(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 April 2022 (14.04.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/076973 A1

(51) International Patent Classification:
C07D 239/94 (2006.01) *A61K 31/517* (2006.01)
C07D 495/04 (2006.01)

(21) International Application Number:
PCT/US2021/071692

(22) International Filing Date:
04 October 2021 (04.10.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/087,780 05 October 2020 (05.10.2020) US

(71) Applicant: **ENLIVEN THERAPEUTICS, INC.** [US/US]; 6200 Lookout Road, Floor 1, Boulder, Colorado 80301-3319 (US).

(72) Inventors: **LYSSIKATOS, Joseph P.**; c/o EnLiven Therapeutics, Inc., 6200 Lookout Road, Floor 1, Boulder, Colorado 80301-3319 (US). **KINTZ, Samuel**; c/o EnLiven Therapeutics, Inc., 6200 Lookout Road, Floor 1, Boulder, Colorado 80301-3319 (US). **REN, Li**; c/o EnLiven Therapeutics, Inc., 6200 Lookout Road, Floor 1, Boulder, Colorado 80301-3319 (US).

(74) Agent: **CHOING, Stephanie** et al.; Morrison & Foerster LLP, 425 Market Street, San Francisco, California 94105 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2022/076973 A1

(54) Title: 7-AZAINDOLE COMPOUNDS FOR INHIBITION OF BCR-ABL TYROSINE KINASES

(57) Abstract: The present disclosure relates to compounds and compositions for inhibition of Bcr-Abl tyrosine kinases, methods of preparing said compounds and compositions, and their use in the treatment of various cancers, such as chronic myeloid leukemia (CML).

7-AZAINDOLE COMPOUNDS FOR INHIBITION OF BCR-ABL TYROSINE KINASES

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to and the benefit of U.S. Provisional Application No. 63/087,780, filed on October 5, 2020, the disclosure of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] Provided herein are compounds and compositions for inhibition of Bcr-Abl tyrosine kinases, methods of preparing said compounds and compositions, and their use in the treatment of various cancers, such as chronic myeloid leukemia (CML).

BACKGROUND

[0003] The cytogenetic abnormality known as the Philadelphia chromosome is highly associated with the occurrence of a number of hematological malignancies, including a majority of chronic myeloid leukemias (CML) and a subset of acute lymphoblastic leukemias (Ph+ ALL). The Philadelphia chromosome is a product of a translocation between the breakpoint cluster region (BCR) gene on chromosome 22 and the Abelson (ABL) tyrosine kinase gene on chromosome 9, resulting in the oncogenic fusion gene product Bcr-Abl. The resultant fusion protein is both overexpressed and harbors constitutive kinase activity that then drives the activation of a number of intracellular signaling cascades to induce the uncontrolled cell growth, division and survival associated with oncogenic transformation. Accordingly, therapeutic intervention employing inhibitors of the Bcr-Abl tyrosine kinase represents a cornerstone of the current treatment paradigm for patients with Philadelphia-positive neoplastic disorders.

[0004] Imatinib (STI-571), a small molecule Bcr-Abl tyrosine kinase inhibitor (Bcr-Abl TKI), was developed as a highly effective treatment for CML in the early 1990s and is still employed today as a first line treatment for CML. However, in more aggressive cases of CML, patients often relapse due to the emergence of resistance. The primary mechanism of this resistance derives from a variety of on-target genetic alterations that drives either aberrant overexpression of the Bcr-Abl fusion or, more commonly, introduce amino acid mutations within the Abl kinase domain that reduce imatinib's binding affinity for the active

site thereby markedly reducing its inhibitory activity. These alterations can either appear stochastically and represent a sub-population within the initial tumor cell population or arise under the selective pressure of inhibitor treatment. One of the predominant on-target Bcr-Abl resistance mutations derives from point mutations that introduce an isoleucine residue for a threonine at position 315 within the Abl kinase domain (T315I) also known as the 'gatekeeper' position. In addition to imatinib, this mutant form of BCR-Abl is profoundly resistant to all second generation Bcr-Abl TKIs (Nilotinib, Dasatinib, Bosutinib, Radotinib). Currently, there exists only one therapeutic option for patients harboring a T315I mutation—the third line Bcr-Abl TKI, Ponatinib. While effective at treating patients with T315I CML, ponatinib suffers from poor selectivity for Bcr-Abl versus a number of other protein kinases. Accordingly, ponatinib has been reported to elicit significant dose-limiting toxicities, which then limits its ability to effectively engage the target to achieve clinical efficacy.

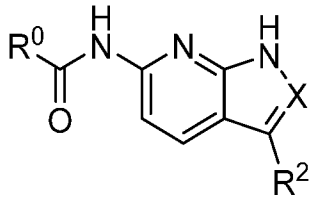
[0005] Besides on- or off-target resistance, intolerance to Bcr-Abl TKIs also represents a major clinical challenge. The doses of more than 50% of Ph+ leukemia patients require modification due to adverse events. In fact, approximately 30% of patients are compelled to dose reduce within the first 6 months of treatment. These drug-related side effects appear early in the course of treatment and, while manageable in most cases, toxicities persist, significantly impacting the patients' quality of life, resulting in decreased compliance. Accordingly, around 40% of patients discontinue first and second generation Bcr-Abl TKIs within the first 5 years of treatment. All of the currently approved Bcr-Abl targeted therapies inhibit other tyrosine kinases, which can lead to potentially debilitating side effects. Specifically, potent inhibition of VEGFRs, PDGFRs, c-Kit and/or the c-Src family can lead to dose-limiting side effects in patients. To address these adverse effects, dose reductions, dose interruptions, and even dose discontinuations are often required during the course of therapy, however such treatment regimens ultimately result in suboptimal therapeutic benefit.

[0006] Accordingly, there remains a substantial unmet medical need for Bcr-Abl TKIs with improved selectivity to improve tolerability and enhanced potency against the wide array of resistance mechanisms in Philadelphia-positive disorders.

SUMMARY OF THE INVENTION

[0007] Provided herein are compounds and compositions that selectively inhibit Bcr-Abl tyrosine kinases and that are useful for treating disorders mediated by Bcr-Abl tyrosine kinases.

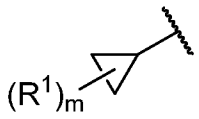
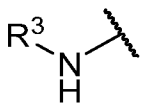
[0008] In one aspect, provided herein is a compound of formula (I),



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

X is N or CR^8;

R^0 is a group  or  ;

m is an integer from 0 to 3;

each R^1 is independently -D, -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, -O-C_1-C_3 alkylene-NR^4R^5, -O-C_1-C_3 alkylene-$NR^{4'}R^{5'}$,C_1-C_3 alkylene-OH, C_0-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene moieties in R^1 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

or

two R^1 are taken together with the carbon atom or carbon atoms to which they are attached to form a 3- to 7-membered heterocyclic ring, wherein the heterocyclic ring contains nitrogen atom and wherein the nitrogen atom is optionally substituted with C_1-C_3 alkyl;

R^2 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein the C_6-C_{14} aryl and 5-to-10-membered heteroaryl are optionally substituted with 1-5 R^6 groups;

R^3 is -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkylene-NR^4R^5, C_1-C_6 alkylene-$NR^{4'}R^{5'}$, C_1-C_6 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_3 alkylene-(C_3-C_6 cycloalkyl), C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-O-(C_1-C_3 alkylene)-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_3 alkylene-(4- to 8-membered heterocycloalkyl), C_1-C_3 alkylene-(C_3-C_7 heterocycloalkyl), C_1-C_3 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, (4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, or (C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, heterocycloalkyl, and heterocycloalkylene moieties in R^3 are optionally substituted with 1-3 fluorine atoms, 1-3 CN groups and/or 1-6 deuterium atoms and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, C_2-C_3 heteroalkyl, 4- to 8-membered heterocycloalkyl, or C_3-C_7 heterocycloalkyl;

each R^4 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-6 deuterium atoms;

each R^5 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-6 deuterium atoms;

each pair of $R^{4'}$ and $R^{5'}$ taken together with the nitrogen atom to which they are attached independently form a 3-to-7-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

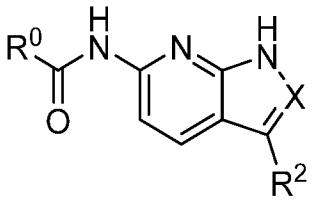
each R^6 is independently halogen, -OR^7, -NR^4R^5, -$NR^{4'}R^{5'}$, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, -CN, $S(O)_nC_1$-C_3 alkyl, or $S(O)_nC_3$-C_6 cycloalkyl,

wherein n is an integer from 0 to 2;

each R^7 is independently -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, or C_1-C_3-alkylene-C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-6 deuterium atoms; and

R^8 is -H, -F, or C_1-C_3 alkyl.

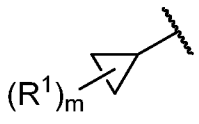
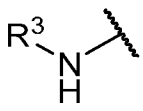
[0009] In another aspect, provided herein is a compound of formula (I),



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

X is N or CR^8;

R^0 is a group  or  ;

m is an integer from 0 to 3;

each R^1 is independently -D, -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, C_0-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene moieties in R^1 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is

independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

R^2 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein the C_6-C_{14} aryl and 5-to-10-membered heteroaryl are optionally substituted with 1-5 R^6 groups;

R^3 is -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkylene-NR^4R^5, C_1-C_6 alkylene-$NR^{4'}R^{5'}$, C_1-C_6 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_3 alkylene-(C_3-C_6 cycloalkyl), C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-O-(C_1-C_3 alkylene)-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_3 alkylene-(C_4-C_6 heterocycloalkyl), C_1-C_3 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_3 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, heterocycloalkyl, and heterocycloalkylene moieties in R^3 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, C_2-C_3 heteroalkyl, or C_4-C_6 heterocycloalkyl;

each R^4 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl;

each R^5 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl;

each pair of $R^{4'}$ and $R^{5'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

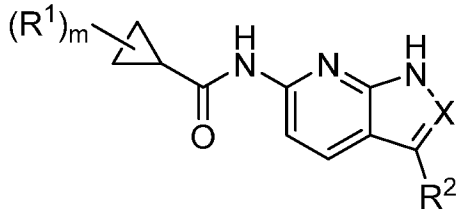
each R^6 is independently halogen, -OR^7, -NR^4R^5, -$NR^{4'}R^{5'}$, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, -CN, $S(O)_nC_1$-C_3 alkyl, or $S(O)_nC_3$-C_6 cycloalkyl,

wherein n is an integer from 0 to 2;

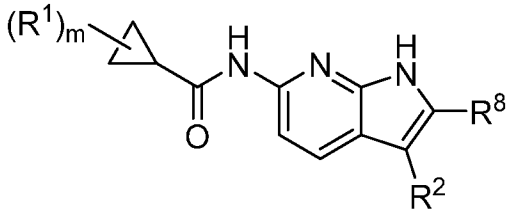
each R^7 is independently -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-6 deuterium atoms; and

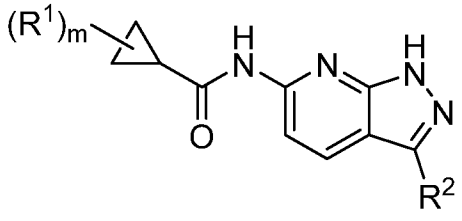
R^8 is -H, -F, or C_1-C_3 alkyl.

[0010] In some embodiments, the compound of formula (I) is a compound of formula (I-A)


(I-A).

[0011] In some embodiments, the compound of formula (I) is a compound of formula (I-A-i) or formula (I-A-ii):


(I-A-i), or


(I-A-ii),

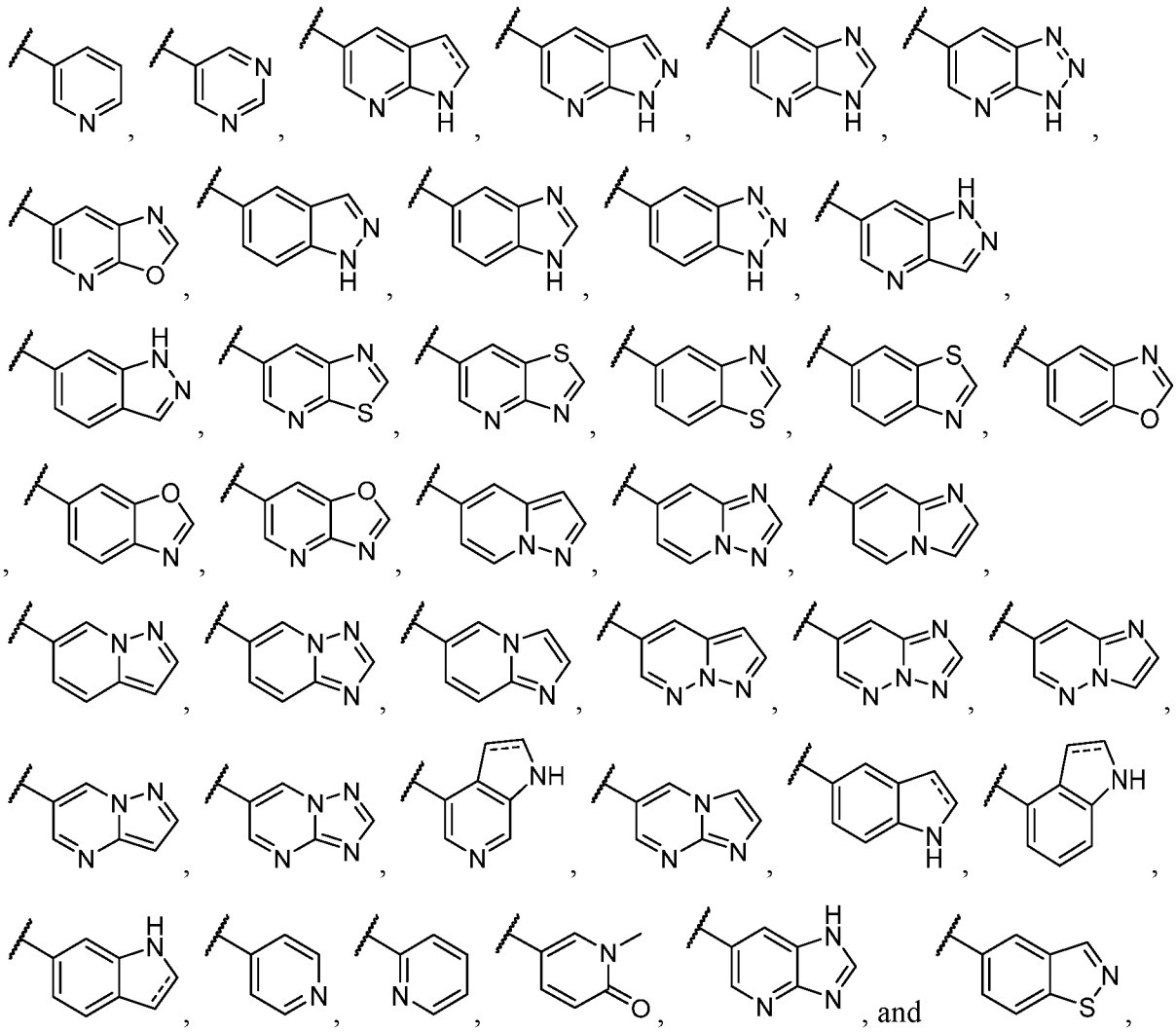
wherein:

m is an integer from 0 to 2;

each R^1 is independently -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, C_0-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene moieties in R^1 are optionally substituted with 1-3 fluorine atoms and/or

1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

R^2 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of:



wherein ═══ indicates a single or double bond, and wherein the C_6-C_{14} aryl and 5-to-10-membered heteroaryl are optionally substituted with 1-5 R^6 groups;

each R^4 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^5 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

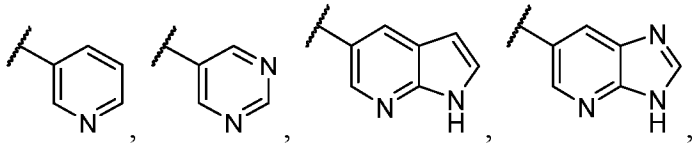
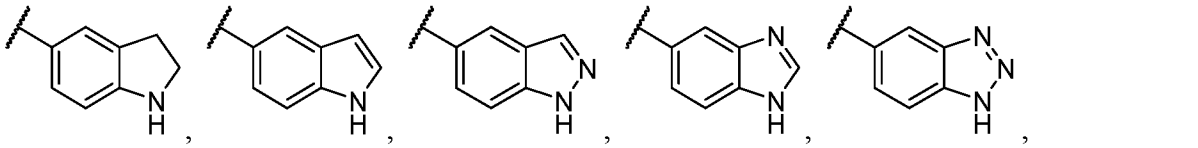
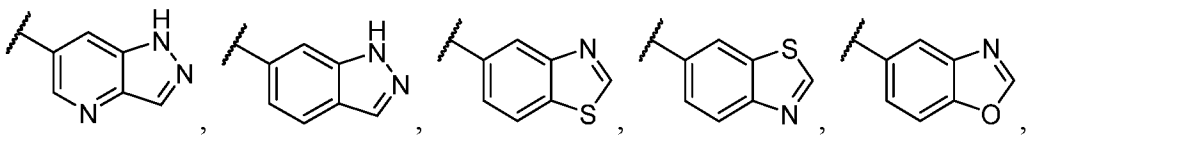
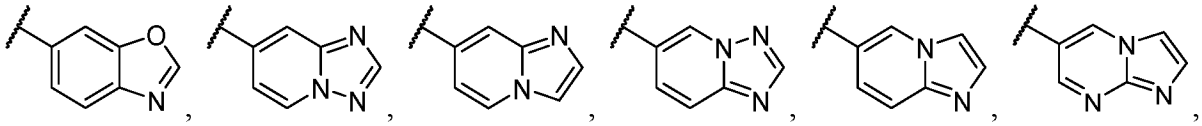
each pair of $R^{4'}$ and $R^{5'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

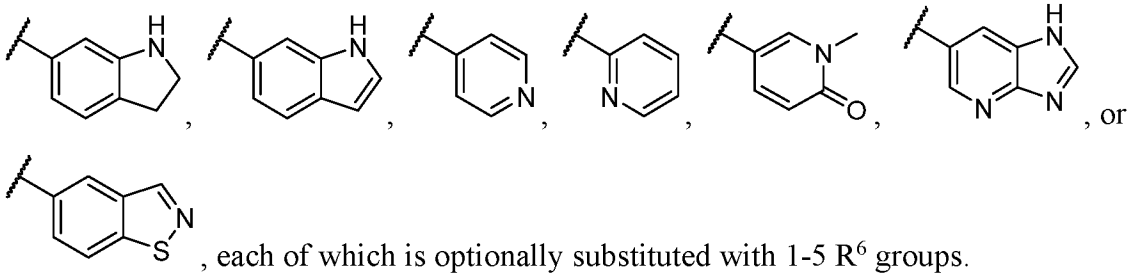
each R^6 is independently halogen, $-OR^7$, $-NR^4R^5$, C_1-C_3 alkyl, $-CF_2H$, $-CF_3$, C_3-C_6 cycloalkyl, or -CN;

each R^7 is independently -H, C_1-C_3 alkyl, $-CD_3$, $-CF_2H$, $-CF_3$, or C_3-C_6 cycloalkyl; and

R^8 is -H, -F, or $-CH_3$.

[0012] In some embodiments, which may be combined with any of the preceding embodiments, each R^1 is independently -F, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, or C_0-C_3 alkylene-CN, wherein each pair of $R^{4'}$ and $R^{5'}$ of R^1 taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl.

[0013] In other embodiments, which may be combined with any of the preceding embodiments, R^2 is phenyl,  ,  ,  ,  .

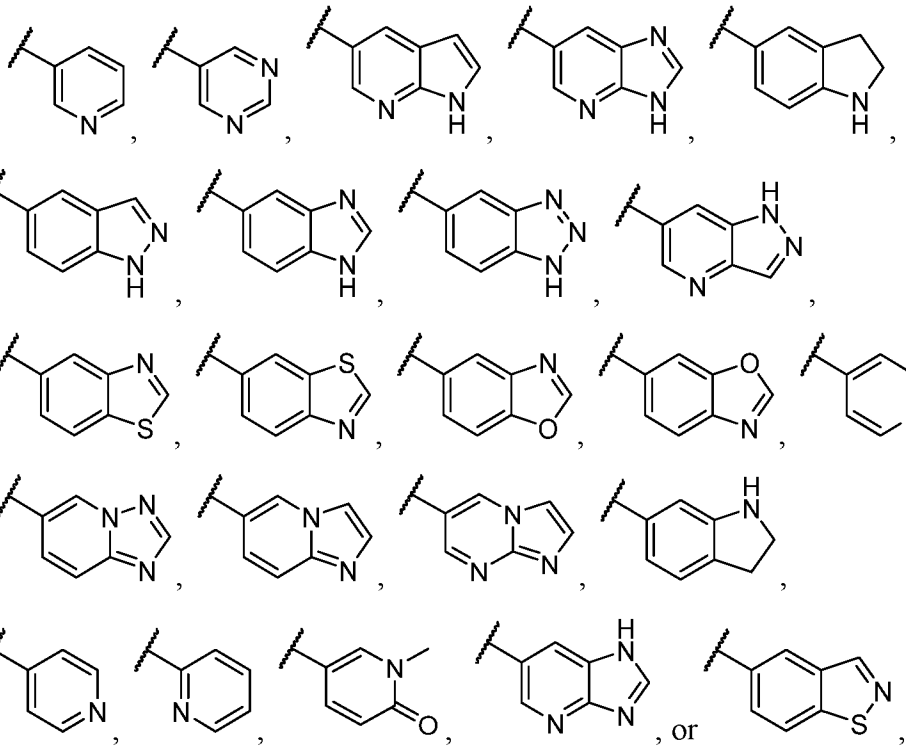


, each of which is optionally substituted with 1-5 R^6 groups.

[0014] In yet other embodiments, which may be combined with any of the preceding embodiments, each $R^6$is independently halogen, $-OR^7$, $-NR^4R^5$, C_1-C_3 alkyl, $-CF_3$, or -CN, wherein each R^4 of R^6 and each R^5 of R^6 are independently -H or C_1-C_3 alkyl; and each R^7 is independently -H, C_1-C_2 alkyl, $-CD_3$, C_1-C_2 haloalkyl, or C_3 cycloalkyl.

[0015] In still yet other embodiments, which may be combined with any of the preceding embodiments, each R^1 is independently -F, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, or C_0-C_3 alkylene-CN, wherein each pair of $R^{4'}$ and $R^{5'}$ of R^1 taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl;

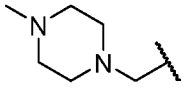
R^2 is phenyl,



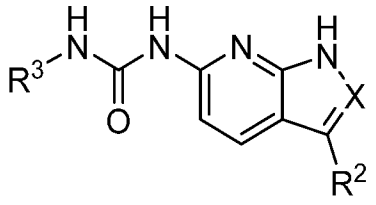
, each of which is optionally substituted with 1-5 R^6 groups;

each R^6 is independently halogen, $-OR^7$, $-NR^4R^5$, C_1-C_3 alkyl, $-CF_3$, or -CN, wherein each R^4 of R^6 and each R^5 of R^6 are independently -H or C_1-C_3 alkyl; and

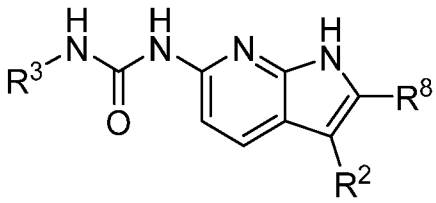
each R^7 is independently -H, C_1-C_2 alkyl, -CD_3, C_1-C_2 haloalkyl, or C_3 cycloalkyl.

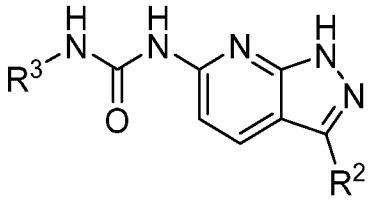
[0016] In still other embodiments, which may be combined with any of the preceding embodiments, each $R^1$is independently F,  , -CH_2OH, -CH_2CH_2OH, -CN, or -CH_2CN. In some embodiments, each R^6 is independently -F, -Cl, -OH, -OCH_3, -OCH_2CH_3, -OCF_3, -OCF_2H, -OCH_2CF_3, -OCD_3, cyclopropyloxy, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -CH_3, -CF_3, or -CN.

[0017] In other embodiments of the present aspect, the compound of formula (I) is a compound of formula (I-B):

 (I-B).

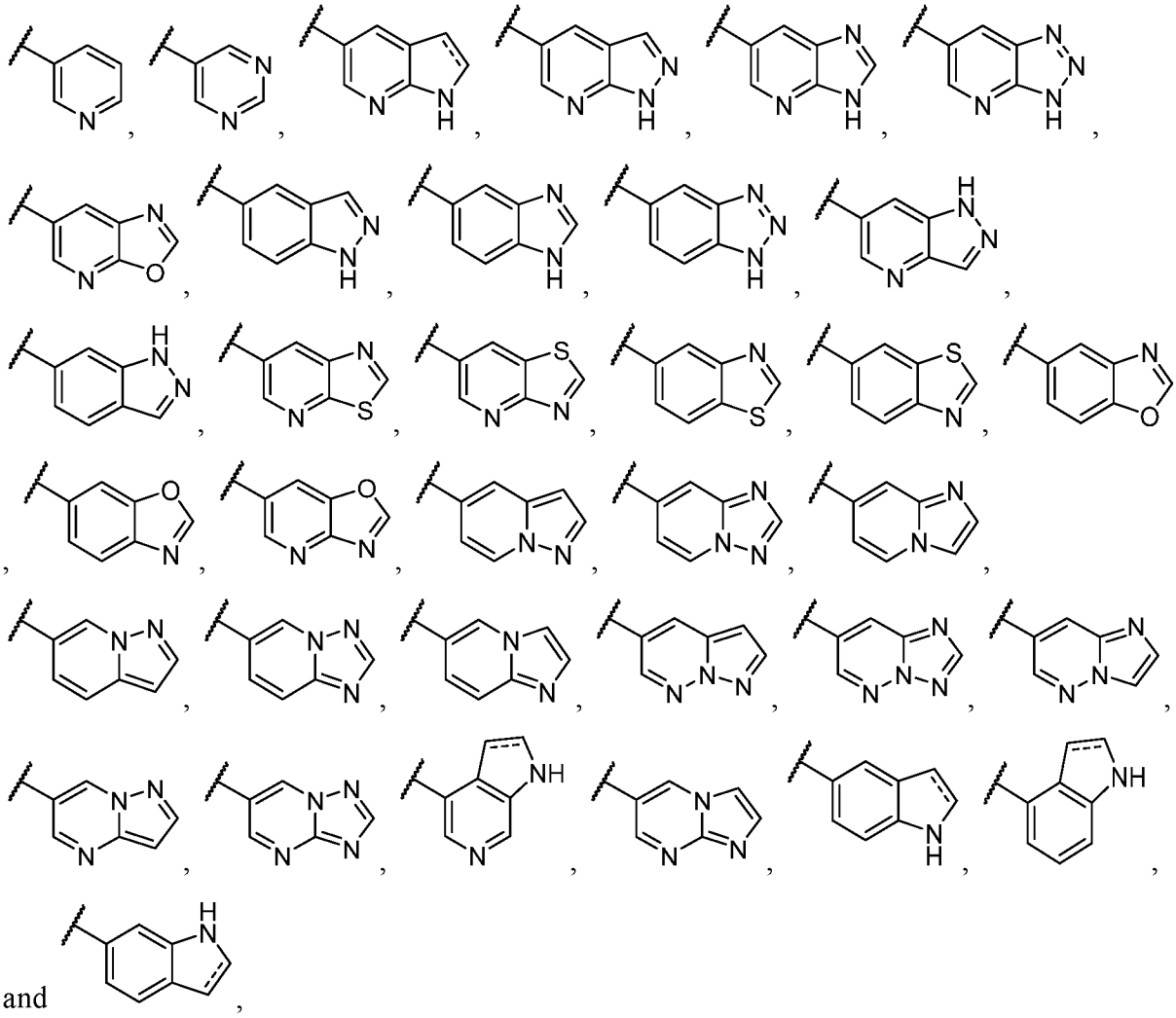
[0018] In some embodiments of the foregoing, the compound of formula (I) is a compound of formula (I-B-i) or formula (I-B-ii):

 (I-B-i), or

 (I-B-ii),

wherein:

R^2 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of:



wherein ≡ indicates a single or double bond, and wherein the C_6-C_{14} aryl and 5-to-10-membered heteroaryl are optionally substituted with 1-5 R^6 groups;

R^3 is C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkyl), C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkyl), C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, heterocycloalkyl, and heterocycloalkylene moieties in R^3 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, C_2-C_3 heteroalkyl, or C_4-C_6 heterocycloalkyl;

each R^4 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

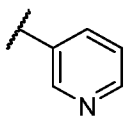
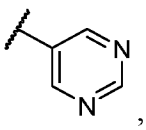
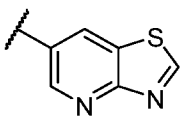
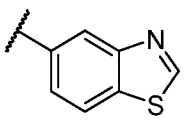
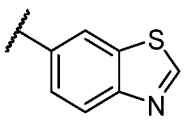
each R^5 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

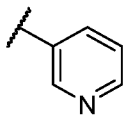
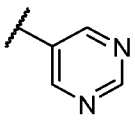
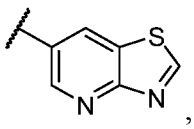
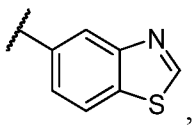
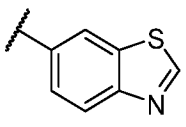
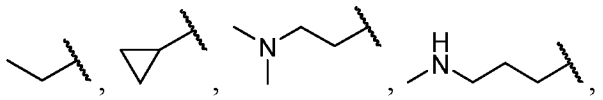
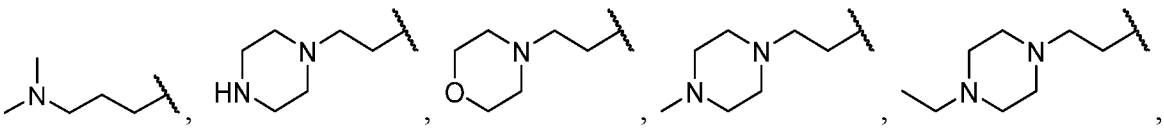
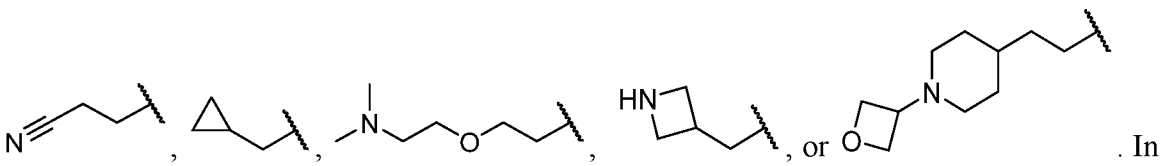
each pair of $R^{4'}$ and $R^{5'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^6 is independently halogen, -OR^7, C_1-C_3 alkyl, -CF_2H, -CF_3, C_3-C_6 cycloalkyl, or -CN;

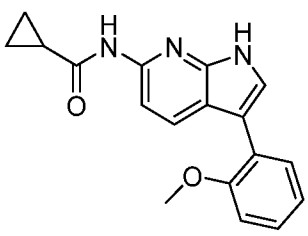
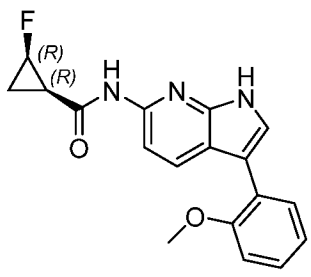
each R^7 is independently -H, C_1-C_3 alkyl, -CD_3, -CF_2H, -CF_3, or C_3-C_6 cycloalkyl; and

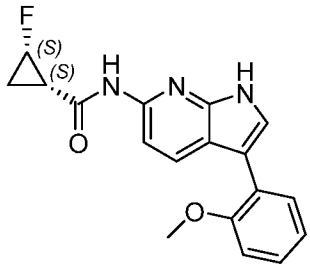
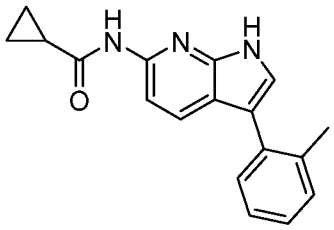
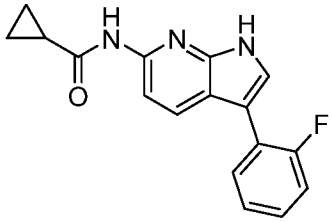
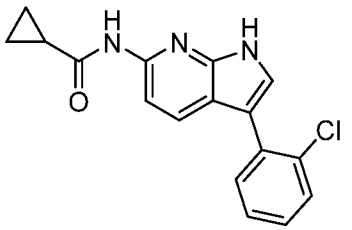
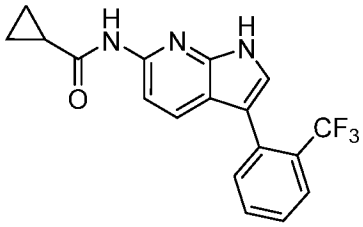
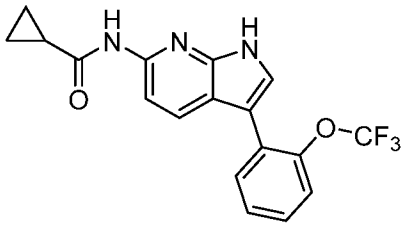
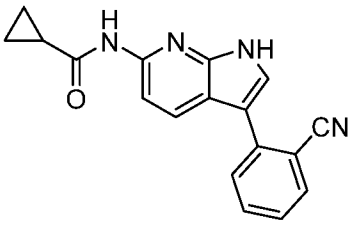
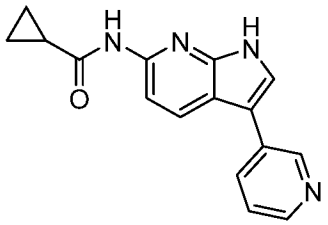
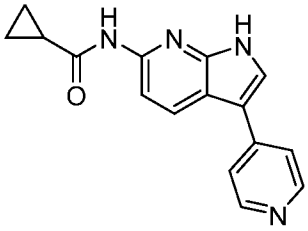
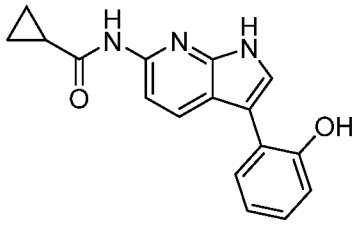
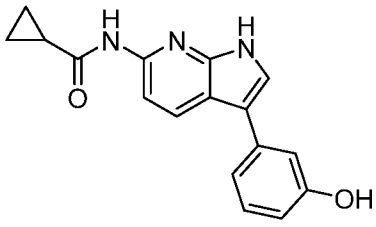
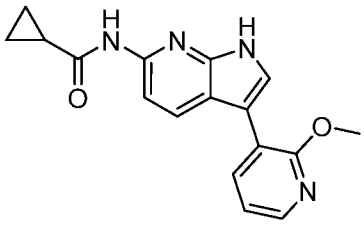
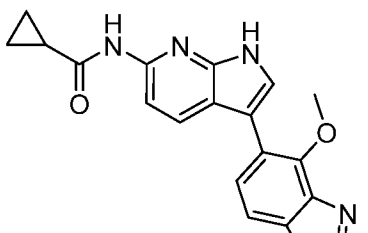
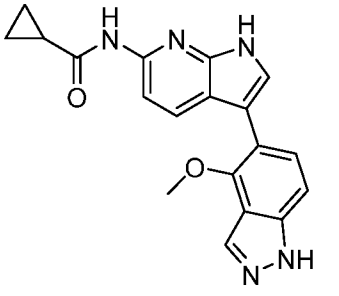
R^8 is -H, -F, or -CH_3.

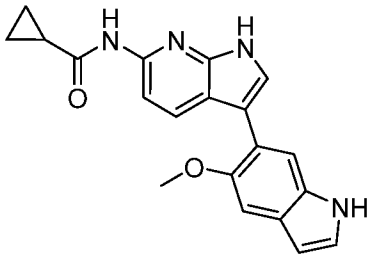
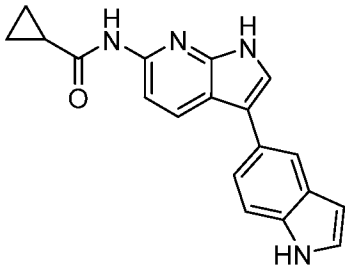
[0019] In some embodiments, which may be combined with any of the preceding embodiments, R^3 is C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkyl), C_1-C_2 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkyl), wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl or C_4-C_6 heterocycloalkyl, wherein the R^4 and R^5 of R^3 are independently -H or C_1-C_3 alkyl, and the $R^{4'}$ and $R^{5'}$ of R^3 taken together with the nitrogen atom to which they are attached form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl. In other embodiments, which may be combined with any of the preceding embodiments, R^2 is phenyl,  ,  ,  ,  , or  , each of which is optionally substituted with 1-5 R^6 groups. In still other embodiments, which may be combined with any of the preceding embodiments, each R^6 is independently halogen or -OR^7; and each R^7 is independently C_1-C_2 alkyl or C_3 cycloalkyl. In yet other embodiments, which

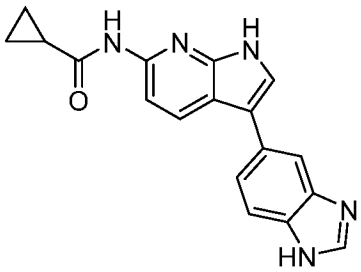
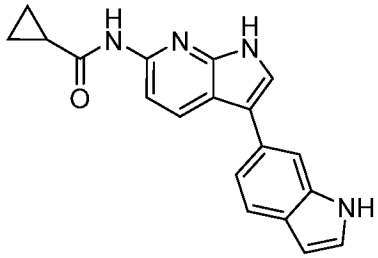
may be combined with any of the preceding embodiments, R^3 is C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkyl), C_1-C_2 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkyl), wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl or C_4-C_6 heterocycloalkyl, wherein the R^4 and R^5 of R^3 are independently -H or C_1-C_3 alkyl, and the $R^{4'}$ and $R^{5'}$ of R^3 taken together with the nitrogen atom to which they are attached form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl; R^2 is phenyl,  ,  ,  ,  , or  , each of which is optionally substituted with 1-5 R^6 groups; each R^6 is independently halogen or -OR^7; and each R^7 is independently C_1-C_2 alkyl or C_3 cycloalkyl. In still yet other embodiments, which may be combined with any of the preceding embodiments, R^3 is  ,  ,  . In still further embodiments, each R^6 is independently -F, -OCH_3, or cyclopropyloxy. In yet other embodiments, which may be combined with any of the preceding embodiments, R^8 is H.

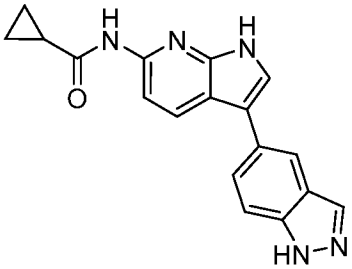
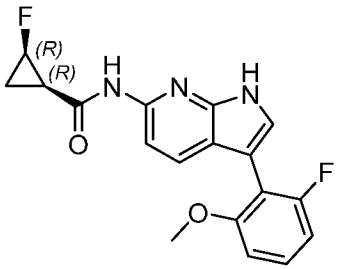
[0020] Also provided herein is a compound which is selected from the group consisting of:

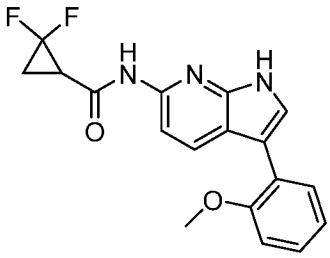
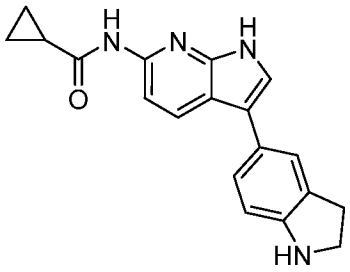
 ;  ;

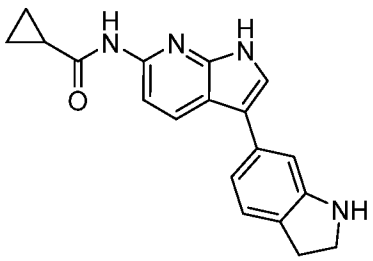
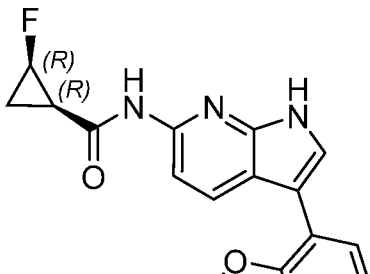

;

;

;

;

;

;

;

;

;

;

;

;

;

;

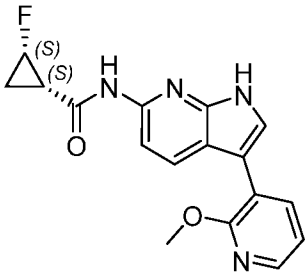
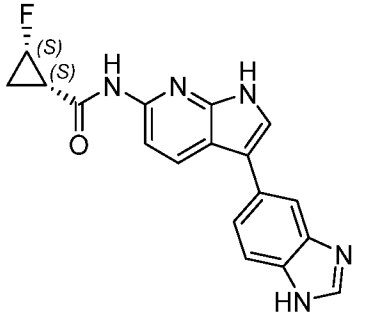

;

;

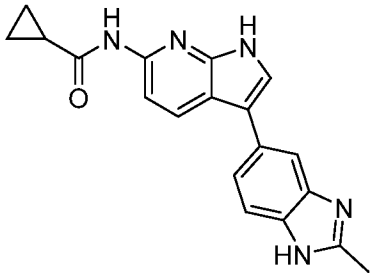
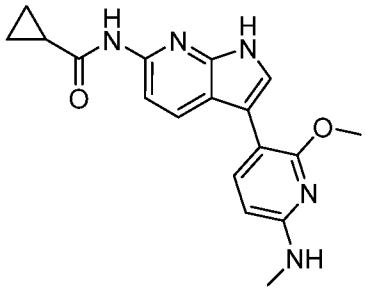

;

;

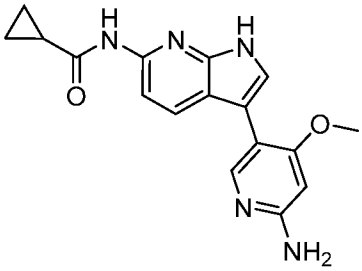
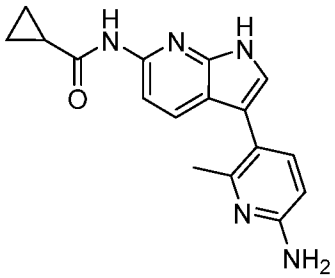

;

;

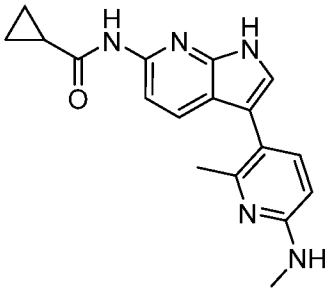
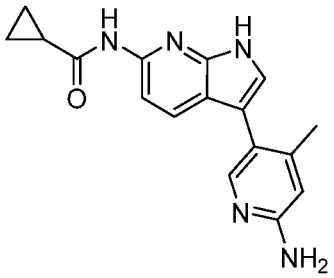

;

;

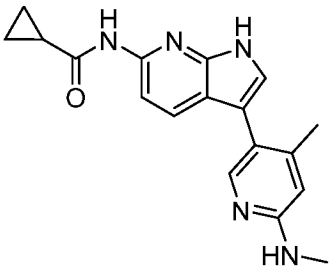
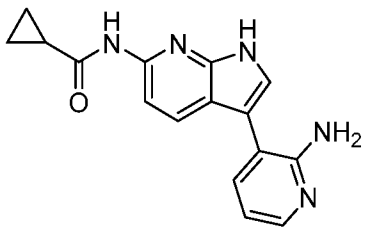

;

;

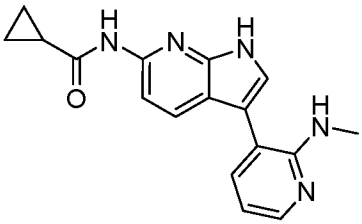
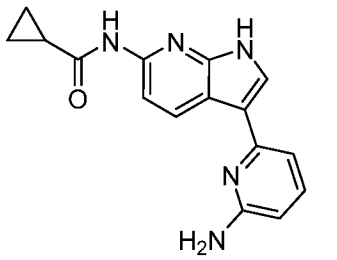

;

;

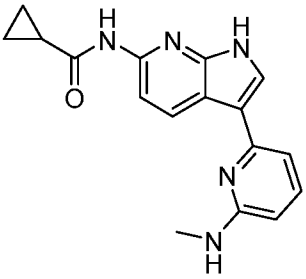
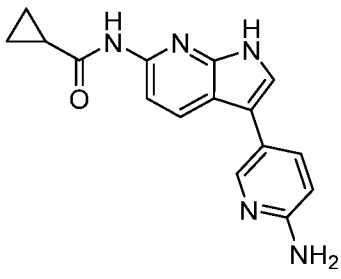

;

;

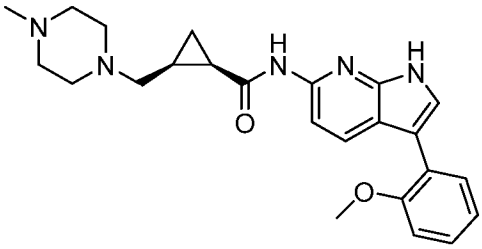
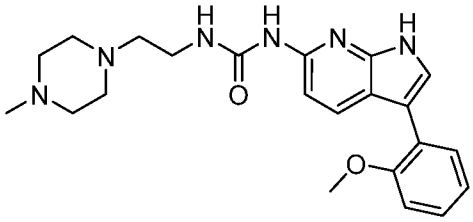
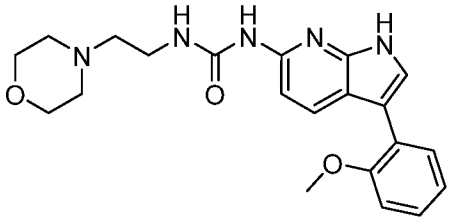
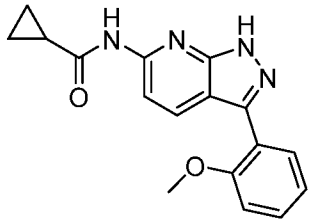
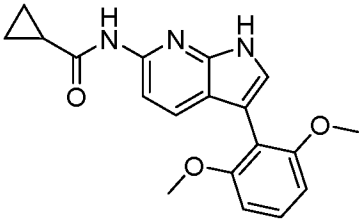
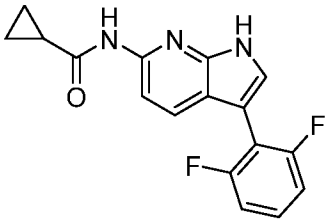
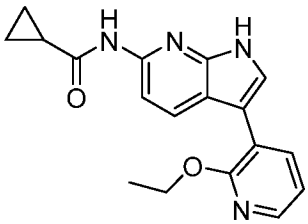
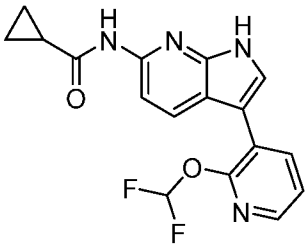
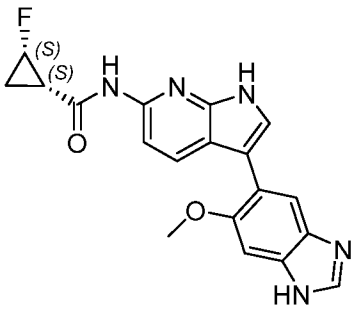
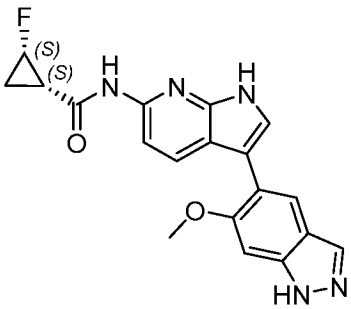
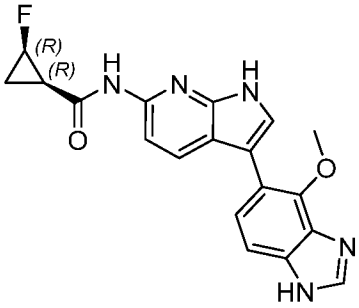
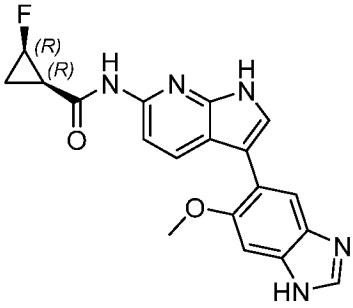
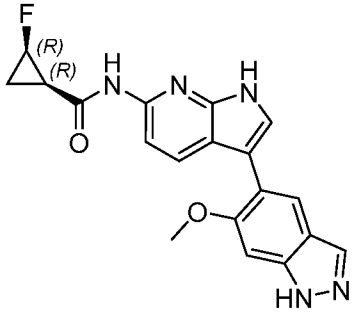
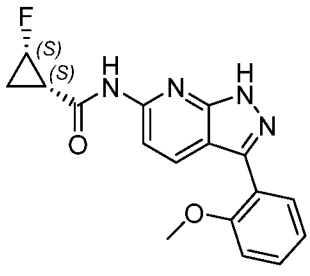

;

;

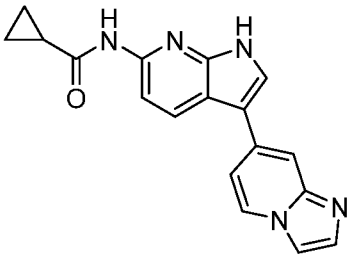
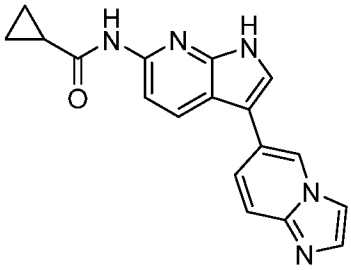

;

;

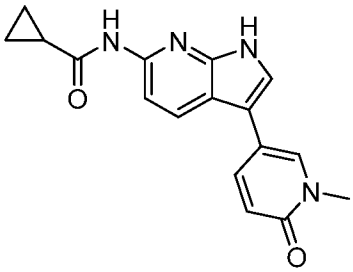
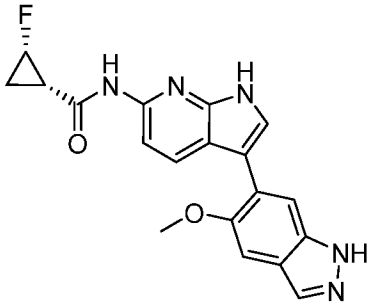

;

;

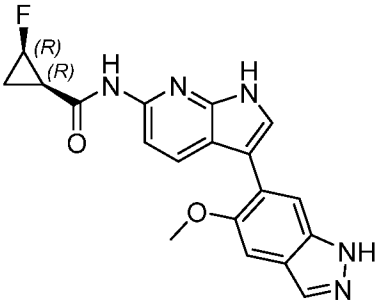
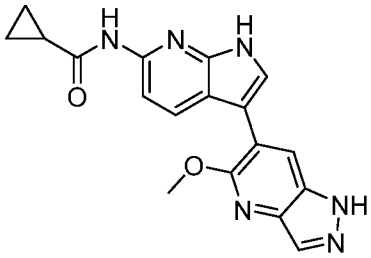

;

;

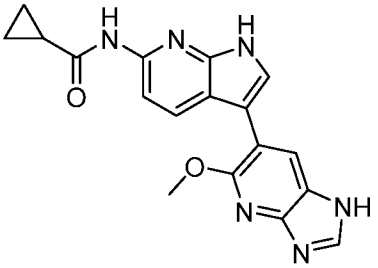
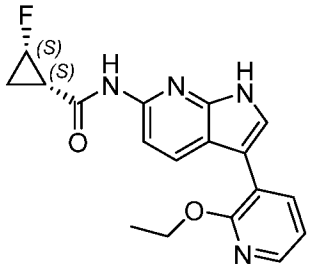

;

;

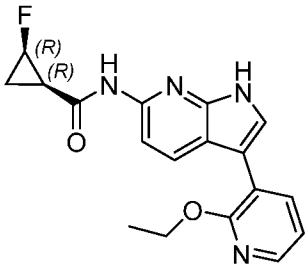
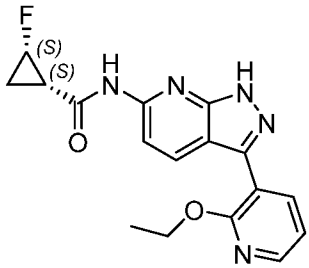

;

;

;

;

;

;

;

;

;

;

;

;

;

;

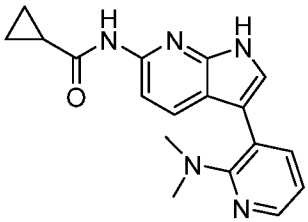
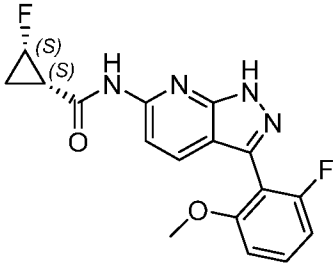

;

;

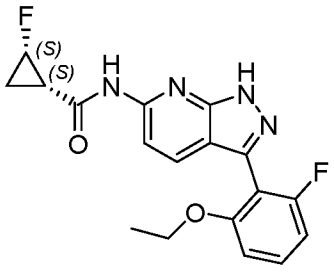
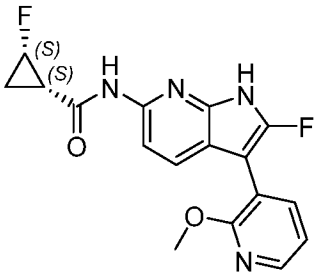

;

;

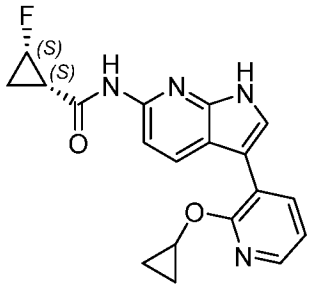
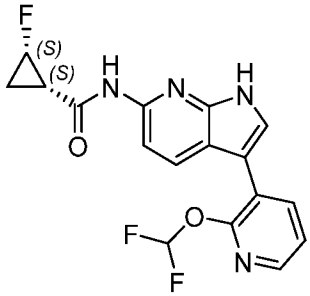

;

;

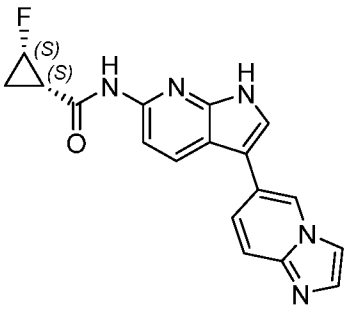
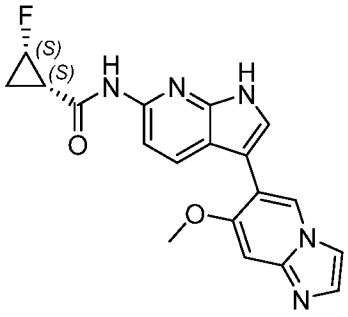

;

;

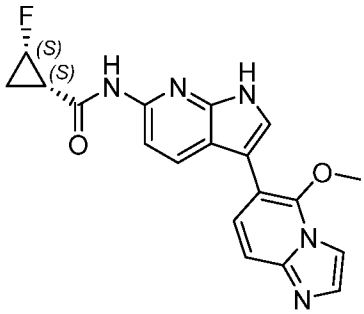
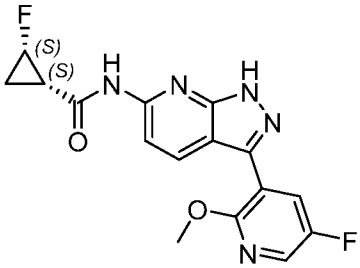

;

;

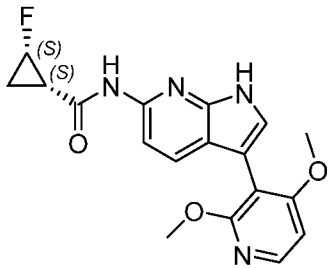
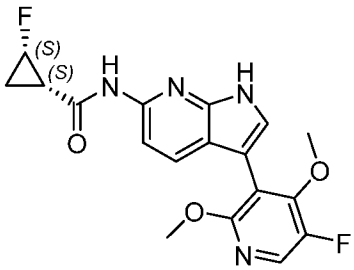

;

;

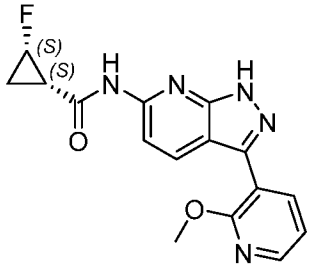
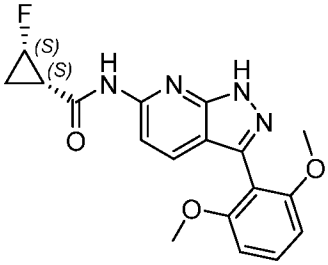

;

;

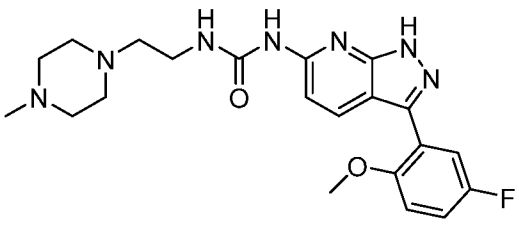
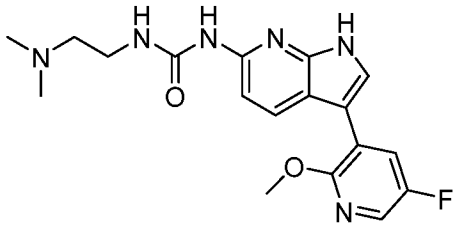

;

;

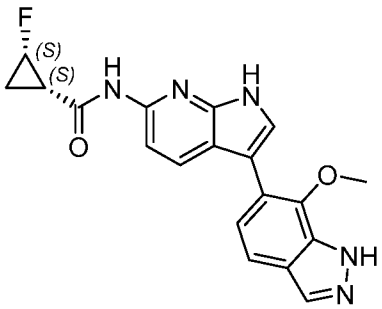
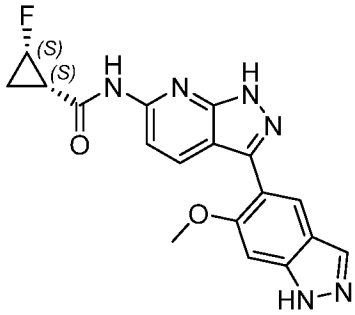

;

;

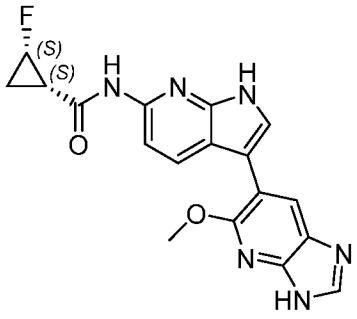
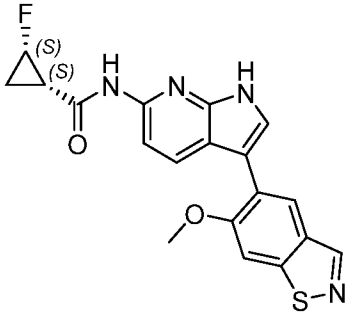

;

;

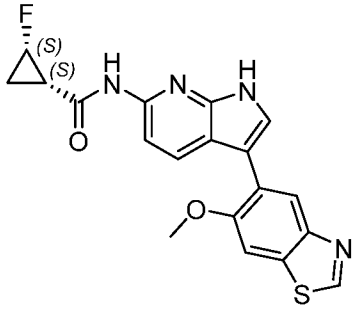
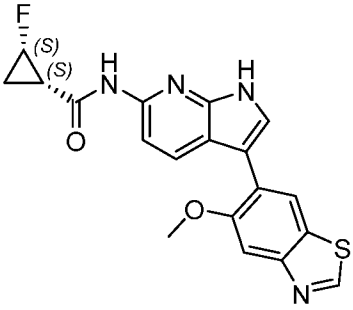

;

;

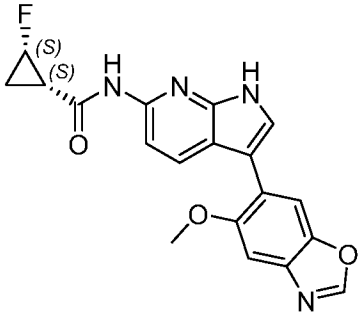
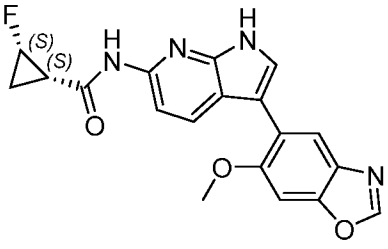

;

;

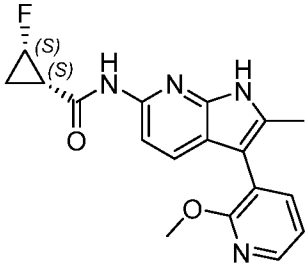
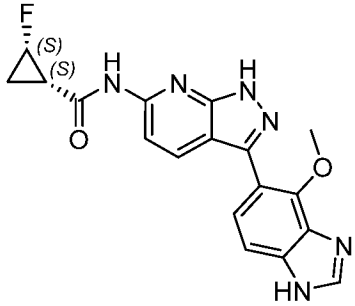

;

;

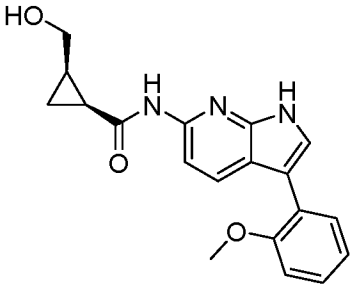
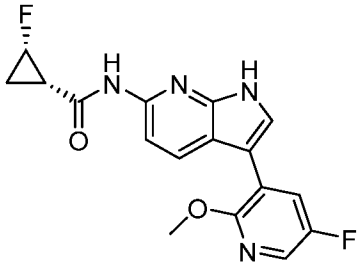

;

;

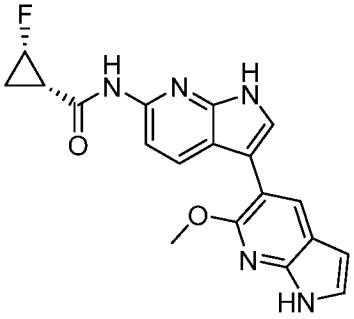
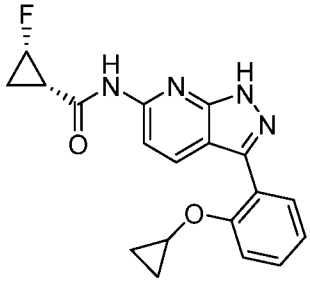

;

;

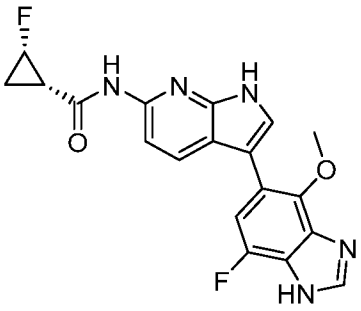
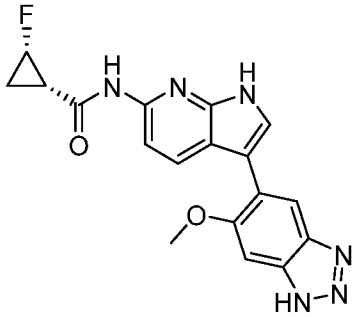

;

;

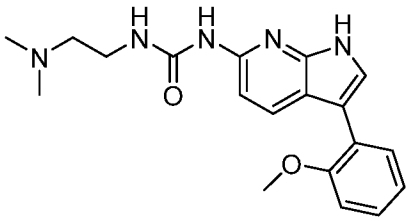
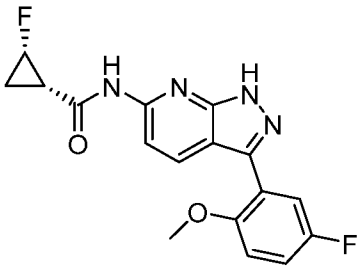

;

;

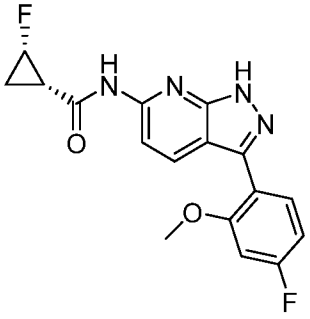
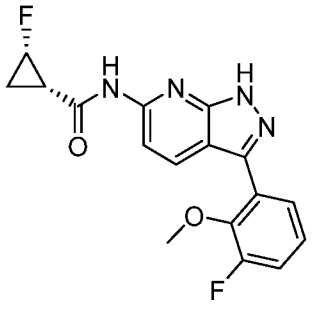

;

;

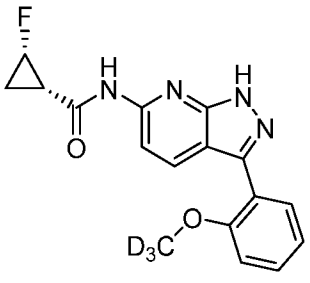
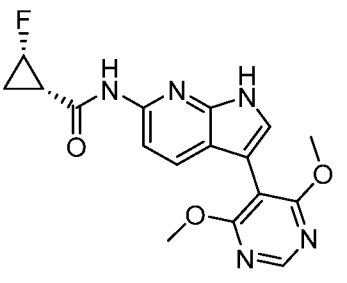

;

;

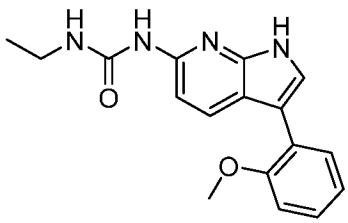
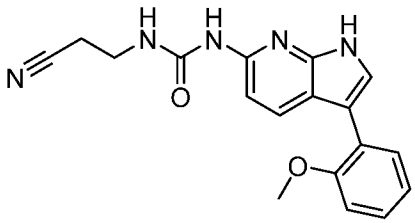
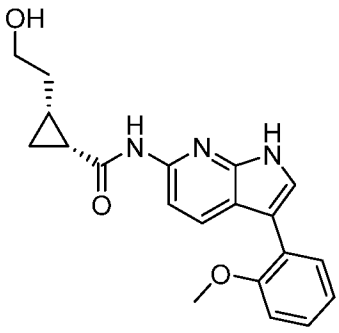
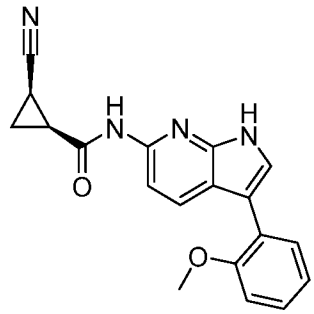
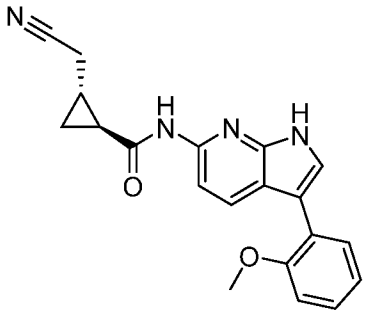
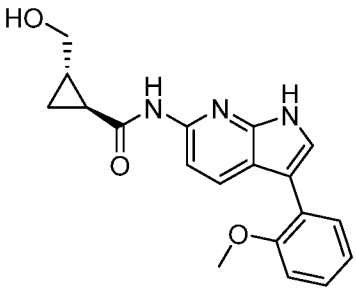
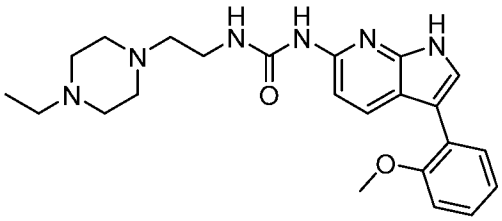
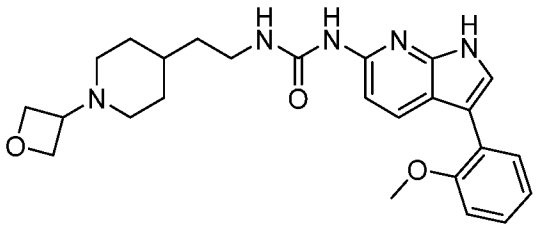
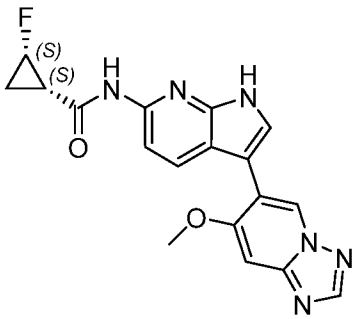
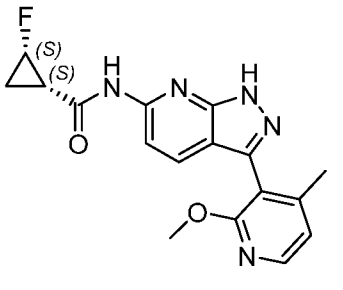
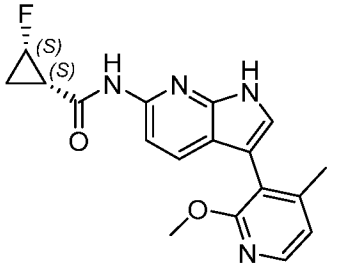
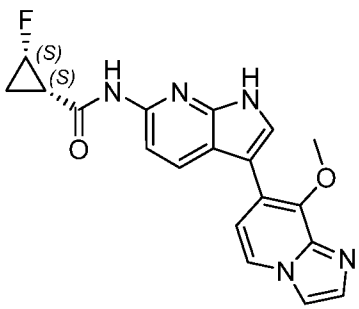

;

;

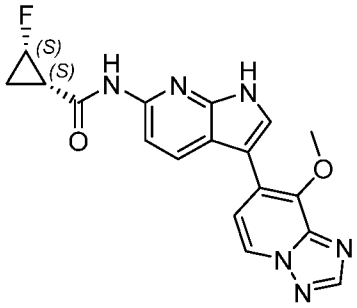
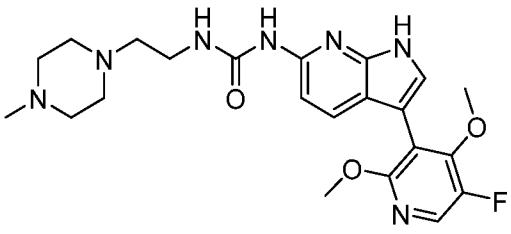
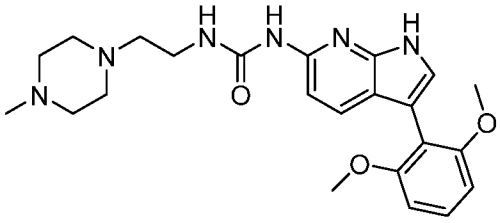
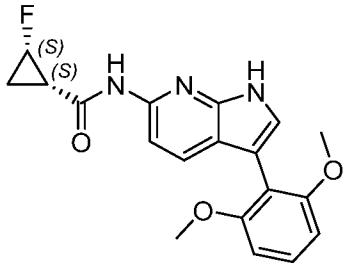
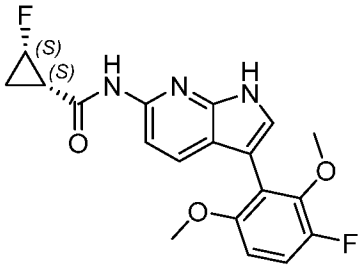
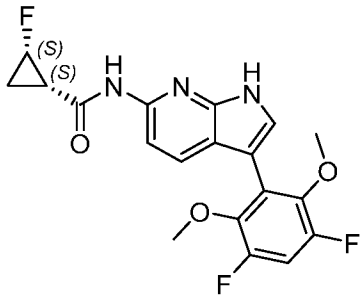
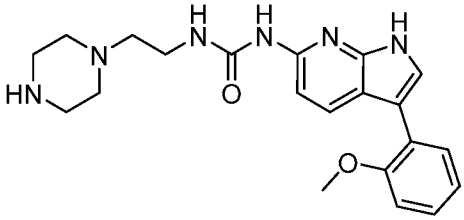
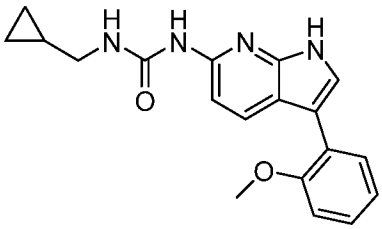
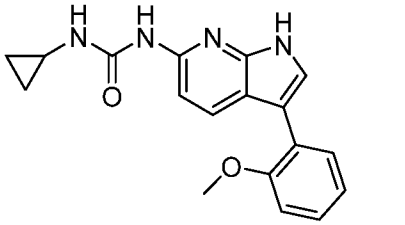
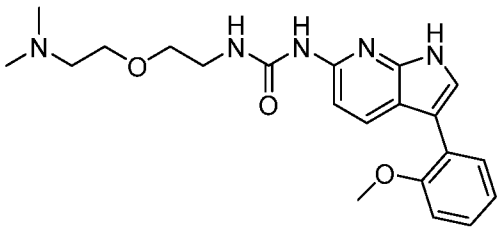
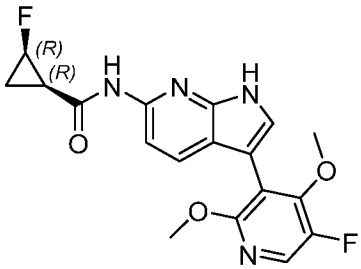
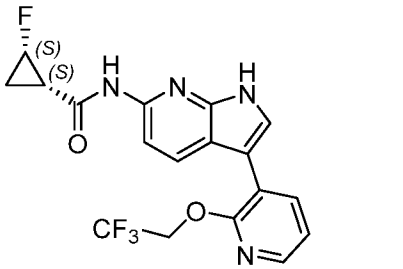

;

;

