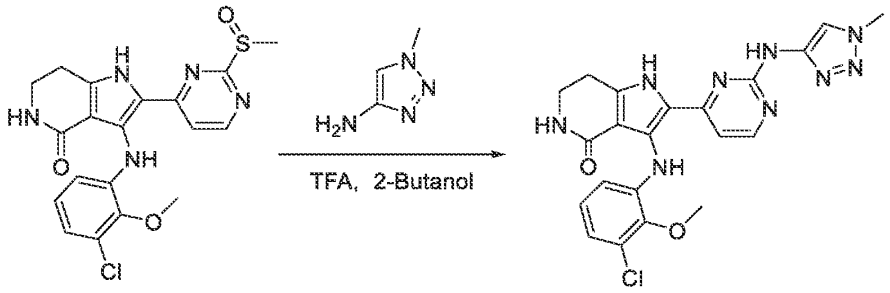


To a stirred mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.185 mmol, 1.00 equiv) and 3-methyl-1,2,3-triazol-4-amine (182 mg, 1.850 mmol, 10 equiv) in 2-Butanol (2 mL) was added TFA (42.24 mg, 0.370 mmol, 2 equiv) in portions at 80 degrees C under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80 degrees C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 52% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(3-methyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (5.7 mg, 6.58%) as a light yellow solid.

LC-MS: M+H found: 466.0.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.48 (s, 1H), 9.80 (s, 1H), 8.26 (dd, J = 5.4, 2.7 Hz, 1H), 8.12 (d, J = 2.6 Hz, 1H), 7.79 (d, J = 2.5 Hz, 1H), 7.21 (d, J = 2.8 Hz, 1H), 6.86 – 6.73 (m, 2H), 6.70 (dd, J = 5.5, 2.6 Hz, 1H), 6.36 – 6.26 (m, 1H), 4.06 (d, J = 2.6 Hz, 3H), 3.90 (d, J = 2.8 Hz, 3H), 3.48 – 3.36 (m, 2H), 2.92 (dt, J = 8.0, 4.0 Hz, 2H).

Example 249. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(1-methyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 511)**

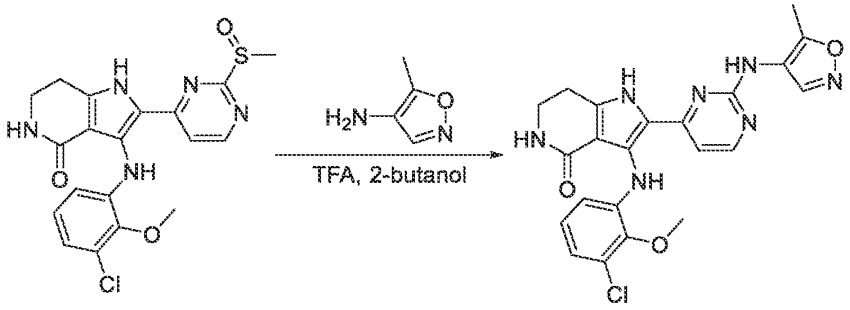


To a stirred mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.185 mmol, 1.00 equiv) and 1-methyl-1,2,3-triazol-4-amine (182 mg, 1.850 mmol, 10 equiv) in 2-Butanol (2 mL) was added TFA (42.24 mg, 0.370 mmol, 2 equiv) in portions at 80 degrees C under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80 degrees C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 44% B in 8 min, 44% B; Wave Length: 254/220 nm; RT1(min): 7.55) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(1-methyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (8.1 mg, 9.32%) as a light yellow solid.

LC-MS: M+H found: 466.0.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.56 (s, 1H), 9.70 (s, 1H), 8.26 (d, J = 5.4 Hz, 1H), 8.20 (s, 1H), 7.80 (s, 1H), 7.22 (d, J = 2.6 Hz, 1H), 6.83 – 6.68 (m, 3H), 6.31 (dd, J = 7.7, 2.0 Hz, 1H), 4.02 (s, 3H), 3.91 (s, 3H), 3.42 (td, J = 6.8, 2.5 Hz, 2H), 2.91 (t, J = 6.7 Hz, 2H).

Example 250. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(5-methyl-1,2-oxazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 510)**

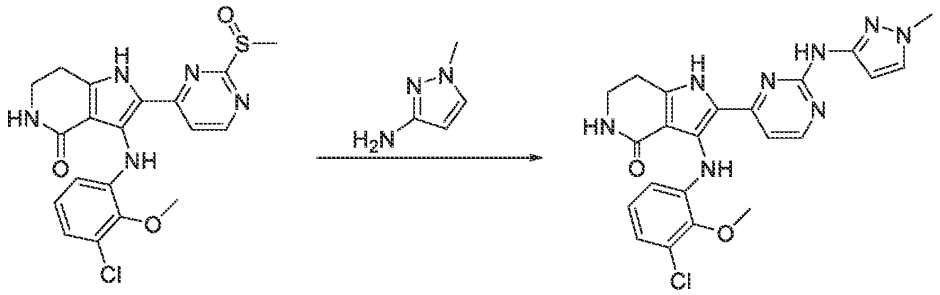


To a stirred mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.232 mmol, 1.00 equiv) in butan-2-ol (2.00 mL) were added 5-methyl-1,2-oxazol-4-amine (114 mg, 1.160 mmol, 5.00 equiv) and TFA (53 mg, 0.464 mmol, 2.00 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for overnight at 80 degrees C. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 58% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(5-methyl-1,2-oxazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (72.2 mg, 64.66%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 465.90.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.43 (s, 1H), 8.88 (s, 1H), 8.72 (s, 1H), 8.19 (d, J = 5.3 Hz, 1H), 7.73 (s, 1H), 7.21 (d, J = 2.5 Hz, 1H), 6.87 - 6.72 (m, 2H), 6.63 (d, J = 5.3 Hz, 1H), 6.31 (dd, J = 7.3, 2.3 Hz, 1H), 3.89 (s, 3H), 3.40 (dd, J = 6.8, 2.5 Hz, 2H), 2.89 (t, J = 6.8 Hz, 2H), 2.39 (s, 3H).

Example 251. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(1-methylpyrazol-3-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 509)**

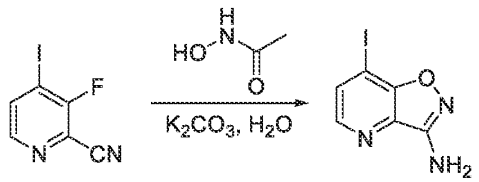


To a stirred mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) and 1-methylpyrazol-3-amine (180 mg, 1.85 mmol, 10 equiv) in 2-Butanol (2 mL) was added TFA (42.24 mg, 0.370 mmol, 2 equiv) in portions at 80 degrees C under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80 degrees C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 12% B to 42% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(1-methylpyrazol-3-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (14.9 mg, 16.66%) as a yellow solid.

LC-MS: M+H found: 465.0.

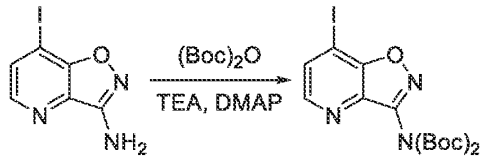
^{1}H NMR (300 MHz, DMSO-d6) δ 11.53 (s, 1H), 9.21 (s, 1H), 8.22 (d, J = 5.5 Hz, 1H), 7.94 (s, 1H), 7.55 (d, J = 2.3 Hz, 1H), 7.18 (s, 1H), 6.88 – 6.75 (m, 2H), 6.68 (d, J = 5.5 Hz, 1H), 6.59 (d, J = 2.3 Hz, 1H), 6.39 (dd, J = 7.0, 2.7 Hz, 1H), 3.88 (s, 3H), 3.75 (s, 3H), 3.41 (d, J = 2.4 Hz, 2H), 2.89 (t, J = 6.8 Hz, 2H).

Example 252. 2-{3-amino-[1,2]oxazolo[4,5-b]pyridin-7-yl}-3-[(3-chloro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 524)**



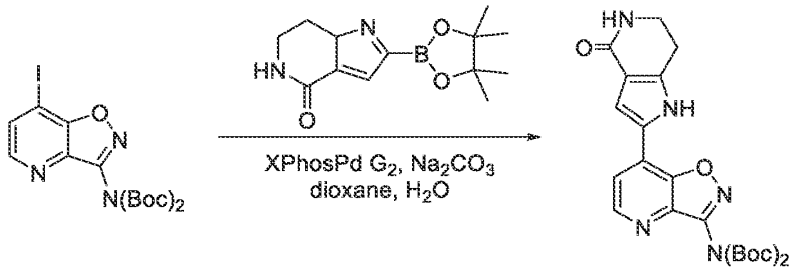
A mixture of 3-fluoro-4-iodopyridine-2-carbonitrile (2 g, 8.06 mmol, 1.00 equiv), acetohydroxamic acid (1.21 g, 16.13 mmol, 2.00 equiv) and K_2CO_3 (2.23 g, 16.13 mmol, 2 equiv) in H_2O (24 mL) was stirred overnight at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The aqueous layer was extracted with CH_2Cl_2 (3x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (12:1) to afford 7-iodo-[1,2]oxazolo[4,5-b]pyridin-3-amine (2 g, 95.01%) as a white solid.

LC-MS: $[M-H]^-$ found: 261.85.



A mixture of 7-iodo-[1,2]oxazolo[4,5-b]pyridin-3-amine (1.2 g, 4.59 mmol, 1.00 equiv), di-tert-butyl dicarbonate (3.01 g, 13.79 mmol, 3.00 equiv), DMAP (0.28 g, 2.29 mmol, 0.50 equiv) and TEA (1.40 g, 13.79 mmol, 3.00 equiv) in DCM (12 mL) was stirred overnight at room temperature under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (15:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-{7-iodo-[1,2]oxazolo[4,5-b]pyridin-3-yl}carbamate (1.65 g, 77.81%) as a white solid.

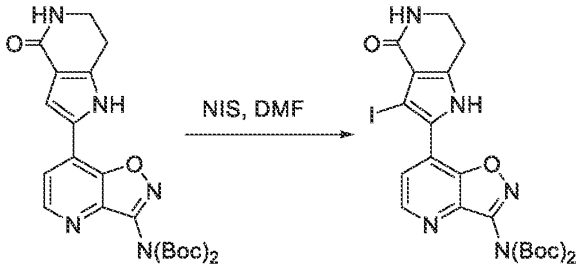
LC-MS: $[M-H]^-$ found: 461.90.



A mixture of tert-butyl N-(tert-butoxycarbonyl)-N-{7-iodo-[1,2]oxazolo[4,5-b]pyridin-3-yl}carbamate (0.8 g, 1.73 mmol, 1.00 equiv), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

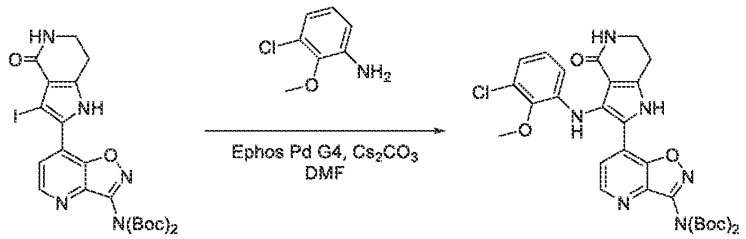
yl)-5H,6H,7H,7aH-pyrrolo[3,2-c]pyridin-4-one (0.68 g, 2.60 mmol, 1.50 equiv), 2nd Generation XPhos Precatalyst (0.14 g, 0.17 mmol, 0.10 equiv) and Na_2CO_3 (0.37 g, 3.47 mmol, 2.00 equiv) in 1,4-dioxane (12.00 mL) and water (3.00 mL) was stirred for 2 h at 50 °C under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (20:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(7-{4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-[1,2]oxazolo[4,5-b]pyridin-3-yl)carbamate (0.7 g, 85.96%) as a yellow solid.

LC-MS: $[M-H]^-$ found: 470.10.



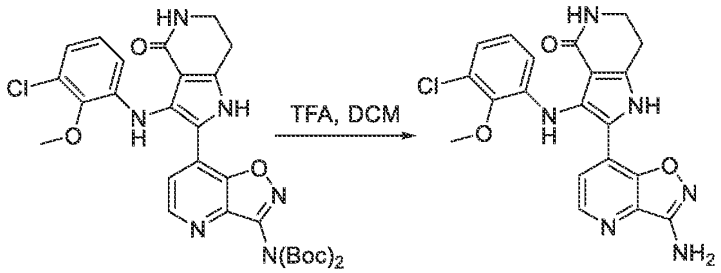
A mixture of tert-butyl N-(tert-butoxycarbonyl)-N-(7-{4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-[1,2]oxazolo[4,5-b]pyridin-3-yl)carbamate (0.7 g, 1.491 mmol, 1 equiv) and NIS (1.01 g, 4.473 mmol, 3 equiv) in DMF (10 mL) was stirred for overnight at room temperature under nitrogen atmosphere.Desired product could be detected by LCMS.The resulting mixture was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (20:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(7-{3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-[1,2]oxazolo[4,5-b]pyridin-3-yl)carbamate (210 mg, 23.66%) as a yellow solid.

LC-MS: $[M+H]^+$ found: 596.10.



A mixture of tert-butyl N-(tert-butoxycarbonyl)-N-(7-{3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-[1,2]oxazolo[4,5-b]pyridin-3-yl)carbamate (180 mg, 0.30 mmol, 1.00 equiv), 3-chloro-2-methoxyaniline (47 mg, 0.30 mmol, 1.00 equiv), EPhos Pd G4 (27 mg, 0.03 mmol, 0.10 equiv) and Cs_2CO_3 (197 mg, 0.60 mmol, 2.00 equiv) in DMF (2.00 mL) was stirred for 1 h at 50 °C under argon atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (15:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(7-{3-[(3-chloro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-[1,2]oxazolo[4,5-b]pyridin-3-yl)carbamate (120 mg, 63.50%) as a yellow solid.

LC-MS: $[M+H]^+$ found: 625.10.

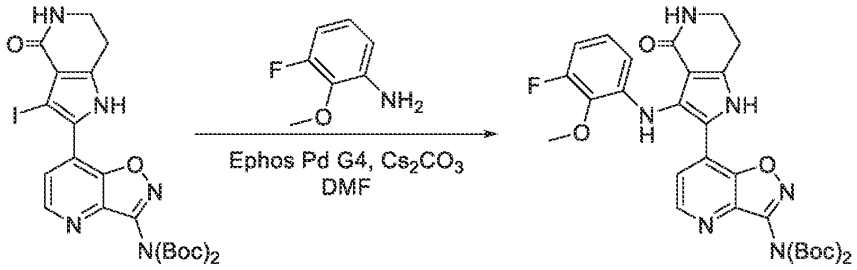


A mixture of tert-butyl N-(tert-butoxycarbonyl)-N-(7-{3-[(3-chloro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-[1,2]oxazolo[4,5-b]pyridin-3-yl)carbamate (120 mg, 0.19 mmol, 1.00 equiv) in TFA (2.00 mL) and DCM (2.00 mL) was stirred for 1 h at room temperature under air atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 33% B to 47% B in 10 min, 47% B; Wave Length: 254/220 nm; RT1(min): 6.0) to afford 2-{3-amino-[1,2]oxazolo[4,5-b]pyridin-7-yl}-3-[(3-chloro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (16.4 mg, 19.79%) as a yellow solid.

LC-MS: $[M+H]^+$ found: 424.90.

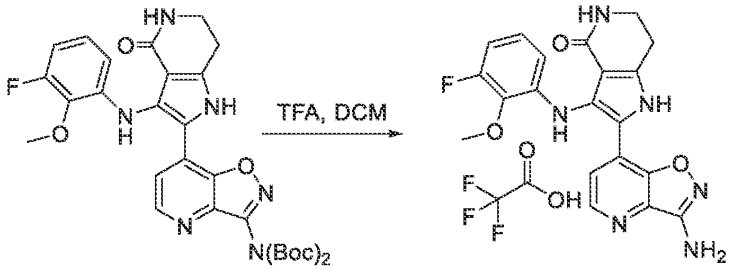
^{1}H NMR (300 MHz, DMSO-d6) δ 11.70 (s, 1H), 8.37 (d, 1H), 7.61 (s, 1H), 7.32 (d, 1H), 7.23 (s, 1H), 6.77-6.63 (m, 2H), 6.56 (s, 2H), 6.19-6.13 (m, 1H), 3.92 (s, 3H), 3.50-3.39 (m, 2H), 3.08-2.89 (m, 2H).

Example 253. 2-{3-amino-[1,2]oxazolo[4,5-b]pyridin-7-yl}-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid **(compound 523)**



A mixture of tert-butyl N-(tert-butoxycarbonyl)-N-(7-{3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-[1,2]oxazolo[4,5-b]pyridin-3-yl)carbamate (150 mg, 0.25 mmol, 1.00 equiv), 3-fluoro-2-methoxyaniline (106 mg, 0.75 mmol, 3.00 equiv), EPhos Pd G4 (23 mg, 0.025 mmol, 0.10 equiv) and Cs_2CO_3 (164 mg, 0.50 mmol, 2.00 equiv) in DMF (2.00 mL) was stirred for 2 h at 50°C under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH2Cl2 / MeOH (20:1) to afford tert-butyl N-(tert-butoxycarbonyl)-N-(7-{3-[(3-fluoro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-[1,2]oxazolo[4,5-b]pyridin-3-yl)carbamate (110 mg, 71.74%) as a yellow solid.

LC-MS: $[M+H]^+$ found: 609.10.



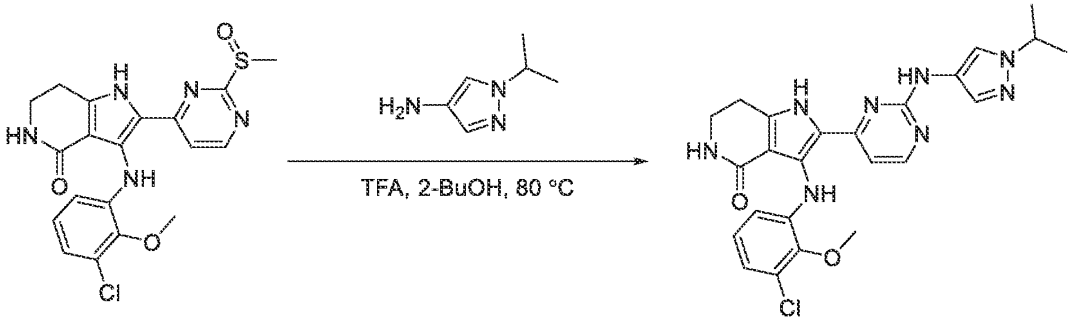
A solution of tert-butyl N-(tert-butoxycarbonyl)-N-(7-{3-[(3-fluoro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-[1,2]oxazolo[4,5-b]pyridin-3-yl)carbamate (110 mg, 0.18 mmol, 1.00 equiv) in DCM (2.00 mL) was added TFA (2.00 mL) at 0 ℃. The reaction was stirred for 1 h at room temperature under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.05%TFA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 47% B in 7 min, 47% B; Wave Length: 254 nm; RT1(min): 6.27) to afford 2-{3-amino-[1,2]oxazolo[4,5-b]pyridin-7-yl}-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid (27.8 mg, 29.38%) as an orange solid.

LC-MS: $[M+H]^+$ found: 409.00.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.62 (s, 1H), 8.37 (d, 1H), 7.60 (s, 1H), 7.31 (d, 1H), 7.24 (s, 1H), 6.67-6.48 (m, 3H), 6.00 (d, 1H), 3.95 (s, 3H), 3.42 (t, 2H), 2.93 (t, 2H).

19F NMR (300 MHz, DMSO-d6) δ -74.76, -132.60.

Example 254. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(1-isopropylpyrazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 516)**



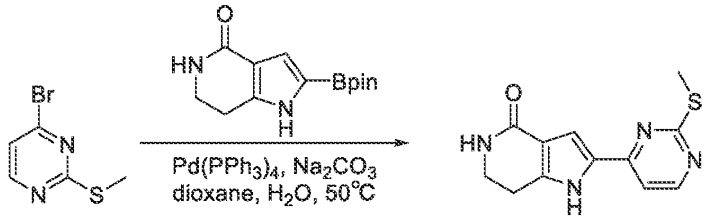
To a stirred mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70 mg, 0.162 mmol, 1.00 equiv) and 1-isopropylpyrazol-4-amine (101.44 mg, 0.810 mmol, 5 equiv) in butan-2-ol (1.8 mL, 24.284 mmol) was added TFA (36.96 mg, 0.324 mmol, 2 equiv) in portions at room temperature under nitrogen atmosphere.The resulting mixture was stirred

for overnight at 80 degrees C under nitrogen atmosphere.The resulting mixture was stirred for overnight at 80 degrees C under nitrogen atmosphere.Desired product could be detected by LCMS.The resulting mixture was concentrated under reduced pressure.The crude product (40 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150 mm 5um, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 19% B to 43% B in 8 min, 43% B; Wave Length: 254/220 nm; RT1(min): 8) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(1-isopropylpyrazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (10.5 mg, 13.04%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 492.95.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.50 (s, 1H), 9.06 (s, 1H), 8.19 (d, *J* = 5.3 Hz, 1H), 7.97 (s, 1H), 7.72 (s, 1H), 7.59 (s, 1H), 7.20 (s, 1H), 6.89 – 6.69 (m, 2H), 6.57 (d, *J* = 5.3 Hz, 1H), 6.32 (dd, *J* = 7.5, 2.1 Hz, 1H), 4.45 (p, *J* = 6.6 Hz, 1H), 3.90 (s, 3H), 3.40 (t, *J* = 6.8 Hz, 2H),2.90 (t, *J* = 6.8 Hz, 2H), 1.41 (d, *J* = 6.6 Hz, 6H).

Example 255. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-{[1-(2,2-difluoroethyl)pyrazol-3-yl]amino}pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 515)**



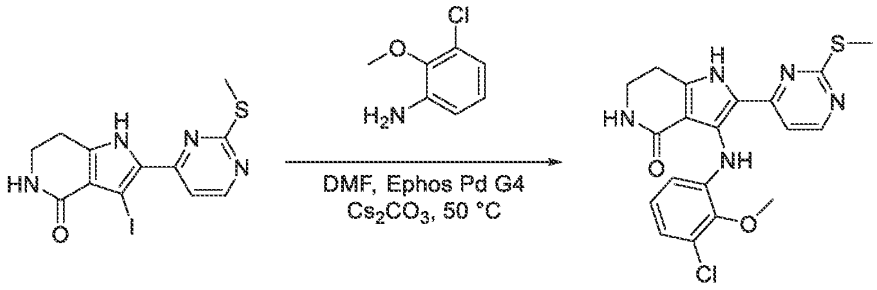
To a solution of 4-bromo-2-(methylsulfanyl)pyrimidine (4.00 g, 19.5 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (6.14 g, 23.4 mmol, 1.20 equiv) in H_2O (40 mL) and dioxane (200 mL) were added Na_2CO_3 (4.13 g, 39.0 mmol, 2.00 equiv) and $Pd(PPh_3)_4$ (2.25 g, 1.95 mmol, 0.10 equiv). After stirring for 2h at 50 degrees C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (4 g, 78.78%)

as a white solid.

LC-MS: $(M+H)^+$ found: 261.00.



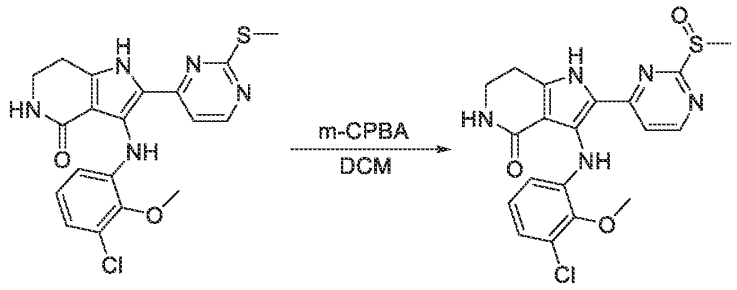
Into a 40-mL vial, was placed 2-[2-(methylsulfanyl) pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (1.00 g, 3.84 mmol, 1.00 equiv), DMF (10 mL), NIS (1.04 g, 4.61 mmol, 1.20 equiv). The resulting solution was stirred for 5 h at room temperature. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The reaction was quenched with sat. Na_2SO_3 (aq.) at 0 degrees C. The precipitated solids were collected by filtration and washed with water (3x50 mL). This resulted in 1.3 g (85.87%) of 3-iodo-2-[2-(methylsulfanyl) pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one as a white solid. LC-MS: $(M+H)^+$ found 386.80.



To a stirred mixture of 3-iodo-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1.00 g, 2.59 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (408 mg, 2.59 mmol, 1.00 equiv) in dioxane (26 mL) were added Ephos Pd G4 (2378 mg, 0.26 mmol, 0.10 equiv) and Cs_2CO_3 (1.69 g, 5.18 mmol, 2.00 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for overnight at 50 degrees C under argon atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was filtered, the filter cake was washed with DCM (2x50 mL). The filtrate was concentrated under reduced pressure. The resulting mixture was diluted with DMF (5mL). The residue was

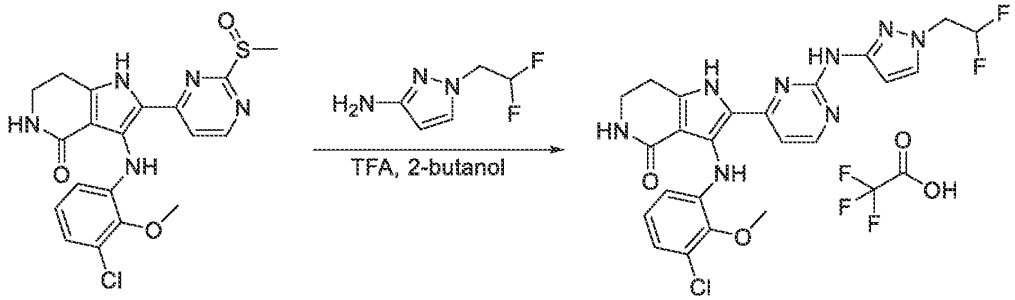
purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, NH3.H2O in water, 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in 580 mg (43.63%) of 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one as a yellow solid.

LC-MS: $(M+H)^+$ found: 416.10.



To a stirred mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (500 mg, 1.20 mmol, 1.00 equiv) in DCM (6 mL) was added m-CPBA (311 mg, 1.80 mmol, 1.50 equiv) in DCM (6 mL) dropwise at 0°C under air atmosphere.The resulting mixture was stirred for 1h at 0°C under air atmosphere.The reaction was quenched by the addition of sat. Na2SO3 (aq.) (5mL) at 0°C.The precipitated solids were collected by filtration and washed with water (1x5 mL).The resulting mixture was washed with 1x5 mL of MeOH.The resulting mixture was washed with 1x5 mL of ethyl ether to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (400 mg, 77.04%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 432.10.

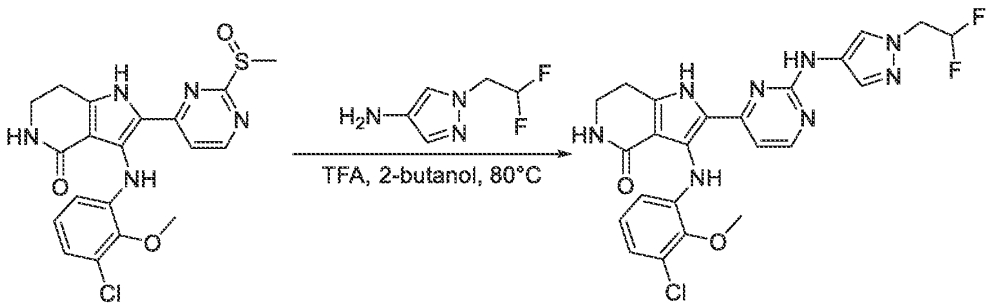


To a stirred mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (350 mg, 0.81 mmol, 1.00 equiv) and 1-(2,2-difluoroethyl)pyrazol-3-amine (596 mg, 4.05 mmol, 5.00 equiv) in butan-2-ol (5.00 mL) was added TFA (185 mg, 1.62 mmol, 2.00 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80 degrees C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product (350 mg) was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water(0.05%FA), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 34% B to 39% B in 8 min, 39% B; Wave Length: 254 nm; RT1(min): 6.88) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-{[1-(2,2-difluoroethyl)pyrazol-3-yl]amino}pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80.7 mg, 18.45%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 515.30.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 10.23 (s, 1H), 8.21 (d, J = 6.0 Hz, 2H), 7.73 (d, J = 2.4 Hz, 1H), 7.22 (s, 1H), 6.93 – 6.75 (m, 3H), 6.66 – 6.19 (m, 3H), 4.62 – 4.50 (m, 2H), 3.85 (s, 3H), 3.50 – 3.32 (m, 2H), 2.90 (t, J = 6.7 Hz, 2H).

Example 256. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-{[1-(2,2-difluoroethyl)pyrazol-4-yl]amino}pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 514)**



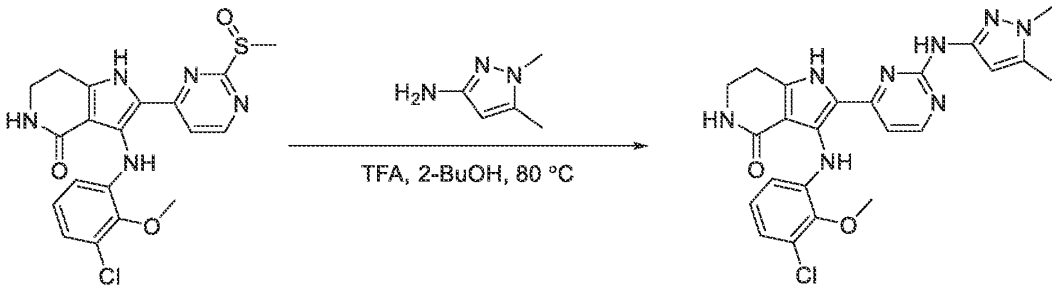
A solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70 mg, 0.16 mmol, 1.00 equiv) in butan-2-ol (3.50 mL) was added 1-(2,2-difluoroethyl) pyrazol-4-amine (71 mg, 0.48 mmol,

3.00 equiv) and TFA (37 mg, 0.32 mmol, 2.00 equiv) dropwise at room temperature under N_2 atmosphere. The resulting mixture was stirred for 2 h at 80 degrees C under N2 atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 29% B to 59% B in 7 min; Wave Length: 254 nm; RT1(min): 6.5; Number Of Runs:2) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-{[1-(2,2-difluoroethyl)pyrazol-4-yl]amino}pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (22 mg, 26.44%) as an off-white solid.

LC-MS: $(M+H)^+$ found: 514.95.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.44 (s, 1H), 9.17 (s, 1H), 8.21 (d, J = 5.1 Hz, 1H), 8.08 (s, 1H), 7.69 (d, J = 7.8 Hz, 2H), 7.21 (s, 1H), 6.83 – 6.74 (m, 2H), 6.60 – 6.54 (m, 1H), 6.37 – 6.30 (m, 2H), 4.62 – 4.51 (m, 2H), 3.91 (s, 3H), 3.43 – 3.40 (m, 2H), 2.90 (t, J = 6.6 Hz, 2H).

Example 257. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(1,5-dimethylpyrazol-3-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 513)**



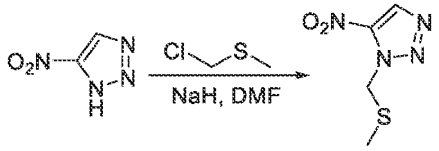
To a stirred mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.185 mmol, 1.00 equiv) and 1,5-dimethylpyrazol-3-amine (41.18 mg, 0.370 mmol, 2 equiv) in butan-2-ol (1.8 mL) was added TFA (42.24 mg, 0.370 mmol, 2 equiv) in portions at room temperature under nitrogen atmosphere.The resulting mixture was stirred for overnight at 80 degrees C under nitrogen atmosphere.Desired product could be detected by LCMS.The

resulting mixture was concentrated under reduced pressure.The crude product (80 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 27% B in 9 min, 27% B; Wave Length: 254/220 nm; RT1(min): 8.13) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(1,5-dimethylpyrazol-3-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (30.2 mg, 33.06%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 478.95.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.50 (s, 1H), 8.37 (s, 1H), 8.10 (d, J = 5.5 Hz, 1H), 7.90 (s, 1H), 7.52 (s, 1H), 7.17 (s, 1H), 6.95 – 6.73 (m, 2H), 6.60 (d, J = 5.5 Hz, 1H), 6.47 – 6.28 (m, 1H), 3.86 (s, 3H), 3.71 (s, 3H), 3.42 (s, 2H), 2.88 (t, J = 6.7 Hz, 2H), 2.14 (s, 3H).

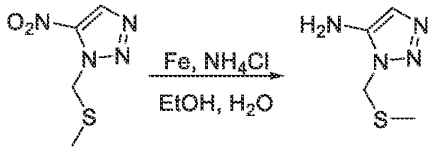
Example 258. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-{[3-(methanesulfonylmethyl)-1,2,3-triazol-4-yl]amino}pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 539)**



To a stirred solution of 4-nitro-3H-1,2,3-triazole (2.00 g, 17.53 mmol, 1 equiv) in DMF (20 mL) were added NaH (0.91 g, 22.79 mmol, 1.30 equiv, 60%) at 0 degrees C under N2 atmosphere. The resulting mixture was stirred for 0.5 h at 0 degrees C. To the above mixture was added chloromethyl methyl sulfide (2.71 g, 28.05 mmol, 1.60 equiv) in portions over 0 °C at N_2. The resulting mixture was stirred for additional 4 h at room temperature. The reaction was monitored by TCL and LCMS. The resulting solution was decolorized by the addition of H2O. The resulting mixture was extracted with EA (3 x 60 mL). The combined organic layers were washed with NaCl (3 x 40 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (9/1) to afford 1-[(methylsulfanyl)methyl]-5-nitro-1,2,3-triazole (900 mg, 29.17%) as a white oil.

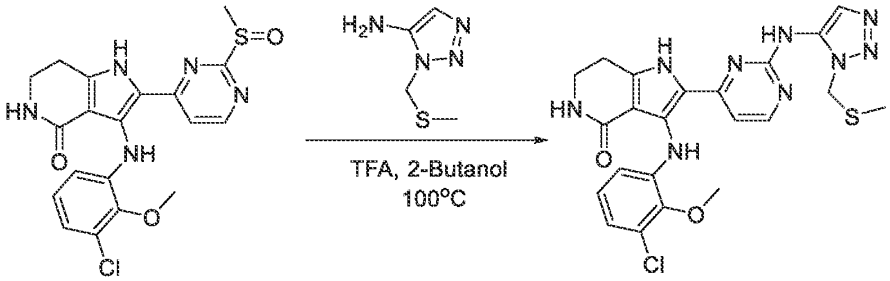
LC-MS: M+H found: 175.00.

^{1}H NMR (400 MHz, Chloroform-d) δ 8.15 (s, 1H), 5.41 (s, 2H), 2.25 (s, 3H).



To a solution of 1-[(methylsulfanyl)methyl]-5-nitro-1,2,3-triazole (0.20 g, 1.15 mmol, 1.00 equiv) and Fe (320 mg, 5.74 mmol, 5.00 equiv) in EtOH (4 mL) and H_2O (1 mL) were added NH_4Cl (614 mg, 11.48 mmol, 10 equiv) and stirred at 70 °C for 2 h. The resulting mixture was filtered, the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EA (1/1) to afford 3-[(methylsulfanyl)methyl]-1,2,3-triazol-4-amine (140 mg, 83.71%) as a yellow solid.

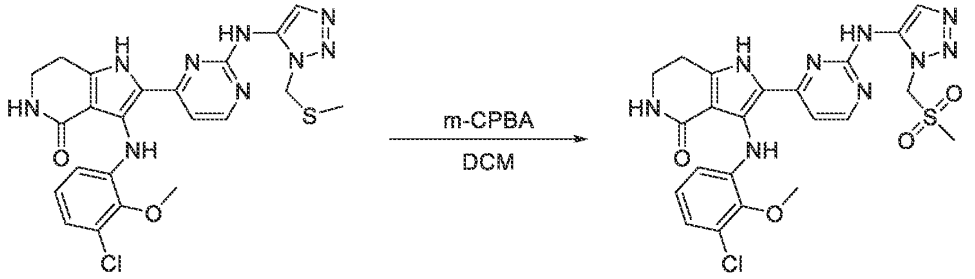
LC-MS: M+H found: 145.05.



To a stirred solution of 3-[(methylsulfanyl)methyl]-1,2,3-triazol-4-amine (100 mg, 0.69 mmol, 1.00 equiv) and 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (75 mg, 0.17 mmol, 0.25 equiv) in 2-butyl-alcohol (3 mL) were added 2-butyl-alcohol (3 mL) and TFA (52.9 mg, 0.46 mmol, 0.67 equiv) at 100 degrees C under N_2 atmosphere. The resulting mixture was stirred for overnight at 100 degrees C. The reaction was monitored by TLC and LCMS. The resulting mixture was concentrated under vacuum. The mixture was neutralized to pH 7 with Na_2CO_3.The resulting mixture was extracted with DCM/MeOH=10/1 (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4. The resulting mixture was filtered and concentrated under reduced pressure. The residue was washed with DCM (2mL), the

precipitated solids were collected by filtration and washed with DCM (3 x 2 mL) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-({3-[(methylsulfanyl)methyl]-1,2,3-triazol-4-yl}amino)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 9.01%) as a yellow solid.

LC-MS: M+H found: 512.05.



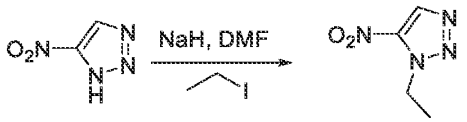
To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-({3-[(methylsulfanyl)methyl]-1,2,3-triazol-4-yl}amino)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70 mg, 0.14 mmol, 1.00 equiv) in DCM (3 mL) were added m-CPBA (58.9 mg, 0.34 mmol, 2.50 equiv) at 0 degrees C under N2 atmosphere. The resulting mixture was stirred for 2 h at 25 degrees C. The reaction was monitored by TCL and LCMS. The resulting solution was decolorized by the addition of Na_2SO_3. The resulting mixture was extracted with DCM/MeOH=10/1 (3 x 50 mL). The combined organic layers were washed with NaCl (3 x 50 mL), dried over anhydrous Na2SO4. The resulting mixture was concentrated under vacuum. The crude product (150 mg) was purified by Prep-HPLC with the following conditions ((2#SHIMADZU (HPLC-01)): Column, XSelect CSH Prep C18 OBD Column, 19*250 mm, 5μm; mobile phase, Water(0.1%FA) and ACN (35% ACN up to 65% in 7 min); Detector, UV(254 nm) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-{[3-(methanesulfonylmethyl)-1,2,3-triazol-4-yl]amino}pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (4.5 mg, 5.81%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 544.05.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.49 (s, 1H), 10.19 (s, 1H), 8.43 (s, 1H), 8.29 (d, J = 5.3 Hz, 1H), 7.78 (s, 1H), 7.24 (s, 1H), 6.85 – 6.68 (m, 3H), 6.31 (dd, J = 7.5, 2.2 Hz, 1H), 5.97 (s, 2H), 3.91 (s, 3H), 3.43 (td, J = 6.8, 2.4 Hz, 2H), 3.13 (s, 3H), 2.93 (t, J = 6.8 Hz,

2H).

Example 259. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(3-ethyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 538)**



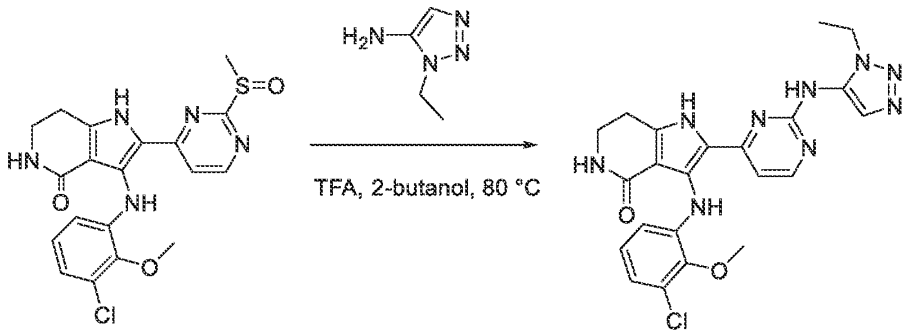
To a stirred solution of 4-nitro-3H-1,2,3-triazole (1.0 g, 8.76 mmol, 1.00 equiv) in dimethylformamide (10 mL) was added NaH (0.37 g, 9.20 mmol, 1.05 equiv, 60%) in portions at 0 degrees C under argon atmosphere. The resulting mixture was stirred for 30 min at 0 degrees C under argon atmosphere. To the above mixture was added ethyl iodide (1.78 g, 11.39 mmol, 1.3 equiv) in portions at 0 degrees C. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched by the addition of Water (10 mL) at 0 degrees C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (3x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford 1-ethyl-5-nitro-1,2,3-triazole (700 mg, 56.18%) as a yellow oil.

^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.71 (s, 1H), 4.59 (q, J = 7.3 Hz, 2H), 1.51 (t, J = 7.3 Hz, 3H).



To a stirred solution of 1-ethyl-5-nitro-1,2,3-triazole (300 mg, 2.11 mmol, 1.00 equiv) in EtOH (10 mL) was added Pd/C (100 mg, 0.09 mmol, 0.04 equiv, 10%) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for overnight at room temperature under hydrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with EtOH (3 x 50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (10:1) to afford 3-ethyl-1,2,3-triazol-4-amine (170 mg, 71.82%) as a yellow oil.

LC-MS: $(M+H)^+$ found: 112.95.

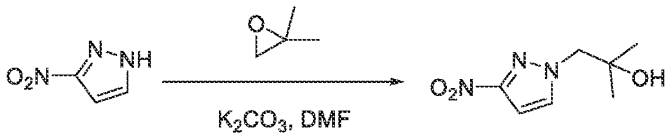


To a stirred mixture of 3-ethyl-1,2,3-triazol-4-amine (64 mg, 0.58 mmol, 5 equiv) and 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50 mg, 0.116 mmol, 1.00 equiv) in butan-2-ol (2 mL) were added TFA (52 mg, 0.46 mmol, 4 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 72 h at 80 degrees C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum and dissolved in DMSO. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 19*250 mm, 10μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH--Preparative; Flow rate: 25 mL/min; Gradient: 61% B to 72% B in 11 min, 72% B; Wave Length: 254 nm; RT1(min): 9.48) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(3-ethyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (5.4 mg, 9.72%) as a white solid.