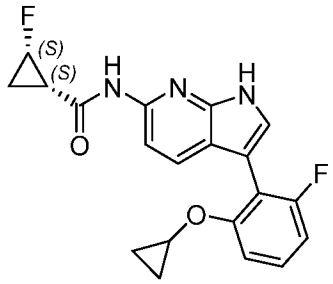
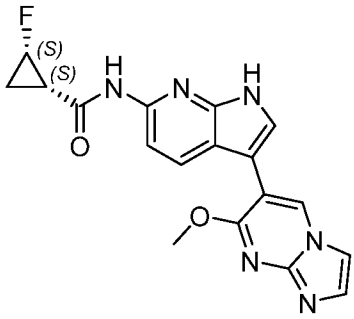
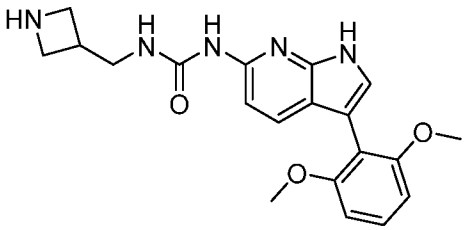
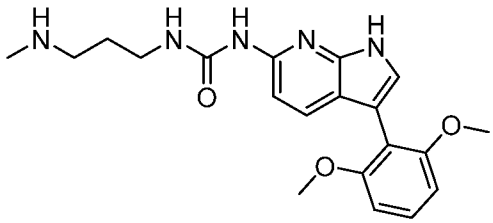
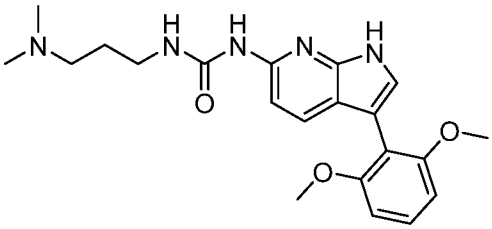
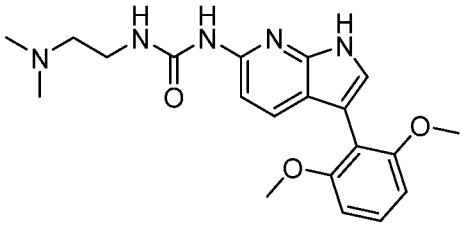
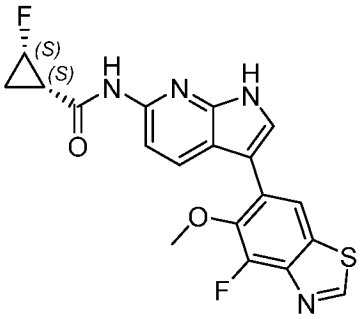
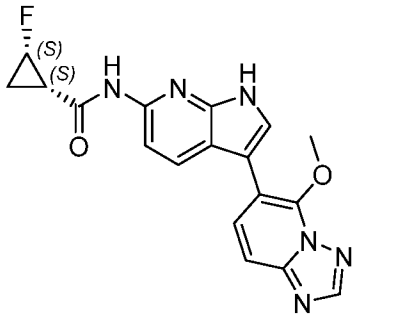
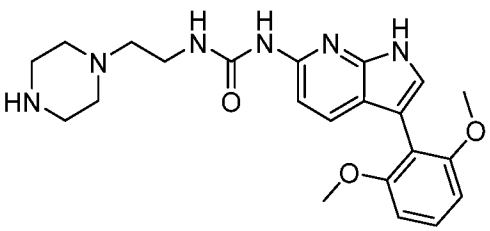
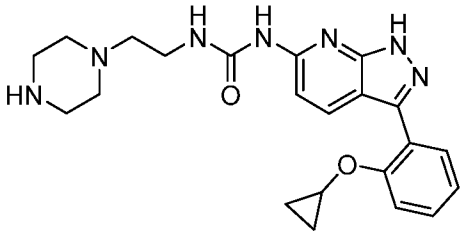
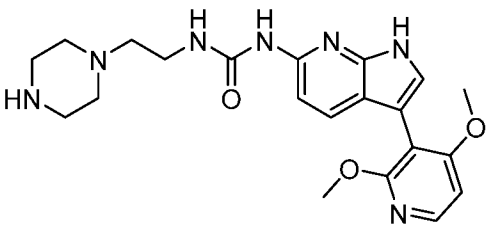
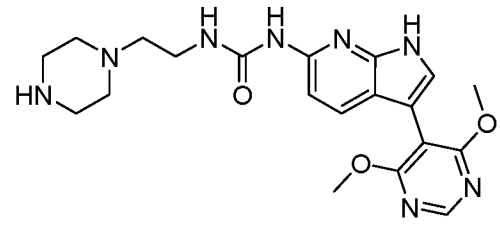
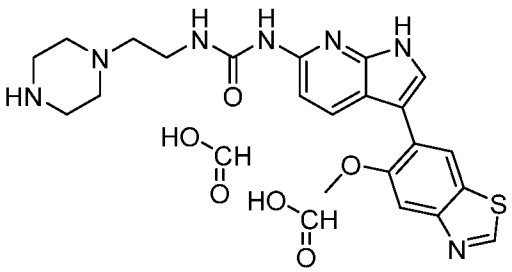
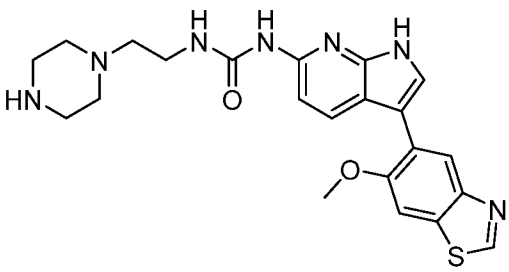

;

;

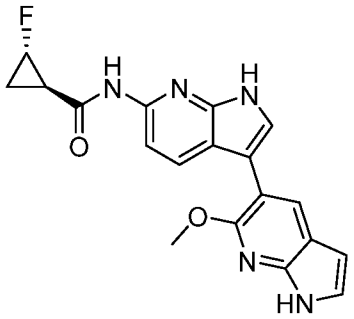
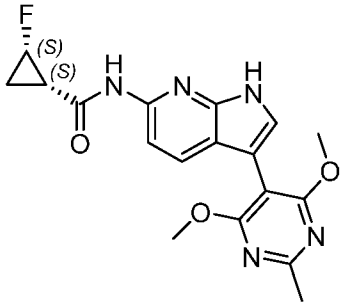
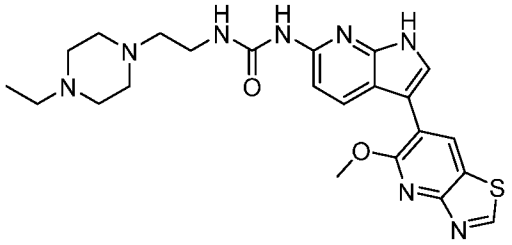
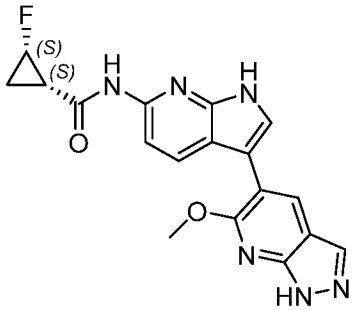
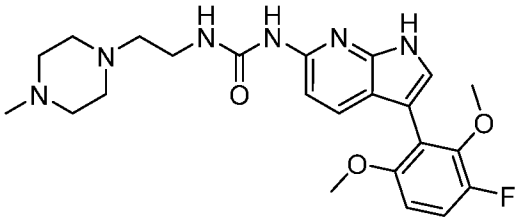
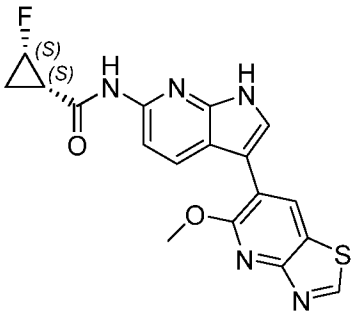
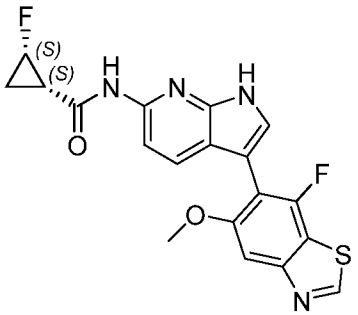
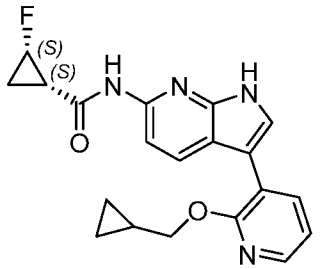
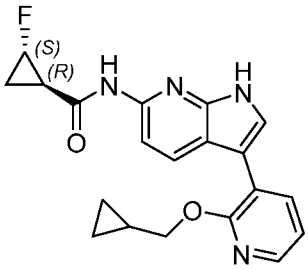
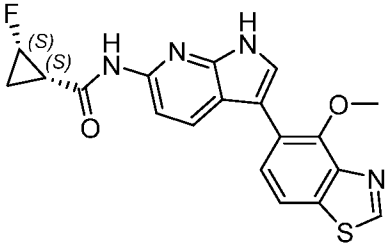
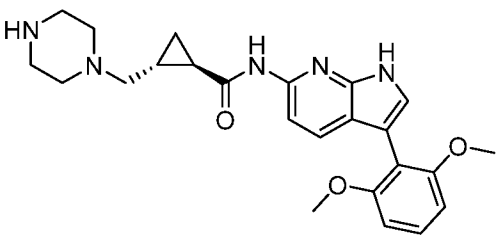
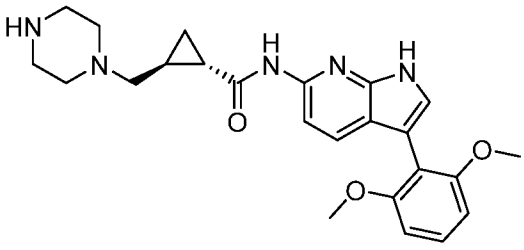

;

;

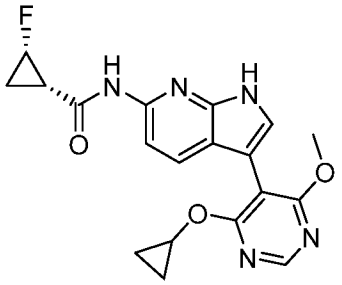
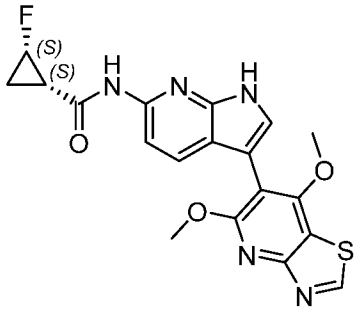

;

;

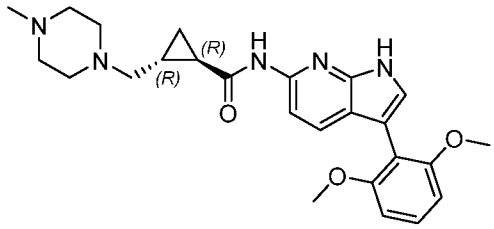
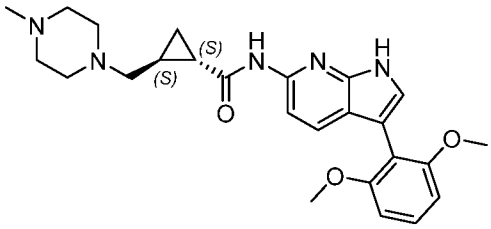

;

;

;

;

;

;

;

;

;

;

;

;

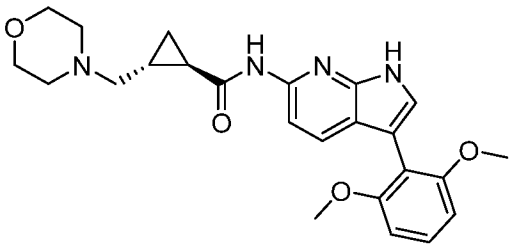
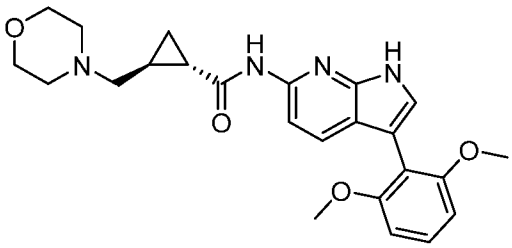

;

;

;

;

;

;

;

;

;

;

;

;

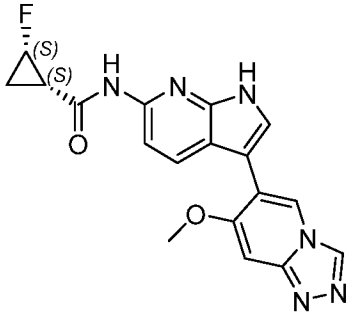
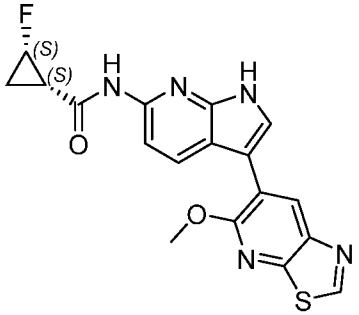

;

;

;

;

;

;

;

;

;

;

;

;

;

;

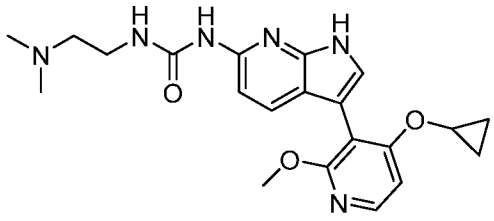
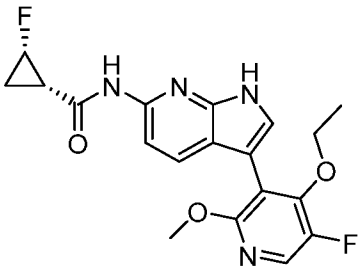

;

;

;

;

;

;

;

;

;

;

;

;

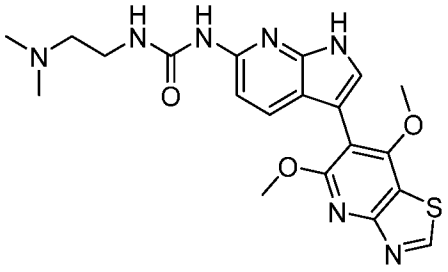
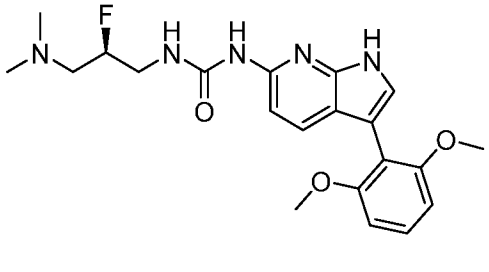

;

;

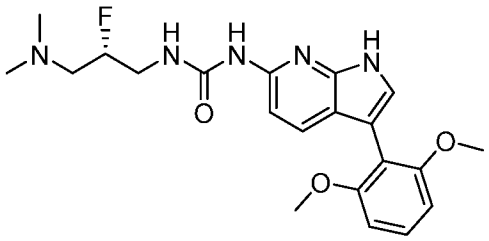
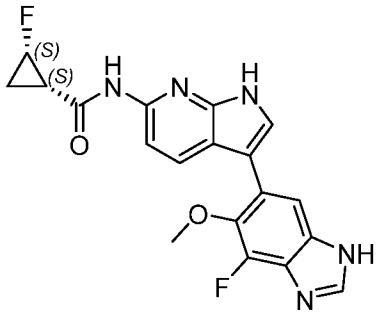
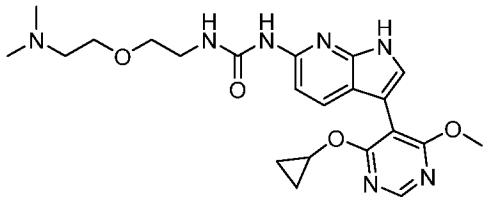
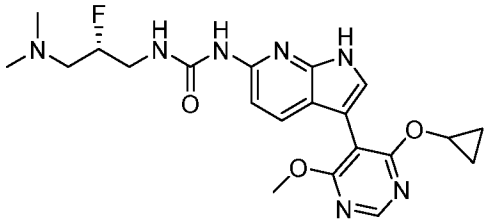
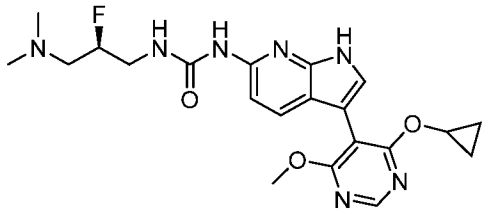
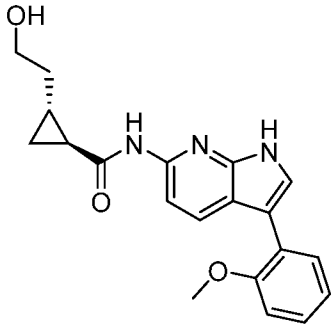
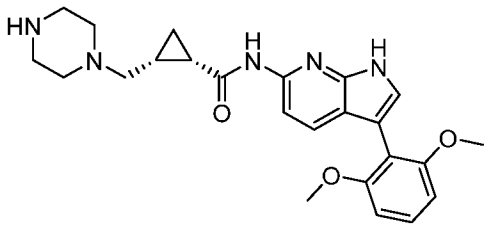
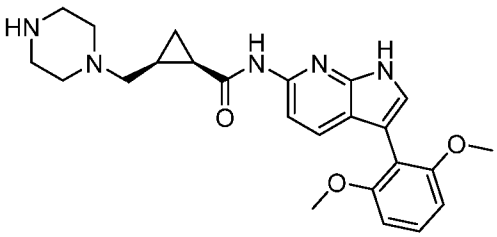
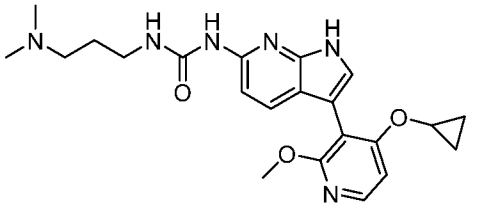
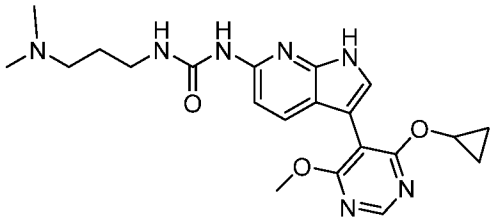
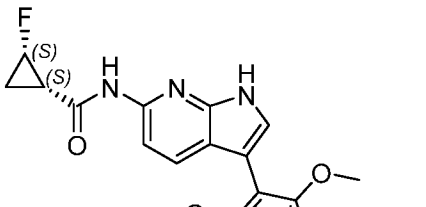
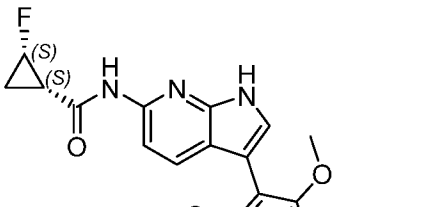
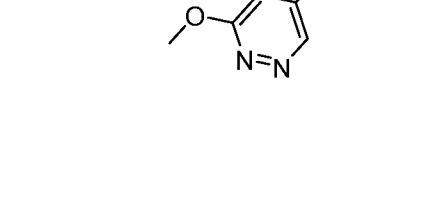
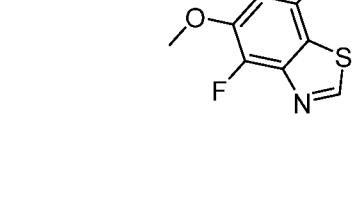

;

;

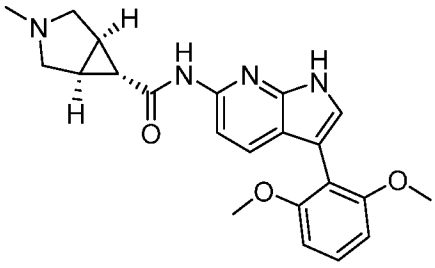
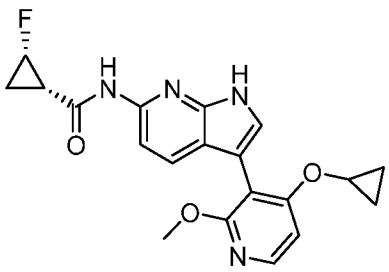
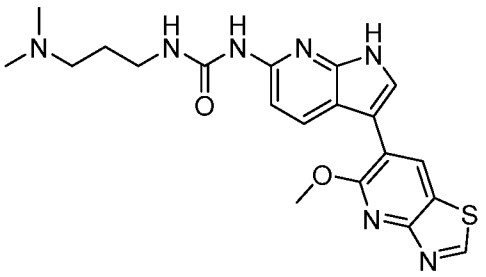
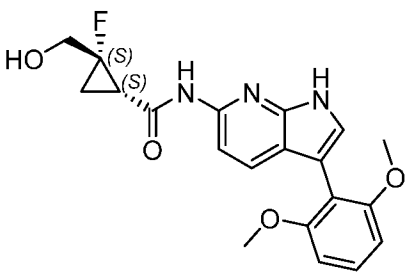
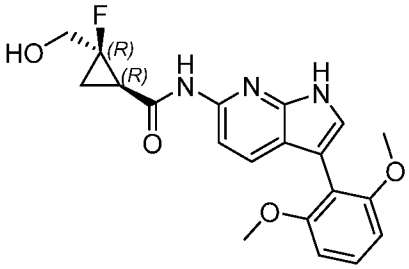
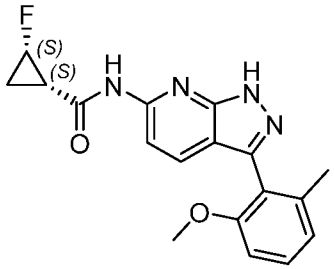
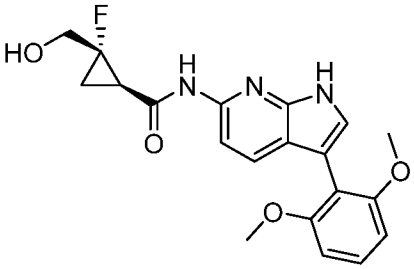
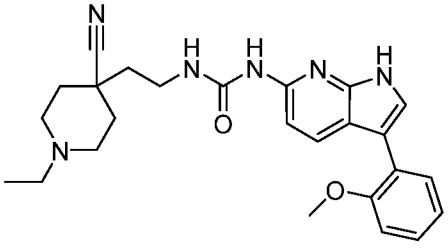
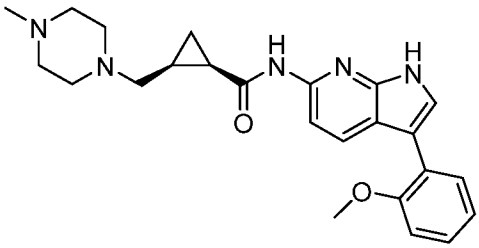
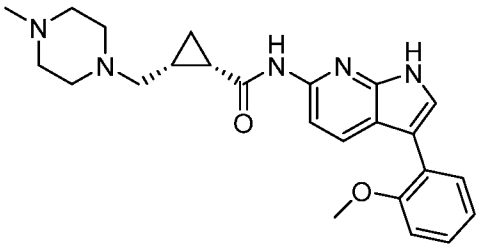
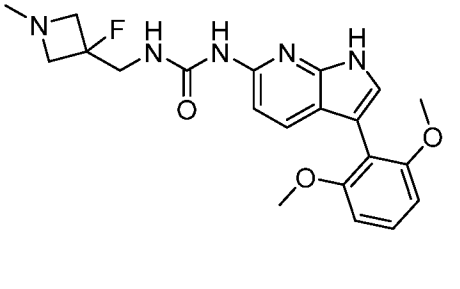

;

;


;

;


;

;


;

;

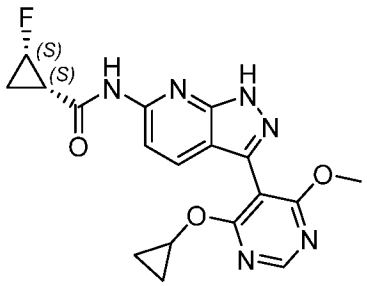
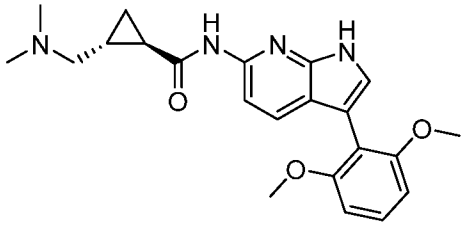
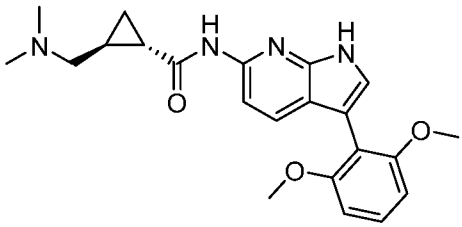
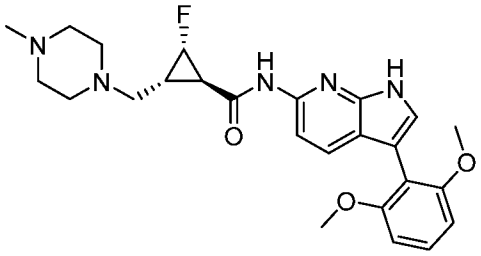
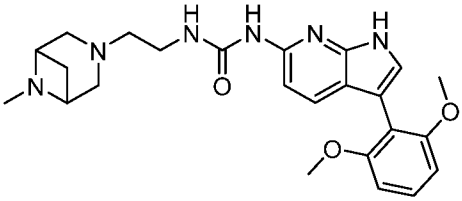
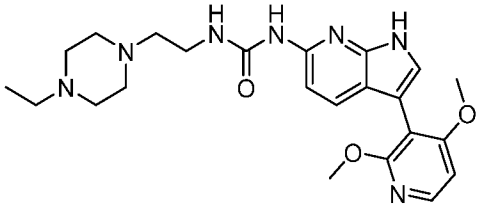
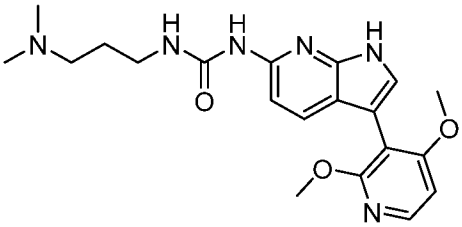
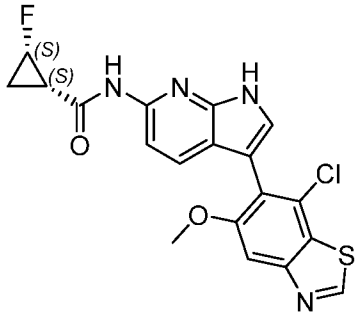
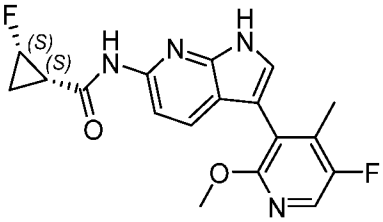
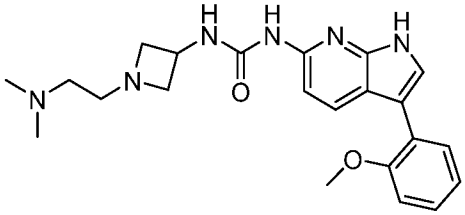
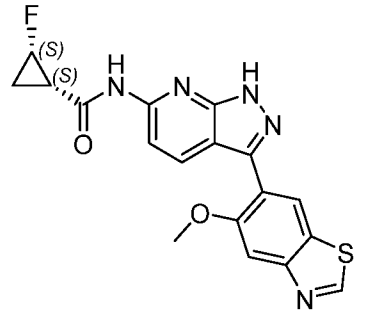
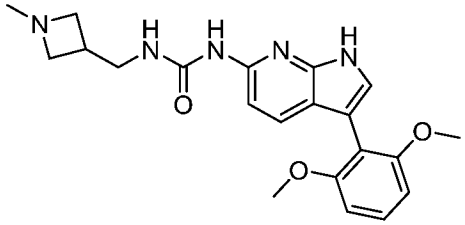
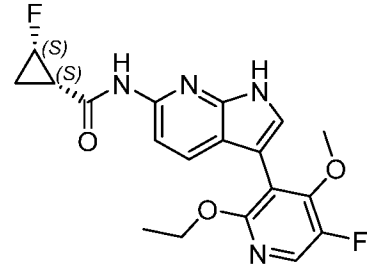
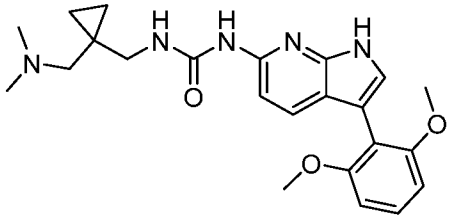

;

;

;

;

;

;

;

;

;

;

;

;

;

;

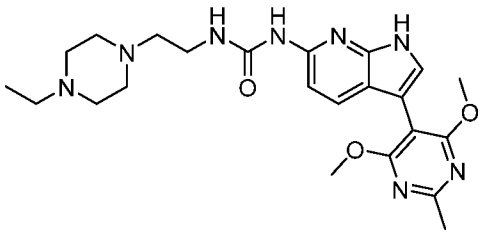
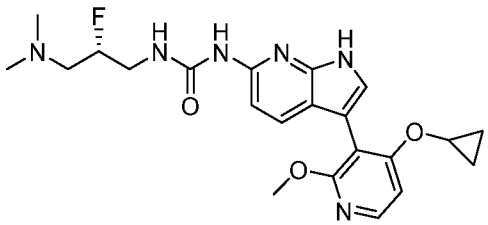
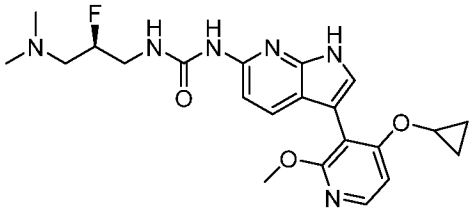
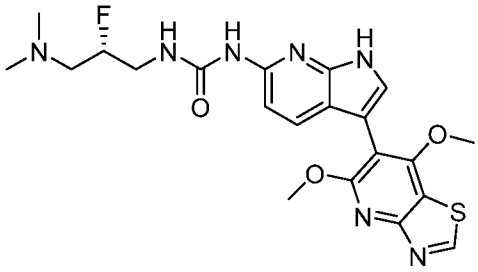
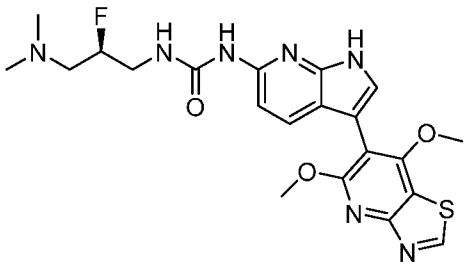
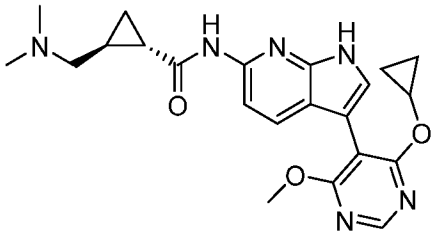
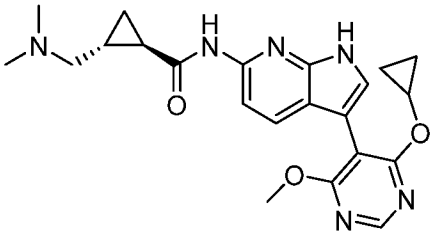
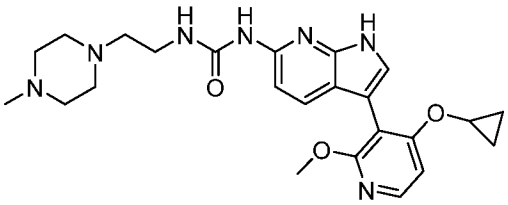
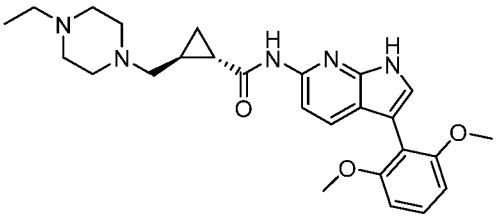
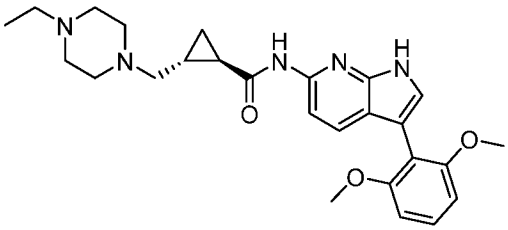
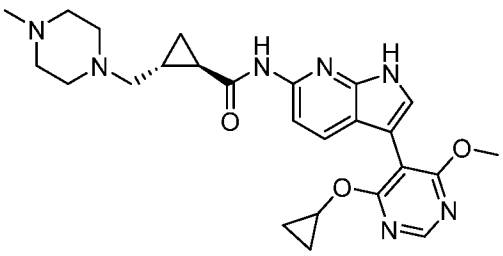
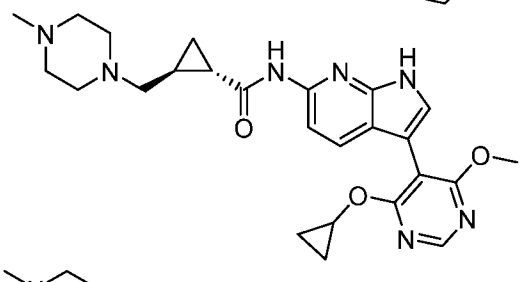
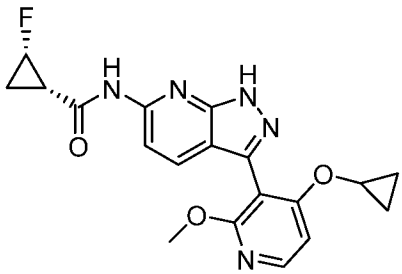
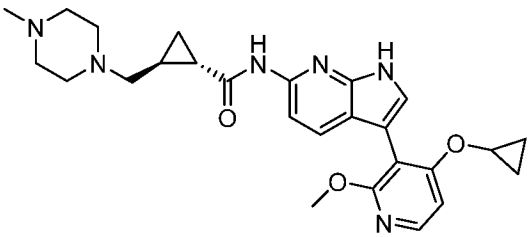

;

;

;

;

;

;

;

;

;

;

;

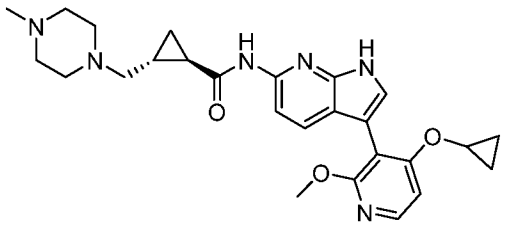
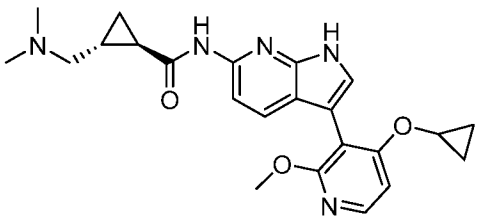
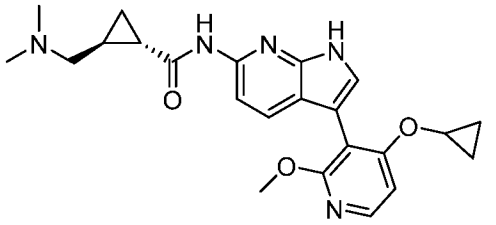
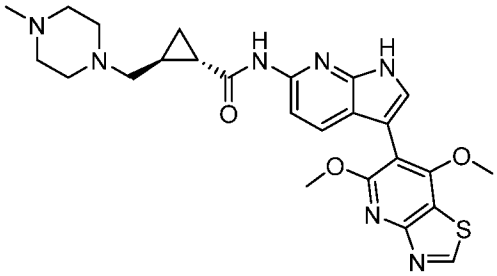
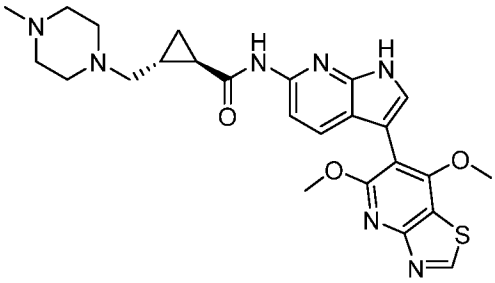
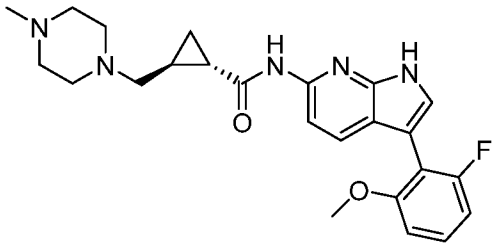
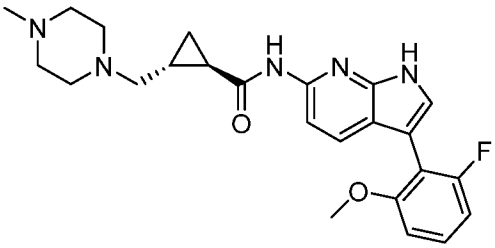
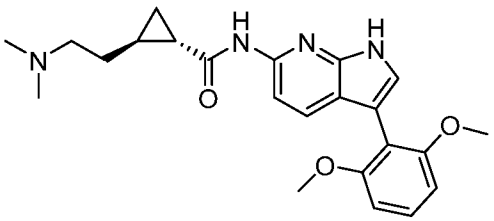
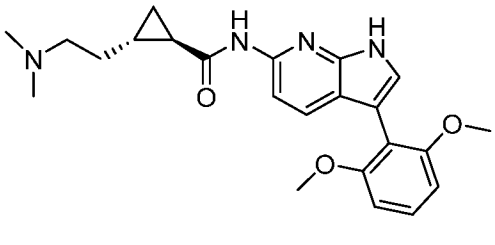
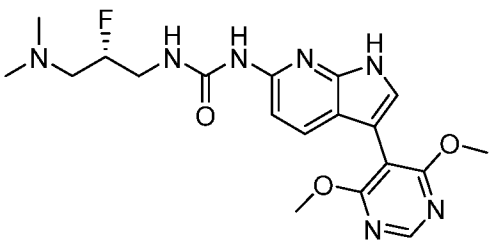
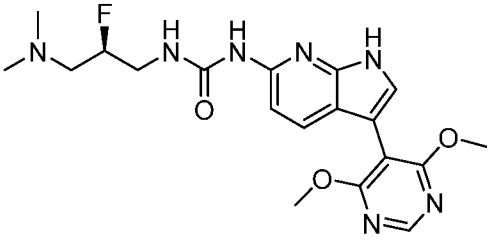
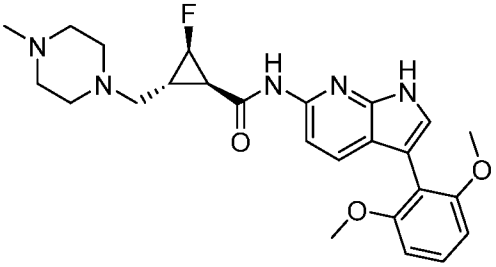
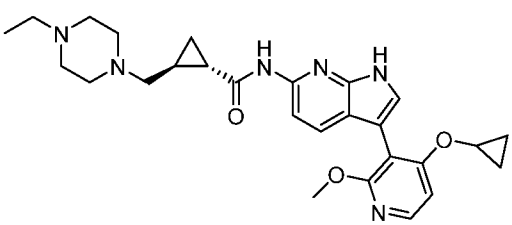
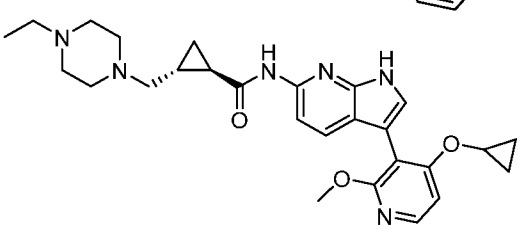
;

;

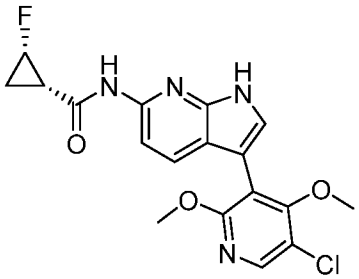
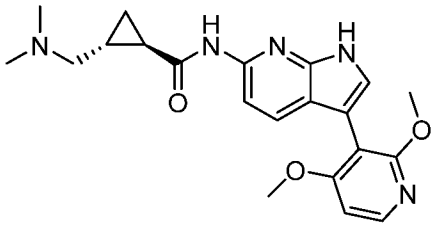
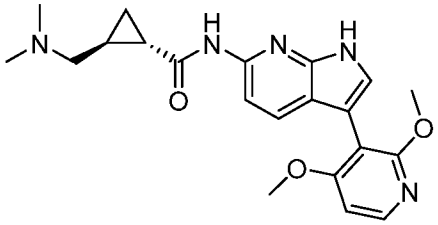
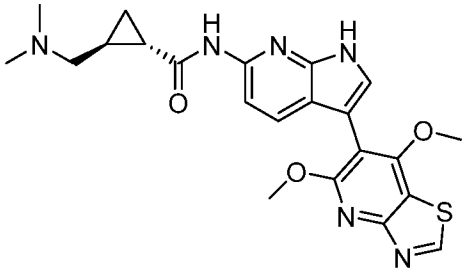
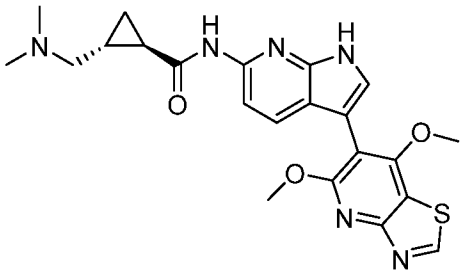
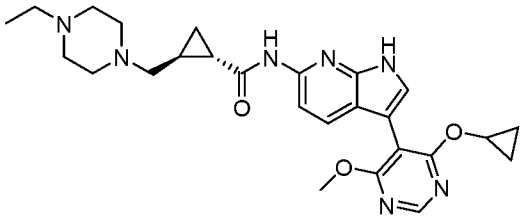
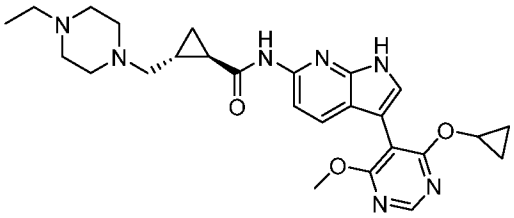
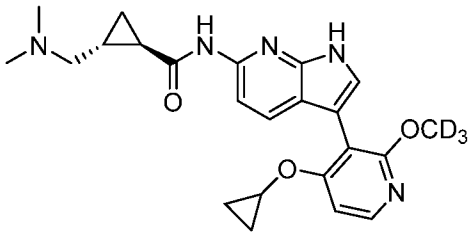
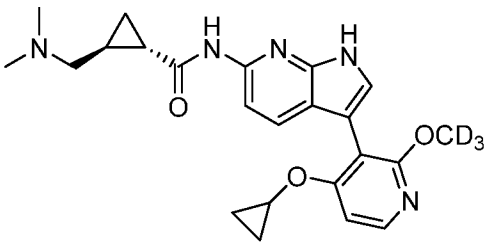
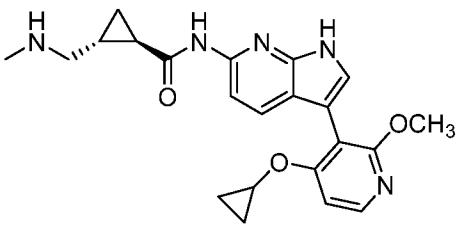
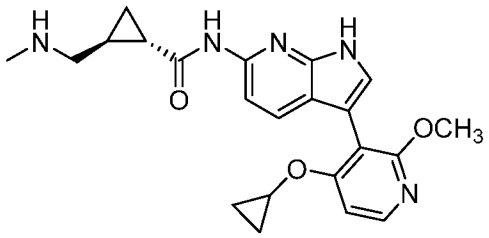
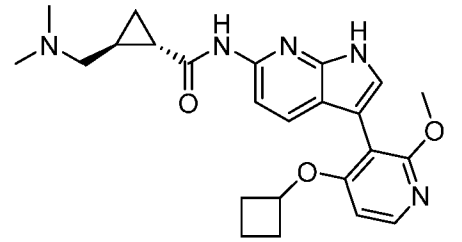
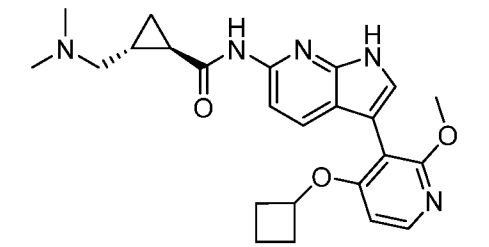
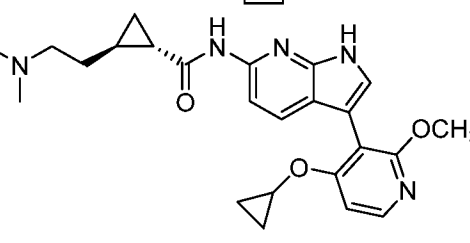
;


;

;

;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;


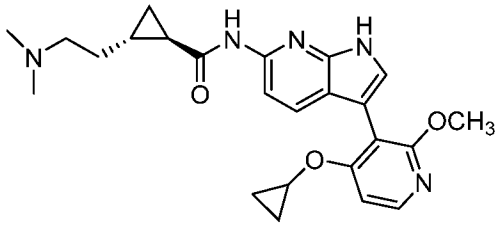
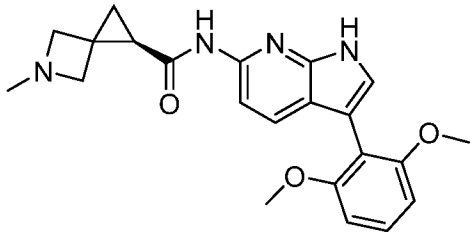
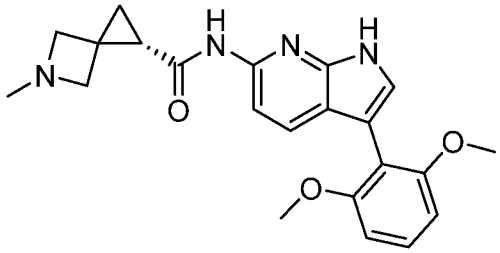
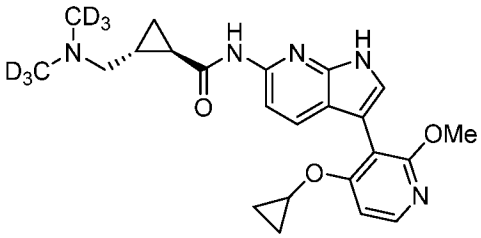
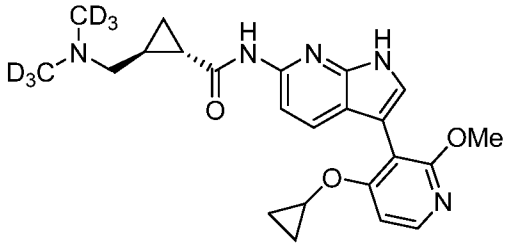
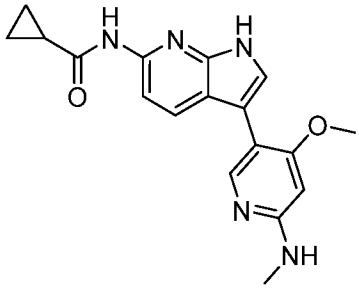
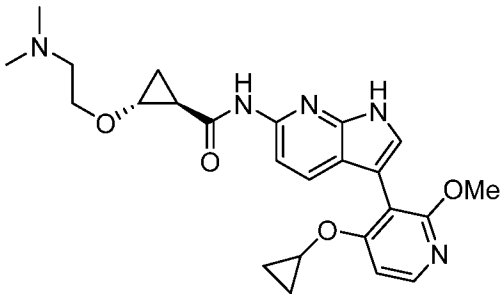
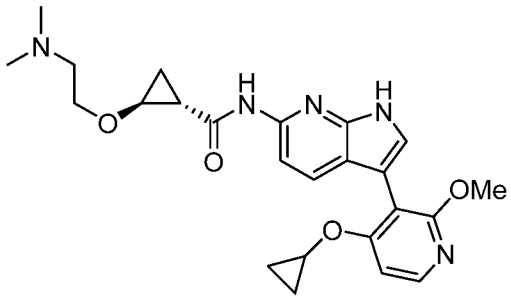
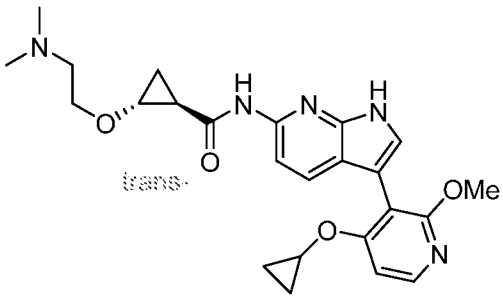
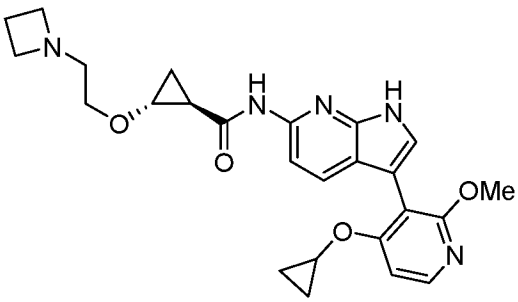
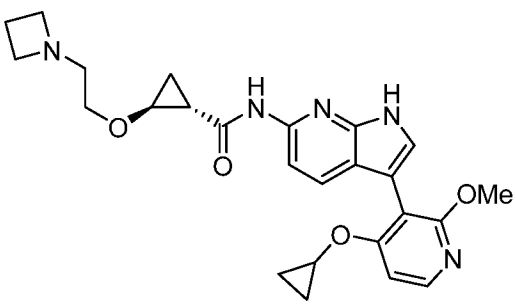
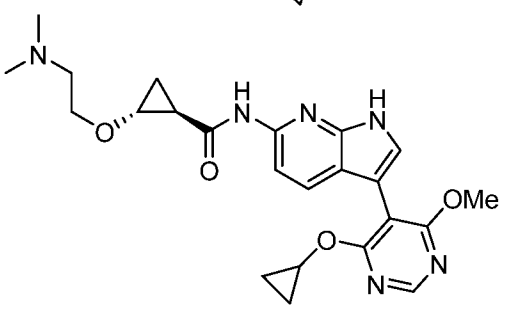

;

;

;

;

;

;

;

;

;

;

;

;

;

;

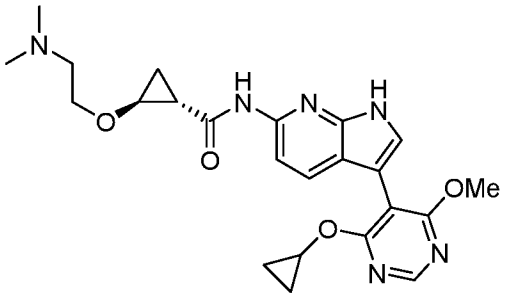
;



;

;

;

;

;

;

;

;

;

;

;

;

;

;

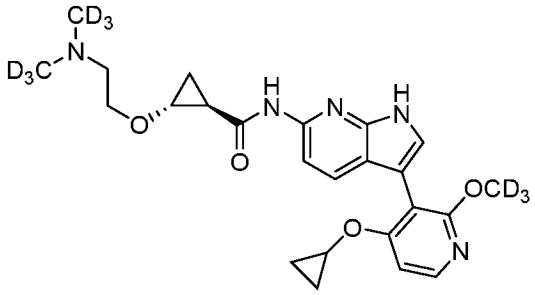
;

;


;

;

;

;

;

;

;

;

;

;

;

;

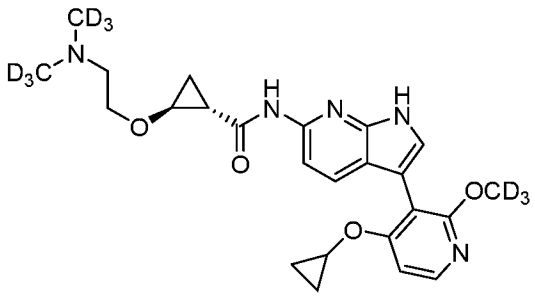


;



;

and



,

or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing.

[0021] In another aspect, provided herin is a pharmaceutical composition comprising a compound of formula (I) as described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0022] In yet another aspect, the present disclosure provides a method of inhibiting Bcr-Abl enzymatic activity in a cell, comprising exposing the cell with an effective amount of a compound of formula (I) as described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) as described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing.

[0023] In still yet another aspect, provided herein is a method of treating chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or a mixed phenotype acute leukemia, in a human in need thereof, comprising administering to the human a compound of formula (I) as described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) as described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing.

[0024] In some embodiments of the present aspect, the leukemia is refractory leukemia. In certain embodiments of the foregoing, the refractory leukemia is associated with a mutation in the Bcr-Abl tyrosine kinase gene resulting in specific amino acid substitutions selected from the group consisting of M244V, L248V, G250E, G250A, Q252H, Q252R, Y253F, Y253H, E255K, E255V, D276G, F311L, T315N, T315A, F317V, F317L, M343T, M351T, E355G, F359A, F359V, V379I, F382L, L387M, H396P, H396R, S417Y, E459K, F486S, and T315I. In still further embodiments of the foregoing, the refractory leukeumia is associated with a mutation in the Bcr-Abl tyrosine kinase gene resulting in specific amino acid substitution T315I. In yet other embodiments, which may be combined with any preceding embodiments of the present aspect, the method further comprises administering one or more pharmaceutical agents including including anti-microtubular therapies, topoisomerase inhibitors, alkylating agents, nucleotide synthesis inhibitors, DNA synthesis inhibtiors, protein synthesis inhibitors, developmental signaling pathway inhibitors, pro-apoptotic agents, Abl myristoyl-pocket binding inhibitors, MEK1/2 inhibitors, AKT inhibitors, PI3K inhibitors and/or radiation.

DETAILED DESCRIPTION

[0025] The following description sets forth exemplary methods, parameters, and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

I. Definitions

[0026] As used herein, the following definitions shall apply unless otherwise indicated. Further, if any term or symbol used herein is not defined as set forth below, it shall have its ordinary meaning in the art.

[0027] The term “excipient” as used herein means an inert or inactive substance that may be used in the production of a drug or pharmaceutical, such as a tablet containing a compound of the present disclosure as an active ingredient. Various substances may be embraced by the term excipient, including without limitation any substance used as a binder, disintegrant, coating, compression/encapsulation aid, cream or lotion, lubricant, solutions for parenteral administration, materials for chewable tablets, sweetener or flavoring, suspending/gelling agent, or wet granulation agent. Binders include, e.g., carbomers,

povidone, xanthan gum, etc.; coatings include, e.g., cellulose acetate phthalate, ethylcellulose, gellan gum, maltodextrin, enteric coatings, etc.; compression/encapsulation aids include, e.g., calcium carbonate, dextrose, fructose dc (dc = "directly compressible"), honey dc, lactose (anhydrate or monohydrate; optionally in combination with aspartame, cellulose, or microcrystalline cellulose), starch dc, sucrose, etc.; disintegrants include, e.g., croscarmellose sodium, gellan gum, sodium starch glycolate, etc.; creams or lotions include, e.g., maltodextrin, carrageenans, etc.; lubricants include, e.g., magnesium stearate, stearic acid, sodium stearyl fumarate, etc.; materials for chewable tablets include, e.g., dextrose, fructose dc, lactose (monohydrate, optionally in combination with aspartame or cellulose), etc.; suspending/gelling agents include, e.g., carrageenan, sodium starch glycolate, xanthan gum, etc.; sweeteners include, e.g., aspartame, dextrose, fructose dc, sorbitol, sucrose dc, etc.; and wet granulation agents include, e.g., calcium carbonate, maltodextrin, microcrystalline cellulose, etc.

[0028] The terms "individual", "subject" and "patient" refer to mammals and includes humans and non-human mammals. Examples of patients include, but are not limited to, mice, rats, hamsters, guinea pigs, pigs, rabbits, cats, dogs, goats, sheep, cows, and humans. In some embodiments, patient refers to a human.

[0029] As used herein, the term "mammal" includes, but is not limited to, humans, mice, rats, guinea pigs, monkeys, dogs, cats, horses, cows, pigs, and sheep.

[0030] "Pharmaceutically acceptable" refers to safe and non-toxic, and suitable for in vivo or for human administration.

[0031] As used herein, the term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon radical, having the number of carbon atoms designated (*e.g.*, C_1-C_6 means one to six carbons). Examples of alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, iso-butyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. In some embodiments, the term "alkyl" may encompass C_1-C_6 alkyl, C_2-C_6 alkyl, C_3-C_6 alkyl, C_4-C_6 alkyl, C_5-C_6 alkyl, C_1-C_5 alkyl, C_2-C_5 alkyl, C_3-C_5 alkyl, C_4-C_5 alkyl, C_1-C_4 alkyl, C_2-C_4 alkyl, C_3-C_4 alkyl, C_1-C_3 alkyl, C_2-C_3 alkyl, or C_1-C_2 alkyl.

[0032] The term "cycloalkyl," "carbocyclic," or "carbocycle" refers to hydrocarbon rings having the indicated number of ring atoms (*e.g.*, C_3-C_6 cycloalkyl means 3-6 carbons) and

being fully saturated or having no more than one double bond between ring vertices. As used herein, "cycloalkyl," "carbocyclic," or "carbocycle" is also meant to refer to bicyclic, polycyclic and spirocyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, pinane, bicyclo[2.2.2]octane, adamantane, norborene, spirocyclic C_{5-12} alkane, etc. In some embodiments, "cycloalkyl" encompasses C_3-C_7 cycloalkyl, C_4-C_7 cycloalkyl, C_5-C_7 cycloalkyl, C_5-C_7 cycloalkyl, C_3-C_6 cycloalkyl, C_4-C_6 cycloalkyl, C_5-C_6 cycloalkyl, C_3-C_5 cycloalkyl, C_4-C_5 cycloalkyl, or C_3-C_4 cycloalkyl. In addition, one ring of a polycyclic cycloalkyl group may be aromatic, provided the polycyclic cycloalkyl group is bound to the parent structure via a non-aromatic carbon. For example, a 1,2,3,4-tetrahydronaphthalen-1-yl group (wherein the moiety is bound to the parent structure via a non-aromatic carbon atom) is a cycloalkyl group, while 1,2,3,4-tetrahydronaphthalen-5-yl (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is not considered a cycloalkyl group.

[0033] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain hydrocarbon radical, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms can optionally be oxidized and the nitrogen heteroatom can optionally be quaternized. The heteroatom(s) O, N and S can be placed at any interior position of the heteroalkyl group. The heteroatom Si can be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. A "heteroalkyl" can contain up to three units of unsaturation, and also include mono- and poly-halogenated variants, or combinations thereof. Examples include $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-O-CF_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, and $-CH=CH=N(CH_3)-CH_3$. Up to two heteroatoms can be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$.

[0034] The term "heterocycloalkyl," "heterocyclic," or "heterocycle" refers to a cycloalkyl radical group having the indicated number of ring atoms (*e.g.*, 5-6 membered heterocycloalkyl) that contain from one to five heteroatoms selected from the group consisting of N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, nitrogen atom(s) are optionally quaternized, as ring atoms. Unless otherwise stated, a "heterocycloalkyl," "heterocyclic," or "heterocycle" ring can be a monocyclic, a bicyclic, bridged or fused ring system, spirocyclic or a polycylic ring system. Non-limiting examples of "heterocycloalkyl," "heterocyclic," or "heterocycle" rings include pyrrolidine, piperidine,

N-methylpiperidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, hydantoin, dioxolane, phthalimide, piperidine, pyrimidine-2,4(1H,3H)-dione, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine-5-oxide, thiomorpholine-S,S-oxide, piperazine, pyran, pyridone, 3-pyrroline, thiopyran, pyrone, tetrahydrofuran, tetrhydrothiophene, quinuclidine, tropane and the like. A "heterocycloalkyl," "heterocyclic," or "heterocycle" group can be attached to the remainder of the molecule through one or more ring carbons or heteroatoms. In some embodiments, "heterocycloalkyl" encompasses 3- to 10-membered heterocycloalkyl, 4- to 10-membered heterocycloalkyl, 5- to 10-membered heterocycloalkyl, 6- to 10-membered heterocycloalkyl, 7- to 10-membered heterocycloalkyl, 8- to 10-membered heterocycloalkyl, 9- to 10-membered heterocycloalkyl, 3- to 9-membered heterocycloalkyl, 4- to 9-membered heterocycloalkyl, 5- to 9-membered heterocycloalkyl, 6- to 9-membered heterocycloalkyl, 7- to 9-membered heterocycloalkyl, 8- to 9-membered heterocycloalkyl, 3- to 8-membered heterocycloalkyl, 4- to 8-membered heterocycloalkyl, 5- to 8-membered heterocycloalkyl, 6- to 8-membered heterocycloalkyl, 7- to 8-membered heterocycloalkyl, 3- to 7-membered heterocycloalkyl, 4- to 7-membered heterocycloalkyl, 5- to 7-membered heterocycloalkyl, 6- to 7-membered heterocycloalkyl, 3- to 6-membered heterocycloalkyl, 4- to 6-membered heterocycloalkyl, 5- to 6-membered heterocycloalkyl, 3- to 5-membered heterocycloalkyl, 4- to 5-membered heterocycloalkyl, or 3- to 4-membered heterocycloalkyl. In other embodiments, "heterocycloalkyl" may be characterized by the number of carbon atoms in the ring, provided that the ring contains at least one heteroatom. For example, in some embodiments, "heterocycloalkyl" encompasses C_3-C_9 heterocycloalkyl, C_3-C_8 heterocycloalkyl, C_3-C_7 heterocycloalkyl, C_3-C_6 heterocycloalkyl, C_3-C_5 heterocycloalkyl, C_3-C_4 heterocycloalkyl, C_4-C_9 heterocycloalkyl, C_4-C_8 heterocycloalkyl, C_4-C_7 heterocycloalkyl, C_4-C_6 heterocycloalkyl, C_4-C_5 heterocycloalkyl, C_5-C_9 heterocycloalkyl, C_5-C_8 heterocycloalkyl, C_5-C_7 heterocycloalkyl, C_5-C_6 heterocycloalkyl, C_6-C_9 heterocycloalkyl, C_6-C_8 heterocycloalkyl, C_6-C_7 heterocycloalkyl, C_7-C_9 heterocycloalkyl, C_7-C_8 heterocycloalkyl, or C_8-C_9 heterocycloalkyl. It should be recognized that "heterocycloalkyl" as described by the number of ring atoms may also be described by number of carbon atoms in the ring. For example, a piperazinyl ring may be described as a C_4 heterocycloalkyl ring or a 6-membered heterocycloalkyl ring; an azetidinyl or oxetanyl ring may each be described as a C_3 heterocycloalkyl ring or a 4-membered heterocycloalkyl ring.

[0035] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by -$CH_2CH_2CH_2CH_2$-. Typically, an alkyl (or

alkylene) group will have from 1 to 24 carbon atoms. In some embodiments, an alkyl (or alkylene) group will have 10 or fewer carbon atoms.

[0036] The term "heteroalkylene" by itself or as part of another substituent means a divalent radical, saturated or unsaturated or polyunsaturated, derived from heteroalkyl, as exemplified by $-CH_2-CH_2-S-CH_2CH_2-$, $-CH_2-S-CH_2-CH_2-NH-CH_2-$, $-O-CH_2-CH=CH-$, $-CH_2-CH=C(H)CH_2-O-CH_2-$ and $-S-CH_2-C\equiv C-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like).

[0037] The term "heterocycloalkylene" by itself or as part of another substituent means a divalent radical, saturated or unsaturated or polyunsaturated, derived from heterocycloalkyl. For heterocycloalkylene groups, heteroatoms can also occupy either or both of the chain termini.

[0038] The terms "alkoxy" and "alkylamino" are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom or an amino group, respectively.

[0039] The term "heterocycloalkoxy" refers to a heterocycloalkyl-O- group in which the heterocycloalkyl group is as previously described herein.

[0040] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "C_1-C_4 haloalkyl" is mean to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, difluoromethyl, and the like.

[0041] The term "haloalkyl-OH" refers to a haloalkyl group as described above which is also substituted by one or more hydroxyl groups. The term "haloalkyl-OH" is meant to include haloalkyl substituted by one hydroxyl group, as well as haloalkyl substituted by multiple hydroxyl groups. For example, the term "haloalkyl-OH" includes $-CH(F)OH$, $-CH_2CFHCH_2OH$, $-CH(OH)CF_3$, and the like.

[0042] The term "alkyl-OH" refers to an alkyl substituted by one or more hydroxyl groups. The term "alkyl-OH" is meant to include alkyl substituted by one hydroxyl group, as

well as alkyl substituted by multiple hydroxyl groups. For example, the term "alkyl-OH" includes -CH_2OH, -$CH(OH)CH_3$, -CH_2CH_2OH, -$C(CH_3)_2OH$, and the like.

[0043] The term "alkyl-CN" refers to an alkyl substituted by one or more cyano groups. The term "alkyl-CN" is meant to include alkyl substituted by one cyano group, as well as alkyl substituted by multiple cyano groups. For example, the term "alkyl-CN" includes -CH_2CN, -CH_2CH_2CN, -$CH(CN)CH_3$, and the like.

[0044] The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon group, which can be a single ring or multiple rings (up to three rings) which are fused together. In some embodiments, "aryl" encompasses C_6-C_{14} aryl, C_8-C_{14} aryl, C_{10}-C_{14} aryl, C_{12}-C_{14} aryl, C_6-C_{12} aryl, C_8-C_{12} aryl, C_{10}-C_{12} aryl, C_6-C_{10} aryl, C_8-C_{10} aryl, or C_6-C_8 aryl. In some embodiments, both rings of a polycyclic aryl group are aromatic (e.g., naphthyl). In other embodiments, polycyclic aryl groups may include a non-aromatic ring fused to an aromatic ring, provided the polycyclic aryl group is bound to the parent structure via an atom in the aromatic ring. Thus, in some embodiments, a 1,2,3,4-tetrahydronaphthalen-5-yl group (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is considered an aryl group, while 1,2,3,4-tetrahydronaphthalen-1-yl (wherein the moiety is bound to the parent structure via a non-aromatic carbon atom) is not considered an aryl group. Similarly, in some embodiments, a 1,2,3,4-tetrahydroquinolin-8-yl group (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is considered an aryl group, while 1,2,3,4-tetrahydroquinolin-1-yl group (wherein the moiety is bound to the parent structure via a non-aromatic nitrogen atom) is not considered an aryl group. However, the term "aryl" does not encompass or overlap with "heteroaryl," as defined herein, regardless of the point of attachment (e.g., both quinolin-5-yl and quinolin-2-yl are heteroaryl groups). In some embodiments, aryl is phenyl or naphthyl. In certain embodiments, aryl is phenyl.

[0045] The term "heteroaryl" refers to aryl groups (or rings) that contain from one to five heteroatoms selected from the group consisting of N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a carbon atom or a heteroatom as valency permits. In some embodiments, both rings of a polycyclic heteroaryl group are aromatic. In other embodiments, polycyclic heteroaryl groups may include a non-aromatic ring (e.g., cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl) fused to a

heteroaryl ring, provided the polycyclic heteroaryl group is bound to the parent structure via an atom in the aromatic ring. For example, in some embodiments, a 4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl group (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is considered a heteroaryl group, while 4,5,6,7-tetrahydrobenzo[d]thiazol-5-yl (wherein the moiety is bound to the parent structure via a non-aromatic carbon atom) is not considered a heteroaryl group.

[0046] Non-limiting examples of aryl groups include phenyl, naphthyl and biphenyl, while non-limiting examples of heteroaryl groups include pyridyl, pyridazinyl, pyrazinyl, pyrimindinyl, triazinyl, quinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalaziniyl, benzotriazinyl, purinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizinyl, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, benzothiaxolyl, benzofuranyl, benzothienyl, indolyl, quinolyl, isoquinolyl, isothiazolyl, pyrazolyl, indazolyl, pteridinyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, thiazolyl, furyl, thienyl and the like. In some embodiments, the term "heteroaryl" encompasses 5- to 10-membered heteroaryl, 6- to 10-membered heteroaryl, 7- to 10-membered heteroaryl, 8- to 10-membered heteroaryl, 9- to 10-membered heteroaryl, 5- to 9-membered heteroaryl, 6- to 9-membered heteroaryl, 7- to 9-membered heteroaryl, 8- to 9-membered heteroaryl, 5- to 8-membered heteroaryl, 6- to 8-membered heteroaryl, 7- to 8-membered heteroaryl, 5- to 7-membered heteroaryl, 6- to 7-membered heteroaryl, or 5- to 6-membered heteroaryl.

[0047] The above terms (*e.g.*, "alkyl," "aryl" and "heteroaryl"), in some embodiments, will include both substituted and unsubstituted forms of the indicated radical. The term "substituted" means that the specified group or moiety bears one or more substituents including, but not limited to, substituents such as alkoxy, acyl, acyloxy, alkoxycarbonyl, carbonylalkoxy, acylamino, amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, cycloalkyl, cycloalkenyl, aryl, heteroaryl, aryloxy, cyano, azido, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, alkyl, alkenyl, alkynyl, heterocycloalkyl, heterocycloalkenyl, aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo and the like. The term "unsubstituted" means that the specified group bears no substituents. Where the term "substituted" is used to describe a structural system, the substitution is meant to occur at any valency-allowed position on the system. When a group or moiety bears more than one substituent, it is understood that the substituents may be the same or different from one another. In some embodiments, a substituted group or moiety bears from one to five substituents. In some

embodiments, a substituted group or moiety bears one substituent. In some embodiments, a substituted group or moiety bears two substituents. In some embodiments, a substituted group or moiety bears three substituents. In some embodiments, a substituted group or moiety bears four substituents. In some embodiments, a substituted group or moiety bears five substituents.

[0048] By "optional" or "optionally" is meant that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" encompasses both "alkyl" and "substituted alkyl" as defined herein. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible, and/or inherently unstable. It will also be understood that where a group or moiety is optionally substituted, the disclosure includes both embodiments in which the group or moiety is substituted and embodiments in which the group or moiety is unsubstituted.

[0049] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

[0050] As used herein, the term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

[0051] As used herein, the term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

[0052] As used herein, a wavy line "〰" that intersects a bond in a chemical structure indicates the point of attachment of the atom to which the wavy bond is connected in the chemical structure to the remainder of a molecule, or to the remainder of a fragment of a molecule.

[0053] As used herein, the representation of a group (*e.g.*, X^a) in parenthesis followed by a subscript integer range (*e.g.*, $(X^a)_{0\text{-}1}$) means that the group can have the number of occurrences as designated by the integer range. For example, $(X^a)_{0\text{-}1}$ means the group X^a can be absent or can occur one time.

[0054] "Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, *e.g.* melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers can separate under high resolution analytical procedures such as electrophoresis and chromatography.

[0055] "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[0056] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. The compounds of the present disclosure can contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the present disclosure, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present disclosure. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (−) are employed to designate the sign of rotation of plane-polarized light by the compound, with (−) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which can occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

[0057] As used herein, the term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions

via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

[0058] As used herein, the term "solvate" refers to an association or complex of one or more solvent molecules and a compound of the present disclosure. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine. The term "hydrate" refers to the complex where the solvent molecule is water. Certain compounds of the present disclosure can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present disclosure.

[0059] The term "co-crystal" as used herein refers to a solid that is a crystalline single phase material composed of two or more different molecular or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts. A co-crystal consists of two or more components that form a unique crystalline structure having unique properties. Co-crystals are typically characterized by a crystalline structure, which is generally held together by freely reversible, non-covalent interactions. As used herein, a co-crystal refers to a compound of the present disclosure and at least one other component in a defined stoichiometric ratio that form a crystalline structure.

[0060] As used herein, the term "protecting group" refers to a substituent that is commonly employed to block or protect a particular functional group on a compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBZ) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include phenylsulfonylethyl, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfenyl)ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see P. G. M. Wuts and T. W. Greene, Greene's Protective Groups in Organic Synthesis 4th edition, Wiley-Interscience, New York, 2006.

[0061] As used herein, the term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N,N′-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S. M., et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0062] The neutral forms of the compounds can be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The

parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present disclosure.

[0063] Certain compounds of the present disclosure possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers, regioisomers and individual isomers (*e.g.*, separate enantiomers) are all intended to be encompassed within the scope of the present disclosure.

[0064] The compounds of the present disclosure can also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the present disclosure also embraces isotopically-labeled variants of the present disclosure which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having the atomic mass or mass number different from the predominant atomic mass or mass number usually found in nature for the atom. All isotopes of any particular atom or element as specified are contemplated within the scope of the compounds of the present disclosure and include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine and iodine, such as ^{2}H ("D"), ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I and ^{125}I. Certain isotopically labeled compounds of the present disclosure (*e.g.*, those labeled with ^{3}H or ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (^{3}H) and carbon-14 (^{14}C) isotopes are useful for their ease of preparation and detectability. Further substitution with heavier isotopes such as deuterium (*i.e.*, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds of the present disclosure can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0065] "Treating" or "treatment" of a disease in a patient refers to inhibiting the disease or arresting its development; or ameliorating or causing regression of the disease. As used herein, "treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. For purposes of this disclosure, beneficial or desired results

include, but are not limited to, one or more of the following: decreasing one more symptoms resulting from the disease or disorder, diminishing the extent of the disease or disorder, stabilizing the disease or disorder (e.g., preventing or delaying the worsening of the disease or disorder), delaying the occurrence or recurrence of the disease or disorder, delay or slowing the progression of the disease or disorder, ameliorating the disease or disorder state, providing a remission (whether partial or total) of the disease or disorder, decreasing the dose of one or more other medications required to treat the disease or disorder, enhancing the effect of another medication used to treat the disease or disorder, delaying the progression of the disease or disorder, increasing the quality of life, and/or prolonging survival of a patient. Also encompassed by "treatment" is a reduction of pathological consequence of the disease or disorder. The methods of the present disclosure contemplate any one or more of these aspects of treatment.

[0066] "Preventing", "prevention", or "prophylaxis" of a disease in a patient refers to preventing the disease from occurring in a patient that is predisposed or does not yet display symptoms of the disease.

[0067] The phrase "therapeutically effective amount" means an amount of a compound of the present disclosure that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

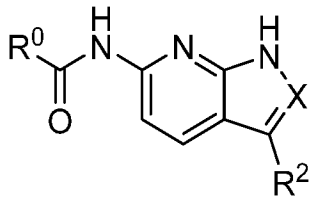
[0068] The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth.

[0069] It is appreciated that certain features of the present disclosure, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables are specifically embraced by the present invention and are disclosed herein just as if each and every combination was individually and explicitly disclosed, to the extent that such combinations embrace compounds that are stable compounds (*i.e.*, compounds that can be isolated, characterized, and tested for biological activity). In addition, all subcombinations of the chemical groups

listed in the embodiments describing such variables are also specifically embraced by the present invention and are disclosed herein just as if each and every such sub-combination of chemical groups was individually and explicitly disclosed herein.

II. Compounds

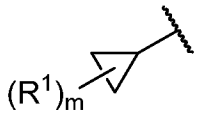
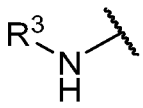
[0070] In one aspect, provided herein is a compound of formula (I),



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

X is N or CR^8;

R^0 is a group  or  ;

m is an integer from 0 to 3;

each R^1 is independently -D, -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, -O-C_1-C_3 alkylene-NR^4R^5, -O-C_1-C_3 alkylene-$NR^{4'}R^{5'}$,C_1-C_3 alkylene-OH, C_0-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^5$, C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene moieties in R^1 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

or

two R^1 are taken together with the carbon atom or carbon atoms to which they are attached to form a 3- to 7-membered heterocyclic ring, wherein the heterocyclic ring contains nitrogen atom and wherein the nitrogen atom is optionally substituted with C_1-C_3 alkyl;

R^2 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein the C_6-C_{14} aryl and 5-to-10-membered heteroaryl are optionally substituted with 1-5 R^6 groups;

R^3 is -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkylene-NR^4R^5, C_1-C_6 alkylene-$NR^{4'}R^{5'}$, C_1-C_6 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_3 alkylene-(C_3-C_6 cycloalkyl), C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-O-(C_1-C_3 alkylene)-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_3 alkylene-(4- to 8-membered heterocycloalkyl), C_1-C_3 alkylene-(C_3-C_7 heterocycloalkyl), C_1-C_3 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, (4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, or (C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, heterocycloalkyl, and heterocycloalkylene moieties in R^3 are optionally substituted with 1-3 fluorine atoms, 1-3 CN groups and/or 1-6 deuterium atoms and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, C_2-C_3 heteroalkyl, 4- to 8-membered heterocycloalkyl, or C_3-C_7 heterocycloalkyl;

each R^4 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-6 deuterium atoms;

each R^5 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-6 deuterium atoms;

each pair of $R^{4'}$ and $R^{5'}$ taken together with the nitrogen atom to which they are attached independently form a 3-to-7-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O,

and S, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

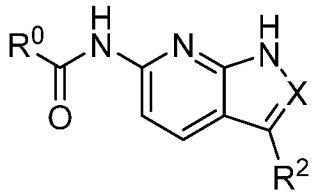
each R^6 is independently halogen, -OR^7, -NR^4R^5, -$NR^{4'}R^{5'}$, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, -CN, $S(O)_nC_1$-C_3 alkyl, or $S(O)_nC_3$-C_6 cycloalkyl,

wherein n is an integer from 0 to 2;

each R^7 is independently -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, or C_1-C_3-alkylene-C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-6 deuterium atoms; and

R^8 is -H, -F, or C_1-C_3 alkyl.