LC-MS: $(M+H)^+$ found: 479.90.

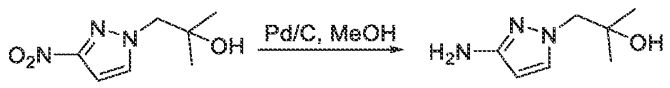
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (s, 1H), 9.67 (s, 1H), 8.33 – 8.17 (m, 2H), 7.81 (s, 1H), 7.21 (s, 1H), 6.83 – 6.65 (m, 2H), 6.70 (d, J = 5.3 Hz, 1H), 6.32 (m, J = 7.7, 2.0 Hz, 1H), 4.36 (q, J = 7.3 Hz, 2H), 3.91 (s, 3H), 3.42 (m, J = 6.8, 2.6 Hz, 2H), 2.90 (t, J = 6.8 Hz, 2H), 1.46 (t, J = 7.3 Hz, 3H).

Example 260. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-{[1-(2-hydroxy-2-methylpropyl)pyrazol-3-yl]amino}pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 537)**



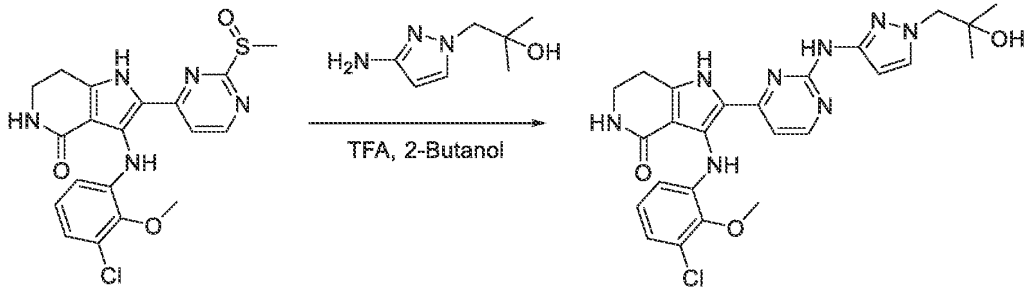
To a stirred mixture of 3-nitro-1H-pyrazole (2 g, 17.69 mmol, 1.00 equiv) and 2,2-dimethyloxirane (2.55 g, 35.37 mmol, 2 equiv) in DMF (20 mL) was added K_2CO_3 (3.67 g, 26.53 mmol, 1.5 equiv) in portions at room temperature under nitrogen atmosphere.The resulting mixture was stirred for 1h at 100 degrees C under nitrogen atmosphere.The resulting mixture was extracted with EtOAc (3 x 20mL). The combined organic layers were washed with brine (1x20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure.The residue was purified by Prep-TLC (PE / EA 3:1) to afford 2-methyl-1-(3-nitropyrazol-1-yl)propan-2-ol (3.1 g, 94.65%) as a colorless oil.

LC-MS: $(M+H)^+$ found: 186.



To a solution of 2-methyl-1-(3-nitropyrazol-1-yl)propan-2-ol (1 g, 5.40 mmol, 1.00 equiv) in 5 mL MeOH was added Pd/C (10%, 100mg) in a pressure tank. The mixture was hydrogenated at room temperature under 30 psi of hydrogen pressure for 1h, filtered through a Celite pad and concentrated under reduced pressure.The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm to afford 1-(3-aminopyrazol-1-yl)-2-methylpropan-2-ol (250 mg, 20.88%) as a off-white solid.

LC-MS: $(M+H)^+$ found: 156.

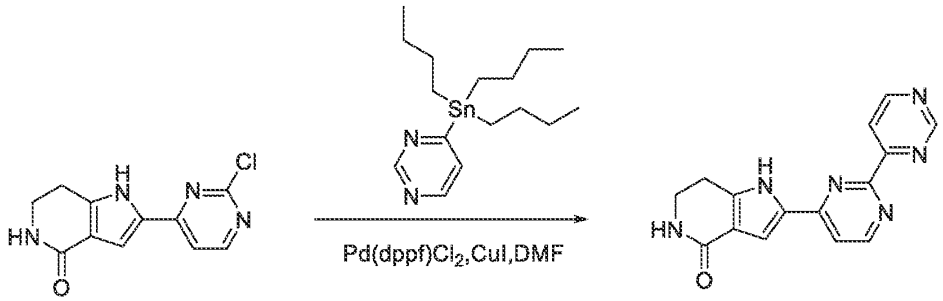


To a stirred mixture of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) and 1-(3-aminopyrazol-1-yl)-2-methylpropan-2-ol (144 mg, 0.93 mmol, 5 equiv) in butan-2-ol (4 mL) was added TFA (42 mg, 0.37 mmol, 2 equiv) in portions at room temperature under nitrogen atmosphere.The resulting mixture was stirred for 3days at 80 degrees C under nitrogen atmosphere.The resulting mixture was concentrated under reduced pressure.The crude product (80mg) was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 50% B in 8 min, 50% B; Wave Length: 254/220 nm; RT1(min): 5.7) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-{[1-(2-hydroxy-2-methylpropyl)pyrazol-3-yl]amino}pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (14.4 mg, 14.79%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 523.30.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.46 (s, 1H), 9.13 (s, 1H), 8.20 (d, J = 5.3 Hz, 1H), 7.82 (s, 1H), 7.52 (d, J = 2.3 Hz, 1H), 7.15 (d, J = 2.7 Hz, 1H), 6.85 – 6.70 (m, 2H), 6.70 – 6.59 (m, 2H), 6.37-6.30 (m, 1H), 4.71 (s, 1H), 3.88 (d, J = 8.3 Hz, 5H), 3.39 (d, J = 2.3 Hz, 2H), 2.87 (t, J = 6.8 Hz, 2H), 1.06 (s, 6H).

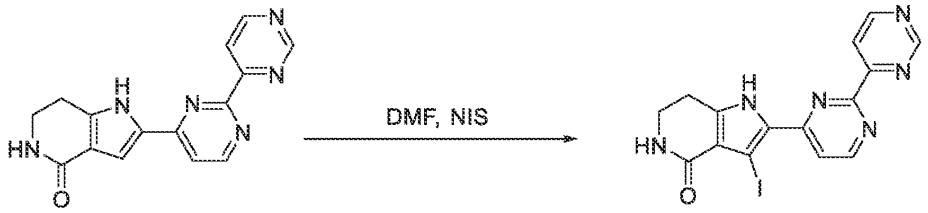
Example 261. 2-{[2,4'-bipyrimidin]-4-yl}-3-[(3-chloro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 546)**



To a stirred solution of 2-(2-chloropyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (200 mg, 0.804 mmol, 1.00 equiv) , $Pd(dppf)Cl_2CH_2Cl_2$ (65.52 mg, 0.080 mmol, 0.1 equiv) and CuI (15.32 mg, 0.080 mmol, 0.1 equiv) in DMF (2 mL) was added 4-

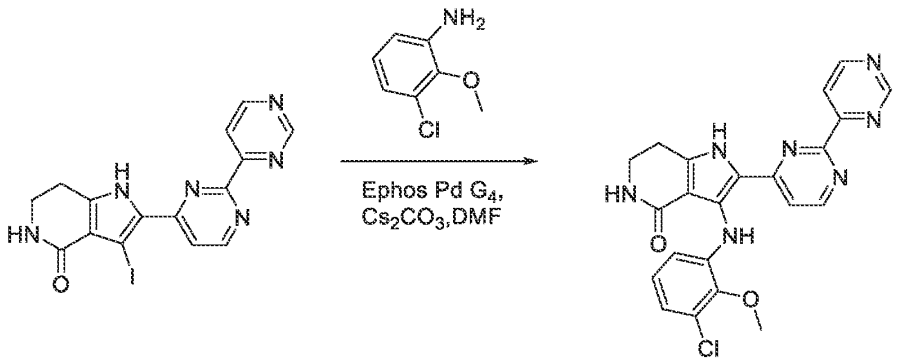
(tributylstannyl)pyrimidine (326.58 mg, 0.884 mmol, 1.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at 130 room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 2-{[2,4'-bipyrimidin]-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (120 mg, 51.04%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 292.95.



To a stirred solution of 2-{[2,4'-bipyrimidin]-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (120.00 mg, 0.411 mmol, 1 equiv) and NIS (92.36 mg, 0.411 mmol, 1 equiv) in DMF (2 mL) at room temperature under nitrogen atmosphere.The resulting mixture was stirred for 1h at 30 °C under nitrogen atmosphere.The reaction was quenched by the addition of sat. Sodium sulfite (aq.) (0.5mL) at 0°C.The resulting mixture was concentrated under vacuum.The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 2-{[2,4'-bipyrimidin]-4-yl}-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (150.00 mg, 87.37%) as a brown solid.

LC-MS: $(M+H)^+$ found: 419.00.



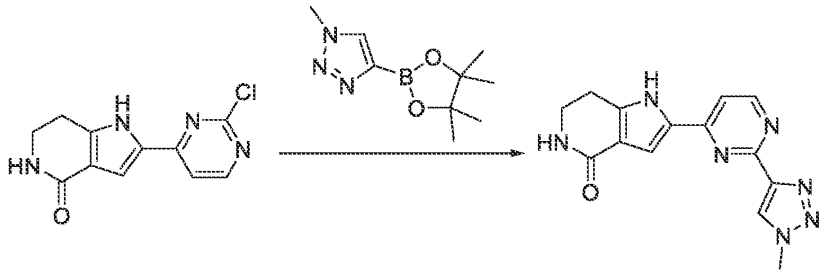
To a stirred mixture of 2-{[2,4'-bipyrimidin]-4-yl}-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-

c]pyridin-4-one (100 mg, 0.239 mmol, 1.00 equiv) and ,3-chloro-2-methoxyaniline (37.69 mg, 0.239 mmol, 1 equiv) in DMF (1.5 mL) were added EPhos Pd G4 (65.89 mg, 0.072 mmol, 0.3 equiv) and Cs_2CO_3 (155.82 mg, 0.478 mmol, 2 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 3h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure. The crude product (50.00 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 50% B in 8 min, 50% B; Wave Length: 254/220 nm; RT1(min): 7.53) to afford 2-{[2,4'-bipyrimidin]-4-yl}-3-[(3-chloro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (13.1 mg, 12.21%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 448.20.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 (s, 1H), 9.37 (d, J = 1.4 Hz, 1H), 9.02 (d, J = 5.2 Hz, 1H), 8.76 (d, J = 5.5 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 7.95 (s, 1H), 7.29 – 7.23 (m, 2H), 6.84 – 6.75 (m, 2H), 6.34 (d, J = 5.8, 1H), 3.93 (s, 3H), 3.45 (t, J = 7.8, 3.9 Hz, 2H), 2.95 (t, J = 6.8 Hz, 2H).

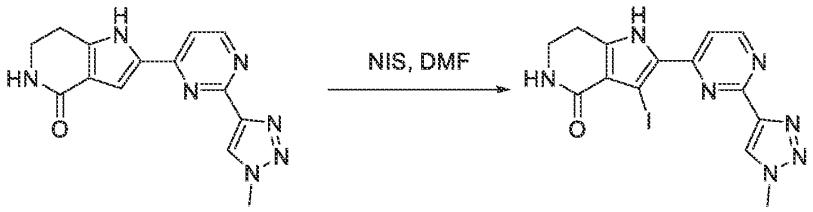
Example 262. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(1-methyl-1,2,3-triazol-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 545)**



To a stirred solution of 2-(2-chloropyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100.00 mg, 0.402 mmol, 1.00 equiv) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3-triazole (100.89 mg, 0.482 mmol, 1.2 equiv) in Toluene (1 mL) and H_2O (0.1 mL) was added $Pd(dppf)Cl_2CH_2Cl_2$ (32.76 mg, 0.040 mmol, 0.1 equiv) at

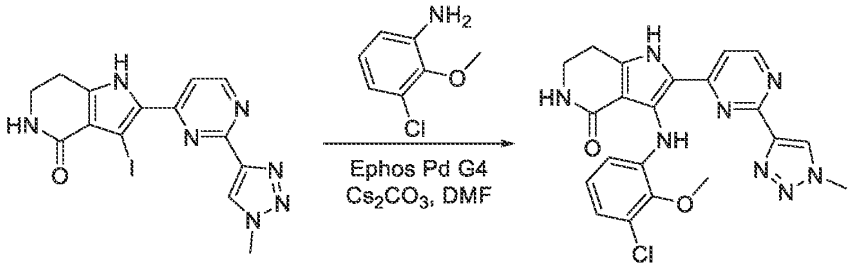
room temperature under argon atmosphere. The resulting mixture was stirred overnight at 50 °C under argon atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 2-[2-(1-methyl-1,2,3-triazol-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (60.00 mg, 50.52%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 296.2.



To a stirred solution of 2-[2-(1-methyl-1,2,3-triazol-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50.00 mg, 0.169 mmol, 1 equiv) in DMF (1 mL) was added NIS (38.09 mg, 0.169 mmol, 1 equiv) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 40 °C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (30:1) to afford 3-iodo-2-[2-(1-methyl-1,2,3-triazol-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70.00 mg, 98.15%) as a brown solid.

LC-MS: $(M+H)^+$ found: 421.90.



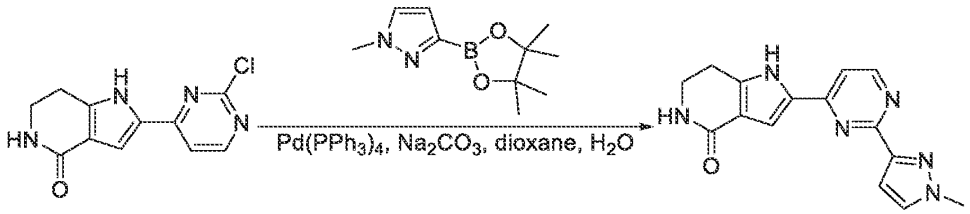
To a stirred mixture of 3-iodo-2-[2-(1-methyl-1,2,3-triazol-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (60 mg, 0.142 mmol, 1.00 equiv) and ,3-chloro-2-methoxyaniline (22.45 mg, 0.142 mmol, 1.00 equiv) in DMF (2 mL) were added EPhos Pd G4 (65.42 mg, 0.071 mmol, 0.50 equiv) and Cs_2CO_3 (92.83 mg, 0.284 mmol,

2.00 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 3h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure that was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford crude 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(1-methyl-1,2,3-triazol-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (40 mg) as a yellow oil. The crude product (40.00mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 49% B in 8 min, 49% B; Wave Length: 254/220 nm; RT1(min): 6.32) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(1-methyl-1,2,3-triazol-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (2.8 mg, 4.21%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 451.05.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.97 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.26 (s, 1H), 7.54 (s, 1H), 6.88 (d, J = 5.5 Hz, 1H),6.84-6.68(m, 2H), 6.38-6.32 (m, 1H), 5.33 (s, 1H), 4.22 (s, 3H), 4.09 (s, 3H), 3.64-3.60 (m, 2H), 3.01 (t, J = 6.8 Hz, 2H).

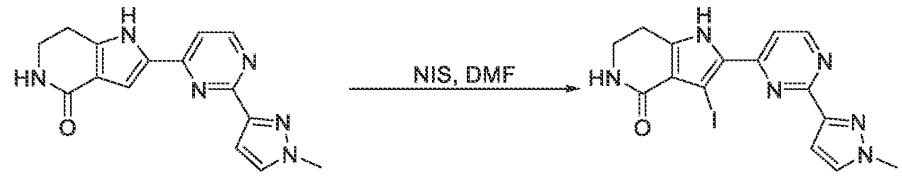
Example 263. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(1-methylpyrazol-3-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 544)**



To a stirred mixture of 2-(2-chloropyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100.00 mg, 0.402 mmol, 1.00 equiv) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (100.41 mg, 0.482 mmol, 1.20 equiv) in dioxane (4.00 mL) and H2O (0.80 mL) were added $Pd(PPh_3)_4$ (46.47 mg, 0.040 mmol, 0.10 equiv) and Na_2CO_3 (85.24 mg, 0.804 mmol, 2.00 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 90 degrees C under

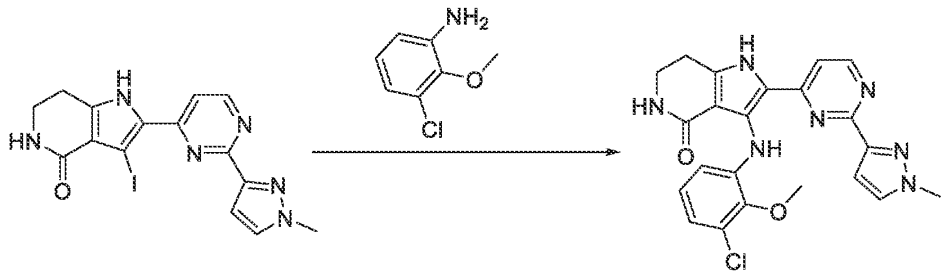
nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 2-[2-(1-methylpyrazol-3-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 83.65%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 294.95.



To a stirred mixture of 2-[2-(1-methylpyrazol-3-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100.00 mg, 0.340 mmol, 1.00 equiv)in DMF (3 mL)was added NIS (76.44 mg, 0.340 mmol, 1.00 equiv) in portions at 0 degrees C under air atmosphere. The resulting mixture was stirred for 4 h at room temperature under air atmosphere. The reaction was monitored by LCMS. The reaction was quenched with sat. sodium hyposulfite (aq.) at 0 degrees C. The precipitated solids were collected by filtration and washed with water (3x10 mL) to afford 3-iodo-2-[2-(1-methylpyrazol-3-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (105.00 mg, 69.86%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 420.85.



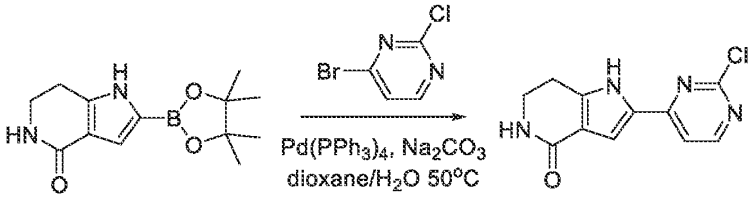
To a stirred mixture of 3-iodo-2-[2-(1-methylpyrazol-3-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100.00 mg, 0.238 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (37.50 mg, 0.238 mmol, 1.00 equiv) in DMF (2.00 mL) were added EPhos Pd G4 (12.73 mg, 0.024 mmol, 0.10 equiv) and Cs_2CO_3 (155.07 mg, 0.476 mmol, 2.00 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was

stirred for 2 h at 50 degrees C under argon atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(1-methylpyrazol-3-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (50.0 mg) as a light yellow solid. The crude product (50 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 58% B in 7 min, 58% B; Wave Length: 254/220 nm; RT1(min): 5.92) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(1-methylpyrazol-3-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (38.0 mg, 35.28%) as a off-white solid.

LC-MS: $(M+H)^+$ found: 451.00.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.86 (s, 1H), 8.55 (d, J = 5.4 Hz, 1H), 7.92 (s, 1H), 7.80 (d, J = 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 - 7.02 (m, 2H), 6.87 - 6.75 (m, 2H), 6.37 (dd, J = 6.1, 3.6 Hz, 1H), 3.93 (d, J = 6.8 Hz, 6H), 3.43 (td, J = 6.5, 2.4 Hz, 2H), 2.93 (t, J = 6.7 Hz, 2H).

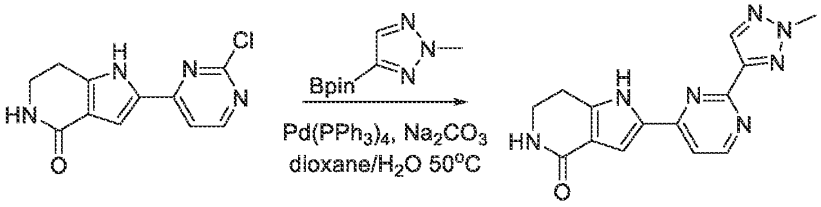
Example 264. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(2-methyl-1,2,3-triazol-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 543)**



To a stirred solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (1626.14 mg, 6.204 mmol, 1.2 equiv) and 4-bromo-2-chloropyrimidine (1000 mg, 5.170 mmol, 1 equiv) in 1,4-dioxane (5 mL) and H_2O (1 mL) was added $Pd(PPh_3)_4$ (1194.84 mg, 1.034 mmol, 0.2 equiv) and Na_2CO_3 (1095.88 mg, 10.340 mmol, 2 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 50 degrees C under nitrogen atmosphere. The

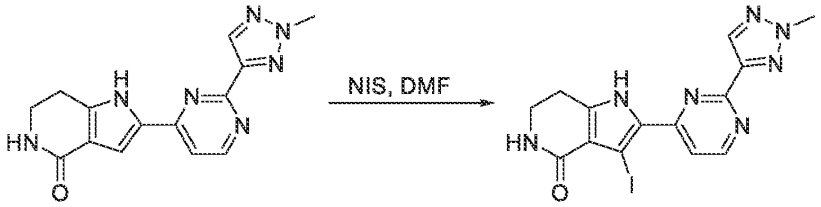
resulting mixture was diluted with water (10 mL). The precipitated solids were collected by filtration and washed with EtOAc (3x5 mL). The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 2-(2-chloropyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (852 mg, 66.27%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 249.2.



To a stirred mixture of 2-(2-chloropyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (200 mg, 0.80 mmol, 1 equiv) and 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3-triazole (201.8 mg, 0.97 mmol, 1.2 equiv) in 1,4-dioxane (5 mL, 0.06 mmol) and H_2O (1 mL) was added $Pd(PPh_3)_4$ (185.9 mg, 0.16 mmol, 0.2 equiv) and Na_2CO_3 (170.5 mg, 1.61 mmol, 2 equiv) at room temperature under argon atmosphere. The resulting mixture was stirred for overnight at 50°C under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The aqueous layer was extracted with EtOAc (3x20mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 2-[2-(2-methyl-1,2,3-triazol-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (150 mg, 63.16%) as a yellow solid.

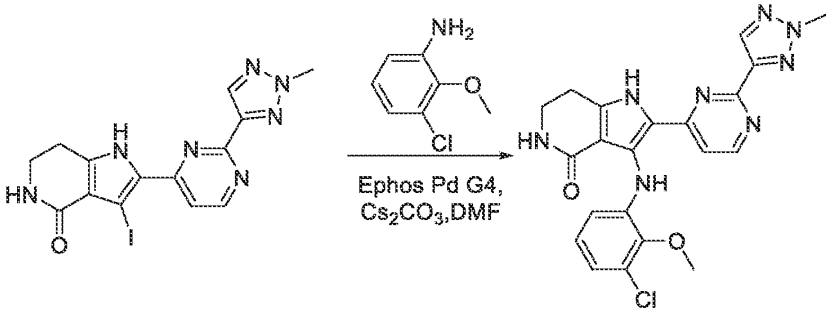
LC-MS: $(M+H)^+$ found: 296.



To a stirred mixture of 2-[2-(2-methyl-1,2,3-triazol-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-

pyrrolo[3,2-c]pyridin-4-one (150 mg, 0.51 mmol, 1 equiv) in DMF (5 mL) was added NIS (137.14 mg, 0.61 mmol, 1.2 equiv) in portions at room temperature under argon atmosphere.The resulting mixture was stirred for 3h at room temperature under argon atmosphere.The reaction was quenched with sat. sodium sulfite (aq.) at room temperature. The precipitated solids were collected by filtration and washed with water (3x10 mL). The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 3-iodo-2-[2-(2-methyl-1,2,3-triazol-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one as a light yellow solid.

LC-MS: $(M+H)^+$ found: 421.9.



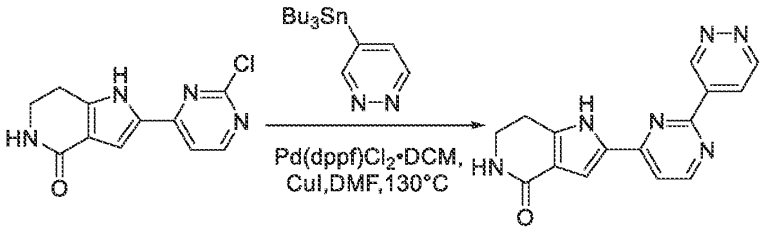
To a stirred mixture of 3-iodo-2-[2-(2-methyl-1,2,3-triazol-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.22 mmol, 1 equiv) and 3-chloro-2-methoxyaniline (36.14 mg, 0.23 mmol, 1.05 equiv) in DMF (2 mL) was added EPhos Pd G4 (20.06 mg, 0.02 mmol, 0.1 equiv) and Cs_2CO_3 (142.33 mg, 0.44 mmol, 2 equiv) at room temperature under argon atmosphere. The resulting mixture was stirred for3 h at 50 °C under argon atmosphere. The resulting mixture was concentrated under vacuum. The crude product (100mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 50% B in 9 min, 50% B; Wave Length: 254/220 nm; RT1(min): 8.85) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(2-methyl-1,2,3-triazol-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (16.5 mg, 16.45%) as a light yellow solid.

LC-MS: $(M+H)^+$ found: 451.00.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.93 (s, 1H), 8.61 (d, J = 5.5 Hz, 1H), 8.40 (s, 1H),

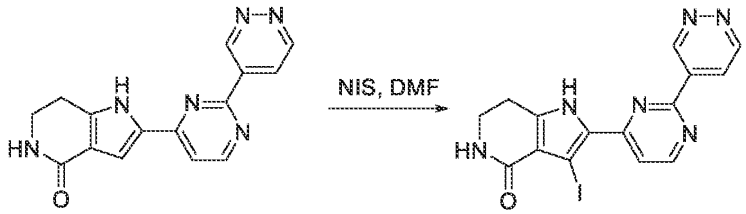
7.94 (s, 1H), 7.25 (t, J = 2.7 Hz, 1H), 7.11 (d, J = 5.5 Hz, 1H), 6.88 – 6.72 (m, 2H), 6.46 – 6.26 (m, 1H), 4.25 (s, 3H), 3.92 (s, 2H), 3.44 (td, J = 6.8, 2.5 Hz, 2H), 2.94 (t, J = 6.7 Hz, 2H).

Example 265. 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(pyridazin-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 542)**



To a solution of 2-(2-chloropyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (150 mg, 0.60 mmol, 1.00 equiv), CuI (11 mg, 0.06 mmol, 0.10 equiv) and Pd(dppf)Cl_2 CH_2Cl_2 (49 mg, 0.06 mmol, 0.10 equiv) in DMF (2.00 mL) were added 4-(tributylstannyl)pyridazine (240 mg, 0.65 mmol, 1.08 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at 130 degrees C under nitrogen atmosphere. The reaction was quenched by the addition of KF (sat.) (5.00 mL) at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 2-[2-(pyridazin-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (110 mg, 62.39%) as a yellow solid.

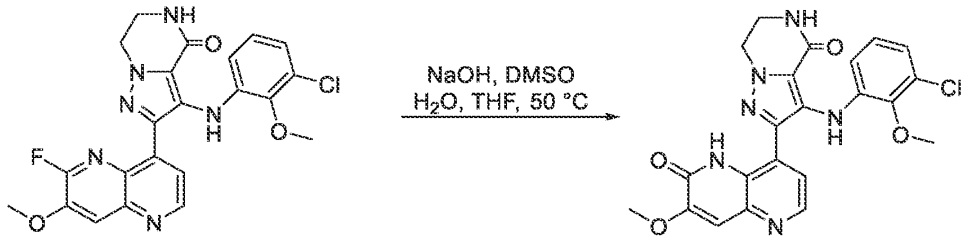
LC-MS: $(M+H)^+$ found: 293.2.



To a stirred solution of 2-[2-(pyridazin-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (90 mg, 0.31 mmol, 1.00 equiv) in DMF (2.00 mL) was added NIS (69 mg, 0.31 mmol, 1.00 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction

was quenched by the addition of Na_2SO_3 (sat.) (2.00 mL) at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 3-iodo-2-[2-(pyridazin-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (70 mg, 54.36%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 418.85.

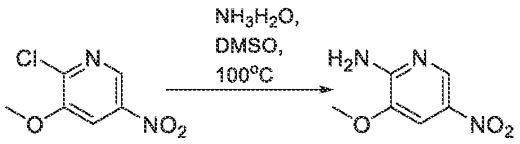


To a stirred solution of 3-iodo-2-[2-(pyridazin-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (60 mg, 0.143 mmol, 1.00 equiv) Cs_2CO_3 (93.49 mg, 0.286 mmol, 2 equiv) and EPhos Pd G4 (39.54 mg, 0.043 mmol, 0.3 equiv) in DMF (2 mL) was added 3-chloro-2-methoxyaniline (20.35 mg, 0.129 mmol, 0.9 equiv) dropwise at room temperature under argon atmosphere.The resulting mixture was stirred for 3 h at 50 °C under argon atmosphere. The resulting mixture was concentrated under reduced pressure.The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford crude product. The crude product (30 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 48% B in 8 min, 48% B; Wave Length: 254/220 nm; RT1(min): 8.85) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-[2-(pyridazin-4-yl)pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (16.5 mg, 25.14%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 447.90.

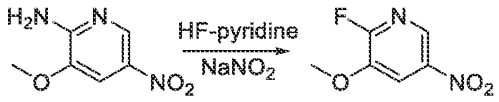
^1H NMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H), 10.23 (s, 1H), 9.45 (d, 1H), 8.74 (d, 1H), 8.55 – 8.49 (m, 1H), 7.86 (s, 1H), 7.31 (s, 1H), 7.16 (d, 1H), 6.85 – 6.76 (m, 2H), 6.34-6.31 (m, 1H), 3.95 (s, 3H), 3.48-3.46 (m, 2H), 2.97 (t, 2H).

Example 266. 3-[(3-fluoro-2-methoxyphenyl)amino]-2-(7-methoxy-6-{[1-(prop-2-enoyl)piperidin-4-yl]oxy}-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 554)**



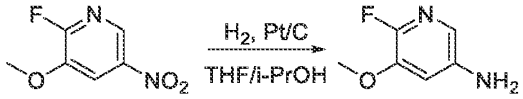
A solution of 2-chloro-3-methoxy-5-nitropyridine (6.6 g, 35.00 mmol, 1.00 equiv) in NH_3H_2O (75 mL) and DMSO (75 mL) was stirred for 8h at 100 degrees C . The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with H_2O (20 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product mixture was used in the next step directly without further purification to afford 3-methoxy-5-nitropyridin-2-amine (5.6 g, 94.60%) as a yellow solid.

LC-MS: $[M-H]^-$ found: 169.9.



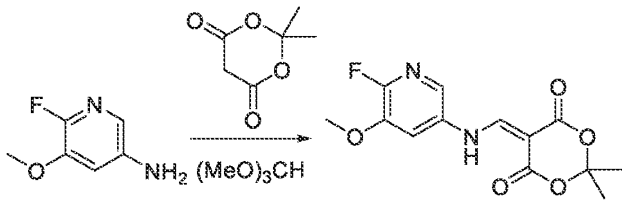
To a stirred solution of 3-methoxy-5-nitropyridin-2-amine (5.5 g, 32.5 mmol, 1 equiv) in 70% wt. HF-pyridine (110 mL) was added sodium nitrite (2.7 g, 39.1 mmol, 1.2 equiv) in portions at 0 degrees C under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched with ice/water at 0 degrees C. The mixture was basified to pH 9 with saturated Na_2CO_3 (aq.). The resulting mixture was extracted with EtOAc (3 x 400mL). The combined organic layers were washed with brine (2 x 200 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with hexane/ EtOAc (1:1) to afford 2-fluoro-3-methoxy-5-nitropyridine (4.2 g, 75%) as a yellow solid.

LC-MS: $[M-H]^-$ found: 173.05.



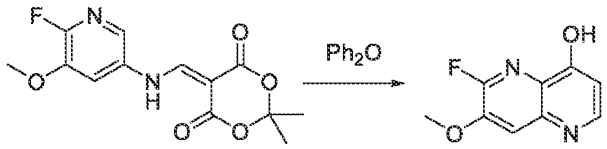
A solution of 2-fluoro-3-methoxy-5-nitropyridine (1 g, 5.81 mmol, 1.00 equiv) and Pt/C (1.13 g, 0.58 mmol, 0.1 equiv, 10%) in THF (2 mL) and i-PrOH (2 mL) was stirred for overnight at 45 degrees C under hydrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered. the filter cake was washed with DCM (2 x 100 mL). The filtrate was concentrated under reduced pressure. This resulted in 6-fluoro-5-methoxypyridin-3-amine (0.8 g, 96.88%) as a yellow solid.

LC-MS: $[M-H]^-$ found 142.90.



A solution of 6-fluoro-5-methoxypyridin-3-amine (3 g, 21.13 mmol, 1 equiv) and meldrum's acid (3.2 g, 21.13 mmol, 1.00 equiv) in trimethyl orthoformate (20 mL) was stirred for 2h at 108 degrees C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. This resulted in 5-{[(6-fluoro-5-methoxypyridin-3-yl)amino]methylidene}-2,2-dimethyl-1,3-dioxane-4,6-dione (6.2 g, 99%) as a brown solid.

LC-MS: $[M+H]^+$ found: 295.1.



A solution of 5-{[(6-fluoro-5-methoxypyridin-3-yl)amino]methylidene}-2,2-dimethyl-1,3-dioxane-4,6-dione (6 g, 20.27 mmol, 1 equiv) in diphenyl-ether (40 mL) was stirred for 1h at 250 degrees C under argon atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with Et_2O (20 mL). The precipitated solids were collected by filtration and washed with Et_2O (2 x 100 mL). This

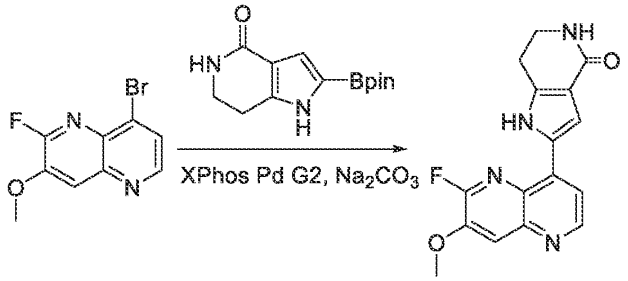
resulted in 6-fluoro-7-methoxy-1,5-naphthyridin-4-ol (3.8 g, 26.33%) as a brown solid.

LC-MS: $[M+H]^+$ found: 195.2.



A solution of 6-fluoro-7-methoxy-1,5-naphthyridin-4-ol (1 g, 5.15 mmol, 1.00 equiv) and PBr_3 (1.39 g, 5.15 mmol, 1.00 equiv) in DMF (28.00 mL) was stirred for 2h at 45 degrees C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with ice/water at 0 degrees C. The resulting mixture was extracted with EtOAc (2 x20 mL). The combined organic layers were washed with brine (1 x 60 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/ EtOAc (1:1) to afford 8-bromo-2-fluoro-3-methoxy-1,5-naphthyridine (1.1 g, 77.6%) as a yellow solid.

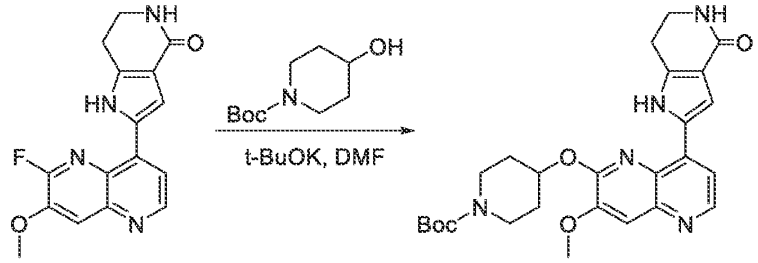
LC-MS: $[M+H]^+$ found: 257.1.



To a solution of 8-bromo-2-fluoro-3-methoxy-1,5-naphthyridine (360 mg, 1.40 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (440 mg, 1.68 mmol, 1.20 equiv) in 1,4-dioxane (4.00 mL) and water (1.00 mL) were added sodium methaneperoxoate sodium (299 mg, 2.80 mmol, 2.00 equiv) and 2nd Generation XPhos Precatalyst (110 mg, 0.14 mmol, 0.10 equiv). After stirring for 4h at 50 degrees C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (10:1) to afford 2-(6-fluoro-7-methoxy-1,5-naphthyridin-4-yl)-

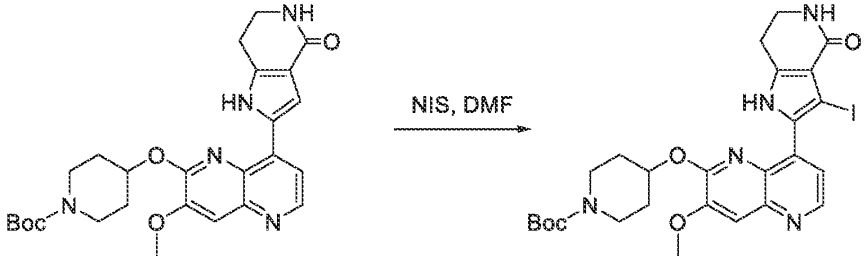
1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (250 mg, 57.16%) as a yellow solid.

LC-MS: $[M+H]^+$ found: 313.1.



To a stirred solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (193.34 mg, 0.960 mmol, 3 equiv) in t-BuOK (1M in THF, 0.35 mL, 0.352 mmol, 1.1 equiv) was added a solution of 2-(6-fluoro-7-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.32 mmol, 1.00 equiv) dropwiseat 0 °C under air atmosphere. The resulting mixture was stirred for overnight at room temperature under air atmosphere. The reaction was quenched with water(2 mL) at room temperature. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford tert-butyl 4-[(3-methoxy-8-{4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-1,5-naphthyridin-2-yl)oxy]piperidine-1-carboxylate (130 mg, 82.26%) as a yellow solid.

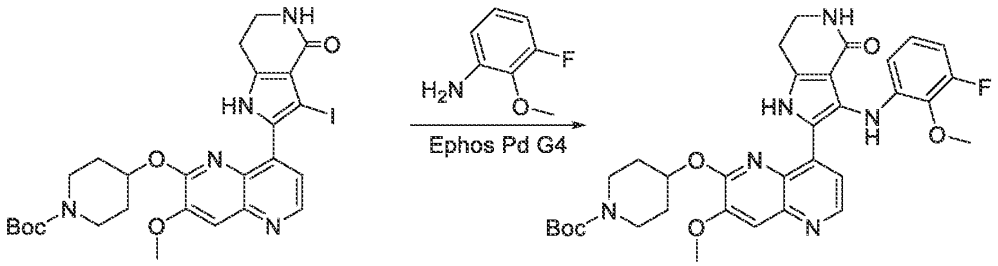
LC-MS: $[M+H]^+$ found: 494.15.



To a stirred solution of tert-butyl 4-[(3-methoxy-8-{4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-1,5-naphthyridin-2-yl)oxy]piperidine-1-carboxylate (120 mg, 0.24 mmol, 1.00 equiv) in dimethylformamide (4.00 mL) was added NIS (54 mg, 0.24 mmol, 1.00 equiv) dropwise at 0 °C under air atmosphere. The resulting mixture was stirred for overnight at room temperature under air atmosphere. The reaction was quenched by the addition of sodium hyposulfite (sat.) (2 mL) at room temperature. The resulting mixture

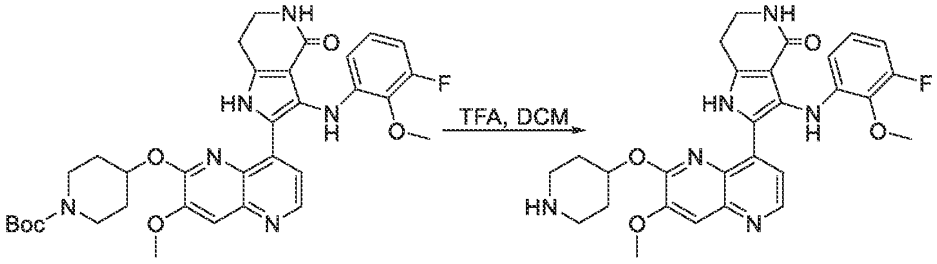
was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford tert-butyl 4-[(8-{3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-3-methoxy-1,5-naphthyridin-2-yl)oxy]piperidine-1-carboxylate (130 mg, 86.32%) as a yellow solid.

LC-MS: $[M+H]^+$ found: 620.05.



To a stirred mixture of caesio methaneperoxoate tert-butyl 4-[(8-{3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-3-methoxy-1,5-naphthyridin-2-yl)oxy]piperidine-1-carboxylate caesium (100 mg, 0.16 mmol, 1.00 equiv), Cs_2CO_3 (115 mg, 0.35 mmol, 2.00 equiv) and 3-fluoro-2-methoxyaniline (50 mg, 0.35 mmol, 2 equiv) in dimethylformamide (2.00 mL) was added Ephos Pd G4 (16 mg, 0.018 mmol, 0.10 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for 30 min at 50°C under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford tert-butyl 4-[(8-{3-[(3-fluoro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-3-methoxy-1,5-naphthyridin-2-yl)oxy]piperidine-1-carboxylate (110 mg, 97.91%) as a yellow solid.

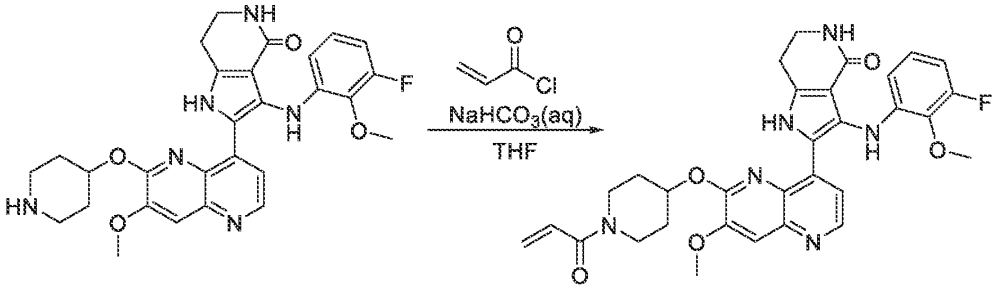
LC-MS: $[M+H]^+$ found: 633.15.



To a stirred solution of tert-butyl 4-[(8-{3-[(3-fluoro-2-methoxyphenyl)amino]-4-oxo-

1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-3-methoxy-1,5-naphthyridin-2-yl)oxy]piperidine-1-carboxylate (100 mg, 0.15 mmol, 1.00 equiv) in DCM (4.00 mL) was added TFA (1.00 mL) dropwise at 0 °C under air atmosphere. The resulting mixture was stirred for 2 h at room temperature under air atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

LC-MS: $[M+H]^+$ found: 533.15.



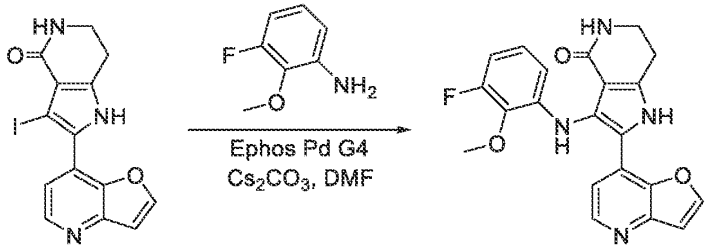
To a stirred solution of 3-[(3-fluoro-2-methoxyphenyl)amino]-2-[7-methoxy-6-(piperidin-4-yloxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (84 mg, 0.15 mmol, 1.00 equiv) in $NaHCO_3$(sat.) (4.00 mL) and tetrahydrofuran (4.00 mL) was added acryloyl chloride (14.28 mg, 0.158 mmol, 1 equiv) dropwise at 0°C under air atmosphere. The resulting mixture was stirred for 2 h at room temperature under air atmosphere. Desired product could be detected by LCMS. The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 46% B in 9 min, 46% B; Wave Length: 254/220 nm; RT1(min): 9.28) to afford 3-[(3-fluoro-2-methoxyphenyl)amino]-2-(7-methoxy-6-{[1-(prop-2-enoyl)piperidin-4-yl]oxy}-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (19.1 mg, 20.06%) as a yellow solid.

LC-MS: $[M+H]^+$ found: 586.95.

^1H NMR (300 MHz, DMSO-d_6) δ 12.31 (s, 1H), 8.41 (d, 1H), 7.74 (d, 2H), 7.46 (d, 1H),

6.69 – 6.48 (m, 3H), 6.31-6.37 (m, 1H), 6.03-6.07 (m, 1H), 5.73-5.77 (m, 1H), 5.50 – 5.44 (m, 1H), 5.29 (s, 1H), 4.14 (d, 3H), 3.88-4.02 (m, 6H), 3.64-3.74 (m, 3H), 3.00 (t, 2H), 2.40-2.20 (d, 4H).

Example 267. 3-[(3-fluoro-2-methoxyphenyl)amino]-2-{furo[3,2-b]pyridin-7-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 553)**



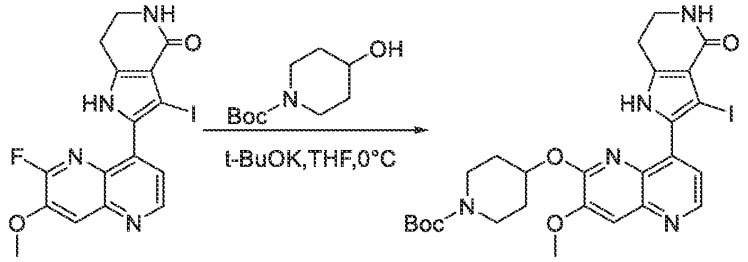
To a stirred mixture of 2-{furo[3,2-b]pyridin-7-yl}-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.211 mmol, 1.00 equiv) and caesio methaneperoxoate caesium (137.92 mg, 0.422 mmol, 2 equiv) in dimethylformamide (2 mL) were added Ephos Pd G4 (19.38 mg, 0.021 mmol, 0.1 equiv) and 3-fluoro-2-methoxyaniline (26.80 mg, 0.190 mmol, 0.9 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for 1 h at 50 degrees C under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM / MeOH (10:1) to afford crude product (62 mg). The crude product (62 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 50% B in 7 min, 50% B; Wave Length: 254/220 nm; RT1(min): 6.12) to afford 3-[(3-fluoro-2-methoxyphenyl)amino]-2-{furo[3,2-b]pyridin-7-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (42.8 mg, 51.02%) as a white solid.

LC-MS: $[M+H]^+$ found: 393.25.

^1H NMR (400 MHz, DMSO-d6) δ 11.58 (s, 1H), 8.33 – 8.29 (m, 2H), 7.54 (s, 1H), 7.23 – 7.11 (m, 3H), 6.59 – 6.43 (m, 2H), 5.99 (d, 1H), 3.92 (s, 3H), 3.42-3.45 (m, 2H), 2.93-2.89 (m, 2H).

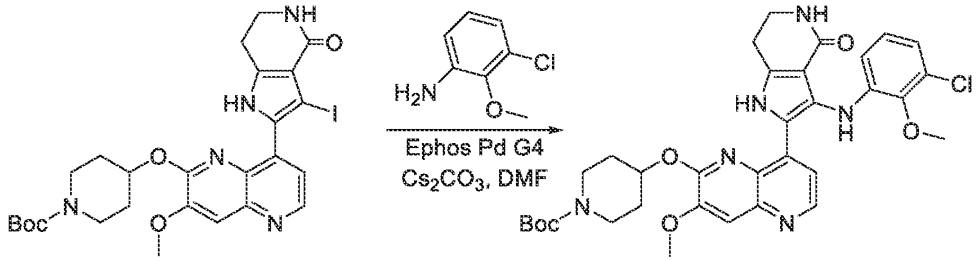
Example 268. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(7-methoxy-6-{[1-(prop-2-

enoyl)piperidin-4-yl]oxy}-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 731)**



To a stirred solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (193 mg, 0.96 mmol, 3.00 equiv) in THF(2.00 mL) was added 2-(6-fluoro-7-methoxy-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.32 mmol, 1.00 equiv) and t-BuOK (1M in THF, 0.35 mL, 0.35 mmol, 1.10 equiv) dropwise at 0 C. The resulting mixture was stirred for overnight at room temperature under air atmosphere. The reaction was quenched with water at room temperature. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (10:1) to afford tert-butyl 4-[(3-methoxy-8-{4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-1,5-naphthyridin-2-yl)oxy]piperidine-1-carboxylate (130 mg, 82.26%) as a yellow solid.

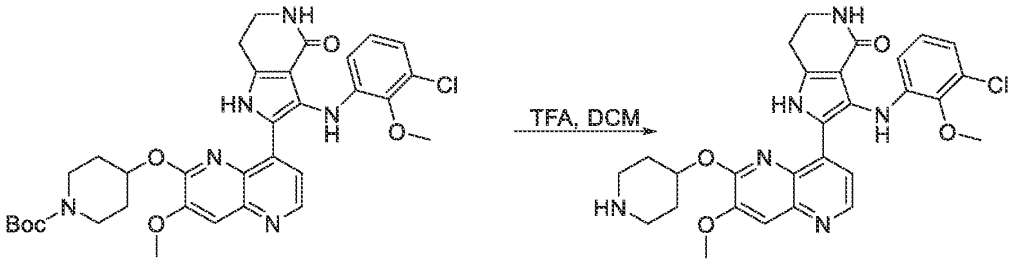
LC-MS: $[M-H]^-$ found: 494.15.



To a stirred mixture of tert-butyl 4-[(8-{3-iodo-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-3-methoxy-1,5-naphthyridin-2-yl)oxy]piperidine-1-carboxylate (120 mg, 0.19 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (30 mg, 0.19 mmol, 1.00 equiv) in dimethylformamide (3.00 mL) were added Ephos Pd G4 (17 mg, 0.02 mmol, 0.10 equiv) and Cs_2CO_3 (126 mg, 0.38 mmol, 2.00 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for 30 min at

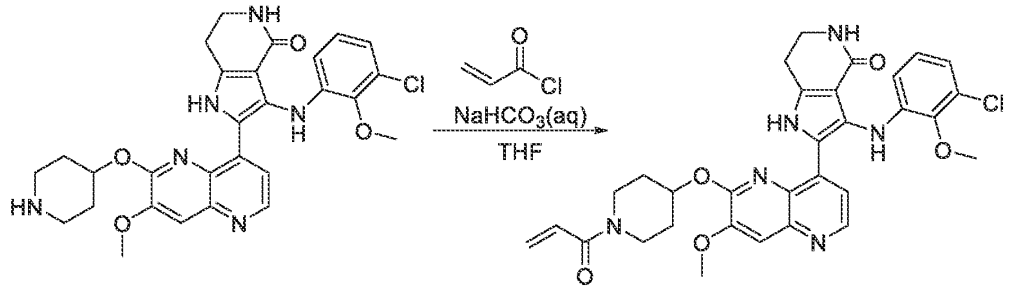
50 °C under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford tert-butyl 4-[(8-{3-[(3-chloro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-3-methoxy-1,5-naphthyridin-2-yl)oxy]piperidine-1-carboxylate (120 mg, 95.43%) as a yellow solid.

LC-MS: $[M-H]^-$ found: 649.30.



To a stirred solution of tert-butyl 4-[(8-{3-[(3-chloro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}-3-methoxy-1,5-naphthyridin-2-yl)oxy]piperidine-1-carboxylate (100 mg, 0.15 mmol, 1.00 equiv) in DCM (0.8 mL) was added TFA (0.20 mL) dropwise at 0° C. The resulting mixture was stirred for 1h at room temperature under air atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification

LC-MS: $[M-H]^-$ found: 549.10.



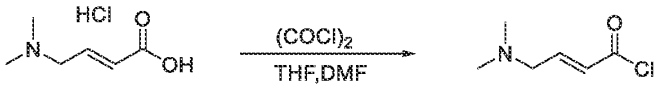
To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-[7-methoxy-6-(piperidin-4-yloxy)-1,5-naphthyridin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (84 mg, 0.15 mmol, 1.00 equiv) in $NaHCO_3$(sat.) (4.00 mL) and THF (4.00 mL) was added acryloyl

chloride (14 mg, 0.15 mmol, 1.00 equiv) dropwise at 0℃. The resulting mixture was stirred for 2h at room temperature under air atmosphere. The resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5 μ m; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 46% B in 10 min, 46% B; Wave Length: 254/220 nm; RT1(min): 9.67) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(7-methoxy-6-{[1-(prop-2-enoyl)piperidin-4-yl]oxy}-1,5-naphthyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (23.2 mg, 24.81%) as a yellow solid.

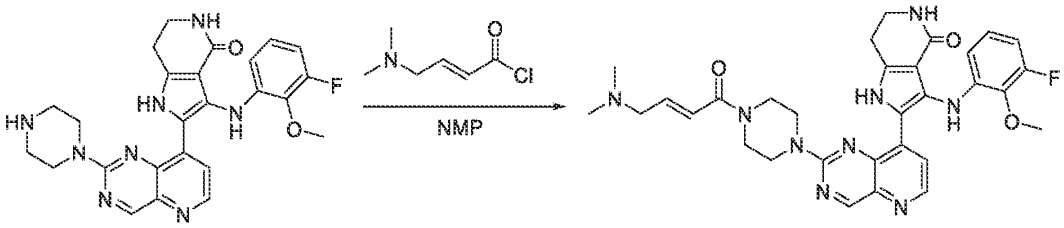
LC-MS: $[M+H]^+$ found: 603.25.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.32 (s, 1H), 8.43 (d, 1H), 7.77 (s, 1H), 7.67 (s, 1H), 7.41 (d, 1H), 6.91-6.75 (m, 1H), 6.69-6.59 (m, 2H), 6.37-6.31 (m, 1H), 6.20-6.17 (m, 1H), 5.77-5.73 (m, 1H), 5.45 (t,1H), 5.28 (s, 1H), 4.12 (s, 3H), 4.03 (s, 3H), 3.99-3.80(m, 3H), 3.75-3.62 (m, 3H), 2.99 (t, 2H), 2.30-2.10 (m, 4H).

Example 269. 2-(2-{4-[(2E)-4-(dimethylamino)but-2-enoyl]piperazin-1-yl}pyrido[3,2-d]pyrimidin-8-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 577)**



To a stirred solution of (2E)-4-(dimethylamino)but-2-enoic acid hydrochloride (100 mg, 0.60 mmol, 1.00 equiv) in THF (3 mL) and DMF 1 drop was added (COCl)2 (84 mg, 0.66 mmol, 1.10 equiv) dropwise at 0°C. The resulting mixture was stirred for 2 h at 0°C. TLC (DCM:MeOH=5:1) showed a new spot was detected. The resulting mixture was used in the next step directly without further purification.

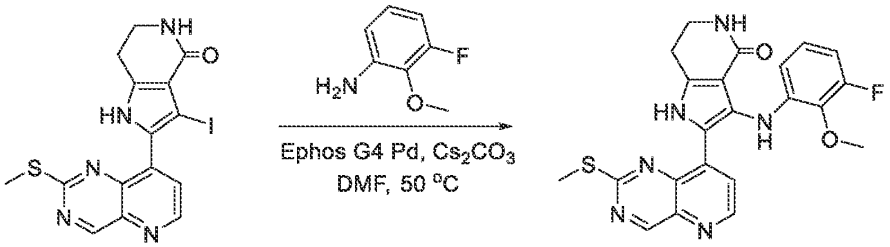


To a stirred solution of 3-[(3-fluoro-2-methoxyphenyl)amino]-2-[2-(piperazin-1-yl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.21 mmol, 1.00 equiv) in NMP (3 mL) was added the solution of (2E)-4-(dimethylamino)but-2-enoyl chloride (30 mg, 0.21 mmol, 1.00 equiv) in 1mL THF dropwise at 0°C. The resulting mixture was stirred for 2 h at 0°C. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 40% B in 10 min, 40% B; Wave Length: 254/220 nm; RT1(min): 9.67) to afford 2-(2-{4-[(2E)-4-(dimethylamino)but-2-enoyl]piperazin-1-yl}pyrido[3,2-d]pyrimidin-8-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (19.0 mg, 14.78%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 600.05.

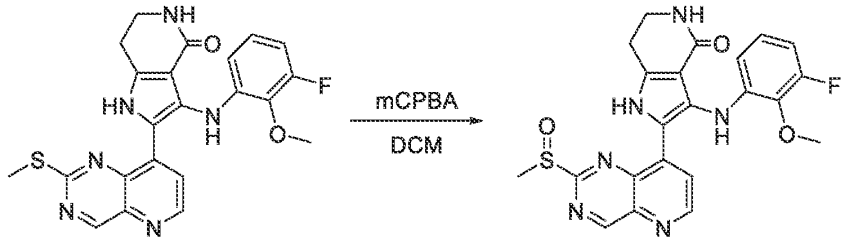
^{1}H NMR (300 MHz, Chloroform-d) δ 12.71 (s, 1H), 9.26 (s, 1H), 8.43 (d, J = 4.9 Hz, 1H), 7.75 (s, 1H), 7.45 (d, J = 4.9 Hz, 1H), 6.02 – 6.90 (m, 1H), 6.73 – 6.40 (m, 3H), 6.08 – 6.01 (m, 1H), 5.30 (d, J = 2.6 Hz, 1H), 4.29 – 3.73 (m, 11H), 3.73 – 3.63 (m, 2H), 3.19 (d, J = 5.8 Hz, 2H), 3.02 (t, J = 6.7 Hz, 2H), 2.35 (s, 6H).

Example 270. 3-[(3-fluoro-2-methoxyphenyl)amino]-2-{2-[4-(prop-2-enoyl)piperazin-1-yl]pyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 576)**



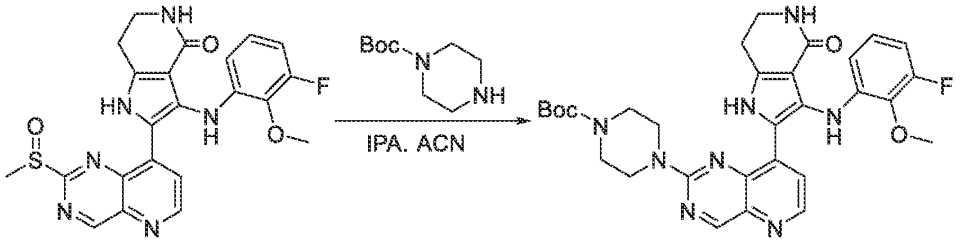
To a solution of 3-iodo-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (330 mg, 0.75 mmol, 1.00 equiv) and 3-fluoro-2-methoxyaniline (117 mg, 0.83 mmol, 1.10 equiv) in DMF was added Cs_2CO_3 (738 mg, 2.26 mmol, 3.00 equiv), EPhos Pd G4 (69 mg, 0.08 mmol, 0.10 equiv). The resulting mixture was stirred for 1 h at 50 °C under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (10:1) to afford 2-bromo-3-[(3-chloro-2-methoxyphenyl)amino]-5H,6H,7H-pyrazolo[1,5-a]pyrazin-4-one (226 mg, 66.47%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 451.



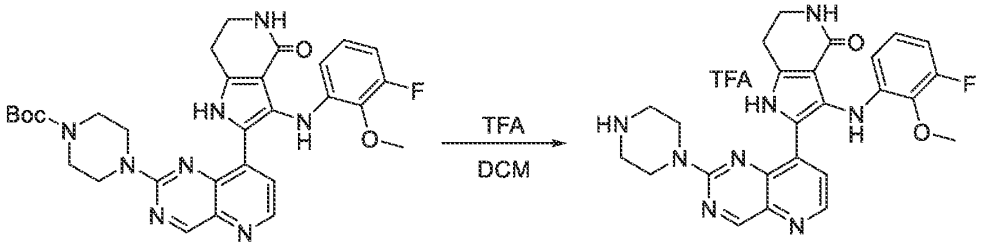
To a sealed tube were added 3-[(3-fluoro-2-methoxyphenyl)amino]-2-[2-(methylsulfanyl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (206 mg, 0.46 mmol, 1.00 equiv) and DCM (15 mL), at 0 °C, m-CPBA (87 mg, 0.50 mmol, 1.10 equiv) in DCM was added and stirred for 1h at room temperature. The reaction was quenched by the addition of Water (20 mL) at 25 °C. The resulting mixture was extracted with CH_2Cl_2 (2x50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give 3-[(3-fluoro-2-methoxyphenyl)amino]-2-{2-methanesulfinylpyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (200 mg). The crude product was used in the next step directly without further purification.

LC-MS: $(M+H)^+$ found: 467.



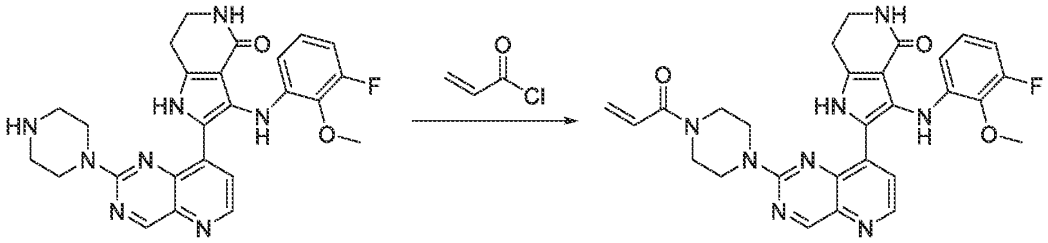
To a sealed tube were added 3-[(3-fluoro-2-methoxyphenyl)amino]-2-{2-methanesulfinylpyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (206 mg, 0.44 mmol, 1.00 equiv), tert-butyl piperazine-1-carboxylate (411 mg, 2.21 mmol, 5.00 equiv) in IPA (5 mL) and ACN (5 mL) stirred overnight at 70 °C under N2 atmosphere. The resulting mixture was concentrated under vacuum to give tert-butyl 4-(8-{3-[(3-fluoro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}pyrido[3,2-d]pyrimidin-2-yl)piperazine-1-carboxylate (400 mg, crude) as brown yellow solid.

LC-MS: $(M+H)^+$ found: 589.



To a stirred solution of tert-butyl 4-(8-{3-[(3-fluoro-2-methoxyphenyl)amino]-4-oxo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-2-yl}pyrido[3,2-d]pyrimidin-2-yl)piperazine-1-carboxylate (400 mg, crude) in DCM (10 mL) was added TFA (3 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2h at room temperature under hydrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography (mobile phase, MeCN in water, 0% to 100%) to afford 3-[(3-fluoro-2-methoxyphenyl)amino]-2-[2-(piperazin-1-yl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one; trifluoroacetic acid (300 mg, 73.27%) as brown solid.

LC-MS: $(M+H)^+$ found: 489.

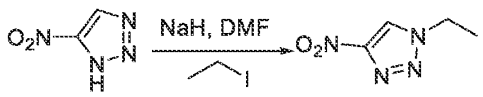


To a stirred solution of 3-[(3-fluoro-2-methoxyphenyl)amino]-2-[2-(piperazin-1-yl)pyrido[3,2-d]pyrimidin-8-yl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.21 mmol, 1.00 equiv) in THF (3 mL) was added $NaHCO_3$ (0.1 mL) at 0°C. To the above mixture was added acryloyl chloride (17 mg, 0.184 mmol, 0.90 equiv) dropwise at 0°C. The resulting mixture was stirred for 2 h at 0°C. Desired product could be detected by LCMS. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 40% B in 10 min, 40% B; Wave Length: 254/220 nm; RT1(min): 9.67) to afford 3-[(3-fluoro-2-methoxyphenyl)amino]-2-{2-[4-(prop-2-enoyl)piperazin-1-yl]pyrido[3,2-d]pyrimidin-8-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (13.8 mg, 11.82%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 543.05.

^1H NMR (300 MHz, Chloroform-d) δ 12.63 (s, 1H), 9.19 (s, 1H), 8.36 (d, J = 4.9 Hz, 1H), 7.69 (s, 1H), 7.38 (d, J = 4.9 Hz, 1H), 6.68 – 6.40 (m, 3H), 6.38 – 6.30 (m, 1H), 6.02 – 5.92 (m, 1H), 5.80 – 5.68 (m, 1H), 5.26 (s, 1H), 4.22 – 3.67 (m, 11H), 3.61 (m, 2H), 2.93 (t, J = 6.7 Hz, 2H).

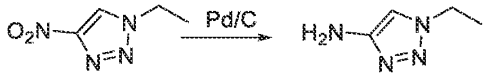
Example 271. 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(1-ethyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 594)**



To a stirred solution of 4-nitro-3H-1,2,3-triazole (1.0 g, 8.77 mmol, 1.00 equiv) in DMF

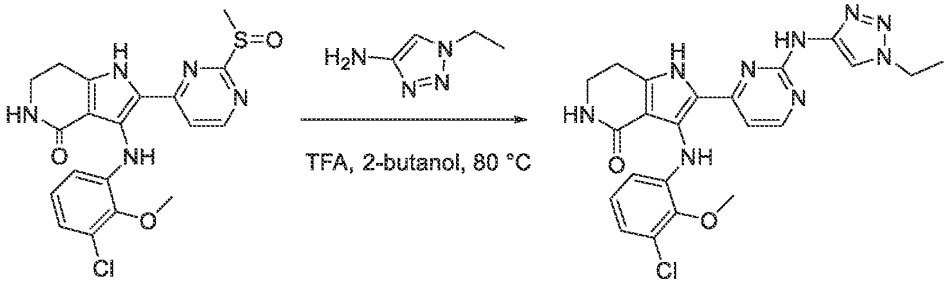
(10 mL) was added NaH (0.37 g, 9.21 mmol, 1.05 equiv, 60%) in portions at 0 degrees C under argon atmosphere. The resulting mixture was stirred for 30 min at 0 degrees C under argon atmosphere. To the above mixture was added ethyl iodide (1.78 g, 11.40 mmol, 1.30 equiv) in portions at 0 degrees C. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched by the addition of Water (10 mL) at 0 degrees C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (3x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford 1-ethyl-4-nitro-1,2,3-triazole (700 mg, 56.18%) as a yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 4.59 (q, J = 7.3 Hz, 2H), 1.51 (t, J = 7.3 Hz, 3H).



To a stirred solution of 1-ethyl-4-nitro-1,2,3-triazole (120 mg, 0.84 mmol, 1.00 equiv) in EtOH (6 mL) was added Pd/C (25 mg, 21% w/w) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for 2h at room temperature under hydrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH (3x30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (2:1) to afford 1-ethyl-1,2,3-triazol-4-amine (90 mg, 95.05%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 113.4.



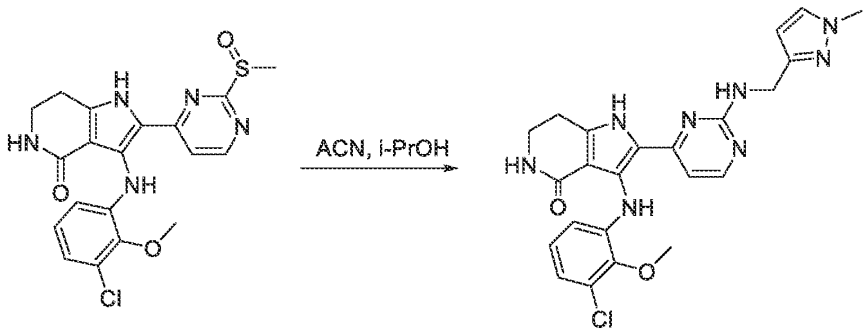
To a stirred solution of 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.19

mmol, 1.00 equiv) in 2-butanol (2 mL) was added 1-ethyl-1,2,3-triazol-4-amine (208 mg, 1.85 mmol, 10.00 equiv) and TFA (42 mg, 0.37 mmol, 2.00 equiv) in portions at room temperature under argon atmosphere. The resulting mixture was stirred for 36 h at 80 degrees C under argon atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product (400 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 55% B in 7 min, 55% B; Wave Length: 254/220 nm; RT1(min): 6.62) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-{2-[(1-ethyl-1,2,3-triazol-4-yl)amino]pyrimidin-4-yl}-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (21.2 mg, 23.13%) as a white solid.

LC-MS: $(M+H)^+$ found: 479.95.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.45 (s, 1H), 9.80 (s, 1H), 8.25 (d, J = 5.3 Hz, 1H), 8.13 (s, 1H), 7.78 (s, 1H), 7.20 (t, J = 2.6 Hz, 1H), 6.83 – 6.72 (m, 2H), 6.70 (d, J = 5.3 Hz, 1H), 6.36 – 6.27 (m, 1H), 4.38 – 4.28 (m, 2H), 3.90 (s, 3H), 3.46 – 3.37 (m, 2H), 2.91 (t, J = 6.8 Hz, 2H), 1.43 (t, J = 7.3 Hz, 3H).

Example 272. 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-[[(1-methylpyrazol-3-yl)methyl]amino]pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 709)**



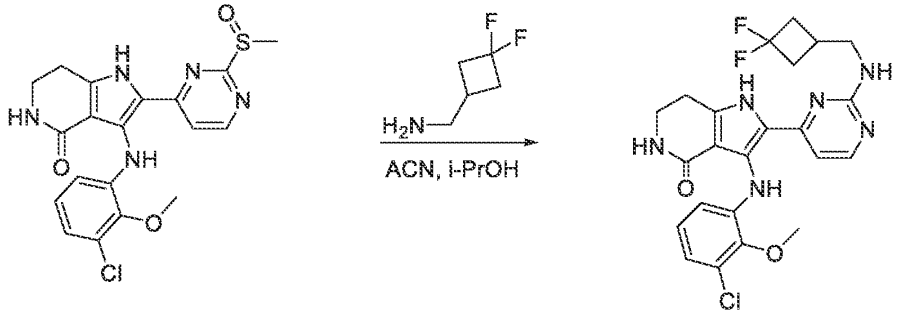
A solution of 3-[(3-chloro-2-methoxyphenyl) amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (80 mg, 0.19 mmol, 1.00 equiv) and (1-methyl-1H-pyrazol-3-yl) methanamine (206 mg, 1.85 mmol, 10.00 equiv) in ACN (1.00

mL) and i-PrOH (1.00 mL) was stirred for overnight at 80 degrees C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product (100mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 52% B in 7 min, 52% B; Wave Length: 254 nm; RT1(min): 6.5) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-2-(2-[[(1-methylpyrazol-3-yl)methyl]amino]pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (4.2 mg, 4.71%) as a light yellow solid.

LC-MS: M+H found: 479.30.

^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.62 (s, 1H), 8.08 (d, *J* = 5.3 Hz, 1H), 7.86 (s, 1H), 7.56 (d, *J* = 2.2 Hz, 1H), 7.14 (s, 1H), 6.83 – 6.72 (m, 3H), 6.47 (d, *J* = 5.3 Hz, 1H), 6.38 – 6.36 (m, 1H), 6.12 (d, *J* = 2.2 Hz, 1H), 4.52 (d, *J* = 5.9 Hz, 2H), 3.87 (s, 3H), 3.79 (s, 3H), 3.46 – 3.36 (m, 2H), 2.89 – 2.87 (m, 2H).

Example 273. 3-[(3-chloro-2-methoxyphenyl) amino]-2-(2-[[(3,3-difluorocyclobutyl) methyl] amino] pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one **(compound 711)**



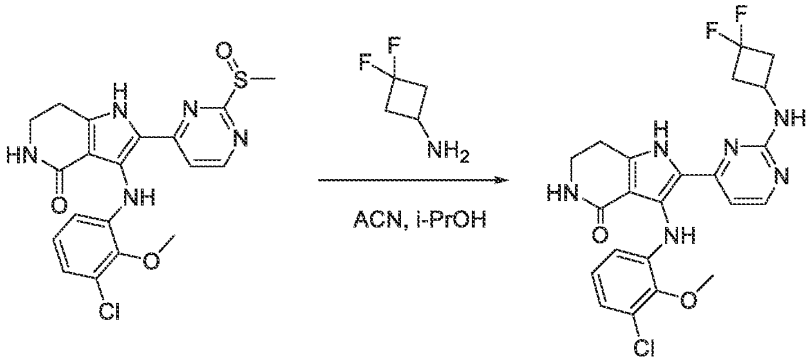
Into a 10-mL sealed tube purged and maintained with an inert atmosphere of argon, was placed 3-[(3-chloro-2-methoxyphenyl) amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (80.00 mg, 0.19 mmol, 1.00 equiv), ACN (1.00 mL, 0.024 mmol, 0.13 equiv), i-PrOH (1.00 mL), 1-(3,3-difluorocyclobutyl) methanamine (224 mg, 1.85 mmol, 10.00 equiv). The resulting solution was stirred for overnight at 110 degrees C. The resulting mixture was concentrated under reduced pressure. The crude product (50mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water(0.1%FA), Mobile

Phase B: ACN; Flow rate: 60 mL/min; Gradient: 19% B to 37% B in 8 min, 37% B; Wave Length: 254/220 nm; RT1(min): 7.68) to afford 3-[(3-chloro-2-methoxyphenyl) amino]-2-(2-[[(3,3-difluorocyclobutyl) methyl] amino] pyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (11.9 mg, 13.13%) as a light yellow solid.

LC-MS: M+H found: 489.30.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.58 (s, 1H), 8.08 (d, J = 5.3 Hz, 1H), 7.97 (s, 1H), 7.12 (t, J = 2.7 Hz, 1H), 6.80 – 6.74 (m, 2H), 6.54 (d, J = 5.3 Hz, 1H), 6.42 – 6.40 (m, 1H), 3.87 (s, 3H), 3.42 – 3.39 (m, 4H), 2.88 (t, J = 6.8 Hz, 2H), 2.58 – 2.52 (m, 2H), 2.38 – 2.26 (m, 3H).

Example 274. 3-[(3-chloro-2-methoxyphenyl) amino]-2-[2-[(3,3-difluorocyclobutyl) amino] pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one **(compound 712)**

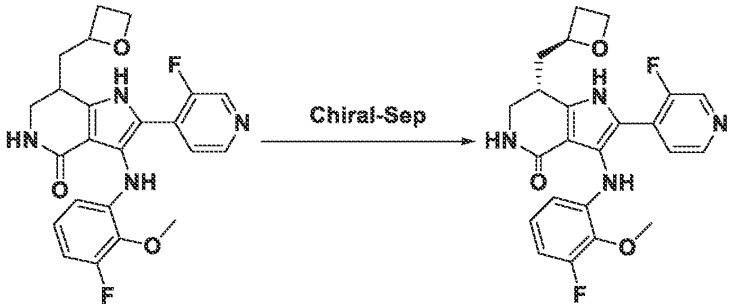


Into a 10-mL sealed tube purged and maintained with an inert atmosphere of argon, was placed 3-[(3-chloro-2-methoxyphenyl) amino]-2-(2-methanesulfinylpyrimidin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (80.00 mg, 0.19 mmol, 1.00 equiv), ACN (1.00 mL), i-PrOH (1.00 mL), 3,3-difluorocyclobutan-1-amine (198 mg, 1.85 mmol, 10.00 equiv). The resulting solution was stirred for overnight at 110 degrees C. The resulting mixture was concentrated under reduced pressure. The crude product (75mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 38% B in 8 min, 38% B; Wave Length: 254/220 nm; RT1(min): 7.55) to afford 3-[(3-chloro-2-methoxyphenyl) amino]-2-[2-[(3,3-difluorocyclobutyl) amino] pyrimidin-4-yl]-1H,5H,6H,7H-pyrrolo[3,2-c] pyridin-4-one (4.6 mg, 5.18%) as a light yellow solid.

LC-MS: M+H found: 475.30.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.55 (s, 1H), 8.09 (d, J = 5.3 Hz, 1H), 7.78 (s, 1H), 7.39 (s, 1H), 7.16 (t, J = 2.7 Hz, 1H), 6.86 – 6.78 (m, 2H), 6.52 (d, J = 5.3 Hz, 1H), 6.34 – 6.32 (m, 1H), 4.41 (brs, 1H), 3.89 (s, 3H), 3.42 – 3.39 (m, 2H), 3.01 – 2.92 (m, 4H), 2.93 – 2.88 (m, 2H).

Example 275. (7S)-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[(2S)-oxetan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(compound 422c)**

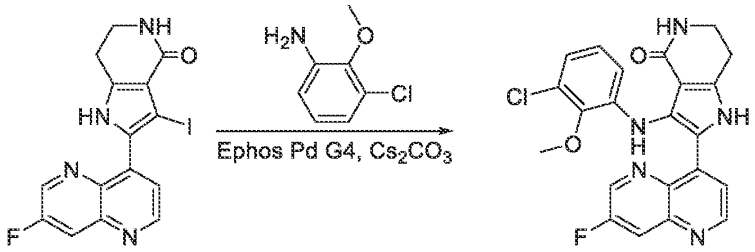


3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-(oxetan-2-ylmethyl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (300 mg) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IA-3, 4.6*50mm, 3um; Mobile Phase A: MtBE(0.1%DEA): EtOH=70: 30; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL). This resulted in (7S)-3-[(3-fluoro-2-methoxyphenyl)amino]-2-(3-fluoropyridin-4-yl)-7-[(2S)-oxetan-2-ylmethyl]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (4.9 mg) as a yellow solid.

LC-MS: (M+H)+ found: 441.

1H NMR (300 MHz, Chloroform-d) δ 11.01 (s, 1H), 8.45 (d, J = 4.3 Hz, 1H), 8.15 (d, J = 5.7 Hz, 1H), 7.73 (s, 1H), 7.43 (t, J = 6.5 Hz, 1H), 6.72 – 6.50 (m, 2H), 6.10 (d, J = 8.0 Hz, 1H), 5.30 (d, J = 11.1 Hz, 2H), 4.89 (q, J = 7.4 Hz, 1H), 4.68 – 4.54 (m, 1H), 4.14 (d, J = 1.4 Hz, 3H), 3.76 – 3.37 (m, 3H), 2.73 (m, 2H), 2.23 (t, J = 11.2 Hz, 1H), 1.83 (d, J = 15.1 Hz, 1H).

Example 276. 2-(7-fluoro-1,5-naphthyridin-4-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(Compound 826)**

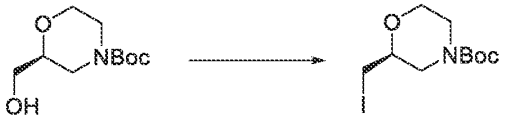


To a stirred solution of 2-(7-fluoro-1,5-naphthyridin-4-yl)-3-iodo-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.25 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (35 mg, 0.22 mmol, 0.90 equiv) in DMF (1.00 mL) was added Ephos Pd G4 (22 mg, 0.02 mmol, 0.10 equiv) dropwise at room temperature under Ar atmosphere. The resulting mixture was stirred for 1 h at 50 degrees C under Ar atmosphere. The reaction was monitored by LCMS. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 46% B in 8 min, 46% B; Wave Length: 254/220 nm; RT1(min): 7.8) to afford 2-(7-fluoro-1,5-naphthyridin-4-yl)-3-[(3-fluoro-2-methoxyphenyl)amino]-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (23 mg, 27.49%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 438.20.

^{1}H NMR (300 MHz, DMSO-d6) δ 12.34 (s, 1H), 9.12 (s, 1H), 8.76 (s, 1H), 8.32 (d, *J* = 8.1 Hz, 1H), 8.01 (s, 1H), 7.54 (s, 1H), 7.26 (s, 1H), 6.71 – 6.67 (m, 2H), 6.18 (d, J = 6.9 Hz, 1H), 3.92 (s, 3H), 3.45 (s, 2H), 2.98 (s, 2H).

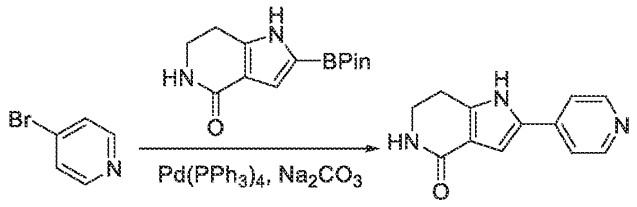
Example 277. (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2R)-4-methylmorpholin-2-yl]methyl}-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(Compound 646)**



Into a 500 mL 3-necked round-bottom flask were added tert-butyl (2S)-2-(hydroxymethyl)morpholine-4-carboxylate (20 g, 92.05 mmol, 1.00 equiv) and PPh_3 (31.39 g, 119.67 mmol, 1.30 equiv) and Imidazole (9.40 g, 138.08 mmol, 1.50 equiv) and

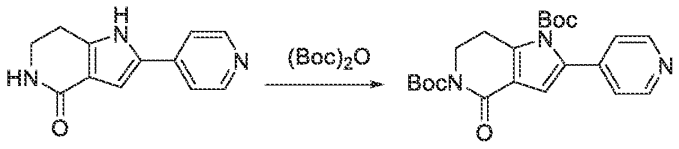
DCM (200 mL) and followed by the addition of I_2 (28.04 g, 110.46 mmol, 1.20 equiv) at room temperature. The resulting mixture was stirred for 5 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The resulting mixture was diluted with ethyl ether (200 mL). The resulting mixture was filtered, the filter cake was washed with ethyl ether (3x50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford tert-butyl (2S)-2-(iodomethyl)morpholine-4-carboxylate (22.3 g, 74.05%) as a white solid.

LC-MS: $(M+H)^+$ found 328.



A solution of 4-bromopyridine (5 g, 31.65 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (9.95 g, 37.98 mmol, 1.20 equiv) and Na_2CO_3 (10.16 g, 94.94 mmol, 3.00 equiv) and tetrakis(triphenylphosphine)palladium(0) (3.66 g, 3.17 mmol, 0.10 equiv) in dioxane (25.00 mL) and H_2O (5.00 mL). The mixture was stirred for overnight at 50 degrees C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The precipitated solids were collected by filtration and washed with water to afford 2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (5 g, 74.09%) as a yellow solid.

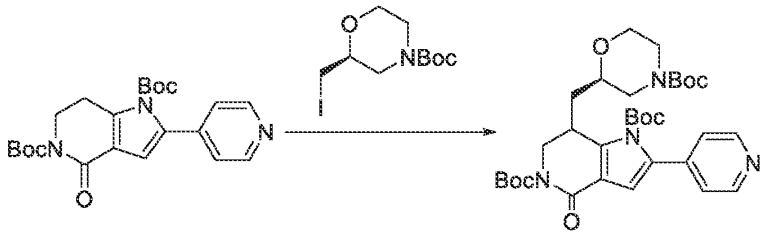
LC-MS: $(M+H)^+$ found 397



To a stirred solution of 2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (6.7 g, 31.42 mmol, 1.00 equiv) and Boc_2O (17.14 g, 78.55 mmol, 2.50 equiv) in THF (100 mL) was added TEA (9.54 g, 94.26 mmol, 3.00 equiv) and DMAP (384 mg, 3.14 mmol, 0.10

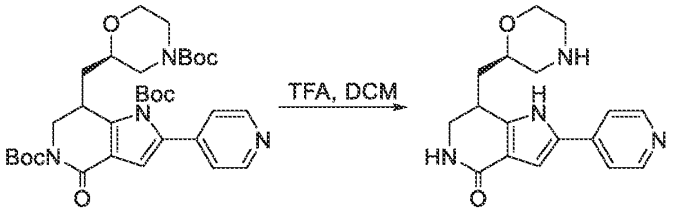
equiv). The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 1,5-di-tert-butyl 4-oxo-2-(pyridin-4-yl)-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (8.7 g, 66.97%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 414



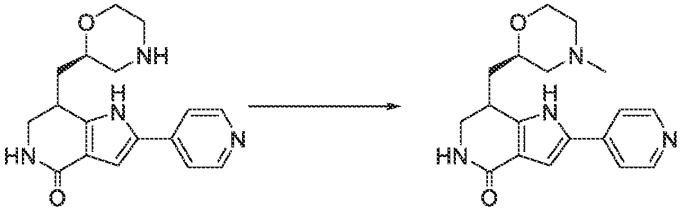
In to a 50 mL round-bottom flask, 1,5-di-tert-butyl 4-oxo-2-(pyridin-4-yl)-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (1.5 g, 3.63 mmol, 1.00 equiv) and tert-butyl (2S)-2-(iodomethyl)morpholine-4-carboxylate (4.75 g, 14.51 mmol, 4.00 equiv) in THF (30 mL) was added LiHMDS (5.44 mL, 5.44 mmol, 1.50 equiv) dropwise at -40 degrees C under Ar_2 atmosphere. The reaction mixture was stirred at -40 degrees C for 5 h. The reaction was quenched with sat. NH_4Cl (aq.) at -40°C. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford crude product. The residue was purified by reverse flash chromatography with the following conditions: column, C18 spherical column; mobile phase, ACN in water, 40% to 90% gradient in 30 min; detector, UV 254 nm. This resulted in 1,5-di-tert-butyl 7-{[(2R)-4-(tert-butoxycarbonyl)morpholin-2-yl]methyl}-4-oxo-2-(pyridin-4-yl)-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (450 mg, 20.24%) as a yellow solid.