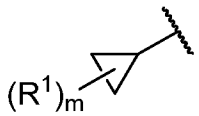
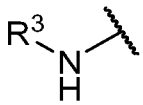
[0071] In one aspect, provided herein is a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

X is N or CR^8;

R^0 is a group  or  ;

m is an integer from 0 to 3;

each R^1 is independently -D, -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, C_0-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-

(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene moieties in R^1 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

R^2 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein the C_6-C_{14} aryl and 5-to-10-membered heteroaryl are optionally substituted with 1-5 R^6 groups;

R^3 is -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkylene-NR^4R^5, C_1-C_6 alkylene-$NR^{4'}R^{5'}$, C_1-C_6 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_3 alkylene-(C_3-C_6 cycloalkyl), C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-O-(C_1-C_3 alkylene)-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_3 alkylene-(C_4-C_6 heterocycloalkyl), C_1-C_3 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_3 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, heterocycloalkyl, and heterocycloalkylene moieties in R^3 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, C_2-C_3 heteroalkyl, or C_4-C_6 heterocycloalkyl;

each R^4 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl;

each R^5 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl;

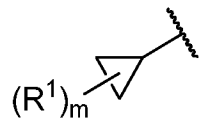
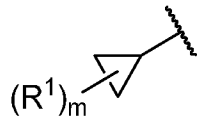
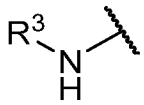
each pair of $R^{4'}$ and $R^{5'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^6 is independently halogen, -OR^7, -NR^4R^5, -$NR^{4'}R^{5'}$, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, -CN, $S(O)_nC_1$-C_3 alkyl, or $S(O)_nC_3$-C_6 cycloalkyl,

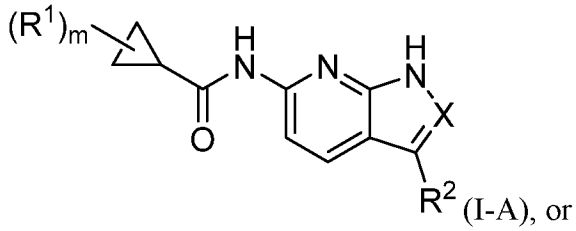
wherein n is an integer from 0 to 2;

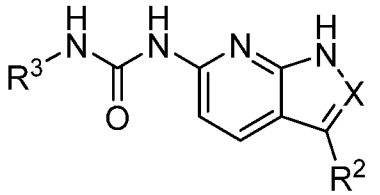
each R^7 is independently -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-6 deuterium atoms; and

R^8 is -H, -F, or C_1-C_3 alkyl.

[0072] In some embodiments of the present aspect, R^0 is  . In some embodiments wherein R^0 is  , m is an integer 0, 1, 2 or 3. In some embodiments, m is 0. In other embodiments, m is 1. In yet other embodiments, m is 2. In still yet other embodiments, m is 3. In other embodiments of the present aspect, R^0 is  .

[0073] In some embodiments, the compound of formula (I) is a compound of formula (I-A) or formula (I-B):


(I-A), or

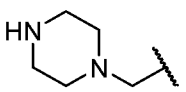
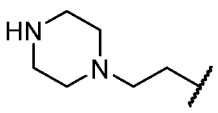
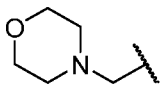

(I-B).

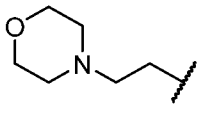
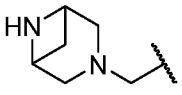
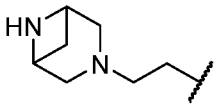
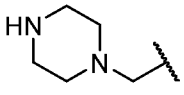
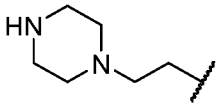
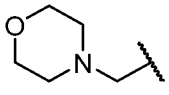
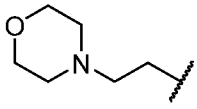
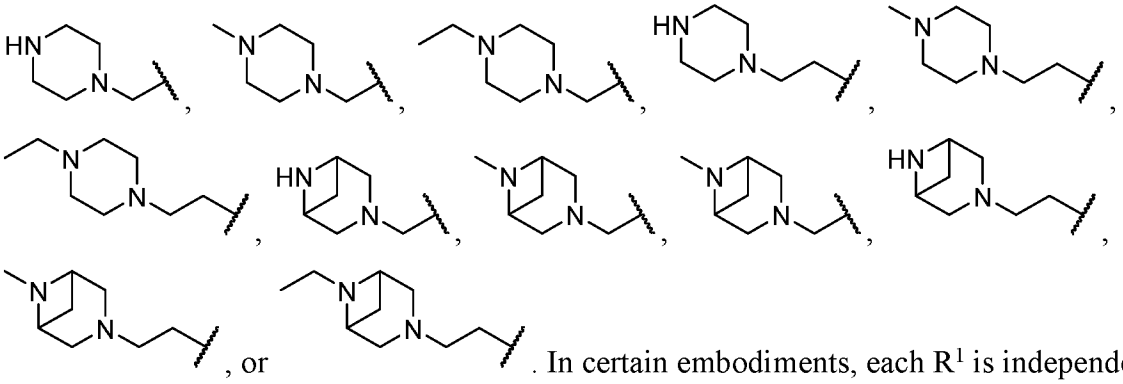
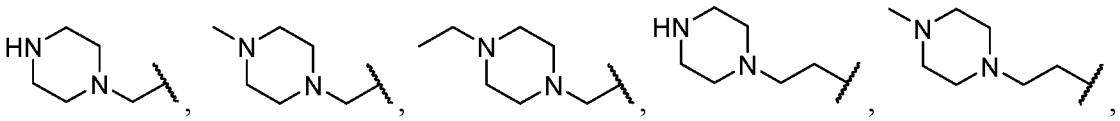
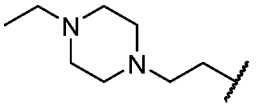
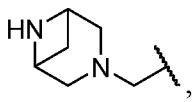
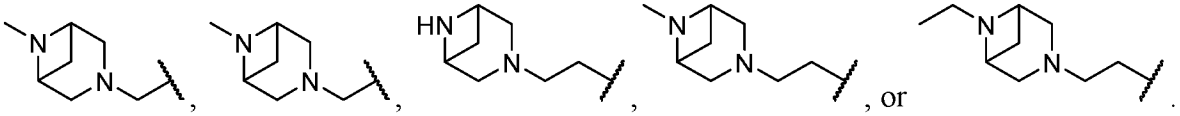
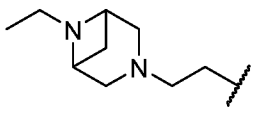
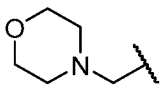
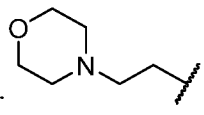
[0074] In some embodiments of the present aspect, X is N or CR^8. In some embodiments, X is N. In some embodiments, X is CR^8.

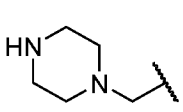
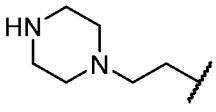
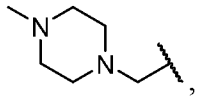
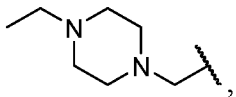
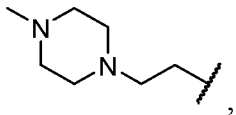
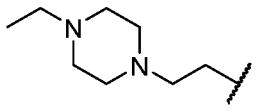
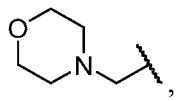
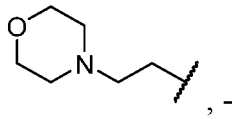
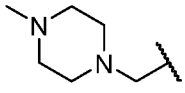
[0075] In some embodiments, each R^1 is independently -D, -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, -O-C_1-C_3 alkylene-NR^4R^5, -O-C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, C_0-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2

alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^5$, C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene moieties in R^1 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl.

[0076] In some embodiments, each R^1 is independently -D, -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, C_0-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene moieties in R^1 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl. In some embodiments, each R^1 is independently -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, C_0-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene moieties in R^1 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl. In some embodiments, each R^1 is independently -D, -F, or C_1-C_3 alkyl. In some embodiments, each R^1 is independently C_1-C_3 alkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, -O-C_1-C_3 alkylene-NR^4R^5, -O-C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, or C_0-C_3 alkylene-CN. In some embodiments, each R^1 is independently C_1-C_3 alkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, or C_0-C_3 alkylene-CN. In some embodiments, each R^1 is independently C_1-C_3 alkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, -O-C_1-C_3

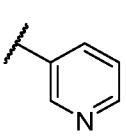
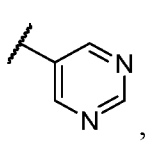
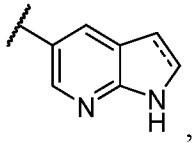
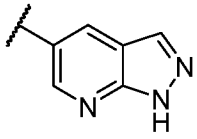
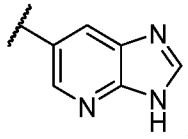
alkylene-NR^4R^5, or -O-C_1-C_3 alkylene-$NR^{4'}R^{5'}$. In some embodiments, each R^1 is independently C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$. In some embodiments, each R^1 is independently C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$. In some embodiments, each R^1 is independently C_1-C_3 alkylene-OH, C_0-C_3 alkylene-CN, or C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH. In some embodiments, each R^1 is independently -F, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, or C_0-C_3 alkylene-CN, wherein each pair of $R^{4'}$ and $R^{5'}$ of R^1 taken together with the nitrogen atom to which they are attached independently form a 3-to-7-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl. In some embodiments, each R^1 is independently -F, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, or C_0-C_3 alkylene-CN, wherein each pair of $R^{4'}$ and $R^{5'}$ of R^1 taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl. In some embodiments, each R^1 is independently C_1-C_3 alkylene-$NR^{4'}R^{5'}$. In certain embodiments, each R^1 is independently optionally substituted –C_1-C_2 alkylene-N-morpholinyl or optionally substituted –C_1-C_2 alkylene-N-piperazinyl. In some embodiments, each R^1 is independently optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted

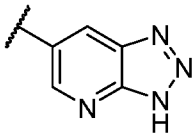
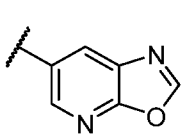
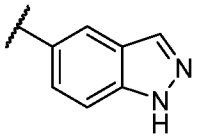
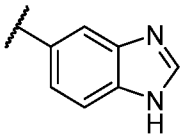
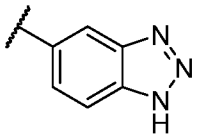
 , optionally substituted  , or optionally substituted  . In certain embodiments, each R^1 is independently optionally substituted  , optionally substituted  , optionally substituted  , or optionally substituted  . In some embodiments, each R^1 is independently  , or . In certain embodiments, each R^1 is independently  , or  . In certain other embodiments, each R^1 is independently  ,  , or  . In still other embodiments, each R^1 is independently  or  . In some embodiments, each R^1 is independently C_1-C_3 alkylene-OH. In certain other embodiments, each R^1 is independently –C_1-C_2 alkylene-OH. In certain embodiments, each R^1 is independently -CH_2OH, -CH_2CH_2OH, -$CH(OH)CH_3$, -$CH_2CH_2CH_2OH$, -$CH_2CH(OH)CH_3$, or -$CH(CN)CH_2CH_3$. In certain other embodiments, each R^1 is independently -CH_2OH or-CH_2CH_2OH. In some embodiments, each R^1 is independently C_0-C_3 alkylene-CN. In certain embodiments, each R^1 is independently -CN, -CH_2CN, -CH_2CH_2CN, -$CH(CN)CH_3$, -$CH_2CH_2CH_2CN$, -$CH_2CH(CN)CH_3$, -$CH(CN)CH_2CH_3$, or -$CH(CH_2CN)CH_3$. In some

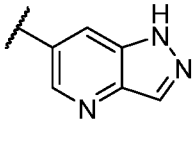
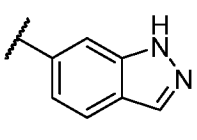
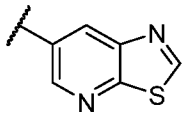
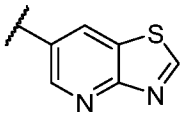
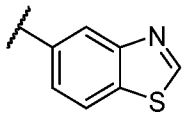
embodiments, each R^1 is independently -F,  ,  ,  ,  ,  ,  ,  ,  , -CH_2OH, -CH_2CH_2OH, -CH_2-$NHCH_3$, -CH_2NHCD_3, -CH_2-$N(CH_3)_2$, -$CH_2N(CD_3)_2$, -CH_2CH_2-$N(CH_3)_2$, -$CH_2CH_2N(CD_3)_2$, -$OCH_2CH_2N(CH_3)_2$, -CN, or -CH_2CN. In some embodiments, each R^1 is independently -F,  , -CH_2OH, -CH_2CH_2OH, -CN, or -CH_2CN.

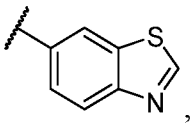
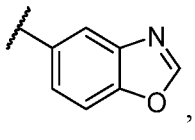
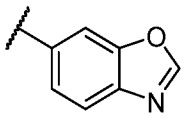
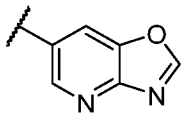
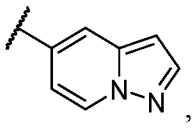
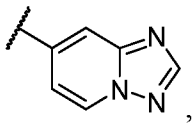
[0077] In other embodiments, two R^1 are taken together with the carbon atom or carbon atoms to which they are attached to form a 3- to 7-membered heterocyclic ring, wherein the heterocyclic ring contains nitrogen atom and wherein the nitrogen atom is optionally substituted with C_1-C_3 alkyl.

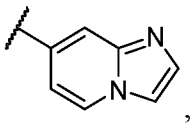
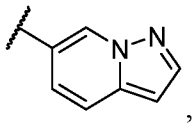
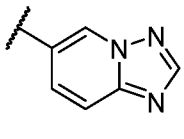
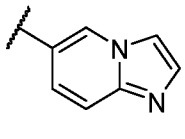
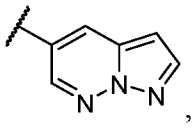
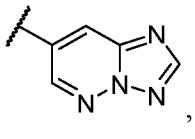
[0078] For example, in some embodiments, two R^1 are present on adjacent carbon atoms and together with the carbon atoms to which they are attached form a 3- to 7-membered heterocyclic ring, such as a pyrrolidinyl ring, wherein the heterocyclic ring contains nitrogen atom and wherein the nitrogen atom is optionally substituted with C_1-C_3 alkyl. In other embodiments, two R^1 are present on the same carbon atom and together with the carbon atoms to which they are attached form a 3- to 7-membered heterocyclic ring, such as a azetidinyl ring, wherein the heterocyclic ring contains nitrogen atom and wherein the nitrogen atom is optionally substituted with C_1-C_3 alkyl.

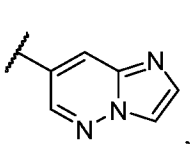
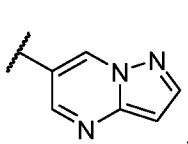
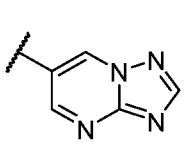
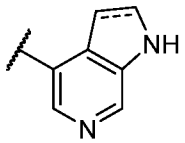
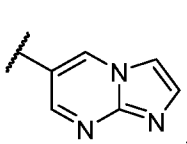
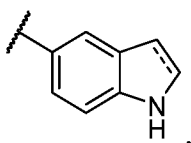
[0079] In some embodiments, R^2 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein the C_6-C_{14} aryl and 5-to-10-membered heteroaryl are optionally substituted with 1-5 R^6 groups. In some embodiments, R^2 is a C_6-C_{14} aryl, wherein said C_6-C_{14} aryl is optionally substituted with 1-5 R^6 groups. In some embodiments, R^2 is phenyl, wherein said phenyl is optionally substituted with 1-5 R^6 groups. In some embodiments, R^2 is 5- to 10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is optionally substituted with 1-5 R^6 groups. In some embodiments, R^2 is a 5-to-10-membered heteroaryl selected from the group consisting of:  ,  ,  ,  ,  ,

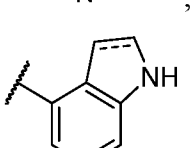
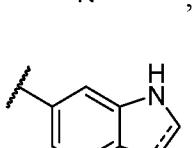
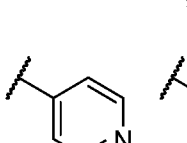
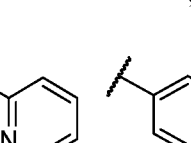
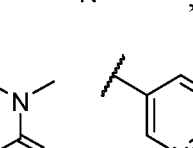
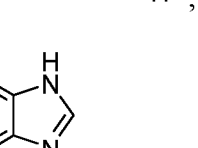
 ,  ,  ,  ,  ,

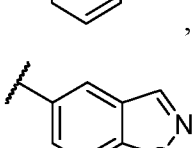
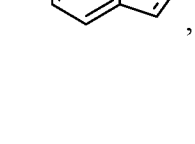
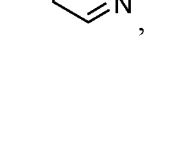
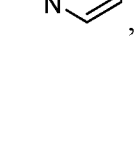
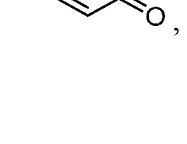
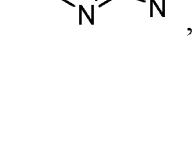
 ,  ,  ,  ,  ,

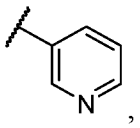
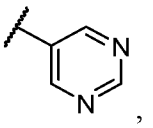
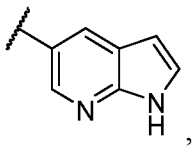
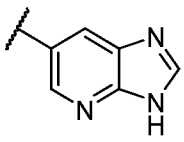
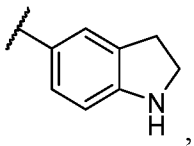
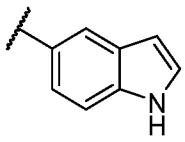
 ,  ,  ,  ,  ,  ,

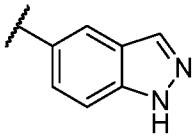
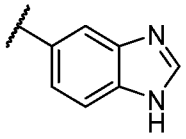
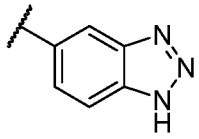
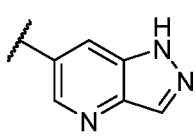
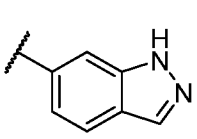
 ,  ,  ,  ,  ,  ,

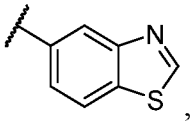
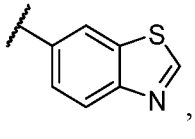
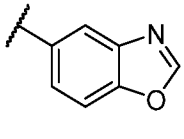
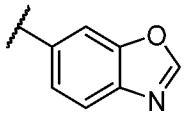
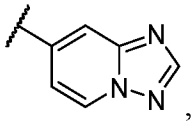
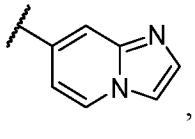
 ,  ,  ,  ,  ,  ,

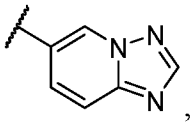
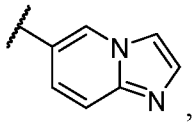
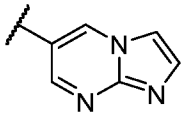
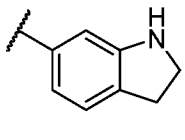
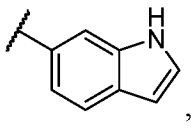
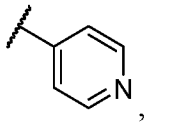
 ,  ,  ,  ,  ,  ,

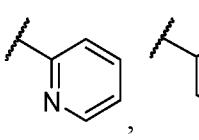
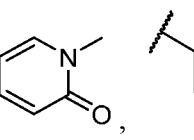
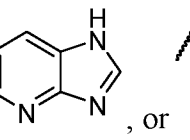
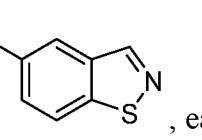
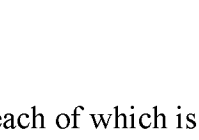
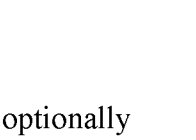
 ,  ,  ,  ,  ,  , and

, wherein ⎓ indicates a single or double bond, and wherein the 5-to-10-membered heteroaryl is optionally substituted with 1-5 R^6 groups. In some embodiments, R^2 is  ,  ,  ,  ,  ,  ,

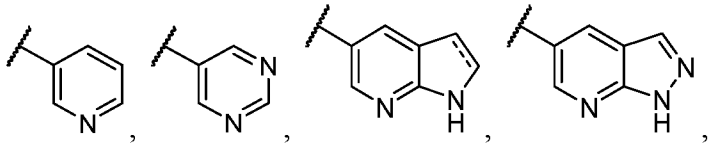
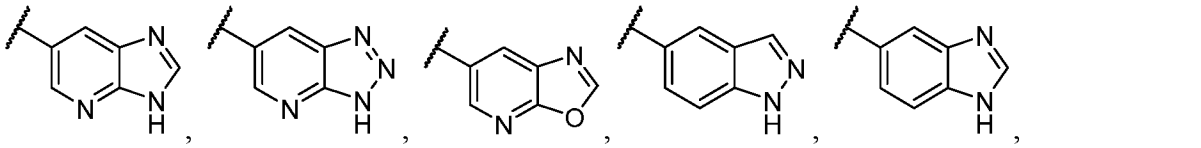
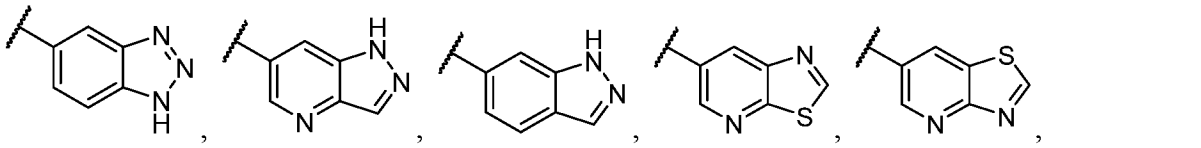
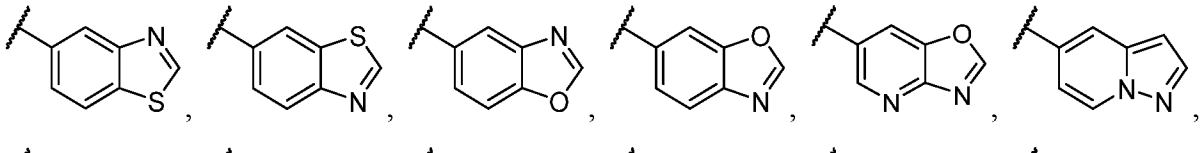
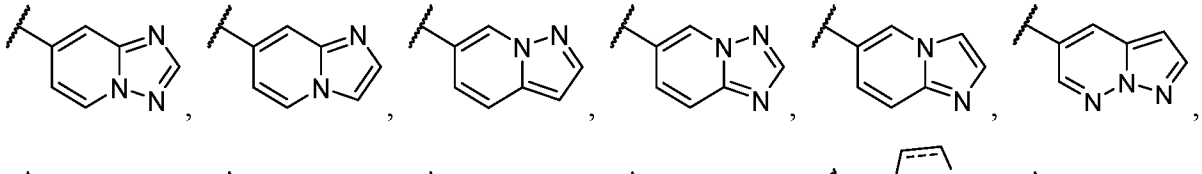
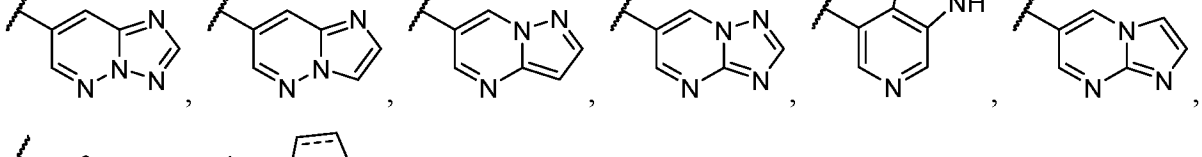
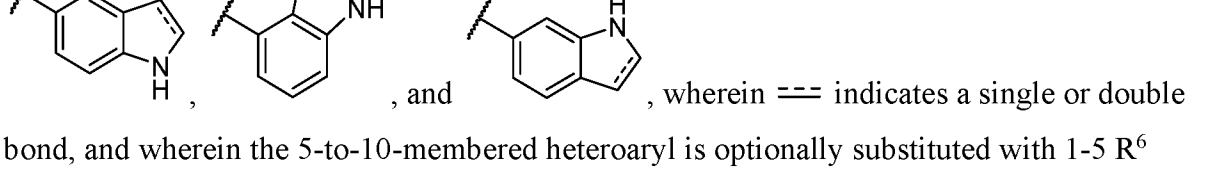
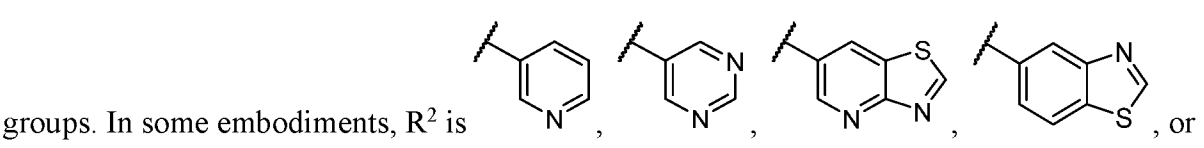
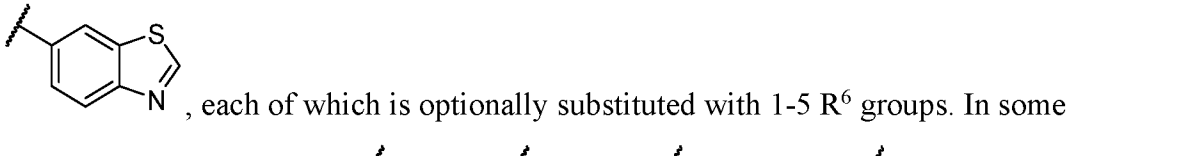
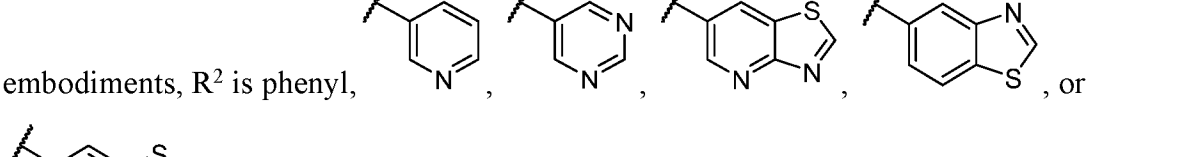
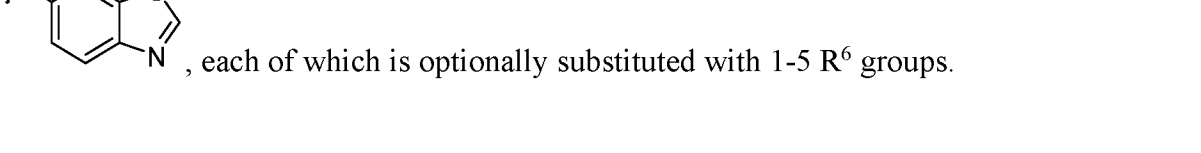
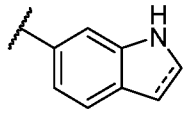
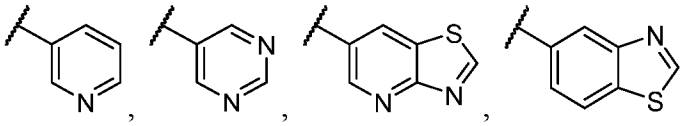
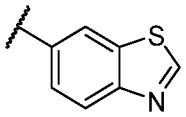
 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,

, , , or  , each of which is optionally

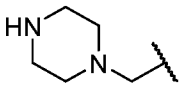
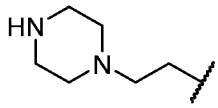
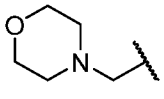
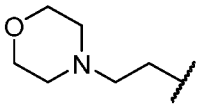
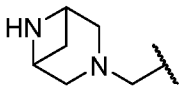
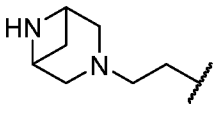
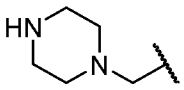
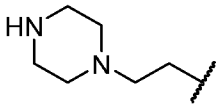
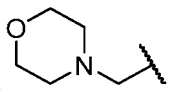
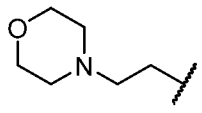
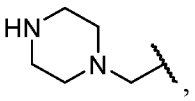
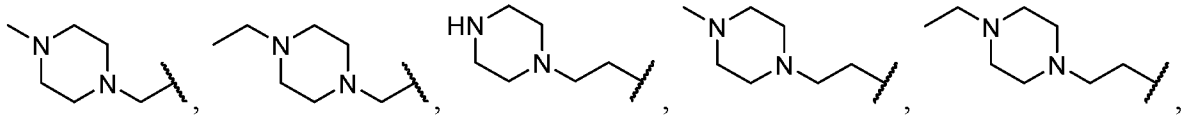
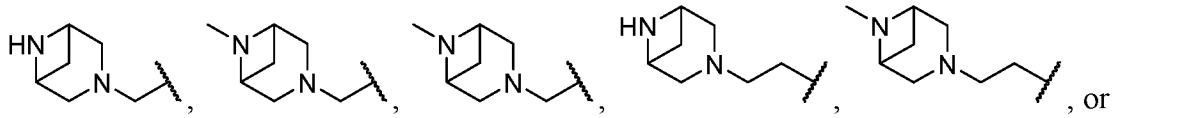
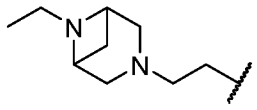
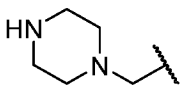
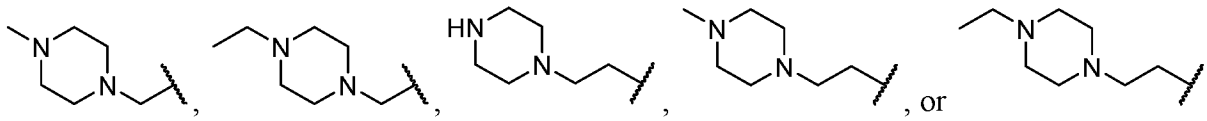
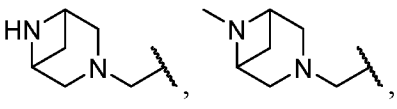
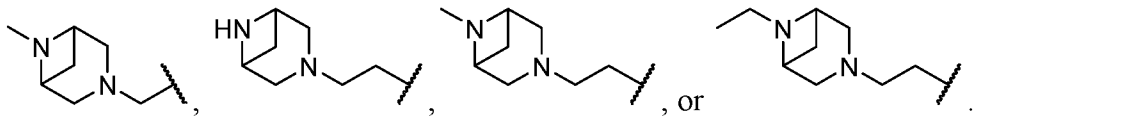
substituted with 1-5 R^6 groups. In some embodiments, R^2 is a 5-to-10-membered heteroaryl selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , wherein ⎓ indicates a single or double bond, and wherein the 5-to-10-membered heteroaryl is optionally substituted with 1-5 R^6 groups. In some embodiments, R^2 is , or , each of which is optionally substituted with 1-5 R^6 groups. In some embodiments, R^2 is phenyl,  , or  , each of which is optionally substituted with 1-5 R^6 groups.

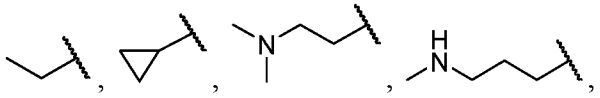
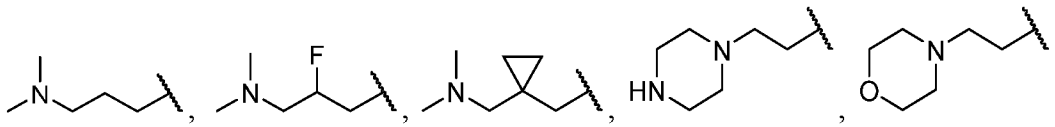
[0080] In some embodiments, R^3 is -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkylene-NR^4R^5, C_1-C_6 alkylene-$NR^{4'}R^{5'}$, C_1-C_6 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_3 alkylene-(C_3-C_6 cycloalkyl), C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-O-(C_1-C_3 alkylene)-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_3 alkylene-(4- to 8-membered heterocycloalkyl), C_1-C_3 alkylene-(C_3-C_7 heterocycloalkyl), C_1-C_3 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, (4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, or (C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, heterocycloalkyl, and heterocycloalkylene moieties in R^3 are optionally substituted with 1-3 fluorine atoms, 1-3 CN groups and/or 1-6 deuterium atoms and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, C_2-C_3 heteroalkyl, 4- to 8-membered heterocycloalkyl, or C_3-C_7 heterocycloalkyl.

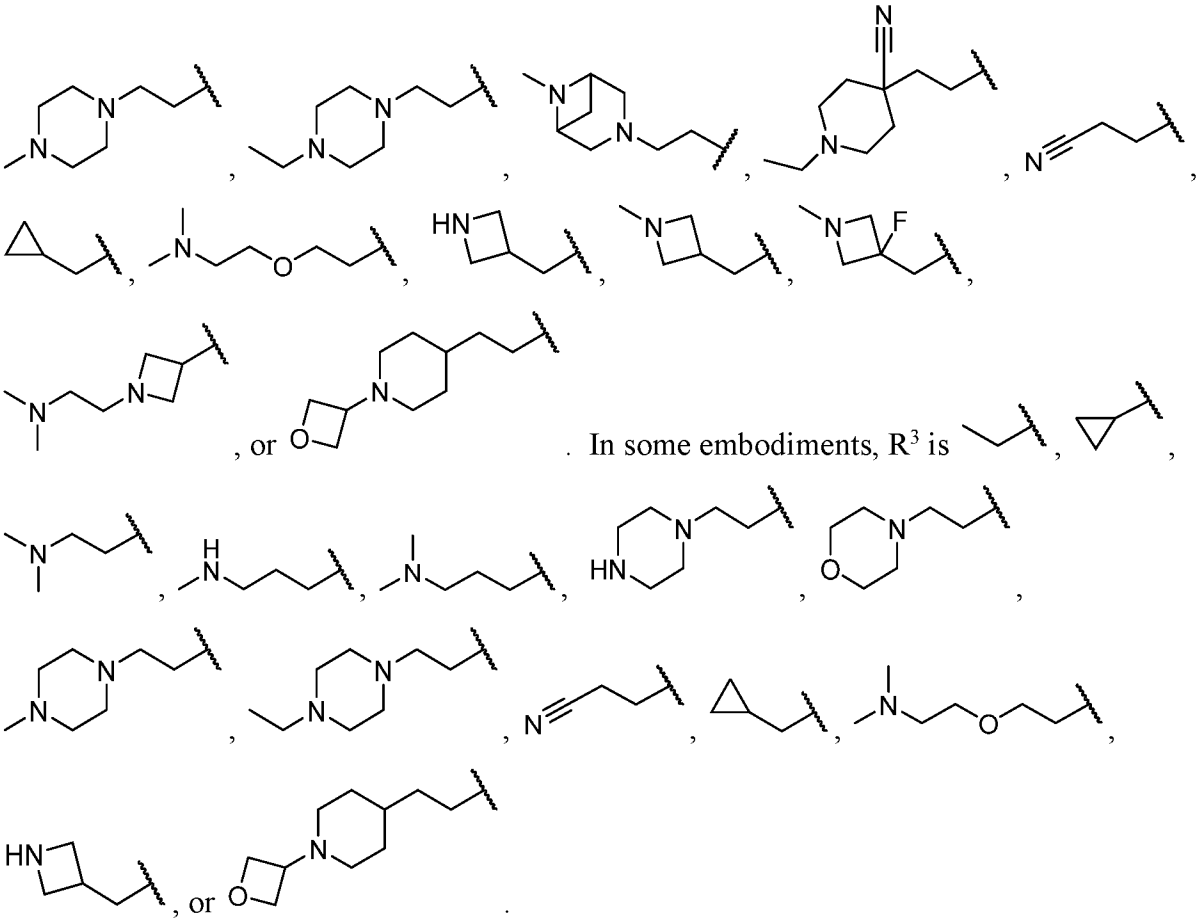
[0081] In some embodiments, R^3 is -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkylene-NR^4R^5, C_1-C_6 alkylene-$NR^{4'}R^{5'}$, C_1-C_6 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_3 alkylene-(C_3-C_6 cycloalkyl), C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-O-(C_1-C_3 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_3 alkylene-(C_4-C_6 heterocycloalkyl), C_1-C_3 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_3 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, heterocycloalkyl, and heterocycloalkylene moieties in R^3 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, C_2-C_3 heteroalkyl, or C_4-C_6 heterocycloalkyl.

[0082] In some embodiments, R^3 is C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkyl), C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5,

C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkyl), C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, heterocycloalkyl, and heterocycloalkylene moieties in R^3 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, C_2-C_3 heteroalkyl, or C_4-C_6 heterocycloalkyl. In some embodiments, R^3 is C_1-C_3 alkylene-(4- to 8-membered heterocycloalkyl), C_1-C_3 alkylene-(C_3-C_7 heterocycloalkyl), C_1-C_3 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, (4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, or (C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 In some embodiments, R^3 is C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkyl), C_1-C_2 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(4- to 8-membered heterocycloalkyl), or C_1-C_3 alkylene-(C_3-C_7 heterocycloalkyl), wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl or C_4-C_6 heterocycloalkyl, wherein the R^4 and R^5 of R^3 taken together with the nitrogen atom to which they are attached independently form a 3-to-7-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl. In some embodiments, R^3 is C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkyl), C_1-C_2 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkyl), wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl or C_4-C_6 heterocycloalkyl, wherein the R^4 and R^5 of R^3 are independently -H or C_1-C_3 alkyl, and the $R^{4'}$ and $R^{5'}$ of R^3 taken together with the nitrogen atom to which they are attached form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl. In some embodiments, each R^1 is

independently optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , optionally substituted  , or optionally substituted  . In certain embodiments, each R^1 is independently optionally substituted  , optionally substituted  , optionally substituted  , or optionally substituted  . In some embodiments, each R^1 is independently  ,  ,  , or  . In certain embodiments, each R^1 is independently  ,  , or  . In certain other embodiments, each R^1 is independently ,  , or .

[0083] In some embodiments, R^3 is  ,  .



[0084] In some embodiments, each R^4 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-6 deuterium atoms. In some embodiments, each R^4 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl. In some embodiments, each R^4 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl. In some embodiments, each R^4 is independently –H. In some embodiments, each R^4 is independently C_1-C_3 alkyl. In certain embodiments, each R^4 is independently $–CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, or $-CH(CH_3)_2$. In some embodiments, each R^4 is independently C_3-C_6 cycloalkyl. In certain embodiments, R^4 is independently cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In some embodiments, each R^4 is independently C_2-C_3 haloalkyl. In certain embodiment, each R^4 is independently C_2-C_3 haloalkyl, wherein the each halogen atom of each C_2-C_3 haloalkyl is independently –F, -Cl, or –Br. In some embodiments, each R^4 is independently C_2-C_3 alkylene-CN. In certain embodiments, each R^4 is independently $-CH_2CH_2CN$, $-CH(CN)CH_3$, $-CH_2CH_2CH_2CN$, $-CH_2CH(CN)CH_3$, $-CH(CN)CH_2CH_3$, or $-CH(CH_2CN)CH_3$. In some embodiments, each R^4 is independently C_2-C_3 heteroalkyl. In certain embodiments, each R^4 is

independently -CH_2CH_2OH, -$CH(OH)CH_3$, -$CH_2CH_2CH_2OH$, -$CH_2CH(OH)CH_3$, or -$CH(OH)CH_2CH_3$, -CH_2OCH_3, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -$CH(OCH_3)CH_3$, -$CH(CH_2OH)CH_3$, -CH_2CH_2 NH_2, -$CH(NH_2)CH_3$, -$CH_2CH_2CH_2$ NH_2, -$CH_2CH(NH_2)CH_3$, or -$CH(NH_2)CH_2CH_3$, -CH_2NHCH_3, -$CH_2NHCH_2CH_3$, -$CH_2CH_2NHCH_3$, -$CH(NHCH_3)CH_3$, -$CH(CH_2NH_2CH_3$, -CH_2CH_2SH, -$CH(SH)CH_3$, -$CH_2CH_2CH_2SH$, -$CH_2CH(SH)CH_3$, or -$CH(SH)CH_2CH_3$, -CH_2SCH_3, -$CH_2SCH_2CH_3$, -$CH_2CH_2SCH_3$, -$CH(SCH_3)CH_3$, or -$CH(CH_2SH)CH_3$.

[0085] In some embodiments, each R^5 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-6 deuterium atoms. In some embodiments, each R^5 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl. In some embodiments, each R^5 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl. In some embodiments, each R^5 is independently –H. In some embodiments, each R^5 is independently C_1-C_3 alkyl. In certain embodiments, each R^5 is independently –CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, or -$CH(CH_3)_2$. In some embodiments, each R^5 is independently C_3-C_6 cycloalkyl. In certain embodiments, R^5 is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In some embodiments, each R^5 is independently C_2-C_3 haloalkyl. In certain embodiment, each R^5 is independently C_2-C_3 haloalkyl, wherein the each halogen atom of each C_2-C_3 haloalkyl is independently –F, -Cl, or –Br. In some embodiments, each R^5 is independently C_2-C_3 alkylene-CN. In certain embodiments, each R^5 is independently -CH_2CH_2CN, -$CH(CN)CH_3$, -$CH_2CH_2CH_2CN$, -$CH_2CH(CN)CH_3$, -$CH(CN)CH_2CH_3$, or -$CH(CH_2CN)CH_3$. In some embodiments, each R^5 is independently C_2-C_3 heteroalkyl. In certain embodiments, each R^5 is independently -CH_2CH_2OH, -$CH(OH)CH_3$, -$CH_2CH_2CH_2OH$, -$CH_2CH(OH)CH_3$, or -$CH(OH)CH_2CH_3$, -CH_2OCH_3, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -$CH(OCH_3)CH_3$, -$CH(CH_2OH)CH_3$, -CH_2CH_2 NH_2, -$CH(NH_2)CH_3$, -$CH_2CH_2CH_2$ NH_2, -$CH_2CH(NH_2)CH_3$, or -$CH(NH_2)CH_2CH_3$, -CH_2NHCH_3, -$CH_2NHCH_2CH_3$, -$CH_2CH_2NHCH_3$, -$CH(NHCH_3)CH_3$, -$CH(CH_2NH_2CH_3$, -CH_2CH_2SH, -$CH(SH)CH_3$, -$CH_2CH_2CH_2SH$, -$CH_2CH(SH)CH_3$, or -$CH(SH)CH_2CH_3$, -CH_2SCH_3, -$CH_2SCH_2CH_3$, -$CH_2CH_2SCH_3$, -$CH(SCH_3)CH_3$, or -$CH(CH_2SH)CH_3$.

[0086] In some embodiments, each pair of $R^{4'}$ and $R^{5'}$ taken together with the nitrogen atom to which they are attached independently form a 3-to-7-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from

the group consisting of N, O, and S, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl. In some embodiments, each pair of $R^{4'}$ and $R^{5'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl. In some embodiments, each pair of $R^{4'}$ and $R^{5'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl.

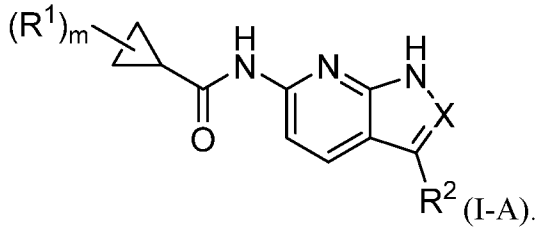
[0087] In some embodiments, each R^6 is independently halogen, $-OR^7$, $-NR^4R^5$, $-NR^{4'}R^{5'}$, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, -CN, $S(O)_nC_1$-C_3 alkyl, or $S(O)_nC_3$-C_6 cycloalkyl, wherein n is an integer from 0 to 2. In some embodiments, each R^6 is independently halogen, $-OR^7$, $-NR^4R^5$, C_1-C_3 alkyl, $-CF_2H$, $-CF_3$, C_3-C_6 cycloalkyl, or –CN. In some embodiments, each R^6 is independently halogen, $-OR^7$, $-NR^4R^5$, C_1-C_3 alkyl, $-CF_3$, or -CN, wherein each R^4 of R^6 and each R^5 of R^6 are independently -H or C_1-C_3 alkyl. In some embodiments, each R^6 is independently -F, -Cl, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-OCD_3$, cyclopropyloxy, cyclobutoxy, $-O-CH_2$-cyclopropyl, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-CH_3$, $-CF_3$, or –CN.In some embodiments, each R^6 is independently -F, -Cl, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-OCD_3$, cyclopropyloxy, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-CH_3$, $-CF_3$, or –CN. In some embodiments, each R^6 is independently halogen or $-OR^7$. In some embodiments, each R^6 is independently -F, $-OCH_3$, or cyclopropyloxy.

[0088] In some embodiments, each R^7 is independently -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, or C_1-C_3-alkylene-C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-6 deuterium atoms. In some embodiments, each R^7 is independently -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-6 deuterium atoms. In some embodiments, each R^7 is independently -H, C_1-C_3 alkyl, $-CD_3$, C_1-C_2 haloalkyl, or C_3-C_6 cycloalkyl. In some embodiments, each R^7 is independently -H, C_1-C_3 alkyl, $-CD_3$, $-CF_2H$, $-CF_3$, or C_3-C_6 cycloalkyl. In some

embodiments, each R^7 is independently -H, C_1-C_2 alkyl, -CD_3, C_1-C_2 haloalkyl, or C_3 cycloalkyl. In some embodiments, each R^7 is independently C_1-C_2 alkyl or C_3 cycloalkyl.

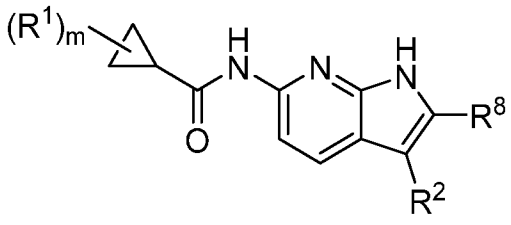
[0089] In some embodiments, R^8 is -H, -F, or C_1-C_3 alkyl. In some embodiments, R^8 is -H, -F, or -CH_3. In some embodiments, R^8 is –H or –F. In some embodiments, R^8 is –H or C_1-C_3 alkyl. In some embodiments, R^8 is -F or C_1-C_3 alkyl. In some embodiments, R^8 is -H, -F, –CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, or -$CH(CH_3)_2$. In some embodiments, R^8 is –H. In some embodiments, R^8 is –F. In some embodiments, R^8 is C_1-C_3 alkyl. In some embodiments, –CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, or -$CH(CH_3)_2$. In some embodiments, R^8 is –CH_3.

[0090] In some embodiments, the compound of formula (I) is a compound of formula (I-A), or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing:

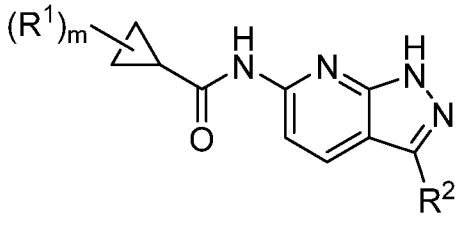


(I-A).

[0091] In some embodiments, the compound of formula (I) or formula (I-A) is a compound of formula (I-A-i) or formula (I-A-ii):



(I-A-i), or



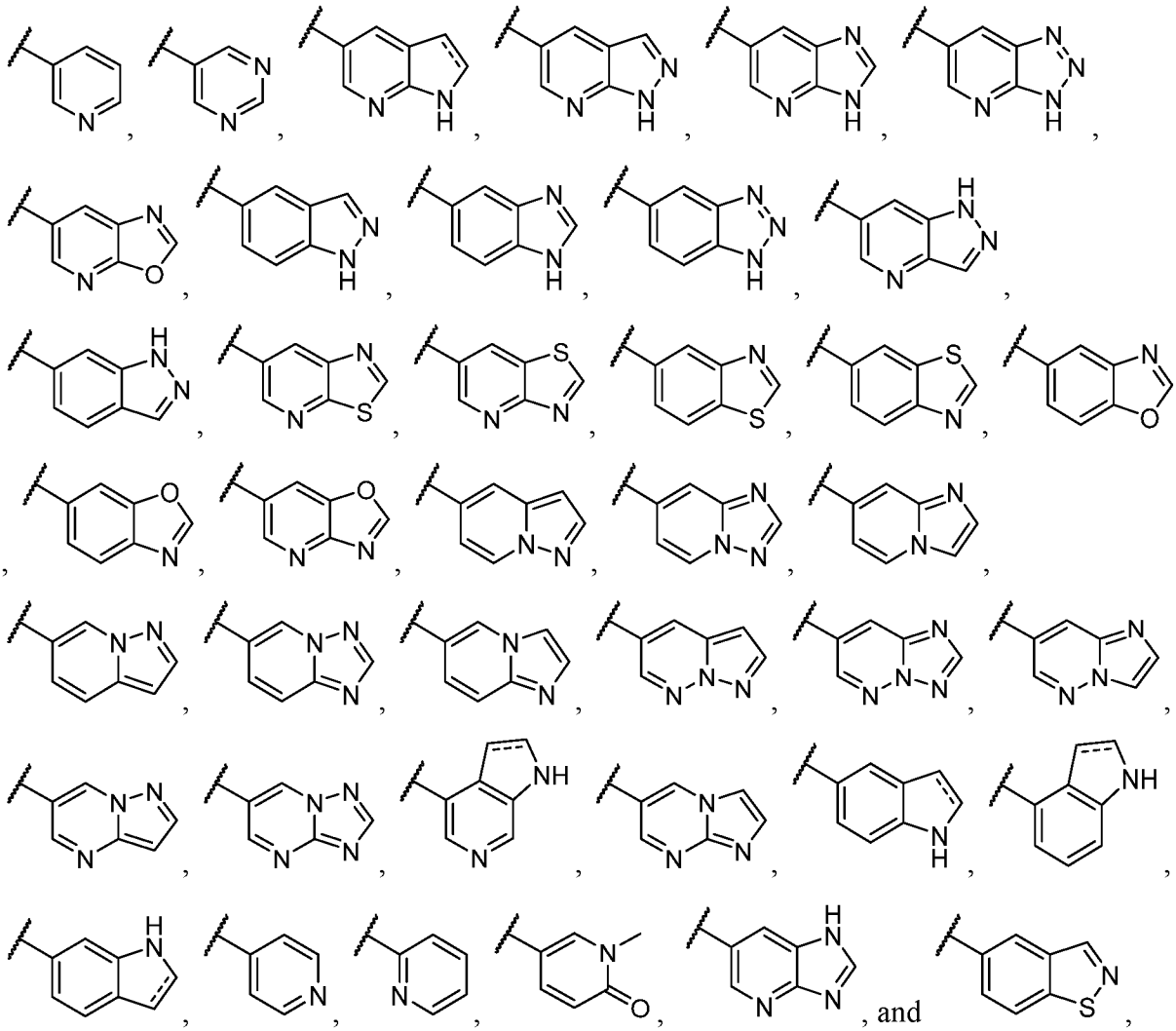
(I-A-ii),

wherein:

m is an integer from 0 to 2;

each R^1 is independently -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, C_0-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene moieties in R^1 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

R^2 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of:



wherein ═══ indicates a single or double bond, and wherein the C_6-C_{14} aryl and 5-to-10-membered heteroaryl are optionally substituted with 1-5 R^6 groups;

each R^4 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^5 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each pair of $R^{4'}$ and $R^{5'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^6 is independently halogen, -OR^7, -NR^4R^5, C_1-C_3 alkyl, -CF_2H, -CF_3, C_3-C_6 cycloalkyl, or -CN;

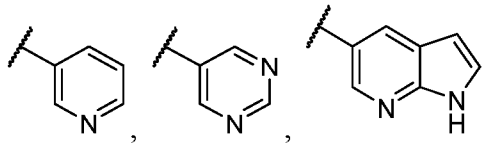
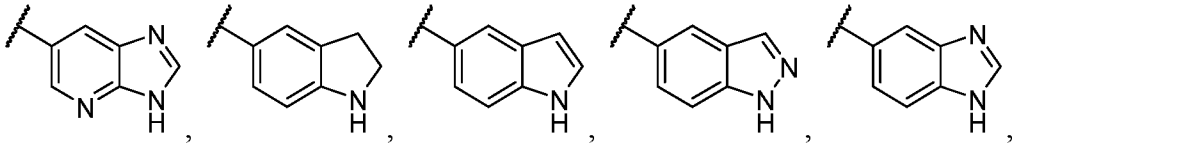
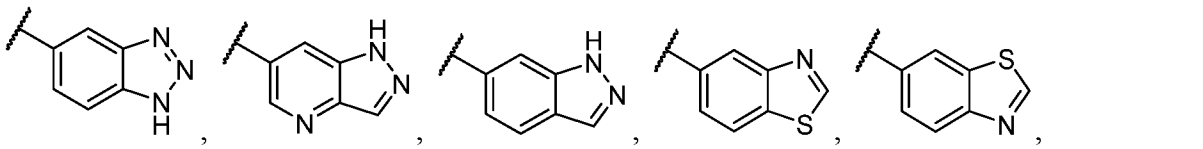
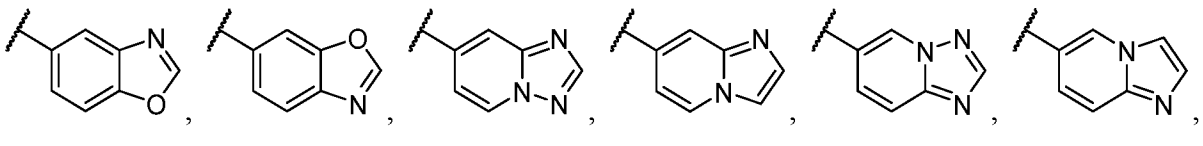
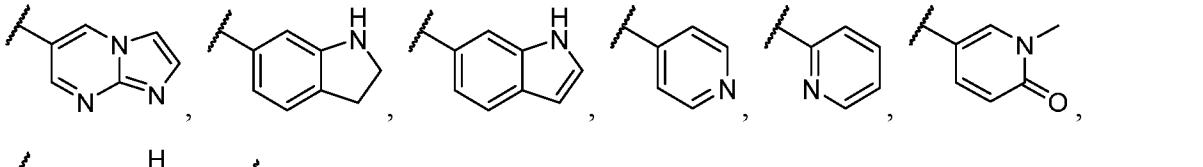
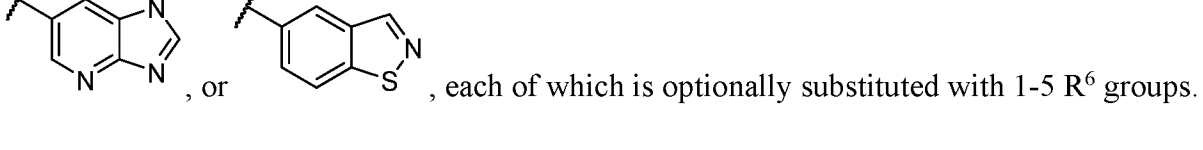
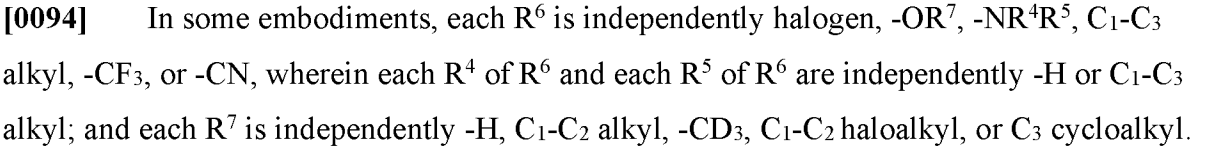
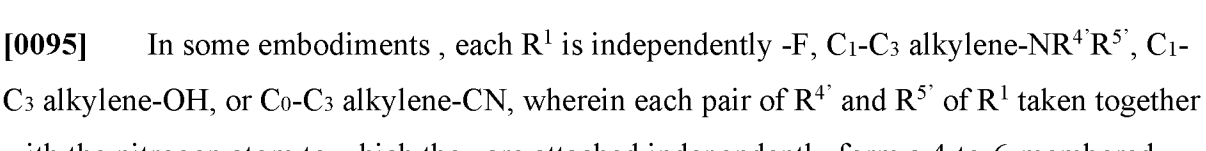
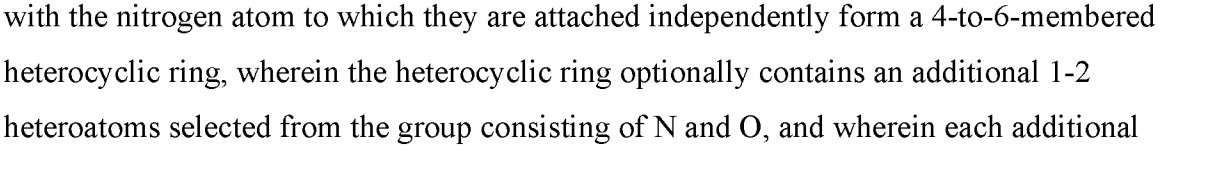
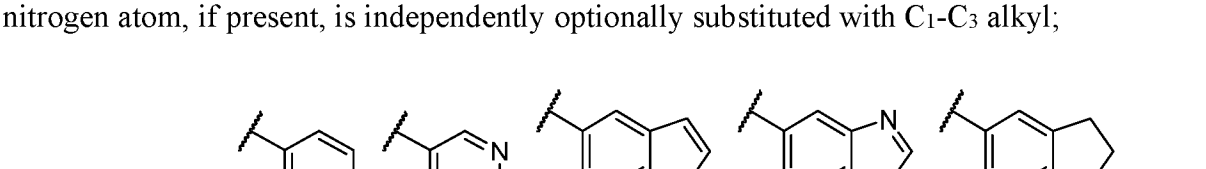
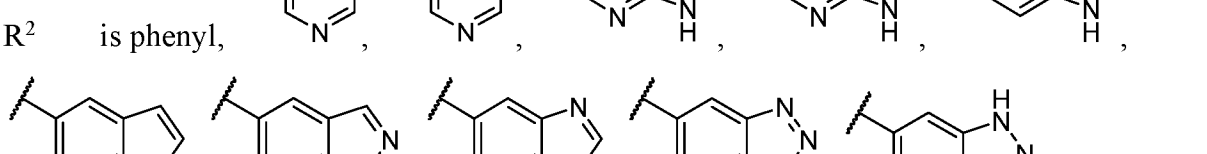
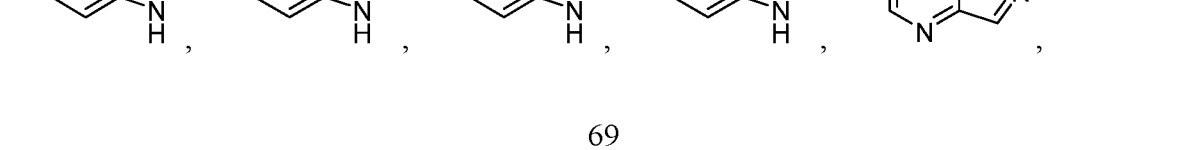
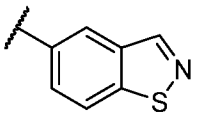
each R^7 is independently -H, C_1-C_3 alkyl, -CD_3, -CF_2H, -CF_3, or C_3-C_6 cycloalkyl; and

R^8 is -H, -F, or -CH_3.

[0092] In some embodiments of the compound of formula (I), formula (I-A), formula (I-A-i),

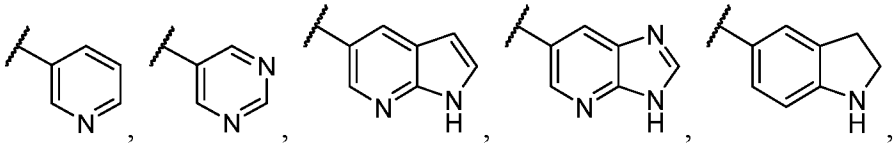
each R^1 is independently -F, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, or C_0-C_3 alkylene-CN,

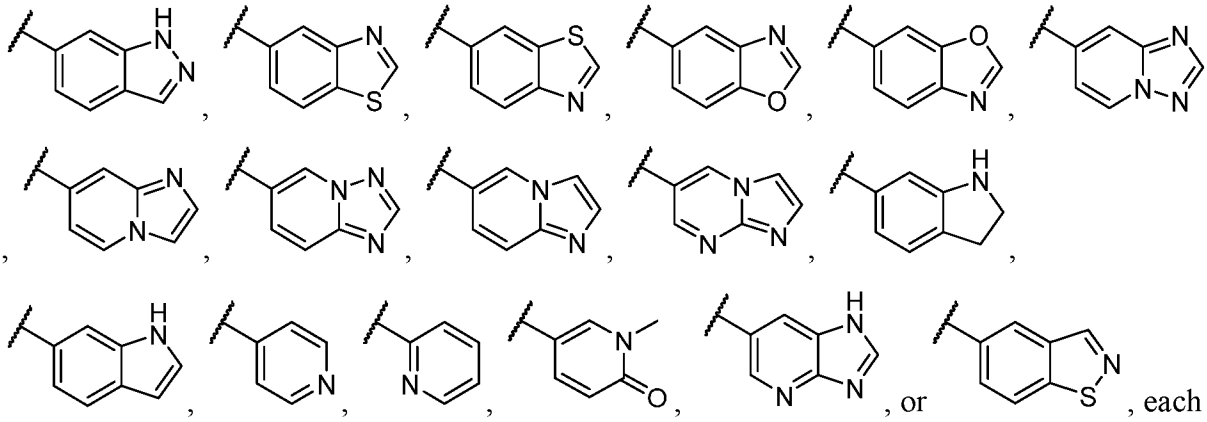
wherein each pair of $R^{4'}$ and $R^{5'}$ of R^1 taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl.

[0093] In some embodiments, R^2 is phenyl,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , or  , each of which is optionally substituted with 1-5 R^6 groups.

[0094] In some embodiments, each R^6 is independently halogen, $-OR^7$, $-NR^4R^5$, C_1-C_3 alkyl, $-CF_3$, or -CN, wherein each R^4 of R^6 and each R^5 of R^6 are independently -H or C_1-C_3 alkyl; and each R^7 is independently -H, C_1-C_2 alkyl, $-CD_3$, C_1-C_2 haloalkyl, or C_3 cycloalkyl.

[0095] In some embodiments , each R^1 is independently -F, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, or C_0-C_3 alkylene-CN, wherein each pair of $R^{4'}$ and $R^{5'}$ of R^1 taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl;

R^2 is phenyl,  , , ,

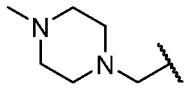


of which is optionally substituted with 1-5 R^6 groups;

each R^6 is independently halogen, $-OR^7$, $-NR^4R^5$, C_1-C_3 alkyl, $-CF_3$, or -CN,

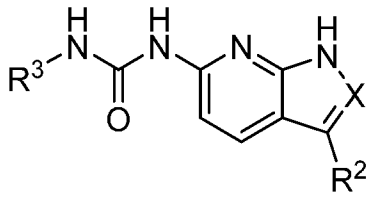
wherein each R^4 of R^6 and each R^5 of R^6 are independently -H or C_1-C_3 alkyl; and

each R^7 is independently -H, C_1-C_2 alkyl, $-CD_3$, C_1-C_2 haloalkyl, or C_3 cycloalkyl.

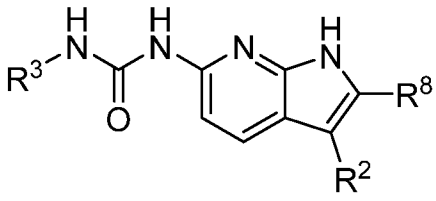
[0096] In some embodiments, each R^1 is independently F,  , $-CH_2OH$, $-CH_2CH_2OH$, -CN, or $-CH_2CN$.

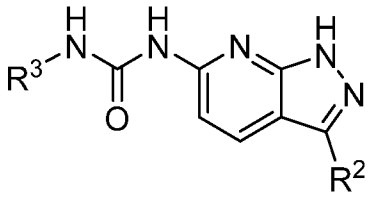
[0097] In some embodiments of the compound of formula (I), formula (I-A), formula (I-A-i), each R^6 is independently -F, -Cl, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, OCD_3, cyclopropyloxy, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-CH_3$, $-CF_3$, or -CN.

[0098] In some embodiments, the compound of formula (I) is a compound of formula (I-B), or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing:

 (I-B).

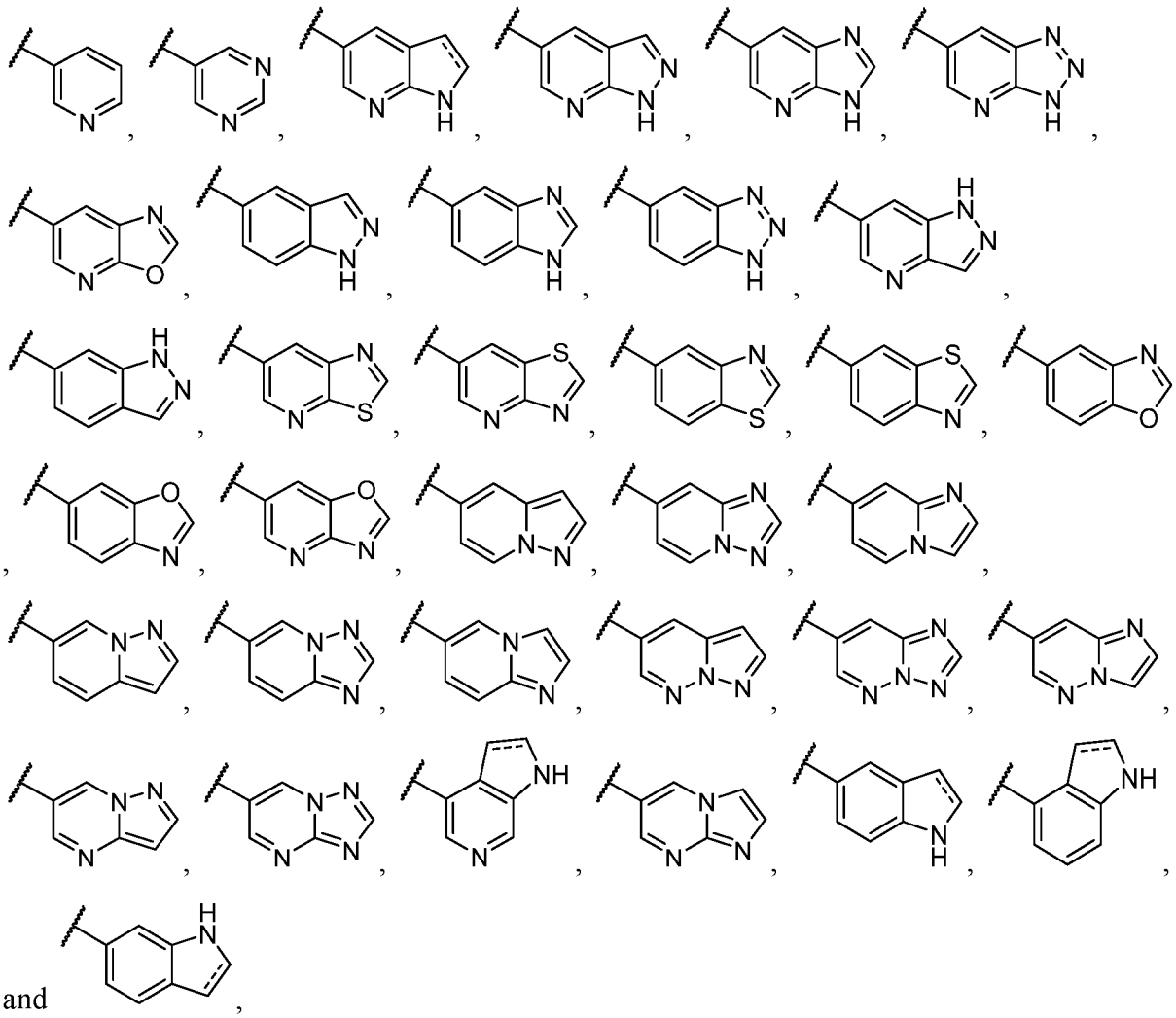
[0099] In some embodiments, wherein the compound of formula (I) or formula (I-B) is a compound of formula (I-B-i) or formula (I-B-ii)


(I-B-i), or


(I-B-ii),

wherein:

R^2 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of:



and ,

wherein ═══ indicates a single or double bond, and wherein the C_6-C_{14} aryl and 5-to-10-membered heteroaryl are optionally substituted with 1-5 R^6 groups;

R^3 is C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkyl), C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkyl), C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, heterocycloalkyl, and heterocycloalkylene moieties in R^3 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, C_2-C_3 heteroalkyl, or C_4-C_6 heterocycloalkyl;

each R^4 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^5 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each pair of $R^{4'}$ and $R^{5'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^6 is independently halogen, -OR^7, C_1-C_3 alkyl, -CF_2H, -CF_3, C_3-C_6 cycloalkyl, or -CN;

each R^7 is independently -H, C_1-C_3 alkyl, -CD_3, -CF_2H, -CF_3, or C_3-C_6 cycloalkyl; and

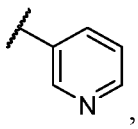
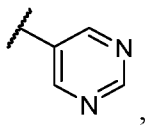
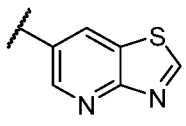
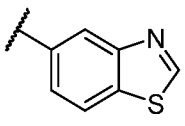
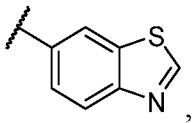
R^8 is -H, -F, or -CH_3.

[0100] In some embodiments, R^3 is C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkyl), C_1-C_2 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkyl), wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl or C_4-C_6 heterocycloalkyl,

wherein the R^4 and R^5 of R^3 are independently -H or C_1-C_3 alkyl, and

the $R^{4'}$ and $R^{5'}$ of R^3 taken together with the nitrogen atom to which they are attached form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl.

[0101] In some embodiments,

R^2 is phenyl,  ,  ,  ,  , or  , each of which is optionally substituted with 1-5 R^6 groups.

[0102] In some embodiments, each R^6 is independently halogen or -OR^7; and

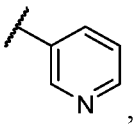
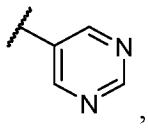
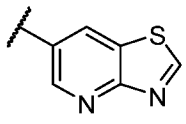
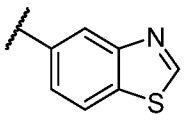
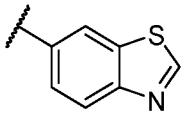
each R^7 is independently C_1-C_2 alkyl or C_3 cycloalkyl.

[0103] In some embodiments of the compound of formula (I-B), formula (I-B-i) or formula (I-B-ii), R^3 is C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkyl), C_1-C_2 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkyl), wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl or C_4-C_6 heterocycloalkyl,

wherein the R^4 and R^5 of R^3 are independently -H or C_1-C_3 alkyl, and

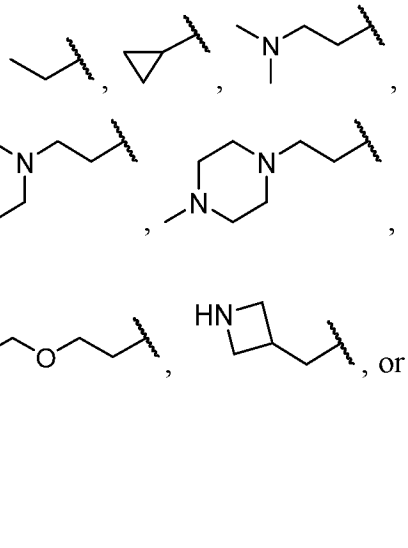
the $R^{4'}$ and $R^{5'}$ of R^3 taken together with the nitrogen atom to which they are attached form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein

each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl;

R^2 is phenyl,  ,  ,  ,  , or  , each of which is optionally substituted with 1-5 R^6 groups;

each R^6 is independently halogen or $-OR^7$; and

each R^7 is independently C_1-C_2 alkyl or C_3 cycloalkyl.

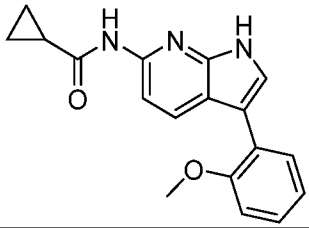
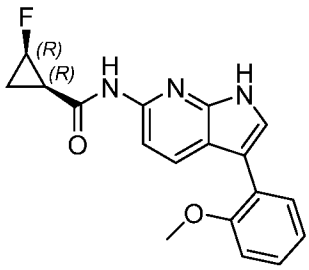
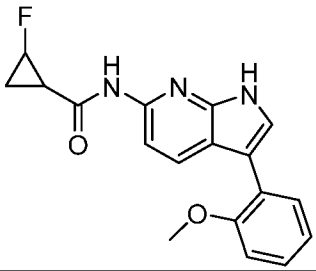
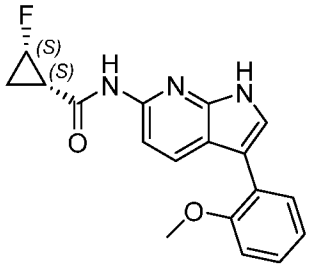
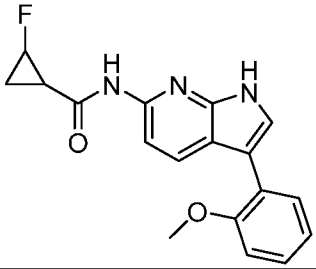
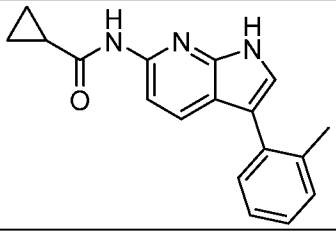
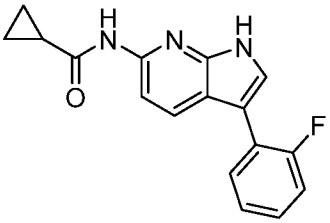
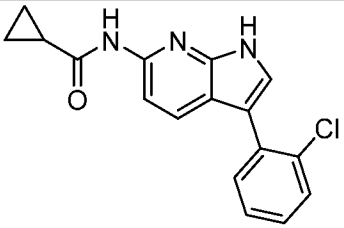
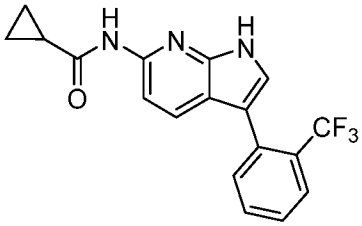
[0104] In some embodiments, R^3 is  .