LC-MS: $(M+H)^+$ found 613.20



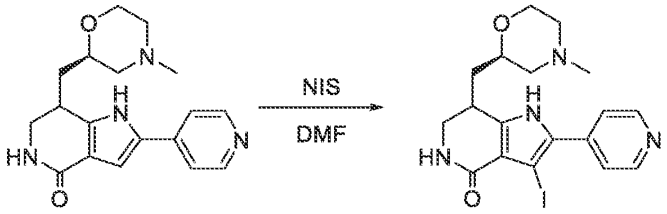
Into a 20 mL vial were added 1,5-di-tert-butyl 7-{[(2R)-4-(tert-butoxycarbonyl)morpholin-2-yl]methyl}-4-oxo-2-(pyridin-4-yl)-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (400 mg, 0.65 mmol, 1.00 equiv) and TFA (0.4 mL) in DCM (2 mL). The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in DMSO. The mixture was neutralized to pH 7 with DIEA. The residue was purified by reverse flash chromatography with the following conditions: column, C18 spherical column; mobile phase, ACN in water, 0% to 50% gradient in 30 min; detector, UV 254 nm. This resulted in 7-[(2R)-morpholin-2-ylmethyl]-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (192 mg, 94.15%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 313.00



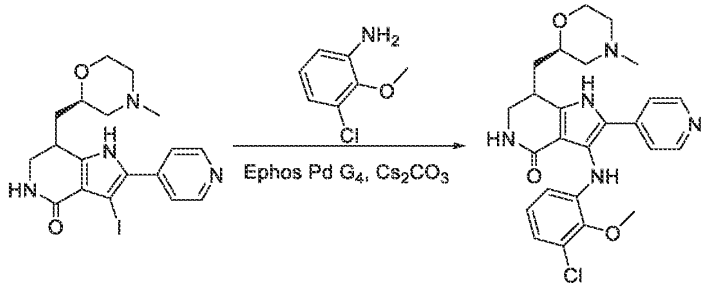
A solution of 7-[(2R)-morpholin-2-ylmethyl]-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (130 mg, 0.42 mmol, 1.00 equiv) in TFE (3 mL) was treated with formaldehyde (94 mg, 1.04 mmol, 2.50 equiv) for 30 min at room temperature under nitrogen atmosphere followed by the addition of $NaBH_4$ (31 mg, 0.83 mmol, 2.00 equiv) at 0 °C. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was quenched with MeOH at 0 °C. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 7-{[(2R)-4-methylmorpholin-2-yl]methyl}-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 73.62%) as a white solid.

LC-MS: $(M+H)^+$ found: 327.00.



To a stirred mixture of 7-{[(2R)-4-methylmorpholin-2-yl]methyl}-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.31 mmol, 1.00 equiv) in ACN (0.3 mL) and DMF (0.3 mL) was added NIS (76 mg, 0.34 mmol, 1.10 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature under nitrogen atmosphere. The reaction was quenched with sat. Na_2SO_3 (aq.) at 0°C. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 20 min; detector, UV 254 nm. This resulted in 3-iodo-7-{[(2R)-4-methylmorpholin-2-yl]methyl}-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 57.73%) as a yellow solid.

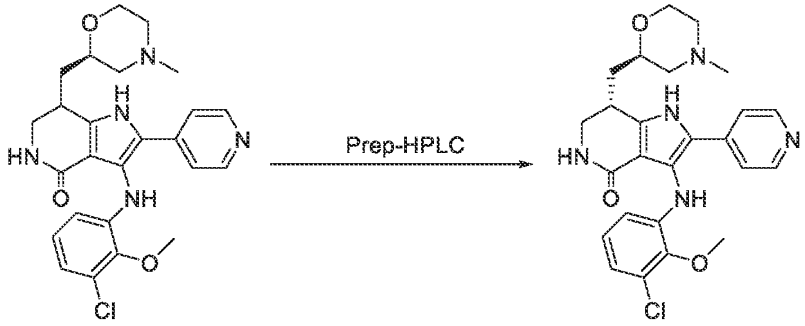
LC-MS: $(M+H)^+$ found: 452.95.



To a stirred mixture of 3-iodo-7-{[(2R)-4-methylmorpholin-2-yl]methyl}-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.18 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (28 mg, 0.18 mmol, 1.00 equiv) in DMF (2 mL) were added EPhos Pd G4 (49 mg, 0.05 mmol, 0.30 equiv) and Cs_2CO_3 (115 mg, 0.35 mmol, 2.00 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 2h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure

that was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2R)-4-methylmorpholin-2-yl]methyl}-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (78 mg, 82.35%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 482.00.

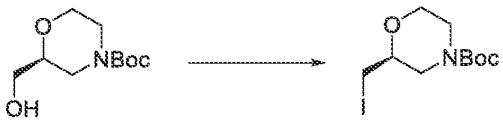


The crude product (78 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 28% B to 42% B in 11 min, 42% B; Wave Length: 254 nm; RT1(min): 8.87) to afford (7R*)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2R)-4-methylmorpholin-2-yl]methyl}-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (12.6 mg, 16.11%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 482.05.

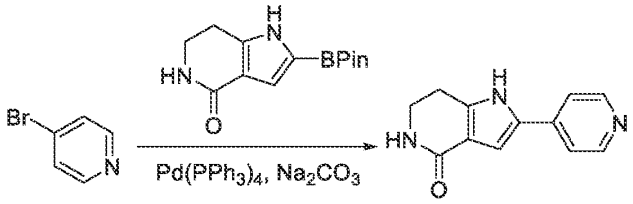
^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.08 (s, 1H), 8.45 – 8.44 (m, 2H), 7.35 (s, 1H), 7.24 – 7.18 (m, 2H), 6.80 – 6.56 (m, 2H), 6.21 – 6.19 (m, 1H), 5.30 (s, 1H), 4.13 – 4.11 (m, 1H), 4.06 (s, 3H), 3.95 – 3.74 (m, 2H), 3.62 – 3.49 (m, 1H), 3.33 – 3.31 (m, 2H), 2.87 – 2.63 (m, 2H), 2.35 (s, 3H), 2.27 – 2.24 (m, 1H), 2.19 – 2.01 (m, 2H), 1.83 – 1.71 (m, 1H).

Example 278. (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2R)-4-methylmorpholin-2-yl]methyl}-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one **(Compound 645)**



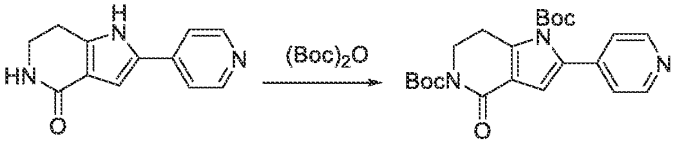
Into a 500 mL 3-necked round-bottom flask were added tert-butyl (2S)-2-(hydroxymethyl)morpholine-4-carboxylate (20 g, 92.05 mmol, 1.00 equiv) and PPh_3 (31.39 g, 119.67 mmol, 1.30 equiv) and Imidazole (9.40 g, 138.08 mmol, 1.50 equiv) and DCM (200 mL) and followed by the addition of I_2 (28.04 g, 110.46 mmol, 1.20 equiv) at room temperature. The resulting mixture was stirred for 5 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum. The resulting mixture was diluted with ethyl ether (200 mL). The resulting mixture was filtered, the filter cake was washed with ethyl ether (3x50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford tert-butyl (2S)-2-(iodomethyl)morpholine-4-carboxylate (22.3 g, 74.05%) as a white solid.

LC-MS: $(M+H)^+$ found 328.



A solution of 4-bromopyridine (5 g, 31.65 mmol, 1.00 equiv) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (9.95 g, 37.98 mmol, 1.20 equiv) and Na_2CO_3 (10.16 g, 94.94 mmol, 3.00 equiv) and tetrakis(triphenylphosphine)palladium(0) (3.66 g, 3.17 mmol, 0.10 equiv) in dioxane (25.00 mL) and H_2O (5.00 mL). The mixture was stirred for overnight at 50 degrees C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The precipitated solids were collected by filtration and washed with water to afford 2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (5 g, 74.09%) as a yellow solid.

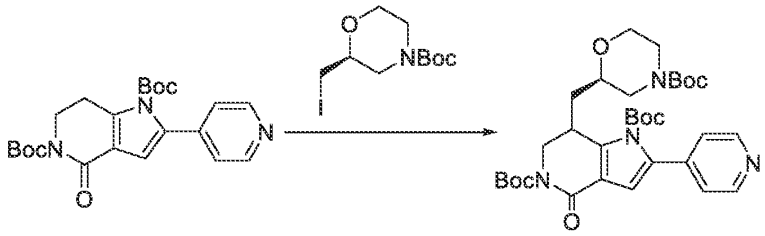
LC-MS: $(M+H)^+$ found 397



To a stirred solution of 2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (6.7 g,

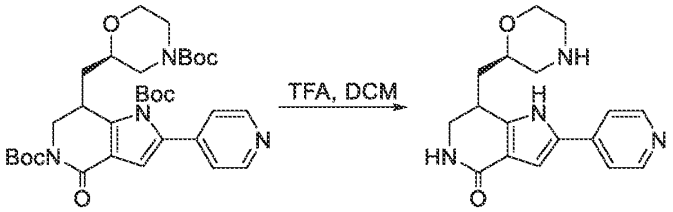
31.42 mmol, 1.00 equiv) and Boc_2O (17.14 g, 78.55 mmol, 2.50 equiv) in THF (100 mL) was added TEA (9.54 g, 94.26 mmol, 3.00 equiv) and DMAP (384 mg, 3.14 mmol, 0.10 equiv). The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 1,5-di-tert-butyl 4-oxo-2-(pyridin-4-yl)-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (8.7 g, 66.97%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 414



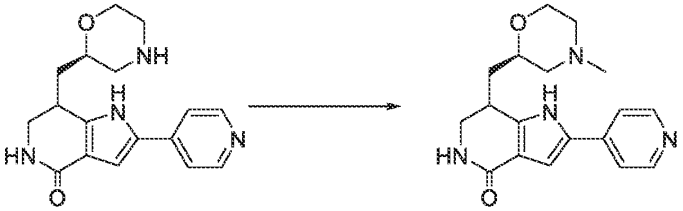
In to a 50 mL round-bottom flask, 1,5-di-tert-butyl 4-oxo-2-(pyridin-4-yl)-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (1.5 g, 3.63 mmol, 1.00 equiv) and tert-butyl (2S)-2-(iodomethyl)morpholine-4-carboxylate (4.75 g, 14.51 mmol, 4.00 equiv) in THF (30 mL) was added LiHMDS (5.44 mL, 5.44 mmol, 1.50 equiv) dropwise at -40 degrees C under Ar_2 atmosphere. The reaction mixture was stirred at -40 degrees C for 5 h. The reaction was quenched with sat. NH_4Cl (aq.) at -40°C. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford crude product. The residue was purified by reverse flash chromatography with the following conditions: column, C18 spherical column; mobile phase, ACN in water, 40% to 90% gradient in 30 min; detector, UV 254 nm. This resulted in 1,5-di-tert-butyl 7-{[(2R)-4-(tert-butoxycarbonyl)morpholin-2-yl]methyl}-4-oxo-2-(pyridin-4-yl)-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (450 mg, 20.24%) as a yellow solid.

LC-MS: $(M+H)^+$ found 613.20



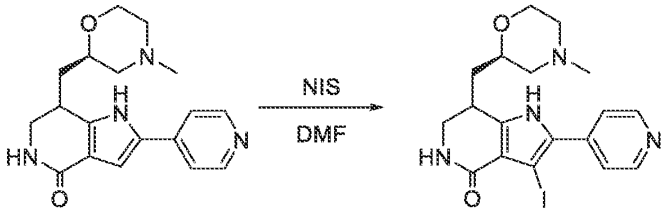
Into a 20 mL vial were added 1,5-di-tert-butyl 7-{[(2R)-4-(tert-butoxycarbonyl)morpholin-2-yl]methyl}-4-oxo-2-(pyridin-4-yl)-6H,7H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylate (400 mg, 0.65 mmol, 1.00 equiv) and TFA (0.4 mL) in DCM (2 mL). The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in DMSO. The mixture was neutralized to pH 7 with DIEA. The residue was purified by reverse flash chromatography with the following conditions: column, C18 spherical column; mobile phase, ACN in water, 0% to 50% gradient in 30 min; detector, UV 254 nm. This resulted in 7-[(2R)-morpholin-2-ylmethyl]-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (192 mg, 94.15%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 313.00



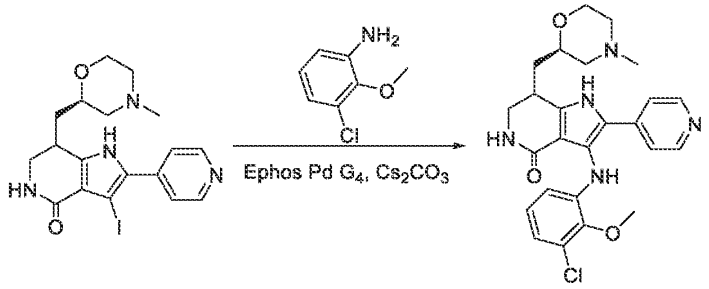
A solution of 7-[(2R)-morpholin-2-ylmethyl]-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (130 mg, 0.42 mmol, 1.00 equiv) in TFE (3 mL) was treated with formaldehyde (94 mg, 1.04 mmol, 2.50 equiv) for 30 min at room temperature under nitrogen atmosphere followed by the addition of $NaBH_4$ (31 mg, 0.83 mmol, 2.00 equiv) at 0 °C. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was quenched with MeOH at 0 °C. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 10:1) to afford 7-{[(2R)-4-methylmorpholin-2-yl]methyl}-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 73.62%) as a white solid.

LC-MS: $(M+H)^+$ found: 327.00.



To a stirred mixture of 7-{[(2R)-4-methylmorpholin-2-yl]methyl}-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (100 mg, 0.31 mmol, 1.00 equiv) in ACN (0.3 mL) and DMF (0.3 mL) was added NIS (76 mg, 0.34 mmol, 1.10 equiv) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature under nitrogen atmosphere. The reaction was quenched with sat. Na_2SO_3 (aq.) at 0°C. The residue was purified by reverse flash chromatography with the following conditions: column, silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 20 min; detector, UV 254 nm. This resulted in 3-iodo-7-{[(2R)-4-methylmorpholin-2-yl]methyl}-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 57.73%) as a yellow solid.

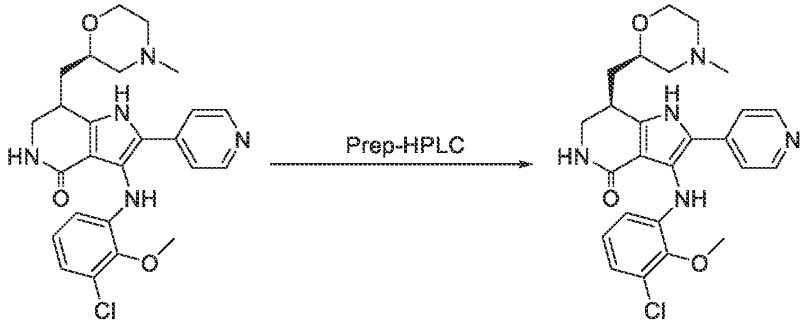
LC-MS: $(M+H)^+$ found: 452.95.



To a stirred mixture of 3-iodo-7-{[(2R)-4-methylmorpholin-2-yl]methyl}-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (80 mg, 0.18 mmol, 1.00 equiv) and 3-chloro-2-methoxyaniline (28 mg, 0.18 mmol, 1.00 equiv) in DMF (2 mL) were added EPhos Pd G4 (49 mg, 0.05 mmol, 0.30 equiv) and Cs_2CO_3 (115 mg, 0.35 mmol, 2.00 equiv) under argon atmosphere. The resulting suspension was backfilled with argon three times and stirred for 2h at 50°C. LCMS confirmed completion of reaction and desired product was observed. The resulting mixture was filtered through a pad of silica and the filter cake was washed with DCM (2x10 mL). The filtrate was concentrated under reduced pressure

that was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (20:1) to afford 3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2R)-4-methylmorpholin-2-yl]methyl}-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (78 mg, 82.35%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 482.00.



The crude product (78 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column, 19*250 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 28% B to 42% B in 11 min, 42% B; Wave Length: 254 nm; RT1(min): 8.87) to afford (7R)-3-[(3-chloro-2-methoxyphenyl)amino]-7-{[(2R)-4-methylmorpholin-2-yl]methyl}-2-(pyridin-4-yl)-1H,5H,6H,7H-pyrrolo[3,2-c]pyridin-4-one (8.4 mg, 10.74%) as a yellow solid.

LC-MS: $(M+H)^+$ found: 482.05.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.75 (s, 1H), 8.45 – 8.44 (m, 2H), 7.32 (s, 1H), 7.26 – 7.23 (m, 2H), 6.80 – 6.62 (m, 2H), 6.21 – 6.19 (m, 1H), 5.40 (s, 1H), 4.14 – 4.11 (m, 1H), 4.05 (s, 3H), 3.96 – 3.82 (m, 2H), 3.55 – 3.20 (m, 3H), 3.10 – 2.82 (m, 2H), 2.43 (s, 3H), 2.38 – 2.36 (m, 1H), 2.10 – 2.05 (m, 1H), 1.98 – 1.88 (m, 1H), 1.76 – 1.64 (m, 1H).

Bioactivity

EXAMPLE A. Inhibitor activity on EGFR-dependent cell growth

Cell lines are generated by transducing Ba/F3 cells with retroviruses containing vectors with EGFR WT, EGFR L858R, EGFR exon 19del, EGFR L858R/C797S, EGFR

exon 20 NPG Ins D770_N771, EGFR exon 20 ASV Ins V769_D770, EGFR exon 20 SVD Ins D770_N771, or EGFR exon 20 FQEA Ins A763_V764 genes and a puromycin selection marker. Transduced cells are selected with puromycin for 7 days and are then be transferred into culture media without Interleukin 3 (IL3). EGFR WT cells are maintained with supplemental EGF. Surviving cells are confirmed to express EGFR by Western blot and maintained as a pool. The IC50 date were included in **Table 6** and **Table 7**.

Study Design

1 Cell seeding

1.1 Cells are harvested from flask into cell culture medium and the cell number counted.

1.2 Cells are diluted with culture medium to the desired density and 40 µL of cell suspension is added into each well of 384-well cell culture plate and the seeding density is 800 (FQEA, exon 19del), 600 (WT, NPG, L858R/C797S), or 400 (ASV, SVD, L858R) cells/well.

2 Compound preparation and treatment

2.1 Test compounds are dissolved to 10 mM in a DMSO stock solution. 45 µL of stock solution is transferred to a 384 polypropylene plate (pp-plate). Perform 3-fold, 10-point dilution via transferring 15 µL compound into 30 µL DMSO using a TECAN (EVO200) liquid handler.

2.2 Spin plates at room temperature at 1,000 RPM for 1 minute.

2.3 Transfer 120 nL of diluted compound from compound source plate into the cell plate.

2.4 After compound treatment for 72 hours, perform CTG detection for compound treatment plates as described in "Detection" section.

3 Detection

3.1 Plates are removed from incubators and equilibrated at room temperature for 15 minutes.

3.2 Thaw the CellTiter Glo reagents and allow to equilibrate to room temperature before the experiment.

3.3 Add 40 μL of CellTiter-Glo reagent into each well (at 1:1 to culture medium). Then place the plates at room temperature for 30 min followed by reading on EnVision.

4 Data analysis

4.1 Inhibition activity is calculated following the formula below:

%Inhibition = 100 x (LumHC – LumSample) / (LumHC –LumLC)

where HC is obtained from cells treated with 0.1% DMSO only; and LC is obtained from culture medium only.

4.2 2. Calculate the IC_{50} by fitting the Curve using Xlfit (v5.3.1.3), equation 201:

Y = Bottom + (Top - Bottom)/(1 + 10^((LogIC_{50} - X)*HillSlope))

EXAMPLE B. Inhibitor Activity on EGFR phosphorylation (pEGFR)

EGFR mutant Ba/F3 cells were generated by transduction with retrovirus containing vectors expressing EGFR L858R, EGFR exon 19del, EGFR L858R/C797S, EGFR exon 20 NPG Ins D770_N771, EGFR exon 20 ASV Ins V769_D770, or EGFR exon 20 SVD Ins D770_N771 genes along with a puromycin selection marker. Transduced cells are selected with puromycin for 7 days and are then be transferred into culture media without Interleukin 3 (IL3). Surviving cells are confirmed to express EGFR by Western blot and maintained as a pool. CUTO14 cells were obtained from Dr. Robert C. Doebele at the University of Colorado. The IC50 date are included in **Table 6** and **Table 7**.

Study Design

1 Cell seeding

1.1 Cells are harvested from flask into cell culture medium and the cell number counted.

1.2 Cells are diluted with culture medium to the desired density and 40 μL of cell suspension is added into each well of 384-well cell culture plate and the seeding density is 50K cells/well (Ba/F3) or 12.5K cells/well (CUTO14).

2 Compound preparation and treatment

2.1 Test compounds are dissolved to 10 mM in a DMSO stock solution. 45 µL of stock solution is transferred to a 384 polypropylene plate (pp-plate). Perform 3-fold, 10-point dilution via transferring 15 µL compound into 30 µL DMSO using a TECAN (EVO200) liquid handler.

2.2 Spin plates at room temperature at 1,000 RPM for 1 minute.

2.3 Transfer 5 nL of diluted compound from compound source plate into the cell plate.

2.4 After compound treatment for 2 hours, perform pEGFR detection by AlphaLISA for compound treatment plates as described in "Detection" section.

3 Detection by pEGFR AlphaLISA (Perkin-Elmer)

3.1 Plates are removed from incubators and equilibrated at room temperature for 10 minutes, and media was removed

3.2 10 µL of lysis buffer is added and plates shaken at 600 rpm for 1 hr.

3.3 Prepare acceptor mix just before use and dispense 5 µL of acceptor mix to all the wells. Shake 350 rpm for 1hr in the dark

3.4 Prepare donor mix under low light conditions prior to use. Dispense 5 µL of donor mix to all the wells. Mix well on the shaker, seal and wrap in aluminum foil and incubate 1.5 hrs at room temperature in the dark

3.5 Transfer 18.5 µL mixture to OptiPlate 384, and read using an Envision.

The IC50 date were included in **Table 6** and **Table 7**.

Table 6. IC50 Data for EGFR Activity and Inhibitor Activity on EGFR phosphorylation (pEGFR)[1]

Compound #	BaF3 ASV IC50	BaF3 SVD IC50	BaF3 NPG IC50	BaF3 FQEA IC50	BaF3 WT IC50	ASV IC50 (pEGFR)	SVD IC50 (pEGFR)	NPG IC50 (pEGFR)	CUTO14 IC50 (pEGFR)
102	++	++	++	++	+	+++	NA	NA	NA
108	+++	+++	+++	++	++	+++	NA	+++	NA
109	+++	+++	+++	+++	+++	+++	NA	+++	NA
110	+++	+++	+++	+++	++	+++	NA	+++	NA
112	++	++	+	++	+	+++	NA	NA	NA
121	+++	+++	+++	NA	++	NA	NA	NA	NA
138	NA	NA	+	NA	+	NA	NA	+	NA

148	+++	+++	+++	++	++	+++	+++	+++	+++
149	+++	+++	+++	+++	+++	NA	NA	+++	NA
150	NA	NA	+	NA	+	NA	NA	+	NA
152	NA	NA	+++	NA	+++	+++	NA	+++	NA
154	NA	NA	+	NA	+++	+	NA	++	NA
156	+	+	+	+	+	+	NA	NA	NA
157	NA	NA	+	NA	++	NA	NA	+	NA
158	NA	NA	+	NA	+	NA	NA	++	NA
159	NA	NA	+	NA	++	NA	NA	+	NA
160	+++	+++	+++	+++	+++	+++	+++	+++	+++
162	+++	++	++	NA	++	NA	NA	NA	NA
192	+	+	NA	+	+	+	NA	NA	NA
193	++	+++	NA	++	++	+++	NA	NA	NA
194	++	++	NA	++	++	+++	NA	NA	NA
195	++	++	++	++	++	+++	NA	+++	NA
196	+	+	NA	++	+	++	NA	NA	NA
197	+	+	NA	+	+	+	NA	NA	NA
198	+	+	NA	+	+	+	NA	NA	NA
199	+	+	++	++	+	++	NA	NA	NA
200	+	+	NA	+	+	++	NA	NA	NA
201	+	+	NA	+	+	+	NA	NA	NA
202	++	++	++	++	++	+++	NA	+++	NA
203	+	+	NA	++	+	+	NA	NA	NA
204	++	++	NA	++	++	++	NA	NA	NA
206	NA	NA	++	NA	++	++	NA	+++	NA
209	++	++	NA	+	+	++	NA	NA	NA
218	++	++	+	++	+	+++	NA	NA	NA
219	+++	+++	+++	+++	+++	+++	NA	NA	NA
220	++	++	++	++	+	++	NA	+++	NA
221	++	++	++	++	+	++	NA	+++	NA
225	++	++	++	+	+	++	NA	NA	NA
239	+	+	NA	+	+	NA	NA	NA	NA
242	+	+	NA	+	+	++	NA	NA	NA
243	++	++	NA	++	+	NA	NA	NA	NA
244	+	+	NA	+	+	++	NA	NA	NA
246	+	+	NA	+	+	+	NA	NA	NA
252	++	++	NA	++	+	NA	NA	NA	NA
255	++	++	NA	++	++	NA	NA	NA	NA
259	+	+	NA	+	+	NA	NA	NA	NA
261	+	+	NA	+	+	++	NA	NA	NA
281	++	++	+++	++	+	NA	NA	+++	NA

282	NA	NA	++	NA	++	+++	NA	+++	NA
283	++	++	++	+++	++	++	NA	+++	NA
284	+	+	NA	+	+	+	NA	NA	NA
285	++	++	++	++	+	+++	NA	+++	NA
286	+	+	+	+	+	+	NA	++	NA
288	+	+	NA	+	+	+	NA	NA	NA
289	+	+	+	+	+	+	NA	NA	NA
290	+++	+++	++	+++	++	+++	NA	+++	NA
292	++	++	++	++	+	+++	NA	NA	NA
293	+	+	NA	+	+	+	NA	NA	NA
295	++	+	+	++	+	++	NA	NA	NA
297	+++	+++	++	++	+	+++	NA	NA	NA
299	++	++	++	++	+	NA	NA	+++	NA
301	+	+	NA	+	+	+	NA	NA	NA
302	+	+	NA	+	+	+	NA	NA	NA
303	+	++	NA	+	+	++	NA	NA	NA
304	++	++	NA	++	+	+++	NA	NA	NA
305	++	++	NA	++	+	+++	NA	NA	NA
306	+	+	NA	++	+	++	NA	NA	NA
307	+	+	NA	+	+	++	NA	NA	NA
308	++	++	++	++	+	+++	NA	+++	NA
316	+++	+++	NA	+++	++	NA	NA	NA	NA
323	+++	+++	NA	+++	++	NA	NA	NA	NA
379	+++	+++	NA	+++	++	NA	NA	NA	NA
408	+++	+++	+++	+++	+++	+++	+++	+++	+++
409	+++	+++	NA	+++	++	NA	NA	NA	NA
410	++	++	NA	++	+	NA	NA	NA	NA
413	+++	+++	NA	+++	+++	NA	NA	NA	NA
417	++	++	NA	++	+	NA	NA	NA	NA
418	++	++	NA	++	+	NA	NA	NA	NA
440	+++	+++	NA	+++	++	NA	NA	NA	NA
441	+++	+++	+++	+++	++	NA	NA	+++	NA
442	+++	+++	+++	+++	++	NA	NA	+++	NA
470	+++	+++	NA	++	++	NA	NA	NA	NA
471	++	++	NA	++	+	NA	NA	NA	NA
472	++	++	NA	+	+	NA	NA	NA	NA
473	++	++	NA	++	+	NA	NA	NA	NA
474	+	+	NA	+	+	NA	NA	NA	NA
475	+	+	NA	+	+	NA	NA	NA	NA
476	+	+	NA	+	+	NA	NA	NA	NA
477	+++	+++	NA	+++	++	NA	NA	NA	NA

478	+++	+++	+++	NA	+++	NA	NA	NA	NA
479	++	++	NA	++	+	NA	NA	NA	NA
480	+++	+++	+++	+++	++	NA	NA	NA	NA
481	+++	+++	+++	+++	++	+++	+++	+++	+++
482	+++	+++	+++	+++	+++	+++	+++	+++	+++
483	+++	+++	+++	++	+	NA	NA	NA	+++
484	+	+	NA	+	+	NA	NA	NA	NA
485	+	+	NA	+	+	NA	NA	NA	NA
486	+	+	NA	+	+	NA	NA	NA	NA
487	++	++	NA	++	+	NA	NA	NA	NA
488	+++	+++	+++	++	+	NA	NA	NA	NA
489	++	++	NA	++	+	NA	NA	NA	NA
490	+	+	+	NA	+	NA	NA	NA	NA
491	+	+	NA	+	+	NA	NA	NA	NA
492	+	+	NA	+	+	NA	NA	NA	NA
493	++	++	NA	++	+	NA	NA	NA	NA
494	+	+	NA	+	+	NA	NA	NA	NA
495	+++	+++	NA	+++	+	NA	NA	NA	NA
496	++	++	NA	++	+	NA	NA	NA	NA
497	++	++	+++	NA	++	NA	NA	NA	NA
498	+	+	++	NA	+	NA	NA	NA	NA
499	+	+	+	NA	+	NA	NA	NA	NA
500	+	+	+	NA	+	NA	NA	NA	NA
501	+++	+++	NA	+++	++	NA	NA	NA	NA
502	++	++	++	++	+	NA	NA	+++	NA
503	+++	+++	NA	+++	++	NA	NA	NA	NA
504	+++	+++	NA	++	++	NA	NA	NA	NA
505	+++	+++	NA	++	+	NA	NA	NA	NA
506	++	++	NA	++	+	NA	NA	NA	NA
507	+++	+++	NA	+++	++	NA	NA	NA	NA
508	+	++	NA	++	+	NA	NA	NA	NA
509	+++	+++	+++	+++	+++	NA	NA	NA	NA
510	+++	+++	NA	++	+	NA	NA	NA	NA
511	+++	+++	+++	+++	++	NA	NA	+++	NA
512	+++	+++	+++	+++	++	+++	+++	+++	+++
513	+++	+++	NA	+++	+++	NA	NA	NA	NA
514	+++	+++	+++	+++	++	+++	+++	+++	++
515	+++	+++	+++	+++	++	+++	+++	+++	+++
516	+++	+++	NA	+++	++	NA	NA	NA	NA
517	+++	+++	NA	++	++	NA	NA	NA	NA
518	+++	+++	NA	+++	++	NA	NA	NA	NA

519	++	++	++	NA	+	NA	NA	NA	NA
520	++	++	NA	+++	++	NA	NA	NA	NA
521	++	++	NA	++	+	NA	NA	NA	NA
522	++	++	++	NA	+	NA	NA	NA	NA
523	++	+++	+++	NA	++	NA	NA	NA	NA
524	+++	+++	+++	NA	++	+++	+++	+++	+++
525	+++	+++	+++	+++	++	+++	+++	+++	+++
526	++	++	++	++	+	NA	NA	NA	NA
527	+++	+++	+++	NA	++	NA	NA	NA	+++
528	++	++	+++	NA	+	NA	NA	NA	NA
529	++	++	++	NA	+	NA	NA	NA	NA
530	+++	+++	+++	NA	++	NA	NA	NA	NA
531	+++	+++	+++	+++	++	NA	NA	NA	+++
532	+++	+++	+++	NA	+	NA	NA	+++	NA
537	+++	+++	+++	NA	++	NA	NA	NA	NA
538	+++	+++	+++	NA	++	NA	NA	NA	NA
539	++	++	++	NA	+	NA	NA	NA	NA
542	+	+	++	NA	+	NA	NA	NA	NA
543	++	+++	+++	NA	+	NA	NA	NA	NA
544	++	++	NA	++	+	NA	NA	NA	NA
545	++	++	+++	NA	+	NA	NA	NA	NA
546	+	++	++	NA	+	NA	NA	NA	NA
551	+++	+++	+++	+++	++	+++	+++	+++	+++
552	+++	+++	+++	NA	+	NA	NA	NA	+++
553	+++	+++	NA	+++	++	NA	NA	NA	NA
554	+++	+++	+++	NA	+++	NA	NA	NA	NA
555	+	+	+	NA	+	NA	NA	NA	NA
556	+++	+++	+++	NA	++	NA	NA	NA	NA
557	+++	+++	+++	NA	+++	NA	NA	+++	NA
558	+++	+++	+++	NA	+++	NA	NA	NA	NA
559	+++	+++	+++	+++	++	NA	NA	NA	+++
560	+++	+++	+++	NA	++	NA	NA	NA	NA
561	+++	+++	+++	NA	++	NA	NA	NA	NA
562	+++	+++	+++	NA	++	NA	NA	NA	+++
563	++	++	++	NA	+	NA	NA	NA	NA
564	++	++	++	NA	+	NA	NA	NA	NA
565	++	++	++	NA	+	NA	NA	NA	NA
566	+++	+++	+++	+++	+++	+++	+++	+++	+++
567	+++	+++	+++	+++	++	+++	+++	+++	+++
568	+++	+++	+++	+++	++	NA	NA	NA	+++
569	+++	+++	+++	+++	++	NA	NA	NA	+++

570	+++	+++	+++	+++	++	+++	+++	+++	+++
571	+++	+++	+++	+++	++	NA	NA	NA	+++
572	++	+++	++	NA	+	NA	NA	NA	NA
573	+++	+++	+++	NA	++	NA	NA	+++	NA
574	+++	+++	+++	NA	+	NA	NA	NA	NA
575	+++	+++	+++	NA	++	NA	NA	NA	NA
576	+++	+++	+++	NA	+++	NA	NA	+++	NA
577	+++	+++	+++	NA	++	NA	NA	NA	NA
585	+++	+++	+++	NA	++	NA	NA	NA	NA
586	+++	+++	+++	NA	++	NA	NA	NA	NA
587	+++	+++	+++	NA	++	NA	NA	NA	NA
588	+++	+++	+++	NA	+++	NA	NA	NA	NA
589	+++	+++	+++	NA	++	NA	NA	NA	NA
590	+	+	++	NA	+	NA	NA	NA	NA
591	+++	+++	+++	NA	++	NA	NA	NA	NA
592	+++	+++	+++	NA	++	NA	NA	NA	+++
593	+++	+++	+++	NA	++	NA	NA	NA	+++
594	+++	+++	+++	NA	++	NA	NA	NA	NA
595	++	++	++	NA	++	NA	NA	NA	NA
603	+++	+++	+++	NA	+	NA	NA	NA	NA
604	+++	+++	+++	+++	++	NA	NA	NA	+++
605	++	++	++	NA	+	NA	NA	NA	NA
606	+++	+++	+++	+++	++	NA	NA	NA	+++
607	+	+	+	NA	+	NA	NA	NA	NA
608	+	+	+	NA	+	NA	NA	NA	NA
609	++	++	+	NA	+	NA	NA	NA	NA
610	+++	+++	+++	NA	++	NA	NA	NA	+++
611	+++	+++	+++	NA	+++	NA	NA	NA	+++
612	+++	+++	+++	NA	++	NA	NA	NA	+++
641	+++	+++	+++	NA	++	NA	NA	NA	+++
642	+++	+++	+++	NA	++	NA	NA	NA	NA
643	+++	+++	+++	NA	+++	NA	NA	NA	+++
644	+++	+++	+++	NA	+++	NA	NA	NA	+++
645	+++	+++	+++	NA	+	NA	NA	NA	+++
646	+	+	+	NA	+	NA	NA	NA	+++
649	++	++	++	NA	+	NA	NA	NA	++
650	++	++	++	NA	+	NA	NA	NA	+++
651	+++	+++	+++	NA	++	NA	NA	NA	+++
652	++	++	++	NA	+	NA	NA	NA	+++
653	++	++	++	NA	+	NA	NA	NA	NA
654	+++	+++	+++	NA	++	NA	NA	NA	NA

655	+++	+++	+++	NA	++	NA	NA	NA	+++
656	+++	+++	+++	NA	+	NA	NA	NA	+++
657	+++	+++	+++	NA	++	NA	NA	NA	+++
658	+++	+++	+++	NA	++	NA	NA	NA	+++
659	+++	+++	+++	NA	+	NA	NA	NA	NA
675	++	++	NA	++	+	NA	NA	NA	NA
676	NA	NA	+	NA	+	NA	NA	NA	NA
677	+++	+++	NA	+++	+++	NA	NA	NA	NA
678	+++	+++	+++	+++	+++	+++	NA	+++	NA
679	+++	+++	+++	+++	+++	NA	NA	NA	NA
680	+++	+++	+++	+++	+++	+++	NA	+++	NA
681	+++	+++	+++	+++	+++	NA	NA	+++	NA
682	NA	NA	+++	NA	+++	NA	NA	+++	NA
683	+++	+++	+++	+++	++	NA	NA	NA	NA
684	+++	+++	+++	+++	++	NA	NA	+++	NA
685	NA	NA	++	NA	++	+++	NA	+++	NA
686	+++	+++	NA	++	++	+++	NA	NA	NA
687	++	++	++	++	+	++	NA	+++	NA
688	+	+	+	+	+	+	NA	NA	NA
689	+	+	+	++	NA	++	NA	NA	NA
690	NA	NA	++	NA	+++	+++	NA	+++	NA
691	++	++	++	++	++	+++	NA	+++	NA
692	++	++	++	++	++	++	NA	+++	NA
693	+	+	NA	+	+	+	NA	NA	NA
694	+++	+++	+++	+++	+++	+++	NA	NA	NA
695	+++	+++	NA	+++	+++	+++	NA	NA	NA
696	+++	+++	+++	+++	+++	+++	NA	NA	NA
697	+++	+++	+++	+++	+++	+++	NA	NA	NA
698	++	+	++	++	+	++	NA	NA	NA
699	+	+	NA	+	+	++	NA	NA	NA
700	+	+	NA	+	+	++	NA	NA	NA
701	+	+	+	+	+	++	NA	NA	NA
702	++	++	++	++	+	++	NA	NA	NA
703	+	+	NA	+	+	++	NA	NA	NA
704	+	+	NA	+	+	+	NA	NA	NA
705	+	+	NA	+	+	+	NA	NA	NA
706	+++	+++	+++	++	++	+++	NA	NA	NA
707	+	+	+	+	+	+	NA	NA	NA
708	+	+	NA	+	+	NA	NA	NA	NA
709	+++	+++	NA	++	++	NA	NA	NA	NA
710	++	++	++	++	+	+++	NA	NA	NA

711	+	+	NA	+	+	++	NA	NA	NA
712	+	+	NA	+	+	++	NA	NA	NA
713	++	++	++	+	+	NA	NA	NA	NA
714	++	++	+++	++	+	NA	NA	NA	NA
715	++	++	NA	++	+	+++	NA	NA	NA
716	++	++	++	++	+	NA	NA	NA	NA
717	++	++	NA	++	++	+++	NA	NA	NA
718	+	+	NA	++	+	++	NA	NA	NA
719	++	+	++	+	+	NA	NA	NA	NA
720	+	+	NA	+	+	NA	NA	NA	NA
721	+	+	+	+	+	++	NA	NA	NA
722	+	+	+	+	+	++	NA	NA	NA
723	++	+	NA	+	+	NA	NA	NA	NA
724	++	++	NA	+	+	NA	NA	NA	NA
725	++	++	+++	++	++	+++	NA	NA	NA
726	+++	+++	+++	+++	+++	+++	+++	+++	+++
727	+++	+++	+++	+++	++	NA	NA	NA	NA
728	+	+	NA	+	+	+	NA	NA	NA
729	++	+++	NA	++	++	NA	NA	NA	NA
730	+++	+++	+++	+++	+++	NA	NA	+++	NA
731	+++	+++	+++	NA	+++	NA	NA	+++	NA
732	+++	+++	+++	+++	+++	NA	NA	NA	NA
733	+++	+++	NA	+++	++	NA	NA	NA	NA
734	+++	+++	+++	+++	++	NA	NA	NA	NA
735	+++	+++	+++	+++	++	NA	NA	NA	NA
736	+++	+++	++	++	++	NA	NA	NA	NA
737	+++	+++	+++	+++	++	NA	NA	NA	NA
738	+++	+++	+++	++	++	NA	NA	NA	NA
739	+++	+++	+++	+++	++	NA	NA	NA	NA
740	+++	+++	NA	+++	+++	NA	NA	NA	NA
741	+++	+++	+++	+++	+++	NA	NA	NA	NA
742	+++	+++	+++	+++	++	NA	NA	NA	NA
743	+++	+++	+++	+++	++	NA	NA	NA	NA
744	+++	+++	NA	+++	+++	NA	NA	NA	NA
745	+++	+++	NA	+++	+++	NA	NA	NA	NA
746	+++	+++	+++	+++	++	NA	NA	NA	NA
747	+++	+++	+++	+++	+++	+++	+++	+++	+++
748	++	++	NA	++	+	NA	NA	NA	NA
749	+++	+++	+++	+++	++	NA	NA	NA	NA
750	+++	+++	+++	+++	++	+++	+++	+++	+++
751	++	++	NA	++	+	NA	NA	NA	NA

752	+++	+++	NA	+++	+++	NA	NA	NA	NA
753	+++	+++	+++	+++	+++	NA	NA	NA	NA
754	+++	+++	+++	+++	+++	NA	NA	NA	NA
755	+++	+++	NA	+++	++	NA	NA	NA	NA
756	+++	++	NA	++	++	NA	NA	NA	NA
757	+++	+++	++	+++	++	NA	NA	+++	NA
758	++	++	++	++	++	NA	NA	NA	NA
759	+++	+++	NA	+++	++	NA	NA	NA	NA
760	+++	+++	NA	+++	+++	NA	NA	NA	NA
761	+++	+++	+++	+++	+++	NA	NA	NA	NA
762	+++	+++	NA	+++	+++	NA	NA	NA	NA
763	+++	+++	++	++	++	NA	NA	NA	NA
764	+++	+++	NA	+++	+++	NA	NA	NA	NA
765	+++	+++	NA	+++	+++	NA	NA	NA	NA
766	+++	+++	+++	+++	++	NA	NA	NA	NA
767	+++	+++	+++	+++	+++	NA	NA	NA	NA
768	+++	+++	NA	+++	++	NA	NA	NA	NA
769	+++	+++	NA	+++	+++	NA	NA	NA	NA
770	+++	+++	NA	+++	+++	NA	NA	NA	NA
771	+++	+++	NA	+++	+++	NA	NA	NA	NA
772	+	+	NA	+	+	NA	NA	NA	NA
773	+	+	NA	+	+	NA	NA	NA	NA
774	+++	+++	NA	+++	+++	NA	NA	NA	NA
775	+++	+++	NA	+++	+++	NA	NA	NA	NA
776	+++	+++	NA	+++	++	NA	NA	NA	NA
777	+++	+++	NA	+++	++	NA	NA	NA	NA
778	++	++	NA	++	+	NA	NA	NA	NA
779	+++	+++	+++	+++	++	NA	NA	NA	NA
780	+++	+++	+++	+++	++	NA	NA	NA	NA
781	++	++	NA	++	+	NA	NA	NA	NA
782	++	++	NA	++	+	NA	NA	NA	NA
783	+++	+++	NA	++	+	NA	NA	NA	NA
784	++	++	NA	++	+	NA	NA	NA	NA
785	+++	+++	NA	+++	++	NA	NA	NA	NA
786	+++	+++	NA	++	++	NA	NA	NA	NA
787	+++	+++	+++	+++	+++	NA	NA	NA	NA
788	+++	+++	+++	+++	+++	NA	NA	NA	NA
789	+	+	NA	+	+	NA	NA	NA	NA
790	+++	+++	+++	NA	++	NA	NA	NA	+++
791	+++	+++	NA	+++	++	NA	NA	NA	NA
792	+++	+++	NA	+++	++	NA	NA	NA	NA

793	+++	+++	NA	+++	++	NA	NA	NA	NA
794	+++	+++	NA	+++	++	NA	NA	NA	NA
795	++	++	NA	++	+	NA	NA	NA	NA
796	+	+	NA	+	+	NA	NA	NA	NA
797	+	+	NA	+	+	NA	NA	NA	NA
798	+++	+++	NA	+++	++	NA	NA	NA	NA
799	+++	+++	NA	+++	++	NA	NA	NA	NA
800	+++	+++	NA	++	++	NA	NA	NA	NA
801	++	+	NA	+	+	NA	NA	NA	NA
802	+	+	NA	+	+	NA	NA	NA	NA
803	+++	+++	NA	+++	++	NA	NA	NA	NA
804	++	+++	NA	+++	++	NA	NA	NA	NA
805	++	+++	NA	+++	++	NA	NA	NA	NA
806	+	+	NA	++	+	NA	NA	NA	NA
807	+++	+++	NA	+++	+++	NA	NA	NA	NA
808	+++	+++	NA	+++	+++	NA	NA	+++	NA
809	+++	+++	NA	+++	++	NA	NA	NA	NA
810	+++	+++	NA	+++	++	NA	NA	NA	NA
811	+	+	NA	+	+	NA	NA	NA	NA
812	++	++	NA	++	+	NA	NA	NA	NA
813	++	++	NA	++	+	NA	NA	NA	NA
814	+++	+++	NA	+++	+++	NA	NA	NA	NA
815	++	++	NA	++	+	NA	NA	NA	NA
816	++	++	NA	++	+	NA	NA	NA	NA
817	+++	+++	+++	+++	++	+++	+++	+++	+++
818	++	++	NA	++	+	NA	NA	NA	NA
819	++	++	NA	++	+	NA	NA	NA	NA
820	++	++	NA	++	+	NA	NA	NA	NA
821	+++	+++	+++	+++	++	NA	NA	NA	NA
822	++	+++	NA	++	+	NA	NA	NA	NA
823	+++	+++	NA	+++	+++	NA	NA	NA	NA
824	++	++	NA	++	+	NA	NA	NA	NA
825	++	+++	NA	++	+	NA	NA	NA	NA
826	+++	+++	NA	+++	++	NA	NA	NA	NA
827	+++	+++	+++	+++	+++	NA	NA	NA	NA
828	+	+	NA	+	+	NA	NA	NA	NA
829	+	+	NA	+	+	NA	NA	NA	NA
830	+++	+++	NA	+++	++	NA	NA	NA	NA
831	+++	+++	+++	+++	++	+++	+++	+++	+++
186a	+++	+++	NA	+++	++	+++	NA	NA	NA
186b	+++	+++	NA	++	++	+++	NA	NA	NA

187a	++	++	NA	++	+	+++	NA	NA	NA
187b	+++	+++	NA	++	++	+++	NA	NA	NA
189a	+++	+++	+++	+++	++	NA	NA	NA	NA
189b	+++	+++	NA	+++	++	NA	NA	NA	NA
310a	+++	+++	+++	+++	+++	NA	NA	NA	NA
310b	+++	+++	NA	+++	+++	NA	NA	NA	NA
421a	++	++	++	++	+	NA	NA	NA	NA
421b	+++	+++	+++	+++	++	+++	+++	+++	+++
422a	+++	+++	+++	++	++	NA	NA	+++	NA
422b	++	++	NA	++	+	NA	NA	NA	NA
422c	++	++	++	++	+	NA	NA	NA	NA
422d	+++	+++	+++	++	++	NA	NA	NA	NA
445a	+++	+++	+++	+++	++	+++	+++	+++	+++
445b	++	++	NA	++	+	NA	NA	NA	NA
447a	+++	+++	NA	+++	++	NA	NA	NA	NA
447b	++	++	NA	++	+	NA	NA	NA	NA
453a	++	++	++	NA	+	NA	NA	NA	+++
453b	+++	+++	+++	NA	++	NA	NA	NA	+++
463a	++	+++	NA	++	+	NA	NA	NA	NA
463b	+++	+++	+++	+++	++	+++	+++	+++	+++
468a	+	+	++	+	+	NA	NA	NA	NA
468b	++	++	NA	++	+	NA	NA	NA	NA
469a	+	+	+	+	+	NA	NA	NA	NA
469b	+	+	+	+	+	NA	NA	NA	NA

[1] "+++" indicates that IC50 < 100 nM;

"++" indicates that 100 nM <= IC50 < 1000 nM;

"+" indicates that IC50 >= 1000 nM;

"NA" indicates that the IC50 data is not available for this compound.