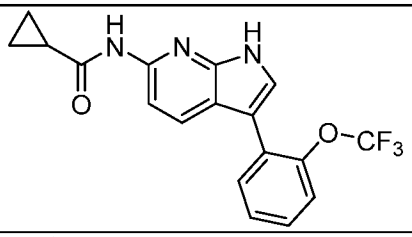
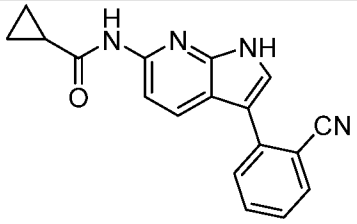
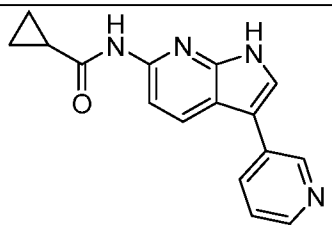
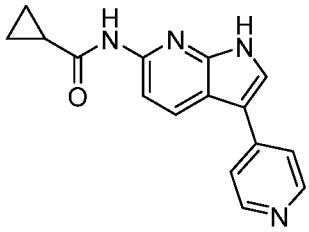
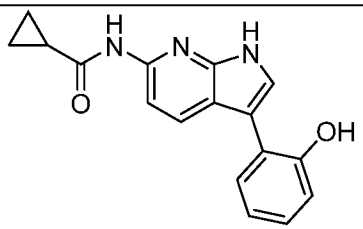
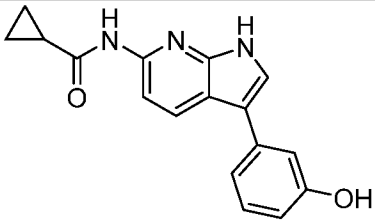
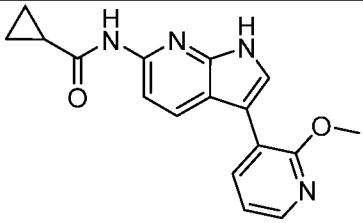
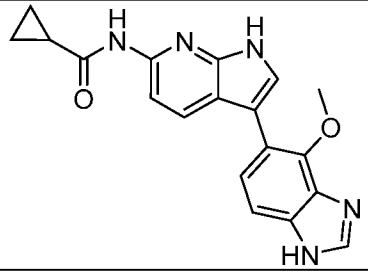
[0105] In some embodiments, each R^6 is independently -F, $-OCH_3$, or cyclopropyloxy. In some embodiments, R^8 is H.

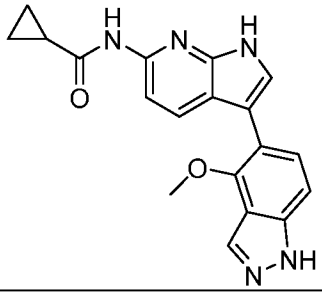
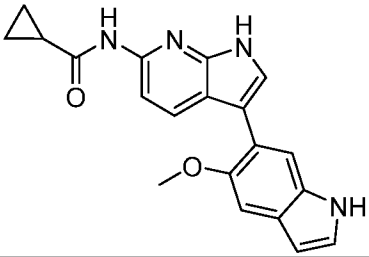
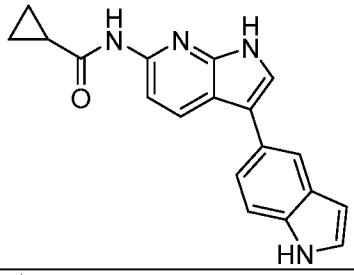
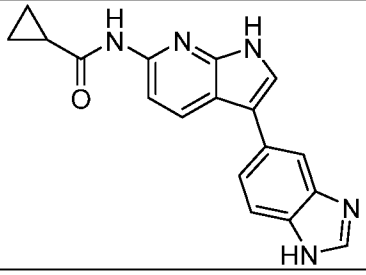
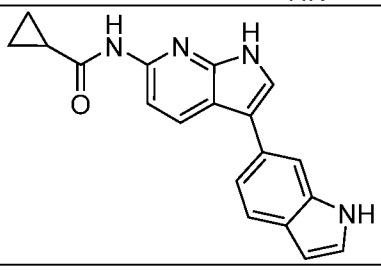
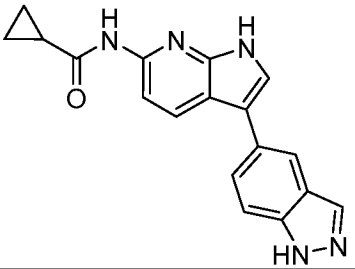
[0106] In some embodiments, provided is a compound selected from the compounds in Table 1, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing.

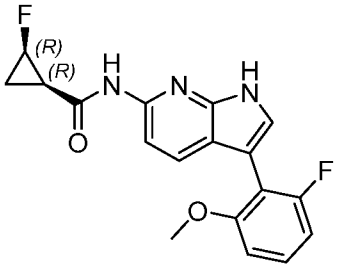
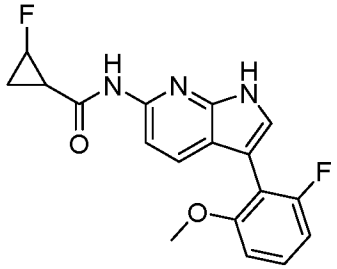
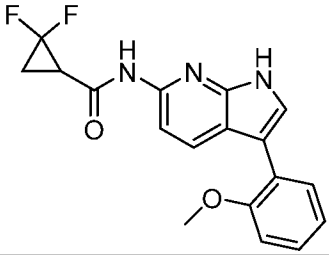
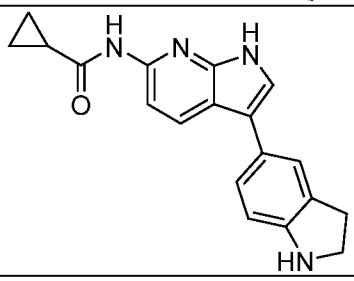
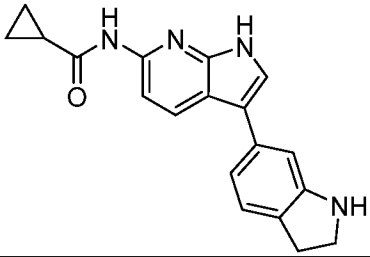
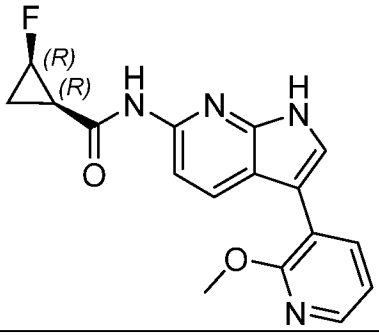
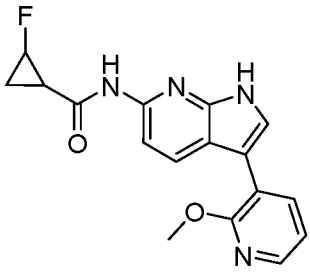
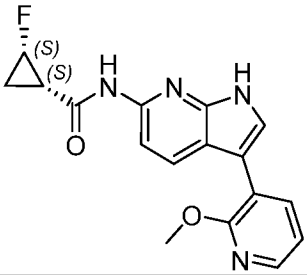
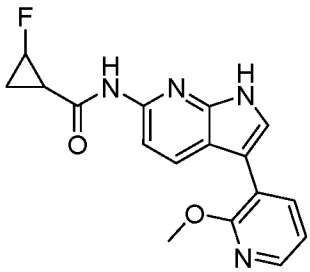
Table 1.

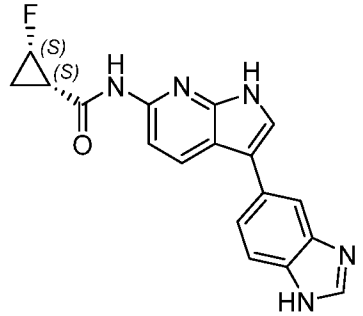
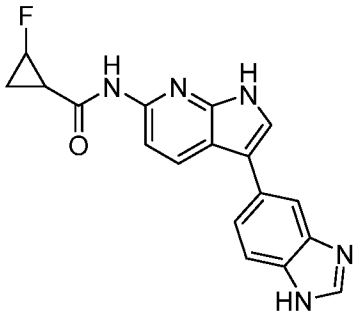
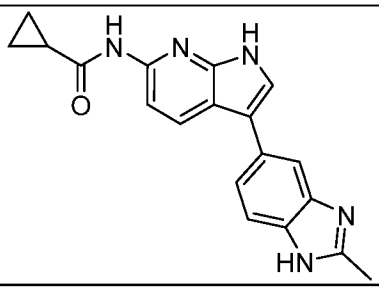
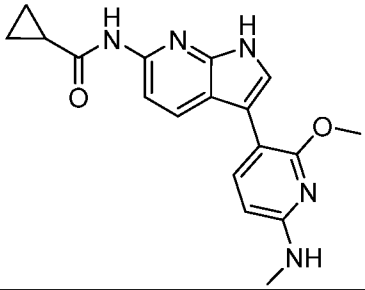
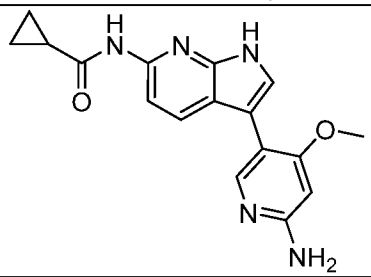
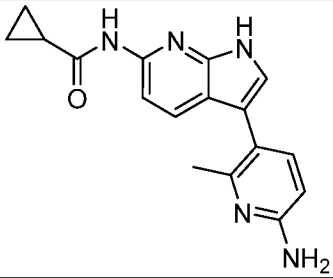
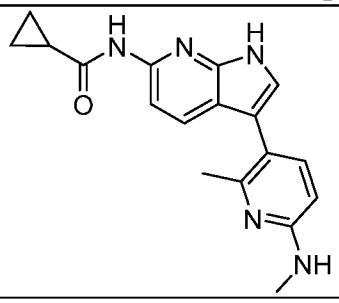
Cmpd No.	Structure	Cmpd No.	Structure

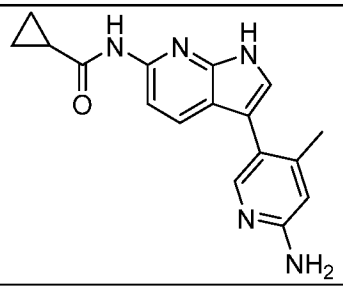
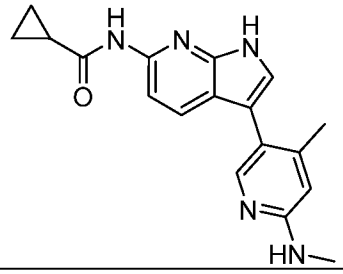
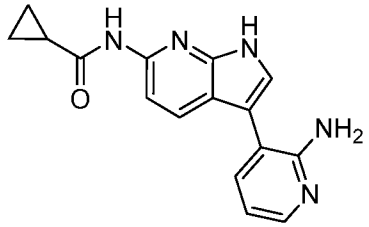
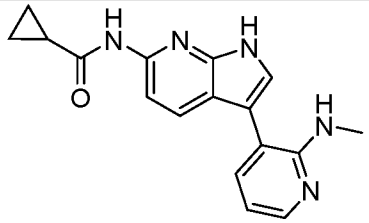
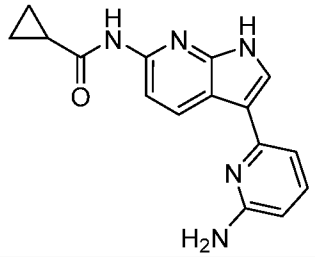
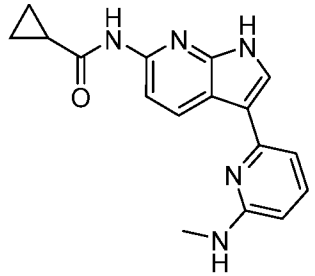
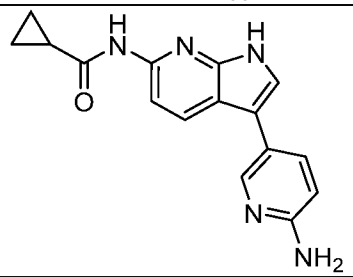
1			
2		**2-1**	
3		**2-1**	
4			
5			
6			
7			

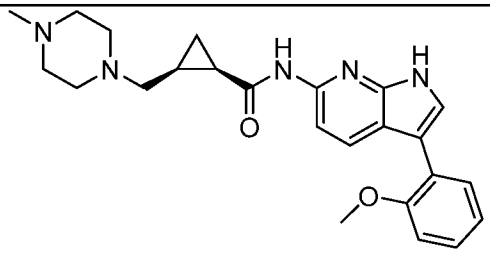
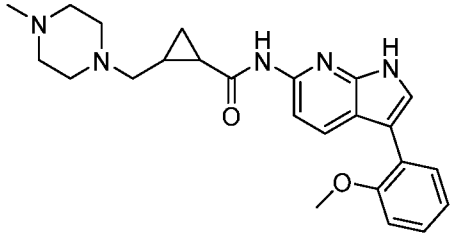
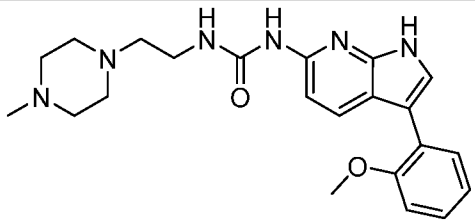
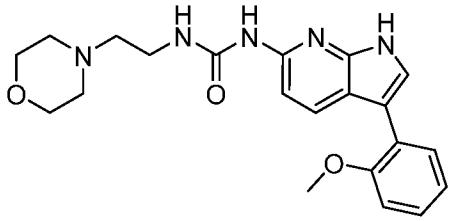
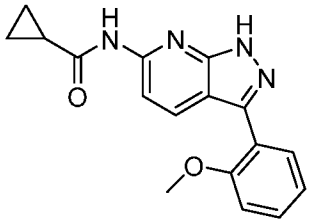
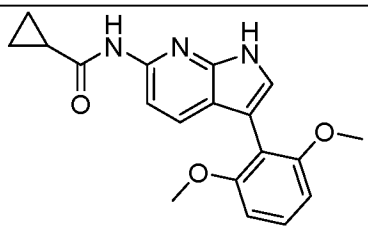
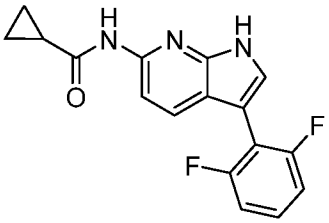
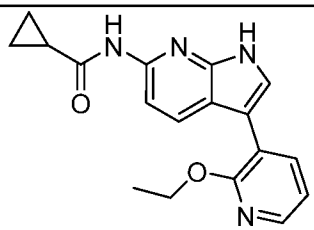
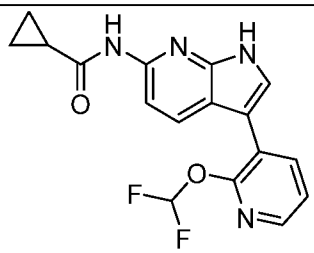
8			
9			
10			
11			
12			
13			
14			
15			

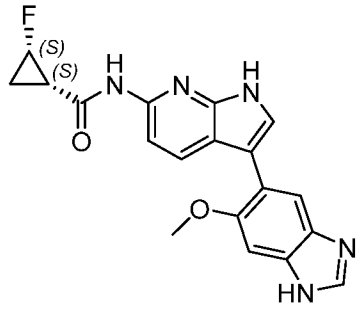
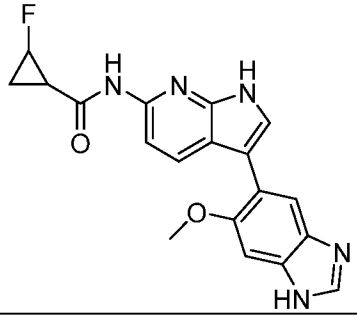
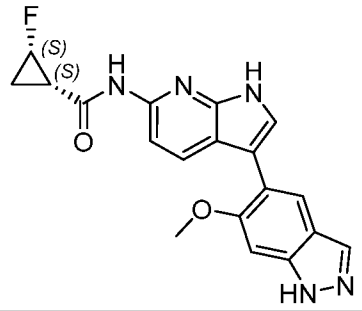
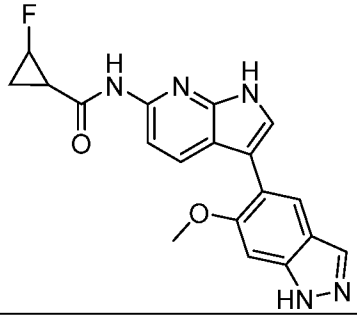
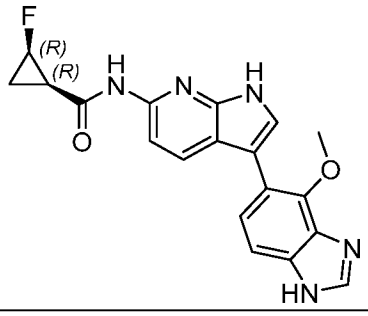
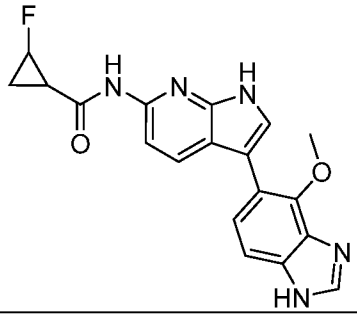
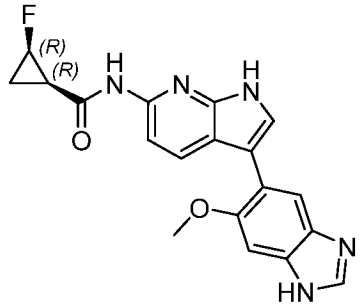
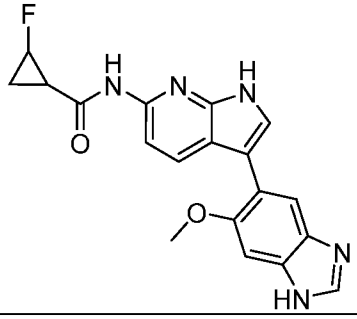
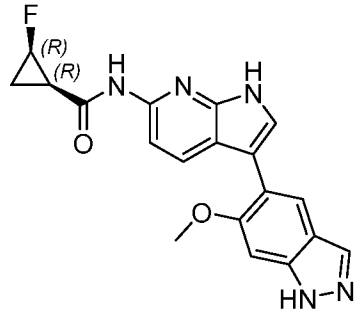
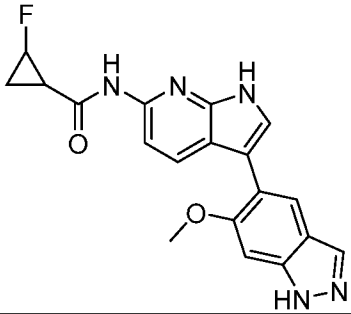
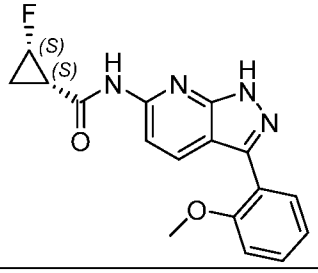
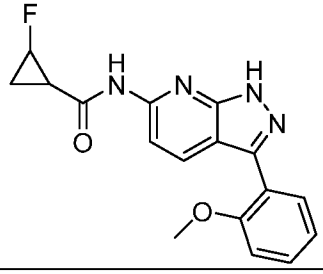
16			
17			
18			
19			
20			
21			

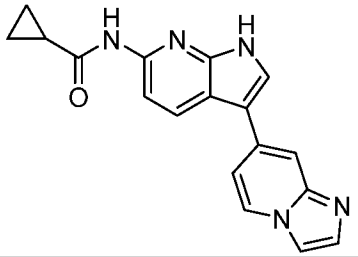
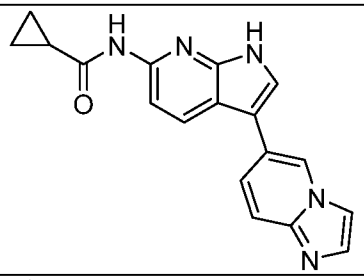
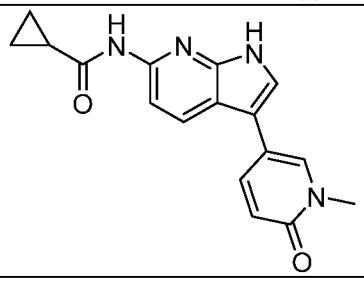
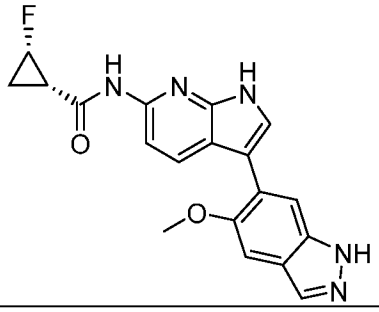
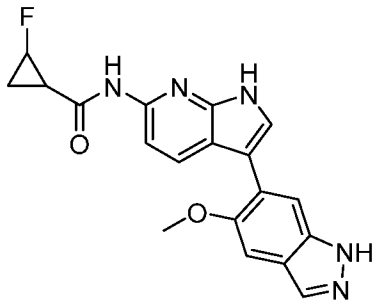
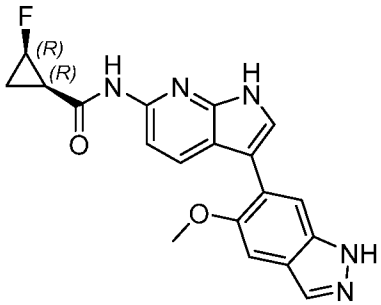
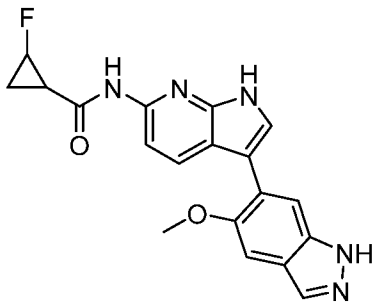
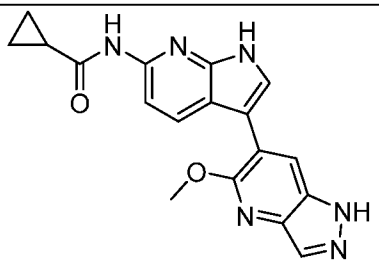
22		22-1	
23			
24			
25			
26		26-1	
27		26-1	

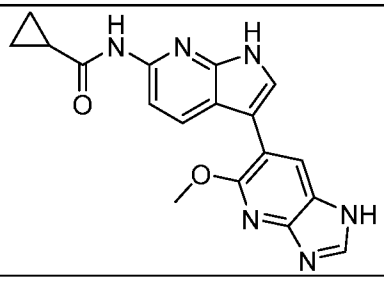
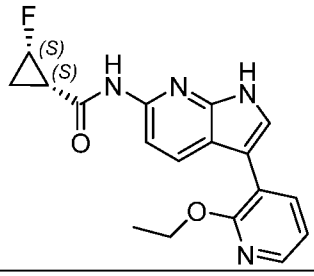
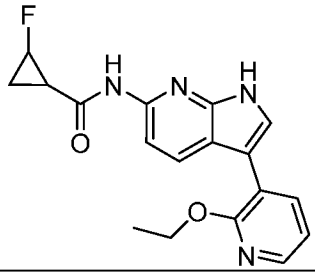
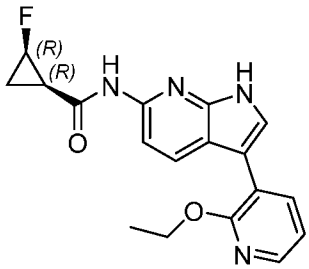
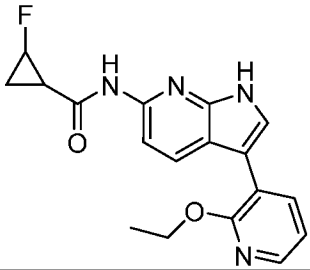
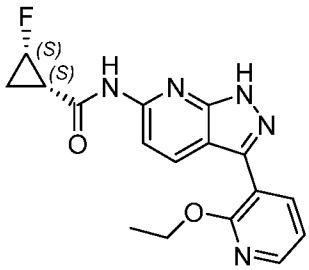
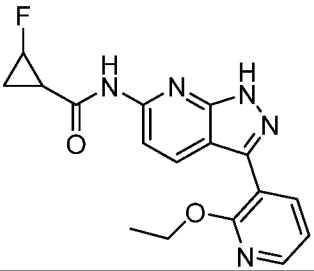
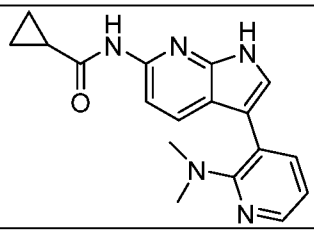
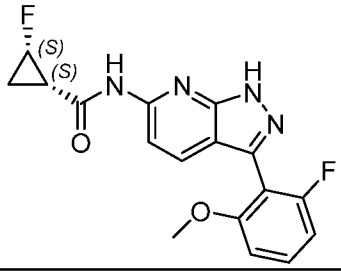
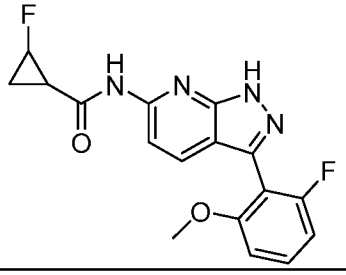
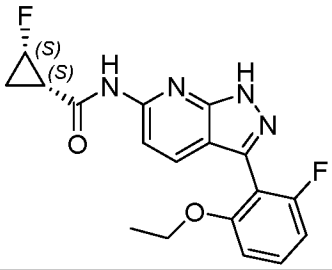
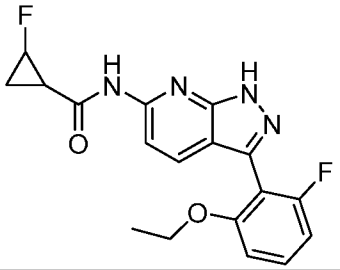
28		**28-1**	
29			
30			
31			
32			
33			

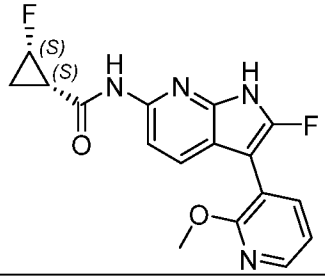
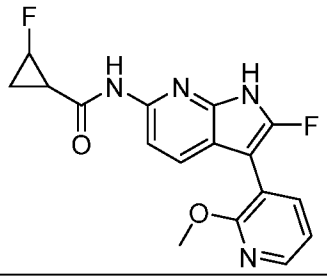
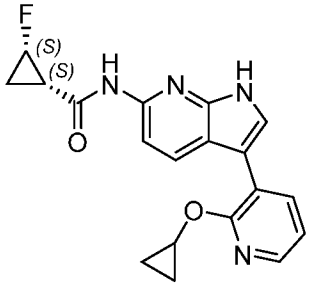
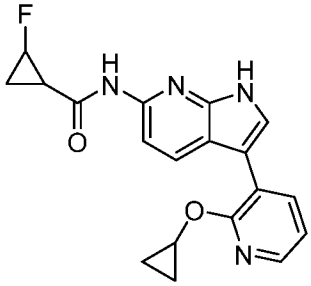
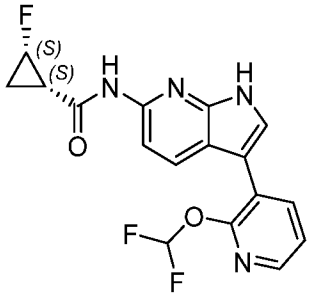
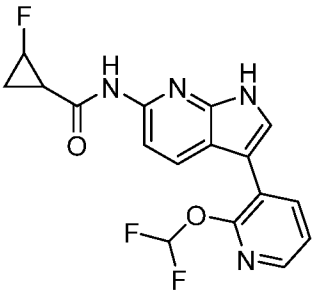
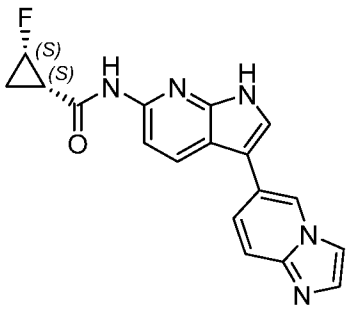
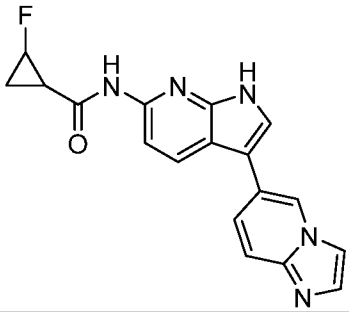
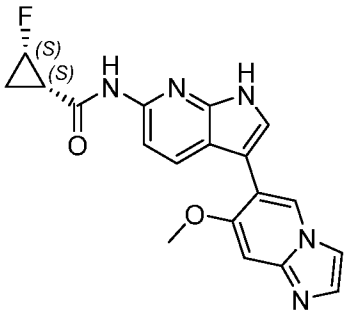
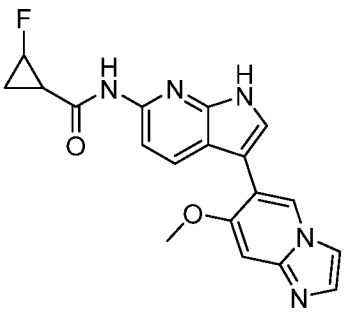
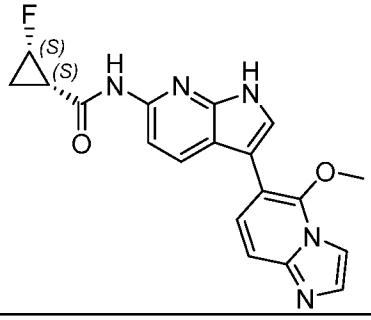
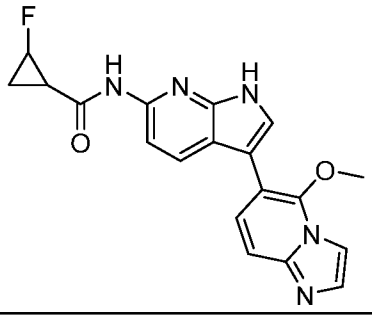
34			
35			
36			
37			
38			
39			
40			

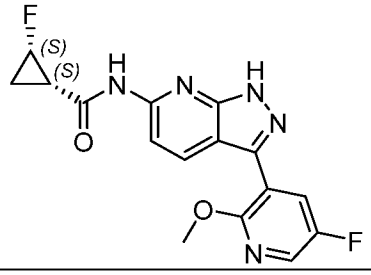
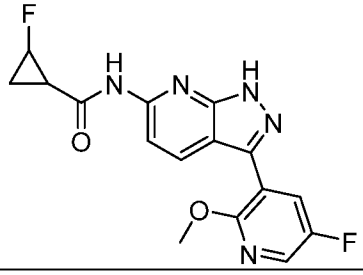
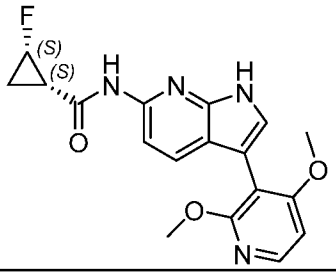
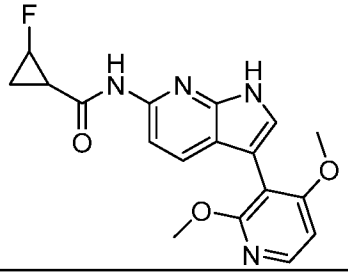
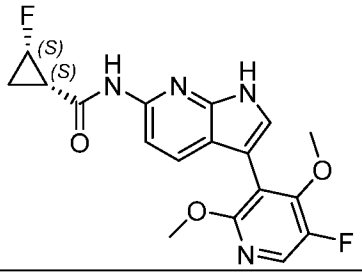
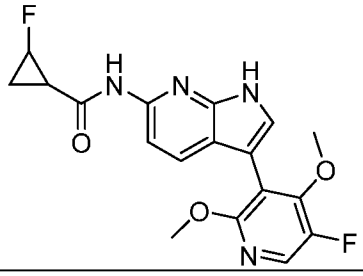
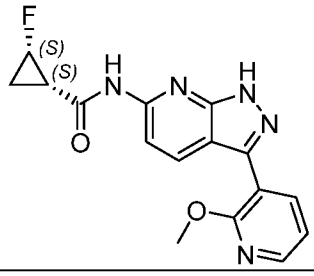
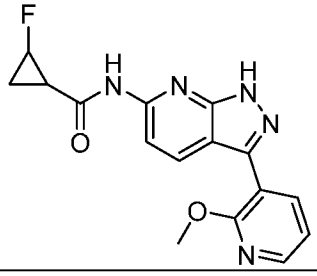
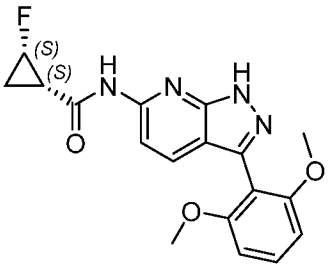
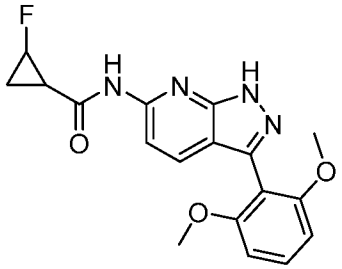
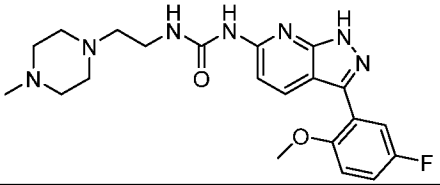
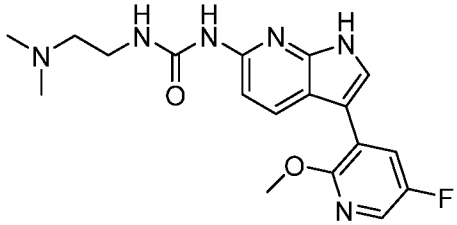
41		41-1	
42			
43			
44			
45			
46			
47			
48			

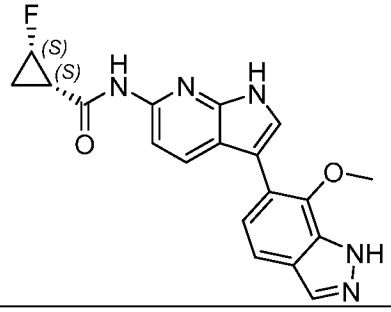
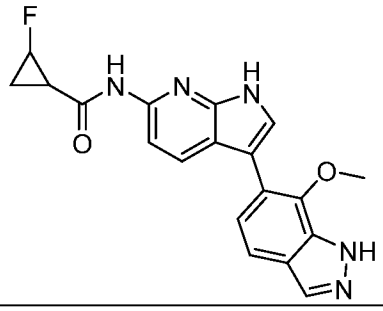
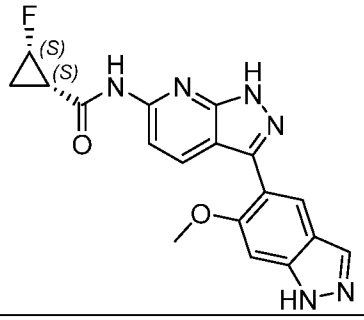
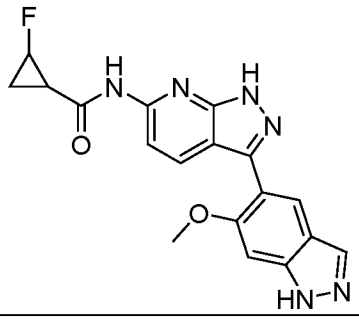
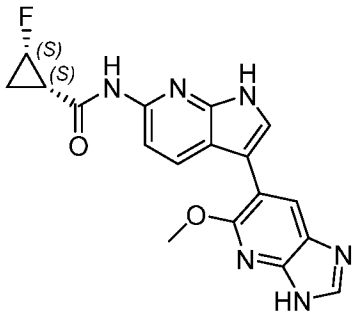
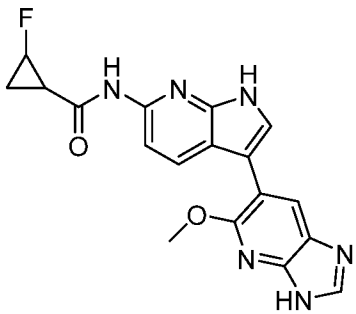
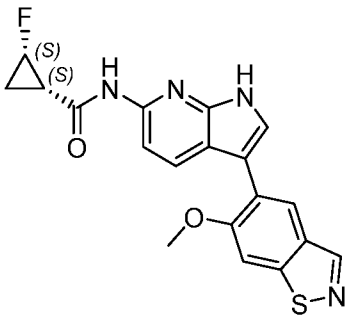
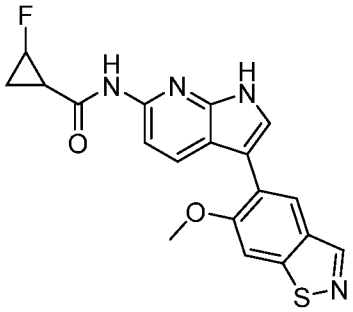
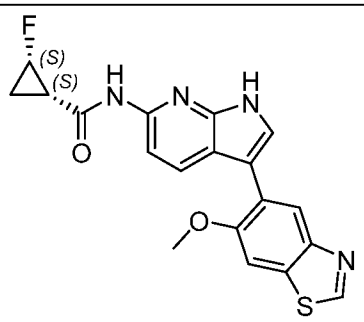
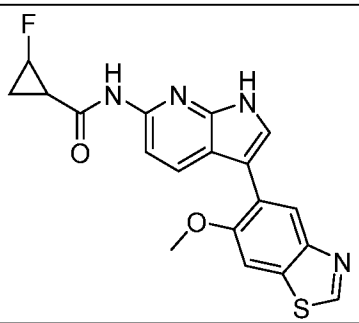
49		**49-1**	
50		**50-1**	
51		**51-1**	
52		**49-1**	
53		**50-1**	
54		**54-1**	

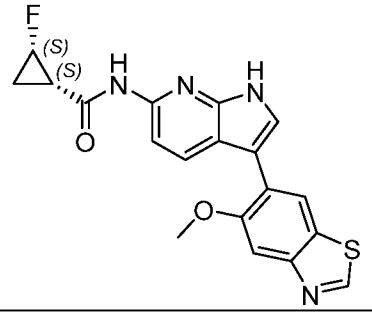
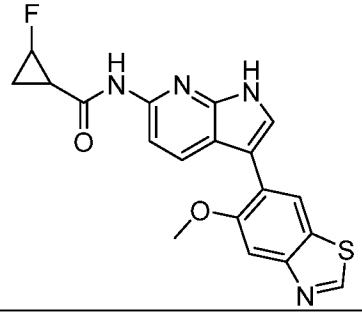
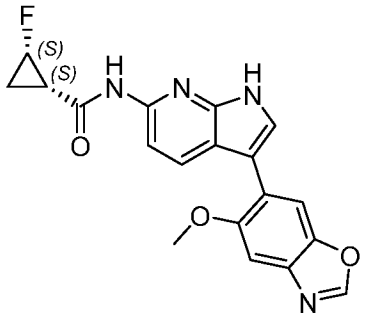
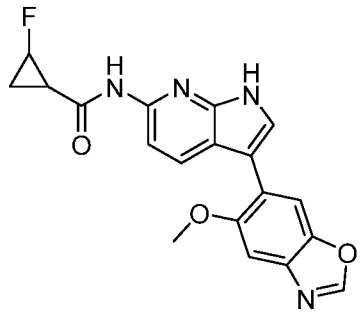
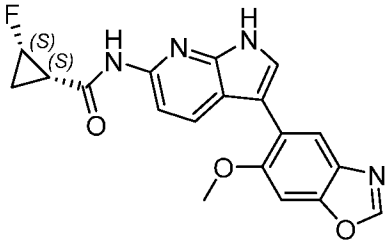
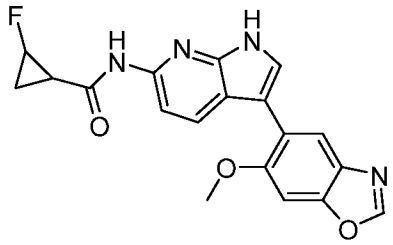
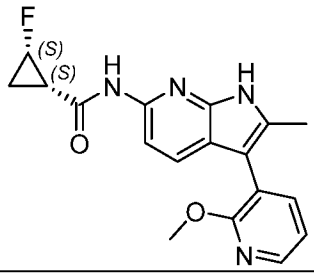
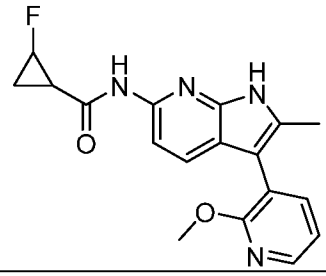
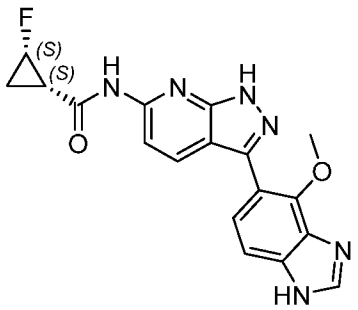
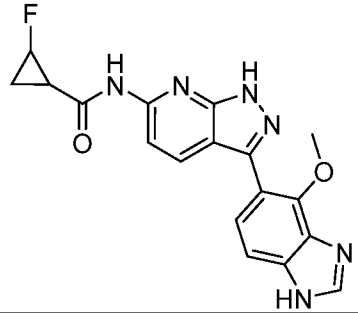
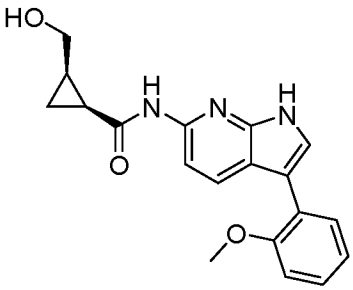
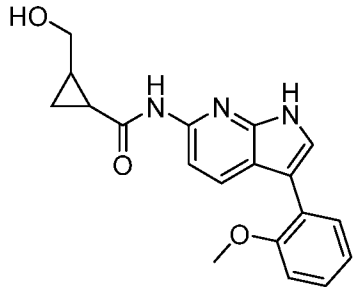
55			
56			
57			
58		**58-1**	
59		**58-1**	
60			

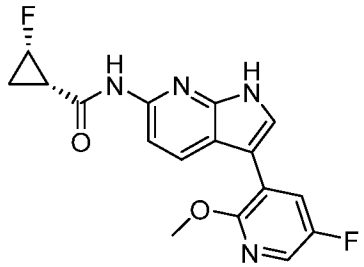
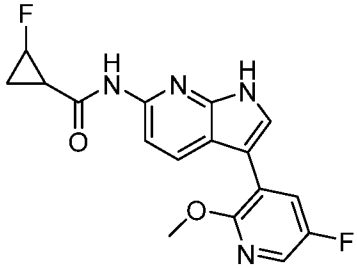
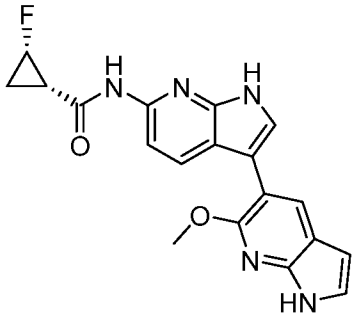
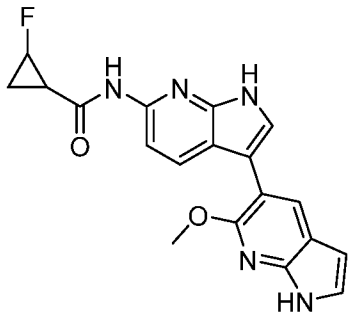
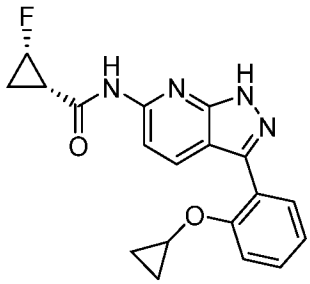
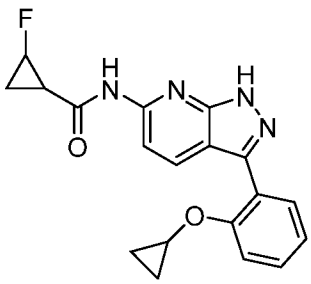
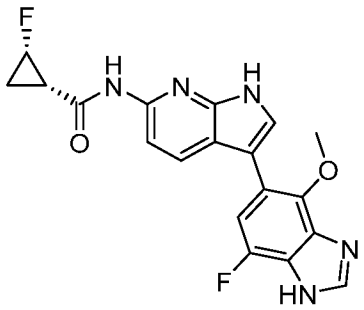
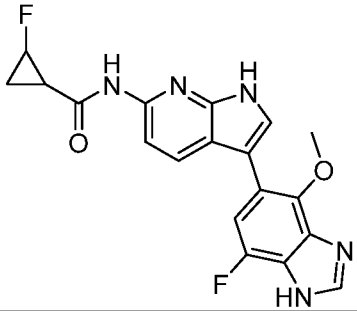
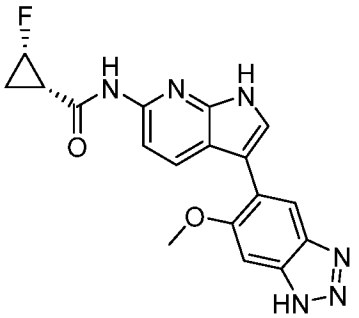
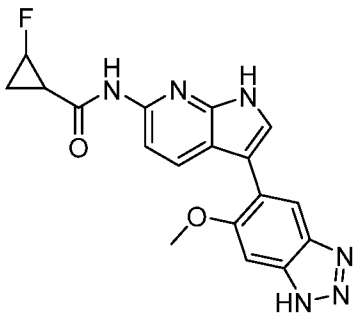
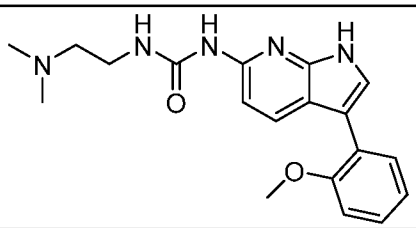
61			
62		62-1	
63		62-1	
64		64-1	
65			
66		66-1	
67		67-1	

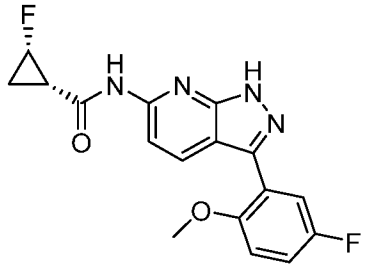
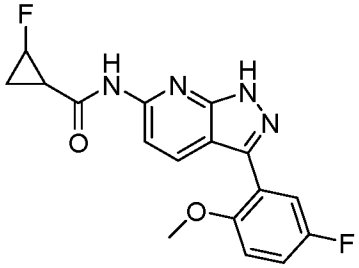
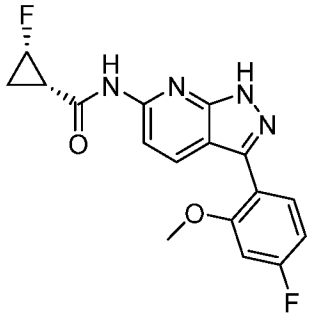
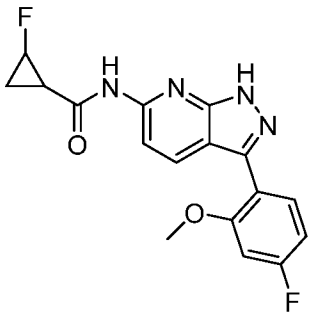
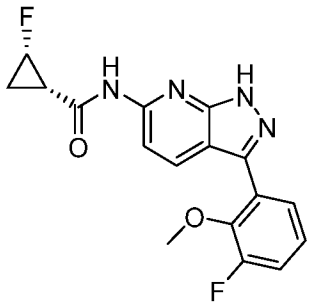
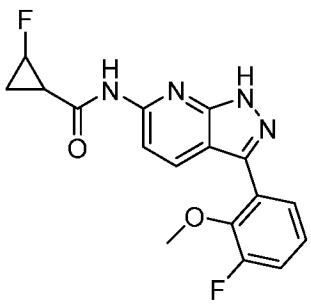
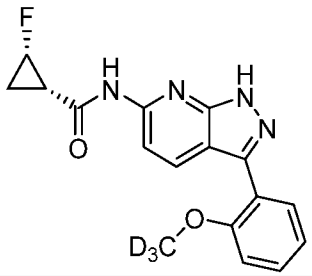
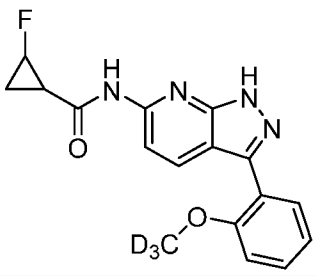
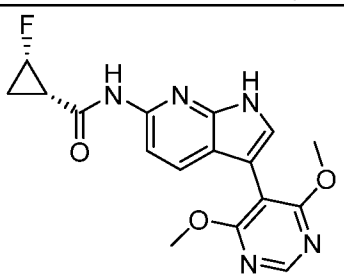
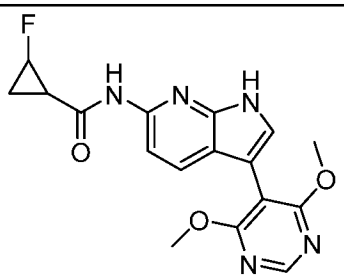
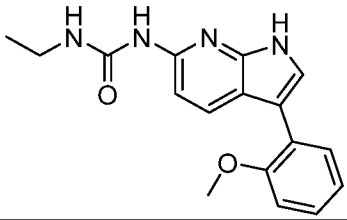
68		**68-1**	
69		**69-1**	
70		**70-1**	
71		**71-1**	
72		**72-1**	
73		**73-1**	

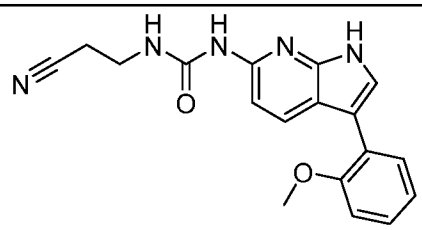
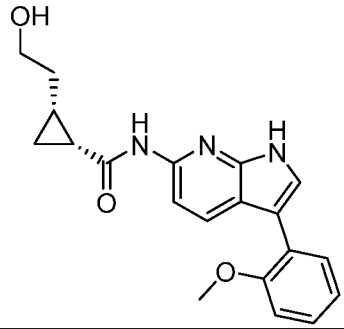
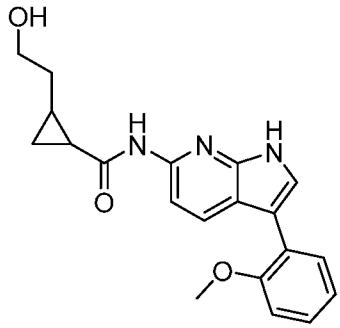
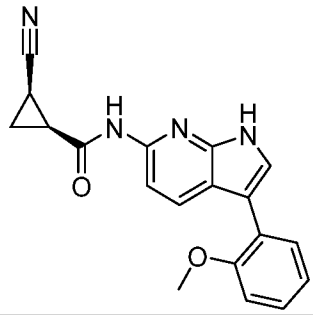
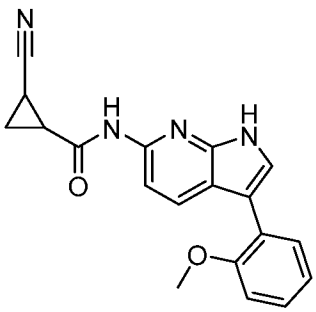
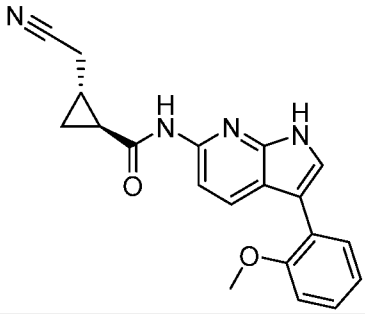
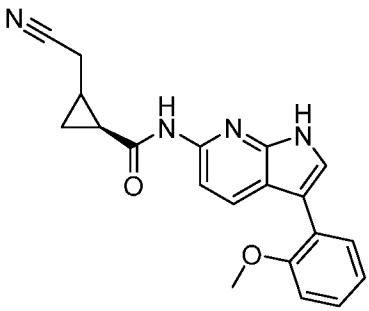
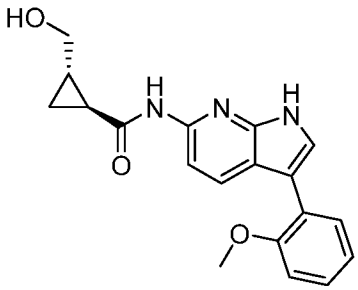
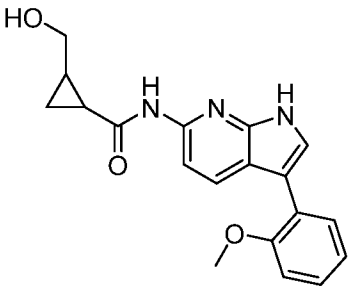
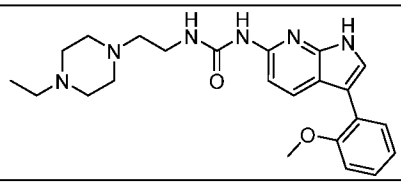
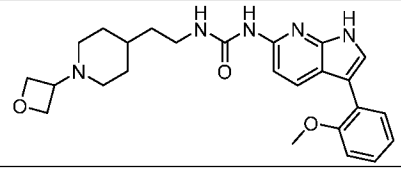
74		**74-1**	
75		**75-1**	
76		**76-1**	
77		**77-1**	
78		**78-1**	
79			
80			

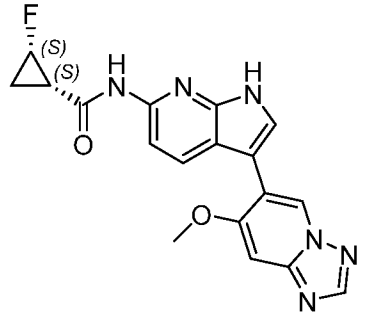
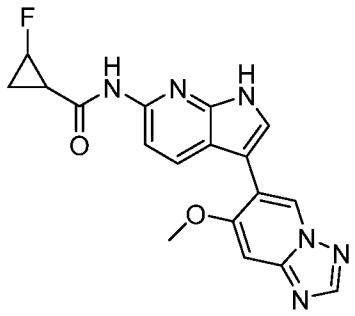
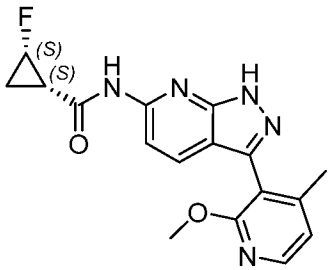
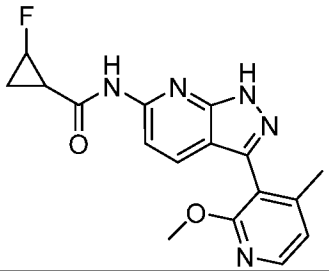
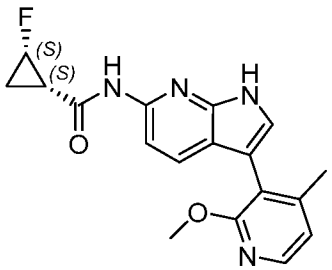
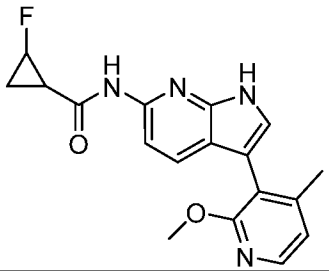
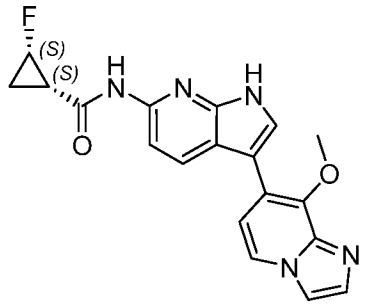
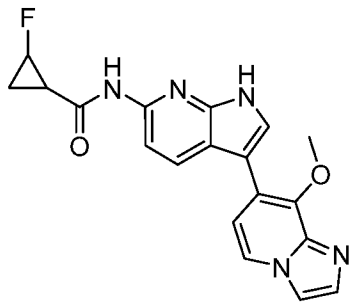
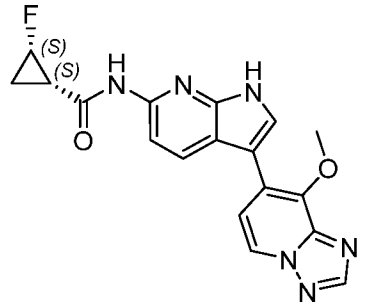
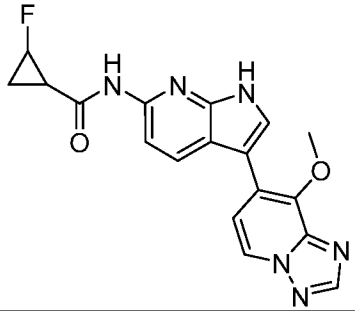
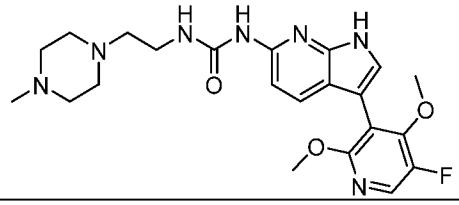
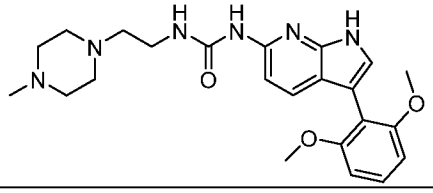
81		**81-1**	
82		**82-1**	
83		**83-1**	
84		**84-1**	
85		**85-1**	

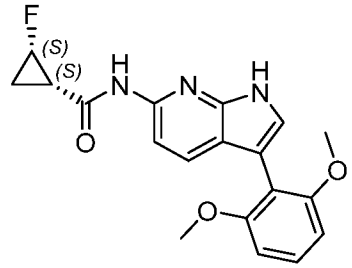
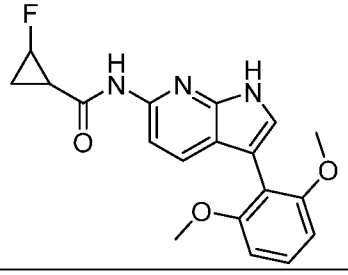
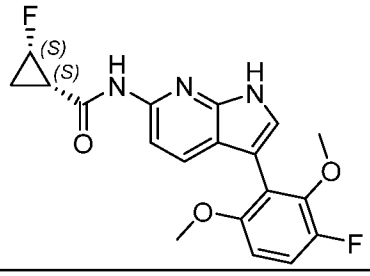
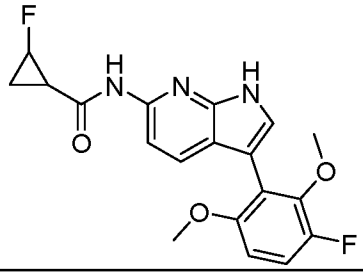
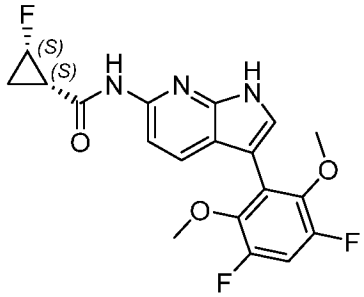
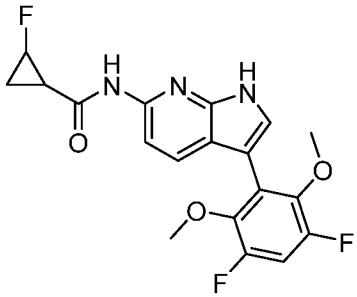
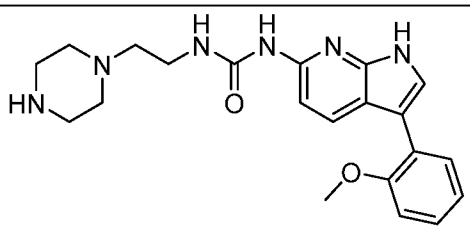
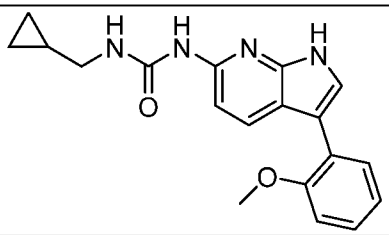
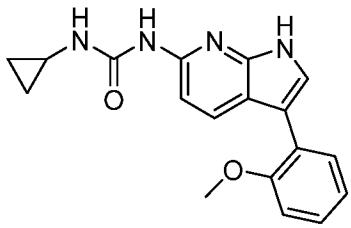
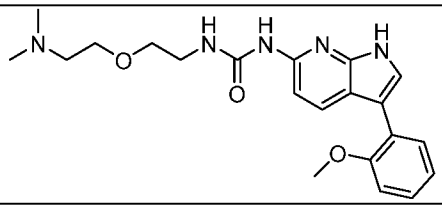
86		**86-1**	
87		**87-1**	
88		**88-1**	
89		**89-1**	
90		**90-1**	
91		**91-1**	

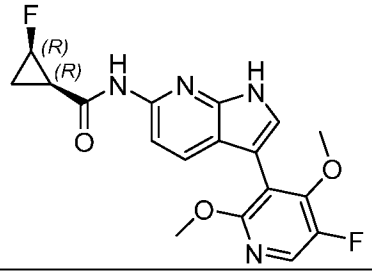
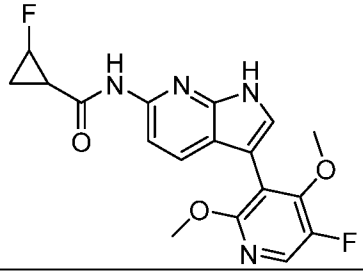
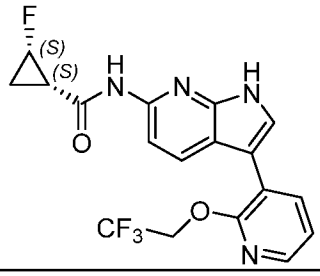
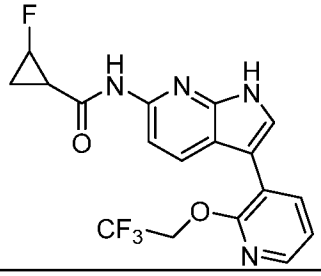
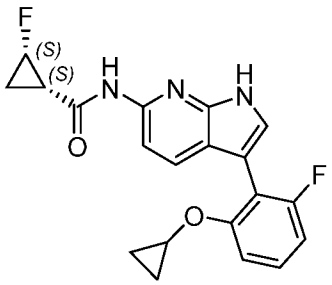
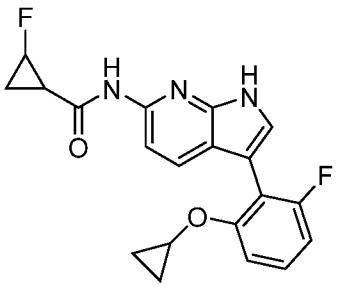
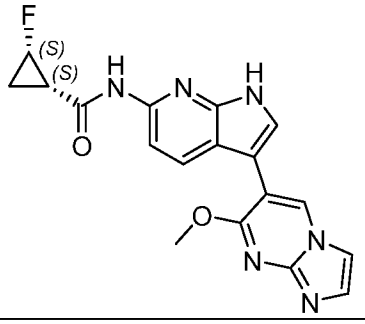
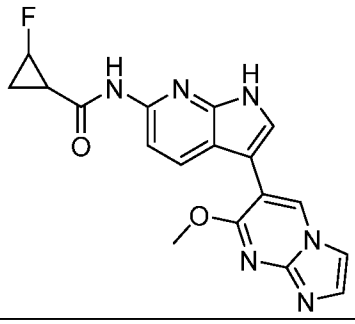
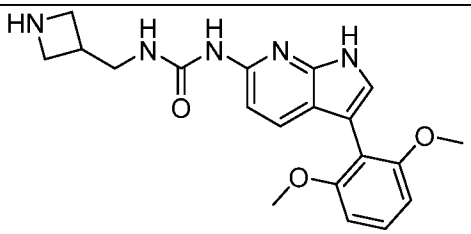
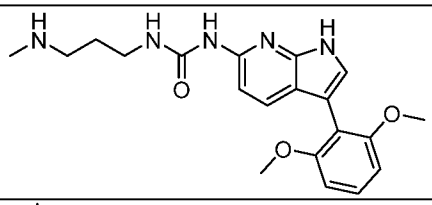
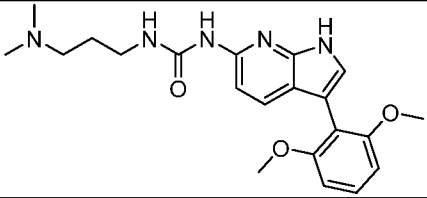
92		**92-1**	
93		**93-1**	
94		**94-1**	
95		**95-1**	
96		**96-1**	
97			

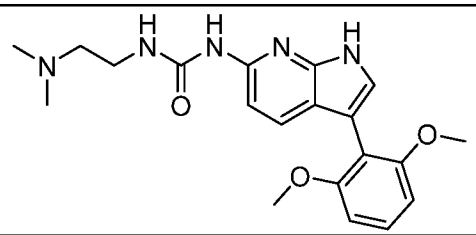
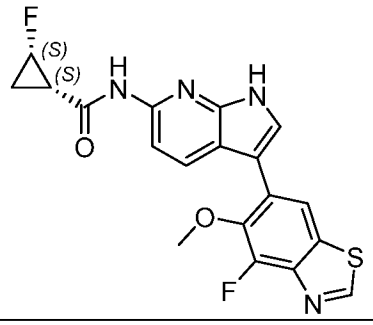
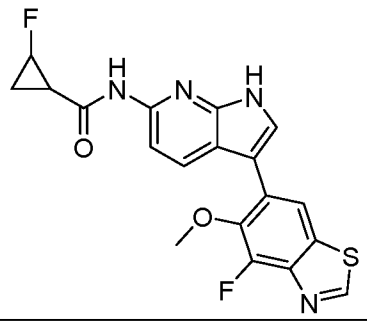
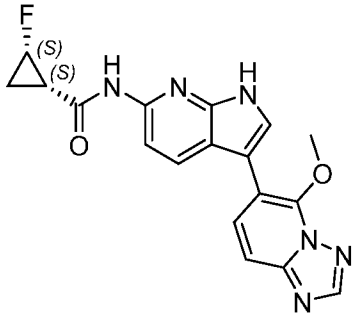
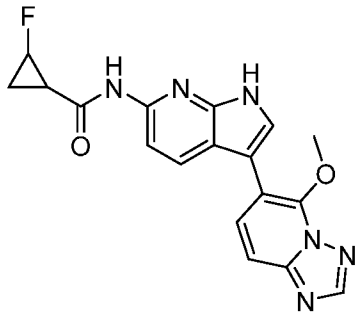
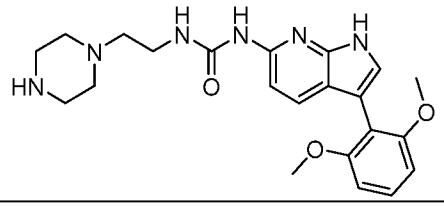
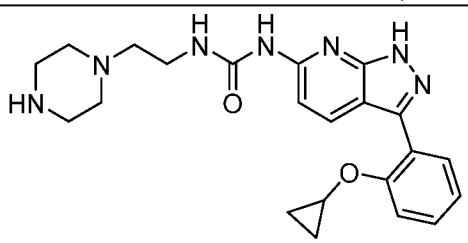
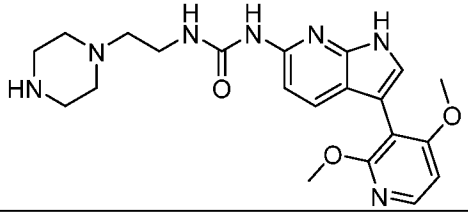
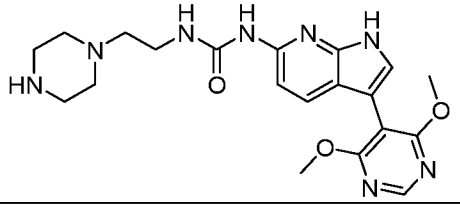
98		**98-1**	
99		**99-1**	
100		**100-1**	
101		**101-1**	
102		**102-1**	
103			

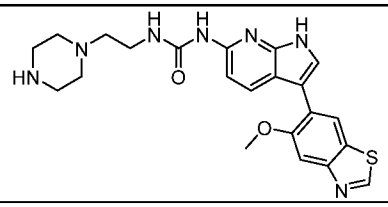
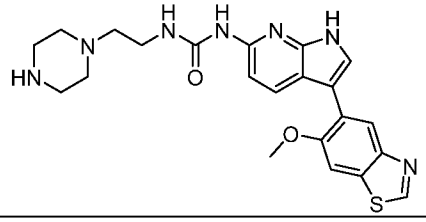
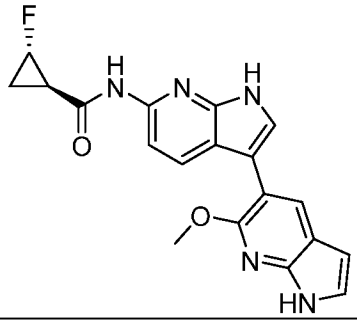
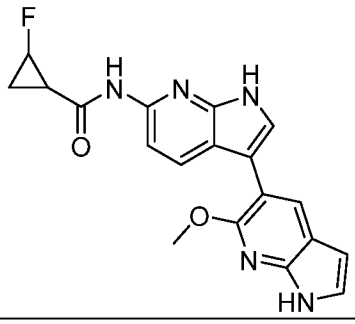
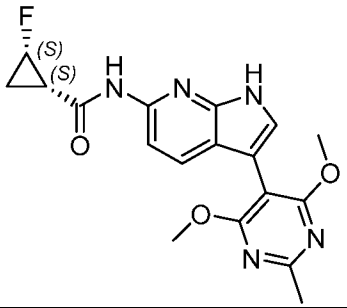
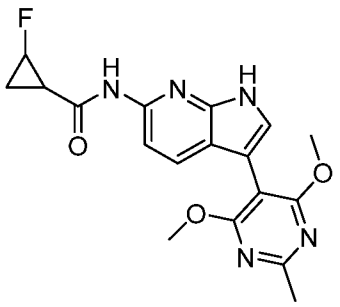
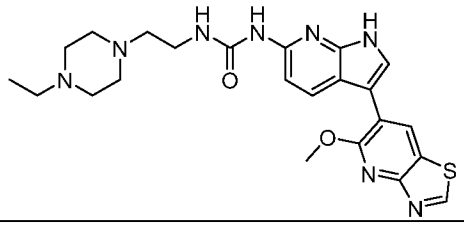
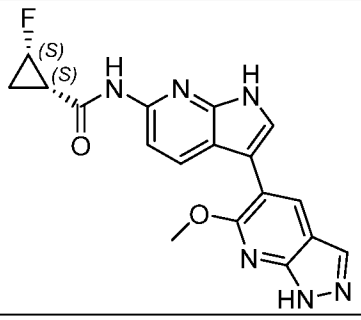
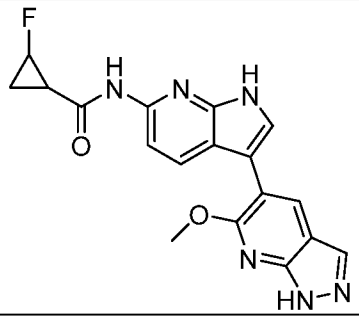
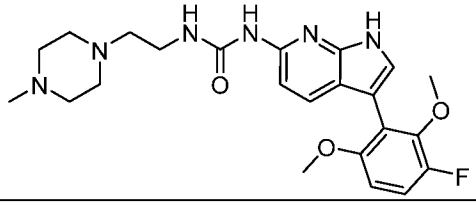
104			
105		**105 -1**	
106		**106 -1**	
107		**107 -1**	
108		**108 -1**	
109			
110			

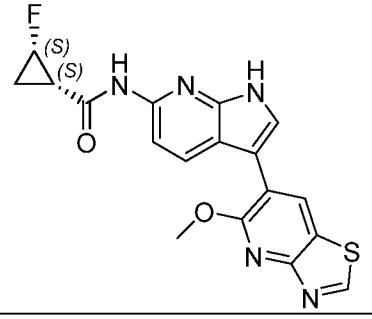
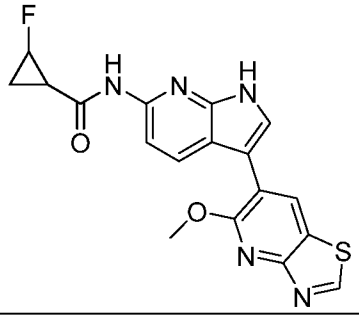
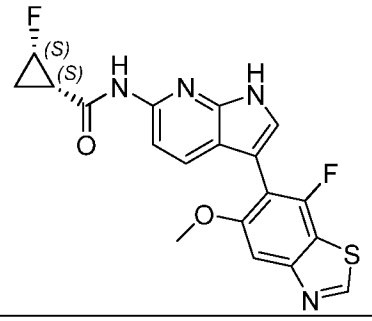
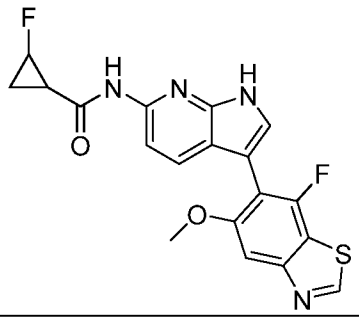
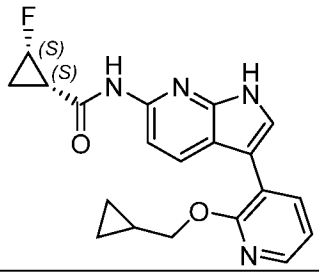
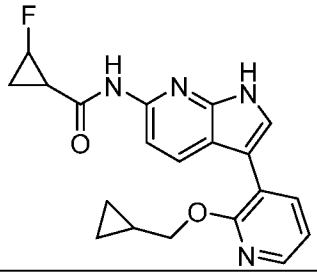
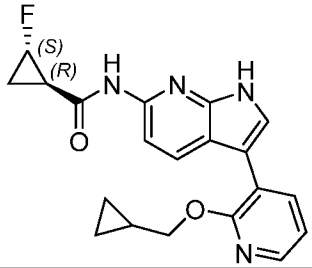
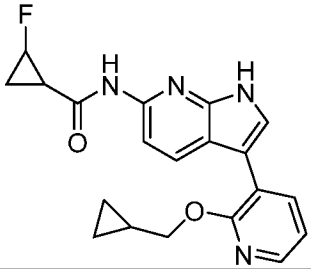
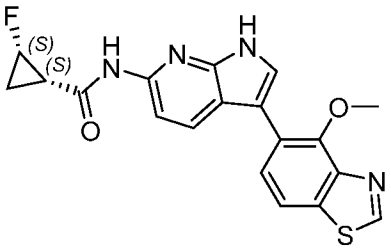
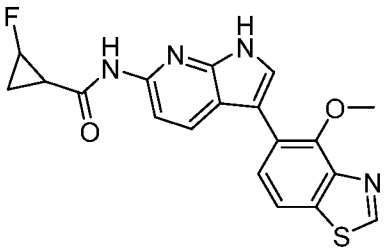
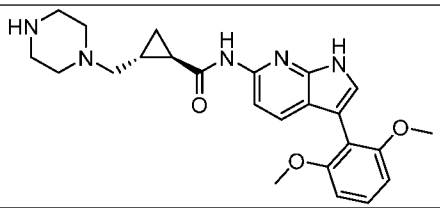
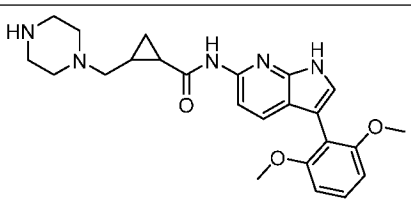
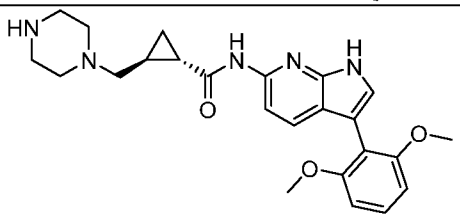
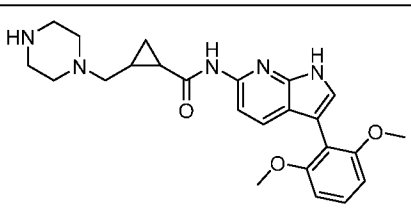
111		**111-1**	
112		**112-1**	
113		**113-1**	
114		**114-1**	
115		**115-1**	
116			
117			