Table 7. IC50 Data for EGFR Activity and Inhibitor Activity on EGFR phosphorylation (pEGFR)[1] - continuted

Compound #	BaF3 L858R IC50	BaF3 Del19 IC50	BaF3 L858R/C797S IC50	L858R IC50 (pEGFR)	Del19 IC50 (pEGFR)	L858R/C797S IC50 (pEGFR)
290	+++	+++	NA	NA	NA	NA
409	+++	+++	+++	+++	+++	+++
480	+++	+++	+++	+++	+++	+++
481	+++	+++	+++	+++	+++	+++
482	+++	+++	+++	+++	+++	+++
483	+++	+++	NA	NA	NA	NA
515	+++	+++	NA	NA	NA	NA
519	+++	+++	+++	+++	+++	+++
525	+++	+++	+++	+++	+++	+++
527	+++	+++	+++	+++	+++	+++
530	+++	+++	+++	+++	+++	+++
531	+++	+++	NA	NA	NA	NA
551	+++	+++	+++	+++	+++	+++
553	+++	+++	NA	NA	NA	NA
559	+++	+++	NA	NA	NA	NA
566	+++	+++	+++	+++	+++	+++
567	+++	+++	NA	NA	NA	NA
568	+++	+++	+++	+++	+++	+++
569	+++	+++	+++	+++	+++	+++
570	+++	+++	+++	+++	+++	+++
571	+++	+++	NA	NA	NA	NA
572	+++	+++	+++	+++	+++	+++
573	+++	+++	NA	NA	NA	NA
575	+++	+++	+++	+++	+++	+++
604	+++	+++	+++	+++	+++	+++
606	+++	+++	+++	+++	+++	+++
611	+++	+++	NA	NA	NA	NA
651	NA	NA	+++	NA	NA	+++
655	+++	+++	NA	NA	NA	NA
656	+++	+++	NA	NA	NA	NA
657	+++	+++	+++	NA	NA	+++
658	+++	+++	+++	NA	NA	+++
679	+++	+++	NA	NA	NA	NA
733	+++	+++	+++	+++	+++	+++
747	+++	+++	+++	+++	+++	+++

749	+++	+++	+++	+++	+++	+++
750	+++	+++	+++	+++	+++	+++
754	+++	+++	NA	NA	NA	NA
766	+++	+++	NA	NA	NA	NA
778	+++	+++	+++	+++	+++	+++
779	+++	+++	NA	NA	NA	NA
780	+++	+++	NA	NA	NA	NA
787	+++	+++	+++	+++	+++	+++
788	+++	+++	+++	+++	+++	+++
794	+++	+++	+++	+++	+++	+++
809	+++	+++	+++	+++	+++	+++
810	+++	+++	NA	NA	NA	NA
817	+++	+++	+++	+++	+++	+++
819	+++	+++	+++	+++	+++	+++
820	+++	+++	+++	+++	+++	+++
821	+++	+++	+++	+++	+++	+++
822	+++	+++	+++	+++	+++	+++
823	+++	+++	NA	NA	NA	NA
827	+++	+++	+++	+++	+++	+++
189a	+++	+++	NA	NA	NA	NA
310a	+++	+++	NA	NA	NA	NA
421b	+++	+++	+++	+++	+++	+++
422a	+++	+++	NA	NA	NA	NA
445a	+++	+++	+++	+++	+++	+++
445b	+++	+++	+++	+++	+++	+++
447a	+++	+++	+++	+++	+++	+++
453a	+++	+++	NA	NA	NA	NA
453b	+++	+++	+++	NA	NA	+++
463b	+++	+++	+++	+++	+++	+++

[1] "+++" indicates that IC50 < 100 nM;

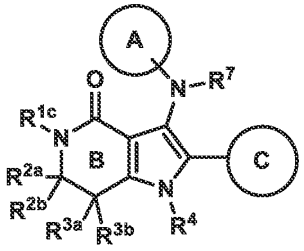
"++" indicates that 100 nM <= IC50 < 1000 nM;

"+" indicates that IC50 >= 1000 nM;

"NA" indicates that the IC50 data is not available for this compound.

WHAT IS CLAIMED IS:

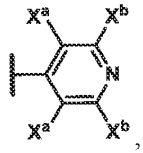
1. A compound of Formula **(I)**:



Formula **(I)**

or a pharmaceutically acceptable salt thereof, wherein:

Ring C is selected from the group consisting of:

- 

, wherein:
  - each $\mathbf{X^b}$ is independently $\mathbf{X^1}$, $\mathbf{R^c}$, or H; and
  - each $\mathbf{X^a}$ is independently selected from the group consisting of: H, halo; cyano; $C_{1\text{-}10}$ alkyl which is optionally substituted with from 1-6 independently selected $\mathbf{R^a}$; $C_{2\text{-}6}$ alkenyl; $-S(O)_{1\text{-}2}(C_{1\text{-}4}$ alkyl); $-S(O)(=NH)(C_{1\text{-}4}$ alkyl); $-NR^cR^f$; –OH; $-S(O)_{1\text{-}2}NR'R''$; $-C_{1\text{-}4}$ thioalkoxy; $-NO_2$; $-C(=O)(C_{1\text{-}10}$ alkyl); $-C(=O)O(C_{1\text{-}4}$ alkyl); $-C(=O)OH$; $-C(=O)NR'R''$; and $-SF_5$;
- 2-pyridyl or 3-pyridyl, each optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;
- 2-pyridonyl or 4-pyridonyl, each optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$, wherein the ring nitrogen atom is optionally substituted with $\mathbf{R^d}$;
- heteroaryl including 6 ring atoms, wherein from 2-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N($\mathbf{R^d}$),

and wherein the heteroaryl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;

- heteroaryl including 5 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;
- bicyclic heteroaryl including 7-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$; and
- C_{6-10} aryl optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;

$\mathbf{X^1}$ is $-(\mathbf{X^2})_{\mathbf{m}}\text{-}\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein: $\mathbf{m}$ is 0 or 1;

$\mathbf{X^2}$ is selected from the group consisting of:

- -O-, -N($\mathbf{R^N}$)-, or $-S(O)_{0-2}$;
-  ;
- $-C_{2-6}$ alkenylene optionally substituted with from 1-3 $\mathbf{R^a}$;
- -C(=O)O-*, -C(=O)N($\mathbf{R^N}$)-*, or $-S(O)_{1-2}N(\mathbf{R^N})$-*;
- -OC(=O)-*, -N($\mathbf{R^N}$)C(=O)-*, or $-N(\mathbf{R^N})S(O)_{1-2}$-*; and

- -OC(=O)N($\mathbf{R}^N$)-*, -N($\mathbf{R}^N$)C(=O)O-*, -N($\mathbf{R}^N$)C(=O)N($\mathbf{R}^N$)-*, or –N($\mathbf{R}^N$)S(O)$_{1-2}$N($\mathbf{R}^N$)-*,

wherein the asterisk represents point of attachment to $\mathbf{L}^1$;

$\mathbf{L}^1$ is selected from the group consisting of: a bond and C$_{1-10}$ alkylene optionally substituted with from 1-6 $\mathbf{R}^a$;

$\mathbf{R}^5$ is selected from the group consisting of:

- H;
- halo;
- -OH;
- -N$\mathbf{R}^e\mathbf{R}^f$;
- -C$_{1-6}$ alkoxy or -S(O)$_{0-2}$(C$_{1-6}$ alkyl), each optionally substituted with from 1-6 $\mathbf{R}^a$;
- -$\mathbf{R}^g$;
- -$\mathbf{L}^5$-$\mathbf{R}^g$;
- -$\mathbf{R}^{g2}$-$\mathbf{R}^W$ or -$\mathbf{R}^{g2}$-$\mathbf{R}^Y$; and
- -$\mathbf{L}^5$-$\mathbf{R}^{g2}$-$\mathbf{R}^W$ or –$\mathbf{L}^5$-$\mathbf{R}^{g2}$-$\mathbf{R}^Y$;

provided that:

when $\mathbf{L}^1$ is a bond, then $\mathbf{R}^5$ is selected from the group consisting of: H, -$\mathbf{R}^g$, -$\mathbf{R}^{g2}$-$\mathbf{R}^W$, and -$\mathbf{R}^{g2}$-$\mathbf{R}^Y$; and

$\mathbf{X}^1$ is other than H, -OH, or NH$_2$;

$\mathbf{L}^5$ is selected from the group consisting of: –O-, -S(O)$_{0-2}$, -NH-, and -N($\mathbf{R}^d$)-;

$\mathbf{R}^W$ is –$\mathbf{L}^W$-$\mathbf{W}$,

wherein $\mathbf{L}^W$ is C(=O), S(O)$_{1-2}$, OC(=O)*, NHC(=O)*, N$\mathbf{R}^d$C(=O)*, NHS(O)$_{1-2}$*, or N$\mathbf{R}^d$S(O)$_{1-2}$*, wherein the asterisk represents point of attachment to $\mathbf{W}$, and

$\mathbf{W}$ is selected from the group consisting of:

- C_{2-6} alkenyl; C_{2-6} alkynyl; or C_{3-10} allenyl, each of which is optionally substituted with from 1-3 $\mathbf{R^a}$ and further optionally substituted with $\mathbf{R^g}$, wherein **W** is attached to $\mathbf{L^W}$ via an sp^2 or sp hybridized carbon atom, thereby providing an α, β-unsaturated system; and
- bicyclo[**x**.**y**.0]cycloalkyl optionally substituted with from 1-2 $\mathbf{R^c}$, wherein **x** is 1 or 2; and **y** is an integer from 1 to 6;

$\mathbf{R^Y}$ is selected from the group consisting of: $\mathbf{-R^g}$ and $\mathbf{-(L^a)_g-R^g}$;

each of $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$ is independently selected from the group consisting of: H; halo; -OH; -C(O)OH or $-C(O)NH_2$; -CN; $\mathbf{-R^b}$; $\mathbf{-L^b-R^b}$, $\mathbf{-NR^eR^f}$; $\mathbf{-R^g}$; $\mathbf{-(L^a)_g-R^g}$; $\mathbf{-(L^a)_g-R^W}$; $\mathbf{-(L^a)_g-R^{g2}-R^W}$; and $-C_{1-6}$ alkoxy or $-C_{1-6}$ thioalkoxy, each optionally substituted with from 1-6 $\mathbf{R^a}$; provided that $\mathbf{R^{1c}}$ is other than halo, –CN, or –C(O)OH; or

two of variables $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$, together with the **Ring B** ring atoms to which each is attached, form a fused saturated or unsaturated ring of 3-12 ring atoms;

- wherein from 0-2 of the ring atoms are each an independently selected heteroatom (in addition to $-N(\mathbf{R^{1c}})-$ when $-N(\mathbf{R^{1c}})-$ forms part of the fused saturated or unsaturated ring), wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, $N(\mathbf{R^d})$, O, and $S(O)_{0-2}$; and
- wherein the fused saturated or unsaturated ring of 3-12 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo, $\mathbf{R^c}$, and $\mathbf{R^W}$; or

one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ combine to form a double bond between the **Ring B** atoms to which each is attached;

Ring A is $\mathbf{R^g}$;

$\mathbf{R^4}$ and $\mathbf{R^7}$ are independently H or $\mathbf{R^d}$;

each occurrence of $\mathbf{R^a}$ is independently selected from the group consisting of: –OH; -halo; $-N\mathbf{R^eR^f}$; C_{1-4} alkoxy; C_{1-4} haloalkoxy; $-C(=O)O(C_{1-4}$ alkyl); $-C(=O)(C_{1-4}$ alkyl); -C(=O)OH; $-CON\mathbf{R'R''}$; $-S(O)_{1-2}N\mathbf{R'R''}$; $-S(O)_{1-2}(C_{1-4}$ alkyl); and cyano;

each occurrence of $\mathbf{R^b}$ is independently C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each of which is optionally substituted with from 1-6 $\mathbf{R^a}$;

each occurrence of $\mathbf{L^b}$ is independently C(=O); C(=O)O; $S(O)_{1-2}$; C(=O)NH*; C(=O)N$\mathbf{R^d}$*; $S(O)_{1-2}NH$*; or $S(O)_{1-2}N(\mathbf{R^d})$*, wherein the asterisk represents point of attachment to $\mathbf{R^b}$;

each occurrence of $\mathbf{R^c}$ is independently selected from the group consisting of: halo; cyano; C_{1-10} alkyl which is optionally substituted with from 1-6 independently selected $\mathbf{R^a}$; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy or C_{1-4} haloalkoxy; C_{1-4} haloalkoxy; -$S(O)_{1-2}(C_{1-4}$ alkyl); -S(O)(=NH)(C_{1-4} alkyl); -N$\mathbf{R^e R^f}$; –OH; -$S(O)_{1-2}$N$\mathbf{R'R''}$; -C_{1-4} thioalkoxy; -NO_2; -C(=O)(C_{1-10} alkyl); -C(=O)O(C_{1-4} alkyl); -C(=O)OH; -C(=O)N$\mathbf{R'R''}$; and –SF_5;

each occurrence of $\mathbf{R^d}$ is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-3 independently selected $\mathbf{R^a}$; -C(O)(C_{1-4} alkyl); -C(O)O(C_{1-4} alkyl); -CON$\mathbf{R'R''}$; -$S(O)_{1-2}$N$\mathbf{R'R''}$; -$S(O)_{1-2}(C_{1-4}$ alkyl); -OH; and C_{1-4} alkoxy;

each occurrence of $\mathbf{R^e}$ and $\mathbf{R^f}$ is independently selected from the group consisting of: H; C_{1-6} alkyl optionally substituted with from 1-3 substituents each independently selected from the group consisting of N$\mathbf{R'R''}$, -OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and halo; -C(O)(C_{1-4} alkyl); -C(O)O(C_{1-4} alkyl); -CON$\mathbf{R'R''}$; -$S(O)_{1-2}$N$\mathbf{R'R''}$; -$S(O)_{1-2}(C_{1-4}$ alkyl); -OH; and C_{1-4} alkoxy;

each occurrence of $\mathbf{R^g}$ is independently selected from the group consisting of:

- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group

consisting of N, N(H), N($\mathbf{R}^d$), O, and S(O)$_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R}^c$;

- heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^d$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R}^c$; and
- C$_{6-10}$ aryl optionally substituted with from 1-4 $\mathbf{R}^c$;

each occurrence of $\mathbf{L}^g$ is independently selected from the group consisting of: -O-, -NH-, -N$\mathbf{R}^d$, -S(O)$_{0-2}$, C(O), and C$_{1-3}$ alkylene optionally substituted with from 1-3 $\mathbf{R}^a$;

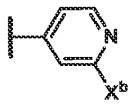
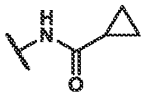
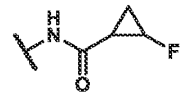
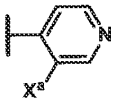
each **g** is independently 1, 2, or 3;

each $\mathbf{R}^{g2}$ is a divalent $\mathbf{R}^g$ group;

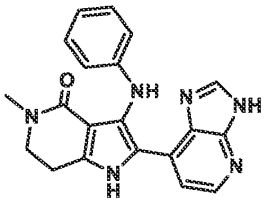
each occurrence of **R'** and **R''** is independently selected from the group consisting of: H; -OH; and C$_{1-4}$ alkyl; and

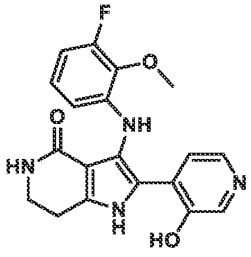
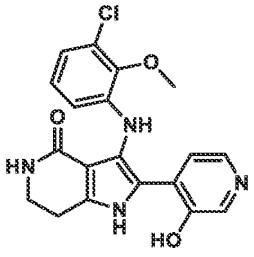
each occurrence of $\mathbf{R}^N$ is independently H, C$_{1-3}$ alkyl, or C$_{3-6}$ cycloalkyl,

provided that one or more of the following applies:

- when $\mathbf{R}^{2a}$ and $\mathbf{R}^{2b}$ are H or methyl; $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$ are H; **Ring C** is  ; and $\mathbf{X}^b$ is H, methyl, NH_2, NHC(=O)Me, NHC(=O)iPr, NHC(=O)NHEt,  ,  , then **Ring A** is other than unsubstituted phenyl;
- when $\mathbf{R}^{2a}$, $\mathbf{R}^{2b}$, $\mathbf{R}^{3a}$, and $\mathbf{R}^{3b}$ are each H; **Ring C** is  ; and $\mathbf{X}^a$ is methyl or F, then **Ring A** is other than unsubstituted phenyl;

- when R^{1c}, R^{2a}, R^{2b}, R^{3a}, and R^{3b} are each H; **Ring C** is  , then **Ring A** is other than 4-fluorophenyl; and

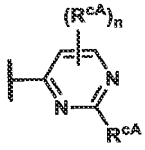
- the compound is other than:  ,

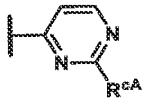
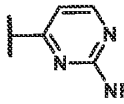
 , or  .

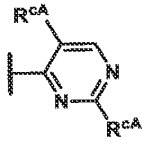
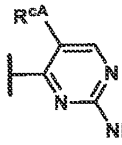
2. The compound of claim 1, wherein **Ring C** is heteroaryl including 6 ring atoms, wherein from 2-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N(R^d), and wherein the heteroaryl is optionally substituted with X^1 and further optionally substituted with from 1-4 R^{cA}, wherein each R^{cA} is an independently selected R^c.

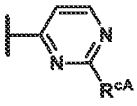
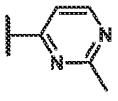
3. The compound of claims 1 or 2, wherein **Ring C** is heteroaryl including 6 ring atoms, wherein from 2-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N(R^d), and wherein the heteroaryl is optionally substituted with from 1-3 R^{cA}, wherein each R^{cA} is an independently selected R^c.

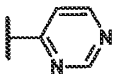
4. The compound of any one of claims 1-3, wherein **Ring C** is pyrimidyl optionally substituted with from 1-3 R^{cA}, such as pyrimidyl substituted with from 1-2 R^{cA}, wherein each R^{cA} is an independently selected R^c.

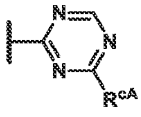
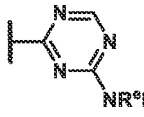
5. The compound of any one of claims 1-4, wherein **Ring C** is  , wherein each R^{cA} is an independently selected R^{c}; and **n** is 0, 1, or 2.

6. The compound of any one of claims 1-5, wherein **Ring C** is  , such as  .

7. The compound of any one of claims 1-5, wherein **Ring C** is  , such as  .

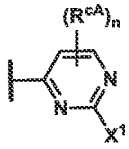
8. The compound of any one of claims 1-6, wherein **Ring C** is  , wherein R^{cA} is C_{1-3} alkyl optionally substituted with from 1-3 independently selected halo. For example, **Ring C** is  .

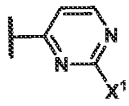
9. The compound of any one of claims 1-4, wherein **Ring C** is  .

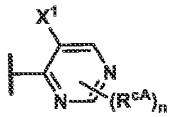
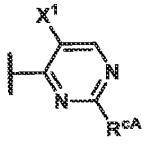
10. The compound of any one of claims 1-3, wherein **Ring C** is triazinyl optionally substituted with from 1-2 R^{cA}, wherein each R^{cA} is an independently selected R^c, such as wherein **Ring C** is  , such as  .

11. The compound of claims 1 or 2, wherein **Ring C** is heteroaryl including 6 ring atoms, wherein from 2-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N(R^d), and wherein the heteroaryl is substituted with X^1 and further optionally substituted with from 1-2 R^{cA}, wherein each R^{cA} is an independently selected R^c.

12. The compound of any one of claims 1-2 or 11, wherein **Ring C** is pyrimidyl substituted with X^1 and further optionally substituted with from 1-2 R^{cA}, wherein each R^{cA} is an independently selected R^c.

13. The compound of any one of claims 1-2 or 11-12, wherein **Ring C** is  , wherein each R^{cA} is an independently selected R^c; and **n** is 0, 1, or 2.

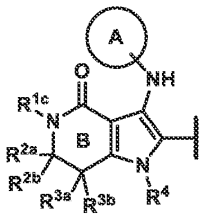
14. The compound of any one of claims 1-2 or 11-13, wherein **Ring C** is  .

15. The compound of any one of claims 1-2 or 11-12, wherein **Ring C** is  , wherein **n** is 0, 1, or 2; and each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$, such as wherein **Ring C** is  .

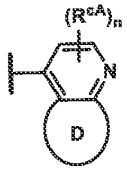
16. The compound of claim 1, wherein **Ring C** is bicyclic heteroaryl including 7-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with $\mathbf{X}^{1}$ and further optionally substituted with from 1-4 $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

17. The compound of claims 1 or 16, wherein **Ring C** is bicyclic heteroaryl including 9-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with $\mathbf{X}^{1}$ and further optionally substituted with from 1-4 $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

18. The compound of any one of claims 1 or 16-17, wherein **Ring C** is bicyclic heteroaryl including 9-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

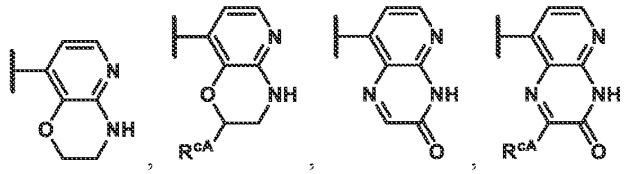
19. The compound of claims 17 or 18, wherein **Ring C** is connected to 

via a 6-membered ring.

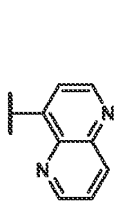
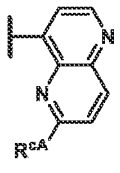
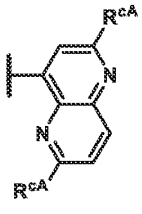
20. The compound of any one of claims 1 or 16-19, wherein **Ring C** is 

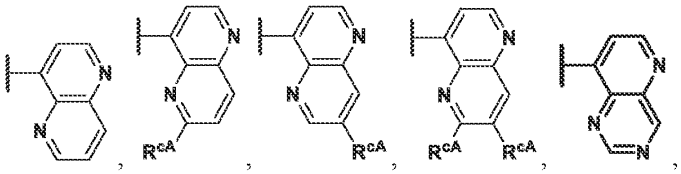
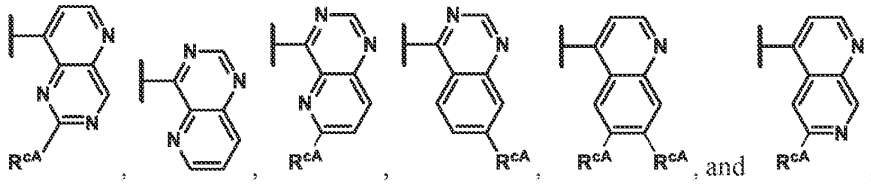
; **Ring D** is a partially unsaturated or aromatic ring including from 5-6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$; **n** is 0, 1, or 2; and each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$.

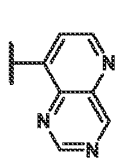
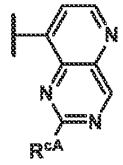
21. The compound of claim 20, wherein **Ring D** is a partially unsaturated or aromatic ring including 6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

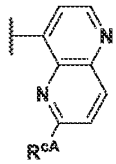
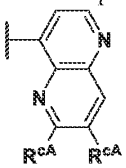
22. The compound of any one of claims 1 or 16-21, wherein **Ring C** is selected from the group consisting of: 

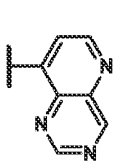
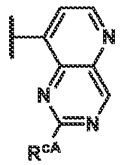
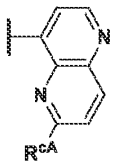
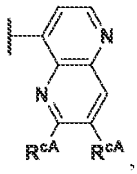
,

 ,  , and  , each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^{c}.

23. The compound of any one of claims 1 or 16-21, wherein **Ring C** is selected from the group consisting of:  ,  , and , each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^{c}.

24. The compound of any one of claims 1, 16-21, or claim 23, wherein **Ring C** is  or  , wherein R^{cA} is an independently selected R^{c}.

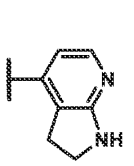
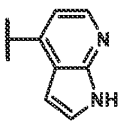
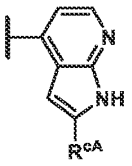
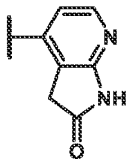
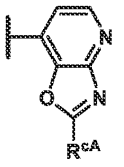
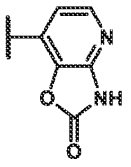
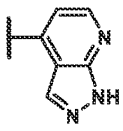
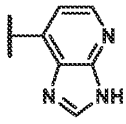
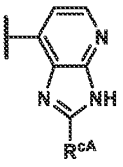
25. The compound of any one of claims 1, 16-21, or claim 23, wherein **Ring C** is  or  , wherein each R^{cA} is an independently selected R^{c}.

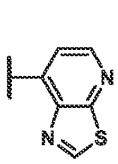
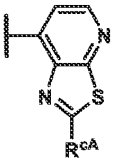
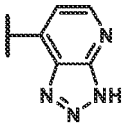
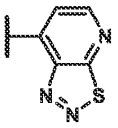
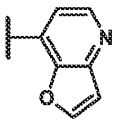
26. The compound of any one of claims 1, 16-21, or claim 23, wherein **Ring C** is selected from the group consisting of:  ,  ,  , and  , wherein:

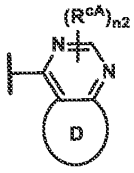
each occurrence of $\mathbf{R}^{cA}$ is independently selected from the group consisting of: halo; $N\mathbf{R}^{e}\mathbf{R}^{f}$; C_{1-4} alkoxy; C_{1-4} haloalkoxy; C_{1-3} alkyl; C_{1-3} alkyl substituted with from 1-3 independently selected halo; C_{1-3} alkyl substituted with C_{1-4} alkoxy; and C_{1-4} alkoxy substituted with C_{1-4} alkoxy;

such as wherein each occurrence of $\mathbf{R}^{cA}$ is independently selected from the group consisting of: C_{1-4} alkoxy; C_{1-4} haloalkoxy; C_{1-3} alkyl; and C_{1-3} alkyl substituted with from 1-3 independently selected halo.

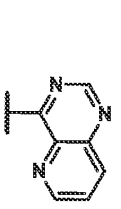
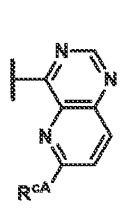
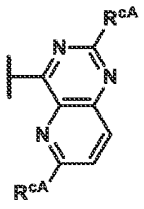
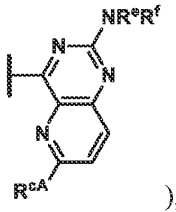
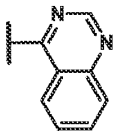
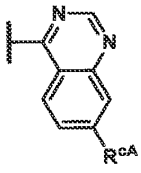
27. The compound of claim 20, wherein **Ring D** is a partially unsaturated or aromatic ring including 5 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and $S(O)_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R}^{cA}$.

28. The compound of any one of claims 1, 16-20, or 27, wherein **Ring C** is selected from the group consisting of:  ,  ,  (e.g., ),  (e.g., ),  ,  ,  ,

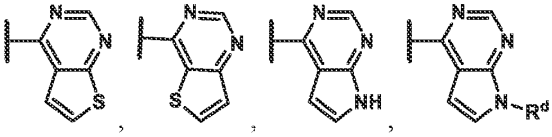
 ,  ,  ,  , and  , each further optionally substituted with $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

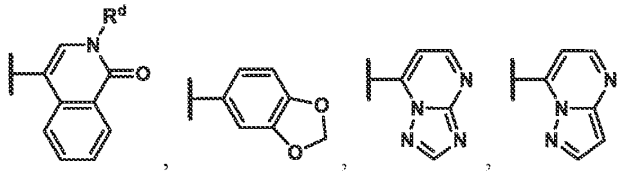
29. The compound of any one of claims 1 or 16-19, wherein **Ring C** is  ; **Ring D** is a partially unsaturated or aromatic ring including from 5-6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R}^{cA}$; **n2** is 0 or 1; and each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{e}$.

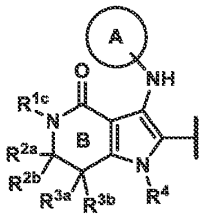
30. The compound of claim 29, wherein **Ring D** is a partially unsaturated or aromatic ring including 6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R}^{cA}$.

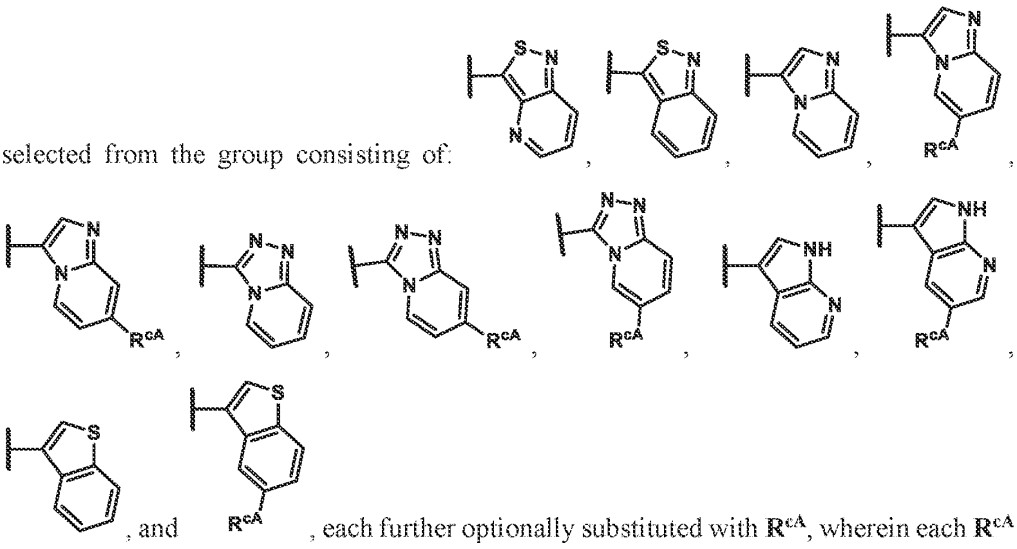
31. The compound of any one of claims 1, 16-19, or 29-30, wherein **Ring C** is selected from the group consisting of:  ,  ,  (e.g., ),  , and  , each further optionally substituted with $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

32. The compound of claim 29, wherein **Ring D** is a partially unsaturated or aromatic ring including 5 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0\text{-}2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

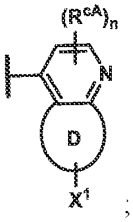
33. The compound of any one of claims 1, 16-19, 29, or 32, wherein **Ring C** is selected from the group consisting of:  , each further optionally substituted with $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$.

34. The compound of any one of claims 1 or 16-19, wherein **Ring C** is selected from the group consisting of:  , each further optionally substituted with $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$.

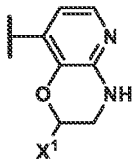
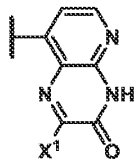
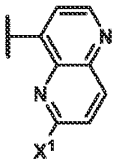
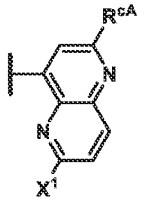
35. The compound of claims 17 or 18, wherein **Ring C** is connected to  via a 5-membered ring.

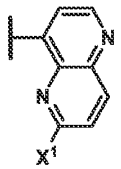
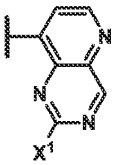
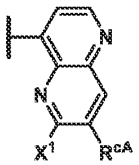
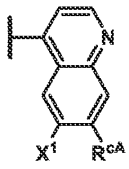
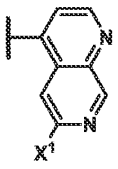
36. The compound of any one of claims 1, 16-18, or 35, wherein **Ring C** is selected from the group consisting of:  , each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^{c}.

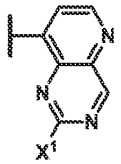
37. The compound of any one of claims 1 or 16-17, wherein **Ring C** is bicyclic heteroaryl including 9-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^{d}), O, and S(O)$_{0-2}$, and wherein the heteroaryl is substituted with X^{1} and further optionally substituted with from 1-4 R^{cA}, wherein each R^{cA} is an independently selected R^{c}.

38. The compound of any one of claims 1, 16-17, 19, or 37, wherein **Ring C** is  ; **Ring D** is a partially unsaturated or aromatic ring including from 5-6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N(R^{d}), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 R^{cA}; **n** is 0, 1, or 2; and each R^{cA} is an independently selected R^{c}.

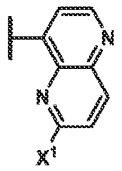
39. The compound of claim 38, wherein **Ring D** is a partially unsaturated or aromatic ring including 6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R}^{cA}$.

40. The compound of any one of claims 1, 16-17, 19, or 37-39, wherein **Ring C** is selected from the group consisting of:  ,  ,  , and  , each further optionally substituted with $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

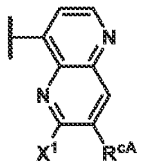
41. The compound compound of any one of claims 1, 17, or 37, wherein **Ring C** is selected from the group consisting of:  ,  ,  ,  , and  each of which is further optionally substituted with from 1-2 $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

42. The compound of any one of claims 1, 17, 37, or 41, wherein **Ring C** is  .

43. The compound of any one of claims 1, 17, 37, or 41, wherein **Ring C** is



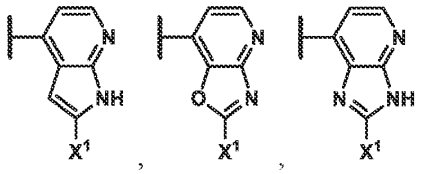
44. The compound of any one of claims 1, 17, 37, or 41, wherein **Ring C** is



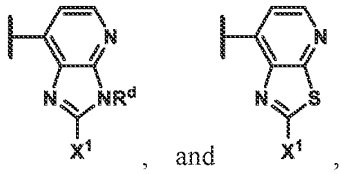
, wherein $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

45. The compound of claim 38, wherein **Ring D** is a partially unsaturated or aromatic ring including 5 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R}^{cA}$.

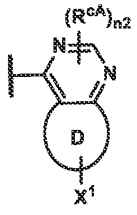
46. The compound of any one of claims 1, 16-17, 19, 37-38, or 45, wherein **Ring C** is selected from the group consisting of:



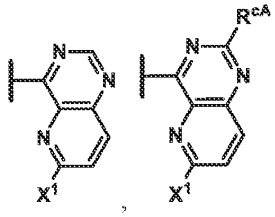
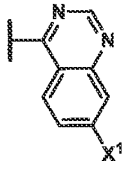
, and



, each further optionally substituted with $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

47. The compound of any one of claims 1, 16-17, 19, or 37, wherein **Ring C** is  ; **Ring D** is a partially unsaturated or aromatic ring including from 5-6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$; **n2** is 0 or 1; and each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$.

48. The compound of claim 47, wherein **Ring D** is a partially unsaturated or aromatic ring including 6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

49. The compound of any one of claims 1, 16-17, 19, or 47-48, wherein **Ring C** is selected from the group consisting of:  , and  , each further optionally substituted with $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$.

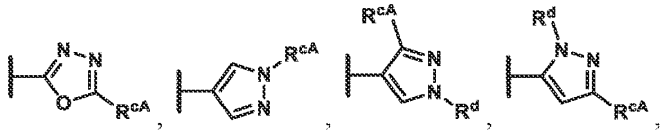
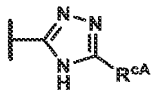
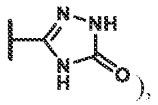
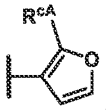
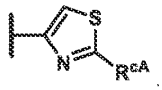
50. The compound of claim 47, wherein **Ring D** is a partially unsaturated or aromatic ring including 5 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

51. The compound of claim 1, wherein **Ring C** is heteroaryl including 5 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is

optionally substituted with X^1 and further optionally substituted with from 1-4 R^{cA}, wherein each R^{cA} is an independently selected R^c.

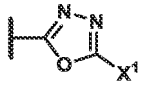
52. The compound of claims 1 or 51, wherein **Ring C** is heteroaryl including 5 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 R^{cA}, wherein each R^{cA} is an independently selected R^c.

53. The compound of any one of claims 1 or 51-52, wherein **Ring C** is selected from the group consisting of: pyrazolyl, imidazolyl, thiazolyl, oxazolyl, triazolyl, furanyl, thiophenyl, oxadiazolyl, and thiadiazolyl, each optionally substituted with from 1-2 R^{cA}, wherein a ring nitrogen atom is optionally substituted with R^d, and each R^{cA} is an independently selected R^c.

54. The compound of any one of claims 1 or 51-53, wherein **Ring C** is selected from the group consisting of:  ,  (e.g., ),  , and  .

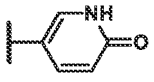
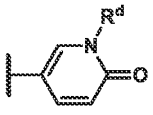
55. The compound of claims 1 or 51, wherein **Ring C** is heteroaryl including 5 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heteroaryl is substituted with X^1 and further optionally substituted with from 1-2 R^{cA}, wherein each R^{cA} is an independently selected R^c.

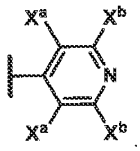
56. The compound of any one of claims 1, 51, or 55, wherein **Ring C** is selected from the group consisting of: pyrazolyl, imidazolyl, thiazolyl, oxazolyl, triazolyl, furanyl, thiophenyl, oxadiazolyl, and thiadiazolyl, each substituted with X^1 and further optionally

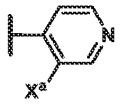
substituted with from 1-2 R^{cA}, wherein a ring nitrogen atom is optionally substituted with R^d, and each R^{cA} is an independently selected R^c, such as wherein **Ring C** is  .

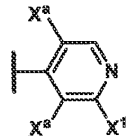
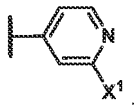
57. The compound of claim 1, wherein **Ring C** is 2-pyridonyl or 4-pyridonyl, each optionally substituted with X^1 and further optionally substituted with from 1-4 R^{cA}, wherein the ring nitrogen atom is optionally substituted with R^d, wherein each R^{cA} is an independently selected R^c.

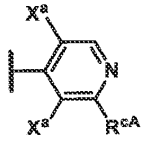
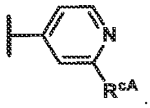
58. The compound of claims 1 or 57, wherein **Ring C** is 2-pyridonyl which is optionally substituted with X^1 and further optionally substituted with from 1-4 R^{cA}, wherein the ring nitrogen atom is optionally substituted with R^d, wherein each R^{cA} is an independently selected R^c.

59. The compound of any one of claims 1 or 57-58, wherein **Ring C** is 2-pyridonyl which is optionally substituted with from 1-4 R^{cA}, wherein the ring nitrogen atom is optionally substituted with R^d, wherein each R^{cA} is an independently selected R^c, such as wherein **Ring C** is  or  .

60. The compound of claim 1, wherein **Ring C** is  .

61. The compound of claim 1 or 60, wherein **Ring C** is  .

62. The compound of claim 1 or 60, wherein **Ring C** is  , such as  .

63. The compound of claim 1 or 60, wherein **Ring C** is  , wherein R^{cA} is an independently selected R^c, such as wherein **Ring C** is  .

64. The compound of any one of claims 1 or 63, wherein each X^a is selected from the group consisting of: H; halo; and C_{1-6} alkyl optionally substituted with from 1-6 R^a.

65. The compound of any one of claims 1 or 63-64, wherein from 1-2, such as 1, occurrence of X^a is independently a substituent other than H.

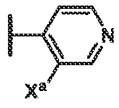
66. The compound of any one of claims 1 or 63-64, wherein one occurrence of X^a is halo, such as –F or –Cl.

67. The compound of any one of claims 1 or 63-66, wherein one occurrence of X^a is –F.

68. The compound of any one of claims 1 or 63-65, wherein one occurrence of X^a is C_{1-3} alkyl optionally substituted with from 1-6 R^a.

69. The compound of any one of claims 1 or 63-65, or 68, wherein one occurrence of $\mathbf{X^a}$ is C_{1-3} alkyl substituted with from 1-3 independently selected halo, such as $-CF_3$ or $-CHF_2$.

70. The compound of any one of claims 1 or 63-64, wherein each $\mathbf{X^a}$ is –H.

71. The compound of any one of claims 1 or 60-61, wherein **Ring C** is 

; wherein $\mathbf{X^a}$ is selected from the group consisting of: -F; -Cl; -H; and C_{1-3} alkyl optionally substituted with from 1-3 independently selected halo.

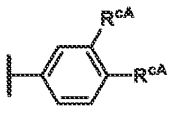
72. The compound of claim 71, wherein $\mathbf{X^a}$ is –F.

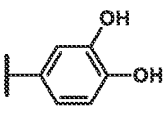
73. The compound of claim 71, wherein $\mathbf{X^a}$ is –Cl.

74. The compound of claim 71, wherein $\mathbf{X^a}$ is –H.

75. The compound of claim 71, wherein $\mathbf{X^a}$ is C_{1-3} alkyl substituted with from 1-3 independently selected halo, such as $-CF_3$ or $-CHF_2$.

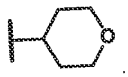
76. The compound of claim 1, wherein **Ring C** is C_{6-10} aryl optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$.

77. The compound of claims 1 or 76, wherein **Ring C** is phenyl optionally substituted with from 1-4 $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$, such as wherein **Ring C** is 

, such as 

.

78. The compound of claim 1, wherein **Ring C** is heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$.

79. The compound of claims 1 or 78, wherein **Ring C** is heterocyclyl including from 4-8, such as 5-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heterocyclyl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$, such as wherein **Ring C** is  .

80. The compound of any one of claims 1-79, wherein **m** is 1.

81. The compound of any one of claims 1-80, wherein $\mathbf{X^2}$ is selected from the group consisting of: -O-, -N($\mathbf{R^N}$)-, and –S(O)$_{0-2}$.

82. The compound of any one of claims 1-81, wherein $\mathbf{X^2}$ is –N($\mathbf{R^N}$)-.

83. The compound of any one of claims 1-82, wherein $\mathbf{X^2}$ is –N(H)-.

84. The compound of any one of claims 1-81, wherein $\mathbf{X^2}$ is –O-.

85. The compound of any one of claims 1-80, wherein $\mathbf{X^2}$ is selected from the group consisting of: -OC(=O)-*, -N($\mathbf{R^N}$)C(=O)-*, and –N($\mathbf{R^N}$)S(O)$_{1-2}$-*.

86. The compound of any one of claims 1-80 or 85, wherein $\mathbf{X^2}$ is -N($\mathbf{R^N}$)C(=O)-*.

87. The compound of any one of claims 1-80 or 85-86, wherein $\mathbf{X^2}$ is –N(H)C(=O)-*.

88. The compound of any one of claims 1-80 or 85, wherein $\mathbf{X^2}$ is –N($\mathbf{R^N}$)S(O)$_2$-*, such as –NHS(O)$_2$-.

89. The compound of any one of claims 1-57, wherein $\mathbf{X^2}$ is selected from the group consisting of: -OC(=O)N($\mathbf{R^N}$)-*, -N($\mathbf{R^N}$)C(=O)O-*, -N($\mathbf{R^N}$)C(=O)N($\mathbf{R^N}$)-*, and –N($\mathbf{R^N}$)S(O)$_{1-2}$N($\mathbf{R^N}$)-*.

90. The compound of any one of claims 1-80 or 89, wherein $\mathbf{X^2}$ is -N($\mathbf{R^N}$)C(=O)O-*, such as –N(H)C(=O)O-*.

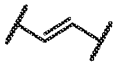
91. The compound of any one of claims 1-80 or 89, wherein $\mathbf{X^2}$ is -N($\mathbf{R^N}$)C(=O)N($\mathbf{R^N}$)-*, such as –N(H)C(=O)N(H)-*.

92. The compound of any one of claims 1-80 or 89, wherein $\mathbf{X^2}$ is -C(=O)O-*, -C(=O)N($\mathbf{R^N}$)-*, or –S(O)$_{1-2}$N($\mathbf{R^N}$)-*.

93. The compound of any one of claims 1-80 or 92, wherein $\mathbf{X^2}$ is –C(=O)N($\mathbf{R^N}$)-*, such as –C(=O)N(H)-*.

94. The compound of any one of claims 1-80, wherein $\mathbf{X^2}$ is  .

95. The compound of any one of claims 1-80, wherein $\mathbf{X^2}$ is C$_{2-6}$ alkenylene optionally substituted with from 1-3 $\mathbf{R^a}$.

96. The compound of any one of claims 1-80 or 95, wherein $\mathbf{X^2}$ is  .

97. The compound of any one of claims 1-79, wherein **m** is 0.

98. The compound of any one of claims 1-97, wherein $\mathbf{L^1}$ is a bond.

99. The compound of any one of claims 1-97, wherein $\mathbf{L^1}$ is C_{1-10} alkylene optionally substituted with from 1-6 $\mathbf{R^a}$.

100. The compound of any one of claims 1-97 or 99, wherein $\mathbf{L^1}$ is C_{1-3} alkylene optionally substituted with from 1-6 $\mathbf{R^a}$, such as wherein $\mathbf{L^1}$ is unsubstituted C_{1-3} alkylene.

101. The compound of any one of claims 1-97 or 99-100, wherein $\mathbf{L^1}$ is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CF_2-$, or –CH(Me)-, such as wherein $\mathbf{L^1}$ is $-CH_2-$, $-CH_2CH_2-$, or –CH(Me)-.

102. The compound of any one of claims 1-97 or 99, wherein $\mathbf{L^1}$ is branched C_{3-6} alkylene optionally substituted with from 1-6 $\mathbf{R^a}$, such as wherein $\mathbf{L^1}$ is  or 

, wherein *aa* is the point of attachment to $\mathbf{R^5}$.

103. The compound of any one of claims 1-97 or 99-102, wherein $\mathbf{R^5}$ is $-C_{1-6}$ alkoxy or $-S(O)_{0-2}(C_{1-6}$ alkyl), each optionally substituted with from 1-6 $\mathbf{R^a}$.

104. The compound of any one of claims 1-97 or 99-103, wherein $\mathbf{R^5}$ is $-C_{1-6}$ alkoxy optionally substituted with from 1-6 $\mathbf{R^a}$.

105. The compound of any one of claims 1-97 or 99-104, wherein $\mathbf{R^5}$ is $-C_{1-3}$ alkoxy, such as methoxy.

106. The compound of any one of claims 1-102, wherein $\mathbf{R^5}$ is H or halo, such as wherein $\mathbf{R^5}$ is H or -F.

107. The compound of any one of claims 1-102 or 106, wherein $\mathbf{R^5}$ is H.

108. The compound of any one of claims 1-97 or 99-102, wherein $\mathbf{R^5}$ is –OH or $-N\mathbf{R^e}\mathbf{R^f}$.

109. The compound of any one of claims 1-97, 99-102, or 108, wherein $\mathbf{R^5}$ is –OH.

110. The compound of any one of claims 1-97, wherein $\mathbf{R^5}$ is -$\mathbf{R^g}$.

111. The compound of any one of claims 1-97 or 110, wherein $\mathbf{R^5}$ is selected from the group consisting of:

- heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R^c}$; and
- C_{6-10} aryl optionally substituted with from 1-4 $\mathbf{R^c}$.

112. The compound of any one of claims 1-97 or 110-111, wherein $\mathbf{R^5}$ is C_{6-10} aryl optionally substituted with from 1-4 $\mathbf{R^c}$.

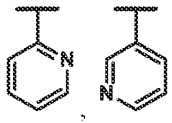
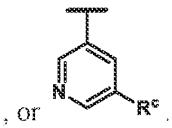
113. The compound of any one of claims 1-97 or 110-112, wherein $\mathbf{R^5}$ is phenyl optionally substituted with from 1-4 $\mathbf{R^c}$.

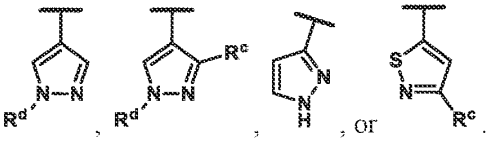
114. The compound of any one of claims 1-102 or 110-113, wherein $\mathbf{R^5}$ is phenyl optionally substituted with from 1-2 independently selected halo, such as –F.

115. The compound of any one of claims 1-97 or 110-111, wherein $\mathbf{R^5}$ is heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R^c}$.

116. The compound of any one of claims 1-97, 110-111, or 115, wherein $\mathbf{R^5}$ is heteroaryl including from 5-6 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R^c}$.

117. The compound of any one of claims 1-97, 110-111, or 115-116, wherein $\mathbf{R^5}$ is heteroaryl including 6 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each

independently selected from the group consisting of N, N(H), and N($\mathbf{R}^d$), and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R}^c$, such as wherein $\mathbf{R}^5$ is  ,  .

118. The compound of any one of claims 1-97, 110-111, or 115-116, wherein $\mathbf{R}^5$ is heteroaryl including 5 ring atoms, wherein from 1-4, such as 2-4, ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^d$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R}^c$, such as wherein $\mathbf{R}^5$ is  .

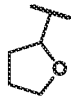
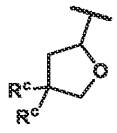
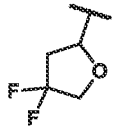
119. The compound of any one of claims 1-97 or 110, wherein $\mathbf{R}^5$ is selected from the group consisting of:

- C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R}^c$; and
- heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^d$), O, and S(O)$_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R}^c$.

120. The compound of any one of claims 1-97, 110, or 119, wherein $\mathbf{R}^5$ is C_{3-10} cycloalkyl or C_{3-10} cycloalkenyl, each of which is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R}^c$.

121. The compound of any one of claims 1-97, 110, or 119-120, wherein $\mathbf{R^5}$ is C_{3-10} cycloalkyl, such as C_{3-6} cycloalkyl, optionally substituted with from 1-4 $\mathbf{R^c}$, such as wherein $\mathbf{R^5}$ is cyclopropyl.

122. The compound of any one of claims 1-97, 110, or 119, wherein $\mathbf{R^5}$ is heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$.

123. The compound of any one of claims 1-97, 110, 119, or 122, wherein $\mathbf{R^5}$ is heterocyclyl including from 4-8, such as 4-6, ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$, such as wherein $\mathbf{R^5}$ is  ,  ,  , such as  , or  .

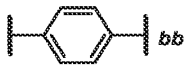
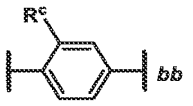
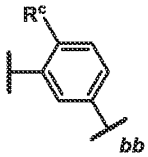
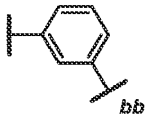
124. The compound of any one of claims 1-97, wherein $\mathbf{R^5}$ is selected from the group consisting of: -$\mathbf{R^{g2}}$-$\mathbf{R^W}$ and –$\mathbf{R^{g2}}$-$\mathbf{R^Y}$.

125. The compound of any one of claims 1-97, or 124, wherein $\mathbf{R^5}$ is –$\mathbf{R^{g2}}$-$\mathbf{R^Y}$.

126. The compound of claims 124 or 125, wherein the –$\mathbf{R^{g2}}$ group present in $\mathbf{R^5}$ is C_{6-10} arylene optionally substituted with from 1-4 $\mathbf{R^c}$.

127. The compound of any one of claims 124-126, wherein the –$\mathbf{R^{g2}}$ group present in $\mathbf{R^5}$ is phenylene optionally substituted with from 1-4 $\mathbf{R^c}$.

128. The compound of any one of claims 124-127, wherein the –$\mathbf{R^{g2}}$ group present in $\mathbf{R^5}$ is 1,3-phenylene or 1,4-phenylene, each optionally substituted with from 1-4

R^c, such as wherein $-R^{g2}$ is  ,  ,  , or  , wherein *bb* is the point of attachment to R^Y.

129. The compound of any one of claims 101-105, wherein the R^Y group present in R^5 is $-R^g$.

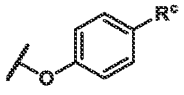
130. The compound of any one of claims 124-129, wherein the R^Y group present in R^5 is heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), $N(R^d)$, O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c.

131. The compound of any one of claims 124-130, wherein the R^Y group present in R^5 is heterocyclyl including from 4-8, such as 4-6, ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), $N(R^d)$, O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c, such as wherein R^Y is  .

132. The compound of any one of claims 1-97 or 99-102, wherein R^5 is $-L^5$-R^g.

133. The compound of any one of claims 1-97, 99-102, or 132, wherein R^5 is –O-R^g.

134. The compound of any one of claims 1-97, 99-102, or 132-133, wherein R^5 is –O-(C_{6-10} aryl) wherein the C_{6-10} aryl is optionally substituted with from 1-4 R^c.

135. The compound of any one of claims 1-97, 99-102, or 132-134, wherein $\mathbf{R^5}$ is –O-phenyl wherein the phenyl is optionally substituted with from 1-2 $\mathbf{R^c}$, such as wherein $\mathbf{R^5}$ is  .

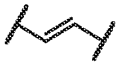
136. The compound of any one of claims 1-79, wherein $\mathbf{X^1}$ is $-(\mathbf{X^2})_m\text{-}\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein:

- **m** is 0 or 1;
- $\mathbf{X^2}$ is $-N(\mathbf{R^N})-$ or -O-;
- $\mathbf{L^1}$ is a bond or $C_{1\text{-}6}$ alkylene optionally substituted with from 1-3 $\mathbf{R^a}$; and
- $\mathbf{R^5}$ is $-\mathbf{R^g}$.

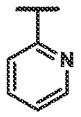
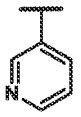
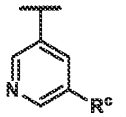
137. The compound of any one of claims 1-79, wherein $\mathbf{X^1}$ is $-\mathbf{X^2}\text{-}\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein:

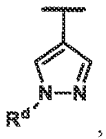
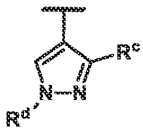
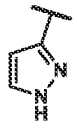
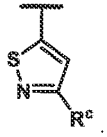
- $\mathbf{X^2}$ is $-N(\mathbf{R^N})C(=O)-*$, $-N(\mathbf{R^N})S(O)_2-*$, $-N(\mathbf{R^N})C(=O)O-*$, or $N(\mathbf{R^N})C(=O)N(\mathbf{R^N})*$;
- $\mathbf{L^1}$ is a bond or $C_{1\text{-}6}$ alkylene optionally substituted with from 1-3 $\mathbf{R^a}$; and
- $\mathbf{R^5}$ is $-\mathbf{R^g}$.

138. The compound of any one of claims 1-79, wherein $\mathbf{X^1}$ is $-\mathbf{X^2}\text{-}\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein:

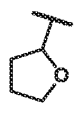
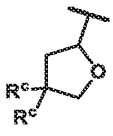
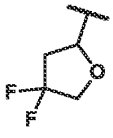
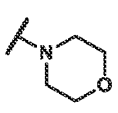
- $\mathbf{X^2}$ is  or  ;
- $\mathbf{L^1}$ is a bond or $C_{1\text{-}6}$ alkylene optionally substituted with from 1-3 $\mathbf{R^a}$; and
- $\mathbf{R^5}$ is $-\mathbf{R^g}$.

139. The compound of any one of claims 136-138, wherein $\mathbf{R^5}$ is phenyl optionally substituted with from 1-4 $\mathbf{R^c}$, such as wherein $\mathbf{R^5}$ is phenyl optionally substituted with from 1-2 independently selected halo, such as –F.

140. The compound of any one of claims 136-138, wherein $\mathbf{R^5}$ is heteroaryl including 6 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N($\mathbf{R^d}$), and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R^e}$, such as wherein $\mathbf{R^5}$ is  ,  , or  .

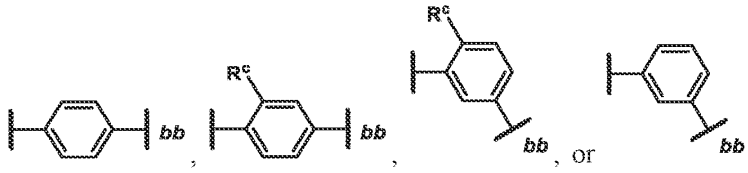
141. The compound of any one of claims 136-138, wherein $\mathbf{R^5}$ is heteroaryl including 5 ring atoms, wherein from 1-4, such as 2-4, ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R^e}$, such as wherein $\mathbf{R^5}$ is  ,  ,  , or  .

142. The compound of any one of claims 136-138, wherein $\mathbf{R^5}$ is C$_{3-10}$ cycloalkyl, such as C$_{3-6}$ cycloalkyl, optionally substituted with from 1-4 $\mathbf{R^e}$, such as wherein $\mathbf{R^5}$ is cyclopropyl.

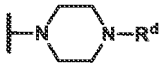
143. The compound of any one of claims 136-138, wherein $\mathbf{R^5}$ is heterocyclyl including from 4-8, such as 4-6, ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^e}$, such as wherein $\mathbf{R^5}$ is  ,  ,  such as  , or  .

144. The compound of any one of claims 1-79, wherein $\mathbf{X^1}$ is $-(\mathbf{X^2})_m\text{-}\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein:

- **m** is 0 or 1;
- $\mathbf{X^2}$ is -N($\mathbf{R^N}$)- or –O-;
- $\mathbf{L^1}$ is a bond or $C_{1\text{-}6}$ alkylene optionally substituted with from 1-3 $\mathbf{R^a}$; and
- $\mathbf{R^5}$ is $-\mathbf{R^{g2}}\text{-}\mathbf{R^Y}$.

145. The compound of claim 144, wherein the $-\mathbf{R^{g2}}$ group present in $\mathbf{R^5}$ is 1,3-phenylene or 1,4-phenylene, each optionally substituted with from 1-4 $\mathbf{R^c}$, such as wherein $-\mathbf{R^{g2}}$ is  , wherein *bb* is the point of attachment to $\mathbf{R^Y}$.

146. The compound of claims 144 or 145, wherein the $\mathbf{R^Y}$ group present in $\mathbf{R^5}$ is $-\mathbf{R^g}$.

147. The compound of any one of claims 144-146, wherein the $\mathbf{R^Y}$ group present in $\mathbf{R^5}$ is heterocyclyl including from 4-8, such as 4-6, ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0\text{-}2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$, such as wherein $\mathbf{R^Y}$ is  .

148. The compound of any one of claims 1-79, wherein $\mathbf{X^1}$ is $-\mathbf{X^2}\text{-}\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein:

- $\mathbf{X^2}$ is -N($\mathbf{R^N}$)-, –O-, -N($\mathbf{R^N}$)C(=O)-*, -N($\mathbf{R^N}$)$S(O)_2$-, -N($\mathbf{R^N}$)C(=O)O-*, or -N($\mathbf{R^N}$)C(=O)N($\mathbf{R^N}$)-*;
- $\mathbf{L^1}$ is $C_{1\text{-}6}$ alkylene optionally substituted with from 1-3 $\mathbf{R^a}$; and

- $\mathbf{R^5}$ is H, halo, C_{1-6} alkoxy optionally substituted with from 1-3 $\mathbf{R^a}$, or –OH.

149. The compound of claim 148, wherein $\mathbf{R^5}$ is H.

150. The compound of claim 148, wherein $\mathbf{R^5}$ is halo, such as –F.

151. The compound of claim 148, wherein $\mathbf{R^5}$ is C_{1-6} alkoxy optionally substituted with from 1-3 $\mathbf{R^a}$, such as wherein $\mathbf{R^5}$ is C_{1-3} alkoxy such as methoxy.

152. The compound of claim 148, wherein $\mathbf{R^5}$ is –OH.

153. The compound of any one of claims 136 or 139-147, wherein **m** is 0.

154. The compound of any one of claims 136 or 139-147, wherein **m** is 1.

155. The compound of any one of claims 136, 139-152, or 154, wherein $\mathbf{X^2}$ is –$N(\mathbf{R^N})$-, such as N(H).

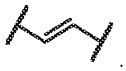
156. The compound of any one of claims 136, 139-152, or 154, wherein $\mathbf{X^2}$ is –O-.

157. The compound of any one of claims 137, 139-143, or 148-152, wherein $\mathbf{X^2}$ is -$N(\mathbf{R^N})C(=O)$-*, such as –N(H)C(=O)-*.

158. The compound of any one of claims 137, 139-143, or 148-152, wherein $\mathbf{X^2}$ is -$N(\mathbf{R^N})S(O)_2$-, such as –$N(H)S(O)_2$-*.

159. The compound of any one of claims 137, 139-143, or 148-152, wherein $\mathbf{X^2}$ is -$N(\mathbf{R^N})C(=O)O$-*, or -$N(\mathbf{R^N})C(=O)N(\mathbf{R^N})$-*, such as –N(H)C(=O)O-* or –N(H)C(=O)N(H)-*.

160. The compound of any one of claims 138-143, wherein $\mathbf{X^2}$ is  .

161. The compound of any one of claims 138-143, wherein $\mathbf{X^2}$ is  .

162. The compound of any one of claims 136-147 or 153-161, wherein $\mathbf{L^1}$ is a bond.

163. The compound of any one of claims 136-161, wherein $\mathbf{L^1}$ is C_{1-3} alkylene, such as $-CH_2-$, $-CH_2CH_2-$, or –CH(Me)-.

164. The compound of any one of claims 136-161, wherein $\mathbf{L^1}$ is branched C_{3-6} alkylene, such as  or  , wherein ***aa*** is the point of attachment to $\mathbf{R^5}$.

165. The compound of any one of claims 1-79, wherein $\mathbf{X^1}$ is $-\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein $\mathbf{L^1}$ is C_{1-6} alkylene optionally substituted with from 1-3 $\mathbf{R^a}$; and $\mathbf{R^5}$ is $-\mathbf{L^5}\text{-}\mathbf{R^g}$.

166. The compound of claim 165, wherein $\mathbf{R^5}$ is $-O\text{-}\mathbf{R^g}$.

167. The compound of claims 165 or 166, wherein $\mathbf{R^5}$ is –O-(phenyl), wherein the phenyl is optionally substituted with from 1-2 $\mathbf{R^c}$.

168. The compound of any one of claims 165-167, wherein $\mathbf{L^1}$ is C_{1-3} alkylene, such as $-CH_2-$, $-CH_2CH_2-$, or –CH(Me)-.

169. The compound of any one of claims 2-168, wherein each occurrence of $\mathbf{R^{cA}}$ is independently selected from the group consisting of: halo; cyano; C_{1-10} alkyl which is optionally substituted with from 1-6 independently selected $\mathbf{R^a}$; C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy or C_{1-4} haloalkoxy; C_{1-4} haloalkoxy; $-S(O)_{1-2}(C_{1-4}$ alkyl); $-N\mathbf{R^e}\mathbf{R^f}$; –OH; $-S(O)_{1-2}N\mathbf{R'}\mathbf{R''}$; $-C_{1-4}$ thioalkoxy; $-C(=O)(C_{1-10}$ alkyl); $-C(=O)O(C_{1-4}$ alkyl); -C(=O)OH; and $-C(=O)N\mathbf{R'}\mathbf{R''}$.

170. The compound of any one of claims 2-169, wherein one occurrence of $\mathbf{R^{cA}}$ is $-N\mathbf{R^e}\mathbf{R^f}$.

171. The compound of any one of claims 2-170, wherein one occurrence of $\mathbf{R}^{cA}$ is $-NH_2$.

172. The compound of any one of claims 2-170, wherein one occurrence of $\mathbf{R}^{cA}$ is $-NH(C_{1-6}$ alkyl), wherein the C_{1-6} alkyl is optionally substituted with from 1-3 substituents each independently selected from the group consisting of $N\mathbf{R'R''}$, -OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and halo.

173. The compound of any one of claims 2-170 or 172, wherein one occurrence of $\mathbf{R}^{cA}$ is –NHMe, $-NHCH_2CF_3$, $-NHCH_2CH_2OH$, or –NHiPr.

174. The compound of any one of claims 2-170, wherein one occurrence of $\mathbf{R}^{cA}$ is $-NHC(=O)C_{1-4}$ alkyl, such as $NHC(=O)CH_3$; or wherein one occurrence of $\mathbf{R}^{cA}$ is $N(C_{1-3}$ alkyl$)_2$ such as NMe_2.

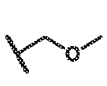
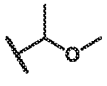
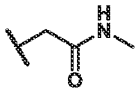
175. The compound of any one of claims 2-169, wherein one occurrence of $\mathbf{R}^{cA}$ is C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy or C_{1-4} haloalkoxy, such as wherein one occurrence of $\mathbf{R}^{cA}$ is OMe or OCH_2CH_2OMe.

176. The compound of any one of claims 2-169, wherein one occurrence of $\mathbf{R}^{cA}$ is C_{1-4} haloalkoxy, such as $-OCH_2CF_3$.

177. The compound of any one of claims 2-169, wherein one occurrence of $\mathbf{R}^{cA}$ is C_{1-4} thioalkoxy, such as $-SCH_3$.

178. The compound of any one of claims 2-169, wherein one occurrence of $\mathbf{R}^{cA}$ is C_{1-6} alkyl, such as methyl; or wherein one occurrence of $\mathbf{R}^{cA}$ is C_{1-6} alkyl substituted with from 1-6 independently selected halo, such as $-CF_3$.

179. The compound of any one of claims 2-169, wherein one occurrence of $\mathbf{R}^{cA}$ is C_{1-6} alkyl substituted with $\mathbf{R}^{a}$, such as C_{1-6} alkyl substituted with C_{1-3} alkoxy or

C(=O)N**R'R"**, such as wherein one occurrence of $\mathbf{R}^{cA}$ is  ,  , or 

180. The compound of any one of claims 2-169, wherein one occurrence of $\mathbf{R}^{cA}$ is halo, such as –F.

181. The compound of any one of claims 2-169, wherein one occurrence of $\mathbf{R}^{cA}$ is –OH.

182. The compound of any one of claims 2-169, wherein one occurrence of $\mathbf{R}^{cA}$ is C(=O)N**R'R"**, such as C(=O)NHMe.

183. The compound of any one of claims 1-182, wherein $\mathbf{R}^{1c}$ is H.

184. The compound of any one of claims 1-183, wherein $\mathbf{R}^{2a}$ and $\mathbf{R}^{2b}$ are both H.

185. The compound of any one of claims 1-183, wherein from 1-2 of $\mathbf{R}^{2a}$ and $\mathbf{R}^{2b}$ is an independently selected substituent that is other than H.

186. The compound of any one of claims 1-183 or 185, wherein one of $\mathbf{R}^{2a}$ and $\mathbf{R}^{2b}$, such as $\mathbf{R}^{2a}$, is a substituent that is other than H.

187. The compound of any one of claims 1-183 or 185-186, wherein one of $\mathbf{R}^{2a}$ and $\mathbf{R}^{2b}$, such as $\mathbf{R}^{2a}$, is $\mathbf{R}^{b}$.

188. The compound of any one of claims 1-183 or 185-187, wherein one of $\mathbf{R}^{2a}$ and $\mathbf{R}^{2b}$, such as $\mathbf{R}^{2a}$, is C_{1-6} alkyl, which is optionally substituted with from 1-6 $\mathbf{R}^{a}$.

189. The compound of any one of claims 1-183 or 185-188, wherein one of $\mathbf{R}^{2a}$ and $\mathbf{R}^{2b}$, such as $\mathbf{R}^{2a}$, is C_{1-3} alkyl, such as methyl or ethyl.

190. The compound of any one of claims 186-189, wherein the other of R^{2a} and R^{2b}, such as R^{2b}, is H.

191. The compound of any one of claims 1-190, wherein R^{3a} and R^{3b} are both H.

192. The compound of any one of claims 1-190, wherein from 1-2 of R^{3a} and R^{3b} is an independently selected substituent that is other than H.

193. The compound of any one of claims 1-190 or 192, wherein one of R^{3a} and R^{3b}, such as R^{3a}, is a substituent that is other than H.

194. The compound of any one of claims 1-190 or 192-193, wherein one of R^{3a} and R^{3b}, such as R^{3a}, is R^{b}.

195. The compound of any one of claims 1-190 or 192-194, wherein one of R^{3a} and R^{3b}, such as R^{3a}, is C_{1-6} alkyl which is optionally substituted with from 1-6 R^{a}.

196. The compound of any one of claims 1-190 or 192-194, wherein one of R^{3a} and R^{3b}, such as R^{3a}, is C_{1-3} alkyl, such as methyl or ethyl.

197. The compound of any one of claims 1-190 or 192-195, wherein one of R^{3a} and R^{3b}, such as R^{3a}, is C_{1-3} alkyl substituted with from 1-3 independently selected halo.

198. The compound of any one of claims 1-190, 192-195, or 197, wherein one of R^{3a} and R^{3b}, such as R^{3a}, is $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CHF_2$, or $-CH_2CH_2F$.

199. The compound of any one of claims 1-190 or 192-195, wherein one of R^{3a} and R^{3b}, such as R^{3a}, is C_{1-3} alkyl substituted with C_{1-4} alkoxy, C_{1-4} haloalkoxy, or $NR^{e}R^{f}$.

200. The compound of any one of claims 1-190, 192-195, or 199, wherein one of R^{3a} and R^{3b}, such as R^{3a}, is $-CH_2OMe$, $-CH_2CH_2OMe$, $-CH(Me)CH_2OMe$, -

$CH_2CH(Me)OMe$, $-CH_2OEt$, $-CH_2CH_2OCHF_2$ $-CH_2NR^eR^f$ (e.g., $-CH_2N(CF_3)Me$), or $-CH_2CH_2NR^eR^f$ (e.g., $-CH_2CH_2NMe_2$).

201. The compound of any one of claims 1-190, 192-195, or 199-200, wherein one of R^{3a} and R^{3b}, such as R^{3a}, is C_{1-3} alkyl substituted with C_{1-4} alkoxy.

202. The compound of any one of claims 1-190, 192-195, or 199-201 wherein one of R^{3a} and R^{3b}, such as R^{3a}, is $-CH_2OMe$, $-CH_2CH_2OMe$, $-CH(Me)CH_2OMe$, $-CH_2CH(Me)OMe$, or $-CH_2OEt$, such as $-CH_2OMe$; such as $-CH_2CH_2OMe$; optionally the other one of R^{3a} and R^{3b}, such as R^{3b} is H.

203. The compound of any one of claims 1-190 or 192-193, wherein one of R^{3a} and R^{3b}, such as R^{3a}, is R^g or $-(L^g)_g$-R^g.

204. The compound of any one of claims 1-190, 192-193, or 203, wherein one of R^{3a} and R^{3b}, such as R^{3a}, is selected from the group consisting of:

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c; and

C_{3-6} cycloalkyl optionally substituted with from 1-4 R^c.

205. The compound of any one of claims 1-190, 192-193, or 203-204, wherein one of R^{3a} and R^{3b}, such as R^{3a}, is selected from the group consisting of: cyclopropyl, cyclobutyl, oxetanyl, and azetidinyl, each of which is optionally substituted with from 1-2 substituents independently selected from the group consisting of: C_{1-3} alkyl and halo, wherein the ring nitrogen of the azetidinyl is optionally substituted with R^d.

206. The compound of any one of claims 1-190, 192-193, or 203, wherein one of R^{3a} and R^{3b}, such as R^{3a}, is $-(C_{1-3}$ alkylene)-R^g or -(C_{1-3} alkylene)-O-R^g, and optionally the R^g group of R^{3a} or R^{3b} is:

C_{3-6} cycloalkyl optionally substituted with from 1-4 $\mathbf{R^c}$, or

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$.

207. The compound of any one of claims 1-190, 192-193, 203, or 206, wherein one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is $-CH_2$-$\mathbf{R^g}$, $-CH_2CH_2\mathbf{R^g}$, or $-CH_2$-O-$\mathbf{R^g}$, wherein the $\mathbf{R^g}$ group of $\mathbf{R^{3a}}$ or $\mathbf{R^{3b}}$ is:

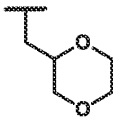
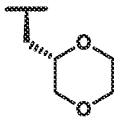
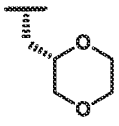
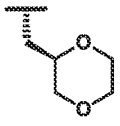
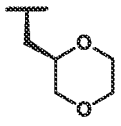
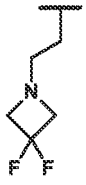
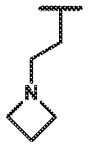
C_{3-6} cycloalkyl optionally substituted with from 1-4 $\mathbf{R^c}$, or

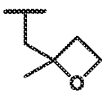
heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$.

208. The compound of any one of claims 1-190, 192-193, 203, or 206-207, wherein one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is $-CH_2$-$\mathbf{R^g}$, $-CH_2CH_2\mathbf{R^g}$, or $-CH_2$-O-$\mathbf{R^g}$, wherein the $\mathbf{R^g}$ group of $\mathbf{R^{3a}}$ or $\mathbf{R^{3b}}$ is selected from the group consisting of:

cyclopropyl, cyclobutyl, oxetanyl, 1,4-dioxanyl, and azetidinyl, each of which is optionally substituted with from 1-2 substituents independently selected from the group consisting of: C_{1-3} alkyl and halo, wherein the ring nitrogen of the azetidinyl is optionally substituted with $\mathbf{R^d}$.

209. The compound of any one of claims 1-190, 192-193, 203 or 206-208, wherein one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is selected from the group consisting of:

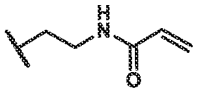
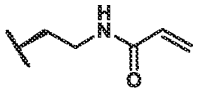
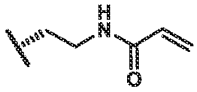
 , such as  ,  ,  , or  ;  ;  ;

 , such as  or  ;  , such as  or  ;  , such as  or   ; and  .

210. The compound of any one of claims 1-190, 192-193 wherein one of $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$, such as $\mathbf{R}^{3a}$, is-$(\mathbf{L}^{s})_{g}$-$\mathbf{R}^{W}$.

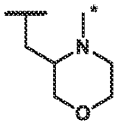
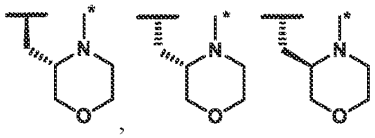
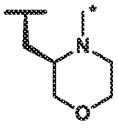
211. The compound any one of claim 1-190, 192-193 or 210, wherein one of $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$, such as $\mathbf{R}^{3a}$, is –(C_{1-3} alkylene)-$\mathbf{R}^{W}$; optionally one of $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$, such as $\mathbf{R}^{3a}$, is –CH_2–$\mathbf{R}^{W}$, or –CH_2CH_2–$\mathbf{R}^{W}$.

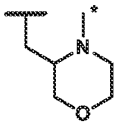
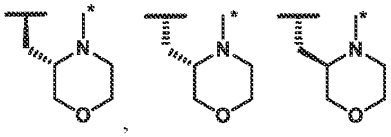
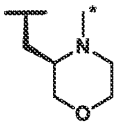
212. The compound of claim 1-190, 192-193 or 210-211, wherein the $\mathbf{R}^{W}$ group of $\mathbf{R}^{3a}$ or $\mathbf{R}^{3b}$ is: C(=O)-CH=CH_2, or -NHC(=O)-CH=CH_2.

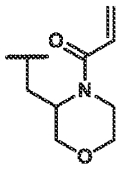
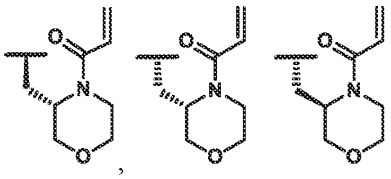
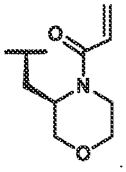
213. The compound of any claims of 1-190, 192-193 or 210-212, wherein one of $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$, such as $\mathbf{R}^{3a}$, is  , such as  or  .

214. The compound of any one of claims 1-190 or 192-193, wherein one of $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$, such as $\mathbf{R}^{3a}$, is -$(\mathbf{L}^{s})_{g}$-$\mathbf{R}^{g2}$-$\mathbf{R}^{W}$.

215. The compound of any one of claims 1-190, 192-193 or 214, wherein one of $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$, such as $\mathbf{R}^{3a}$, is -(C_{1-3} alkylene)-$\mathbf{R}^{g2}$-$\mathbf{R}^{W}$, and optionally one of $\mathbf{R}^{3a}$ and $\mathbf{R}^{3b}$, such as $\mathbf{R}^{3a}$, is -CH_2-$\mathbf{R}^{g2}$-$\mathbf{R}^{W}$, or -CH_2CH_2-$\mathbf{R}^{g2}$-$\mathbf{R}^{W}$.

216. The compound of any one of claims 1-190, 192-193 or 214-215, wherein the R^{g2} group of R^{3a} or R^{3b} is  , such as  , or  , wherein the waveline represents the point of attachment to L^g (e.g., -CH_2- or -CH_2CH_2-) and the asterisk represents the point of attachment to R^W; and wherein the R^W group of R^{3a} or R^{3b} is -C(=O)-CH=CH_2, or -NHC(=O)-CH=CH_2.

217. The compound of any one of claims 1-190, 192-193 or 214-216, wherein one of R^{3a} and R^{3b}, such as R^{3a}, is -CH_2-R^{g2}-R^W, and wherein the R^{g2} group of R^{3a} or R^{3b} is  , such as  , or  , wherein the waveline represents the point of attachment to L^g (e.g., -CH_2- or -CH_2CH_2-) and the asterisk represents the point of attachment to R^W; and wherein the R^W group of R^{3a} or R^{3b} is -C(=O)-CH=CH_2, or -NHC(=O)-CH=CH_2.

218. The compound of any one of claims 1-190, 192-193 or 214-217, wherein one of R^{3a} and R^{3b}, such as R^{3a}, is  , such as  , or  .

219. The compound of any one of claims 1-190 or 193-218 wherein the other of R^{3a} and R^{3b} is –H.

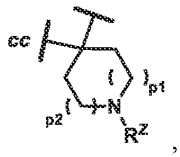
220. The compound of any one of claims 1-190 or 193-218, wherein the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is C_{1-3} alkyl, such as methyl; or wherein the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is halo, such as -F.

221. The compound of any one of claims 1-190, wherein $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, together with the **Ring B** ring atom to which each is attached, form a fused saturated or unsaturated ring of 3-12 ring atoms;

- wherein from 0-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and $S(O)_{0-2}$; and
- wherein the fused saturated or unsaturated ring of 3-12 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo, $\mathbf{R^c}$, and $\mathbf{R^w}$.