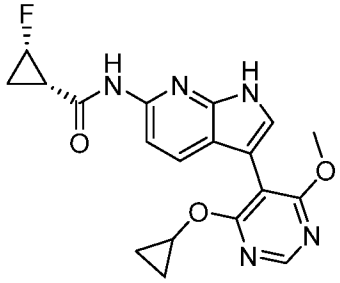
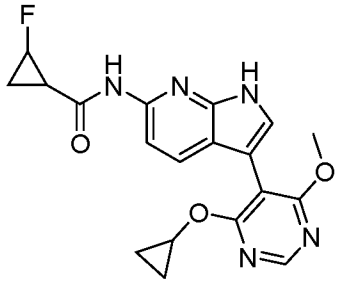
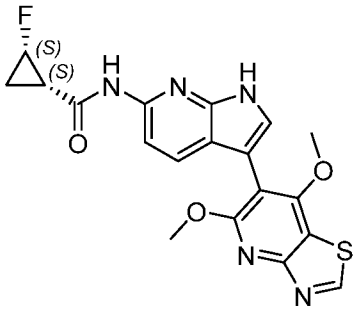
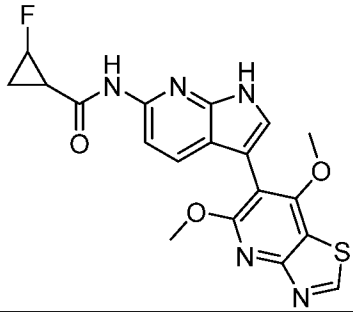
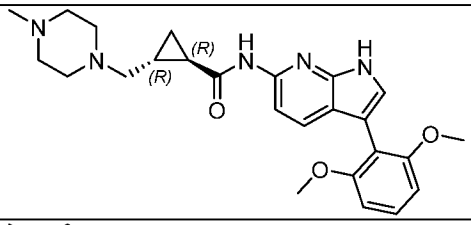
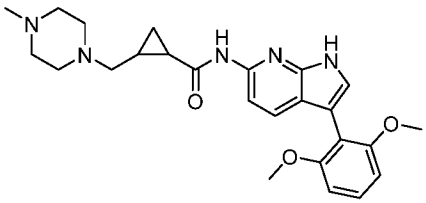
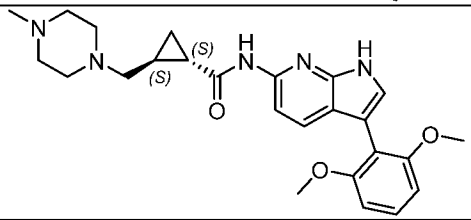
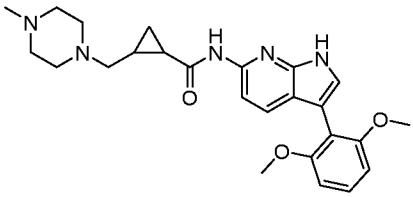
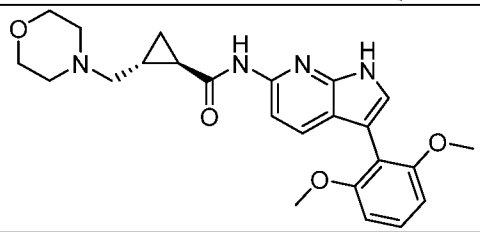
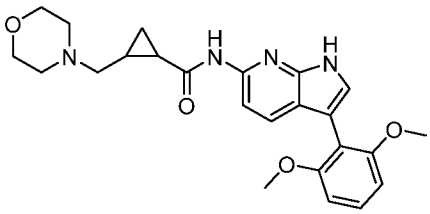
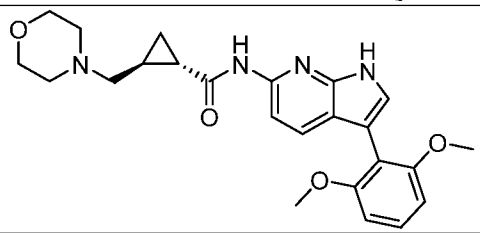
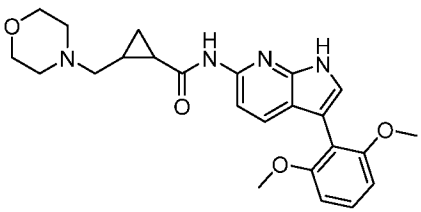
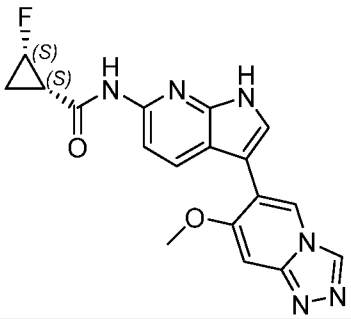
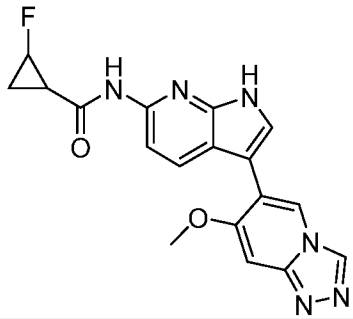
118		**118 -1**	
119		**119 -1**	
120		**120 -1**	
121			
122			
123			
124			

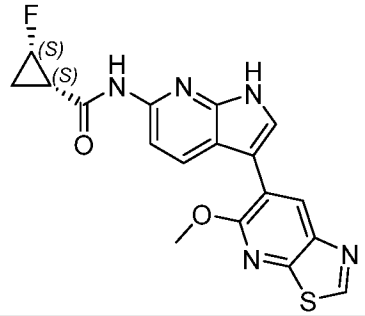
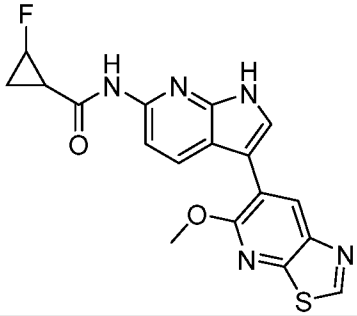
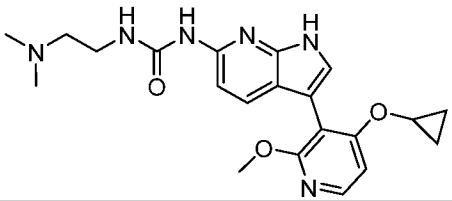
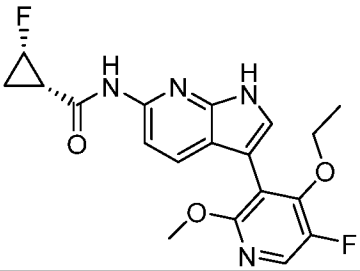
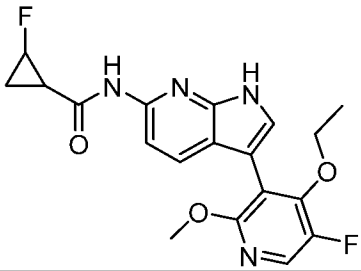
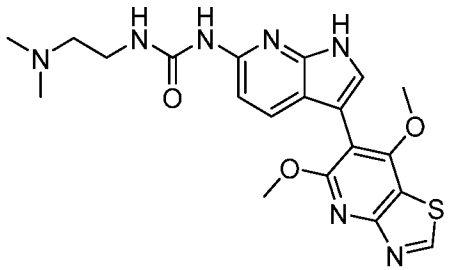
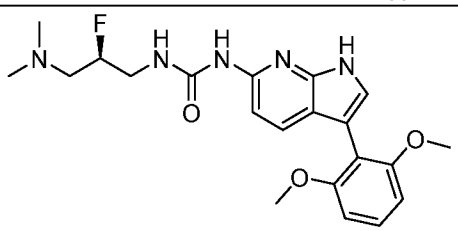
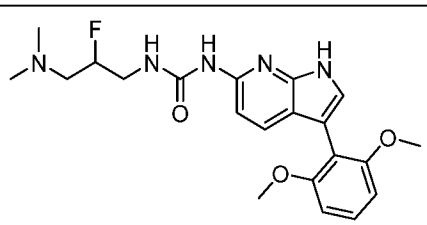
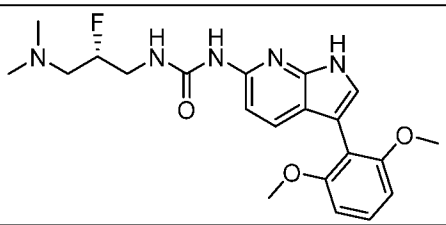
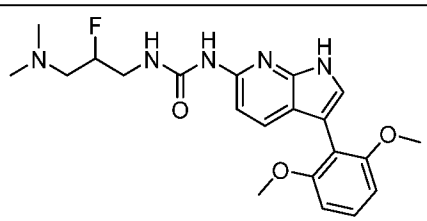
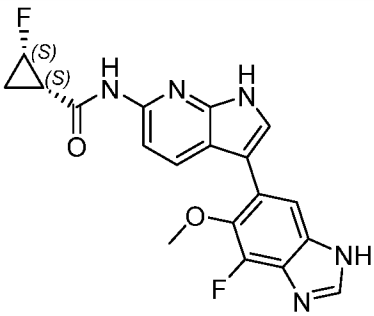
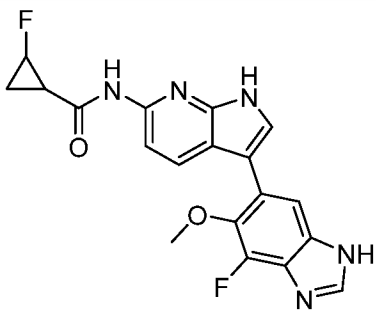
125		**125 -1**	
126		**126 -1**	
127		**127 -1**	
128		**128 -1**	
129			
130			
131			

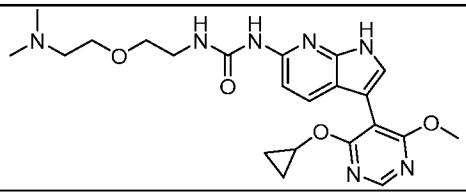
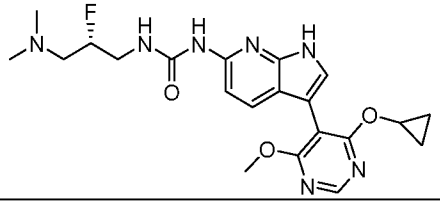
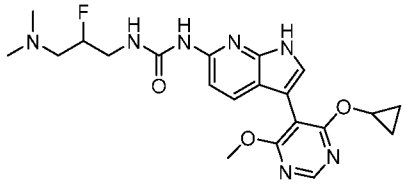
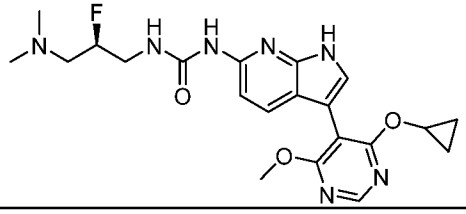
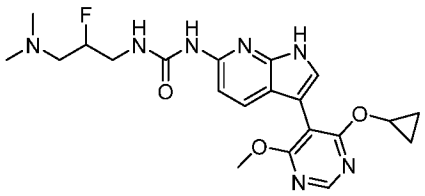
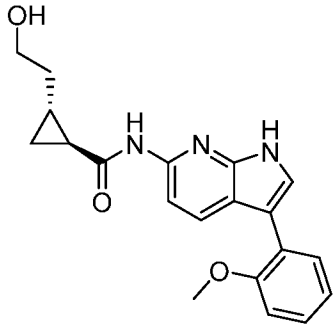
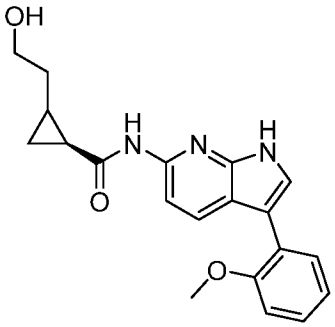
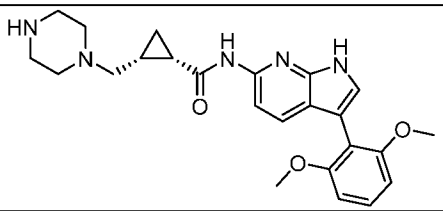
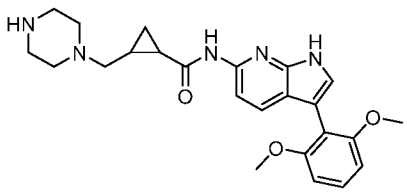
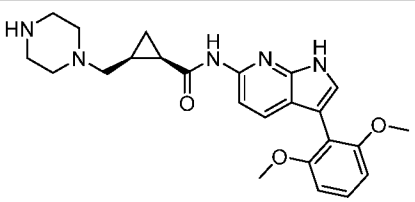
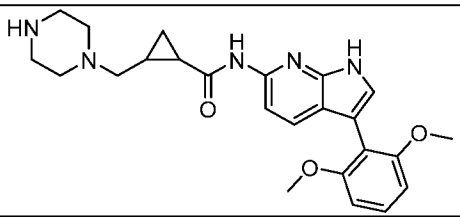
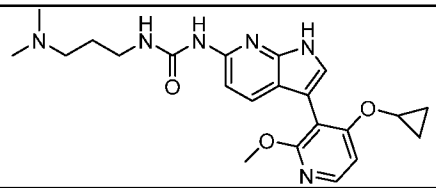
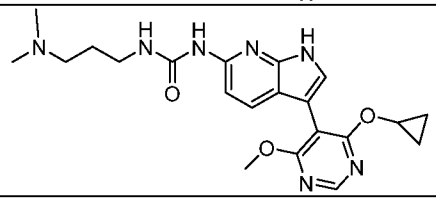
132			
133		**133 -1**	
134		**134 -1**	
135			
136			
137			
138			

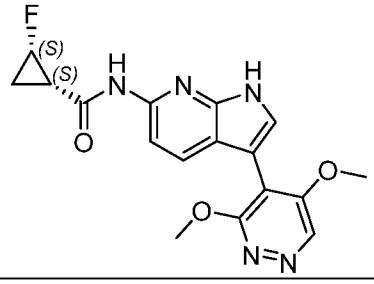
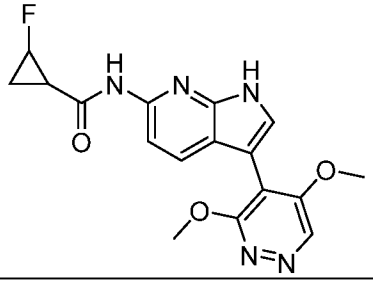
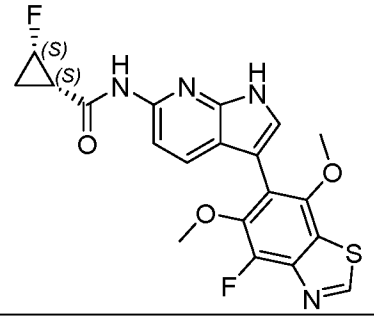
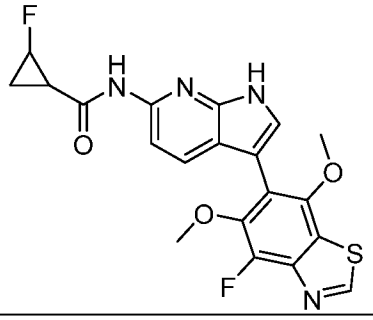
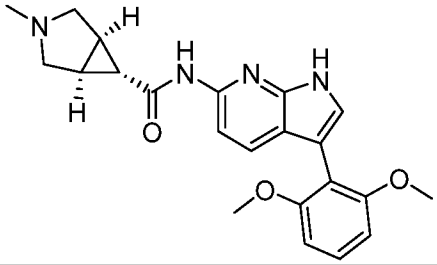
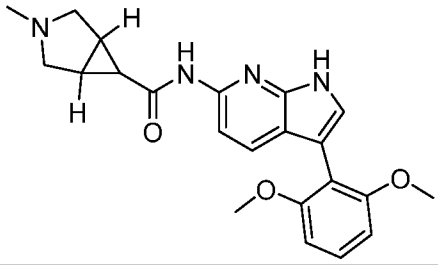
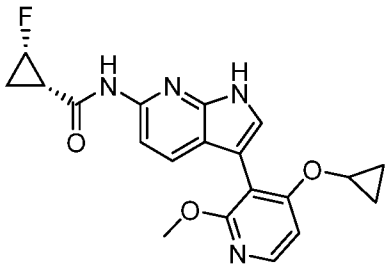
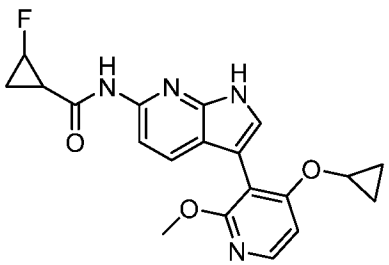
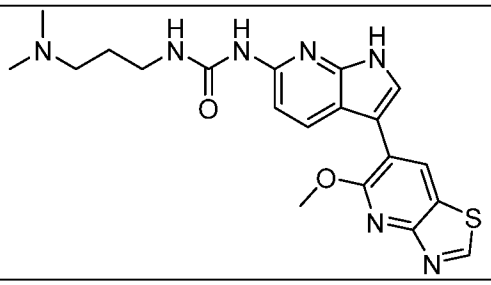
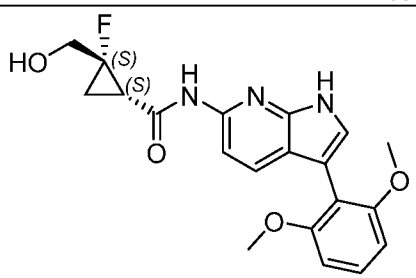
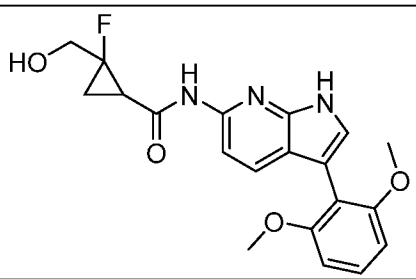
139			
140			
141		**141 -1**	
142		**142 -1**	
143			
144		**144 -1**	
145			

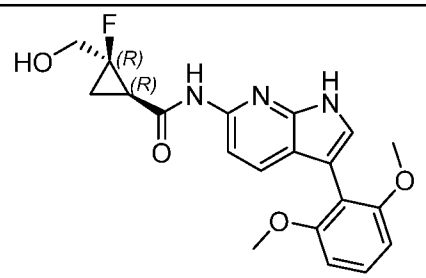
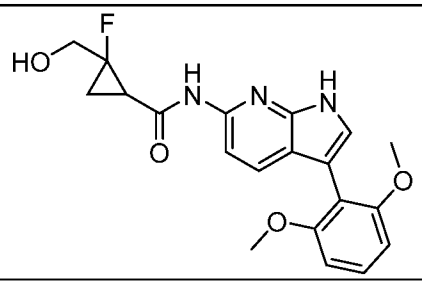
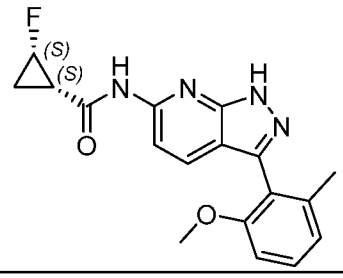
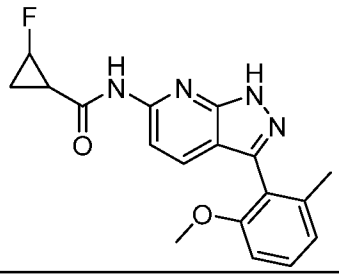
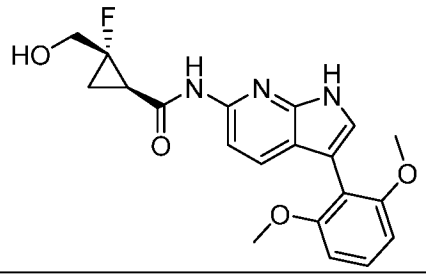
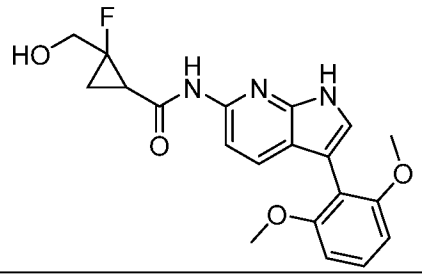
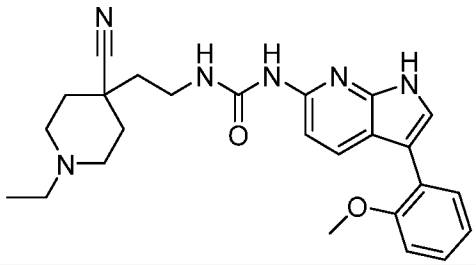
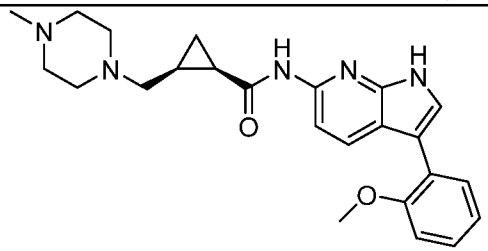
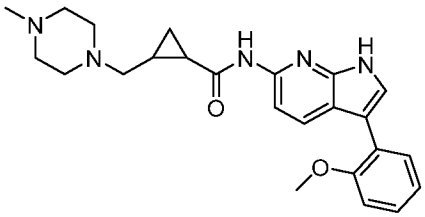
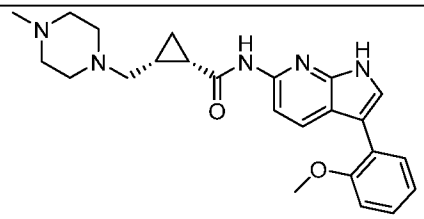
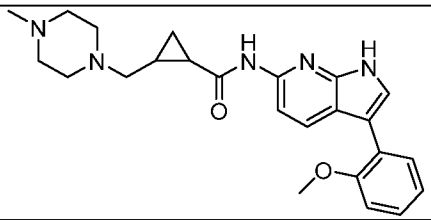
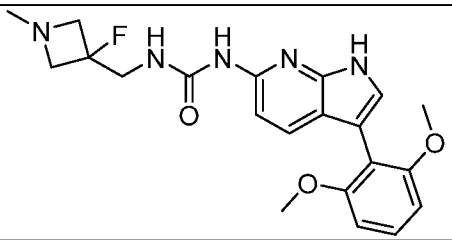
146		**146 -1**	
147		**147 -1**	
148		**148 -1**	
149		**148 -1**	
150		**150 -1**	
151		**151 -1**	
152		**151 -1**	

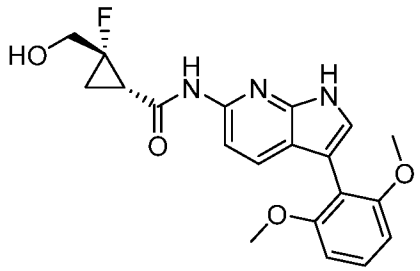
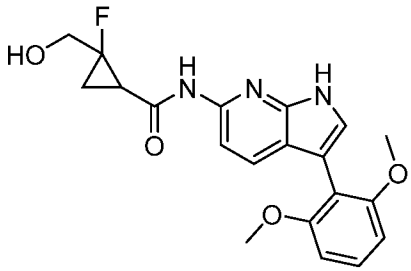
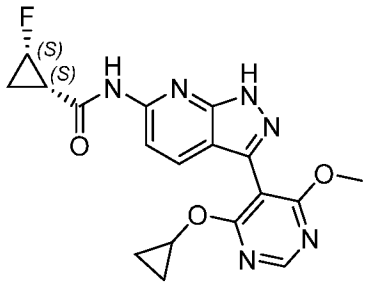
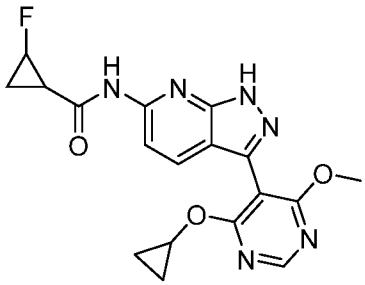
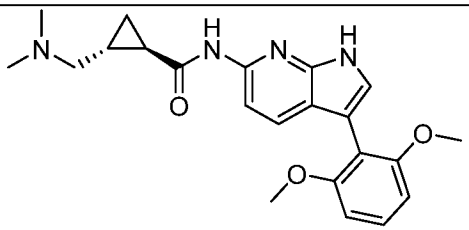
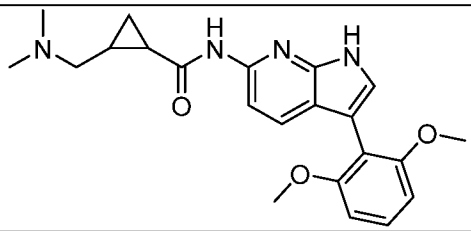
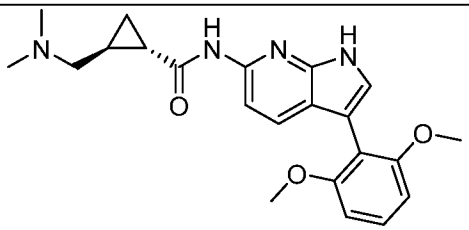
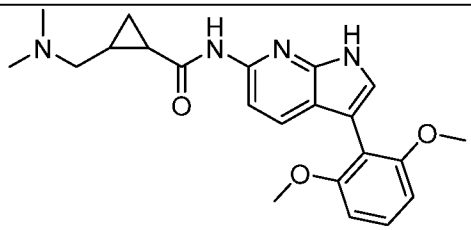
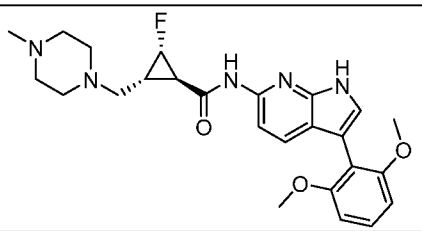
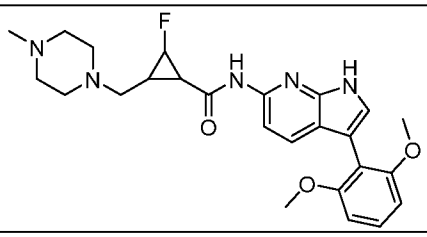
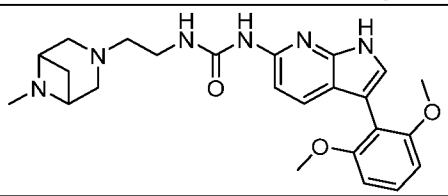
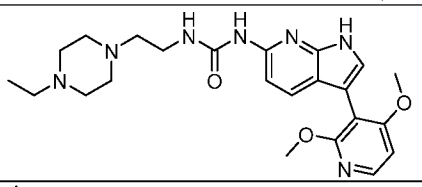
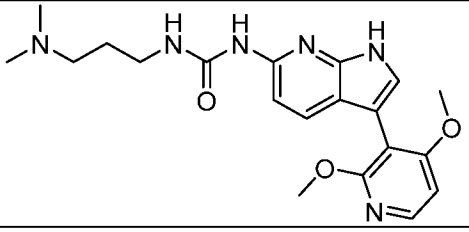
153		153-1	
154		154-1	
155		155-1	
156		155-1	
157		157-1	
158		157-1	
159		159-1	

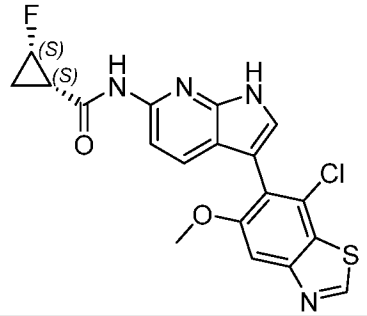
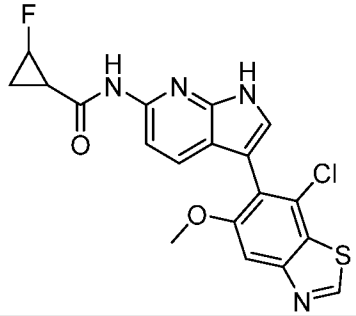
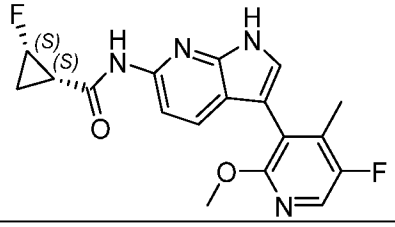
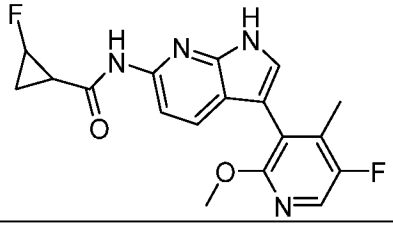
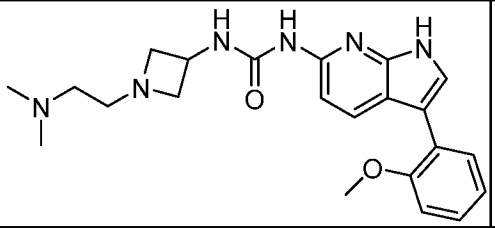
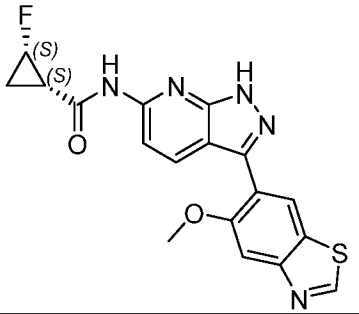
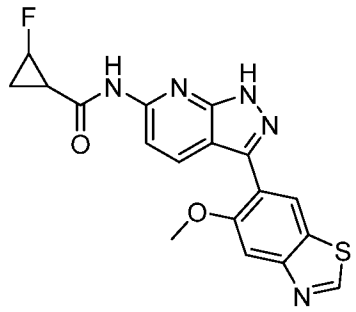
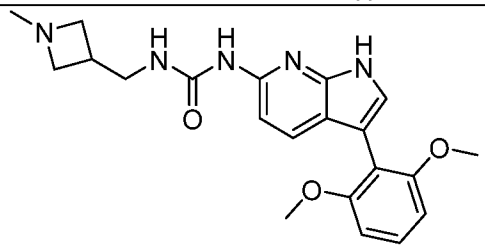
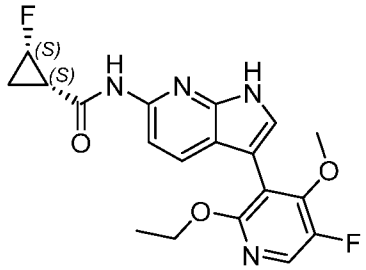
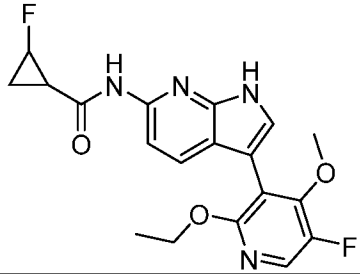
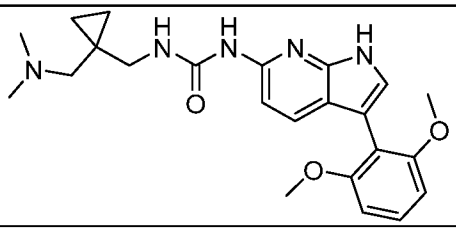
160		160-1	
161			
162		162-1	
163			
164		164-1	
165		164-1	
166		166-1	

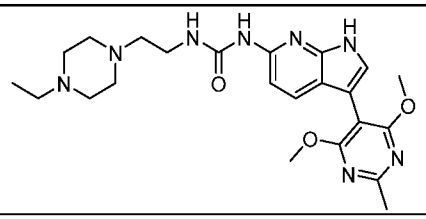
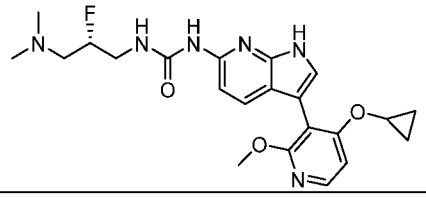
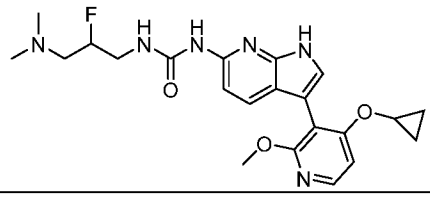
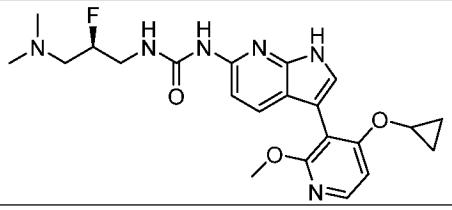
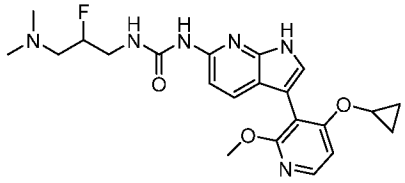
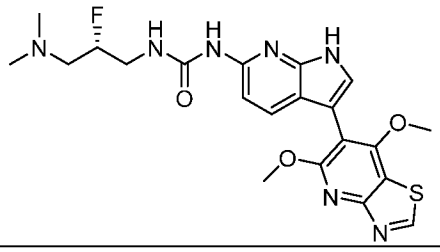
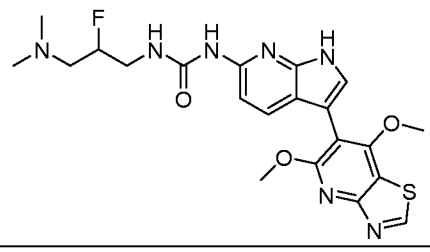
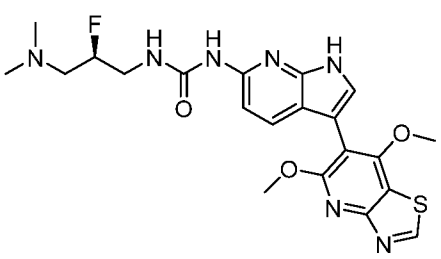
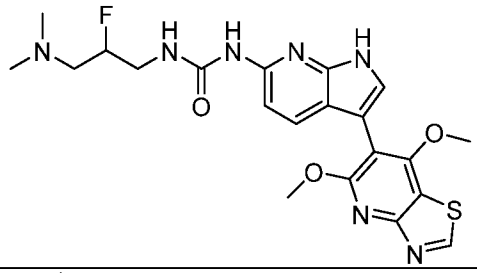
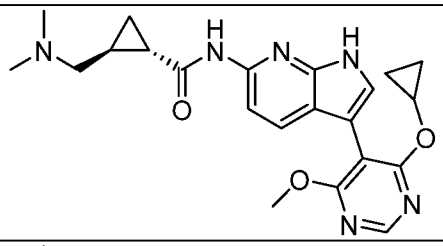
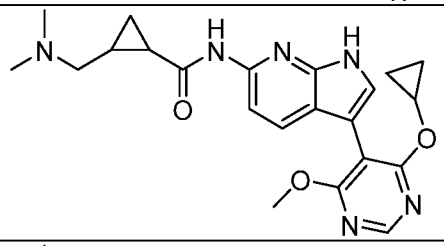
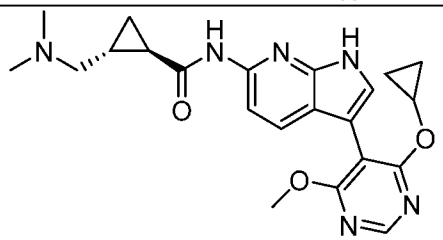
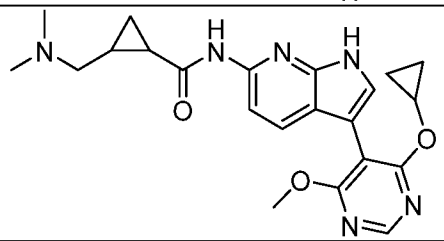
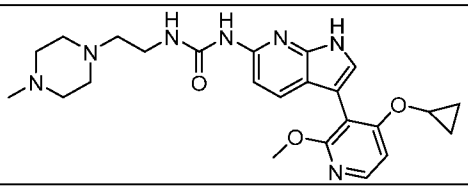
167			
168		**168-1**	
169		**168-1**	
170		**170-1**	
171		**171-1**	
172		**171-1**	
173			
174			

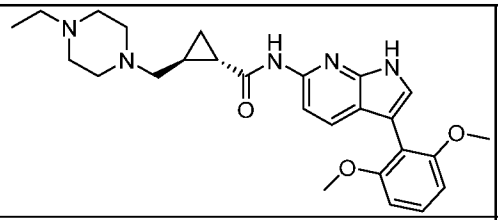
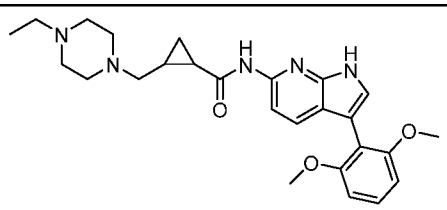
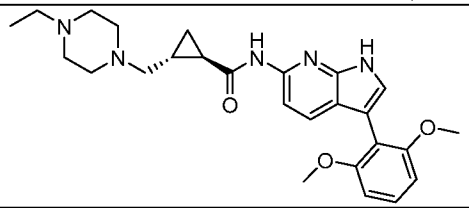
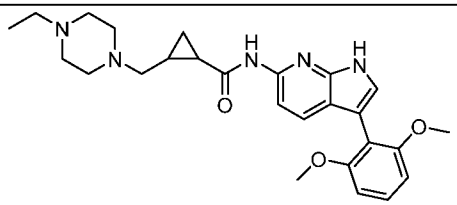
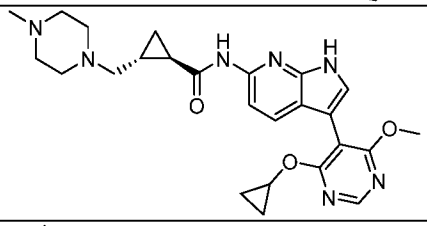
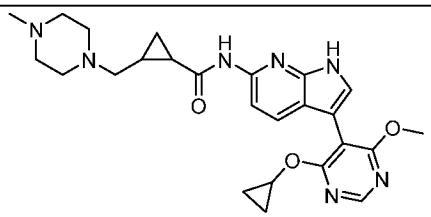
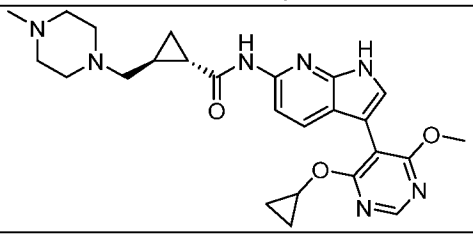
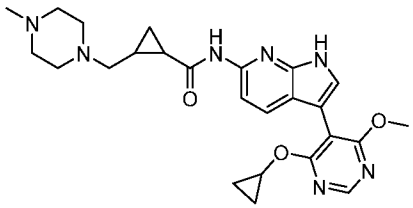
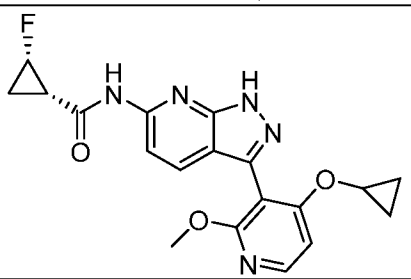
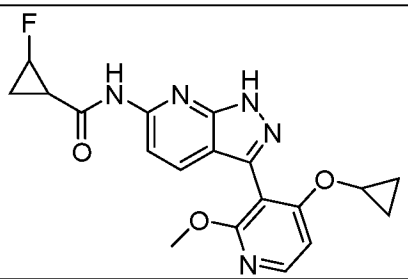
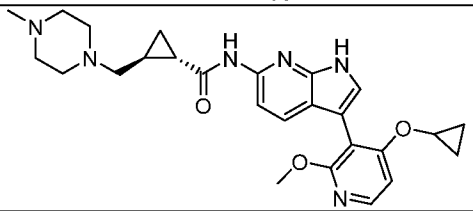
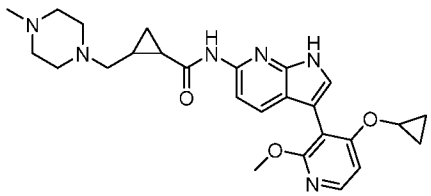
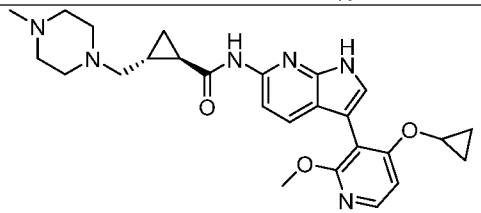
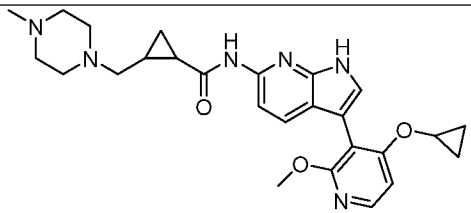
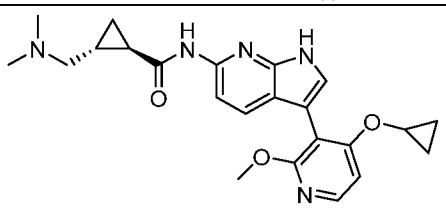
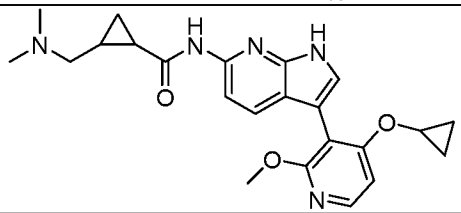
175		**175 -1**	
176		**176 -1**	
177		**177 -1**	
178		**178 -1**	
179			
180		**180 -1**	

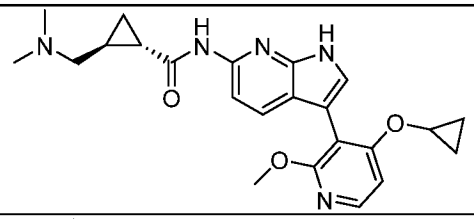
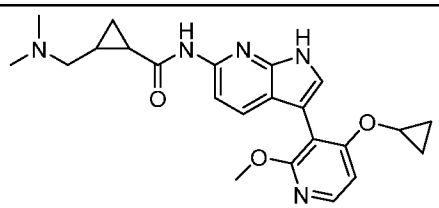
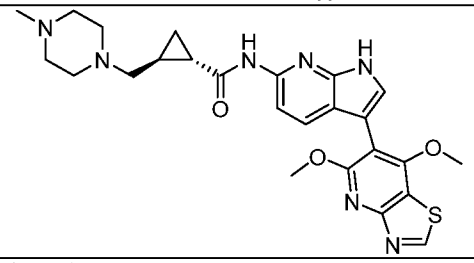
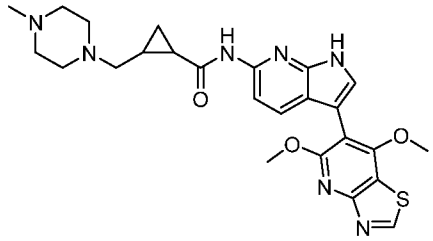
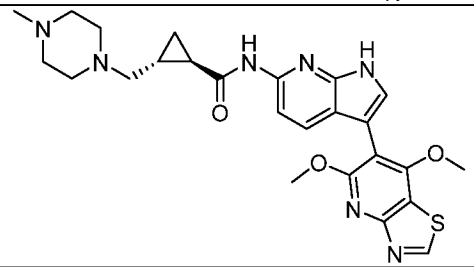
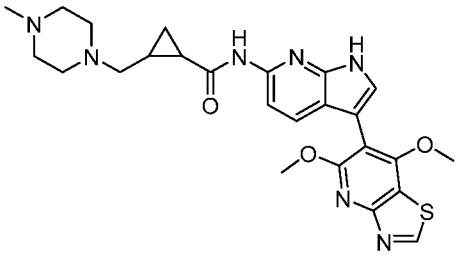
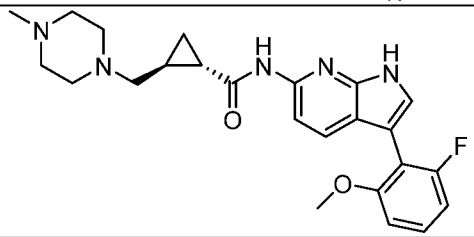
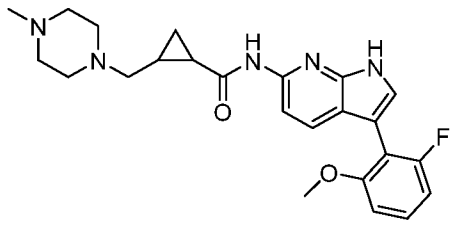
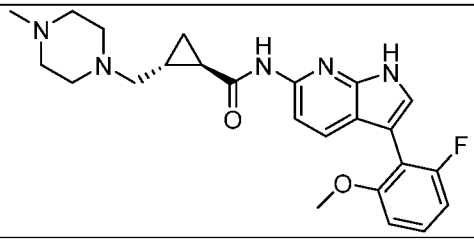
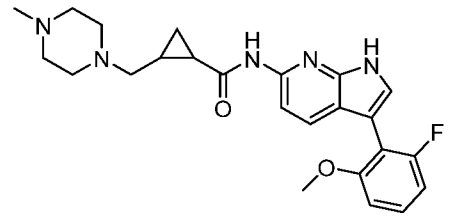
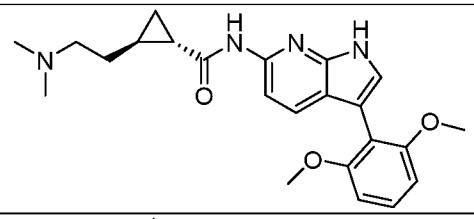
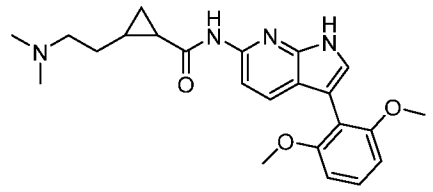
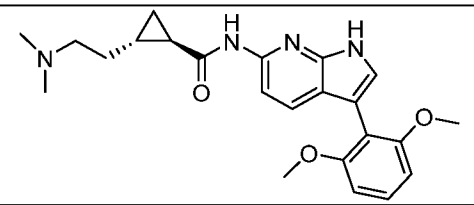
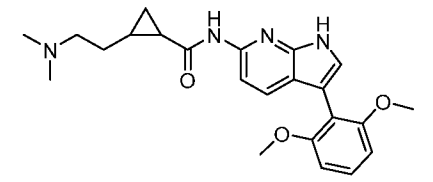
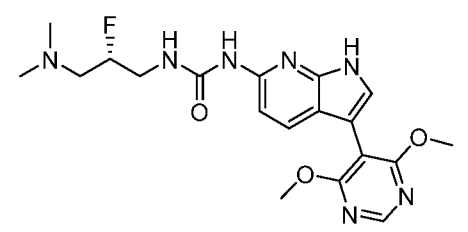
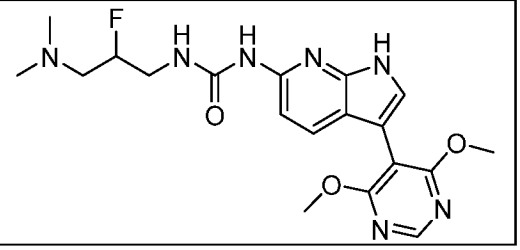
181		**180-1**	
182		**182-1**	
183		**180-1**	
184			
185		**41-1**	
186		**41-1**	
187			

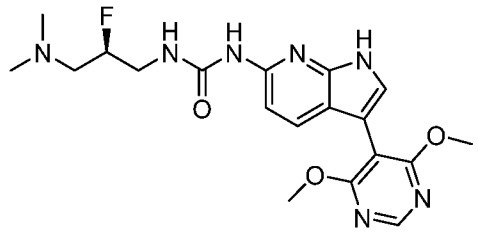
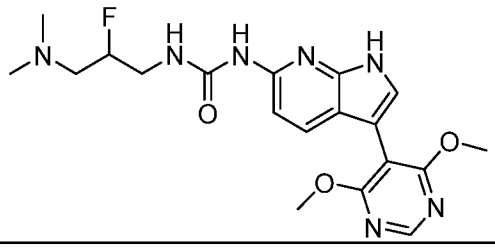
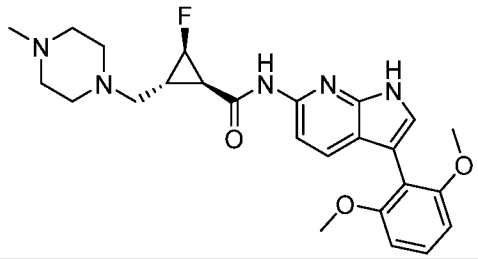
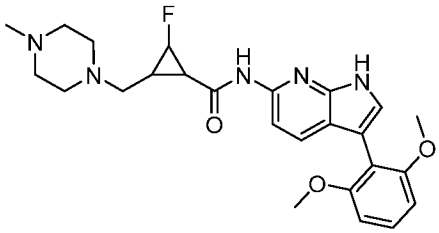
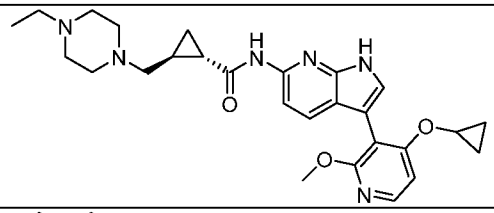
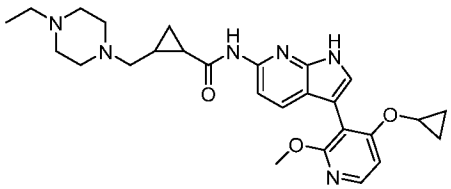
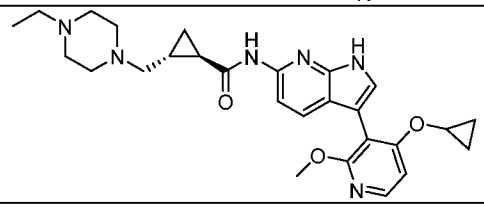
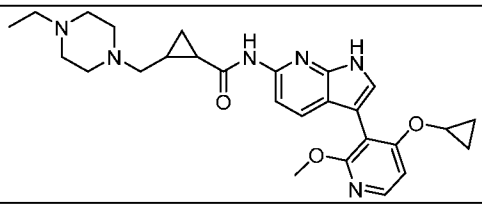
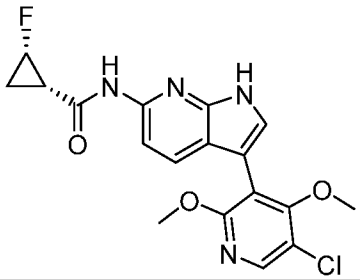
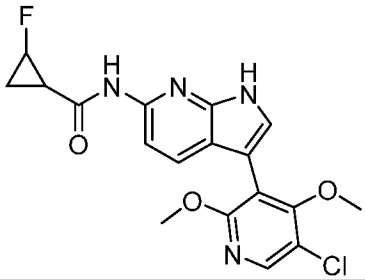
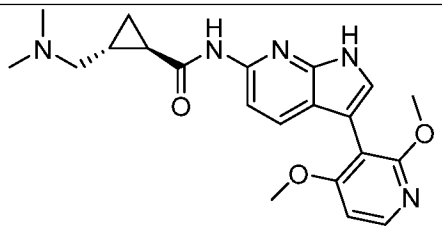
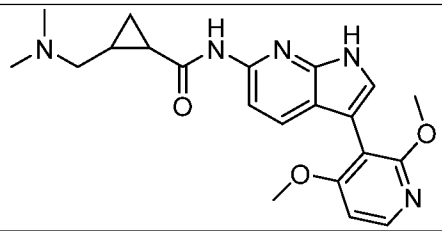
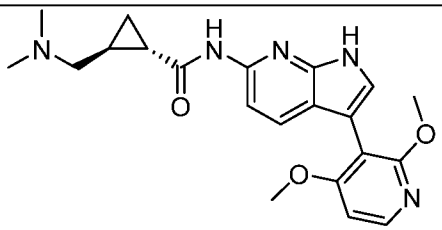
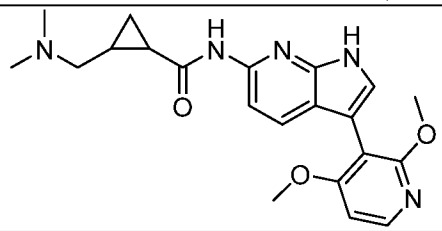
188		**180-1**	
189		**189-1**	
190		**190-1**	
191		**190-1**	
192		**192-1**	
193			
194			
195			

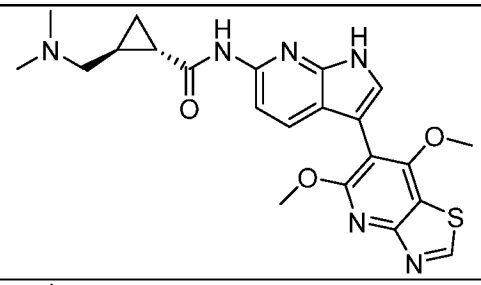
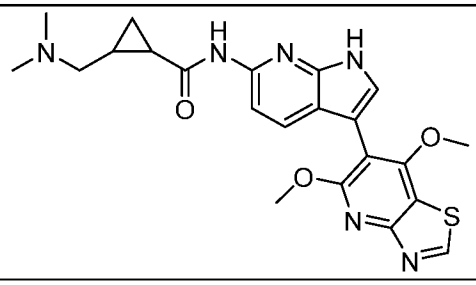
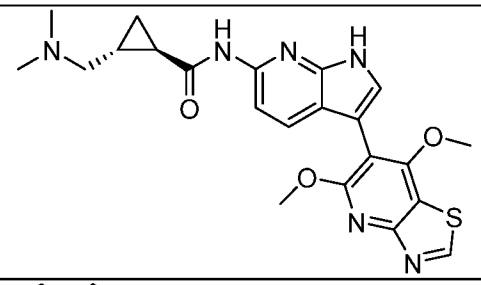
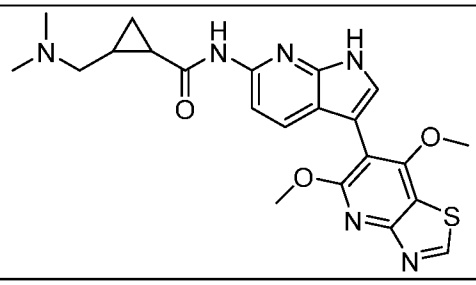
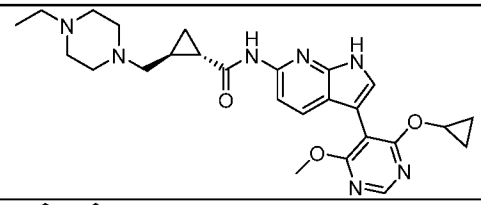
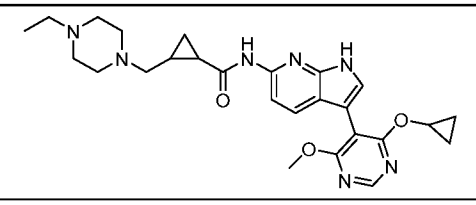
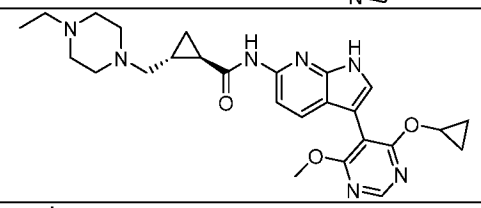
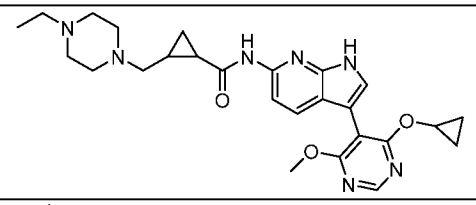
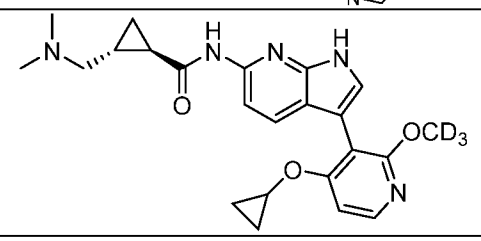
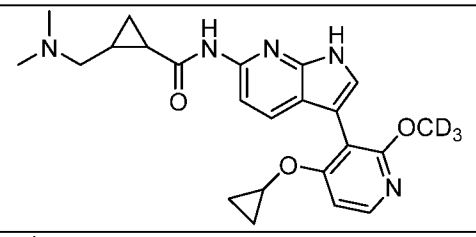
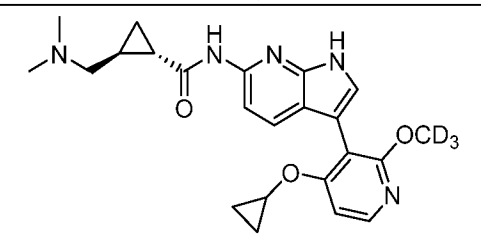
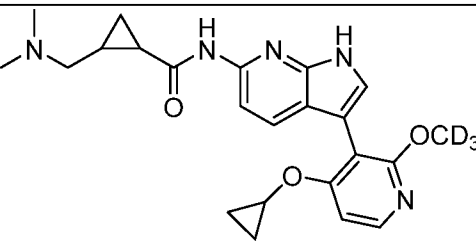
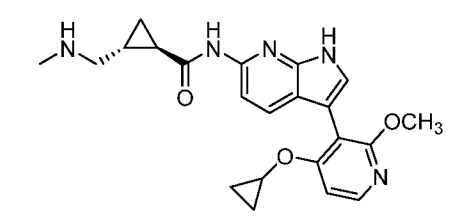
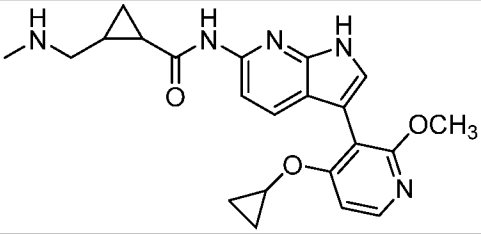
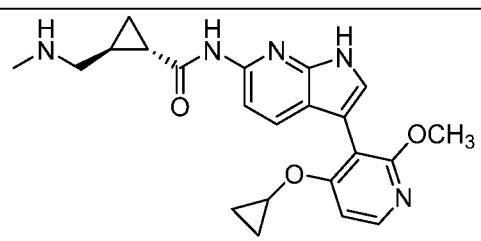
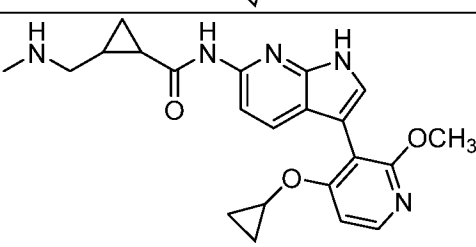
196		**196 -1**	
197		**197 -1**	
198			
199		**199 -1**	
200			
201		**201 -1**	
202			

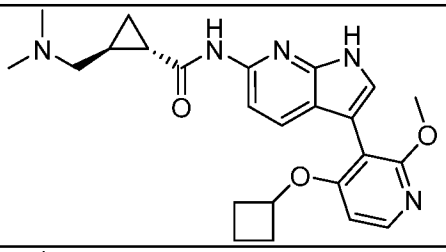
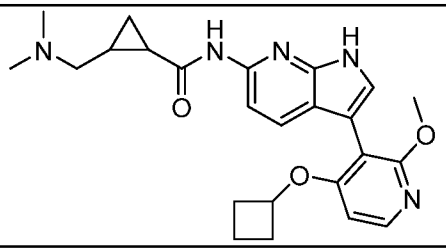
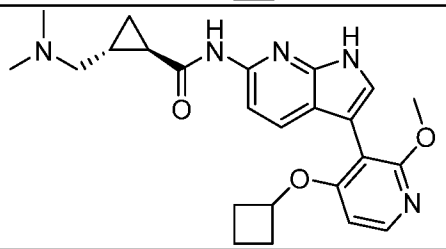
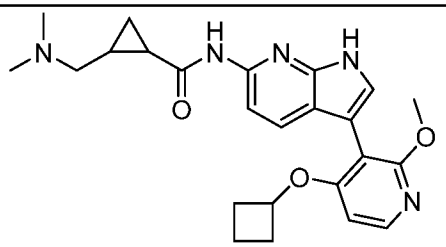
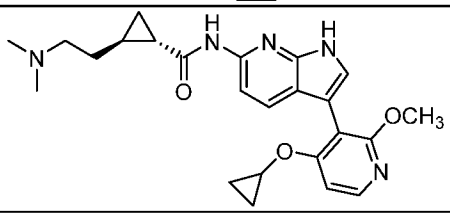
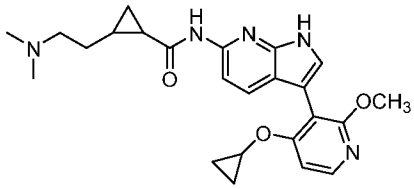
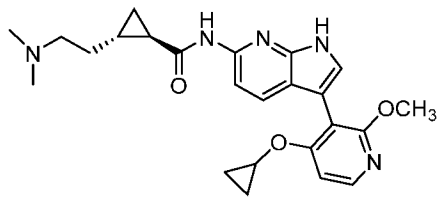
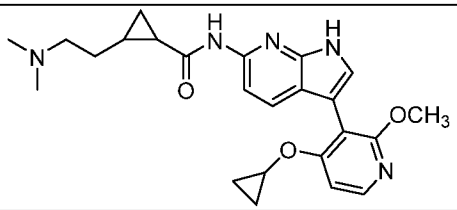
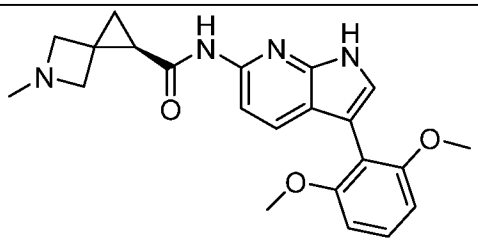
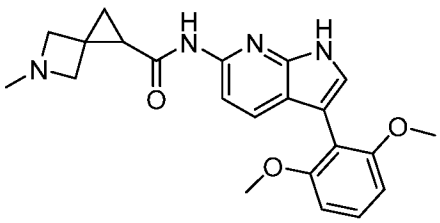
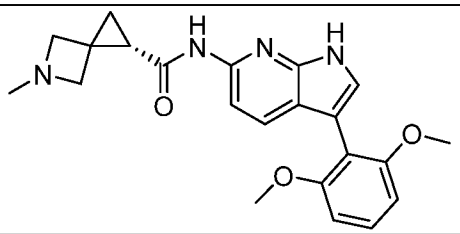
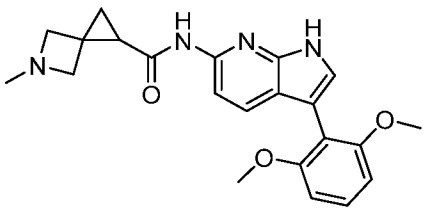
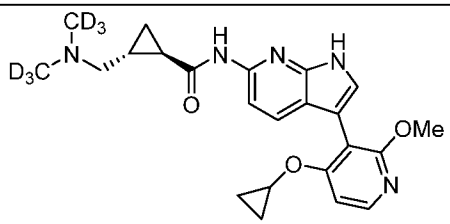
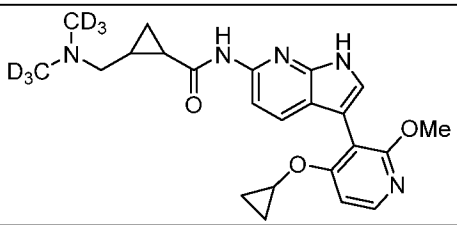
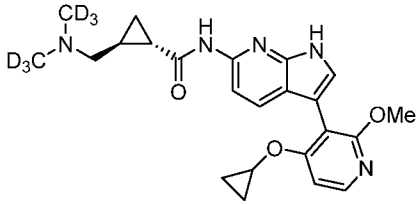
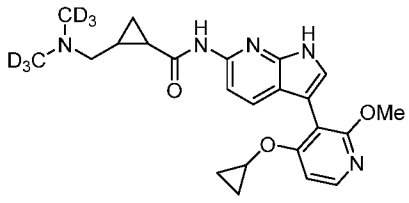
203			
204		**204-1**	
205		**204-1**	
206		**206-1**	
207		**206-1**	
208		**208-1**	
209		**208-1**	
210			

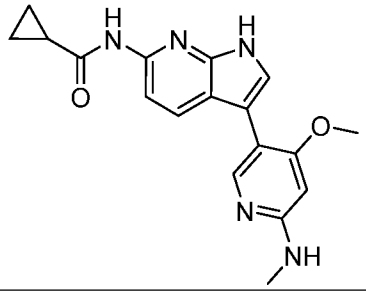
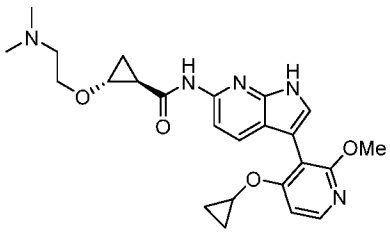
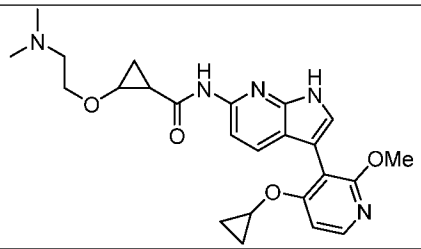
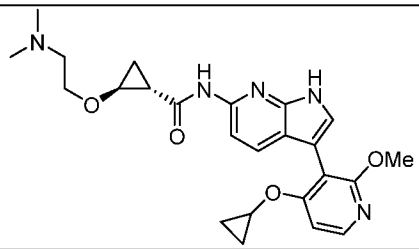
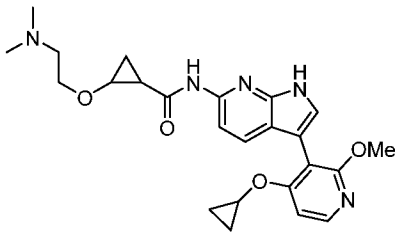
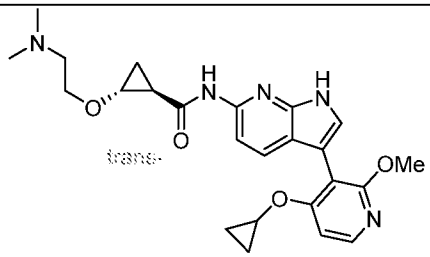
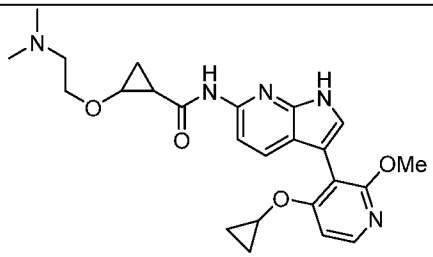
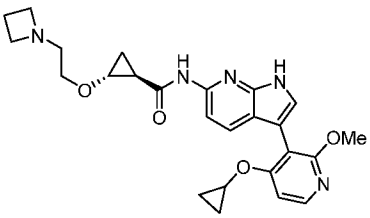
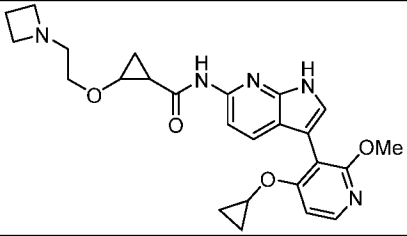
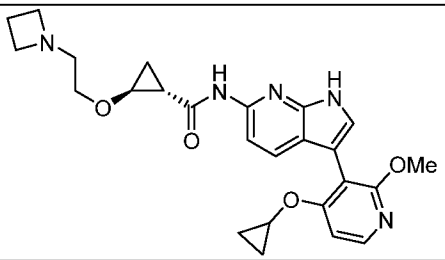
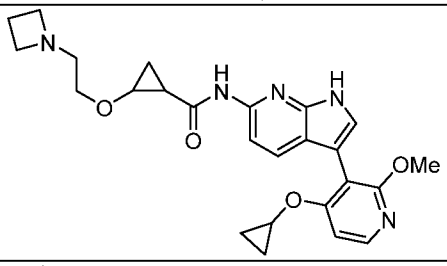
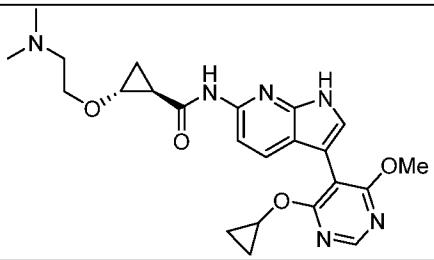
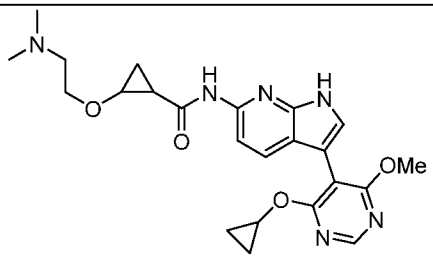
211		211-1	
212		211-1	
213		213-1	
214		213-1	
215		215-1	
216		216-1	
217		216-1	
218		218-1	

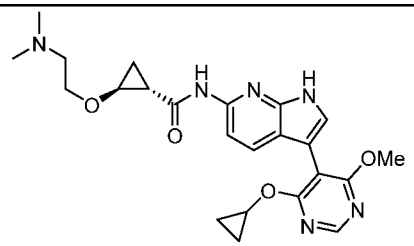
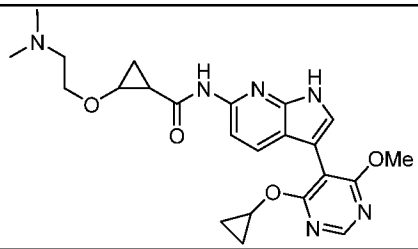
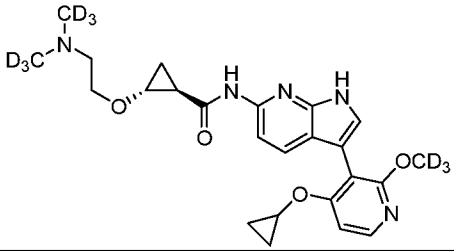
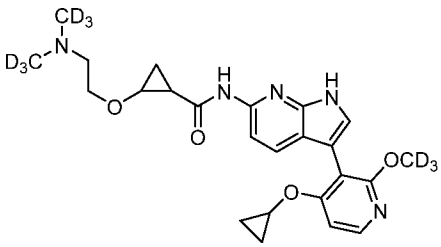
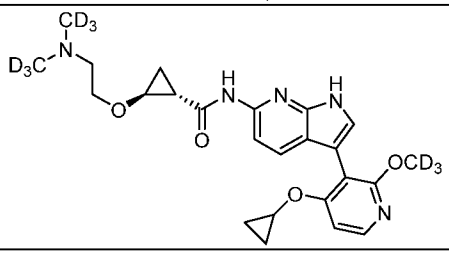
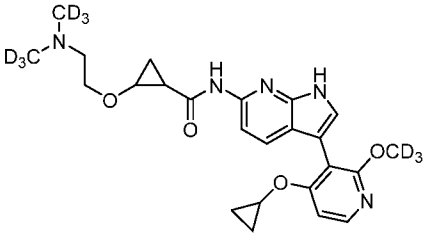
219		218-1	
220		220-1	
221		220-1	
222		222-1	
223		222-1	
224		224-1	
225		224-1	
226		226-1	

227		**226-1**	
228		**192-1**	
229		**229-1**	
230		**229-1**	
231		**231-1**	
232		**232-1**	
233		**232-1**	

234		**234-1**	
235		**234-1**	
236		**236-1**	
237		**236-1**	
238		**238-1**	
239		**238-1**	
240		**240-1**	
241		**240-1**	

242		**242 -1**	
243		**242 -1**	
244		**244 -1**	
245		**244 -1**	
246		**246 -1**	
247		**246 -1**	
248		**248 -1**	
249		**248 -1**	

250			
251		251-1	
252		251-1	
253		251-1	
254		254-1	
255		254-1	
256		256-1	

257		256-1	
258		258-1	
259		258-1	

[0107] Although certain compounds described in Table 1 are presented as specific stereoisomers and/or in a non-stereochemical form, it is understood that any or all non-stereochemical forms and any or all stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms of any of the compounds of Table 1 are herein described. In some embodiments, the compound described herein is selected from Compound Nos. 1-259.

[0108] This disclosure also includes all salts, such as pharmaceutically acceptable salts, of compounds referred to herein. This disclosure also includes any or all of the stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms, such as N-oxides, solvates, hydrates, or isotopomers, of the compounds described. The present disclosure also includes co-crystals of the compounds described herein. Unless stereochemistry is explicitly indicated in a chemical structure or name, the structure or name is intended to embrace all possible stereoisomers of a compound depicted. In addition, where a specific stereochemical form is depicted, it is understood that other stereochemical forms are also embraced by the invention. All forms of the compounds are also embraced by the invention, such as crystalline or non-crystalline forms of the compounds. Compositions comprising a compound of the invention are also intended, such as a composition of substantially pure compound, including a specific stereochemical form

thereof. Compositions comprising a mixture of compounds of the invention in any ratio are also embraced by the invention, including mixtures of two or more stereochemical forms of a compound of the invention in any ratio, such that racemic, non-racemic, enantioenriched and scalemic mixtures of a compound are embraced.