222. The compound of any one of claims 1-190 or 221, wherein $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, together with the **Ring B** ring atom to which each is attached, form a fused saturated ring of 4-8 ring atoms;

- wherein from 0-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and $S(O)_{0-2}$; and
- wherein the fused saturated ring of 4-8 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo, $\mathbf{R^c}$, and $\mathbf{R^w}$.

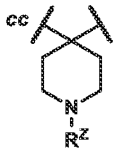
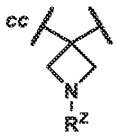
223. The compound of any one of claims 1-190 or 221-222, wherein $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, together with the **Ring B** ring atom to which each is attached, form: 

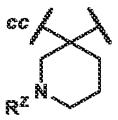
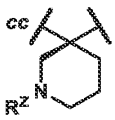
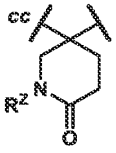
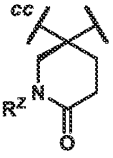
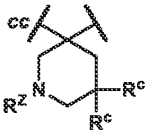
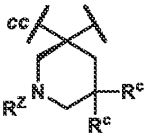
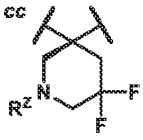
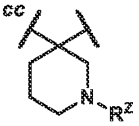
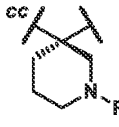
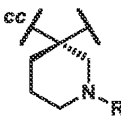
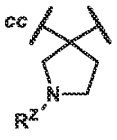
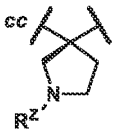
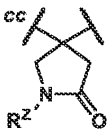
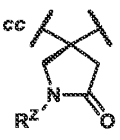
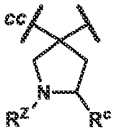
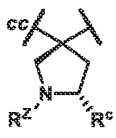
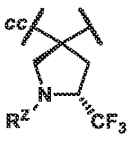
, which is optionally substituted with from 1-2 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$, wherein:

p1 and **p2** are independently 0, 1, or 2;

R^Z is H, R^d, C(=O)-**W**, or $S(O)_2$**W**; and

cc represents the point of attachment to C($R^{2a}R^{2b}$).

224. The compound of any one of claims 1-190 or 221-223, wherein R^{3a} and R^{3b}, together with the **Ring B** ring atom to which each is attached, form  or  , wherein R^Z is H, R^d, C(=O)-**W**, or $S(O)_2$**W**; and *cc* represents the point of attachment to C($R^{2a}R^{2b}$).

225. The compound of any one of claims 1-190 or 221-223, wherein R^{3a} and R^{3b}, together with the **Ring B** ring atom to which each is attached, form a fused ring selected from the group consisting of:  such as  ;  such as  ;  such as  (e.g., );  such as  or  ;  such as  ;  such as  ; and  such as  (e.g., ), wherein R^Z is H, R^d, C(=O)-**W**, or $S(O)_2$**W**; and *cc* represents the point of attachment to C($R^{2a}R^{2b}$).

226. The compound of any one of claims 223-225, wherein $\mathbf{R^Z}$ is H.

227. The compound of any one of claims 223-225, wherein $\mathbf{R^Z}$ is $\mathbf{R^d}$.

228. The compound of any one of claims 223-225 or 227, wherein $\mathbf{R^Z}$ is C_{1-6} alkyl optionally substituted with from 1-3 independently selected $\mathbf{R^a}$.

229. The compound of any one of claims 223-225, wherein $\mathbf{R^Z}$ is C(=O)-**W** or $S(O)_2$**W**.

230. The compound of any one of claims 223-225 or 229, wherein **W** is C_{2-4} alkenyl.

231. The compound of any one of claims 223-225 or 229-230, wherein $\mathbf{R^Z}$ is $C(=O)\text{-}CH_2{=}CH_2$.

232. The compound of any one of claims 1-190, wherein $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ together with the **Ring B** ring atom to which each is attached form a fused C_{3-6} cycloalkyl, wherein the fused C_{3-6} cycloalkyl is optionally substituted with from 1-2 $\mathbf{R^c}$.

233. The compound of any one of claims 1-190 or 232, wherein $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ together with the **Ring B** ring atom to which each is attached form a fused cyclopropyl or cyclobutyl.

234. The compound of any one of claims 1-190, wherein $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ together with the **Ring B** ring atom to which each is attached, form a fused saturated ring of 4-6 ring atoms;

wherein from 1-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and $S(O)_{0-2}$; and

wherein the fused saturated ring of 4-6 ring atoms is optionally substituted with from 1-2 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$.

235. The compound of any one of claims 1-190 or 234, wherein $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, together with the **Ring B** ring atom to which each is attached, form  ,  , or  .

236. The compound of any one of claims 1-183, wherein one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ (such as $\mathbf{R^{2a}}$) and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ (such as $\mathbf{R^{3a}}$) taken together with the **Ring B** ring atoms to which each is attached, form a fused saturated or unsaturated ring of 3-12 ring atoms;

wherein from 0-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and S(O)$_{0-2}$; and

wherein the fused saturated or unsaturated ring of 3-12 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$.

237. The compound of any one of claims 1-183 or 236, wherein one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ (such as $\mathbf{R^{2a}}$) and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ (such as $\mathbf{R^{3a}}$) taken together with the **Ring B** ring atoms to which each is attached, form a fused saturated ring of 3-8 ring atoms;

wherein from 0-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and S(O)$_{0-2}$; and

wherein the fused saturated ring of 3-8 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$.

238. The compound of any one of claims 1-183 or 236-237, wherein one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ (such as $\mathbf{R^{2a}}$) and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ (such as $\mathbf{R^{3a}}$) taken together with the **Ring B** ring atoms to which each is attached, form a fused C$_{3-6}$ cycloalkyl which is optionally substituted with from 1-2 $\mathbf{R^c}$.

239. The compound of any one of claims 1-183 or 236-238, wherein one of R^{2a} and R^{2b} (such as R^{2a}) and one of R^{3a} and R^{3b} (such as R^{3a}) taken together with the **Ring B** ring atoms to which each is attached, form a fused cyclopropyl or cyclobutyl.

240. The compound of any one of claims 1-183, wherein one of R^{2a} and R^{2b} (such as R^{2a}) and one of R^{3a} and R^{3b} (such as R^{3a}) combine to form a double bond between the **Ring B** atoms to which each is attached.

241. The compound of any one of claims 236-240, wherein the other of R^{2a} and R^{2b} and the other of R^{3a} and R^{3b} are each H.

242. The compound of any one of claims 1-183 or 240, wherein the other one of R^{3a} and R^{3b} is R^g or $-(L^g)_g$-R^g.

243. The compound of any one of claims 1-183, 240 or 242, wherein the other one of R^{3a} and R^{3b} is $-(L^g)_g$-R^g.

244. The compound of any one of claims 1-183, 240 or 242-243, wherein the other one of R^{3a} and R^{3b} is $-(C_{1-3}$ alkylene)-R^g or -(C_{1-3} alkylene)-O-R^g, and optionally the R^g group of R^{3a} or R^{3b} is:

C_{3-6} cycloalkyl optionally substituted with from 1-4 R^c, or

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c.

245. The compound of any one of claims 1-183, 240 or 242-244, wherein the other one of R^{3a} and R^{3b}, such as R^{3a}, is $-CH_2$-R^g, $-CH_2CH_2R^g$, or $-CH_2$-O-R^g, wherein the R^g group of R^{3a} or R^{3b} is:

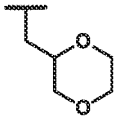
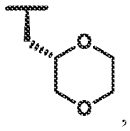
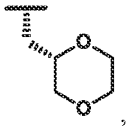
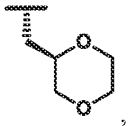
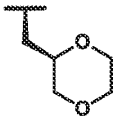
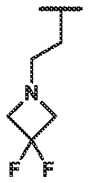
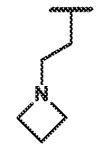
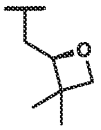
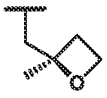
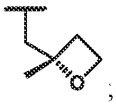
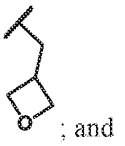
C_{3-6} cycloalkyl optionally substituted with from 1-4 R^c, or

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O,

and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c.

246. The compound of any one of claims 1-183, 240 or 242-245, wherein the other one of R^{3a} and R^{3b}, such as R^{3a}, is $-CH_2-R^g$, $-CH_2CH_2R^g$, or $-CH_2-O-R^g$, wherein the R^g group of R^{3a} or R^{3b} is selected from the group consisting of:

cyclopropyl, cyclobutyl, oxetanyl, 1,4-dioxanyl, and azetidinyl, each of which is optionally substituted with from 1-2 substituents independently selected from the group consisting of: C_{1-3} alkyl and halo, wherein the ring nitrogen of the azetidinyl is optionally substituted with R^d.

247. The compound of any one of claims 1-183, 240 or 242-245, wherein the other one of R^{3a} and R^{3b}, such as R^{3a}, is selected from the group consisting of:  , such as  ,  ,  , or  ;  ;  ;  , such as  or  ;  , such as  or  ;  , such as  or  ;  ; and  .

248. The compound of any one of claims 1-183, wherein R^{1c}, R^{2a}, and R^{2b} are each H; one of R^{3a} and R^{3b}, such as R^{3a}, is C_{1-3} alkyl optionally substituted with from 1-3 R^a; and the other of R^{3a} and R^{3b} is H, optionally each R^a substituent present in R^{3a} or R^{3b}

is independently selected from the group consisting of: halo, C_{1-4} alkoxy, and C_{1-4} haloalkoxy.

249. The compound of any one of claims 1-183, wherein $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is C_{1-3} alkyl optionally substituted with from C_{1-4} alkoxy; optionally one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is -CH_2CH_2-OMe; and the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is H.

250. The compound of any one of claims 1-183, wherein $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; and $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ are independently selected C_{1-3} alkyl.

251. The compound of any one of claims 1-183, wherein $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, such as $\mathbf{R^{3a}}$, is $-\mathbf{R^g}$, $-(C_{1-3}$ alkylene)-$\mathbf{R^g}$, or $-(C_{1-3}$ alkylene)-O-$\mathbf{R^g}$,

optionally wherein the $\mathbf{R^g}$ group of $\mathbf{R^{3a}}$ or $\mathbf{R^{3b}}$ is:

C_{3-6} cycloalkyl optionally substituted with from 1-4 $\mathbf{R^c}$, or

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$; and

the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is H.

252. The compound of any one of claims 1-183, wherein $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; and $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ taken together with the **Ring B** ring carbon atom to which each is attached form a fused C_{3-6} (such as C_3 or C_4) cycloalkyl, wherein the fused cycloalkyl ring is optionally substituted with from 1-2 $\mathbf{R^c}$.

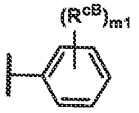
253. The compound of any one of claims 1-183, wherein $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; and $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ together with the **Ring B** ring atom to which each is attached, form a fused saturated ring of 4-6 ring atoms;

- wherein from 1-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and S(O)$_{0-2}$; and
- wherein the fused saturated ring of 4-6 ring atoms is optionally substituted with from 1-2 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$.

254. The compound of any one of claims 1-183, wherein $\mathbf{R^{1c}}$ is H; one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ (such as $\mathbf{R^{2a}}$) and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ (such as $\mathbf{R^{3a}}$) taken together with the **Ring B** ring atoms to which each is attached, form a fused C$_{3-6}$ (such as C$_3$ or C$_4$) cycloalkyl which is optionally substituted with from 1-2 $\mathbf{R^c}$; and the other of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ and the other of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ are each H.

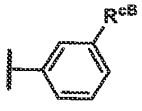
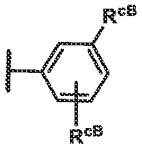
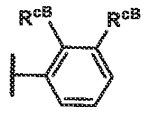
255. The compound of any one of claims 1-183, wherein $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$ are each H.

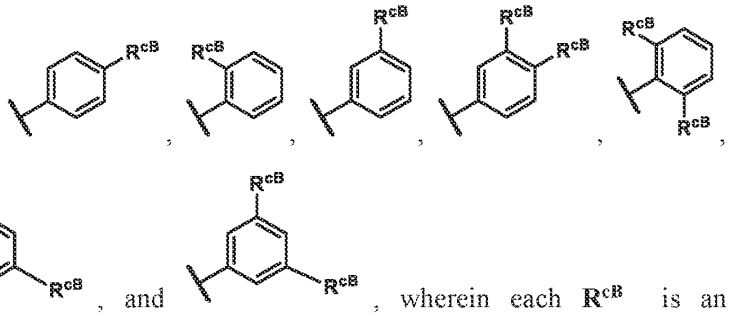
256. The compound of any one of claims 1-238, wherein $\mathbf{R^4}$ is H; and $\mathbf{R^7}$ is H.

257. The compound of any one of claims 1-256, wherein **Ring A** is  , wherein each $\mathbf{R^{cB}}$ is an independently selected $\mathbf{R^c}$; and **m1** is 0, 1, 2, 3, or 4.

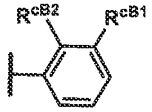
258. The compound of claim 257, wherein **m1** is 1, 2, or 3.

259. The compound of claims 257 or 258, wherein **m1** is 1 or 2, such as 2.

260. The compound of any one of claims 1-259, wherein **Ring A** is  or  (e.g., ), wherein each $\mathbf{R^{cB}}$ is an independently selected $\mathbf{R^c}$.

261. The compound of any one of claims 1-259, wherein **Ring A** is selected from the group consisting of:  , wherein each $\mathbf{R}^{cB}$ is an independently selected $\mathbf{R}^{c}$.

262. The compound of any one of claims 257-261, wherein each $\mathbf{R}^{cB}$ is independently selected from the group consisting of: -halo, such as -Cl and -F; -CN; C_{1-4} alkoxy; C_{1-4} haloalkoxy; C_{1-3} alkyl; and C_{1-3} alkyl substituted with from 1-6 independently selected halo.

263. The compound of any one of claims 1-256, wherein **Ring A** is  , wherein $\mathbf{R}^{cB1}$ is $\mathbf{R}^{c}$; and $\mathbf{R}^{cB2}$ is H or $\mathbf{R}^{c}$, optionally wherein $\mathbf{R}^{cB1}$ and $\mathbf{R}^{cB2}$ are each independently selected from the group consisting of: -halo, such as -Cl and -F; -CN; C_{1-4} alkoxy; C_{1-4} haloalkoxy; C_{1-3} alkyl; and C_{1-3} alkyl substituted with from 1-6 independently selected halo.

264. The compound of claim 263, wherein $\mathbf{R}^{cB1}$ is halo, such as –F or –Cl, such as –F.

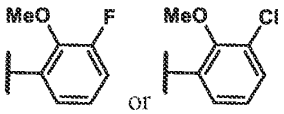
265. The compound of claim 263, wherein $\mathbf{R}^{cB1}$ is C_{1-3} alkyl or C_{1-3} alkyl substituted with from 1-6 independently selected halo, such as wherein $\mathbf{R}^{cB1}$ is methyl, –CHF_2, or –CF_3.

266. The compound of any one of claims 263-265, wherein $\mathbf{R}^{cB2}$ is selected from the group consisting of: halo; -CN; C_{1-4} alkoxy; C_{1-4} haloalkoxy; C_{1-3} alkyl; and C_{1-3} alkyl substituted with from 1-6 independently selected halo.

267. The compound of any one of claims 263-266, wherein $\mathbf{R}^{cB2}$ is C_{1-4} alkoxy or C_{1-4} haloalkoxy.

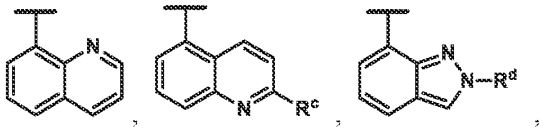
268. The compound of any one of claims 263-267, wherein $\mathbf{R}^{cB2}$ is selected from the group consisting of cyano; C_{1-3} alkyl; and C_{1-3} alkyl substituted with from 1-6 independently selected halo, such as wherein $\mathbf{R}^{cB2}$ is cyano, methyl, ethyl, $-CHF_2$, $-CF_3$, or $-CH_2CHF_2$.

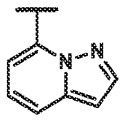
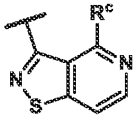
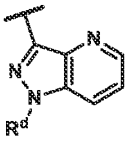
269. The compound of any one of claims 1-256, or 263-268, wherein **Ring A** is



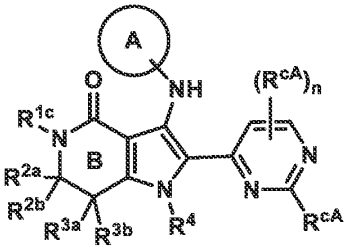
270. The compound of any one of claims 1-256, wherein **Ring A** is heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^d$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R}^e$.

271. The compound of any one of claims 1-256 or 270, wherein **Ring A** is bicyclic heteroaryl including from 9-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^d$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R}^e$.

272. The compound of any one of claims 1-256 or 270-271, wherein **Ring A** is selected from the group consisting of: 

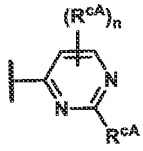
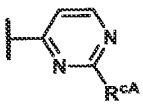
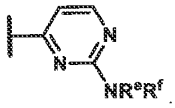
 ,  , and  , each of which is further optionally substituted with R^c.

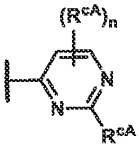
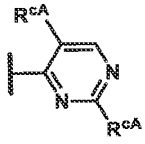
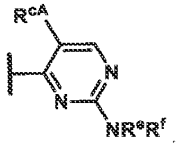
273. The compound of claim 1, wherein the compound is a compound of Formula **(I-a)**:

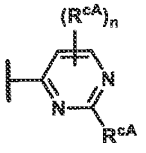
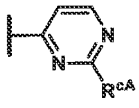
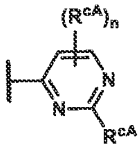
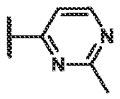

Formula **(I-a)**

or a pharmaceutically acceptable salt thereof,

wherein: each R^{cA} is an independently selected R^c; and **n** is 0, 1, or 2.

274. The compound of claim 273, wherein  is  , such as  .

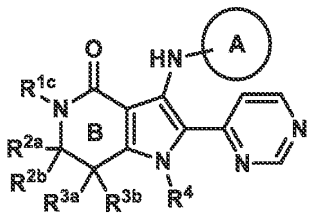
275. The compound of claims 273 or 274, wherein  is  , such as  .

276. The compound of any one of claims 273 or 274, wherein  is  , wherein R^{cA} is C_{1-3} alkyl optionally substituted with from 1-3 independently selected halo; optionally wherein  is  .

277. The compound of any one of claims 273-276, wherein one of R^{3a} and R^{3b}, such as R^{3a}, is C_{1-3} alkyl substituted with C_{1-4} alkoxy; optionally wherein the other one of of R^{3a} and R^{3b}, such as R^{3b} is H.

278. The compound of any one of claims 276 wherein one of R^{3a} and R^{3b}, such as R^{3a}, is –CH_2OMe, -CH_2CH_2OMe, -$CH(Me)CH_2OMe$, -$CH_2CH(Me)OMe$, or -CH_2OEt; optionally wherein one of R^{3a} and R^{3b}, such as R^{3a} is -CH_2CH_2OMe.

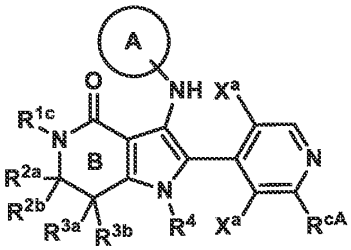
279. The compound of claim 1, wherein the compound is a compound of Formula **(I-b)**:



Formula **(I-b)**

or a pharmaceutically acceptable salt thereof.

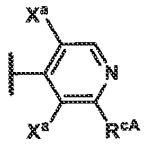
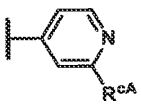
280. The compound of claim 1, wherein the compound is a compound of Formula **(I-c)**:



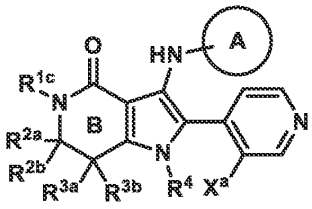
Formula (**I-c**)

or a pharmaceutically acceptable salt thereof,

wherein: R^{cA} is an independently selected R^c.

281. The compound of claim 280, wherein  is  .

282. The compound of claim 1, wherein the compound is a compound of Formula (**I-d**):



Formula (**I-d**)

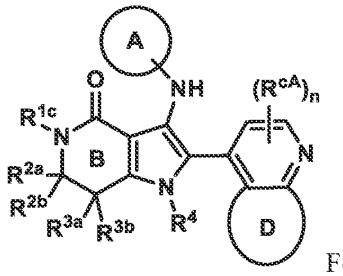
or a pharmaceutically acceptable salt thereof, wherein:

X^a is selected from the group consisting of: H; -F; -Cl; C_{1-6} alkyl; and C_{1-3} alkyl substituted with from 1-3 independently selected halo.

283. The compound of claim 282, wherein X^a is –F.

284. The compound of claim 82, wherein X^a is C_{1-3} substituted with from 1-3 independently selected halo, such as $–CF_2H$ or $–CF_3$.

285. The compound of claim 1, wherein the compound is a compound of Formula (**I-e**):



Formula **(I-e)**

or a pharmaceutically acceptable salt thereof,

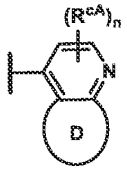
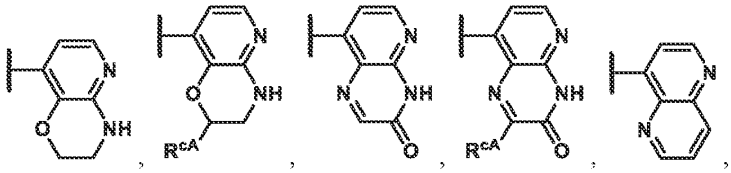
wherein:

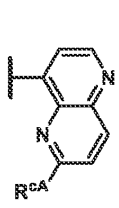
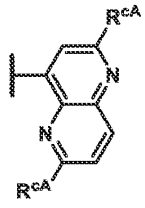
each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^{c}}$;

n is 0, 1, or 2; and

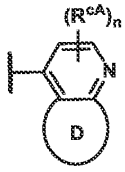
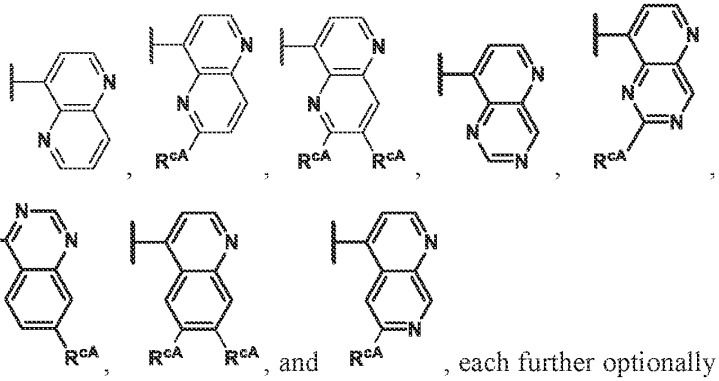
Ring D is a partially unsaturated or aromatic ring including from 5-6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^{d}}$), O, and S(O)$_{0\text{-}2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

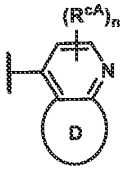
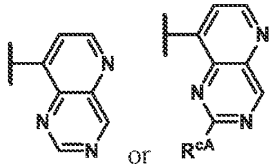
286. The compound of claim 285, wherein **Ring D** is a partially unsaturated or aromatic ring including 6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^{d}}$), O, and S(O)$_{0\text{-}2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

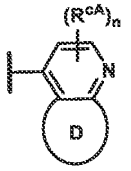
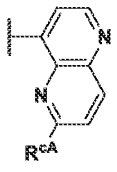
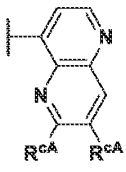
287. The compound of claims 285 or 286, wherein  is selected from the group consisting of: 

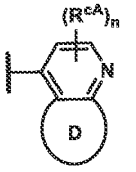
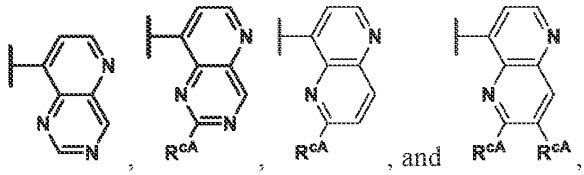



, and , each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^{c}.

288. The compound of claims 285 or 286, wherein  is selected from the group consisting of:  , and , each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^{c}.

289. The compound of any one of claims 285-288, wherein  is  or , wherein R^{cA} is an independently selected R^{c}.

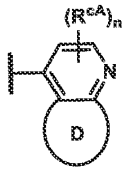
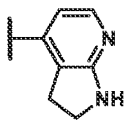
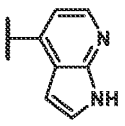
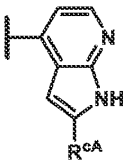
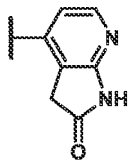
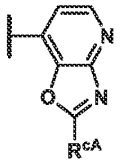
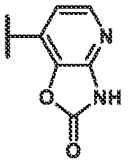
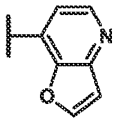
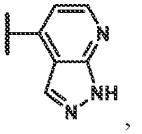
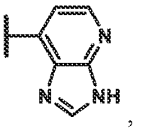
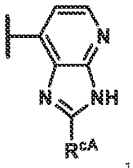
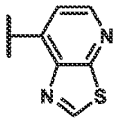
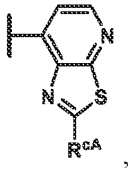
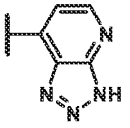
290. The compound of any one of claims 285-288, wherein  is  or  , wherein each R^{cA} is an independently selected R^{c}.

291. The compound of any one of claims 285-288, wherein  is selected from the group consisting of:  , and , wherein:

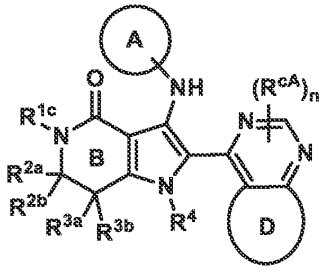
each occurrence of R^{cA} is independently selected from the group consisting of: halo; $NR^{e}R^{f}$; C_{1-4} alkoxy; C_{1-4} haloalkoxy; C_{1-3} alkyl; C_{1-3} alkyl substituted with from 1-3 independently selected halo; C_{1-3} alkyl substituted with C_{1-4} alkoxy; and C_{1-4} alkoxy substituted with C_{1-4} alkoxy;

such as wherein each occurrence of R^{cA} is independently selected from the group consisting of: C_{1-4} alkoxy; C_{1-4} haloalkoxy; C_{1-3} alkyl; and C_{1-3} alkyl substituted with from 1-3 independently selected halo.

292. The compound of claim 285, wherein **Ring D** is a partially unsaturated or aromatic ring including 5 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), $N(R^{d})$, O, and $S(O)_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 R^{cA}.

293. The compound of claims 285 or 292, wherein  is selected from the group consisting of:  ,  ,  (e.g., ),  (e.g., ),  ,  ,  ,  ,  ,  ,  , and  , each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^c.

294. The compound of claim 1, wherein the compound is a compound of Formula **(I-f)**:



Formula **(I-f)**

or a pharmaceutically acceptable salt thereof,

wherein:

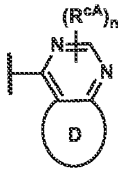
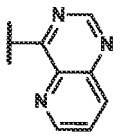
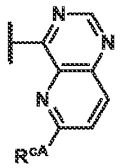
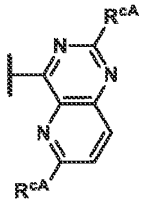
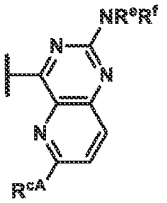
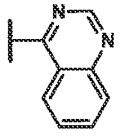
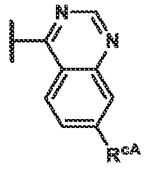
each R^{cA} is an independently selected R^c;

n is 0 or 1; and

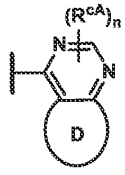
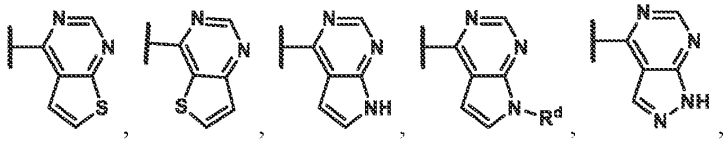
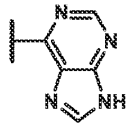
Ring D is a partially unsaturated or aromatic ring including from 5-6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the

group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R}^{cA}$.

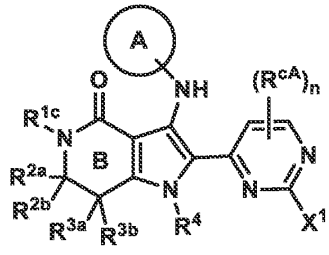
295. The compound of claim 294, wherein **Ring D** is a partially unsaturated or aromatic ring including 6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R}^{cA}$.

296. The compound of claims 294 or 295, wherein  is selected from the group consisting of:  ,  ,  (e.g., ),  , and  , each further optionally substituted with $\mathbf{R}^{cA}$, wherein each $\mathbf{R}^{cA}$ is an independently selected $\mathbf{R}^{c}$.

297. The compound of claim 294, wherein **Ring D** is a partially unsaturated or aromatic ring including 5 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R}^{cA}$.

298. The compound of claims 294 or 297, wherein  is selected from the group consisting of:  , and  , each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^{c}.

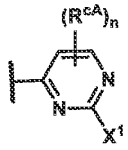
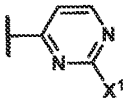
299. The compound of claim 1, wherein the compound is a compound of Formula **(I-g)**:



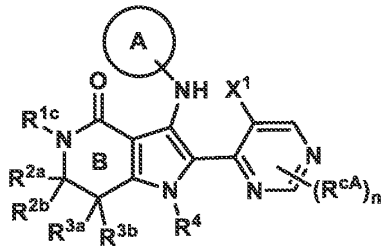
Formula **(I-g)**

or a pharmaceutically acceptable salt thereof,

wherein: each R^{cA} is an independently selected R^{c}; and **n** is 0, 1, or 2.

300. The compound of claim 299, wherein  is  .

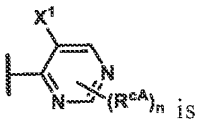
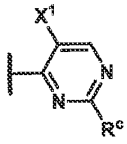
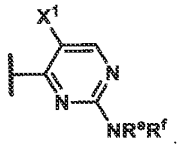
301. The compound of claim 1, wherein the compound is a compound of Formula **(I-h)**:



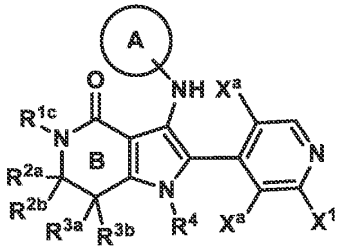
Formula (**I-h**)

or a pharmaceutically acceptable salt thereof,

wherein: each R^{cA} is an independently selected R^c; and **n** is 0, 1, or 2.

302. The compound of claim 301, wherein  is  , such as  .

303. The compound of claim 1, wherein the compound is a compound of Formula (**I-i**):

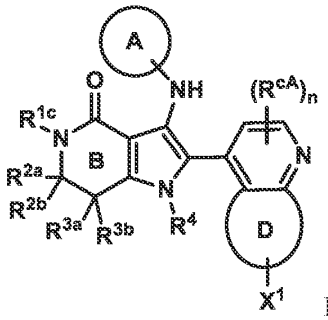


Formula (**I-i**)

or a pharmaceutically acceptable salt thereof.

304. The compound of claim 303, wherein each X^a is H.

305. The compound of claim 1, wherein the compound is a compound of Formula (**I-j**):



Formula (I-j)

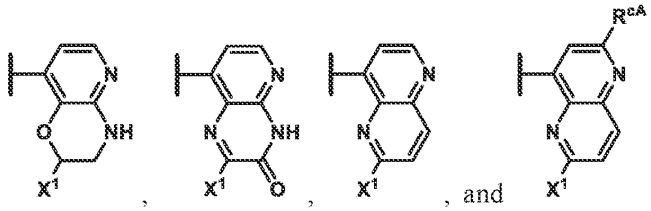
or a pharmaceutically acceptable salt thereof;

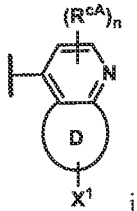
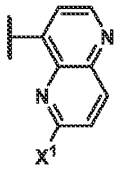
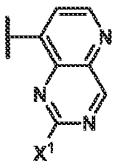
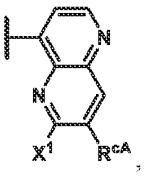
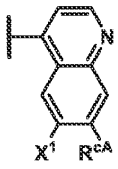
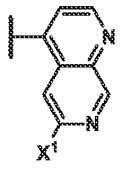
wherein **n** is 0, 1, or 2;

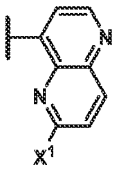
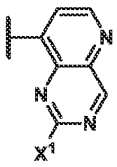
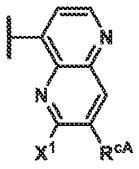
each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^{c}}$; and

Ring D is a partially unsaturated or aromatic ring including from 5-6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^{d}}$), O, and S(O)$_{0\text{-}2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

306. The compound of claim 305, wherein **Ring D** is a partially unsaturated or aromatic ring including 6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^{d}}$), O, and S(O)$_{0\text{-}2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

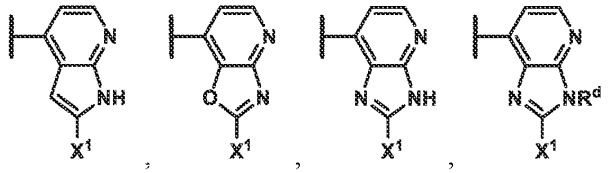
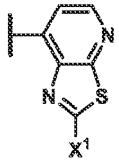
307. The compound of claims 305 or 306, wherein  is selected from the group consisting of:  , and , each further optionally substituted with $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^{c}}$.

308. The compound of any one of claims 305 or 306, wherein  is selected from the group consisting of: consisting of:  ,  ,  ,  , and  each of which is further optionally substituted with from 1-2 R^{cA}, wherein each R^{cA} is an independently selected R^{c}.

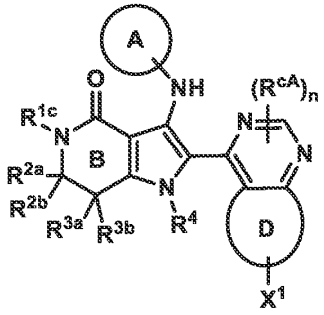
309. The compound of any one of claims 305, 306 or 308, wherein  is selected from the group consisting of: consisting of:  ,  , and  .

310. The compound of claim 305, wherein **Ring D** is a partially unsaturated or aromatic ring including 5 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N(R^{d}), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 R^{cA}.



311. The compound of claims 305 or 310, wherein is selected from the group consisting of:  , and  , each further optionally substituted with R^{cA}, wherein each R^{cA} is an independently selected R^{c}.

312. The compound of claim 1, wherein the compound is a compound of Formula **(I-k)**:



Formula **(I-k)**

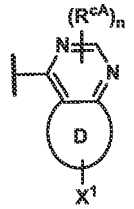
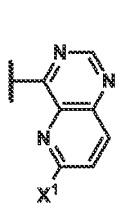
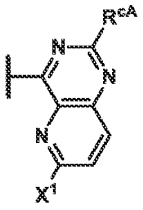
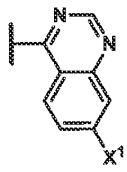
or a pharmaceutically acceptable salt thereof;

wherein **n** is 0 or 1;

each R^{cA} is an independently selected R^{c}; and

Ring D is a partially unsaturated or aromatic ring including from 5-6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N(R^{d}), O, and $S(O)_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 R^{cA}.

313. The compound of claim 312, wherein **Ring D** is a partially unsaturated or aromatic ring including 6 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

314. The compound of claims 312 or 313, wherein  is selected from the group consisting of:  ,  , and  , each further optionally substituted with $\mathbf{R^{cA}}$, wherein each $\mathbf{R^{cA}}$ is an independently selected $\mathbf{R^c}$.

315. The compound of claim 312, wherein **Ring D** is a partially unsaturated or aromatic ring including 5 ring atoms, wherein from 0-2 of the ring atoms are heteroatoms each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, wherein **Ring D** is optionally substituted with from 1-2 $\mathbf{R^{cA}}$.

316. The compound of any one of claims 273-315, wherein each occurrence of $\mathbf{R^{cA}}$ is independently selected from the group consisting of: halo; cyano; C$_{1-10}$ alkyl which is optionally substituted with from 1-6 independently selected $\mathbf{R^a}$; C$_{1-4}$ alkoxy optionally substituted with C$_{1-4}$ alkoxy or C$_{1-4}$ haloalkoxy; C$_{1-4}$ haloalkoxy; -S(O)$_{1-2}$(C$_{1-4}$ alkyl); -N$\mathbf{R^eR^f}$; –OH; -S(O)$_{1-2}$N$\mathbf{R'R''}$; -C$_{1-4}$ thioalkoxy; -C(=O)(C$_{1-10}$ alkyl); -C(=O)O(C$_{1-4}$ alkyl); -C(=O)OH; and -C(=O)N$\mathbf{R'R''}$.

317. The compound of any one of claims 273-316, wherein one occurrence of $\mathbf{R^{cA}}$ is –N$\mathbf{R^eR^f}$.

318. The compound of any one of claims 273-317, wherein one occurrence of $\mathbf{R}^{cA}$ is $-NH_2$.

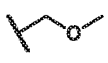
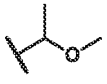
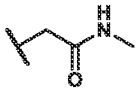
319. The compound of any one of claims 273-317, wherein one occurrence of $\mathbf{R}^{cA}$ is $-NH(C_{1-6}$ alkyl), wherein the C_{1-6} alkyl is optionally substituted with from 1-3 substituents each independently selected from the group consisting of N**R'R''**, -OH, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and halo, such as wherein one occurrence of $\mathbf{R}^{cA}$ is –NHMe, -$NHCH_2CF_3$, -$NHCH_2CH_2OH$, or –NHiPr.

320. The compound of any one of claims 273-317, wherein one occurrence of $\mathbf{R}^{cA}$ is $-NHC(=O)C_{1-4}$ alkyl, such as $NHC(=O)CH_3$; or wherein one occurrence of $\mathbf{R}^{cA}$ is $N(C_{1-3}$ alkyl$)_2$ such as NMe_2.

321. The compound of any one of claims 273-316, wherein one occurrence of $\mathbf{R}^{cA}$ is C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy or C_{1-4} haloalkoxy, such as wherein one occurrence of $\mathbf{R}^{cA}$ is OMe or OCH_2CH_2OMe; or wherein one occurrence of $\mathbf{R}^{cA}$ is C_{1-4} haloalkoxy, such as $-OCH_2CF_3$.

322. The compound of any one of claims 273-316, wherein one occurrence of $\mathbf{R}^{cA}$ is C_{1-4} thioalkoxy, such as $-SCH_3$.

323. The compound of any one of claims 273-316, wherein one occurrence of $\mathbf{R}^{cA}$ is C_{1-6} alkyl, such as methyl; or wherein one occurrence of $\mathbf{R}^{cA}$ is C_{1-6} alkyl substituted with from 1-6 independently selected halo, such as $-CF_3$.

324. The compound of any one of claims 273-316, wherein one occurrence of $\mathbf{R}^{cA}$ is C_{1-6} alkyl substituted with $\mathbf{R}^{a}$, such as C_{1-6} alkyl substituted with C_{1-3} alkoxy or C(=O)N**R'R''**, such as wherein one occurrence of $\mathbf{R}^{cA}$ is  ,  , or  .

325. The compound of any one of claims 273-316, wherein one occurrence of R^{cA} is halo, such as –F.

326. The compound of any one of claims 273-316, wherein one occurrence of R^{cA} is –OH.

327. The compound of any one of claims 273-316, wherein one occurrence of R^{cA} is C(=O)N**R'R"**, such as C(=O)NHMe.

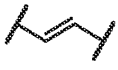
328. The compound of any one of claims 299-327, wherein X^1 is $-(X^2)_m-L^1-R^5$, wherein:

- **m** is 0 or 1;
- X^2 is –N(R^N)- or -O-;
- L^1 is a bond or C_{1-6} alkylene optionally substituted with from 1-3 R^a; and
- R^5 is –R^g.

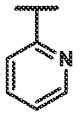
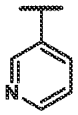
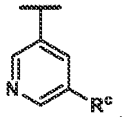
329. The compound of any one of claims 299-327, wherein X^1 is $-X^2-L^1-R^5$, wherein:

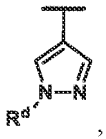
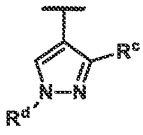
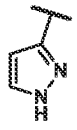
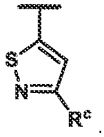
- X^2 is -N(R^N)C(=O)*, -N(R^N)S(O)$_2$*, -N(R^N)C(=O)O-*, or -N(R^N)C(=O)N(R^N)-*;
- L^1 is a bond or C_{1-6} alkylene optionally substituted with from 1-3 R^a; and
- R^5 is –R^g.

330. The compound of any one of 299-327, wherein X^1 is $-X^2-L^1-R^5$, wherein:

- X^2 is  or  ;
- L^1 is a bond or C_{1-6} alkylene optionally substituted with from 1-3 R^a; and
- R^5 is –R^g.

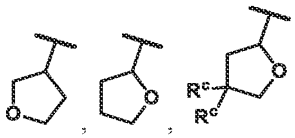
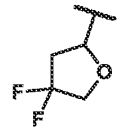
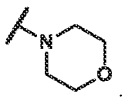
331. The compound of any one of claims 328-330, wherein R^5 is phenyl optionally substituted with from 1-4 R^c, such as wherein R^5 is phenyl optionally substituted with from 1-2 independently selected halo, such as –F.

332. The compound of any one of claims 328-330, wherein R^5 is heteroaryl including 6 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N(R^d), and wherein the heteroaryl is optionally substituted with from 1-4 R^c, such as wherein R^5 is  ,  , or  .

333. The compound of any one of claims 328-330, wherein R^5 is heteroaryl including 5 ring atoms, wherein from 1-4, such as 2-4, ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 R^c, such as wherein R^5 is  ,  ,  , or  .