[0109] In the descriptions herein, it is understood that every description, variation, embodiment, or aspect of a moiety can be combined with every description, variation, embodiment, or aspect of other moieties the same as if each and every combination of descriptions is specifically and individually listed. For example, every description, variation, embodiment, or aspect provided herein with respect to R^0 of formula (I) may be combined with every description, variation, embodiment, or aspect of X, m, R^1, R^2, R^3, R^4, $R^{4'}$, R^5, $R^{5'}$, R^6, R^7, and/or R^8, the same as if each and every combination were specifically and individually listed. It is also understood that all descriptions, variations, embodiments or aspects of formula (I), where applicable, apply equally to other formulae detailed herein, and are equally described, the same as if each and every description, variation, embodiment or aspect were separately and individually listed for all formulae. For example, all descriptions, variations, embodiments, or aspects of formula (I), where applicable, apply equally to any of formulae (I-A), (I-A-i), (I-B), (I-B-i) and (I-B-ii) detailed herein, and are equally described, the same as if each and every description, variation, embodiment or aspect were separately and individually listed for all formulae.

III. General Synthetic Methods

[0110] The compounds of the present disclosure may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter (such as the schemes provided in the Examples below). In the following process descriptions, the symbols when used in the formulae depicted are to be understood to represent those groups described above in relation to the formulae herein.

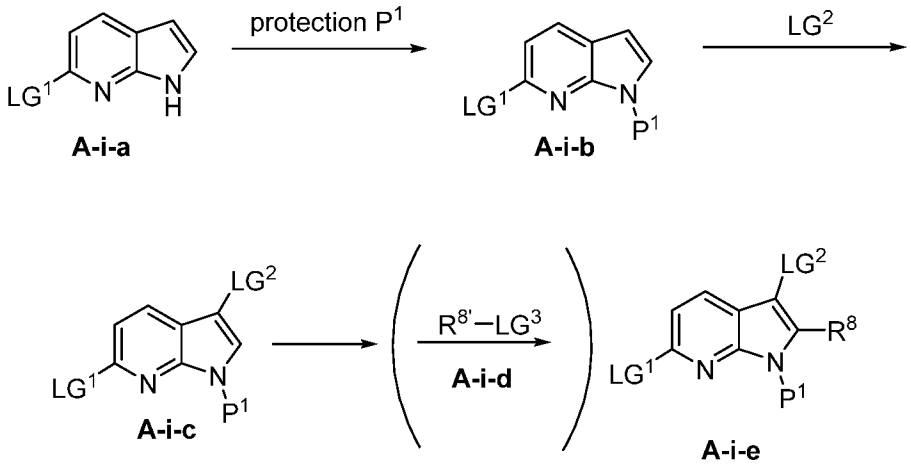
[0111] The intermediates described in the following preparations may contain a number of nitrogen, hydroxy, and acid protecting groups such as esters. The variable protecting group may be the same or different in each occurrence depending on the particular reaction conditions and the particular transformations to be performed. The protection and deprotection conditions are well known to the skilled artisan and are described in the literature. S*ee e.g.*, Greene and Wuts, *Protective Groups in Organic Synthesis*, (T. Greene and P. Wuts, eds., 2d ed. 1991).

[0112] Certain stereochemical centers have been left unspecified and certain substituents have been eliminated in the following schemes for the sake of clarity and are not intended to limit the teaching of the schemes in any way. Furthermore, individual isomers, enantiomers, and diastereomers may be separated or resolved by one of ordinary skill in the art at any convenient point in the synthesis of compounds of the invention, by methods such as selective crystallization techniques or chiral chromatography (*See e.g.*, J. Jacques, et al., "*Enantiomers, Racemates, and Resolutions*", John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen," *Stereochemistry of Organic Compounds*", Wiley-Interscience, 1994).

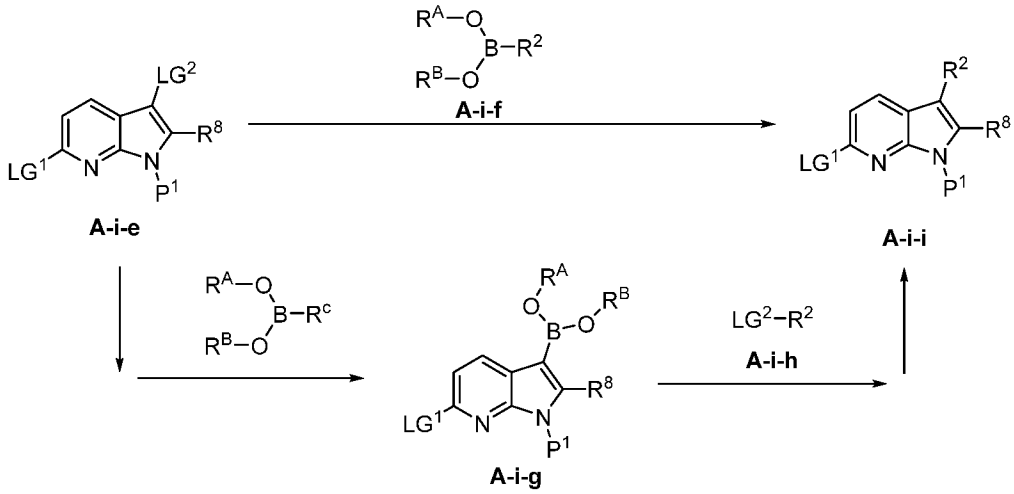
[0113] The compounds of the present invention, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, may be prepared by a variety of procedures known in the art, some of which are illustrated in the Examples below. The specific synthetic steps for each of the routes described may be combined in different ways, to prepare compounds of the present disclosure, or salts thereof. The products of each step can be recovered by conventional methods well known in the art, including extraction, evaporation, precipitation, chromatography, filtration, trituration, and crystallization. The reagents and starting materials are readily available to one of ordinary skill in the art. Others may be made by standard techniques of organic and heterocyclic chemistry which are analogous to the syntheses of known structurally-similar compounds and the procedures described in the Examples which follow including any novel procedures.

[0114] Compounds of formula (I) can be prepared according to Scheme A, Scheme B, Scheme C, Scheme D, Scheme E, or Scheme F, wherein X, m, R^1, R^2, R^3, R^4, $R^{4'}$, R^5, $R^{5'}$, R^6, R^7, and/or R^8 are as defined for formula (I) or any applicable variation thereof as detailed herein.

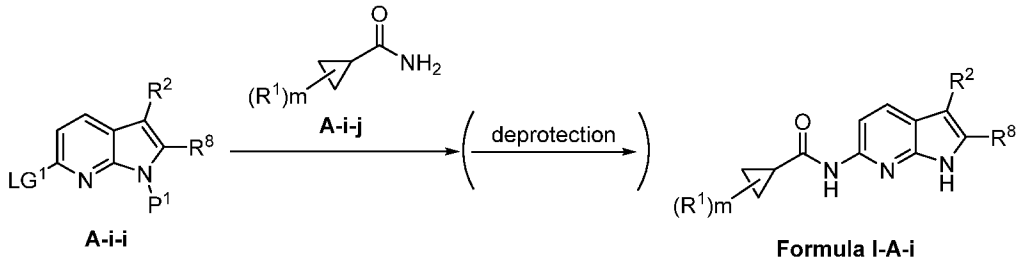
Scheme A- Part I.



Scheme A- Part II.



Scheme A- Part III.



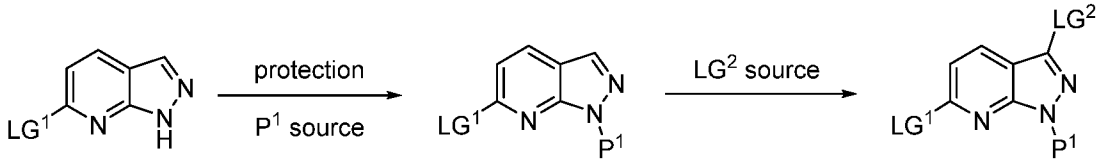
[0115] Compounds of formula (**I-A-i**) may be prepared according to the general synthetic scheme shown in Scheme A, Parts I-III. In Scheme A, Part I, 7-azaindole compounds of general formula **A-i-a**, wherein LG^1 is a leaving group (such as chloro or bromo), are protected at the secondary nitrogen with a protecting group P^1 (*e.g.*, with a Boc- or SEM-group) to give the compounds of general formula **A-i-b**. A suitable leaving group LG^2 (such as iodo) is added to the protected compounds of general formula **A-i-b** in preparation for the installation of the R^2 moiety. The resulting compounds of general formula **A-i-c** are further

subjected to reactions to introduce substituent $R^{8'}$ onto the 7-azaindole core as required to produce the intermediate compounds of general formula **A-i-e**. As shown in Scheme A, $R^{8'}$ has the same definition as R^8 as described herein, except that $R^{8'}$ does not include hydrogen.

[0116] In Part II of Scheme A, the R^2 aryl or heteroaryl moiety is added to the compounds of general formula **A-i-e**, at the position occupied by LG^2, to yield the further intermediate compounds of general formula **A-i-i** . The installation of the R^2 moiety may be achieved, for example, by two routes as shown above. In the first route, the compounds of general formula **A-i-e** are reacted with a suitable boronic acid derivative comprising the desired R^2 group **A-i-f**, wherein R^A and R^B are independently selected from the group consisting of halogen, OH, and O-(C_1-C_6 alkyl), or R^A and R^B are taken together with the boron atom to which they are attached to form a 5-10 membered heterocycle**,** to give the intermediate compounds of formula **A-i-i**. In the second route, the compounds of formula **A-i-e** are directly reacted with boronic acid or a derivative thereof, wherein R^c is a suitable leaving group (such as O-C_1-C_3 alkyl, or another boronic acid or derivative thereof, *i.e.*, in a diboron compound), to give the 7-azaindolyl-boronate compounds of formula **A-i-g**. The resulting boronate compounds are further reacted with an R^2-containing substrate (**A-i-h**) to give compounds of formula **A-i-i**.

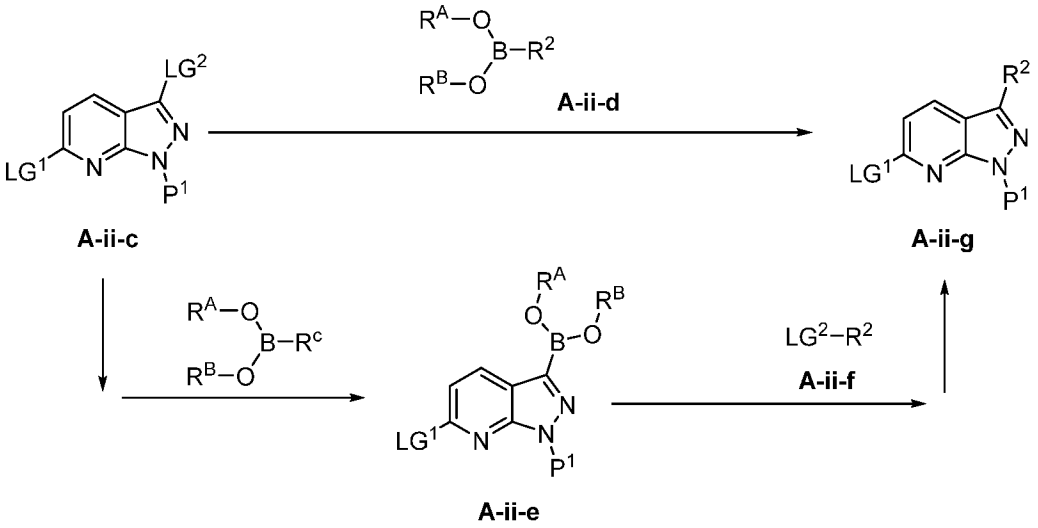
[0117] In Part III of Scheme A, the compounds of formula **A-i-i** are reacted with suitable cyclopropanecarboxamides of formula **A-i-j** to provide compounds of formula **I-A-i**.

Scheme B- Part I.

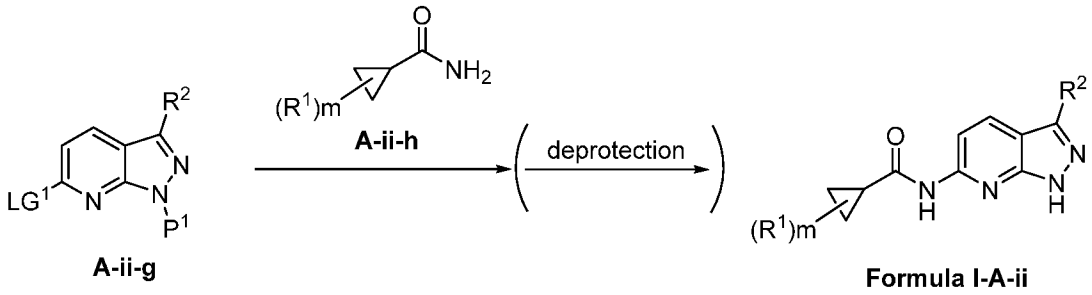


A-ii-a **A-ii-b** **A-ii-c**

Scheme B- Part II.



Scheme B- Part III.



[0118] Similar to Scheme A, Scheme B describes the preparation of compounds of formula (**I-A-ii**) having a 7-azaindazolyl core. Compounds of formula (**I-A-ii**) may be prepared according to the general synthetic scheme shown in Scheme B, Parts I-III. In Scheme B, Part I, 7-azaindazole compounds of general formula **A-ii-a**, wherein LG^1 is a leaving group (such as chloro or bromo), are protected at the secondary nitrogen with a protecting group P^1 (*e.g.*, with a Boc- or SEM-group) to give the compounds of general formula **A-ii-b**. A suitable leaving group LG^2 (such as iodo) is added to the protected compounds of general formula **A-ii-b** in preparation for the installation of the R^2 moiety.

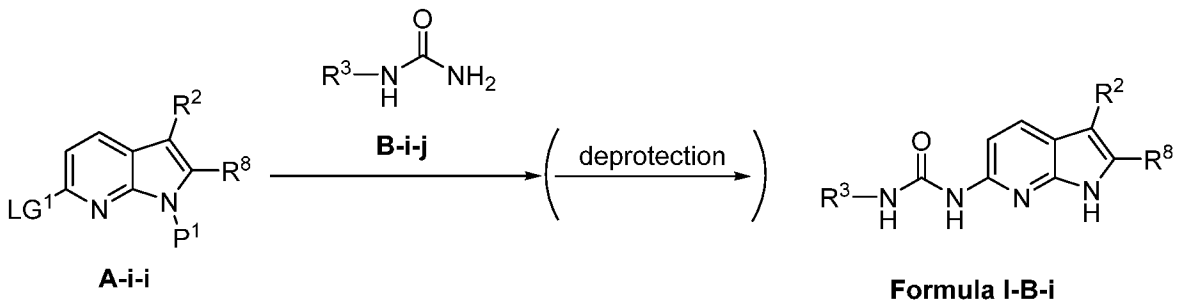
[0119] In Part II of Scheme B, the R^2 aryl or heteroaryl moiety is added to the compounds of general formula **A-ii-c**, at the position occupied by LG^2, to yield the further intermediate compounds of general formula **A-ii-g**. The installation of the R^2 moiety may be achieved, for example, by two routes as shown above. In the first route, the compounds of general formula **A-ii-c** are reacted with a suitable boronic acid derivative comprising the desired R^2 group **A-ii-d**, wherein R^A and R^B are independently selected from the group consisting of halogen, OH, and O-(C_1-C_6 alkyl), or R^A and R^B are taken together with the boron atom to which they are attached to form a 5-10 membered heterocycle, to give the

intermediate compounds of formula **A-ii-g**. In the second route, the compounds of formula **A-ii-c** are directly reacted with boronic acid or a derivative thereof, wherein R^c is a suitable leaving group (such as O-C_1-C_3 alkyl, or another boronic acid or derivative thereof, *i.e.*, in a diboron compound), to give the 7-azaindazolyl-boronate compounds of formula **A-ii-e**. The resulting boronate compounds are further reacted with an R^2-containing substrate (**A-ii-f**) to give compounds of formula **A-ii-g**.

[0120] In Part III of Scheme B, the compounds of formula **A-ii-g** are reacted with suitable cyclopropanecarboxamides of formula **A-ii-h** to provide compounds of formula **I-A-ii**.

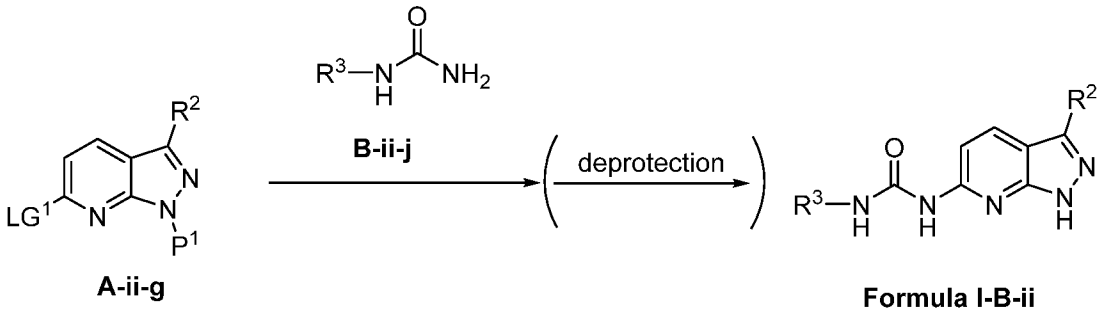
[0121] Compounds of formula (I-B) may also be prepared according to the general synthetic schemes shown in Scheme C and Scheme D. In Scheme C, the 7-azaindolyl compounds of formula **A-i-i** obtained from Scheme A (Parts I and II) are reacted with suitable urea compounds of formula **B-i-j** to provide compounds of formula **I-B-i**. In Scheme D, the 7-azaindazolyl compounds of formula **A-ii-g** obtained from Scheme B (Parts I and II) are reacted with suitable urea compounds of formula **B-ii-j** to provide compounds of formula **I-B-ii**.

Scheme C.



A-i-i **Formula I-B-i**

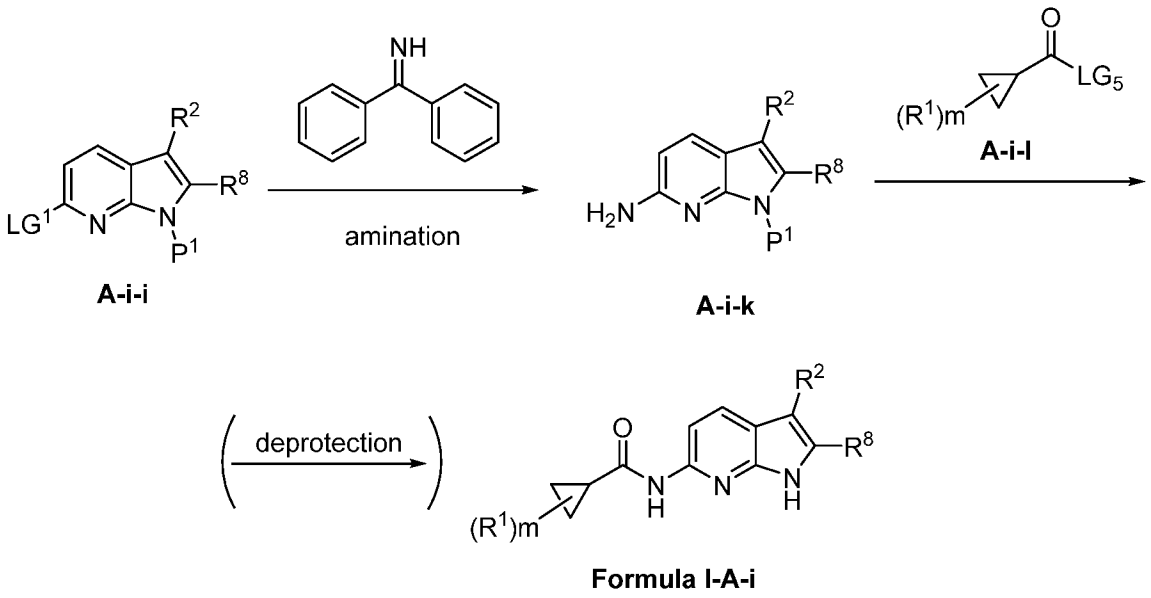
Scheme D.



A-ii-g **Formula I-B-ii**

[0122] Alternatively, the addition of the cyclopropylcarboxamidyl or urea moiety as described in Scheme A (Part III), Scheme B (Part III), Scheme C and Scheme D may be substituted with the methods as described in Scheme E, Scheme F, Scheme G and Scheme H, respectively.

Scheme E.

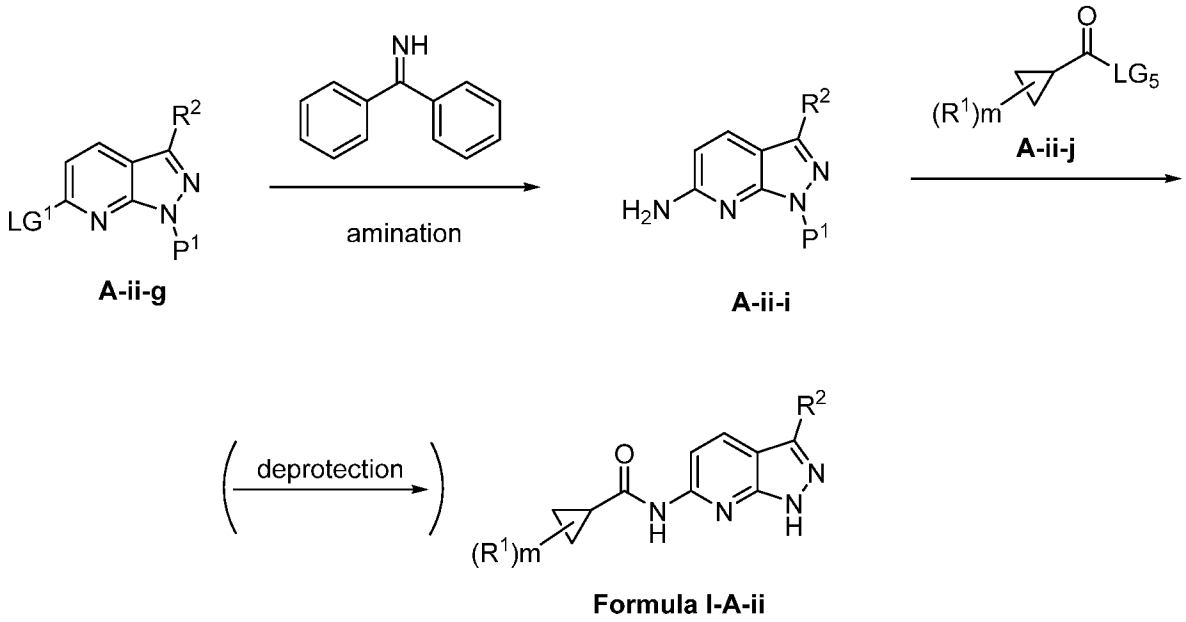


A-i-i

A-i-k

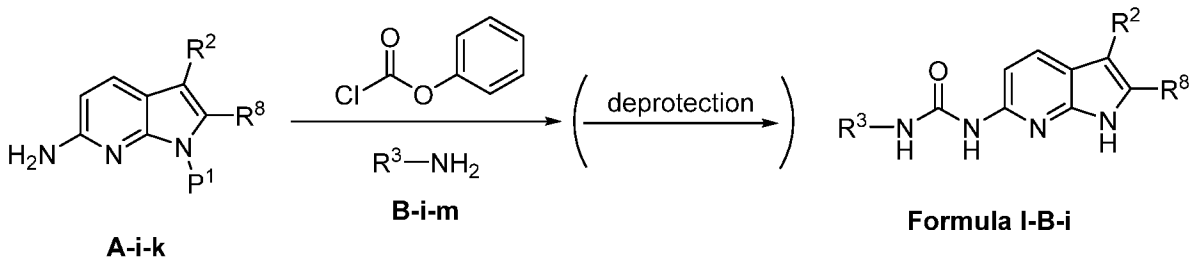
[0123] In Scheme E, the intermediate compounds of general formula **A-i-i** are aminated (such as with diphenylmethanimine) to give the compounds of general formula **A-i-k**. The resulting compounds of general formula **A-i-k** are subsequently reacted with a cyclopropanecarboxylic acid or derivative thereof **A-i-l** (wherein LG^3 may be –OH, Cl-, -O-C_1-C_6 alkyl, etc.) to give the desired compounds of formula (**I-A-i**). Similarly, in Scheme F, the intermediate compounds of general formula **A-ii-g** are aminated (such as with diphenylmethanimine) to give the compounds of general formula **A-ii-i**. The resulting compounds of general formula **A-ii-i** are subsequently reacted with a cyclopropanecarboxylic acid or derivative thereof **A-ii-j** (wherein LG^3 may be –OH, Cl-, -O-C_1-C_6 alkyl, etc.) to give the desired compounds of formula (**I-A-ii**).

Scheme F.

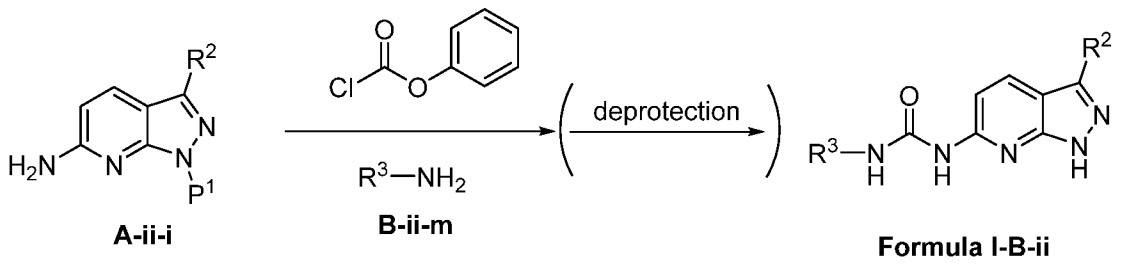


[0124] Compounds of general formula (I-B) may also be prepared from the compounds of general formulae **A-i-k** and **A-ii-i** as described in Schemes G and F. In Scheme G, the compounds of general formula **A-i-k** are reacted with carboxylic acid derivatives (*e.g.*, phenyl carbonylchloridate and R^3-containing free amines **B-i-m** in successive steps to give the desired urea compounds of general formula **I-B-i**. Similarly, in Scheme H, the compounds of general formula **A-ii-i** are reacted with carboxylic acid derivatives and R^3-containing free amines **B-ii-m** in successive steps to give the desired urea compounds of general formula **I-B-ii**.

Scheme G.



Scheme H.



IV. Pharmaceutical Compositions and Formulations

[0125] Any of the compounds described herein may be formulated as a pharmaceutically acceptable composition.

[0126] Pharmaceutical compositions of any of the compounds detailed herein are embraced by this disclosure. Thus, the present disclosure includes pharmaceutical compositions comprising a compound as detailed herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, and a pharmaceutically acceptable carrier or excipient. In one aspect, the pharmaceutically acceptable salt is an acid addition salt, such as a salt formed with an inorganic or organic acid. Pharmaceutical compositions may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration or a form suitable for administration by inhalation.

[0127] A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions comprising a compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, as detailed herein are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, as detailed herein is in substantially pure form. In one variation, "substantially pure" intends a composition that contains no more than 35% impurity, wherein the impurity denotes a compound other than the compound comprising the majority of the composition or a salt thereof. For example, a composition of a substantially pure compound selected from a compound of Table 1 intends a composition that contains no more than 35% impurity, wherein the impurity denotes a compound other than the compound of Table 1. In one variation, a composition of substantially pure compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is provided wherein the composition contains no more than 25% impurity. In another variation, a composition of substantially pure compound, or a pharmaceutically

acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is provided wherein the composition contains or no more than 20% impurity. In still another variation, a composition of substantially pure compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is provided wherein the composition contains or no more than 10% impurity. In a further variation, a composition of substantially pure compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is provided wherein the composition contains no more than 5% impurity. In another variation, a composition of substantially pure compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is provided wherein the composition contains no more than 3% impurity. In still another variation, a composition of substantially pure compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is provided wherein the composition contains no more than 1% impurity. In a further variation, a composition of substantially pure compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is provided wherein the composition contains no more than 0.5% impurity. In yet other variations, a composition of substantially pure compound means that the composition contains no more than 15% , no more than 10%, no more than 5% , no more than 3%, or no more than 1% impurity, which impurity may be the compound in a different stereochemical form. For instance, and without limitation, a composition of substantially pure (S) compound means that the composition contains no more than 15% or no more than 10% or no more than 5% or no more than 3% or no more than 1% of the (R) form of the compound.

[0128] In one variation, the compounds herein are synthetic compounds prepared for administration to an individual. In another variation, compositions are provided containing a compound in substantially pure form. In another variation, the present disclosure embraces pharmaceutical compositions comprising a compound detailed herein and a pharmaceutically acceptable carrier. In another variation, methods of administering a compound are provided. The purified forms, pharmaceutical compositions and methods of administering the compounds are suitable for any compound or form thereof detailed herein. In some embodiments, the compounds and compositions as provided herein are sterile. Methods for sterilization known in the art may be suitable for any compounds or form thereof and compositions thereof as detailed herein.

[0129] A compound detailed herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, may be formulated for any available delivery route, including an oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal or rectal), parenteral (*e.g.*, intramuscular, subcutaneous or intravenous), topical or transdermal delivery form. A compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, may be formulated with suitable carriers to provide delivery forms that include, but are not limited to, tablets, caplets, capsules (such as hard gelatin capsules or soft elastic gelatin capsules), cachets, troches, lozenges, gums, dispersions, suppositories, ointments, cataplasms (poultices), pastes, powders, dressings, creams, solutions, patches, aerosols (*e.g.*, nasal spray or inhalers), gels, suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions or water-in-oil liquid emulsions), solutions and elixirs.

[0130] A compound detailed herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, can be used in the preparation of a formulation, such as a pharmaceutical formulation, by combining the compound or compounds, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, with a pharmaceutically acceptable carrier. Depending on the therapeutic form of the system (*e.g.*, transdermal patch vs. oral tablet), the carrier may be in various forms. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants. Formulations comprising the compound may also contain other substances which have valuable therapeutic properties. Pharmaceutical formulations may be prepared by known pharmaceutical methods. Suitable formulations can be found, *e.g.*, in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, PA, 20th ed. (2000), which is incorporated herein by reference.

[0131] A compound detailed herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, may be administered to individuals in a form of generally accepted oral compositions, such as tablets, coated tablets, and gel capsules in a hard or in soft shell, emulsions or suspensions. Examples of carriers, which may be used for the preparation of such compositions, are lactose, corn starch or its derivatives, talc, stearate or its salts, etc. Acceptable carriers for gel capsules with soft shell are, for instance, plant oils, wax, fats, semisolid and liquid poly-ols, and so on. In addition,

pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants.

[0132] Any of the compounds, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, described herein can be formulated in a tablet in any dosage form described, for example, a compound as described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, can be formulated as a 10 mg tablet.

[0133] Compositions comprising a compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, provided herein are also described. In one variation, the composition comprises a compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, and a pharmaceutically acceptable carrier or excipient. I n another variation, a composition of substantially pure compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is provided. In some embodiments, the composition is for use as a human or veterinary medicament. In some embodiments, the composition is for use in a method described herein. In some embodiments, the composition is for use in the treatment of a disease or disorder described herein.

[0134] Compositions formulated for co-administration of a compound provided herein and one or more additional pharmaceutical agents are also described. The co-administration can be simultaneous or sequential in any order. A compound provided herein may be formulated for co-administration with the one or more additional pharmaceutical agents in the same dosage form (*e.g.*, single tablet or single i.v.) or separate dosage forms (*e.g.*, two separate tablets, two separate i.v., or one tablet and one i.v.). Furthermore, co-administration can be, for example, 1) concurrent delivery, through the same route of delivery (*e.g.*, tablet or i.v.), 2) sequential delivery on the same day, through the same route or different routes of delivery, or 3) delivery on different days, through the same route or different routes of delivery.

V. Methods of Use

[0135] Compounds and compositions detailed herein, such as a pharmaceutical composition containing a compound of formula (I) or any variation thereof provided herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, and a pharmaceutically acceptable carrier or excipient, may be used in methods of administration and treatment as provided herein. The compounds and compositions may also be used in *in vitro* methods, such as *in vitro* methods of administering a compound or composition to cells for screening purposes and/or for conducting quality control assays.

[0136] In one aspect, provided herein is a method of inhibiting Bcr-Abl tyrosine kinase enzymatic activity, comprising contacting an effective amount of a compound or composition provided herein, to the Bcr-Abl tyrosine kinase. In some embodiments, provided herein is a method of inhibiting Bcr-Abl tyrosine kinase in a cell, comprising administering an effective amount of a compound or composition of the disclosure to the cell. In some embodiments, provided herein is a method of inhibiting Bcr-Abl tyrosine kinase in an individual in need thereof, comprising administering an effective amount of a compound or composition of the disclosure to the individual. In some variations, the compounds provided herein are selective for inhibiting Bcr-Abl tyrosine kinase. As such, in some embodiments, provided herein is a method of selectively inhibiting Bcr-Abl tyrosine kinase, as compared to other tyrosine kinases, including but not limited to c-KIT, FGFR, PDGFR, SRC, CSFR1, or VEGFR.

[0137] The compounds and compositions described herein may be used in a method of treating a disease or disorder mediated by Bcr-Abl tyrosine kinase activity. In some embodiments, the compound or composition is administered according to a dosage described herein.

[0138] In some embodiments, provided herein is a method for treating a disease or disorder mediated by Bcr-Abl tyrosine kinase activity comprising administering to an individual in need of treatment an effective amount of a compound of formula (I) or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing. In some embodiments, the disease or disorder is a cancer mediated by Bcr-Abl tyrosine kinase activity. In some embodiments, the disease or disorder is chronic myeloid leukemia (CML), acute myeloid leukemia (AML), or acute lymphoblastic leukemia (ALL). In some embodiments, the disease or disorder is a cancer, such as leukemia. In some variations, the cancer is chronic myeloid leukemia (CML),

Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL), acute myelogenous leukemia (AML), or mixed phenotype acute leukemia.

[0139] In certain embodiments, the leukemia is chronic myeloid leukemia. Chronic myeloid leukemia may be characterized by the state of disease progression, as determined by blast cells. In still further embodiments, the chronic myeloid leukemia is chronic phase CML, accelerated phase CML, or blastic phase CML. In some embodiments, the chronic myeloid leukemia is refractory chronic myeloid leukemia.

[0140] In some embodiments, the disease or disorder mediated by Bcr-Abl tyrosine kinase activity is refractory or resistant to first-line treatment, second-line treatment, and/or third-line treatment. In certain embodiments, the condition mediated by Bcr-Abl tyrosine kinase activity is refractory or resistant to treatment with one or more Bcr-Abl tyrosine kinase inhibitors selected from the group consisting of imatinib, nilotinib, dasatinib, bafetinib, bosutinib, radotinib, asciminib, and ponatinib. First-line treatment as described herein includes the use of imatinib; second- and third-line treatments as described herein include the use of nilotinib, dasatinib, bafetinib, bosutinib, radotinib, asciminib, and/or ponatinib. In some variations of the foregoing, the chronic myeloid leukemia is refractory chronic myeloid leukemia.

[0141] Resistant subtypes of Bcr-Abl tyrosine kinase-mediated diseases or disorders may be associated with any number of Bcr-Abl dependent or Bcr-Abl independent resistance mechanisms. In some embodiments wherein the disease or disorder mediated by Bcr-Abl tyrosine kinase activity is refractory to treatment, the disease or disorder is characterized as being associated with one or more Bcr-Abl dependent resistance mechanisms. Bcr-Abl dependent resistance mechanisms include, but are not limited to, one or more point mutations at positions M244, L248, G250, G250, Q252, Q252, Y253, Y253, E255, E255, D276, F311, T315, T315, F317, F317, M343, M351, E355, F359, F359, V379, F382, L387, H396, H396, S417, E459, F486, or T315 in the Bcr-Abl tyrosine kinase. In certain variations, the refractory disease or disorder mediated by Bcr-Abl tyrosine kinase is associated with one or more specific point mutations in the Bcr-Abl tyrosine kinase selected from the group consisting of: M244V, L248V, G250E, G250A, Q252H, Q252R, Y253F, Y253H, E255K, E255V, D276G, F311L, T315N, T315A, F317V, F317L, M343T, M351T, E355G, F359A, F359V, V379I, F382L, L387M, H396P, H396R, S417Y, E459K, F486S, and T315I. In certain embodiments, the refractory disease or disorder mediated by Bcr-Abl tyrosine kinase

is associated with a T315I mutation. In still further embodiments, the refractory disease or disorder mediated by Bcr-Abl tyrosine kinase is associated with a T315I mutation at the onset of treatment and I315M mutation following ponatinib. In other embodiments, the refractory disease or disorder mediated by Bcr-Abl tyrosine kinase is associated with one or more P-loop mutations (M244V, G250E, Q252H, Y253H/F, E255K/V).

[0142] In some embodiments, provided is a method for treating cancer in an individual in need thereof, comprising administering to the individual an effective amount of a compound of formula (I), or any variation thereof as described herein. In some embodiments, the cancer is leukemia. In some embodiments, the cancer is chronic myeloid leukemia (CML), Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL), acute myelogenous leukemia (AML), or mixed phenotype acute leukemia. In some embodiments, the cancer is chronic myeloid leukemia (CML). In certain embodiments, the leukemia is chronic myeloid leukemia. In still further embodiments, the chronic myeloid leukemia is refractory chronic myeloid leukemia. In certain embodiments of the foregoing, the chronic myeloid leukemia is refractory chronic myeloid leukemia associated with a T315I mutation.

[0143] In one aspect, provided herein is a method of treating cancer in an individual in need thereof, wherein modulation of Bcr-Abl tyrosine kinase activity inhibits or ameliorates the pathology and/or symptomology of the cancer, comprising administering to the individual a therapeutically effective amount of a compound or composition provided herein. In one embodiment, provided herein is a method of treating cancer, wherein modulation of Bcr-Abl tyrosine kinase activity inhibits the pathology and/or symptomology of the cancer, in an individual, comprising administering to the individual a therapeutically effective amount of a compound or composition provided herein. In one embodiment, provided herein is a method of treating a cancer, wherein modulation of Bcr-Abl tyrosine kinase activity ameliorates the pathology and/or symptomology of the cancer, in an individual, comprising administering to the individual a therapeutically effective amount of a compound or composition provided herein.

[0144] In another aspect, provided herein is a method of preventing cancer, wherein modulation of Bcr-Abl tyrosine kinase activity prevents the pathology and/or symptomology of the cancer, in an individual, comprising administering to the individual a therapeutically effective amount of a compound or composition provided herein. In another aspect, provided herein is a method of delaying the onset and/or development of a cancer that is mediated by

Bcr-Abl tyrosine kinase activity in an individual (such as a human) who is at risk for developing the cancer. It is appreciated that delayed development may encompass prevention in the event the individual does not develop the cancer.

[0145] In one aspect, provided herein is a method of delaying the onset and/or development of cancer in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound or composition provided herein. In some embodiments, the cancer is a leukemia. In certain embodiments, the cancer is chronic myeloid leukemia (CML), Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL), acute myelogenous leukemia (AML), or mixed phenotype acute leukemia. In some embodiments, the cancer is chronic myeloid leukemia. In still further embodiments, the chronic myeloid leukemia is refractory chronic myeloid leukemia. In still yet other embodiments, the chronic myeloid leukemia is refractory chronic myeloid leukemia associated with a T315I mutation. In one aspect, provided herein is a method of delaying the onset and/or development of chronic myeloid leukemia in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound or composition provided herein. In one variation, provided herein is a method of delaying the onset and/or development of refractory chronic myeloid in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound or composition provided herein. In one variation, provided herein is a method of delaying the onset and/or development of refractory chronic myeloid leukemia associated with a T315I mutation in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound or composition provided herein.

[0146] In one aspect, provided herein is a compound of formula (I) or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, for use in therapy. In some embodiments, provided herein is a compound of formula (I) or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or pharmaceutical composition comprising such compound, for use in the treatment of cancer. In some embodiments, provided is a compound of formula (I) or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or a pharmaceutical composition comprising such compound, for use in the treatment of chronic myeloid leukemia (CML), Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL), acute myelogenous leukemia (AML), or mixed phenotype acute

leukemia. In some embodiments, provided is a compound of formula (I) or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or a pharmaceutical composition comprising such compound, for use in the treatment of chronic myeloid leukemia (CML). In some embodiments, provided is a compound of formula (I) or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or a pharmaceutical composition comprising such compound, for use in the treatment of refractory chronic myeloid leukemia (CML). In some embodiments, provided is a compound of formula (I) or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or a pharmaceutical composition comprising such compound, for use in the treatment of refractory chronic myeloid leukemia associated with a T315I mutation.

[0147] In another embodiment, provided herein is a compound of formula (I) or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, for use in the manufacture of a medicament for the treatment of cancer. In another embodiment, provided herein is a compound of formula (I) or any variation thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, for use in the manufacture of a medicament for the treatment of chronic myeloid leukemia (CML), Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL), acute myelogenous leukemia (AML), or mixed phenotype acute leukemia. In some embodiments, the medicament is for the treatment of chronic myeloid leukemia. In some embodiments, the medicament is for the treatment of refractory chronic myeloid leukemia. In some embodiments, the medicament is for the treatment of refractory chronic myeloid leukemia associated with a T315I mutation.

[0148] In some embodiments, the individual is a mammal. In some embodiments, the individual is a primate, dog, cat, rabbit, or rodent. In some embodiments, the individual is a primate. In some embodiments, the individual is a human. In some embodiments, the human is at least about or is about any of 18, 21, 30, 50, 60, 65, 70, 75, 80, or 85 years old. In some embodiments, the human is a child. In some embodiments, the human is less than about or about any of 21, 18, 15, 10, 5, 4, 3, 2, or 1 years old.

[0149] In some embodiments, the method further comprises administering one or more additional pharmaceutical agents. In some embodiments, the method further comprises

administering radiation. In some embodiments, the method further comprises administering one or more additional pharmaceutical agents, including anti-microtubular therapies (e.g. paclitaxel, vincristine), topoisomerase inhibitors (e.g. adriamycin), alylating agents (e.g. busulfan, cyclophosphamide), nucleotide synthesis inhibitors (hyroxyurea), DNA synthesis inhibtiors (e.g. cytarabine), protein synthesis inhibitors (e.g. omacetaxine), developmental signaling pathway inhibitors (e.g. sonidegib, Hedgehog pathway), pro-apoptotic agents (e.g. venetoclax), Abl myristoyl-pocket binding inhibitors (e.g. asciminib), MEK1/2 inhibitors (e.g. trametinib, binimetinib), AKT inhibitors (e.g. ipatasertib), PI3K inhibitors (e.g. apelisib)and radiation.

VI. Dosing and Method of Administration

[0150] The dose of a compound described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, administered to an individual (such as a human) may vary with the particular compound or salt thereof, the method of administration, and the particular cancer, such as type and stage of cancer, being treated. In some embodiments, the amount of the compound, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, is a therapeutically effective amount.

[0151] The compounds provided herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, may be administered to an individual via various routes, including, *e.g.*, intravenous, intramuscular, subcutaneous, oral, and transdermal.

[0152] The effective amount of the compound may in one aspect be a dose of between about 0.01 and about 100 mg/kg. Effective amounts or doses of the compounds of the present disclosure may be ascertained by routine methods, such as modeling, dose escalation, or clinical trials, taking into account routine factors, *e.g.*, the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the disease to be treated, the subject's health status, condition, and weight. An exemplary dose is in the range of about from about 0.7 mg to 7 g daily, or about 7 mg to 350 mg daily, or about 350 mg to 1.75 g daily, or about 1.75 to 7 g daily.

[0153] Any of the methods provided herein may in one aspect comprise administering to an individual a pharmaceutical composition that contains an effective amount of a compound

provided herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, and a pharmaceutically acceptable excipient.

[0154] A compound or composition provided herein may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer, which in some variations may be for the duration of the individual's life. In one variation, the compound is administered on a daily or intermittent schedule. The compound can be administered to an individual continuously (for example, at least once daily) over a period of time. The dosing frequency can also be less than once daily, *e.g.*, about a once weekly dosing. The dosing frequency can be more than once daily, *e.g.*, twice or three times daily. The dosing frequency can also be intermittent, including a 'drug holiday' (*e.g.*, once daily dosing for 7 days followed by no doses for 7 days, repeated for any 14 day time period, such as about 2 months, about 4 months, about 6 months or more). Any of the dosing frequencies can employ any of the compounds described herein together with any of the dosages described herein.

VII. Articles of Manufacture and Kits

[0155] The present disclosure further provides articles of manufacture comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, a composition described herein, or one or more unit dosages described herein in suitable packaging. In certain embodiments, the article of manufacture is for use in any of the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

[0156] The present disclosure further provides kits for carrying out the methods of the present disclosure, which comprises one or more compounds described herein or a composition comprising a compound described herein. The kits may employ any of the compounds disclosed herein. In one variation, the kit employs a compound described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, thereof. The kits may be used for any one or more of the uses described herein, and, accordingly, may contain instructions for the treatment of any disease or described herein, for example for the treatment of cancer, including chronic myeloid leukemia (CML), Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL), acute

myelogenous leukemia (AML), or mixed phenotype acute leukemia. In some embodiments, the cancer is chronic myeloid leukemia. In some embodiments, the cancer is refractory chronic myeloid leukemia. In certain embodiments of the foregoing, the cancer is refractory chronic myeloid leukemia associated with a T315I mutation.

[0157] The kits optionally further comprise a container comprising one or more additional pharmaceutical agents and which kits further comprise instructions on or in the package insert for treating the subject with an effective amount of the one or more additional pharmaceutical agents.

[0158] Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any compound described herein. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit.

[0159] The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a compound as disclosed herein and/or an additional pharmaceutically active compound useful for a disease detailed herein to provide effective treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (*e.g.*, hospital pharmacies and compounding pharmacies).

[0160] The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (*e.g.*, magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the methods of the present disclosure. The instructions included with the kit generally include information as to the components and their administration to an individual.

EXAMPLES

[0161] It is understood that the present disclosure has been made only by way of example, and that numerous changes in the combination and arrangement of parts can be resorted to by those skilled in the art without departing from the spirit and scope of present disclosure.

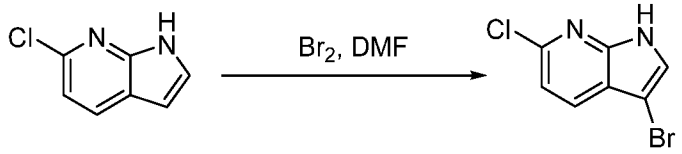
Synthetic Examples

[0162] The chemical reactions in the Examples described can be readily adapted to prepare a number of other compounds disclosed herein, and alternative methods for preparing the compounds of this disclosure are deemed to be within the scope of this disclosure. For example, the synthesis of non-exemplified compounds according to the present disclosure can be successfully performed by modifications apparent to those skilled in the art, *e.g.*, by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, or by making routine modifications of reaction conditions, reagents, and starting materials. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the present disclosure.

[0163] Abbreviations used in the Examples include the following: ACN: acetonitrile; Brettphos: 2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl; dppf: 1,1'-ferrocenediyl-bis(diphenylphosphine); DCM: dichloromethane; DIAD: diisopropylazodicarboxylate; DIEA: N,N-diisopropylethylamine; DMAP: 4-dimethylaminopyridine; DMF: dimethylformamide; DMF-DMA: N,N-dimethylformamide dimethylacetal; DMSO: dimethyl sulfoxide; EDA; ethylenediamine; EtOAc: ethyl acetate; EtOH: ethanol or ethyl alcohol; F-TEDA-BF_4: 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); ^{1}H NMR: proton nuclear magnetic resonance; HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate, Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium; LCMS: liquid chromatography–mass spectrometry; LDA: lithium diisopropylamide; LiHMDS: lithium hexamethyldisilazide; MeOH: methanol or methyl alcohol; NBS: N-bromosuccinimide; NIS: N-iodosuccinimide; NNMP: N-methyl-2-pyrrolidone; OAc: acetate; Py: pyridine; TBAB: tetra-n—butylammonium bromide; TBAF: tetra-n-butylammonium fluoride; TEA: triethylamine; TFA: trifluoroacetic acid; THF: tetrahydrofuran; and TLC: thin-layer chromatography.

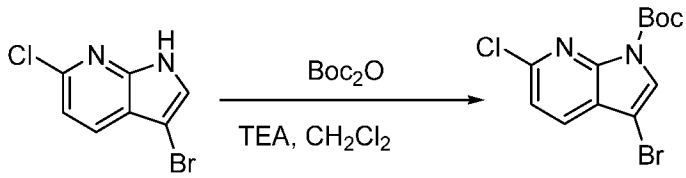
Example S1. Compound 1

Step 1: Synthesis of 3-bromo-6-chloro-1H-pyrrolo[2,3-b]pyridine.



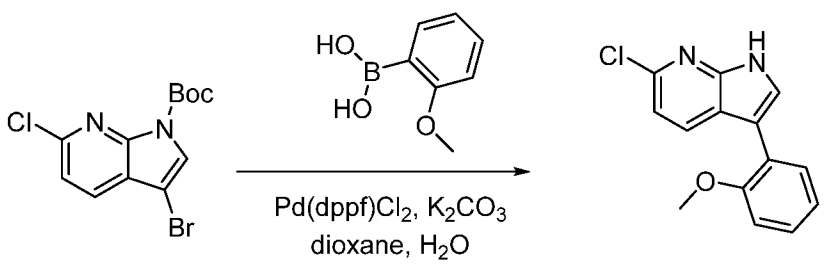
[0164] To a solution of 6-chloro-1H-pyrrolo[2,3-b]pyridine (500.0 mg, 3.28 mmol) in DMF (5.0 mL) was added Br_2 (549.9 mg, 3.44 mmol) dropwise at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 3 h under N_2. After the reaction was completed, the reaction was quenched with aq.$NaHSO_3$ at 10 °C. The pH value of the mixture was adjusted to 8 with aq.$NaHCO_3$. The resulting mixture was filtered. The solid was washed with H_2O, collected and dried to afford 3-bromo-6-chloro-1H-pyrrolo[2,3-b]pyridine (620.0 mg, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =230.9.

Step 2: Synthesis of tert-butyl 3-bromo-6-chloro-1H-pyrrolo[2,3-b]pyridine-1-carboxylate.



[0165] To a solution of 3-bromo-6-chloro-1H-pyrrolo[2,3-b]pyridine (620.0 mg, crude) in CH_2Cl_2 (10.0 mL) was added Boc_2O (759.9 mg, 3.48 mmol) and TEA (758.9 mg, 7.50 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (85/15, v/v) to afford tert-butyl 3-bromo-6-chloro-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (850.0 mg, 96%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =331.0.

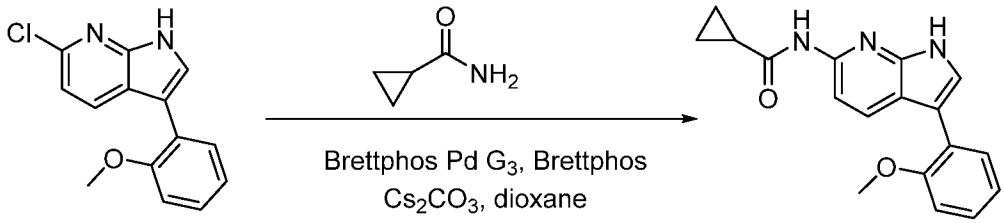
Step 3: Synthesis of 6-chloro-3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine.



[0166] To a solution of tert-butyl 3-bromo-6-chloro-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (500.0 mg, 1.51 mmol) in 1,4-dioxane/H_2O (20.0/2.0 mL) was added (2-

methoxyphenyl)boronic acid (275.0 mg, 1.81 mmol), K_2CO_3 (625.2 mg, 4.52 mmol) and Pd(dppf)Cl_2 (110.3 mg, 0.15 mmol). The resulting mixture was stirred at 100 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (83/17, v/v) to afford 6-chloro-3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine (190.0 mg, 49%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =259.1.

Step 4: Synthesis of N-(3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (Compound 1)

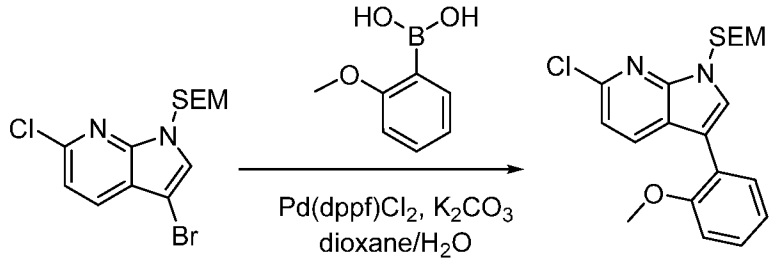


1

[0167] To a stirred solution of 6-chloro-3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine (140.0 mg, 0.54 mmol) in 1,4-dioxane (15.0 mL) was added cyclopropanecarboxamide (184.2 mg, 2.17 mmol), BrettPhos (58.1 mg, 0.11 mmol), Cs_2CO_3 (529.0 mg, 1.62 mmol) and BrettPhos Pd G3 (49.1 mg, 0.05 mmol). The resulting mixture was stirred at 100 °C for 4 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (95/5, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:27% B to 57% B in 7 min; 254 nm) to afford N-(3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (14.6 mg, 9%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =308.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.55 (s, 1H), 10.58 (s, 1H), 7.98 - 7.87 (m, 2H), 7.56 - 7.52 (m, 2H), 7.35 - 7.19 (m, 1H), 7.11 (d, J = 8.1 Hz, 1H), 7.07 - 6.92 (m, 1H), 3.81 (s, 3H), 2.11 - 1.98 (m, 1H), 0.97 - 0.73 (m, 4H).

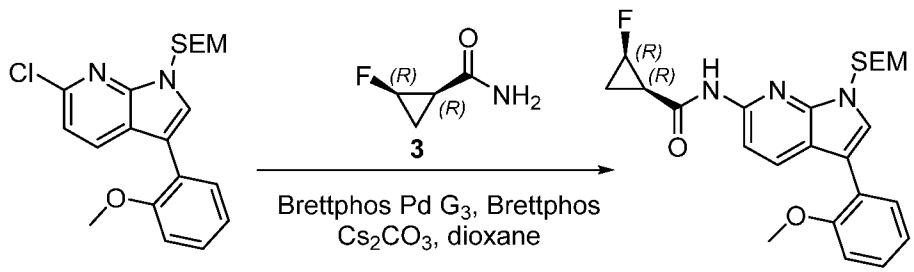
Example S2. Compound 2

Step 1: Synthesis of 6-chloro-3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine.



[0168] To a solution of 3-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (600.0 mg, 1.66 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added (2-methoxyphenyl)boronic acid (302.5 mg, 1.99 mmol), K_2CO_3 (687.7 mg, 4.98 mmol) and $Pd(dppf)Cl_2$ (121.4 mg, 0.17 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 3 h under N_2. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford 6-chloro-3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (390.0 mg, 60%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =389.1.

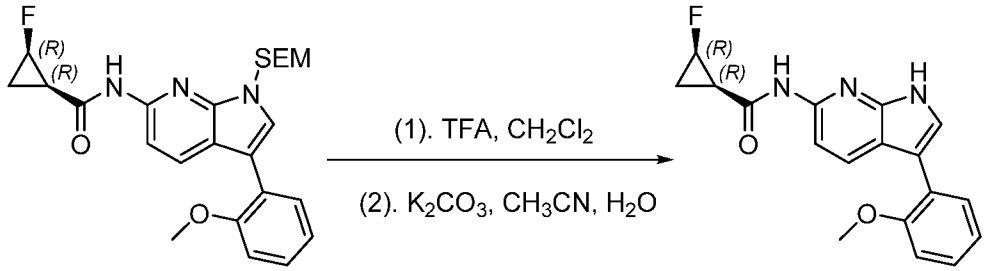
Step 2: Synthesis of (1R,2R)-2-fluoro-N-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide.



[0169] To a solution of 6-chloro-3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (190.0 mg, 0.49 mmol) in 1,4-dioxane (10.0 mL) was added (1R,2R)-2-fluorocyclopropane-1-carboxamide (251.8 mg, 2.44 mmol), BrettPhos (52.4 mg, 0.10 mmol), Cs_2CO_3 (477.4 mg, 1.47 mmol) and BrettPhos Pd G3 (44.3 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h under N_2. After the reaction was completed, the resulting mixture was diluted

with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (67/33, v/v) to afford (1R,2R)-2-fluoro-N-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (110.0 mg, 49%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =456.2.

Step 3: Synthesis of (1R,2R)-2-fluoro-N-(3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 2)

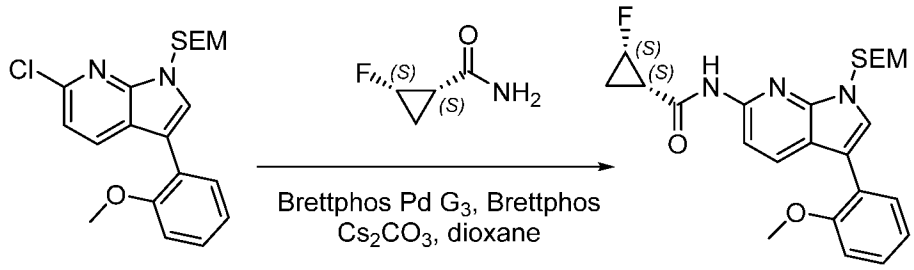


2

[0170] To a solution of (1R,2R)-2-fluoro-N-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (100.0 mg, 0.22 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated in vacuo. The residue was re-dissolved in ACN/H_2O (5.0/1.0 mL). Then K_2CO_3 (380.7 mg, 2.76 mmol) was added to the mixture. The mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions(Column: YMC-Actus Triart C18, 30x250 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:39% B to 52% B in 7 min; 254 nm) to afford (1R,2R)-2-fluoro-N-(3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (14.0 mg, 20%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =326.1. ^1H NMR(300 MHz, DMSO-d_6): δ 11.58 (s, 1H), 10.64 (s, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.58 - 7.53 (m, 2H), 7.31 - 7.25 (m, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.06 - 7.00 (m, 1H), 5.10 - 4.78 (m, 1H), 3.82 (s, 3H), 2.30 - 2.15 (m, 1H), 1.75 - 1.67 (m, 1H), 1.25 - 1.08 (m, 1H).

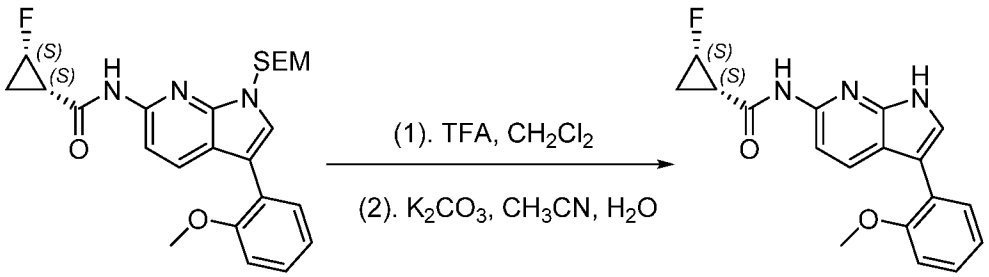
Example S3. Compound 3

Step 1: Synthesis of (1S,2S)-2-fluoro-N-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide.



[0171] To a solution of 6-chloro-3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (190.0 mg, 0.49 mmol) in 1,4-dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (251.8 mg, 2.44 mmol), BrettPhos (52.4 mg, 0.10 mmol), Cs_2CO_3 (477.4 mg, 1.47 mmol) and BrettPhos Pd G3 (44.3 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (67/33, v/v) to afford (1S,2S)-2-fluoro-N-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (100.0 mg, 45%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =456.2.

Step 2: Synthesis of (1S,2S)-2-fluoro-N-(3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 3)



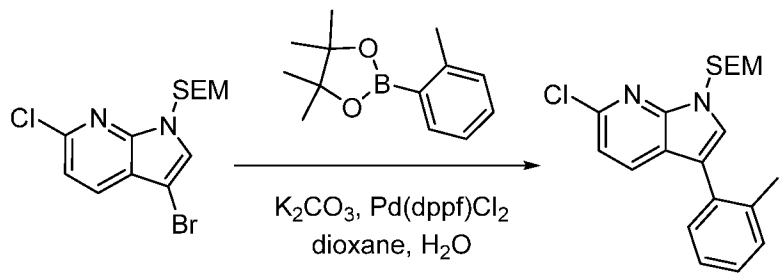
3

[0172] To a solution of (1S,2S)-2-fluoro-N-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide

(100.0 mg, 0.22 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated in vacuo. The residue was re-dissolved in ACN/H_2O (5.0/1.0 mL). Then K_2CO_3 (380.7 mg, 2.76 mmol) was added to the mixture. The reaction mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions(Column: YMC-Actus Triart C18, 30x250 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:39% B to 52% B in 7 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (10.6 mg, 14%) as a light pink solid. LCMS (ESI, m/z): $[M+H]^+$ =326.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.57 (s, 1H), 10.63 (s, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.89 (d, J = 8.7 Hz, 1H), 7.57 - 7.52 (m, 2H), 7.30 - 7.24 (m, 1H), 7.12 - 7.09 (m, 1H), 7.05 - 7.00 (m, 1H), 5.05 - 4.80 (m, 1H), 3.82 (s, 3H), 2.27 - 2.21 (m, 1H), 1.70 - 1.61 (m, 1H), 1.19 - 1.12 (m, 1H).

Example S4. Compound 4

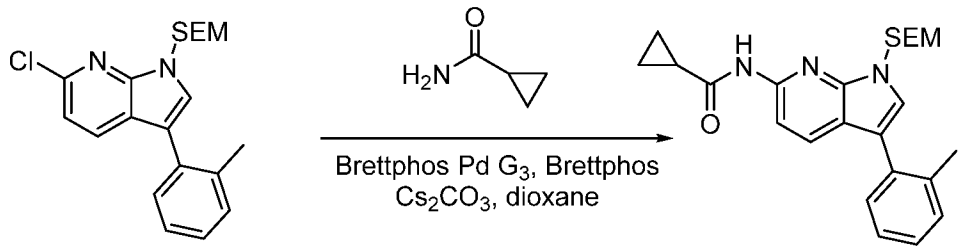
Step 1: Synthesis of 6-chloro-3-(2-methylphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine.



[0173] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 0.83 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 4,4,5,5-tetramethyl-2-(2-methylphenyl)-1,3,2-dioxaborolane (217.0 mg, 0.99 mmol), K_2CO_3 (343.9 mg, 2.49 mmol) and $Pd(dppf)Cl_2$ (121.4 mg, 0.17 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced

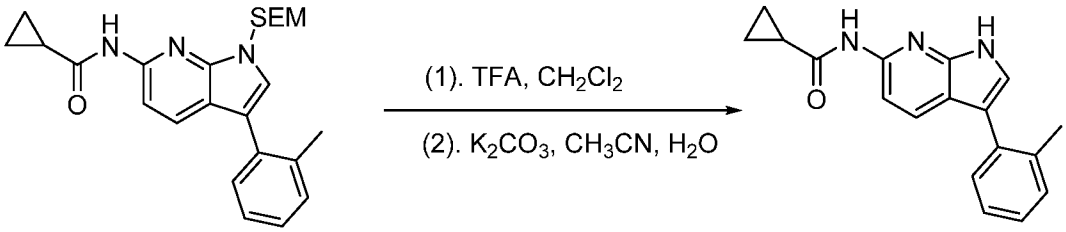
pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (90/10, v/v) to afford 6-chloro-3-(2-methylphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (150.0 mg, 49%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =373.1.

Step 2: Synthesis of N-[3-(2-methylphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide.



[0174] To a solution of 6-chloro-3-(2-methylphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (120.0 mg, 0.32 mmol) in dioxane (8.0 mL) was added cyclopropanecarboxamide (136.9 mg, 1.60 mmol), BrettPhos (69.0 mg, 0.13 mmol), Cs_2CO_3 (314.5 mg, 0.97 mmol) and BrettPhos Pd G3 (58.3 mg, 0.06 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (80/20, v/v) to afford N-[3-(2-methylphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (120.0 mg, 88%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =422.2.

Step 3: Synthesis of N-[3-(2-methylphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 4)

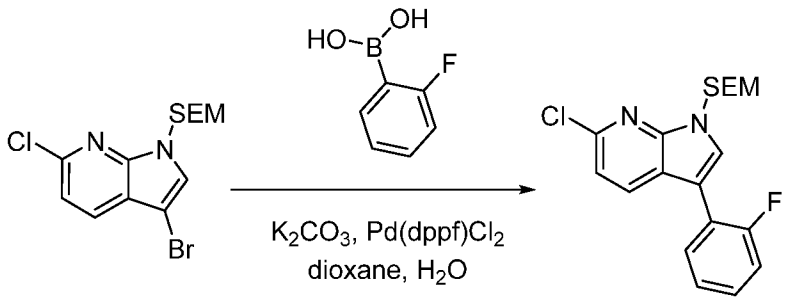


4

[0175] To a solution of N-[3-(2-methylphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (100.0 mg, 0.24 mmol) in DCM (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in ACN/H_2O (5.0/1.0 mL). Then K_2CO_3 (163.6 mg, 1.18 mmol) was added to the mixture. The mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30x250 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:48% B to 58% B in 7 min; 254 nm) to afford N-[3-(2-methylphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (13.6 mg, 20%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =292.1. ^1H NMR (400 MHz, DMSO-d_6): δ 11.59 (s, 1H), 11.60 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.78 (s, 1H), 7.42 (d, J = 2.4 Hz, 1H) ,7.37 - 7.31 (m, 2H), 7.25 - 7.22 (m, 2H), 2.31 (s, 3H), 2.06 - 2.02 (m, 1H), 0.82 - 0.80 (m, 4H).

Example S5. Compound 5

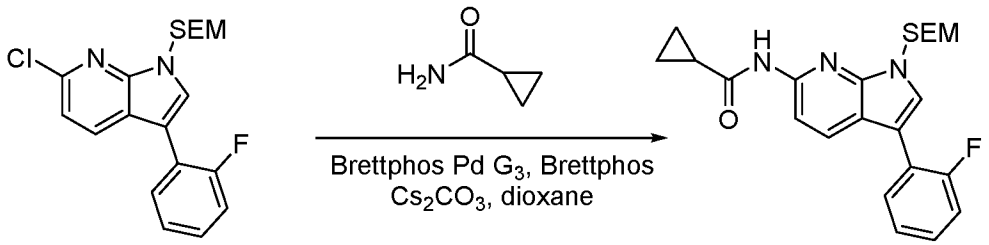
Step 1: Synthesis of 6-chloro-3-(2-fluorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine.



[0176] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 0.83 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 2-fluorophenylboronic acid (139.2 mg, 1.01 mmol), K_2CO_3 (343.8 mg, 2.49 mmol) and Pd(dppf)Cl_2 (60.7 mg, 0.08 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 3 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The

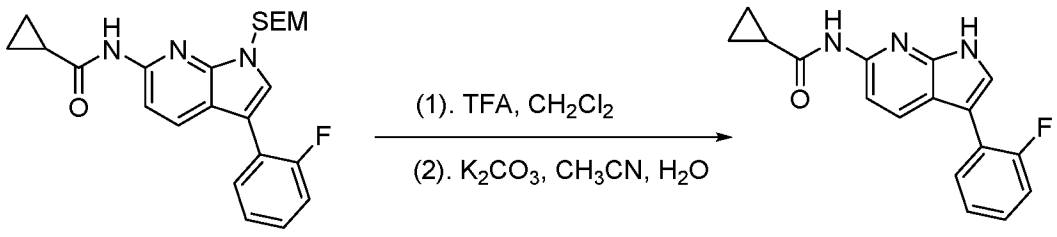
combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (93/7, v/v) to afford 6-chloro-3-(2-fluorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (220.0 mg, 70%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =377.1.

Step 2: Synthesis of N-[3-(2-fluorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide.



[0177] To a solution of 6-chloro-3-(2-fluorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (170.0 mg, 0.45 mmol) in 1,4-dioxane (5.0 mL) was added cyclopropanecarboxamide (115.1 mg, 1.35 mmol), Cs_2CO_3 (440.8 mg, 1.35 mmol), Brettphos (48.42 mg, 0.09 mmol) and Brettphos Pd G3 (40.9 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (83/17, v/v) to afford N-[3-(2-fluorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (210.0 mg, 62%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =426.1.

Step 3: Synthesis of N-[3-(2-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 5)

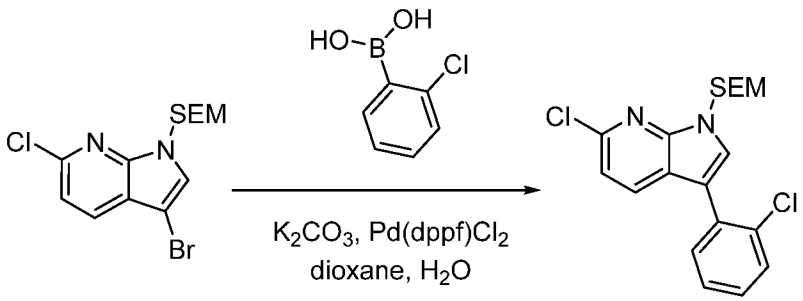


5

[0178] To a solution of N-[3-(2-fluorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (150.0 mg, 0.35 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated in vacuo. The residue was re-dissolved in ACN/H_2O (5.0/1.0 mL). Then K_2CO_3 (487.1 mg, 3.53 mmol) was added to the mixture. The mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:38% B to 68% B in 7 min; 254 nm) to afford N-[3-(2-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (54.7 mg, 52%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =296.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.80 (s, 1H), 10.65 (s, 1H), 8.08 - 8.05 (m, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.76 - 7.70 (m, 1H), 7.66 (s, 1H), 7.34 - 7.26 (m, 3H), 2.08 - 2.03 (m, 1H), 0.86 - 0.76 (m, 4H).

Example S6. Compound 6

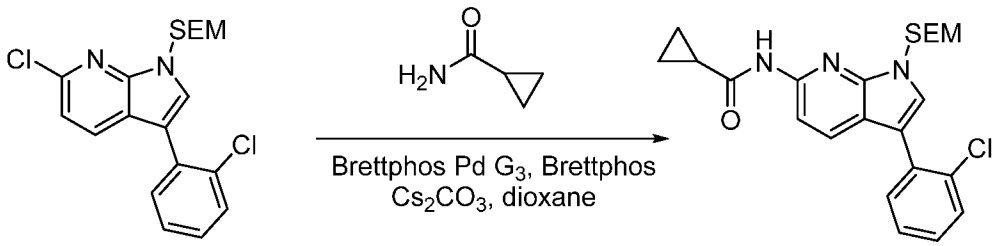
Step 1: Synthesis of 6-chloro-3-(2-chlorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine



[0179] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 0.83 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 2-chlorophenylboronic acid (155.6 mg, 0.99 mmol), K_2CO_3 (343.9 mg, 2.49 mmol) and $Pd(dppf)Cl_2$ (60.7 mg, 0.08 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 3 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was

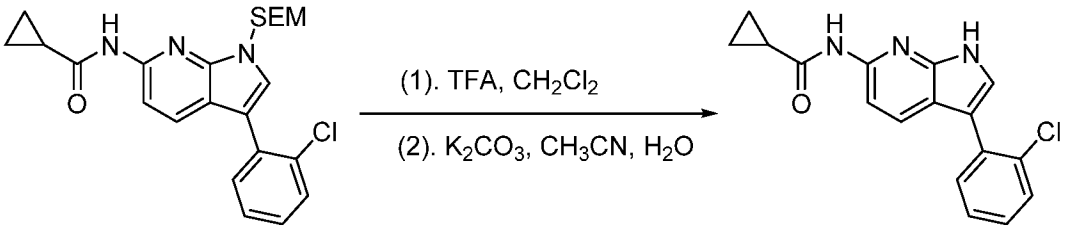
concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford 6-chloro-3-(2-chlorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (210.0 mg, 64%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =393.1.

Step 2: Synthesis of N-[3-(2-chlorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide



[0180] To a solution of 6-chloro-3-(2-chlorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (110.0 mg, 0.28 mmol) in 1,4-dioxane (3.0 mL) was added cyclopropanecarboxamide (23.8 mg, 0.28 mmol), BrettPhos (30.0 mg, 0.06 mmol), Cs_2CO_3 (273.3 mg, 0.38 mmol) and BrettPhos Pd G3 (25.4 mg, 0.03 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 3 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford N-[3-(2-chlorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (105.0 mg, 85%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =442.2.

Step 3: Synthesis of N-[3-(2-chlorophenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 6)

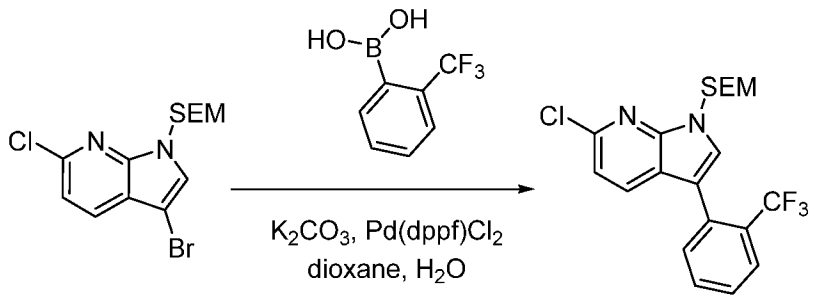


6

[0181] To a solution of N-[3-(2-chlorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (105.0 mg, 0.24 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The mixture was evaporated in vacuo. The residue was re-dissolved with ACN/H_2O (5.0/3.0 mL). Then K_2CO_3 (328.3 mg, 2.38 mmol) was added to the mixture. The mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column, 5 um, 19x250 mm; Mobile Phase A:Water (0.05% FA), Mobile Phase B:MeOH--HPLC; Flow rate: 25 mL/min; Gradient:54% B to 70% B in 10 min; 254 nm) to afford N-[3-(2-chlorophenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (8.1 mg, 10%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =312.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.79 (s, 1H), 10.64 (s, 1H), 7.98 - 7.91 (m, 1H), 7.87 - 7.84 (m, 1H), 7.60 - 7.57 (m, 3H), 7.49 - 7.30 (m, 2H), 2.10 - 2.00 (m, 1H), 0.83 - 0.79 (m, 4H).

Example S7. Compound 7

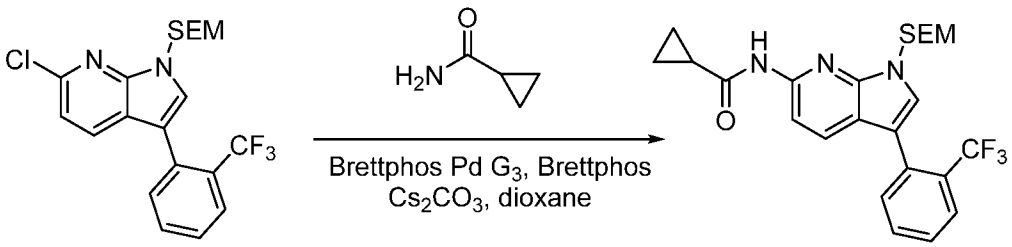
Step 1: Synthesis of 6-chloro-3-[2-(trifluoromethyl)phenyl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine.



[0182] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 0.83 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 2-(trifluoromethyl)phenylboronic acid (189.0 mg, 0.99 mmol), K_2CO_3 (343.8 mg, 2.49 mmol) and $Pd(dppf)Cl_2$ (60.7 mg, 0.08 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by

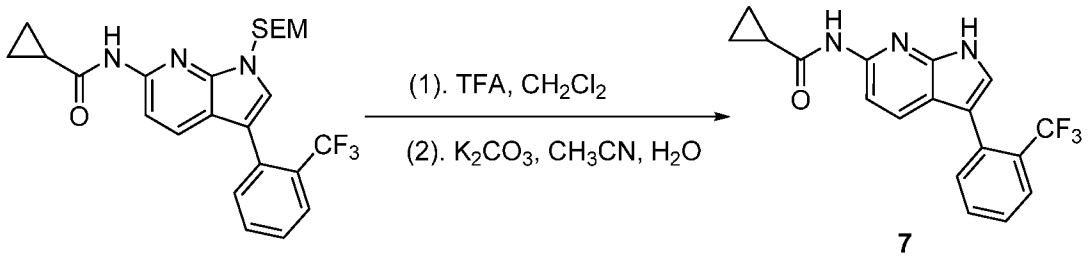
flash column chromatography with petroleum ether/ethyl acetate (94/6, v/v) to afford 6-chloro-3-[2-(trifluoromethyl)phenyl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 84%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =427.1.