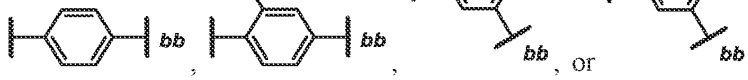
334. The compound of any one of claims 328-330, wherein R^5 is C$_{3-10}$ cycloalkyl, such as C$_{3-6}$ cycloalkyl, optionally substituted with from 1-4 R^c, such as wherein R^5 is cyclopropyl.

335. The compound of any one of claims 328-330, wherein R^5 is heterocyclyl including from 4-8, such as 4-6, ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N(R^d), O, and S(O)$_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents

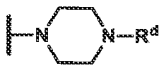
independently selected from the group consisting of oxo and R^c, such as wherein R^5 is  such as  , or  .

336. The compound of any one of claims 299-327, wherein X^1 is $-(X^2)_m-L^1-R^5$, wherein:

- **m** is 0 or 1;
- X^2 is $-N(R^N)-$ or $-O-$;
- L^1 is a bond or C_{1-6} alkylene optionally substituted with from 1-3 R^a; and
- R^5 is $-R^{g2}-R^Y$.

337. The compound of claim 336, wherein the $-R^{g2}$ group present in R^5 is 1,3-phenylene or 1,4-phenylene, each optionally substituted with from 1-4 R^c, such as wherein $-R^{g2}$ is  , wherein *bb* is the point of attachment to R^Y.

338. The compound of claims 336 or 337, wherein the R^Y group present in R^5 is $-R^g$.

339. The compound of any one of claims 336-338, wherein the R^Y group present in R^5 is heterocyclyl including from 4-8, such as 4-6, ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), $N(R^d)$, O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and R^c, such as wherein R^Y is  .

340. The compound of any one of claims 329-337, wherein $\mathbf{X^1}$ is $-\mathbf{X^2}\text{-}\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein:

- $\mathbf{X^2}$ is -N($\mathbf{R^N}$)-, –O-, -N($\mathbf{R^N}$)C(=O)-*, -N($\mathbf{R^N}$)S(O)$_2$-, -N($\mathbf{R^N}$)C(=O)O-*, or -N($\mathbf{R^N}$)C(=O)N($\mathbf{R^N}$)-*;
- $\mathbf{L^1}$ is $C_{1\text{-}6}$ alkylene optionally substituted with from 1-3 $\mathbf{R^a}$; and
- $\mathbf{R^5}$ is H, halo, $C_{1\text{-}6}$ alkoxy optionally substituted with from 1-3 $\mathbf{R^a}$, or –OH.

341. The compound of claim 340, wherein $\mathbf{R^5}$ is H.

342. The compound of claim 340, wherein $\mathbf{R^5}$ is halo, such as –F.

343. The compound of claim 340, wherein $\mathbf{R^5}$ is $C_{1\text{-}6}$ alkoxy optionally substituted with from 1-3 $\mathbf{R^a}$, such as wherein $\mathbf{R^5}$ is $C_{1\text{-}3}$ alkoxy such as methoxy.

344. The compound of claim 340, wherein $\mathbf{R^5}$ is –OH.

345. The compound of any one of claims 329 or 331-339, wherein **m** is 0.

346. The compound of any one of claims 329 or 331-339, wherein **m** is 1.

347. The compound of any one of claims 329, 331-334 or 346 wherein $\mathbf{X^2}$ is –N($\mathbf{R^N}$)-, such as N(H).

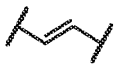
348. The compound of any one of claims 329, 331-334 or 346, wherein $\mathbf{X^2}$ is –O-.

349. The compound of any one of claims 329, 331-335 or 340-344, wherein $\mathbf{X^2}$ is -N($\mathbf{R^N}$)C(=O)-*, such as –N(H)C(=O)-*.

350. The compound of any one of claims 329, 331-335 or 340-344, wherein $\mathbf{X^2}$ is -N($\mathbf{R^N}$)S(O)$_2$-, such as –N(H)S(O)$_2$-*.

351. The compound of any one of claims 329, 331-335 or 340-344, wherein $\mathbf{X^2}$ is -N($\mathbf{R^N}$)C(=O)O-*, or -N($\mathbf{R^N}$)C(=O)N($\mathbf{R^N}$)-*, such as –N(H)C(=O)O-* or –N(H)C(=O)N(H)-*.

352. The compound of any one of claims 330-335, wherein $\mathbf{X^2}$ is  .

353. The compound of any one of claims 330-335, wherein $\mathbf{X^2}$ is  .

354. The compound of any one of claims 263-274 or 280-288, wherein $\mathbf{L^1}$ is a bond.

355. The compound of any one of claims 328-353, wherein $\mathbf{L^1}$ is C_{1-3} alkylene, such as –CH_2-, -CH_2CH_2-, or –CH(Me)-.

356. The compound of any one of claims 328-353, wherein $\mathbf{L^1}$ is branched C_{3-6} alkylene, such as  or  , wherein ***aa*** is the point of attachment to $\mathbf{R^5}$.

357. The compound of any one of claims 299-327, wherein $\mathbf{X^1}$ is –$\mathbf{L^1}$-$\mathbf{R^5}$, wherein $\mathbf{L^1}$ is C_{1-6} alkylene optionally substituted with from 1-3 $\mathbf{R^a}$, and $\mathbf{R^5}$ is –$\mathbf{L^5}$-$\mathbf{R^g}$.

358. The compound of claim 357, wherein $\mathbf{R^5}$ is –O-$\mathbf{R^g}$.

359. The compound of claims 357 or 358, wherein $\mathbf{R^5}$ is –O-(phenyl), wherein the phenyl is optionally substituted with from 1-2 $\mathbf{R^c}$.

360. The compound of any one of claims 357-359, wherein $\mathbf{L^1}$ is C_{1-3} alkylene, such as –CH_2-, -CH_2CH_2-, or –CH(Me)-.

361. The compound of any one of claims 273-360, wherein $\mathbf{R^{1c}}$ is H.

362. The compound of any one of claims 273-361, wherein $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are both H.

363. The compound of any one of claims 273-361, wherein $\mathbf{R^{2a}}$ is a substituent that is other than H.

364. The compound of any one of claims 273-361 or 363, wherein $\mathbf{R^{2a}}$ is C_{1-6} alkyl which is optionally substituted with from 1-6 $\mathbf{R^a}$, such as wherein $\mathbf{R^{2a}}$ is C_{1-3} alkyl, such as methyl or ethyl.

365. The compound of claims 363 or 364, wherein $\mathbf{R^{2b}}$ is H.

366. The compound of any one of claims 273-365, wherein $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ are both H.

367. The compound of any one of claims 273-365, wherein $\mathbf{R^{3a}}$ is a substituent that is other than H.

368. The compound of any one of claims 273-365 or 367, wherein $\mathbf{R^{3a}}$ is C_{1-6} alkyl which is optionally substituted with from 1-6 $\mathbf{R^a}$, such as wherein $\mathbf{R^{3a}}$ is C_{1-3} alkyl, such as methyl or ethyl.

369. The compound of any one of claims 273-365 or 367, wherein $\mathbf{R^{3a}}$ is C_{1-3} alkyl substituted with from 1-3 independently selected halo, such as wherein $\mathbf{R^{3a}}$ is $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CHF_2$, or $-CH_2CH_2F$.

370. The compound of any one of claims 273-365 or 367, wherein $\mathbf{R^{3a}}$ is C_{1-3} alkyl substituted with C_{1-4} alkoxy, C_{1-4} haloalkoxy, or $N\mathbf{R^c}\mathbf{R^f}$, such as wherein $\mathbf{R^{3a}}$ is $-CH_2OMe$, $-CH_2CH_2OMe$, $-CH(Me)CH_2OMe$, $-CH_2CH(Me)OMe$, $-CH_2OEt$, $-CH_2N\mathbf{R^c}\mathbf{R^f}$ (e.g., $-CH_2N(CF_3)Me$), or $-CH_2CH_2N\mathbf{R^c}\mathbf{R^f}$ (e.g., $-CH_2CH_2NMe_2$).

371. The compound of any one of claims 273-365 or 367, wherein $\mathbf{R^{3a}}$ is selected from the group consisting of:

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^e}$; and

C_{3-6} cycloalkyl optionally substituted with from 1-4 $\mathbf{R^e}$.

372. The compound of any one of claims 273-365 or 367, wherein $\mathbf{R^{3a}}$ is –(C_{1-3} alkylene)-$\mathbf{R^g}$ or -(C_{1-3} alkylene)-O-$\mathbf{R^g}$, and optionally the $\mathbf{R^g}$ group of $\mathbf{R^{3a}}$ is:

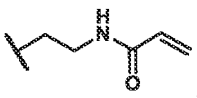
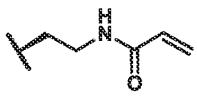
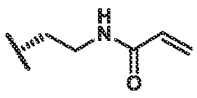
C_{3-6} cycloalkyl optionally substituted with from 1-4 $\mathbf{R^e}$, or

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^e}$.

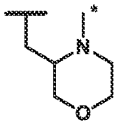
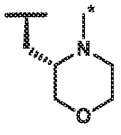
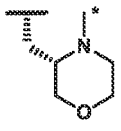
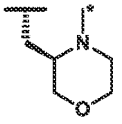
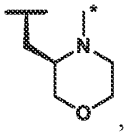
373. The compound of claims 273-365, 367 or 372, wherein $\mathbf{R^{3a}}$ is –CH_2-$\mathbf{R^g}$, or –$CH_2CH_2\mathbf{R^g}$, wherein $\mathbf{R^g}$ is 1,4-dioxanyl.

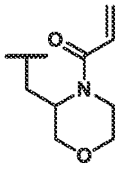
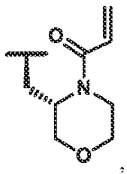
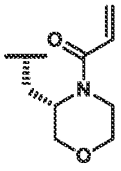
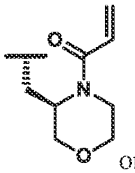
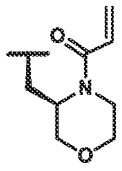
374. The compound of any one of claims 273-365 or 367, wherein $\mathbf{R^{3a}}$ is-$(\mathbf{L^g})_g$-$\mathbf{R^W}$.

375. The compound of any one of claims 273-365, 367 or 374, wherein $\mathbf{R^{3a}}$ is-CH_2CH_2-$\mathbf{R^W}$, wherein the $\mathbf{R^W}$ group is C(=O)-CH=CH_2, or -NHC(=O)-CH=CH_2.

376. The compound of any one of claims 273-365, 367 or 374-375, wherein $\mathbf{R^{3a}}$ is  , such as  or  .

377. The compound of any one of claims 273-365, or 367, wherein $\mathbf{R^{3a}}$ is -$(\mathbf{L^g})_g$-$\mathbf{R^{g2}}$-$\mathbf{R^W}$.

378. The compound of any one of claims 273-365, 367 or 377, wherein R^{3a} is -CH_2-R^{g2}-R^W, wherein the R^{g2} group is  , such as  ,  ,  or  , wherein the waveline represents the point of attachment to -CH_2- and the asterisk represents the point of attachment to R^W; and optionally the R^W group is C(=O)-CH=CH_2.

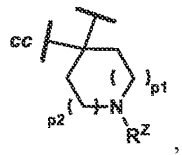
379. The compound of any one of claims 273-365, 367 or 377-378, wherein R^{3a} is  , such as  ,  ,  or  .

380. The compound of claims 273-365, or 367-379, wherein R^{3b} is H.

381. The compound of any one of claims 273-365, or 367-379, wherein R^{3b} is C_{1-3} alkyl, such as methyl.

382. The compound of any one of claims 273-365, wherein R^{3a} and R^{3b}, together with the **Ring B** ring atom to which each is attached, form a fused saturated ring of 4-8 ring atoms;

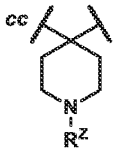
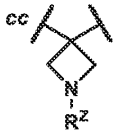
- wherein from 0-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N(R^d), O, and S(O)$_{0-2}$; and
- wherein the fused saturated ring of 4-8 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo, R^c, and R^W.

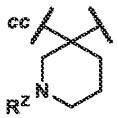
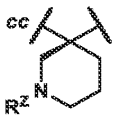
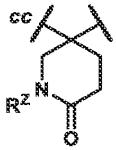
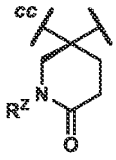
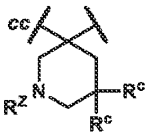
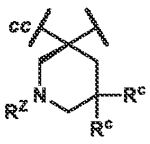
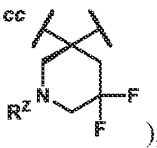
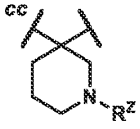
383. The compound of any one of claims 273-365 or 382, wherein R^{3a} and R^{3b}, together with the **Ring B** ring atom to which each is attached, form:  , which is optionally substituted with from 1-2 substituents independently selected from the group consisting of oxo and R^c, wherein:

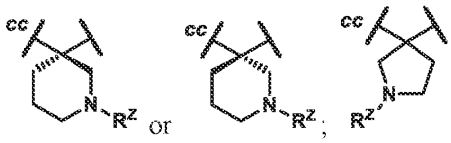
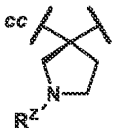
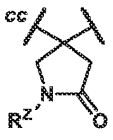
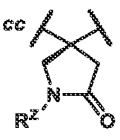
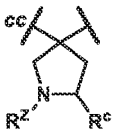
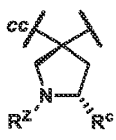
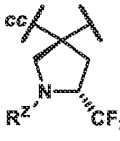
p1 and **p2** are independently 0, 1, or 2;

R^Z is H, R^d, C(=O)-**W**, or $S(O)_2$**W**; and

cc represents the point of attachment to C($R^{2a}R^{2b}$).

384. The compound of any one of claims 273-365 or 382-383, wherein R^{3a} and R^{3b}, together with the **Ring B** ring atom to which each is attached, form  or  , wherein R^Z is H, R^d, C(=O)-**W**, or $S(O)_2$**W**; and *cc* represents the point of attachment to C($R^{2a}R^{2b}$).

385. The compound of any one of claims 273-365 or 382-383, wherein R^{3a} and R^{3b}, together with the **Ring B** ring atom to which each is attached, form a fused ring selected from the group consisting of:  such as  ;  such as  ;  such as  (e.g., );  such as

 or ; such as  ;  such as  ; and  such as  (e.g., ),wherein $\mathbf{R^Z}$ is H, $\mathbf{R^d}$, C(=O)-**W**, or $S(O)_2\mathbf{W}$; and *cc* represents the point of attachment to $C(\mathbf{R^{2a}R^{2b}})$.

386. The compound any one of claims 383-385, wherein $\mathbf{R^Z}$ is H.

387. The compound of any one of claims 383-385, wherein $\mathbf{R^Z}$ is C_{1-6} alkyl optionally substituted with from 1-3 independently selected $\mathbf{R^a}$.

388. The compound of any one of claims 383-385, wherein $\mathbf{R^Z}$ is C(=O)-**W** or $S(O)_2\mathbf{W}$, optionally wherein **W** is C_{2-4} alkenyl.

389. The compound of any one of claims 273-365, wherein $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ together with the **Ring B** ring atom to which each is attached form a fused C_{3-6} cycloalkyl, wherein the fused C_{3-6} cycloalkyl is optionally substituted with from 1-2 $\mathbf{R^c}$.

390. The compound of any one of claims 273-365, wherein $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ together with the **Ring B** ring atom to which each is attached, form a fused saturated ring of 4-6 ring atoms;

- wherein from 1-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, $N(\mathbf{R^d})$, O, and $S(O)_{0-2}$; and
- wherein the fused saturated ring of 4-6 ring atoms is optionally substituted with from 1-2 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$.

391. The compound of any one of claims 273-361, wherein $\mathbf{R^{2a}}$ and $\mathbf{R^{3a}}$ taken together with the **Ring B** ring atoms to which each is attached, form a fused C_{3-6} (e.g., C_3 or C_4) cycloalkyl which is optionally substituted with from 1-2 $\mathbf{R^c}$.

392. The compound of any one of claims 273-362, wherein $\mathbf{R^{2b}}$ and $\mathbf{R^{3b}}$ are each H.

393. The compound of any one of claims 273-362, wherein $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; $\mathbf{R^{3a}}$ is C_{1-3} alkyl optionally substituted with from 1-3 $\mathbf{R^a}$; and $\mathbf{R^{3b}}$ is H, optionally each $\mathbf{R^a}$ substituent present in $\mathbf{R^{3a}}$ is independently selected from the group consisting of: halo, C_{1-4} alkoxy, and C_{1-4} haloalkoxy.

394. The compound of any one of claims 273-362 or 393, wherein $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; and $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ are independently selected C_{1-3} alkyl.

395. The compound of any one of claims 273-362, wherein $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; $\mathbf{R^{3a}}$, is $-\mathbf{R^g}$, $-(C_{1-3}$ alkylene$)$-$\mathbf{R^g}$, or $-(C_{1-3}$ alkylene$)$-O-$\mathbf{R^g}$,

optionally wherein the $\mathbf{R^g}$ group of $\mathbf{R^{3a}}$ is:

C_{3-6} cycloalkyl optionally substituted with from 1-4 $\mathbf{R^c}$, or

heterocyclyl including from 4-6 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$; and

$\mathbf{R^{3b}}$ is H.

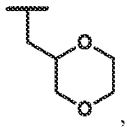
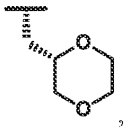
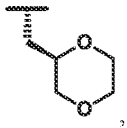
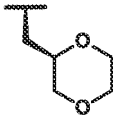
396. The compound of any one of claims 273-362, wherein $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; and $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ taken together with the **Ring B** ring carbon atom to which each is attached form a fused C_{3-6} (such as C_3 or C_4) cycloalkyl, wherein the fused cycloalkyl ring is optionally substituted with from 1-2 $\mathbf{R^c}$.

397. The compound of any one of claims 273-362, wherein $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, and $\mathbf{R^{2b}}$ are each H; and $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ together with the **Ring B** ring atom to which each is attached, form a fused saturated ring of 4-6 ring atoms;

- wherein from 1-2 of the ring atoms are each an independently selected heteroatom, wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and S(O)$_{0-2}$; and
- wherein the fused saturated ring of 4-6 ring atoms is optionally substituted with from 1-2 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$.

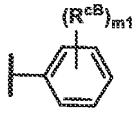
398. The compound of any one of claims 273-361, wherein $\mathbf{R^{1c}}$ is H; $\mathbf{R^{2a}}$ and $\mathbf{R^{3a}}$ taken together with the **Ring B** ring atoms to which each is attached, form a fused C_{3-6} (e.g., C_3 or C_4) cycloalkyl which is optionally substituted with from 1-2 $\mathbf{R^c}$; and $\mathbf{R^{2b}}$ and $\mathbf{R^{3b}}$ are each H.

399. The compound of any one of claims 273-361, wherein $\mathbf{R^{1c}}$ is H; $\mathbf{R^{2a}}$ and $\mathbf{R^{3a}}$ combine to form a double bond between the **Ring B** atoms to which each is attached; and $\mathbf{R^{2b}}$ is H; and $\mathbf{R^{3b}}$ is $-(\mathbf{L^g})_g\text{-}\mathbf{R^g}$.

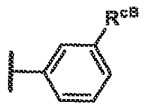
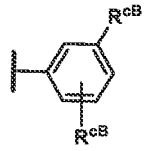
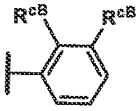
400. The compound of any one of claims 273-361 or 399, wherein $\mathbf{R^{1c}}$ is H; $\mathbf{R^{2a}}$ and $\mathbf{R^{3a}}$ combine to form a double bond between the **Ring B** atoms to which each is attached; and $\mathbf{R^{2b}}$ is H; and $\mathbf{R^{3b}}$ is  , such as  ,  ,  , or  .

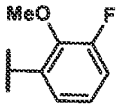
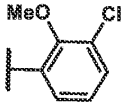
401. The compound of any one of claims 273-362, wherein $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$ are each H.

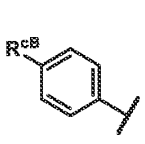
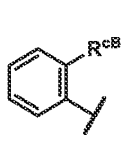
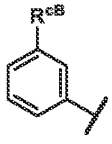
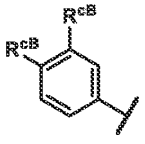
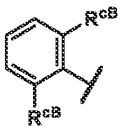
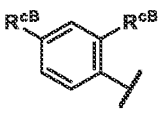
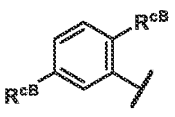
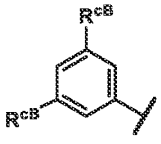
402. The compound of any one of claims 273-401, wherein $\mathbf{R^4}$ is H.

403. The compound of any one of claims 273-402, wherein **Ring A** is  , wherein each $\mathbf{R^{cB}}$ is an independently selected $\mathbf{R^c}$; and **m1** is 0, 1, 2, 3, or 4.

404. The compound of claim 403, wherein **m1** is 1, 2, or 3, such as 1 or 2.

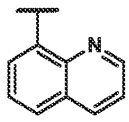
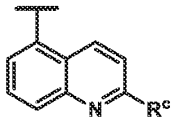
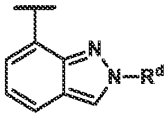
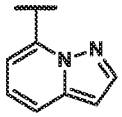
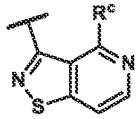
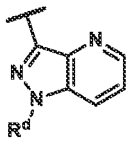
405. The compound of any one of claims 273-404, wherein **Ring A** is  or  (e.g., ), wherein each $\mathbf{R^{cB}}$ is an independently selected $\mathbf{R^c}$.

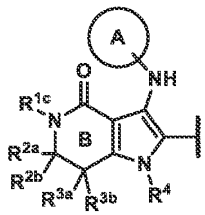
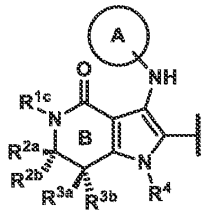
406. The compound of any one of claims 273-405, wherein **Ring A** is  or  .

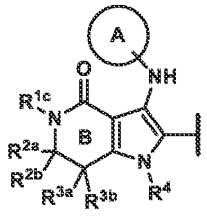
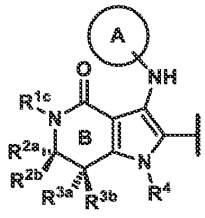
407. The compound of any one of claims 273-404, wherein **Ring A** is selected from the group consisting of:  ,  ,  ,  ,  ,  ,  , and  , wherein each $\mathbf{R^{cB}}$ is an independently selected $\mathbf{R^c}$.

408. The compound of any one of claims 403-407, wherein each $\mathbf{R}^{cB}$ is independently selected from the group consisting of: -halo, such as -Cl and -F; -CN; C_{1-4} alkoxy; C_{1-4} haloalkoxy; C_{1-3} alkyl; and C_{1-3} alkyl substituted with from 1-6 independently selected halo.

409. The compound of any one of claims 273-402, wherein **Ring A** is bicyclic heteroaryl including from 9-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R}^{d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with from 1-4 $\mathbf{R}^{c}$, such as wherein:

Ring A is selected from the group consisting of:  ,  ,  ,  ,  , and  , each of which is further optionally substituted with $\mathbf{R}^{c}$.

410. The compound of any one of claims 1-409, wherein the  moiety is  .

411. The compound of any one of claims 1-409, wherein the  moiety is  .

412. The compound of claim 1, wherein the compound is selected from the group consisting of the compounds delineated in **Table C1**, or a pharmaceutically acceptable salt thereof.

413. A pharmaceutical composition comprising a compound of any one of claims 1-412, or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable diluent or carrier.

414. A method for treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-412, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 413.

415. A method for treating cancer in a subject in need thereof, the method comprising (a) determining that the cancer is associated with a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same; and (b) administering to the subject a therapeutically effective amount of a compound of any one of claims 1-412, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 413.

416. A method of treating an EGFR-associated cancer in a subject, the method

comprising administering to a subject identified or diagnosed as having an EGFR-associated cancer a therapeutically effective amount of a compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 383.

417. A method of treating an EGFR-associated cancer in a subject, the method comprising:

(a) determining that the cancer in the subject is an EGFR-associated cancer; and

(b) administering to the subject a therapeutically effective amount of a compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 413.

418. A method of treating a subject, the method comprising administering a therapeutically effective amount of a compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 413, to a subject having a clinical record that indicates that the subject has a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same.

419. The method of any one of claims 415 and 417, wherein the step of determining that the cancer in the subject is an EGFR-associated cancer includes performing an assay to detect dysregulation in an *EGFR* gene, an EGFR kinase protein, or expression or activity or level of any of the same in a sample from the subject.

420. The method of claim 419, further comprising obtaining a sample from the subject.

421. The method of claim 420, wherein the sample is a biopsy sample.

422. The method of any one of claims 419-421, wherein the assay is selected

from the group consisting of sequencing, immunohistochemistry, enzyme-linked immunosorbent assay, and fluorescence in situ hybridization (FISH).

423. The method of claim 422, wherein the FISH is break apart FISH analysis.

424. The method of claim 422, wherein the sequencing is pyrosequencing or next generation sequencing.

425. The method of any one of claims 415, 418, and 419, wherein the dysregulation in an *EGFR* gene, an EGFR kinase protein, or expression or activity or level of any of the same is one or more point mutations in the *EGFR* gene.

426. The method of claim 425, wherein the one or more point mutations in an *EGFR* gene results in the translation of an EGFR protein having one or more amino acid substitutions at one or more of the following amino acid positions exemplified in **Table 1a** and **1b**.

427. The method of claim 426, wherein the one or more point mutations is selected from the mutations in **Table 1a** and **1b** (e.g., L858R, G719S, G719C, G719A, L861Q, a deletion in exon 19 and/or an insertion in exon 20).

428. The method of claim 426, wherein the one or more point mutations is an EGFR inhibitor resistance mutation (e.g., L718Q, L747S, D761Y, T790M, C797S, T854A).

429. The method of claim 426, wherein the one or more point mutations in an *EGFR* gene include a deletion in exon 19 of a human *EGFR* gene.

430. The method of claim 426, wherein the one or more mutations is an EGFR insertion in exon 20 of a human *EGFR* gene.

431. The method of claim 428, wherein the insertion in exon 20 of a human EGFR gene is selected from: V769_D770insX, D770_N771insX, N771_P772insX, P772_H773insX, and H773_V774insX.

432. The method of claims 428 or 429, wherein the insertion in exon 20 of a human *EGFR* gene is selected from: Y772_A775dup, A775_G776insYVMA, G776delinsVC, G776delinsVV, V777_G778insGSP, and P780_Y781insGSP.

433. The method of any one of claims 426, 427 and 329-432, wherein the EGFR-associated cancer is selected from the group consisting of: oral cancer, oropharyngeal cancer, nasopharyngeal cancer, respiratory cancer, urogenital cancer, gastrointestinal cancer, central or peripheral nervous system tissue cancer, an endocrine or neuroendocrine cancer, a hematopoietic cancer, glioma, sarcoma, carcinoma, lymphoma, melanoma, fibroma, meningioma, brain cancer, oropharyngeal cancer, nasopharyngeal cancer, renal cancer, biliary cancer, pheochromocytomaLi-Fraumeni tumor, thyroid cancer, parathyroid cancer, pituitary tumors, adrenal gland tumors, osteogenic sarcoma tumors, breast cancer, lung cancer, head and neck cancer, prostate cancer, esophageal cancer, tracheal cancer, liver cancer, bladder cancer, stomach cancer, pancreatic cancer, ovarian cancer, uterine cancer, cervical cancer, testicular cancer, colon cancer, rectal cancer and skin cancer.

434. The method of any one of claims 417 and 419-433, wherein the EGFR-associated cancer is selected from the group consisting of: lung cancer, pancreatic cancer, head and neck cancer, melanoma, colon cancer, renal cancer, leukemia, glioblastoma, or breast cancer.

435. The method of claim 433 or 434, wherein the lung cancer is non-small cell lung cancer.

436. The method of any one of claims 414-435, wherein the cancer is a HER2-associated cancer.

437. The method of claim 436, wherein the HER2-associated cancer is associated with a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same.

438. The method of any one of claims 436 and 437, wherein determining that the cancer in the subject is a HER2-associated cancer includes performing an assay to detect dysregulation in a *HER2* gene, a HER2 kinase protein, or expression or activity or level of any of the same in a sample from the subject.

439. The method of claim 438, further comprising obtaining a sample from the subject.

440. The method of claim 439, wherein the sample is a biopsy sample.

441. The method of any one of claims 438-440, wherein the assay is selected from the group consisting of sequencing, immunohistochemistry, enzyme-linked immunosorbent assay, and fluorescence in situ hybridization (FISH).

442. The method of claim 441, wherein the sequencing is pyrosequencing or next generation sequencing.

443. The method of any one of claims 437-442, wherein the dysregulation in a *HER2* gene, a HER2 kinase protein, or expression or activity or level of any of the same is one or more point mutations in the *HER2* gene.

444. The method of claim 443, wherein the one or more point mutations in a *HER2* gene results in the translation of a HER2 protein having one or more amino acid substitutions at one or more of the following amino acid positions exemplified in **Table 3**.

445. The method of claim 444, wherein the one or more point mutations is selected from the mutations in **Table 3** (e.g., S310F, S310Y, R678Q, R678W, R678P,

I767M, V773M, V777L, and V842I).

446. The method of any one of claims 414-445, wherein the cancer is selected from the group consisting of: non-small cell lung cancer, pancreatic cancer, and colorectal cancer.

447. The method of any one of claims 414-446, further comprising administering an additional therapy or therapeutic agent to the subject.

448. The method of claim 447, wherein the additional therapy or therapeutic agent is selected from radiotherapy, cytotoxic chemotherapeutics, kinase targeted-therapeutics, apoptosis modulators, signal transduction inhibitors, immune-targeted therapies, and angiogenesis-targeted therapies.

449. The method of claim 448, wherein said additional therapeutic agent is selected from one or more kinase targeted therapeutics.

450. The method of claim 449, wherein said additional therapeutic agent is a tyrosine kinase inhibitor.

451. The method of claim 450, wherein said additional therapeutic agent is a second EGFR inhibitor.

452. The method of claim 447, wherein said additional therapeutic agent is selected from osimertinib, gefitinib, erlotinib, afatinib, lapatinib, neratinib, AZD-9291, CL-387785, CO-1686, WZ4002, and combinations thereof.

453. The method of claim 447, wherein said additional therapeutic agent is a second compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 413.

454. The method of claim 447, wherein said additional therapeutic agent is a HER2 inhibitor.

455. The method of claim 454, wherein the HER2 inhibitor is selected from trastuzumab, pertuzumab, trastuzumab emtansine, lapatinib, KU004, neratinib, dacomitinib, afatinib, tucatinib, erlotinib, pyrotinib, poziotinib, CP-724714, CUDC-101, sapitinib (AZD8931), tanespimycin (17-AAG), IPI-504, PF299, pelitinib, S- 22261 1, and AEE-788.

456. The method of any one of claims 447-455, wherein the compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 413, and the additional therapeutic agent are administered simultaneously as separate dosages.

457. The method of any one of claims 447-455, wherein the compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 413, and the additional therapeutic agent are administered as separate dosages sequentially in any order.

458. A method of treating a subject having a cancer, wherein the method comprises:

(a) administering one or more doses of a first EGFR inhibitor to the subject for a period of time;

(b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one EGFR inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor of step (a); and

(c) administering a compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has been determined to have a cancer cell that has at least one

EGFR inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor of step (a); or

(d) administering additional doses of the first EGFR inhibitor of step (a) to the subject if the subject has not been determined to have a cancer cell that has at least one EGFR inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor of step (a).

459. The method of claim 458, wherein the anticancer agent in step (c) is a second EGFR inhibitor, an immunotherapy, a HER2 inhibitor, or a combination thereof.

460. The method of claim 458, wherein the anticancer agent in step (c) is the first EGFR inhibitor administered in step (a).

461. The method of claim 458, wherein the subject is administered additional doses of the first inhibitor of EGFR of step (a), and the method further comprises (e) administering another anticancer agent to the subject.

462. The method of claim 461, wherein the anticancer agent of step (e) is a second EGFR inhibitor, an immunotherapy, or a combination thereof.

463. The method of claim 461, wherein the anticancer agent of step (e) is a compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof.

464. The method of any one of claims 458-463, wherein the EGFR inhibitor resistance mutation is a substitution at amino acid position 718, 747, 761, 790, 797, or 854 (e.g., L718Q, L747S, D761Y, T790M, C797S, T854A).

465. A method of treating an EGFR-associated cancer in a subject, the method comprising administering to a subject identified or diagnosed as having an EGFR-associated cancer that has one or more EGFR inhibitor resistance mutations a therapeutically effective amount of a compound of any one of claims 1-412 or a

pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 413.

466. A method of treating an EGFR-associated cancer in a subject, the method comprising:

(a) determining that the cancer in the subject has one or more EGFR inhibitor resistance mutations; and

(b) administering to the subject a therapeutically effective amount of a compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 413.

467. A method of treating a subject having a cancer, wherein the method comprises:

(a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first EGFR inhibitor has one or more EGFR inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor that was previously administered to the subject; and

(b) administering a compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has been determined to have a cancer cell that has at least one EGFR inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first modulator of EGFR that was previously administered to the subject; or

(c) administering additional doses of the first modulator of EGFR to the subject if the subject has not been determined to have a cancer cell that has at least one EGFR modulator resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first modulator of EGFR previously administered to the subject.

468. The method of claim 467, wherein the anticancer agent of step (b) is a second EGFR innhibitor, an immunotherapy, a HER2 inhibitor, or a combination thereof.

469. The method of claim 467, wherein the anticancer agent of step (b) is the first EGFR inhibitor previously administered to the subject.

470. The method of claim 467, wherein the subject is administered additional doses of the first EGFR inhibitor previously administered to the subject, and the method further comprises (d) administering another anticancer agent to the subject.

471. The method of claim 470, wherein the anticancer agent of step (d) is a second EGFR inhibitor, an immunotherapy, or a combination thereof.

472. The method of claim 470, wherein the anticancer agent of step (d) is a compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof.

473. The method of claim 472, wherein the second EGFR inhibitor is selected from osimertinib, gefitinib, erlotinib, afatinib, lapatinib, neratinib, AZD-9291, CL-387785, CO-1686, WZ4002, and combinations thereof.

474. The method of any one of claims 465-473, wherein the cancer is selected from the group consisting of: non-small cell lung cancer, pancreatic cancer, and colorectal cancer.

475. The method of any one of claims 465-474, wherein the cancer is associated with a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same.

476. The method of claim 475, wherein the dysregulation in a *HER2* gene, a HER2 kinase protein, or expression or activity or level of any of the same is one or more point mutations in the *HER2* gene.

477. The method of claim 476, wherein the one or more point mutations in a

HER2 gene results in the translation of a HER2 protein having one or more amino acid substitutions at one or more of the following amino acid positions exemplified in **Table 3**.

478. The method of claim 477, wherein the one or more point mutations is selected from the mutations in **Table 3** (e.g., S310F, S310Y, R678Q, R678W, R678P, I767M, V773M, V777L, and V842I).

479. A method for modulating EGFR in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound of any one of claims 1-412, or a pharmaceutically acceptable salt thereof.

480. The method of claim 479, wherein the contacting occurs in vivo.

481. The method of claim 479, wherein the contacting occurs in vitro.

482. The method of any one of claims 479-481, wherein the mammalian cell is a mammalian cancer cell.

483. The method of claim 482, wherein the mammalian cancer cell is a mammalian EGFR-associated cancer cell.

484. The method of any one of claims 479-483, wherein the cell has a dysregulation of an *EGFR* gene, an EGFR kinase protein, or expression or activity or level of any of the same.

485. The method of claim 484, wherein the dysregulation in an *EGFR* gene, an EGFR kinase protein, or expression or activity or level of any of the same is one or more point mutations in the *EGFR* gene.

486. The method of claim 485, wherein the one or more point mutations in an *EGFR* gene results in the translation of an EGFR protein having one or more amino acid

substitutions at one or more of the following amino acid positions exemplified in **Table 1a** and **1b**.

487. The method of claim 486, wherein the one or more point mutations is selected from the mutations in **Table 1a** and **1b** (e.g., L858R, G719S, G719C, G719A, L861Q, a deletion in exon 19 and/or an insertion in exon 20).

488. The method of claim 485, wherein the one or more point mutations is an EGFR inhibitor resistance mutation (e.g., L718Q, L747S, D761Y, T790M, C797S, T854A).

489. The method of claim 485, wherein the one or more point mutations in an *EGFR* gene include a deletion in exon 19 of a human *EGFR* gene.

490. The method of claim 485, wherein the one or more point mutations is an EGFR insertion in exon 20 of a human *EGFR* gene.

491. The method of claim 490, wherein the insertion in exon 20 of a human *EGFR* gene is selected from: A767_V769insX, V769_D770insX, D770_N771insX, N771_P772insX, P772_H773insX, and H773_V774insX.

492. The method of claim 491, wherein the insertion in exon 20 of a human *EGFR* gene is selected from: A767_V769dupASV, V769_D770insASV, D770_N771insNPG, D770_N771insNPY, D770_N771insSVD, D770_N771insGL, N771_H773dupNPH, N771_P772insN, N771_P772insH, N771_P772insV, P772_H773insDNP, P772_H773insPNP, H773_V774insNPH, H773_V774insH, H773_V774insPH, H773_V774insAH, and P772_H773insPNP.

493. A method for treating cancer in a subject in need thereof, the method comprising (a) determining that the cancer is associated with a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same; and (b)

administering to the subject a therapeutically effective amount of a compound of any one of claims 1-412, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 413.

494. A method of treating a HER2-associated cancer in a subject, the method comprising administering to a subject identified or diagnosed as having a HER2-associated cancer a therapeutically effective amount of a compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 413.

495. A method of treating a HER2-associated cancer in a subject, the method comprising:

(a) determining that the cancer in the subject is a HER2-associated cancer; and

(b) administering to the subject a therapeutically effective amount of a compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 413.

496. A method of treating a subject, the method comprising administering a therapeutically effective amount of a compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 413, to a subject having a clinical record that indicates that the subject has a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same.

497. The method of any one of claims 493 and 495, wherein the step of determining that the cancer in the subject is a HER2-associated cancer includes performing an assay to detect dysregulation in a *HER2* gene, a HER2 kinase protein, or expression or activity or level of any of the same in a sample from the subject.

498. The method of claim 497, further comprising obtaining a sample from the subject.

499. The method of claim 498, wherein the sample is a biopsy sample.

500. The method of any one of claims 493-499, wherein the assay is selected from the group consisting of sequencing, immunohistochemistry, enzyme-linked immunosorbent assay, and fluorescence in situ hybridization (FISH).

501. The method of claim 500, wherein the FISH is break apart FISH analysis.

502. The method of claim 500, wherein the sequencing is pyrosequencing or next generation sequencing.

503. The method of any one of claims 493, 496, and 497, wherein the dysregulation in a *HER2* gene, a HER2 kinase protein, or expression or activity or level of any of the same is one or more point mutations in the *HER2* gene.

504. The method of claim 503, wherein the one or more point mutations in a *HER2* gene results in the translation of a HER2 protein having one or more amino acid substitutions at one or more of the following amino acid positions exemplified in **Table 3**.

505. The method of claim 503, wherein the one or more point mutations is selected from the mutations in **Table 3** (e.g., S310F, S310Y, R678Q, R678W, R678P, I767M, V773M, V777L, and V842I).

506. The method of any one of claims 492, 495, and 496, wherein the dysregulation in a *HER2* gene, a HER2 kinase protein, or expression or activity or level of any of the same is an insertion in exon 20 of the human *HER2* gene.

507. The method of claim 506, wherein the insertion in exon 20 of the human *HER2* gene is deletions at an amino acid position selected from: 774, 775, 776, 777, 778, and 780.

508. The method of claim 507, wherein the insertion in exon 20 of a human *HER2* gene is selected from: M774AYVM, M774del insWLV, A775_G776insYVMA, A775_G776insAVMA, A775_G776insSVMA, A775_G776insVAG, A775insV G776C, A775_G776insI, G776del insVC2, G776del insVV, G776del insLC, G776C V777insC, G776C V777insV, V777_G778insCG, G778_S779insCPG, and P780_Y781insGSP.

509. The method of any one of claims 494, 495, and 497, wherein the HER2-associated cancer is selected from the group consisting of: colon cancer, lung cancer, or breast cancer.

510. The method of claim 509, wherein the lung cancer is non-small cell lung cancer.

511. The method of any one of claims 496-510, further comprising administering an additional therapy or therapeutic agent to the subject.

512. The method of claim 511, wherein the additional therapy or therapeutic agent is selected from radiotherapy, cytotoxic chemotherapeutics, kinase targeted-therapeutics, apoptosis modulators, signal transduction inhibitors, immune-targeted therapies and angiogenesis-targeted therapies.

513. The method of claim 511, wherein said additional therapeutic agent is a second compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 413.

514. The method of claim 511, wherein said additional therapeutic agent is selected from one or more kinase targeted therapeutics.

515. The method of claim 511, wherein said additional therapeutic agent is a tyrosine kinase inhibitor.

516. The method of claim 511, wherein said additional therapeutic agent is an EGFR inhibitor.

517. The method of claim 511, wherein said additional therapeutic agent is selected from osimertinib, gefitinib, erlotinib, afatinib, lapatinib, neratinib, AZD-9291, CL-387785, CO-1686, WZ4002, and combinations thereof.

518. The method of claim 511, wherein said additional therapeutic agent is a HER2 inhibitor.

519. The method of claim 518, wherein the HER2 inhibitor is selected from trastuzumab, pertuzumab, trastuzumab emtansine, lapatinib, KU004, neratinib, dacomitinib, afatinib, tucatinib, erlotinib, pyrotinib, poziotinib, CP-724714, CUDC-101, sapitinib (AZD8931), tanespimycin (17-AAG), IPI-504, PF299, pelitinib, S- 22261 1, and AEE-788.

520. The method of any one of claims 514-519, wherein the compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 413, and the additional therapeutic agent are administered simultaneously as separate dosages.

521. The method of any one of claims 514-519, wherein the compound of any one of claims 1-412 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 413, and the additional therapeutic agent are administered as separate dosages sequentially in any order.