Step 2: Synthesis of N-[3-[2-(trifluoromethyl)phenyl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide.



[0183] To a solution of 6-chloro-3-[2-(trifluoromethyl)phenyl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (250.0 mg, 0.59 mmol) in 1,4-dioxane (5.0 mL) was added cyclopropanecarboxamide (149.5 mg, 1.76 mmol), Cs_2CO_3 (572.4 mg, 1.76 mmol), BrettPhos (62.8 mg, 0.12 mmol) and Brettphos Pd G3 (53.1 mg, 0.06 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (84/16, v/v) to afford N-[3-[2-(trifluoromethyl)phenyl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (200.0 mg, 71%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =476.2.

Step 3: Synthesis of N-[3-[2-(trifluoromethyl)phenyl]-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 7)



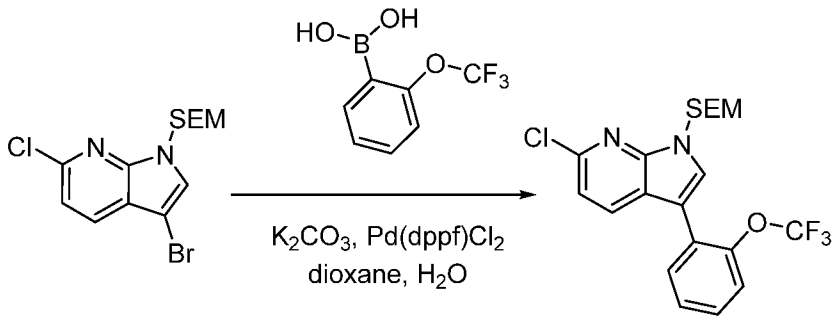
7

[0184] The solution of N-[3-[2-(trifluoromethyl)phenyl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (200.0 mg, 0.42 mmol) in CH_2Cl_2/TFA (5.0 mL/5.0 mL) was stirred at room temperature for 1 h.

The mixture was evaporated in vacuo. The residue was re-dissolved in ACN/H_2O (5.0/1.0mL).Then K_2CO_3 (581.2 mg, 4.21 mmol) was added to the mixture. The mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30x250 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:48% B to 61% B in 7 min; 254 nm) to afford N-[3-[2-(trifluoromethyl)phenyl]-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (21.0 mg, 14%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =346.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.70 (s, 1H), 10.64 (s, 1H), 7.90 - 7.84 (m, 2H), 7.73 - 7.70 (m, 2H), 7.60 - 7.56 (m, 2H), 7.37 (s, 1H), 2.05 - 1.95 (m, 1H), 0.85 - 0.75 (m, 4H).

Example S8. Compound 8

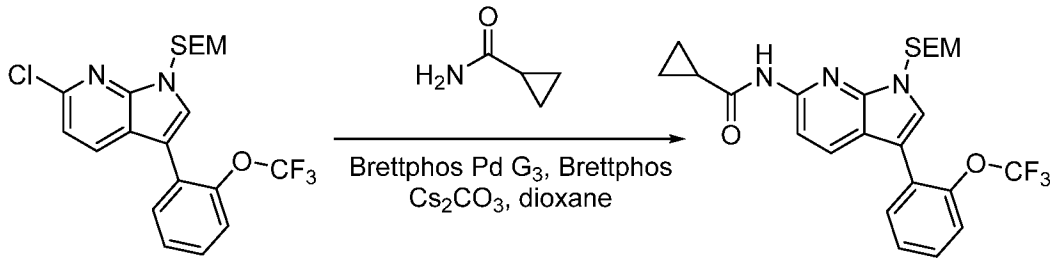
Step 1: Synthesis of 6-chloro-3-[2-(trifluoromethoxy)phenyl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine.



[0185] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 0.83 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 2-(trifluoromethoxy)phenylboronic acid (204.9 mg, 0.99 mmol), K_2CO_3 (343.8 mg, 2.49 mmol) and $Pd(dppf)Cl_2$ (60.7 mg, 0.08 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 3 h under N_2. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford 6-

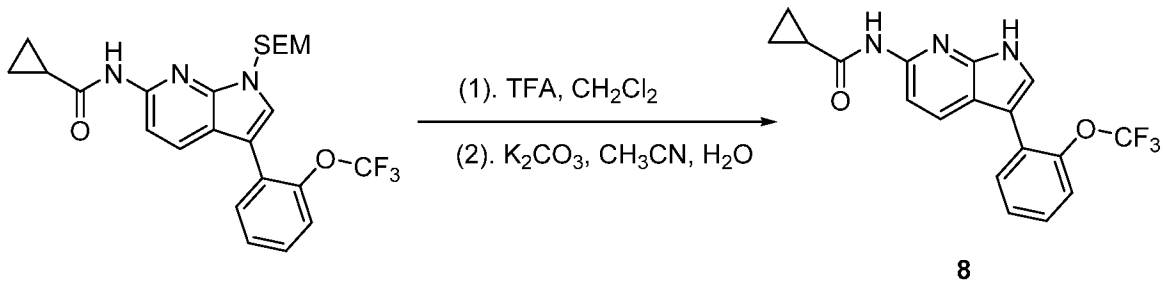
chloro-3-[2-(trifluoromethoxy)phenyl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (290.0 mg, 78%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =443.1.

Step 2: Synthesis of N-[3-[2-(trifluoromethoxy)phenyl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide.



[0186] To a solution of 6-chloro-3-[2-(trifluoromethoxy)phenyl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (240.0 mg, 0.54 mmol) in 1,4-dioxane (5.0 mL) was added cyclopropanecarboxamide (138.3 mg, 1.63 mmol), BrettPhos (58.2 mg, 0.11 mmol), Cs_2CO_3 (529.6 mg, 1.63 mmol) and BrettPhos Pd G3 (49.1 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 3 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford N-[3-[2-(trifluoromethoxy)phenyl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (155.0 mg, 58%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =492.2.

Step 3: Synthesis of N-[3-[2-(trifluoromethoxy)phenyl]-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 8)



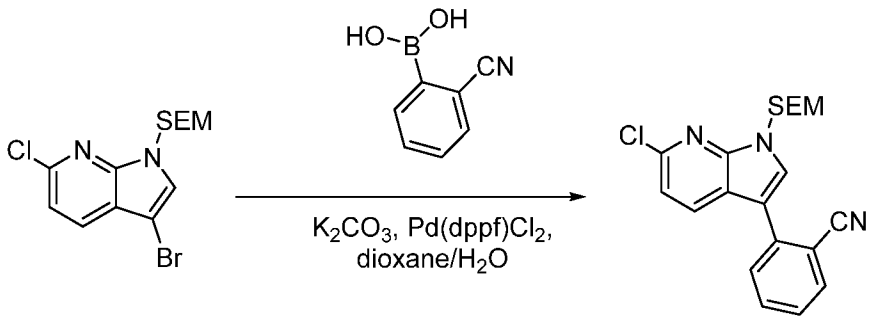
8

[0187] To a solution of N-[3-[2-(trifluoromethoxy)phenyl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (155.0 mg, 0.32 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The

resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the reaction mixture was evaporated in vacuo. The residue was dissolved with ACN/H_2O (5.0/3.0 mL). Then K_2CO_3 (435.8 mg, 3.45 mmol) was added to the mixture. The mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions(Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:36% B to 56% B in 11 min; 254 nm) to afford N-[3-[2-(trifluoromethoxy)phenyl]-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (13.7 mg, 12%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =362.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.79 (s, 1H), 10.66 (s, 1H), 7.99 - 7.92 (m, 2H), 7.75 - 7.71 (m, 1H), 7.60 (d, J = 2.4 Hz, 1H), 7.51 - 7.42 (m, 3H), 2.05 - 1.95 (m, 1H), 0.83 - 0.79 (m, 4H).

Example S9. Compound 9

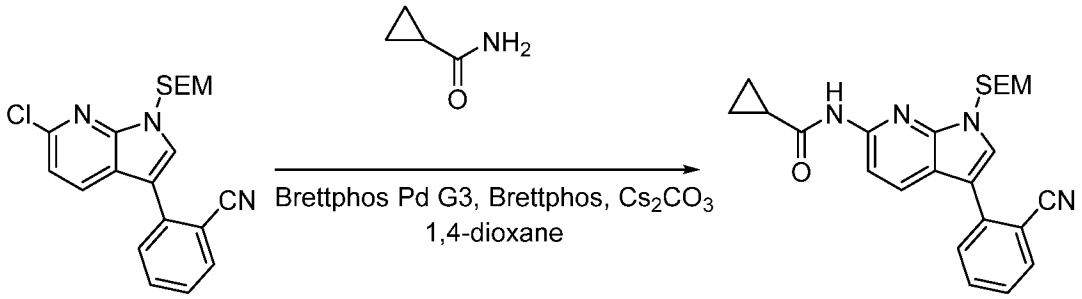
Step 1: Synthesis of 2-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)benzonitrile



[0188] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 0.83 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 2-cyanophenylboronic acid (146.2 mg, 1.00 mmol), K_2CO_3 (343.9 mg, 2.49 mmol) and Pd(dppf)Cl_2 (60.7 mg, 0.08 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 3 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (65/35, v/v) to afford 2-(6-chloro-1-[[2-

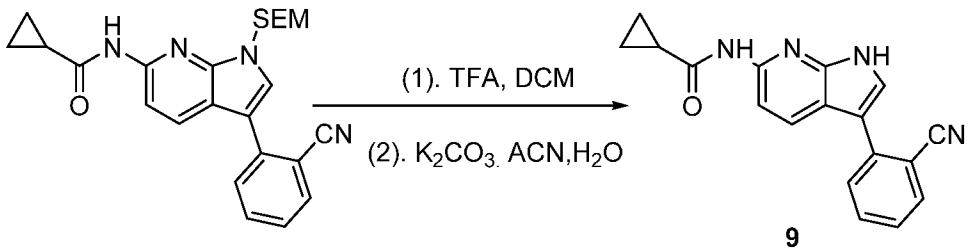
(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)benzonitrile (190.0 mg, 59%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =384.1.

Step 2: Synthesis N-[3-(2-cyanophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide.



[0189] To a solution of 2-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)benzonitrile (140.0 mg, 0.37 mmol) in 1,4-dioxane (5.0 mL) was added cyclopropanecarboxamide (93.1 mg, 1.09 mmol), Cs_2CO_3 (356.4 mg, 1.09 mmol), Brettphos (39.14 mg, 0.07 mmol) and Brettphos Pd G3 (33.1 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (7/3, v/v) to afford N-[3-(2-cyanophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (150.0 mg, 95%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =433.2.

Step 3: Synthesis of N-[3-(2-cyanophenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 9)



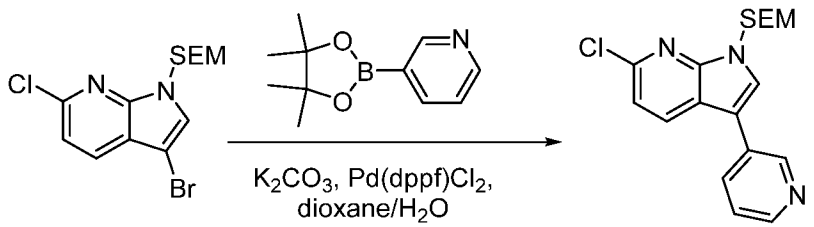
9

[0190] To a solution of N-[3-(2-cyanophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (150.0 mg, 0.35 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL). The resulting mixture stirred

at room temperature for 1 h. The reaction mixture was evaporated in vacuo. The residue was re-dissolved in ACN/H_2O (5.0/1.0 mL). Then K_2CO_3 (239.6 mg, 1.73 mmol) was added to the mixture. The mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:25% B to 42% B in 11 min; 254 nm) to afford N-[3-(2-cyanophenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (24.9 mg, 18%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =303.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.93 (s, 1H), 10.68 (s, 1H), 8.02 - 7.91 (m, 3H), 7.79 - 7.76 (m, 3H), 7.51 - 7.46 (m, 1H), 2.06 - 2.03 (m, 1H), 0.83 - 0.79 (m, 4H).

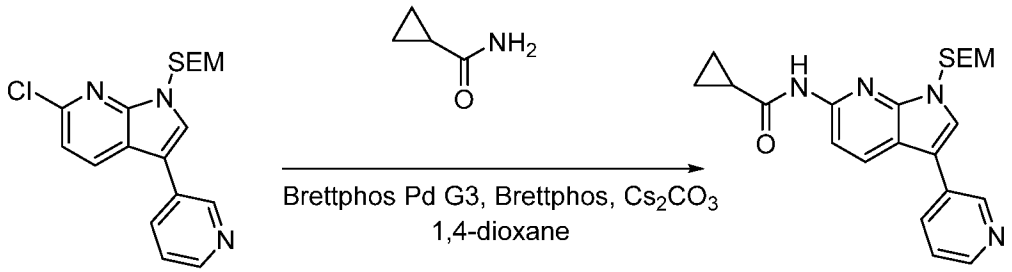
Example S10. Compound 10

Step 1: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridine.



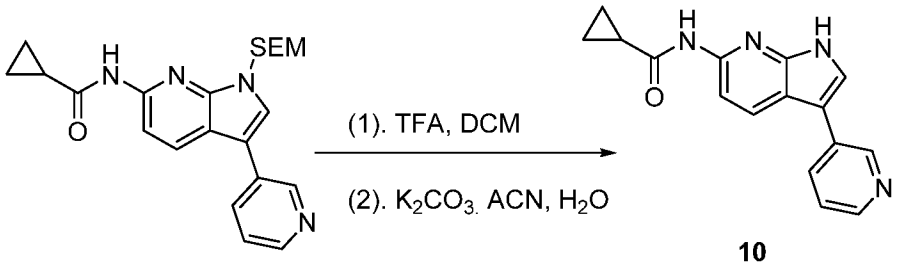
[0191] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 0.83 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (204.1 mg, 1.0 mmol), K_2CO_3 (343.9 mg, 2.49 mmol) and $Pd(dppf)Cl_2$ (60.7 mg, 0.08 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 3 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/9, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridine (290.0 mg, 97%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =360.1.

Step 2: Synthesis of N-[3-(pyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide



[0192] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridine (250.0 mg, 0.69 mmol) in 1,4-dioxane (5.0 mL) was added cyclopropanecarboxamide (177.3 mg, 2.08 mmol), Cs_2CO_3 (678.9 mg, 2.08 mmol), Brettphos (74.6 mg, 0.14 mmol) and Brettphos Pd G3 (62.9 mg, 0.07 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (14/86, v/v) to afford N-[3-(pyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (200.0 mg, 70%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =409.2.

Step 3: Synthesis of N-[3-(pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 10)



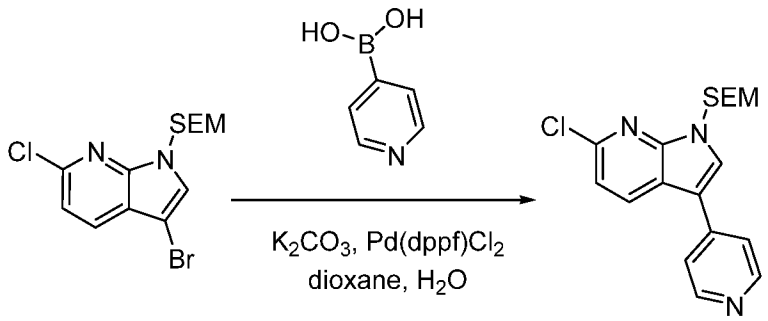
10

[0193] To a solution of N-[3-(pyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (150.0 mg, 0.37 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated in vacuo. The residue was re-dissolved in ACN/H_2O (5.0/1.0 mL). Then K_2CO_3 (253.7 mg, 1.84 mmol) was added to the mixture. The mixture was stirred at room temperature for another 16 h. After the

reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH F-Phenyl OBD column, 19x250 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:25 mL/min; Gradient:32% B to 51% B in 7 min; 254 nm) to afford N-[3-(pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (18.3 mg, 18%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =279.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.82 (s, 1H), 10.66 (s, 1H), 8.97 (d, J = 1.5 Hz, 1H), 8.44 (d, J = 3.3 Hz, 1H), 8.30 (d, J = 8.7 Hz, 1H), 8.13 - 8.11 (m, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.46 - 7.42 (m, 1H), 2.19 - 1.90 (m, 1H), 0.84 - 0.80 (m, 4H).

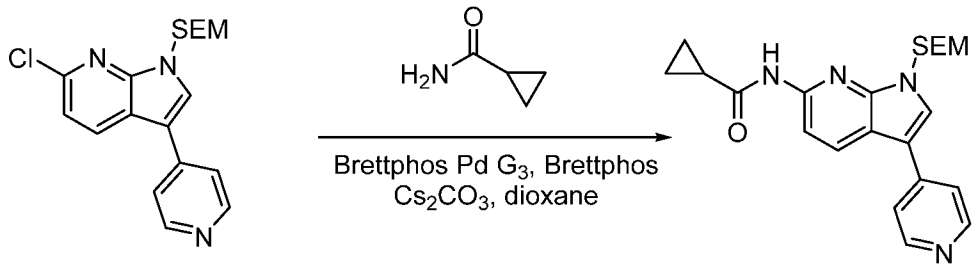
Example S11. Compound 11

Step 1: Synthesis of 4-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridine.



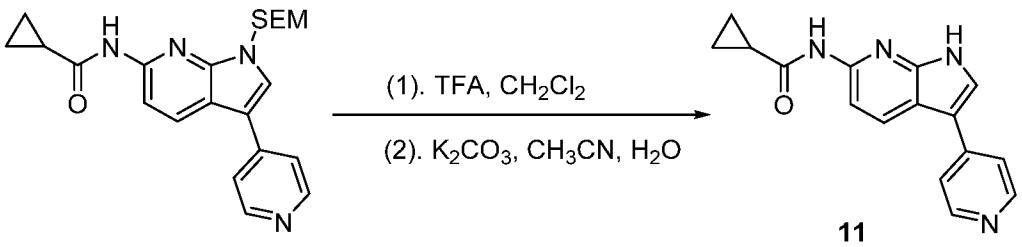
[0194] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (280.0 mg, 0.77 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added pyridin-4-ylboronic acid (95.1 mg, 0.77 mmol), K_2CO_3 (320.9 mg, 2.32 mmol) and $Pd(dppf)Cl_2$ (113.3 mg, 0.16 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (70/30, v/v) to afford 4-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridine (114.0 mg, 41%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =360.1.

Step 2: Synthesis of N-[3-(pyridin-4-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide



[0195] To a solution of 4-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridine (120.0 mg, 0.33 mmol) in dioxane (8.0 mL) was added cyclopropanecarboxamide (141.9 mg, 1.67 mmol), BrettPhos (71.6 mg, 0.13 mmol), Cs_2CO_3 (325.9 mg, 1.00 mmol) and BrettPhos Pd G3 (60.5 mg, 0.07 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (64/36, v/v) to afford N-[3-(pyridin-4-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (100.0 mg, 73%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =409.2.

Step 3: Synthesis of N-[3-(pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 11)

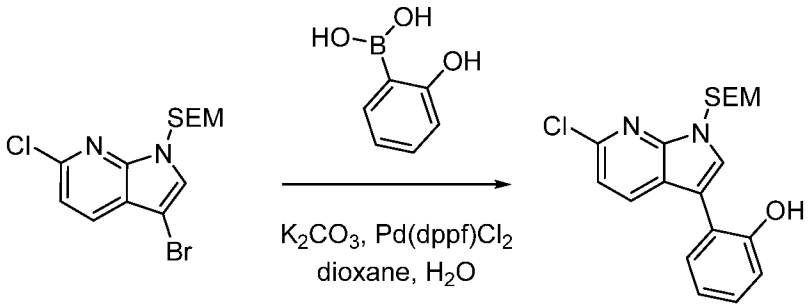


[0196] To a stirred mixture of N-[3-(pyridin-4-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (100.0 mg, 0.25 mmol) in DCM (3.0 mL) was added TFA (3.0 mL). The resulting mixture was stirred at room temperature for 3 h. The mixture was evaporated in vacuo. The residue was re-dissolved in ACN/H_2O (5.0/1.0 mL). Then K_2CO_3 (182.7 mg, 1.32 mmol) was added to the mixture. The mixture was stirred at room temperature for 16 h. After the reaction was

completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH F-Phenyl OBD column, 19x250 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:25 mL/min; Gradient:30% B to 60% B in 7 min; 254 nm) to afford N-[3-(pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (12.8 mg, 10%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =279.1. ^1H NMR (400 MHz, DMSO-d_6): δ 11.95 (s, 1H), 10.65 (s, 1H), 8.53 (d, J = 4.8 Hz, 2H), 8.39 (d, J = 8.8 Hz, 1H), 8.08 (s, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 4.8 Hz, 2H), 2.05 - 1.97 (m, 1H), 0.83 - 0.79 (m, 4H).

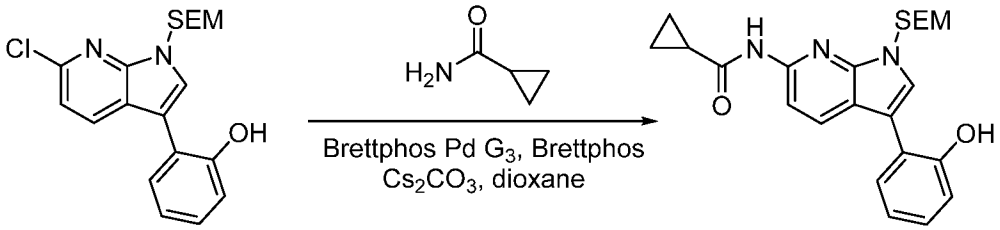
Example S12. Compound 12

Step 1: Synthesis of 2-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)phenol



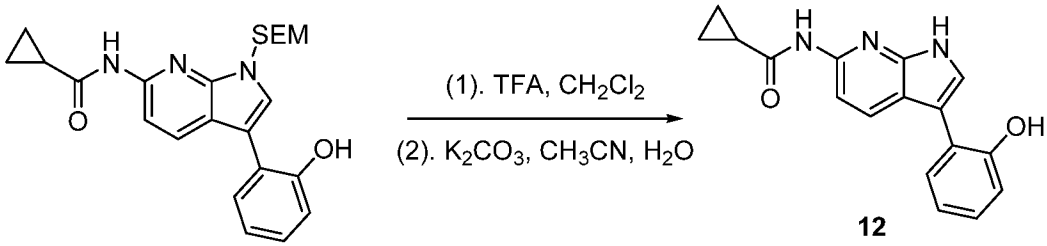
[0197] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (280.0 mg, 0.77 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 2-hydroxyphenylboronic acid (106.8 mg, 0.77 mmol), K_2CO_3 (320.9 mg, 2.32 mmol) and $Pd(dppf)Cl_2$ (113.3 mg, 0.16 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (89/11, v/v) to afford 2-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)phenol (110.0 mg, 38%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =375.1.

Step 2: Synthesis of N-[3-(2-hydroxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide



[0198] To a solution of 2-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)phenol (110.0 mg, 0.29 mmol) in dioxane (8.0 mL) was added cyclopropanecarboxamide (124.8 mg, 1.47 mmol), BrettPhos (63.0 mg, 0.12 mmol), Cs_2CO_3 (286.8 mg, 0.88 mmol) and BrettPhos Pd G3 (53.2 mg, 0.06 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (63/37, v/v) to afford N-[3-(2-hydroxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (52.0 mg, 42%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =424.2.

Step 3: Synthesis of N-[3-(2-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 12)

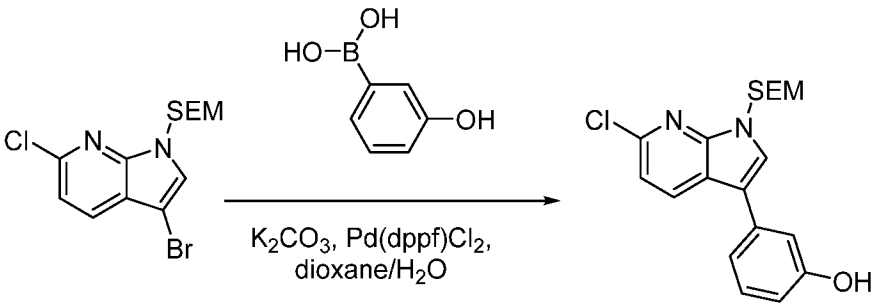


[0199] To a stirred mixture of N-[3-(2-hydroxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (110.0 mg, 0.26 mmol) in DCM (3.0 mL) was added TFA (3.0 mL). The resulting mixture was stirred at room temperature for 3 h. The mixture was evaporated in vacuo. The residue was re-dissolved in ACN/H_2O (5.0/1.0 mL). Then K_2CO_3 (107.7 mg, 0.78 mmol) was added to the mixture. The mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by

Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:24% B to 35% B in 12 min; 254 nm)to afford N-[3-(2-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (16.9 mg, 20%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =294.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.47 (s, 1H), 10.55 (s, 1H), 9.48 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.61 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.08 - 7.05 (m, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.89 - 6.86 (m, 1H), 2.05 - 1.97 (m, 1H), 0.82 - 0.78 (m, 4H).

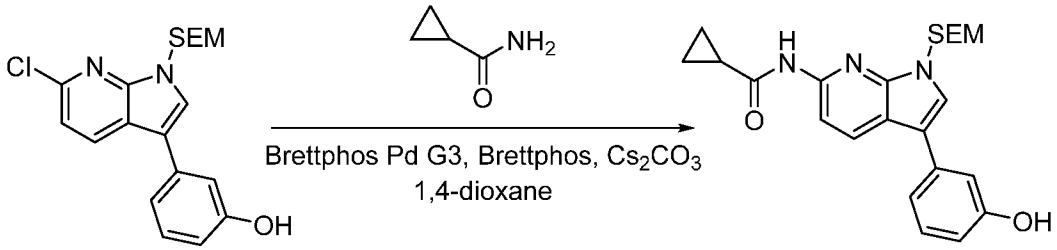
Example S13. Compound 13

Step 1: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)phenol



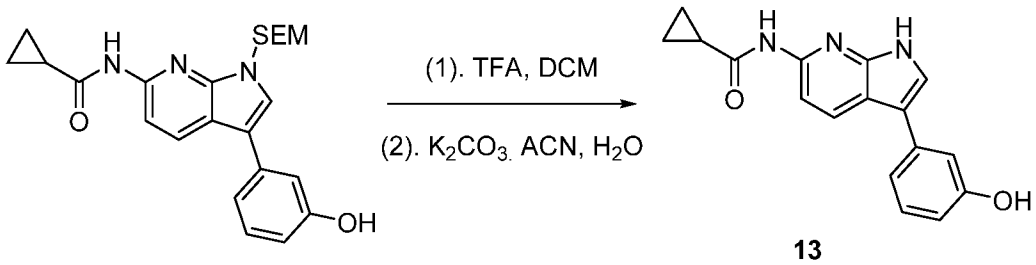
[0200] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 0.83 mmol) in 1,4-dioxane/ H_2O (5.0/1.0 mL) was added 3-hydroxyphenylboronic acid (137.3 mg, 0.99 mmol), K_2CO_3 (343.9 mg, 2.49 mmol) and $Pd(dppf)Cl_2$ (60.7 mg, 0.08 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (88/12, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)phenol (230.0 mg, 73%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =375.1.

Step 2: Synthesis of N-[3-(3-hydroxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide



[0201] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)phenol (200.0 mg, 0.53 mmol) in 1,4-dioxane (5.0 mL) was added cyclopropanecarboxamide (136.2 mg, 1.60 mmol), Cs_2CO_3 (521.4 mg, 1.60 mmol), Brettphos (57.3 mg, 0.11 mmol) and Brettphos Pd G3 (48.4 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (7/3, v/v) to afford N-[3-(3-hydroxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (220.0 mg, 97%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =424.2.

Step 3: Synthesis of N-[3-(3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 13)



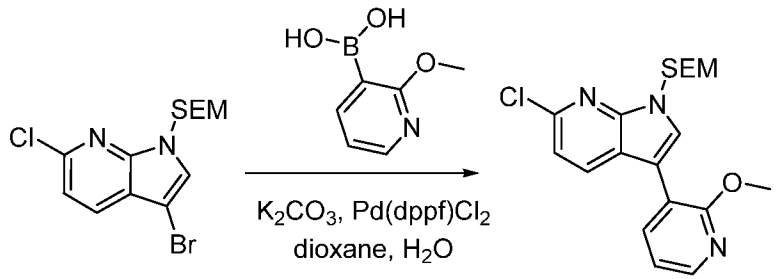
13

[0202] The solution of N-[3-(3-hydroxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (170.0 mg, 0.40 mmol) in CH_2Cl_2/TFA (5.0 mL/5.0 mL) was stirred at room temperature for 1 h. The mixture was evaporated in vacuo. The residue was re-dissolved in ACN/H_2O (5.0/1.0 mL). Then K_2CO_3 (554.7 mg, 4.01 mmol) was added to the mixture. The mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following

conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:29% B to 32% B in 8 min; 254 nm) to afford N-[3-(3-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (34.0 mg, 28%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =294.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.62 (s, 1H), 10.62 (s, 1H), 9.38 (s, 1H), 8.18 (d, J = 8.7 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 2.7 Hz, 1H), 7.24 - 7.19 (m, 1H), 7.14 - 7.11 (m, 2H), 6.67 - 6.63 (m, 1H), 2.08 - 2.03 (m, 1H), 0.83 - 0.79 (m, 4H).

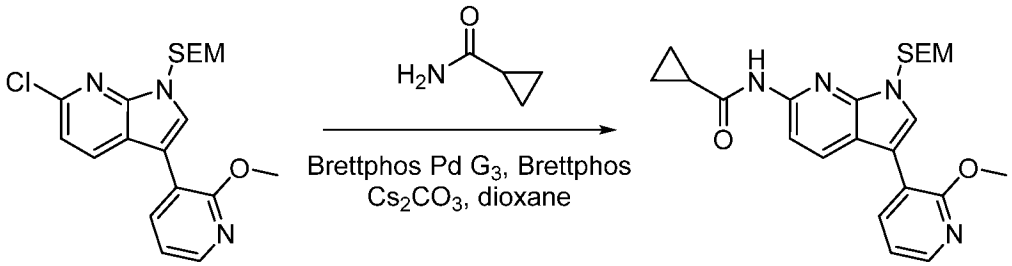
Example S14. Compound 14

Step 1: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-methoxypyridine



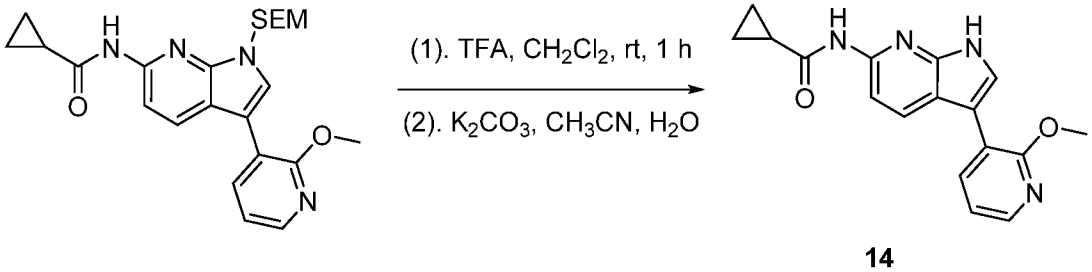
[0203] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (500.0 mg, 1.38 mmol) in 1,4-dioxane/H_2O (10.0/2.0 mL) was added 2-methoxypyridin-3-ylboronic acid (211.4 mg, 1.38 mmol), K_2CO_3 (57.3 mg, 0.42 mmol) and Pd(dppf)Cl_2 (112.9 mg, 0.14 mmol). The resulting mixture was stirred at 80 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/EtOAc (80/20, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-methoxypyridine (250.0 mg, 46%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =390.1.

Step 2: Synthesis of N-(3-(2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide.



[0204] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-methoxypyridine (235.0 mg, 0.60 mmol) in 1,4-dioxane (8.0 mL) was added cyclopropanecarboxamide (205.2 mg, 2.41 mmol), BrettPhos (64.7 mg, 0.12 mmol), Cs_2CO_3 (589.0 mg, 1.81 mmol) and Brettphos Pd G3 (54.6 mg, 0.06 mmol). The resulting mixture was stirred at 100 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with ether/ethyl acetate (75/25, v/v) to afford N-(3-(2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (250.0 mg, 94%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =439.2.

Step 3: Synthesis of N-[3-(2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 14)



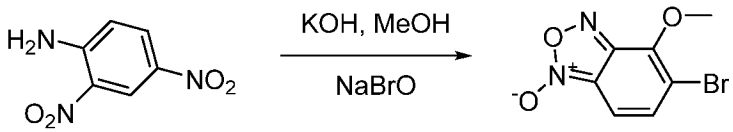
14

[0205] To a solution of N-[3-(2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (250.0 mg, 0.57 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL). The resulting mixture was stirred at room temperature for 1 h. The mixture was concentrated under vacuum. The residue was re-dissolved in ACN (6.0 mL) and H_2O (0.5 mL). Then K_2CO_3 (393.9 mg, 2.85 mmol) was added to the mixture. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with ether/ethyl acetate (82/18, v/v)

and then purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 Column, 30×250 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 56% B in 10 min; 254 nm) to afford N-[3-(2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (51.0 mg, 29%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 309.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.68 (s, 1H), 10.59 (s, 1H), 8.11 - 8.07 (m, 2H), 8.01 - 7.91 (m, 2H), 7.72 (d, J = 2.7 Hz, 1H), 7.10 - 7.06 (m, 1H), 3.95 (s, 3H), 2.08 - 2.01 (m, 1H), 0.87 - 0.79 (m, 4H).

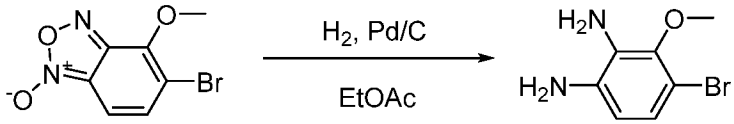
Example S15. Compound 15

Step 1: Synthesis of 5-bromo-4-methoxy-2,1,3-benzoxadiazol-1-ium-1-olate



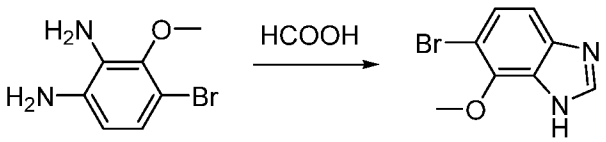
[0206] To a mixture of 2,4-dinitroaniline (10.0 g, 54.61 mmol) and KOH (9.2 g, 163.80 mmol) in MeOH (1.0 L) was added dropwise a solution of potassium hydroxide (64.9 g, 546.12 mmol) in H_2O (1.0 L) 50 °C under N_2. The resulting mixture was stirred at 50 °C for 3 h. After the reaction was completed, the reaction was cooled to room temperature and then filtered. The precipitated solid was collected and dried to afford 5-bromo-4-methoxy-2,1,3-benzoxadiazol-1-ium-1-olate (2.1 g, 16%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =244.9.

Step 2: Synthesis of 4-bromo-3-methoxybenzene-1,2-diamine



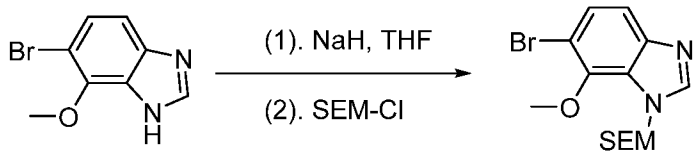
[0207] To a solution of 5-bromo-4-methoxy-2,1,3-benzoxadiazol-1-ium-1-olate (1.2 g, 4.90 mmol) in EtOAc (30.0 mL) was added Pd/C (0.1 g, dry). The resulting mixture was stirred at room temperature for 16 h under H_2. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure to afford 4-bromo-3-methoxybenzene-1,2-diamine (623.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =217.0.

Step 3: Synthesis of 5-bromo-4-methoxy-3H-1,3-benzodiazole.



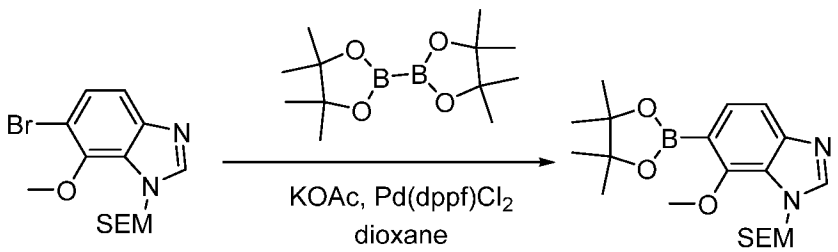
[0208] The solution of 4-bromo-3-methoxybenzene-1,2-diamine (623.0 mg, 2.87 mmol) in HCOOH (10.0 mL) was stirred at 100 °C for 2 h. After the reaction was completed, the reaction was diluted with H_2O. The pH value of the mixture was adjusted to 8 with NaOH (aq.) and then extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (10/1, v/v) to afford 5-bromo-4-methoxy-3H-1,3-benzodiazole (495.0 mg, 75%) as a red solid. LCMS (ESI, m/z): $[M+H]^+$ =227.0.

Step 4: Synthesis of 6-bromo-7-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole



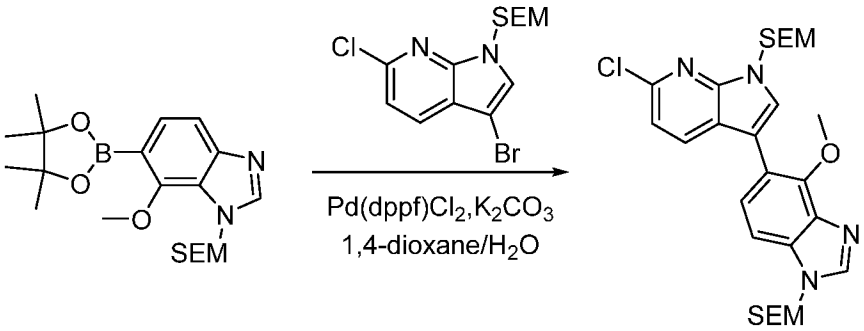
[0209] To a solution of 5-bromo-4-methoxy-3H-1,3-benzodiazole (710.0 mg, 3.13 mmol) in THF (20.0 mL) was added NaH (375.2 mg, 60%) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. Then SEM-Cl (782.0 mg, 4.69 mmol) was added dropwise to the mixture at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h under N_2. After the reaction was completed, the reaction was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 6-bromo-7-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (790.0 mg, crude) as a black oil. LCMS (ESI, m/z): $[M+H]^+$ =357.1.

Step 5: Synthesis of 7-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole.



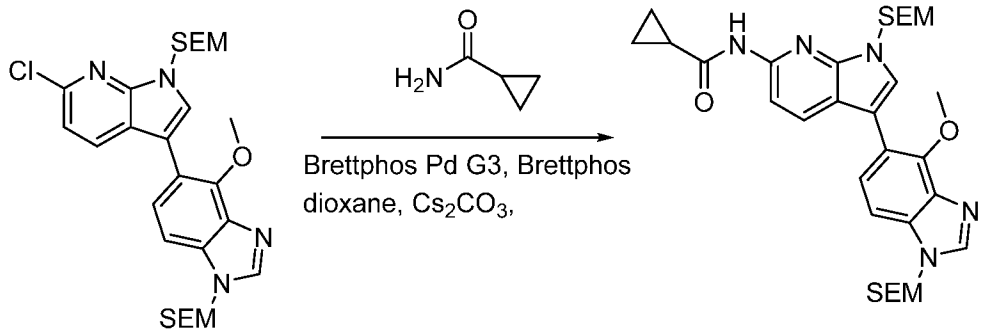
[0210] To a solution of 6-bromo-7-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (740.0 mg, 2.07 mmol) in dioxane (20.0 mL) was added bis(pinacolato)diboron (1577.7 mg, 6.21 mmol), KOAc (609.7 mg, 6.21 mmol) and $Pd(dppf)Cl_2$ (169.1 mg, 0.21 mmol) at room temperature under N_2. The resulting mixture was stirred at 85 °C for 16 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (6/1, v/v) to afford 7-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (270.0 mg, 32%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =405.2.

Step 6: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole.



[0211] To a solution of 7-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (405.0 mg, 1.00 mmol) in dioxane/H_2O (10.0 mL/2.0 mL) was added 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (301.9 mg, 0.84 mmol), K_2CO_3 (346.0 mg, 2.50 mmol) and $Pd(dppf)Cl_2$ (68.2 mg, 0.08 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (140.0 mg, 30%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =559.2.

Step 7: Synthesis of N-[3-(4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide.



[0212] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (122.0 mg, 0.22 mmol) in 1,4-dioxane (6.0 mL) was added cyclopropanecarboxamide (92.8 mg, 1.09 mmol), BrettPhos (23.4 mg, 0.04 mmol), Cs_2CO_3 (213.2 mg, 0.65 mmol) and BrettPhos Pd G3 (19.7 mg, 0.02 mmol) at room temperature under N_2. The resulting mixture was irradiated with microwave radiation at 120 °C for 1.5 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford N-[3-(4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6- yl]cyclopropanecarboxamide (109.0 mg, 82%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =608.3.

Step 8: Synthesis of N-[3-(4-methoxy-1H-1,3-benzodiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 15)

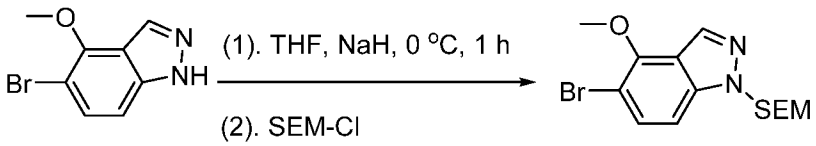


[0213] To a solution of N-[3-(4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-

yl]cyclopropanecarboxamide (109.0 mg, 0.18 mmol) in DMF (5.0 mL) was added ethane-1,2-diamine (53.8 mg, 0.90 mmol) and TBAF (0.5 mL, 0.01 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions Column: (Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 16% B to 38% B in 6 min; 254 nm) to afford N-[3-(4-methoxy-1H-1,3-benzodiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (9.1 mg, 15%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =348.2. ^1H NMR (300 MHz, DMSO-d_6): δ 12.49 (s, 1H), 11.47 (s, 1H), 10.58 (s, 1H), 8.21 - 8.18 (m, 1H), 7.97 - 7.87 (m, 2H), 7.47 (s, 1H), 7.36 - 7.33 (m, 1H), 7.26 - 7.24 (m, 1H), 4.22 (s, 2H), 3.66 (s, 1H), 2.10 - 2.01 (m, 1H), 0.83 - 0.79 (m, 4H).

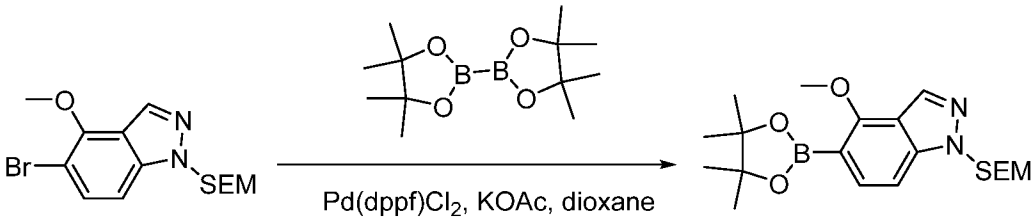
Example S16. Compound 16

Step 1: Synthesis of 5-bromo-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole.



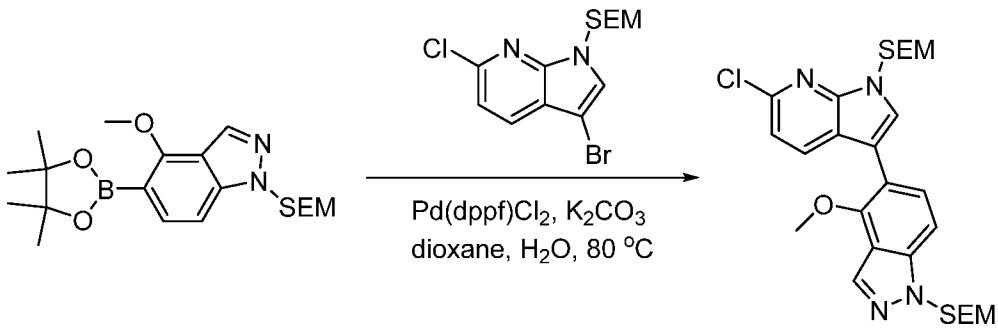
[0214] To a mixture of 5-bromo-4-methoxy-1H-indazole (1.0 g, 4.40 mmol) in THF (10.0 mL) was added NaH (0.3 g, 60%) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. Then SEM-Cl (1.1 g, 6.62 mmol) was added dropwise to the mixture at 0 °C. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford 5-bromo-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole (2.5 g, crude) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ = 357.1.

Step 2: Synthesis of 4-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy] methyl]indazole.



[0215] To a mixture of 5-bromo-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole (2.4 g, 6.71 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (5.1 g, 20.16 mmol) in dioxane (30.0 mL) was added $Pd(dppf)Cl_2$ (0.5 g, 0.67 mmol) and KOAc (1.9 g, 20.17 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford 4-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy] methyl]indazole (750.0 mg, 27%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =405.2.

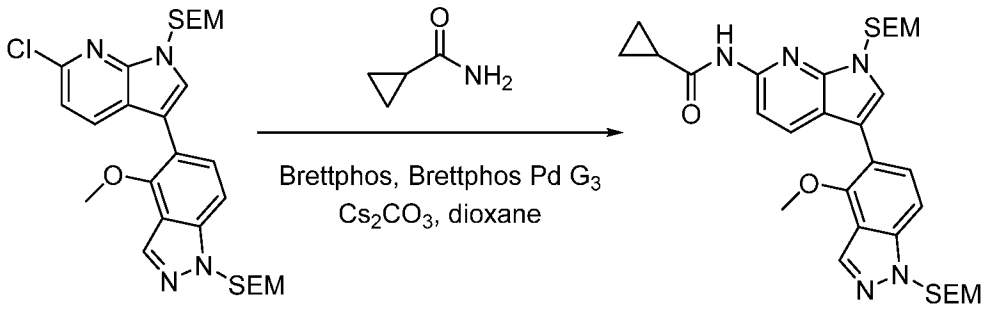
Step 3: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl] indazole



[0216] To a mixture of 4-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole (660.0 mg, 1.63 mmol) and 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (400.0 mg, 1.11 mmol) in dioxane/H_2O (10.0/1.0 mL) was added $Pd(dppf)Cl_2$ (90.0 mg, 0.11 mmol) and K_2CO_3 (460.0 mg, 3.33 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to

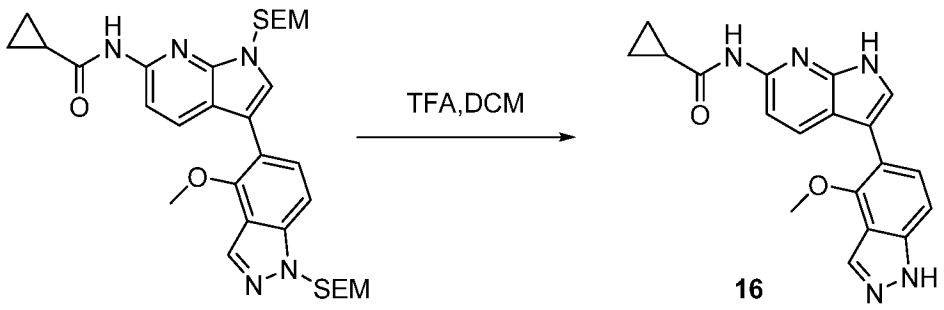
afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl] indazole (330.0 mg, 36%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =559.2.

Step 4: Synthesis of N-[3-(4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide.



[0217] To a mixture of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole (300.0 mg, 0.53 mmol) and cyclopropanecarboxamide (182.6 mg, 2.14 mmol) in dioxane (5.0 mL) was added BrettPhos Pd G3 (48.6 mg, 0.05 mmol), BrettPhos (57.5 mg, 0.10 mmol) and Cs_2CO_3 (699.1 mg, 2.14 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford N-[3-(4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (220.0 mg, 67%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =608.3.

Step 5: Synthesis of N-[3-(4-methoxy-1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 16)

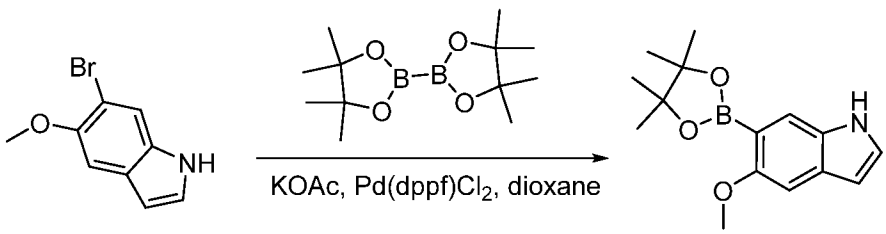


16

[0218] To a mixture of N-[3-(4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (190.0 mg, 0.31 mmol) in DCM (3.0 mL) was added TFA (1.0 mL). The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in CH_3CN/H_2O (5.0/1.0 mL). Then K_2CO_3 (500.0 mg. 3.62 mmol) was added to the mixture. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30x150 mm, 5 um; 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 7 min; 254 nm) to afford N-[3-(4-methoxy-1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (17.1 mg, 15%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =348.1. ^1H NMR (300 MHz, DMSO-d_6): δ 13.22 (s, 1H), 11.35 (s, 1H), 10.45 (s, 1H), 8.43 (s, 1H), 7.88 - 7.74 (m, 3H), 7.26 (d, J = 8.7 Hz, 1H), 6.77 (d, J = 2.1 Hz, 1H), 4.25 (s, 3H), 2.11 - 2..02 (m, 1H), 0.87 - 0.79 (m, 4H).

Example S17. Compound 17

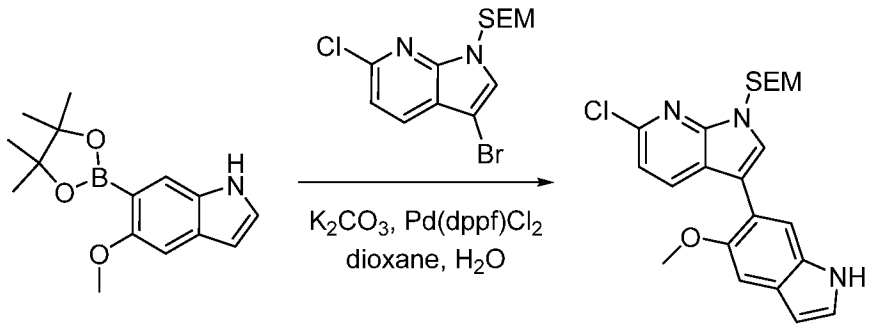
Step 1: Synthesis of 5-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole



[0219] To a solution of 6-bromo-5-methoxy-1H-indole (1.0 g, 4.42 mmol) in 1,4-dioxane (8.0 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.4 g, 13.27 mmol), KOAc (1.3 g, 13.22 mmol) and $Pd(dppf)Cl_2$ (0.4 g, 0.44 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (90/10, v/v) to afford 5-

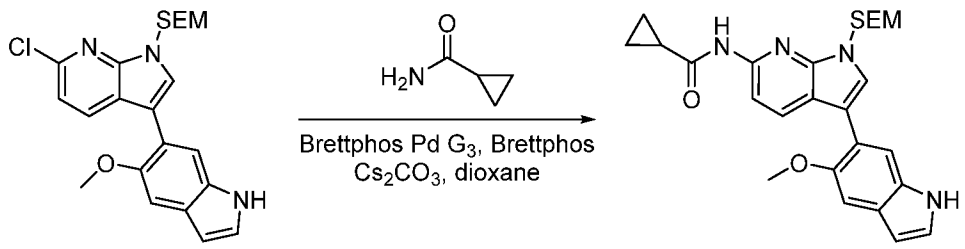
methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (900.0 mg, 74%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =274.2.

Step 2: Synthesis of 6-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-methoxy-1H-indole.



[0220] To a solution of 5-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (350.0 mg, 1.28 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (579.4 mg, 1.28 mmol), K_2CO_3 (531.3 mg, 3.84 mmol) and Pd(dppf)Cl_2 (104.6 mg, 0.13 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (89/11, v/v) to afford 6-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-methoxy-1H-indole (200.0 mg, 36%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =428.1.

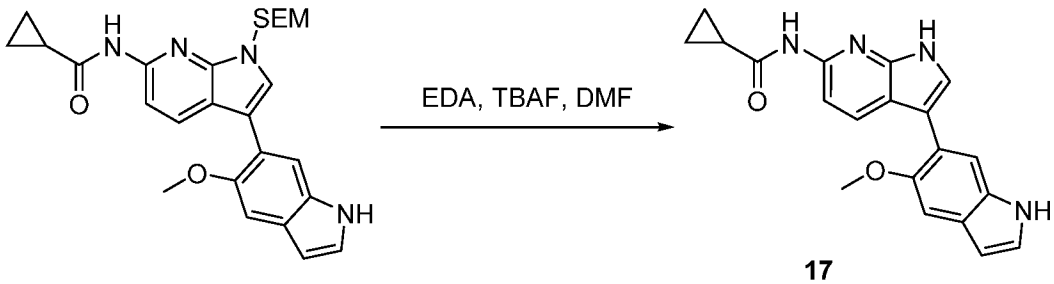
Step 3: Synthesis of N-[3-(5-methoxy-1H-indol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide.



[0221] To a solution of 6-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-methoxy-1H-indole (180.0 mg, 0.42 mmol) in dioxane (3.0 mL) was added cyclopropanecarboxamide (143.1 mg, 1.68 mmol), BrettPhos (90.3 mg, 0.17 mmol), Cs_2CO_3

(411.1 mg, 1.26 mmol) and BrettPhos Pd G3 (76.2 mg, 0.08 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (81/19, v/v) to afford N-[3-(5-methoxy-1H-indol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (159.0 mg, 79%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =477.2.

Step 4: Synthesis of N-[3-(5-methoxy-1H-indol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 17)

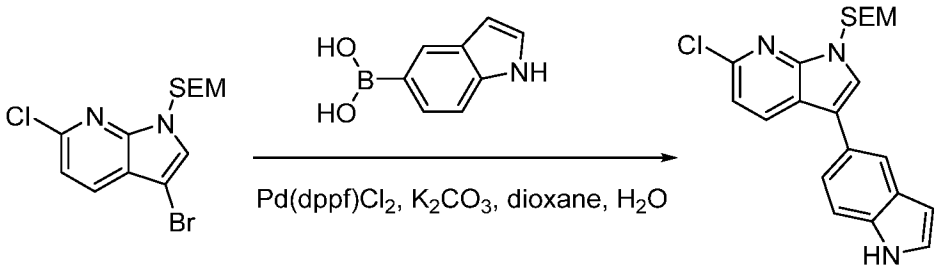


17

[0222] To a solution of N-[3-(5-methoxy-1H-indol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (150.0 mg, 0.31 mmol) in DMF (2.0 mL) was added EDA (94.5 mg, 1.57 mmol) and TBAF (246.8 mg, 0.94 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 54% B in 8 min; 254 nm) to afford N-[3-(5-methoxy-1H-indol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (14.9 mg, 14%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =347.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.43 (s, 1H), 10.85 (s, 1H), 10.56 (s, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.50 (s, 2H), 7.28 (s, 1H), 7.18 (s, 1H), 6.37 (s, 1H), 3.78 (s, 3H), 2.07 - 2.03 (m, 1H), 0.83 - 0.77 (m, 4H).

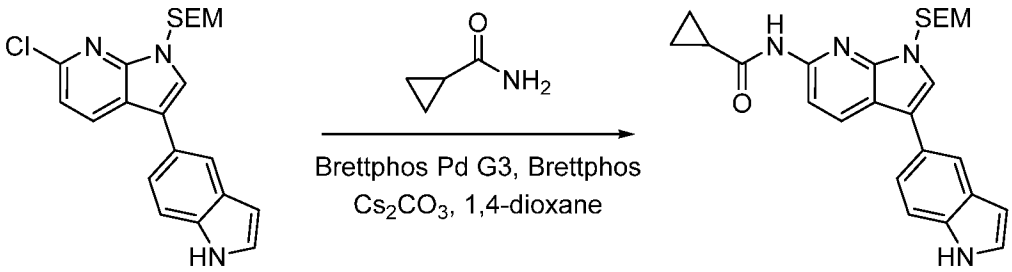
Example S18. Compound 18

Step 1: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-1H-indole



[0223] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (500.0 mg, 1.38 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 1H-indol-5-ylboronic acid (222.5 mg, 1.38 mmol), K_2CO_3 (573.1 mg, 4.15 mmol) and $Pd(dppf)Cl_2$ (225.7 mg, 0.27 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (84/16, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-1H-indole (220.0 mg, 40%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =398.1.

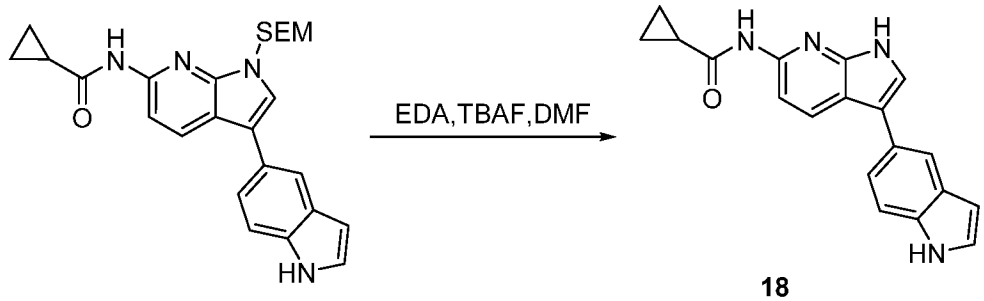
Step 2: Synthesis of N-[3-(1H-indol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide.



[0224] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-1H-indole (200.0 mg, 0.50 mmol) in dioxane (3.0 mL) was added cyclopropanecarboxamide (128.3 mg, 1.51 mmol), BrettPhos (107.9 mg, 0.20 mmol), Cs_2CO_3 (491.2 mg, 1.51 mmol) and BrettPhos Pd G3 (91.1 mg, 0.10 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and

filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (79/21, v/v) to afford N-[3-(1H-indol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (150.0 mg, 66%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =447.2.

Step 3: Synthesis of N-[3-(1H-indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 18)

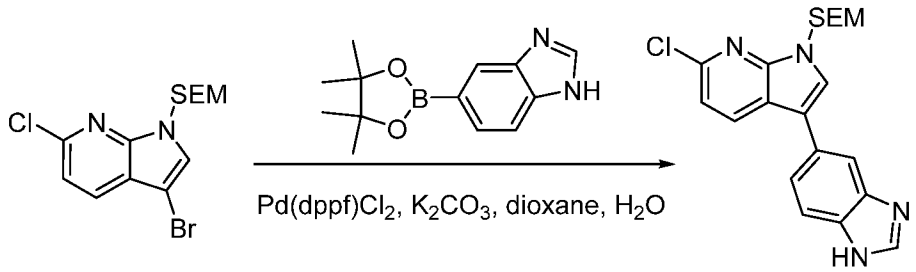


18

[0225] To a solution of N-[3-(1H-indol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (100.0 mg, 0.22 mmol) in DMF (2.0 mL) was added EDA (40.4 mg, 0.67 mmol) and TBAF (292.7 mg, 1.12 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 49% B in 9 min; 254 nm) to afford N-[3-(1H-indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (26.7 mg, 38%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =317.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.45 (s, 1H), 11.04 (s, 1H), 10.58 (s, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.83 (s, 1H), 7.58 (d, J = 1.6 Hz, 1H), 7.46 - 7.41 (m, 2H), 7.33 (d, J = 2.4 Hz, 1H), 6.46 (s, 1H), 2.07 - 2.03 (m, 1H), 0.83 - 0.79 (m, 4H).

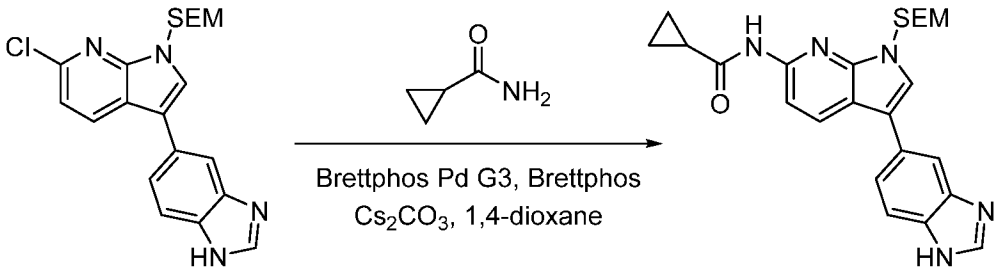
Example S19. Compound 19

Step 1: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-1H-1,3-benzodiazole.



[0226] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (500.0 mg, 1.38 mmol) in 1,4-dioxane/ H_2O (5.0/1.0 mL) was added 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-1,3-benzodiazole (404.9 mg, 1.66 mmol), K_2CO_3 (573.1 mg, 4.15 mmol) and $Pd(dppf)Cl_2$ (112.9 mg, 0.14 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with ethyl acetate /MeOH (10/1, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-1H-1,3-benzodiazole (280.0 mg, 50%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =399.1.

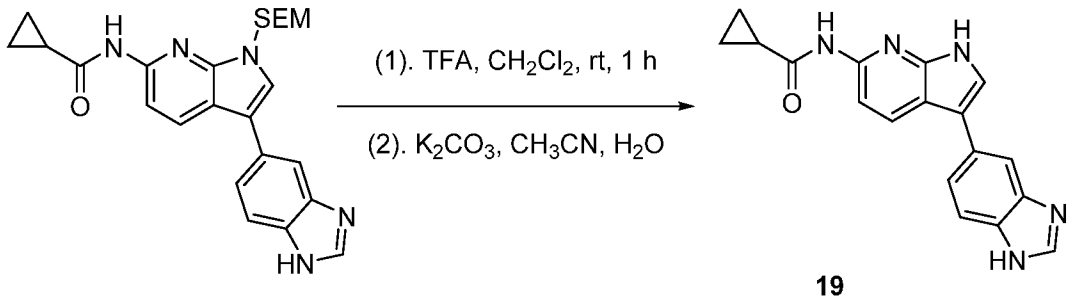
Step 2: Synthesis of N-[3-(1H-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide.



[0227] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-1H-1,3-benzodiazole (280.0 mg, 0.70 mmol) in 1,4-dioxane (10.0 mL) was added cyclopropanecarboxamide (1194.5 mg, 14.04 mmol), BrettPhos (75.34 mg, 0.14 mmol), Cs_2CO_3 (686.0 mg, 2.10 mmol) and BrettPhos Pd G3 (63.6 mg, 0.07 mmol) at room temperature under N_2. The resulting mixture was irradiated with microwave radiation at 120 °C for 1.5 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with ethyl acetate/MeOH

(10/1, v/v) to afford N-[3-(1H-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (250.0 mg, 79%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =448.2.

Step 3: Synthesis of N-[3-(1H-1,3-benzodiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 19)

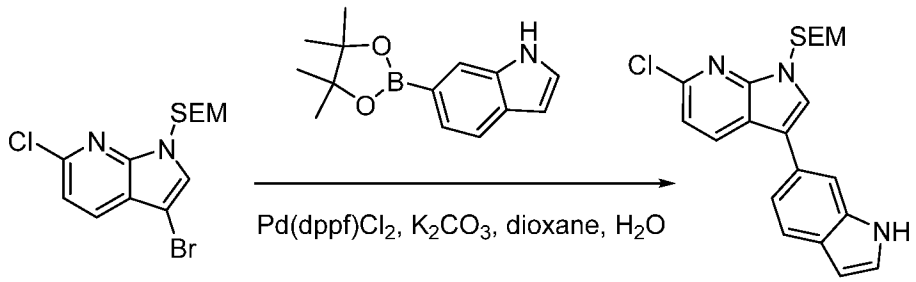


19

[0228] To a solution of N-[3-(1H-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (400.0 mg, 0.89 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated in vacuo. The residue was re-dissolved in ACN/H_2O (10.0/2.0 mL). Then K_2CO_3 (1235.0 mg, 8.94 mmol) was added to the mixture. The mixture was stirred at room temperature for another 16 h. After the reaction was completed, the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30x250 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 45% B in 10 min; 254 nm) to afford N-[3-(1H-1,3-benzodiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (9.0 mg, 3%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =318.1. ^1H NMR (300 MHz, DMSO-d_6): δ 12.41 - 12.35 (m, 1H), 11.59 - 11.55 (m, 1H), 10.60 (s, 1H), 8.25 - 8.19 (m, 2H), 7.97 - 7.54 (m, 5H), 2.08 - 2.03 (m, 1H), 0.84 - 0.79 (m, 4H).

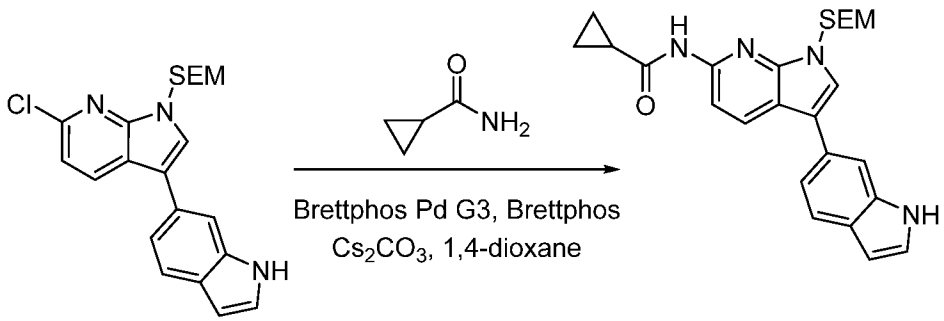
[0229] ***Example S20. Compound 20***

Step 1: Synthesis of 6-chloro-3-(1H-indol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine.



[0230] To a solution of 3-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (500.0 mg, 1.38 mmol) in dioxane/H_2O (8.0/2.0 mL) was added 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (336.0 mg, 1.38 mmol), K_2CO_3 (573.1 mg, 4.15 mmol) and $Pd(dppf)Cl_2$ (101.1 mg, 0.14 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 6-chloro-3-(1H-indol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (160.0 mg, 29%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =398.1.

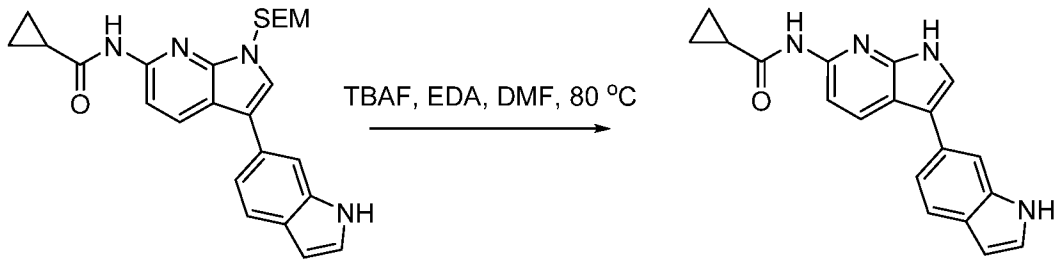
Step 2: Synthesis of N-(3-(1H-indol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide.



[0231] To a solution of 6-chloro-3-(1H-indol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (160.0 mg, 0.40 mmol) in 1,4-dioxane (10.0 mL) was added cyclopropanecarboxamide (684.3 mg, 8.04 mmol), Cs_2CO_3 (393.0 mg, 1.21 mmol) and Brettphos (43.2 mg, 0.08 mmol), BrettPhos Pd G3 (36.4 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and

filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (6/1, v/v) to afford N-(3-(1H-indol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (130.0 mg, 72%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =447.2.

Step 3: Synthesis of N-(3-(1H-indol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (Compound 20)

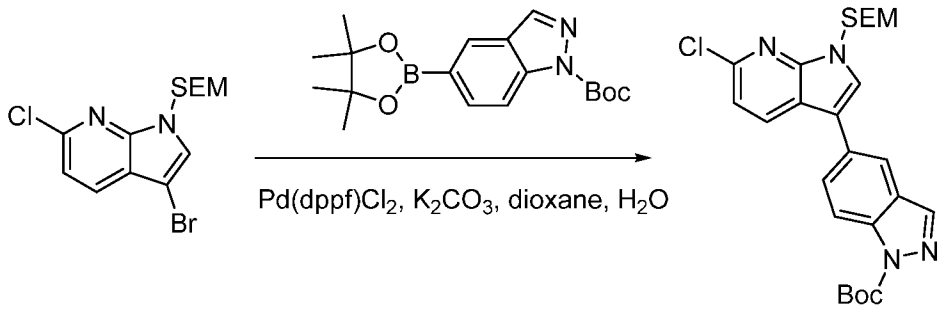


20

[0232] To a solution of N-(3-(1H-indol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (100.0 mg, 0.22 mmol) in DMF (5.0 mL) was added TBAF (0.6 mL) and EDA (67.2 mg, 1.12 mmol). The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with 5 - 100% CH_3CN in H_2O and then purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 57% B in 8 min; 220 nm) to afford N-(3-(1H-indol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (1.4 mg, 1%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =317.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.53 (s, 1H), 11.01 (s, 1H), 10.61 (s, 1H), 8.23 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.68 - 7.63 (m, 2H), 7.59 (d, J = 8.1 Hz, 1H), 7.36 - 7.33 (m, 2H), 6.43 (s, 1H), 2.08 - 1.98 (m, 1H), 0.84 - 0.79 (m, 4H).

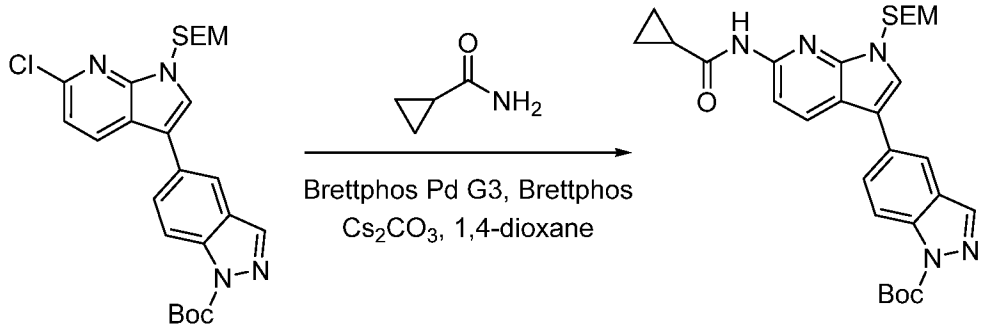
[0233] ***Example S21. Compound 21***

Step 1: Synthesis of tert-butyl 5-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-1H-indazole-1-carboxylate.



[0234] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (500.0 mg, 1.38 mmol) in dioxane/H_2O (8.0/2.0 mL) was added tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole-1-carboxylate (475.8 mg, 1.38 mmol), K_2CO_3 (573.1 mg, 4.15 mmol) and Pd(dppf)Cl_2 (101.1 mg, 0.14 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford tert-butyl 5-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-1H-indazole-1-carboxylate (140.0 mg, 20%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =499.2.

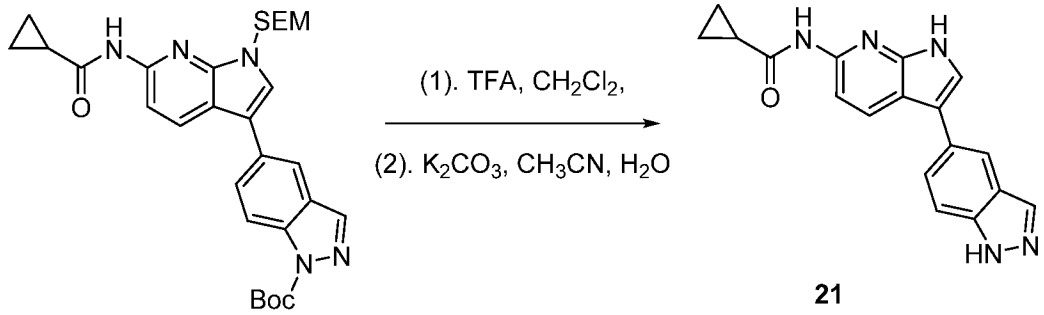
Step 2: Synthesis of tert-butyl 5-(6-(cyclopropanecarboxamido)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-1H-indazole-1-carboxylate.



[0235] To a solution of tert-butyl 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)indazole-1-carboxylate (110.0 mg, 0.22 mmol) in 1,4-dioxane (10.0 mL) was added cyclopropanecarboxamide (375.2 mg, 4.41 mmol), Cs_2CO_3 (215.4 mg, 0.66 mmol), Brettphos (23.7 mg, 0.04 mmol) and BrettPhos Pd

G3 (20.0 mg, 0.02 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford tert-butyl 5-(6-(cyclopropanecarboxamido)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-1H-indazole-1-carboxylate (110.0 mg, 91%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =548.3.

Step 3: Synthesis of N-(3-(1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (Compound 21)

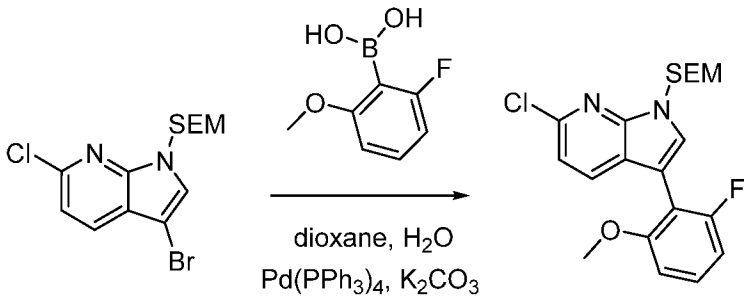


[0236] To a solution of tert-butyl 5-(6-(cyclopropanecarboxamido)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-1H-indazole-1-carboxylate (110.0 mg, 0.20 mmol,) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL). The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in CH_3CN/H_2O (20.0/20.0 mL). Then K_2CO_3 (277.6 mg, 2.00 mmol) was added to the mixture. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/2, v/v) and then purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 39% B in 8 min; 254 nm) to afford N-[3-(1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (9.3 mg, 14%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =318.2. ^1H NMR (400 MHz, DMSO-d_6): δ 13.02 (s, 1H), 11.58 (s, 1H), 10.62 (s, 1H), 8.29

(d, J = 8.8 Hz, 1H), 8.09 - 8.05 (m, 2H), 7.96 (d, J = 8.8 Hz, 1H), 7.74 - 7.71 (m, 2H), 7.60 (d, J = 8.8 Hz, 1H), 2.07 - 1.99 (m, 1H), 0.85 - 0.80 (m, 4H).

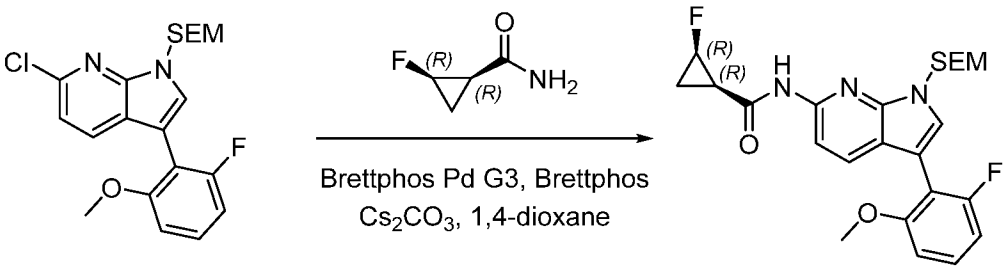
Example S22. Compound 22

Step 1: Synthesis of 6-chloro-3-(2-fluoro-6-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine.



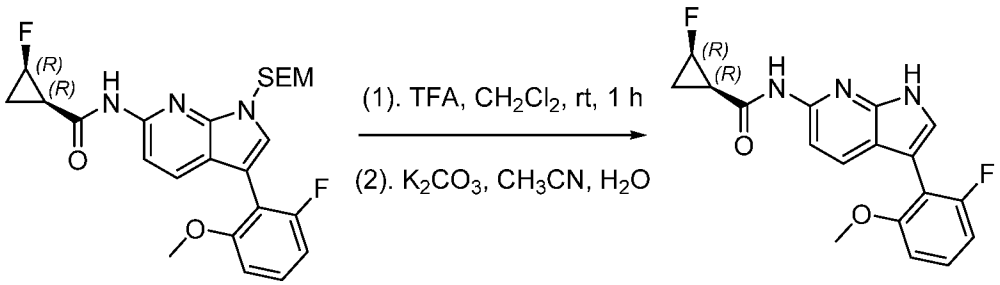
[0237] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (500.0 mg, 1.38 mmol) in 1,4-dioxane/ H_2O (8.0/2.0 mL) was added 2-fluoro-6-methoxyphenylboronic acid (281.9 mg, 1.66 mmol), K_2CO_3 (382.1 mg, 2.76 mmol) and $Pd(PPh_3)_4$ (159.7 mg, 0.14 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 6-chloro-3-(2-fluoro-6-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (220.0 mg, 39%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =407.1.

Step 2: Synthesis of (1R,2R)-2-fluoro-N-[3-(2-fluoro-6-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide.



[0238] To a solution of 6-chloro-3-(2-fluoro-6-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (250.0 mg, 0.61 mmol) in 1,4-dioxane (6.0 mL) was added (1R,2R)-2-fluorocyclopropane-1-carboxamide (316.7 mg, 3.07 mmol), BrettPhos (66.0 mg, 0.12 mmol), Cs_2CO_3 (600.5 mg, 1.84 mmol) and BrettPhos Pd G3 (55.7 mg, 0.06 mmol) at room temperature. The resulting mixture was irradiated with microwave radiation at 120 °C for 1.5 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with ether/ethyl acetate (3/2, v/v) to afford (1R,2R)-2-fluoro-N-[3-(2-fluoro-6-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (146.0 mg, 50%) as a brown yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =474.2.

Step 3: Synthesis of (1R,2R)-2-fluoro-N-[3-(2-fluoro-6-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 22)



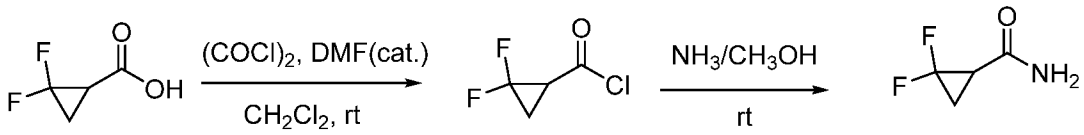
22

[0239] To a solution of (1R,2R)-2-fluoro-N-[3-(2-fluoro-6-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (146.0 mg, 0.31 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The mixture was evaporated under reduced pressure. The residue was re-dissolved in ACN/H_2O (10.0/2.0 mL). Then K_2CO_3 (426.1 mg, 3.08 mmol) was added to the mixture. The mixture was stirred at room temperature for another 16 h. After the reaction was completed, the reaction mixture was filtered. The filtrate 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31% B to 61% B in 10 min; 254 nm) to afford (1R,2R)-2-

fluoro-N-[3-(2-fluoro-6-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (10.8 mg, 10%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =344.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.67 (s, 1H), 10.63 (s, 1H), 7.88 - 7.86 (m, 1H), 7.70 - 7.68 (m, 1H), 7.46 (s, 1H), 7.37 - 7.31 (m, 1H), 6.99 - 6.90 (m, 2H), 5.03 - 4.82 (m, 1H), 3.78 (s, 3H), 2.27 - 2.20 (m, 1H), 1.71 - 1.63 (m, 1H), 1.20 - 1.05 (m, 1H).

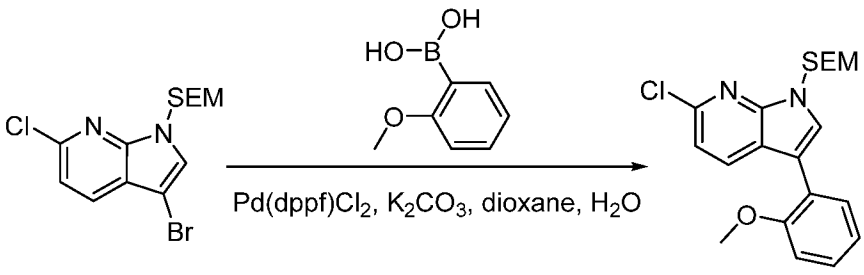
Example S23. Compound 23

Step 1: Synthesis of 2,2-difluorocyclopropane-1-carboxamide.



[0240] To a solution of 2,2-difluorocyclopropane-1-carboxylic acid (800.0 mg, 6.55 mmol) in DCM (10.0 mL) was added DMF (0.1 mL) and oxalyl chloride (998.1 mg, 7.86 mmol). The resulting mixture was stirred at room temperature for 1 h. Then NH_3(g)/MeOH (10.0 mL, 7 mol/L) was added to the mixture. The mixture was stirred at room temperature for another 0.5 h. After the reaction was completed, the reaction mixture was concentrated under reduced pressure to afford 2,2-difluorocyclopropane-1-carboxamide (790.0 mg, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =122.0.

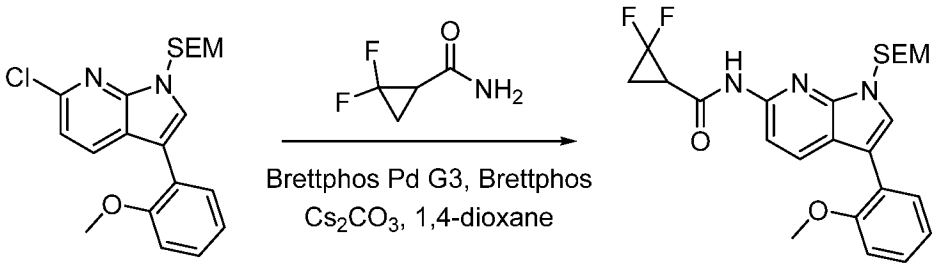
Step 2: Synthesis of 6-chloro-3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine.



[0241] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (500.0 mg, 1.38 mmol) in 1,4-dioxane/H_2O (20.0/4.0 mL) was added 2-methoxyphenylboronic acid (252.1 mg, 1.66 mmol), K_2CO_3 (573.1 mg, 4.15 mmol) and $Pd(dppf)Cl_2$ (112.9 mg, 0.14 mmol). The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was

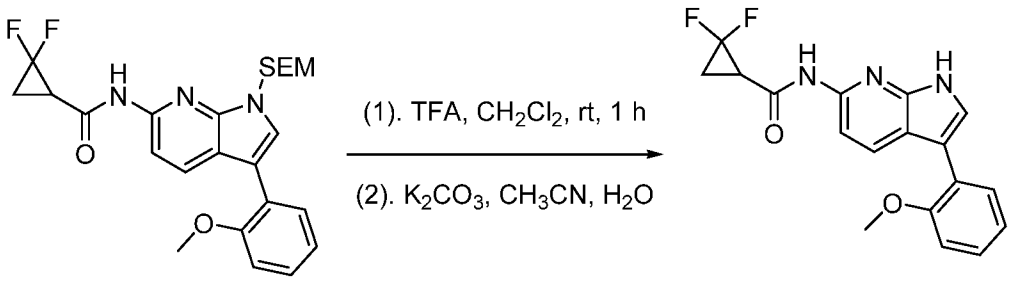
washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford 6-chloro-3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (230.0 mg, 42%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =389.1.

Step 3: Synthesis of 2,2-difluoro-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide.



[0242] To a solution of 6-chloro-3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (170.0 mg, 0.44 mmol) in 1,4-dioxane (6.0 mL) was added 2,2-difluorocyclopropane-1-carboxamide (264.6 mg, 2.19 mmol), Cs_2CO_3 (427.2 mg, 1.31 mmol), BrettPhos (46.9 mg, 0.09 mmol) and BrettPhos Pd G3 (396.2 mg, 0.48 mmol). The resulting mixture was irradiated with microwave radiation at 120 °C for 1.5 h under N_2. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 2,2-difluoro-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (120.0 mg, 57%) as a brown yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =474.2.

Step 4: Synthesis of 2,2-difluoro-N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 23)

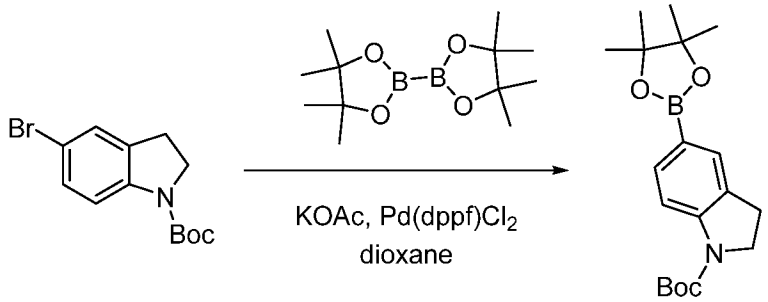


23

[0243] To a solution of 2,2-difluoro-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (120.0 mg, 0.25 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL). The resulting mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated under reduced pressure. The residue was re-dissolved in ACN/H_2O (10.0/2.0 mL). Then K_2CO_3 (350.2 mg, 2.53 mmol) was added to the mixture. The mixture was stirred at room temperature for another 16 h. After the reaction was completed, the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep Phenyl OBD Column, 19×150 mm, 5 um, 13 nm; 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 10 min; 254 nm) to afford 2,2-difluoro-N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (14.7 mg, 16%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =344.1. ^1H NMR (400 MHz, DMSO-d_6): δ 11.64 (s, 1H), 10.82 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.54 (d, J = 7.2 Hz, 1H), 7.30 - 7.26 (m, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.05 - 7.01 (m, 1H), 3.82 (s, 3H), 3.06 - 2.98 (m, 1H), 2.09 - 1.95 (m, 2H).

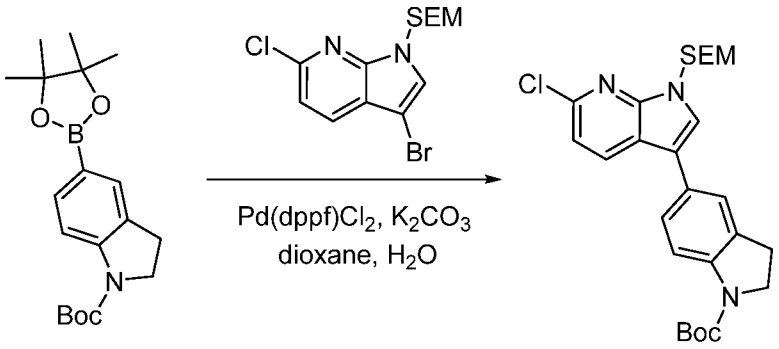
Example S24. Compound 24

Step 1: Synthesis of tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydroindole-1-carboxylate.



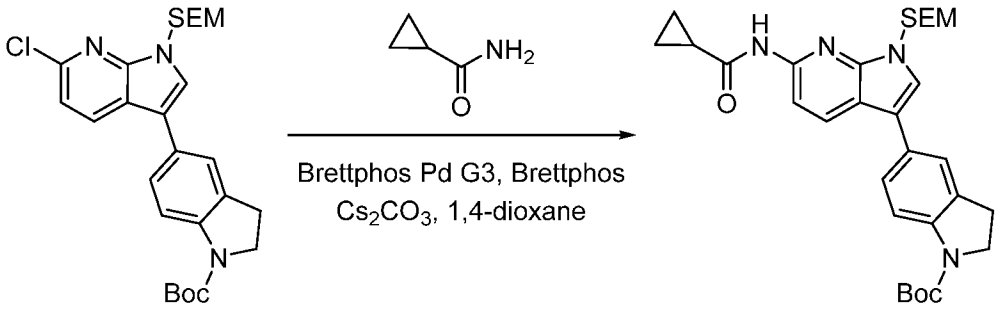
[0244] To a solution of tert-butyl 5-bromo-2,3-dihydroindole-1-carboxylate (1.0 g, 3.35 mmol) in 1,4-dioxane (10.0 mL) was added bis(pinacolato)diboron (2.6 g, 10.06 mmol), KOAc (987.4 mg, 10.06 mmol) and $Pd(dppf)Cl_2$ (112.6 mg, 0.15 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (89/11, v/v) to afford tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydroindole-1-carboxylate (1.0 g, 73%) as a red solid. LCMS (ESI, m/z): $[M+H]^+$ =346.2.

Step 2: Synthesis of tert-butyl 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2,3-dihydroindole-1-carboxylate.



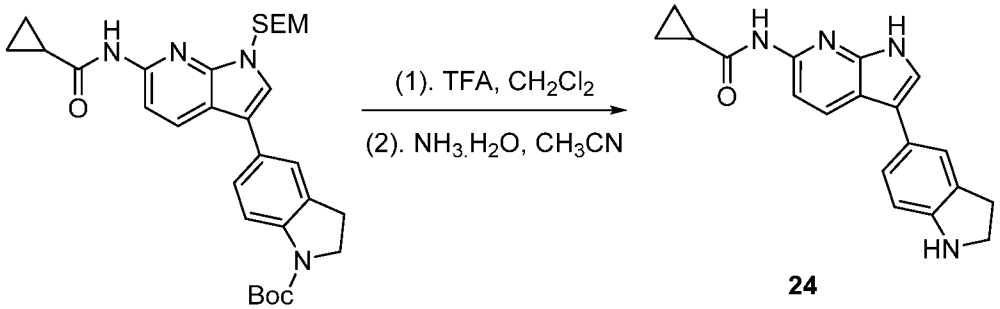
[0245] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (360.0 mg, 0.99 mmol) in 1,4-dioxane/H_2O (5.0 mL/1.0 mL) was added tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydroindole-1-carboxylate (412.3 mg, 1.19 mmol), K_2CO_3 (412.6 mg, 2.99 mmol), and $Pd(dppf)Cl_2$ (72.8 mg, 0.10 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (68/32, v/v) to afford tert-butyl 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2,3-dihydroindole-1-carboxylate (260.0 mg, 52%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =500.2.

Step 3: Synthesis of tert-butyl 5-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2,3-dihydroindole-1-carboxylate.



[0246] To a solution of tert-butyl 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2,3-dihydroindole-1-carboxylate (200.0 mg, 0.40 mmol) in 1,4-dioxane (5.0 mL) was added cyclopropanecarboxamide (40.8 mg, 0.48 mmol), Cs_2CO_3 (390.9 mg, 1.20 mmol), BrettPhos (42.9 mg, 0.08 mmol) and Brettphos Pd G3 (36.2 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (52/48, v/v) to afford tert-butyl 5-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2,3-dihydroindole-1-carboxylate (200.0 mg, 91%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =549.2.

Step 4: Synthesis of N-[3-(2,3-dihydro-1H-indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 24)



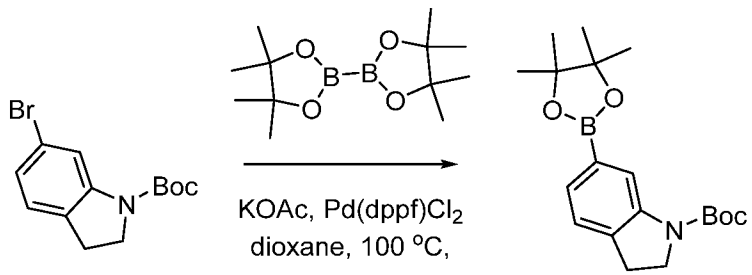
24

[0247] To a solution of tert-butyl 5-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2,3-dihydroindole-1-carboxylate

(200.0 mg, 0.36 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL). The mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated in vacuo. The residue was re-dissolved in $CH_3CN/NH_3.H_2O$ (5.0/5.0 mL). The mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5 um; 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; 254 nm) to afford N-[3-(2,3-dihydro-1H-indol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (5.2 mg, 4%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =319.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.38 (s, 1H), 10.57 (s, 1H), 8.14 (d, J = 8.7 Hz, 1H), 7.89 (d, J = 8.7 Hz, 1H), 7.47 (d, J = 2.4 Hz, 1H), 7.37 (s, 1H), 7.25 (d, J = 7.8 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 5.47 (s, 1H), 3.47 - 3.42 (m, 2H), 3.00 - 2.97 (m, 2H), 2.08 - 1.92 (m, 1H), 0.83 - 0.78 (m, 4H).

Example S25. Compound 25

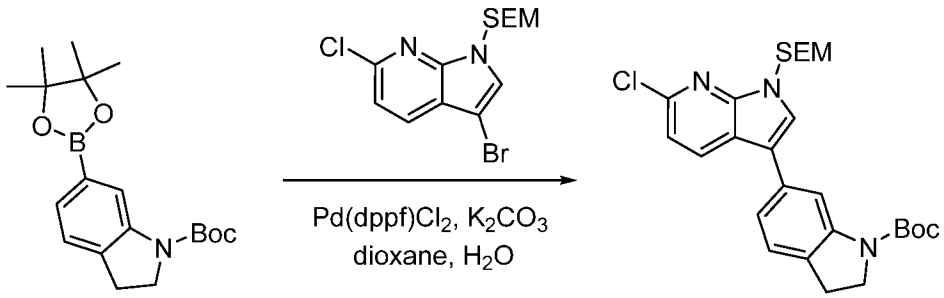
Step 1: Synthesis of tert-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydroindole-1-carboxylate.



[0248] A mixture of tert-butyl 6-bromo-2,3-dihydroindole-1-carboxylate (1.0 g, 3.35 mmol), bis(pinacolato)diboron (1.3 g, 5.03 mmol), KOAc (1.0 g, 10.06 mmol) and $Pd(dppf)Cl_2$ (0.3 g, 0.34 mmol) in dioxane (25.0 mL) was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (89/11, v/v) to

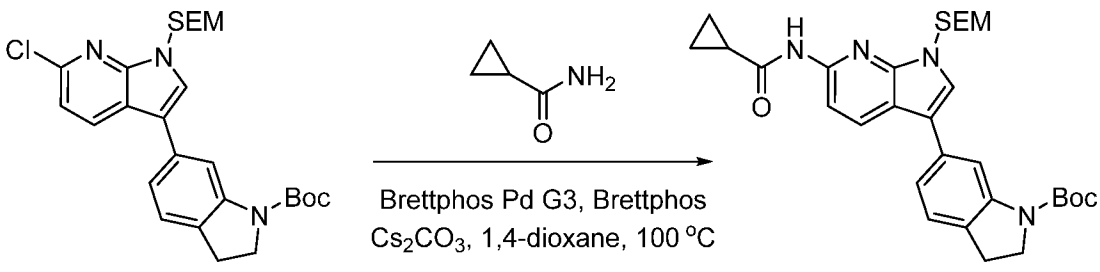
afford tert-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydroindole-1-carboxylate (1.1 g, 95%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 346.2.

Step 2: Synthesis of tert-butyl 6-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2,3-dihydroindole-1-carboxylate.



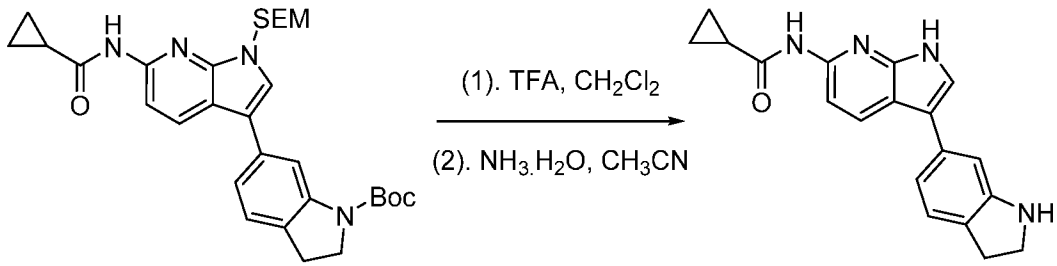
[0249] To a solution of tert-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydroindole-1-carboxylate (1.1 g, 3.19 mmol) in dioxane (20.0 mL) and H_2O (4.0 mL) was added 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (1.4 g, 3.87 mmol), K_2CO_3 (1.3 g, 9.42 mmol) and $Pd(dppf)Cl_2$ (0.2 g, 0.27 mmol). The mixture was stirred at 100 °C for 3 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (92/8, v/v) to afford tert-butyl 6-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2,3-dihydroindole-1-carboxylate (919.0 mg, 57%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 500.2.

Step 3: Synthesis of tert-butyl 6-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2,3-dihydroindole-1-carboxylate.



[0250] A mixture of tert-butyl 6-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2,3-dihydroindole-1-carboxylate (500.0 mg, 1.00 mmol), cyclopropanecarboxamide (255.3 mg, 3.00 mmol), Cs_2CO_3 (977.2 mg, 3.00 mmol), BrettPhos (107.3 mg, 0.20 mmol) and BrettPhos Pd G3 (90.6 mg, 0.10 mmol) in dioxane (10.0 mL) was stirred at 100 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (71/29, v/v) to afford tert-butyl 6-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2,3-dihydroindole-1-carboxylate (437.4 mg, 79%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 549.3.

Step 4: Synthesis of N-[3-(2,3-dihydro-1H-indol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 25)



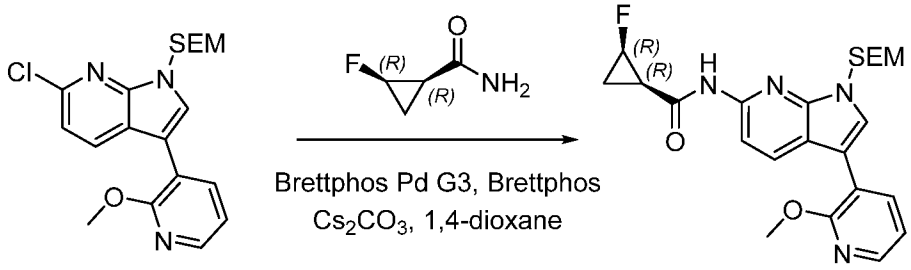
25

[0251] To a solution of tert-butyl 6-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2,3-dihydroindole-1-carboxylate (200.0 mg, 0.36 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL). The mixture was stirred at room temperature for 2 h. The mixture was evaporated in vacuo. The residue was re-dissolved in CH_3CN (5.0 mL). Then $NH_3.H_2O$ (5.0 mL) was add to the mixture. The mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (94/6, v/v) and then purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient:

28% B to 49% B in 7 min; 254 nm; RT1:6.27min) to afford N-[3-(2,3-dihydro-1H-indol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (13.1 mg, 11%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 319.2. ^1H NMR (400 MHz, CD_3OD): δ 8.21 - 8.19 (m, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.43 (s, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.03 - 7.00 (m, 2H), 3.55 - 3.49 (m, 2H), 3.06 - 3.02 (m, 2H), 1.95 - 1.85 (m, 1H), 1.03 - 0.99 (m, 2H), 0.96 - 0.88 (m, 2H).

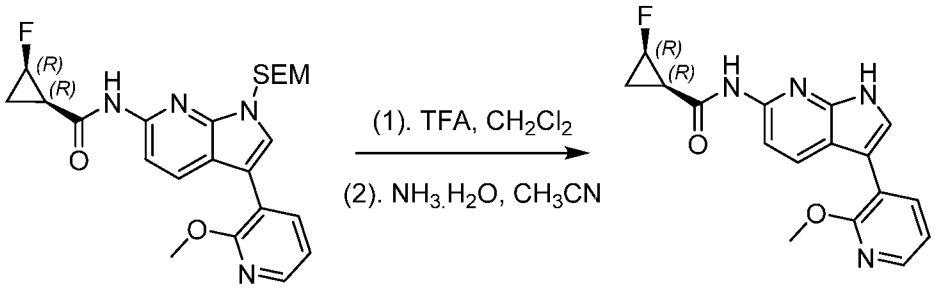
Example S26. Compound 26

Step 1: Synthesis of (1R,2R)-2-fluoro-N-(3-(2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide.



[0252] To a solution of 6-chloro-3-(2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (240.0 mg, 0.61 mmol) in dioxane (10.0 mL) were added Cs_2CO_3 (601.5 mg, 1.84 mmol), (1R,2R)-2-fluorocyclopropane-1-carboxamide (317.2 mg, 3.07 mmol), BrettPhos (132.1 mg, 0.24 mmol) and Brettphos Pd G3 (111.5 mg, 0.12 mmol) under N_2. The mixture was irradiated with microwave radiation at 100 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with ether/ethyl acetate (88/12, v/v) to afford (1R,2R)-2-fluoro-N-(3-(2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (230.0 mg, 81%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =457.2.

Step 2: Synthesis of (1R,2R)-2-fluoro-N-(3-(2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 26)

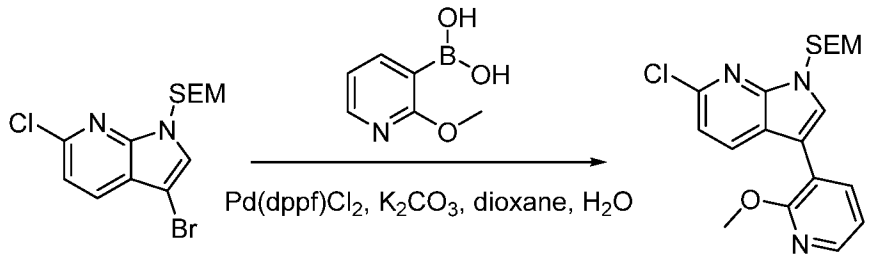


26

[0253] To a solution of (1R,2R)-2-fluoro-N-[3-(2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (230.0 mg, 0.50 mmol) in CH_2Cl_2 (15.0 mL) was added TFA (15.0 mL). The resulting mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated under vacuum. The residue was re-dissolved in CH_3CN (15.0 mL). Then NH_3H_2O (30.0 mL) was added to the mixture. The mixture was stirred at room temperature for another 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (80/20, v/v) and then purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 49% B in 8 min; 220 nm) to afford (1R,2R)-2-fluoro-N-(3-(2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (55.5 mg, 33%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 327.2 ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.70 (s, 1H), 10.64 (s, 1H), 8.13 - 8.07 (m, 2H), 8.01 - 7.90 (m, 2H), 7.72 (d, J = 2.7 Hz, 1H), 7.10 - 7.06 (m, 1H), 5.05 - 4.80 (m, 1H), 3.95 (s, 3H), 2.26 - 2.21 (m, 1H), 1.71 - 1.61 (m, 1H), 1.19 - 1.08 (m, 1H).

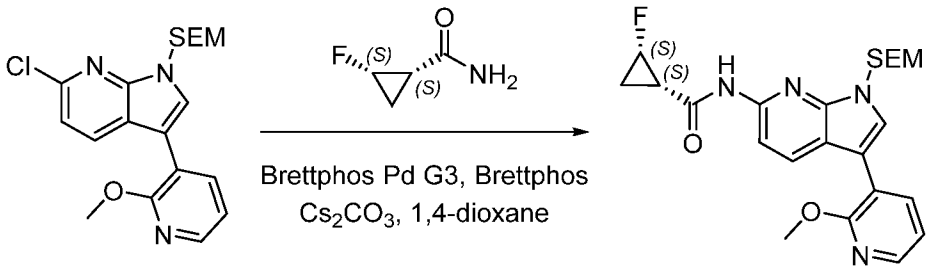
Example S27. Compound 27

Step 1: Synthesis of 6-chloro-3-(2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine.



[0254] A mixture of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (3.0 g, 8.29 mmol), 2-methoxypyridin-3-ylboronic acid (735.6 mg, 4.81 mmol), K_2CO_3 (2.0 g, 14.43 mmol) and $Pd(dppf)Cl_2$ (606.8 mg, 0.82 mmol) in dioxane (20.0 mL)/H_2O (2.0 mL) was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (7/3, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-methoxypyridine (1400.0 mg, 43%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =390.0.

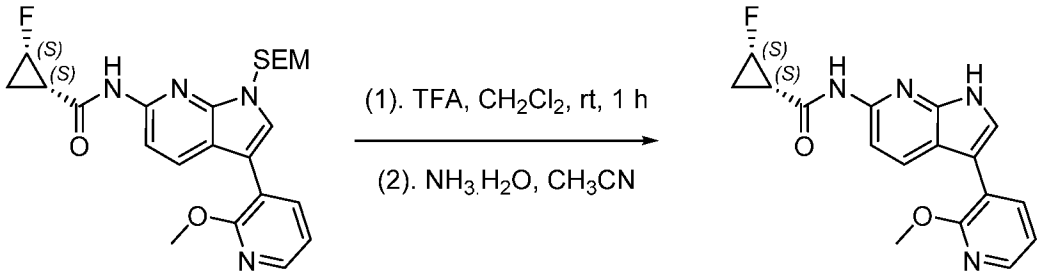
Step 2: Synthesis of (1S,2S)-2-fluoro-N-(3-(2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide.



[0255] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-methoxypyridine (400.0 mg, 1.02 mmol) in dioxane (8.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (634.5 mg, 6.15 mmol), BrettPhos (220.2 mg, 0.41 mmol), Cs_2CO_3 (1002.6 mg, 3.07 mmol) and Brettphos Pd G3 (185.9 mg, 0.20 mmol). The final reaction mixture was irradiated with microwave radiation at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (7/3, v/v) to afford (1S,2S)-2-fluoro-N-[3-(2-methoxypyridin-3-yl)-1-[[2-

(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (125.0 mg, 26%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =457.0.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-(3-(2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 27)

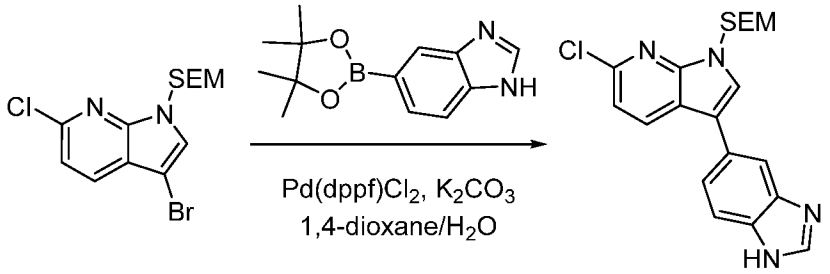


27

[0256] A mixture of (1S,2S)-2-fluoro-N-[3-(2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (100.0 mg, 0.21 mmol) and TFA (5.0 mL) in CH_2Cl_2 (5.0 mL) was stirred at room temperature for 1 h. The resulting mixture was concentrated under vacuum. The residue was dissolved in CH_3CN (5.0 mL). Then NH_3H_2O (5.0 mL) was added to the mixture. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 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 46% B in 7 min; 220 nm) to afford (1S,2S)-2-fluoro-N-[3-(2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (18.8 mg, 26%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =327.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.72 (s, 1H), 10.65 (s, 1H), 8.14 - 8.08 (m, 2H), 8.02 - 7.91 (m, 2H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.11 - 7.07 (m, 1H), 5.05 - 4.81 (m, 1H), 3.96 (s, 3H), 2.27 - 2.22 (m, 1H), 1.71 - 1.62 (m, 1H), 1.20 - 1.13 (m, 1H).

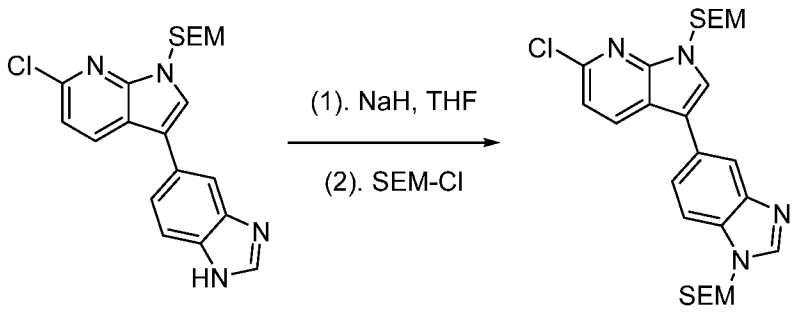
Example S28. Compound 28

Step 1: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-1H-1,3-benzodiazole.



[0257] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (500.0 mg, 1.38 mmol) in 1,4-dioxane/H_2O (15.0/3.0 mL) was added 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-1,3-benzodiazole (674.8 mg, 2.77 mmol), K_2CO_3 ((573.1 mg, 4.15 mmol) and $Pd(dppf)Cl_2$ (112.9 mg, 0.14 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (12/1, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-1H-1,3-benzodiazole (177.0 mg, 32%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =399.1.

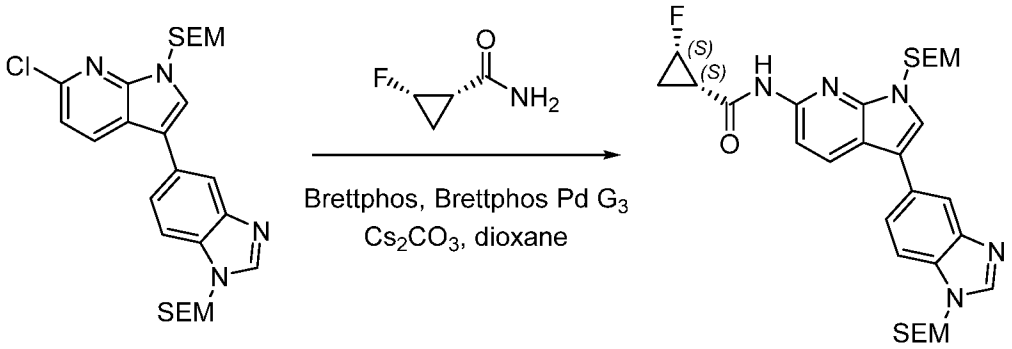
Step 2: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole.



[0258] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-1H-1,3-benzodiazole (297.0 mg, 0.74 mmol) in THF (20.0 mL) was added NaH (186.2 mg, 60%) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. Then SEM-Cl (186.2 mg, 1.12 mmol) was added dropwise to the mixture at 0 °C under N_2. The resulting mixture was stirred at 0 °C for another 1 h. After the reaction was completed, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The

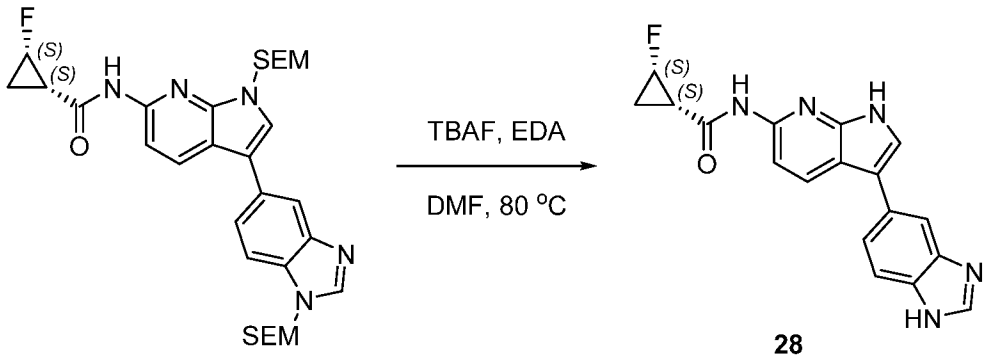
filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (200.0 mg, 50%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =529.2.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-(1-[[2-(trimethylsilyl)ethoxy]methyl]-3-(1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide.



[0259] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (189.0 mg, 0.36 mmol) in 1,4-dioxane (8.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (184.1 mg, 1.79 mmol), BrettPhos (38.3 mg, 0.07 mmol), Cs_2CO_3 (349.1 mg, 1.07 mmol) and BrettPhos Pd G3 (32.4 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was irradiated with microwave radiation at 120 °C for 1.5 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1S,2S)-2-fluoro-N-(1-[[2-(trimethylsilyl)ethoxy]methyl]-3-(1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (166.0 mg, 78%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =596.3.

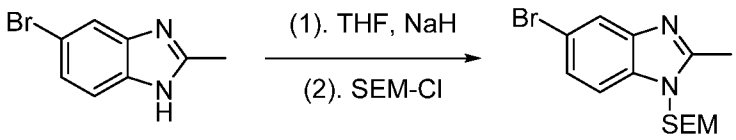
Step 4: Synthesis of (1S,2S)-N-[3-(1H-1,3-benzodiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 28)



[0260] To a solution of (1S,2S)-2-fluoro-N-(1-[[2-(trimethylsilyl)ethoxy]methyl]-3-(1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (166.0 mg, 0.28 mmol) in DMF (8.0 mL) was added ethane-1,2-diamine (83.7 mg, 1.39 mmol) and TBAF (0.8 mL, 0.28 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 19% B to 39% B in 6 min; 254 nm) to (1S,2S)-N-[3-(1H-1,3-benzodiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (7.7 mg, 8%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =336.1. ^1H NMR (300 MHz, DMSO-d_6): δ 12.40 - 12.35 (m, 1H), 11.63 (s, 1H), 10.78 (s, 1H), 8.26 - 8.19 (m, 2H), 7.91 - 7.89 (m, 2H), 7.77 - 7.70 (m, 2H), 7.56 - 7.54 (m, 1H), 5.01 - 4.78 (m, 1H), 2.59 - 2.50 (m, 1H), 1.54 - 1.46 (m, 1H), 1.28 - 1.22 (m, 1H).

Example S29. Compound 29

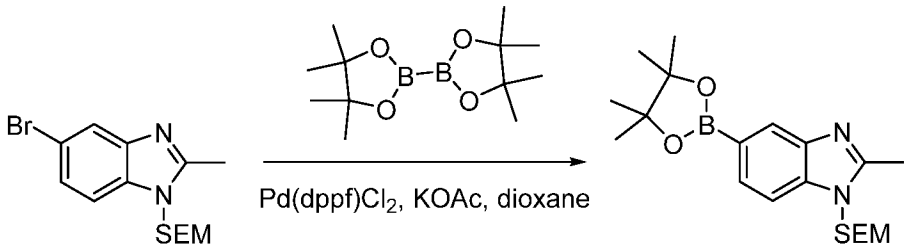
Step 1: Synthesis of 5-bromo-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole



[0261] To a solution of 5-bromo-2-methyl-1H-benzo[d]imidazole (500.0 mg, 2.37 mmol) in THF (20.0 mL) was added NaH (284.3 mg, 60%) at 0 °C under N_2. The resulting mixture

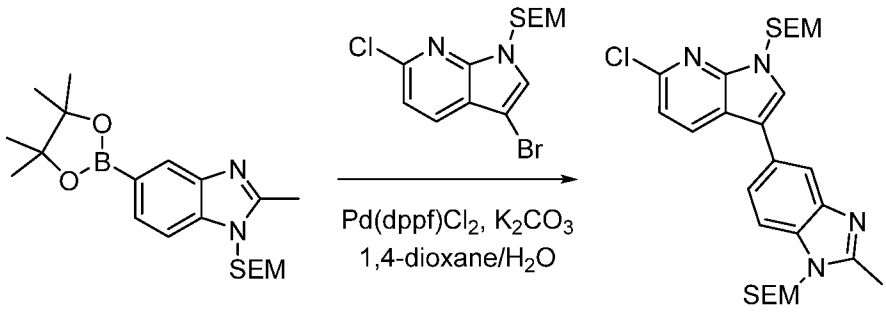
was stirred at 0 °C for 1 h. Then SEM-Cl (592.4 mg, 3.55 mmol) was added dropwise to the mixture at 0 °C under N_2. The resulting mixture was stirred at 0 °C for another 1 h. After the reaction was completed, the resulting mixture was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (63/37, v/v) to afford 5-bromo-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole (710.0 mg, 87%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =341.1.

Step 2: Synthesis of 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole.



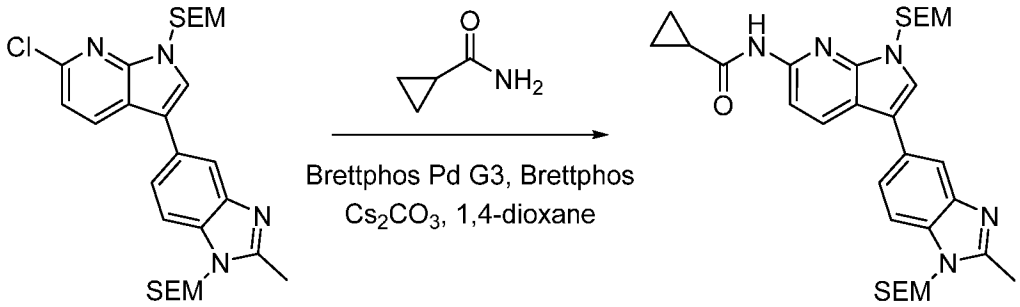
[0262] To a solution of 5-bromo-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole (660.0 mg, 1.93 mmol) in 1,4-dioxane (15.0 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1473.1 mg, 5.80 mmol), KOAc (569.3 mg, 5.80 mmol) and $Pd(dppf)Cl_2$ (141.5 mg, 0.19 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (45/55, v/v) to afford 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole (620.0 mg, 80%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =389.2.

Step 3: Synthesis of 5-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole.



[0263] To a solution of 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole (570.0 mg, 1.47 mmol) in 1,4-dioxane/H_2O (20.0/4.0 mL) was added 3-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (530.9 mg, 1.47 mmol), K_2CO_3 (608.5 mg, 4.40 mmol) and $Pd(dppf)Cl_2$ (107.4 mg, 0.15 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (43/57, v/v) to afford 5-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole (790.0 mg, 99%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =543.2.

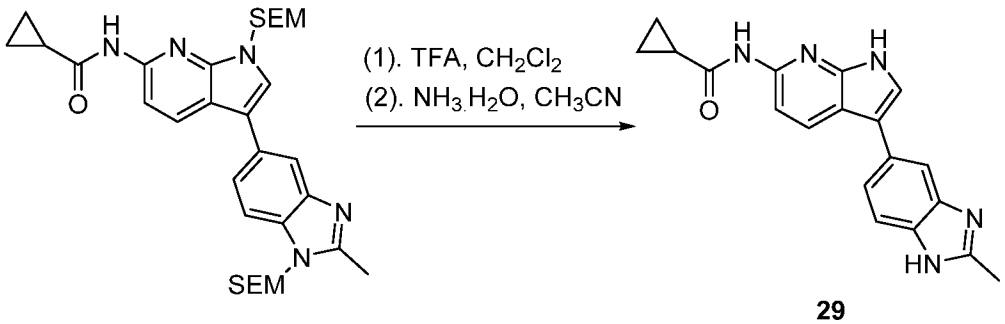
Step 4: Synthesis of N-(3-(2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide.



[0264] To a solution of 5-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole (750.0 mg, 1.38 mmol) in 1,4-dioxane (15.0 mL) was added cyclopropanecarboxamide (587.5 mg, 6.90 mmol), Cs_2CO_3 (1349.4 mg, 4.14 mmol), BrettPhos (148.2 mg, 0.28 mmol) and

BrettPhos Pd G3 (125.2 mg, 0.14 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (35/66, v/v) to afford N-(3-(2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (600.0 mg, 73%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =592.3.

Step 5: Synthesis of N-(3-(2-methyl-1H-benzo[d]imidazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (Compound 29)



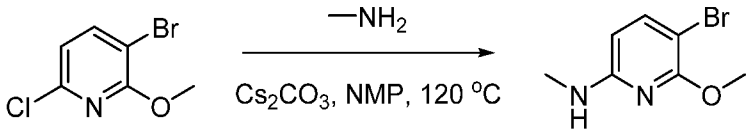
29

[0265] To a solution of N-(3-(2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (550.0 mg, 0.93mmol) in CH_2Cl_2 (10.0 mL) was added TFA (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (10.0 mL and $NH_3.H_2O$ (10.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 16% B to 40% B in 8 min; 254 nm) to afford N-(3-(2-methyl-1H-benzo[d]imidazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (26.7 mg, 8%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =332.2. ^1H NMR (300 MHz,

CD_3OD): δ 8.25 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.74 (s, 1H), 7.57 - 7.51 (m, 3H), 2.60 (s, 3H), 1.94 - 1.89 (m, 1H), 1.05 - 0.96 (m, 2H), 0.94 - 0.91 (m, 2H).

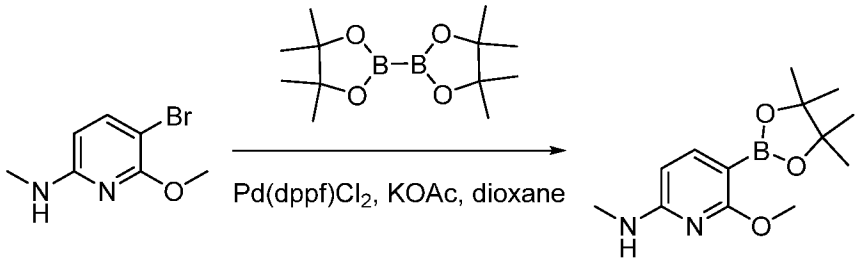
Example S30. Compound 30

Step 1: Synthesis of 5-bromo-6-methoxy-N-methylpyridin-2-amine.



[0266] To a mixture of 3-bromo-6-chloro-2-methoxypyridine (1.0 g, 4.49 mmol) and methylamine (1.4 g, 45.07 mmol) in NMP (15.0 mL) was added Cs_2CO_3 (4.3 g, 13.47 mmol) at room temperature. The resulting mixture was stirred at 120 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford 5-bromo-6-methoxy-N-methylpyridin-2-amine (950.0 mg, 97%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =217.0.

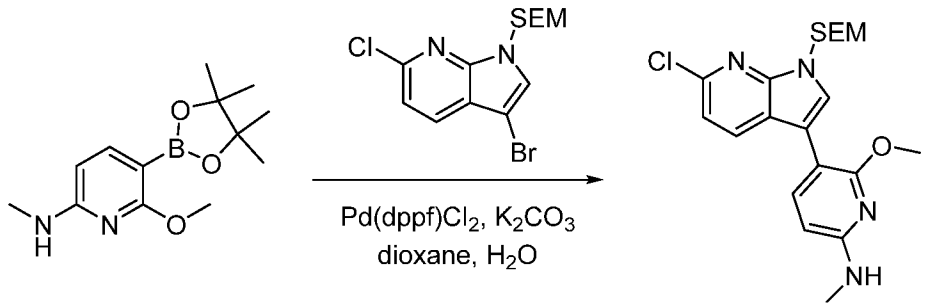
Step 2: Synthesis of 6-methoxy-N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine.



[0267] To a mixture of 5-bromo-6-methoxy-N-methylpyridin-2-amine (900.0 mg, 4.14 mmol) and bis(pinacolato)diboron (3.1 g, 12.43 mmol) in dioxane (20.0 mL) were added $Pd(dppf)Cl_2$ (303.3 mg, 0.41 mmol) and KOAc (1.2 g, 12.43 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column

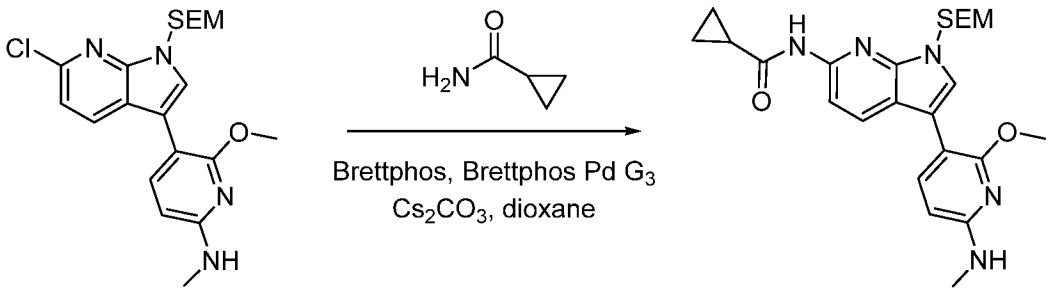
chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford 6-methoxy-N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (180.0 mg, 16%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =265.2.

Step 3: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-N-methylpyridin-2-amine.



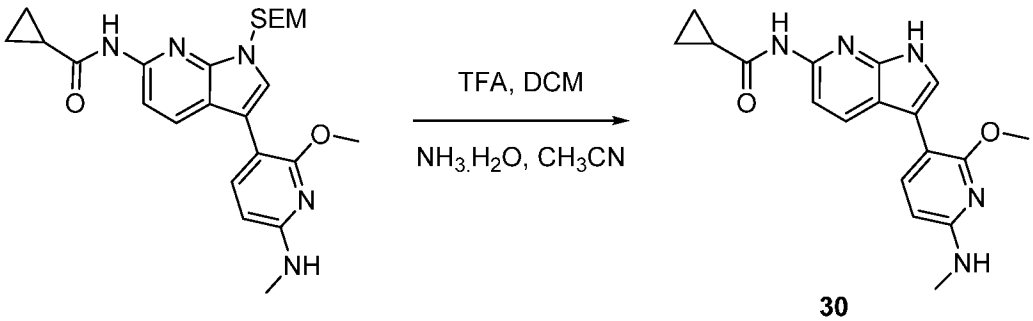
[0268] To a mixture of 6-methoxy-N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (160.0 mg, 0.62 mmol) and 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (150.0 mg, 0.41 mmol) in dioxane (4.0 mL) was added $Pd(dppf)Cl_2$ (30.0 mg, 0.041 mmol) and K_2CO_3 (170.0 mg, 2.08 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-N-methylpyridin-2-amine (70.0 mg, 28%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =419.2.

Step 4: Synthesis of N-[3-[2-methoxy-6-(methylamino)pyridin-3-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide.



[0269] To a mixture of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-N-methylpyridin-2-amine (40.0 mg, 0.09 mmol) and cyclopropanecarboxamide (32.5 mg, 0.38 mmol) in dioxane (3.0 mL) was added BrettPhos (10.2 mg, 0.02 mmol) BrettPhos Pd G3 (8.6 mg, 0.01 mmol) and Cs_2CO_3 (93.3 mg, 0.28 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford N-[3-[2-methoxy-6-(methylamino)pyridin-3-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl] pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (40.0 mg, 89%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =468.2.

Step 5: Synthesis of N-[3-[2-methoxy-6-(methylamino)pyridin-3-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 30)



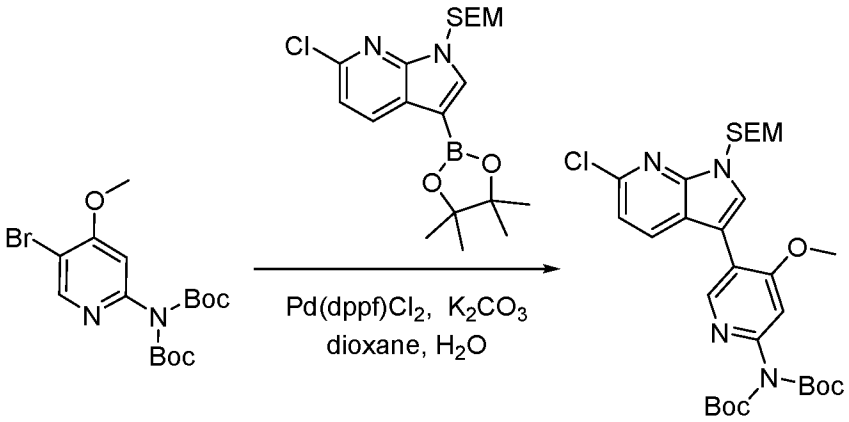
30

[0270] To a solution of N-[3-[2-methoxy-6-(methylamino)pyridin-3-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (100.0 mg, 0.21 mmol) in DCM (2.0 mL) was added TFA (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added $NH_3.H_2O$ (2.0 mL) and ACN (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; 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 10

min; 254 nm) to afford N-[3-[2-methoxy-6-(methylamino)pyridin-3-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (28.4 mg, 39%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =338.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.36 (s, 1H), 10.53 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.7 Hz, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 6.39 - 6.34 (m, 1H), 6.10 (d, J = 8.1 Hz, 1H), 3.87 (s, 3H), 2.82 (d, J = 4.5 Hz, 3H), 2.06 - 2.01 (m, 1H), 0.83 - 0.75 (m, 4H).

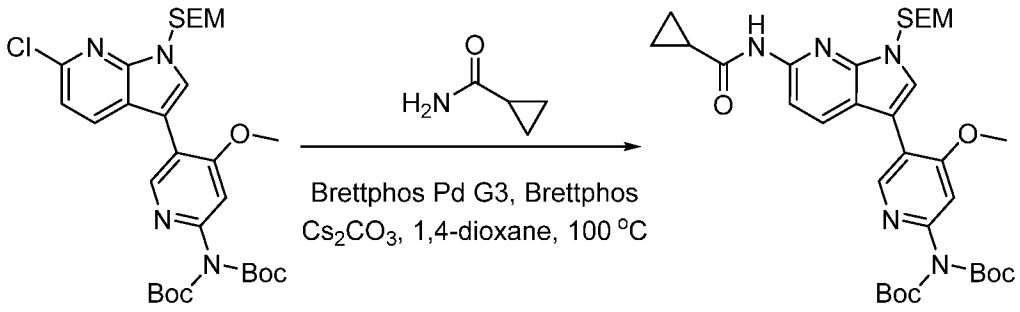
Example S31. Compound 31

Step 1: Synthesis of tert-butyl N-(tert-butoxycarbonyl)-N-[5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxypyridin-2-yl]carbamate.



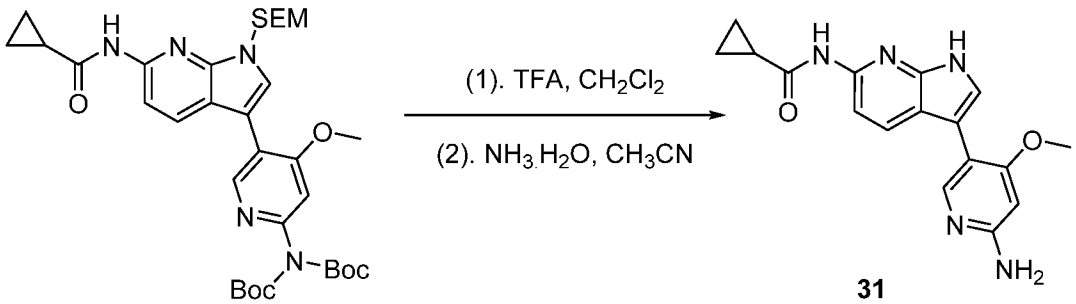
[0271] To a solution of tert-butyl N-(5-bromo-4-methoxypyridin-2-yl)-N-(tert-butoxycarbonyl)carbamate (402.5 mg, 1.00 mmol) in dioxane/H_2O (15.0 / 3.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (340.0 mg, 0.83 mmol), K_2CO_3 (344.8 mg, 2.50 mmol), Pd(dppf)Cl_2 (67.9 mg, 0.08 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford tert-butyl N-(tert-butoxycarbonyl)-N-[5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxypyridin-2-yl]carbamate (330.0 mg, 66%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =605.2.

Step 2: Synthesis of tert-butyl N-(tert-butoxycarbonyl)-N-[5-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxypyridin-2-yl]carbamate.



[0272] To a solution of tert-butyl N-(tert-butoxycarbonyl)-N-[5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxypyridin-2-yl]carbamate (282.0 mg, 0.47 mmol) in 1,4-dioxane (15.0 mL) was added cyclopropanecarboxamide (198.3 mg, 2.33 mmol), BrettPhos (50.0 mg, 0.03 mmol), Cs_2CO_3 (455.46 mg, 1.40 mmol) and BrettPhos Pd G3 (42.3 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was irradiated with microwave radiation at 120 °C for 1.5 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to tert-butyl N-(tert-butoxycarbonyl)-N-[5-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxypyridin-2- yl]carbamate (80.0 mg, 26%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =654.3.

Step 3: Synthesis of N-[3-(6-amino-4-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 31)

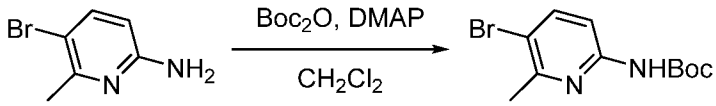


31

[0273] To a solution of tert-butyl N-(tert-butoxycarbonyl)-N-[5-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxypyridin-2-yl]carbamate (80.0 mg, 0.12 mmol) in CH_2Cl_2 (4.0 mL) was added TFA (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (5.0 mL) and $NH_3.H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions Column: (Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate: 60 mL/min; Gradient: 14% B to 36% B in 7 min; 254 nm) to afford N-[3-(6-amino-4-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (10.8 mg, 27%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =324.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.33 (s, 1H), 10.47 (s, 1H), 7.84 - 7.78 (m, 3H), 7.29 (d, J = 2.1 Hz, 1H), 6.09 (s, 1H), 5.78 (s, 2H), 3.70 (s, 3H), 1.96 - 1.92 (m, 1H), 0.75 - 0.68 (m, 4H).

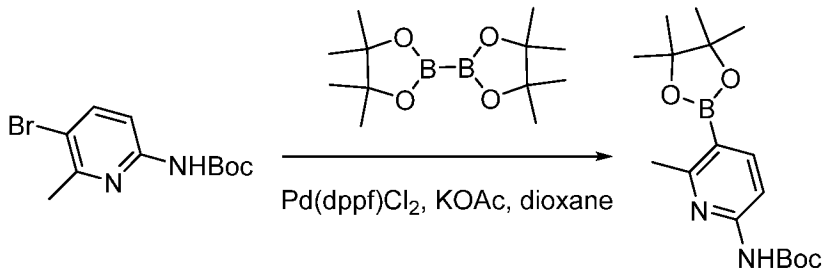
Example S32. Compound 32

Step 1: Synthesis of tert-butyl (5-bromo-6-methylpyridin-2-yl)carbamate.



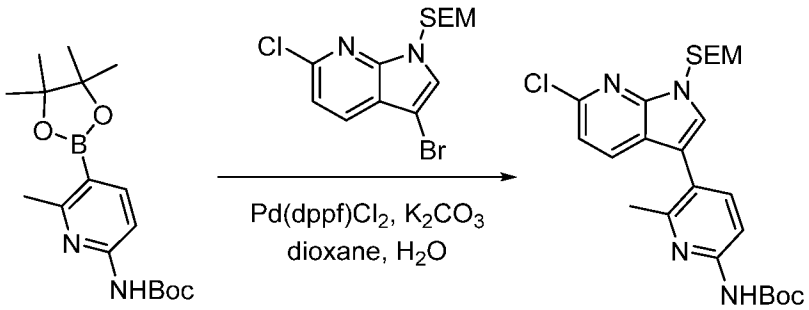
[0274] To a solution of 5-bromo-6-methylpyridin-2-amine (5.0 g, 26.73 mmol) in CH_2Cl_2 (100.0 mL) was added Boc_2O (5.8 g, 26.73 mmol) and DMAP (3.3 g, 26.73 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford tert-butyl (5-bromo-6-methylpyridin-2-yl)carbamate (4.0 g, 52%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =287.0.

Step 2: Synthesis of tert-butyl (6-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate



[0275] To a solution of tert-butyl (5-bromo-6-methylpyridin-2-yl)carbamate (2.0 g, 6.97 mmol) in dioxane (40.0 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (5.3 g, 20.89 mmol), KOAc (2.1 g, 20.89 mmol) and $Pd(dppf)Cl_2$ (0.5 g, 0.70 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford tert-butyl (6-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (2.0 g, 85%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =335.2.

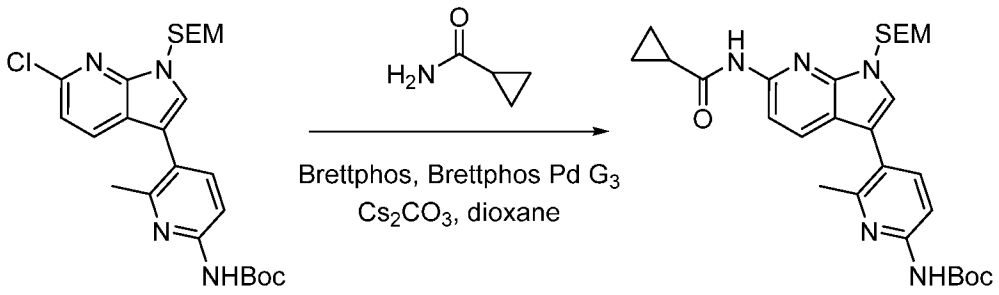
Step 3: Synthesis of tert-butyl (5-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-methylpyridin-2-yl)carbamate:



[0276] To a solution of tert-butyl (6-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (500.0 mg, 1.50 mmol) in dioxane/H_2O (10.0/1.0 mL) was added 3-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (541.2 mg, 1.50 mmol), K_2CO_3 (620.3 mg, 4.49 mmol) and $Pd(dppf)Cl_2$ (109.5 mg, 0.15 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford tert-butyl

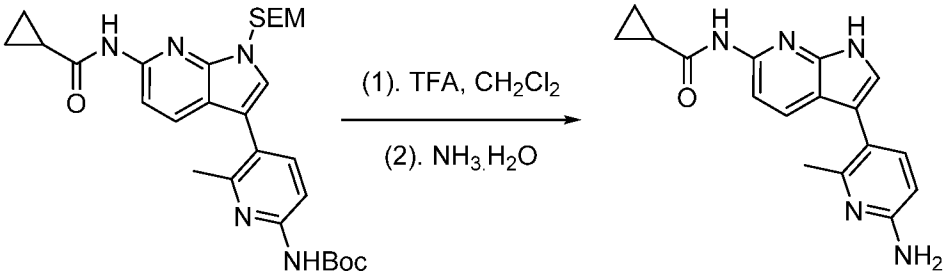
(5-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-methylpyridin-2-yl)carbamate (170.0 mg, 23%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =489.2.

Step 4: Synthesis of tert-butyl (5-(6-(cyclopropanecarboxamido)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-methylpyridin-2-yl)carbamate:



[0277] To a solution of tert-butyl (5-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-methylpyridin-2-yl)carbamate (130.0 mg, 0.27 mmol) in dioxane (10.0 mL) was added cyclopropanecarboxamide (135.7 mg, 1.60 mmol), Cs_2CO_3 (259.8 mg, 0.80 mmol), Brettphos (28.5 mg, 0.05 mmol) and BrettPhos Pd G3 (24.1 mg, 0.03 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford tert-butyl (5-(6-(cyclopropanecarboxamido)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-methylpyridin-2-yl)carbamate (130.0 mg, 90%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =538.3.

Step 5: Synthesis of N-(3-(6-amino-2-methylpyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (Compound 32)

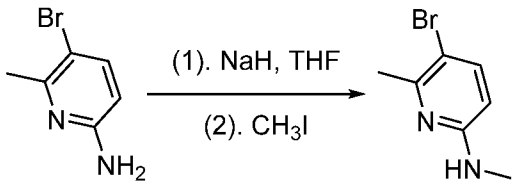


32

[0278] To a solution of tert-butyl (5-(6-(cyclopropanecarboxamido)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-methylpyridin-2-yl)carbamate (250.0 mg, 0.47 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in CH_3CN (5.0 mL) and $NH_3 \cdot H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 6% to 17% in 7 min; 254 nm) to afford N-(3-(6-amino-2-methylpyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (27.8 mg, 19%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =308.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.46 (s, 1H), 10.57 (s, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.36 - 7.30 (m, 2H), 6.38 (d, J = 8.4 Hz, 1H), 5.86 (s, 2H), 2.27 (s, 3H), 2.07 - 2.01 (m, 1H), 0.84 - 0.81 (m, 4H).

Example S33. Compound 33

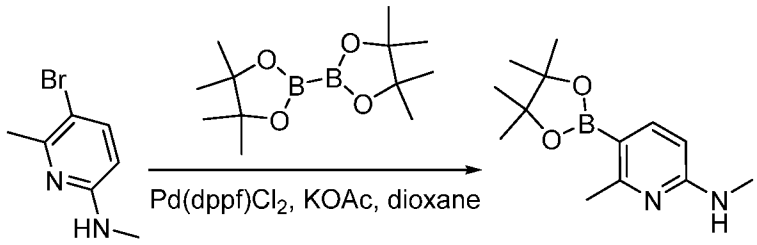
Step 1: Synthesis of 5-bromo-N,6-dimethylpyridin-2-amine:



[0279] To a solution of 5-bromo-6-methylpyridin-2-amine (10.0 g, 53.46 mmol) in THF (100.0 mL) was added NaH (1.9 g, 60%) at 0 °C under N_2. The resulting mixture was stirred

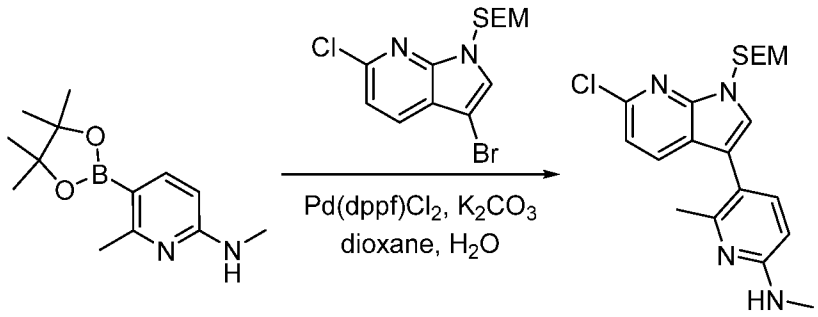
at 0 °C for 1 h under N_2. Then CH_3I (7.6 g, 53.46 mmol) was added dropwise to the mixture at 0 °C under N_2. The resulting mixture was stirred at 0 °C for another 1 h. After the reaction was completed, the reaction was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford 5-bromo-N,6-dimethylpyridin-2-amine (3.3 g, 30%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =201.0.

Step 2: Synthesis of N,6-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine:



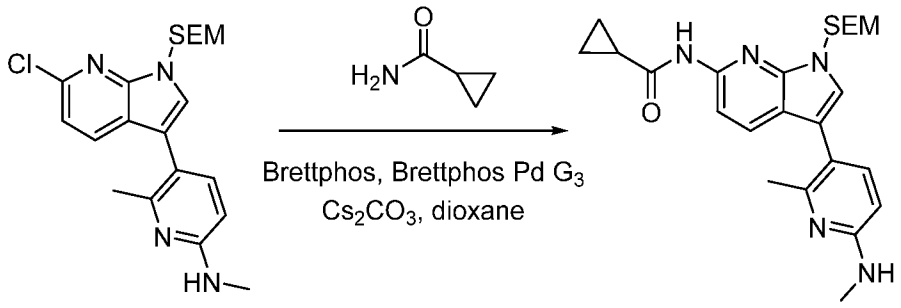
[0280] To a solution of 5-bromo-N,6-dimethylpyridin-2-amine (2.0 g, 9.95 mmol) in dioxane (40.0 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (7.6 g, 29.84 mmol), KOAc (8.9 g, 29.84 mmol) and $Pd(dppf)Cl_2$ (0.7 g, 1.00 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/9, v/v) to afford N,6-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (750.0 mg, 30%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =249.2.

Step 3: Synthesis of 5-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-N,6-dimethylpyridin-2-amine:



[0281] To a solution of N,6-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (500.0 mg, 2.02 mmol) in dioxane/H_2O (10.0/1.0 mL) was added 3-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (728.9 mg, 2.02 mmol), K_2CO_3 (835.5 mg, 6.05 mmol) and $Pd(dppf)Cl_2$ (147.4 mg, 0.20 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 5-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-N,6-dimethylpyridin-2-amine (250.0 mg, 30%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =403.2.

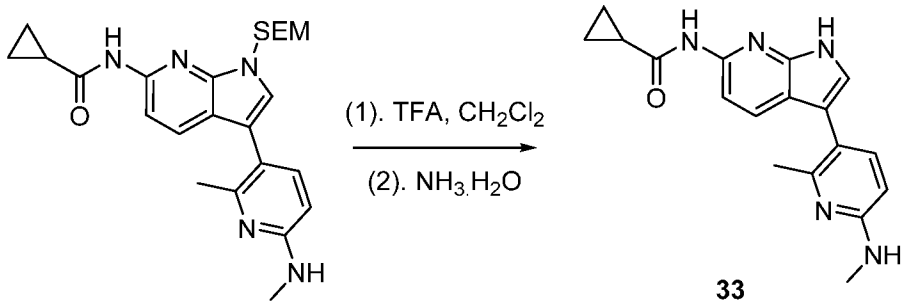
Step 4: Synthesis of N-(3-(2-methyl-6-(methylamino)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide:



[0282] To a solution of 5-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-N,6-dimethylpyridin-2-amine (200.0 mg, 0.50 mmol) in dioxane (10.0 mL) was added cyclopropanecarboxamide (253.4 mg, 2.98 mmol), Cs_2CO_3 (485.1mg, 1.49 mmol), Brettphos (53.3 mg, 0.10 mmol) and BrettPhos Pd G3 (45.0 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction

was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford N-(3-(2-methyl-6-(methylamino)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (150.0 mg, 66%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =452.2.

Step 5: Synthesis of N-(3-(2-methyl-6-(methylamino)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (Compound 33)

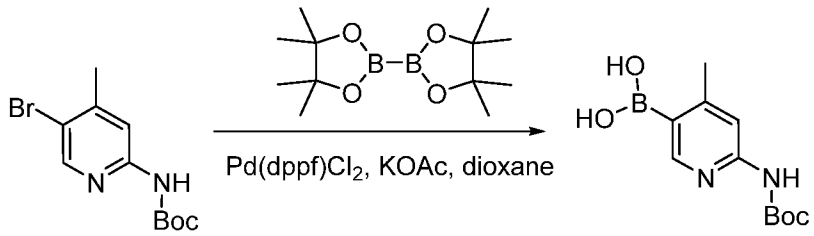


[0283] To a solution of N-(3-(2-methyl-6-(methylamino)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (130.0 mg, 0.29 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in CH_3CN (5.0 mL) and $NH_3 \cdot H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate: 60 mL/min; Gradient: 24% to 44% in 7 min; 254 nm) to afford N-(3-(2-methyl-6-(methylamino)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (44.1 mg, 47%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =322.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.46 (d, J = 1.5 Hz, 1H), 10.57 (s, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H),

6.36 - 6.31 (m, 2H), 2.79 (d, J = 4.8 Hz, 3H), 2.30 (s, 3H), 2.08 - 2.00 (m, 1H), 0.85 - 0.75 (m, 4H).

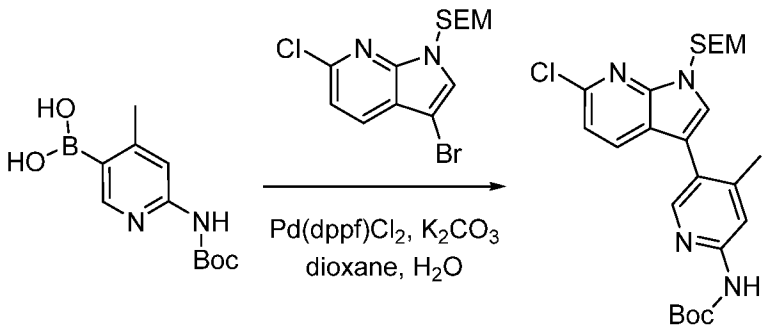
Example S34. Compound 34

Step 1: Synthesis of 6-[(tert-butoxycarbonyl)amino]-4-methylpyridin-3-ylboronic acid:



[0284] To a solution of tert-butyl N-(5-bromo-4-methylpyridin-2-yl)carbamate (500.0 mg, 1.71 mmo) in dioxane (10.0 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1326.4 mg, 5.24 mmol), Pd(dppf)Cl_2 (254.8 mg, 0.38 mmol) and KOAc (512.6 mg, 5.24 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/2, v/v) to afford 6-[(tert-butoxycarbonyl)amino]-4-methylpyridin-3-ylboronic acid (400.0 mg, 69%) as a yellow oil.. LCMS (ESI, m/z): $[M+H]^+$ =253.1.

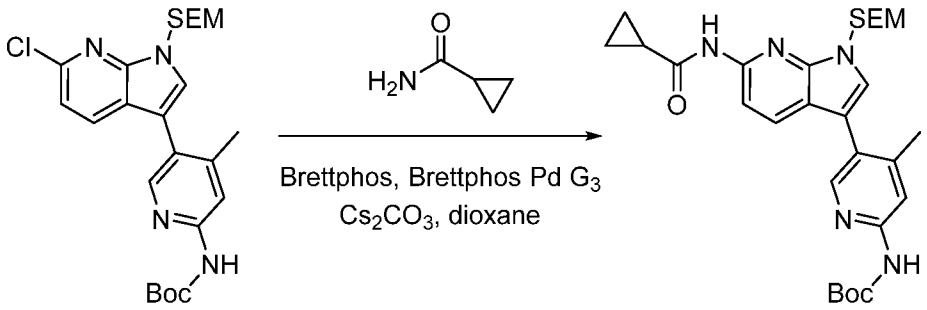
Step 2: Synthesis of tert-butyl N-[5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methylpyridin-2-yl]carbamate:



[0285] To a solution of 6-[(tert-butoxycarbonyl)amino]-4-methylpyridin-3-ylboronic acid (300.0 mg, 1.19 mmol) in dioxane/H_2O (10.0 mL/1.0 mL) was added 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (344.4 mg, 0.95 mmol), Pd(dppf)Cl_2

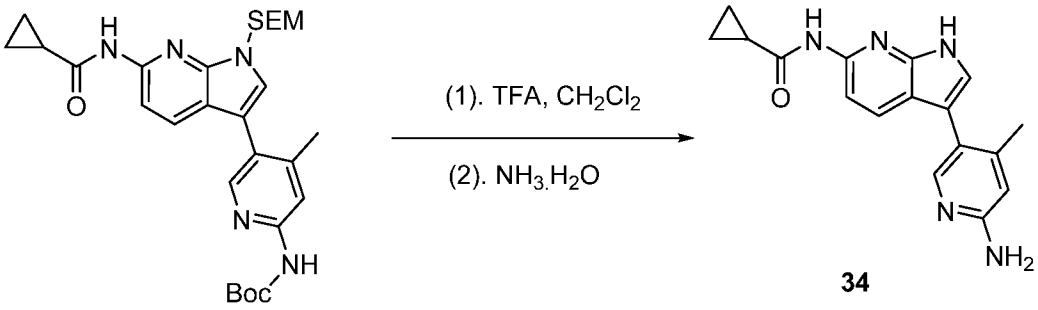
(87.0 mg, 0.19 mmol) and K_2CO_3 (493.4 mg, 3.57 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford tert-butyl N-[5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methylpyridin-2-yl]carbamate (130.0 mg, 22%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =489.2.

Step 3: Synthesis of tert-butyl N-[5-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methylpyridin-2-yl]carbamate:



[0286] To a solution of tert-butyl N-[5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methylpyridin-2-yl]carbamate (110.0 mg, 0.25 mmol) in dioxane (10.0 mL) was added cyclopropanecarboxamide (57.4 mg, 0.65 mmol), BrettPhos Pd G3 (20.9 mg, 0.02 mmol), BrettPhos (24.4 mg, 0.05 mmol) and Cs_2CO_3 (219.8 mg, 0.67 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford tert-butyl N-[5-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methylpyridin-2-yl]carbamate (78.0 mg, 64%) as a white oil. LCMS (ESI, m/z): $[M+H]^+$ =538.3.

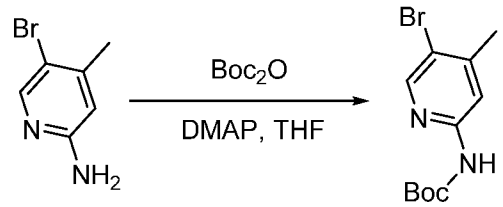
Step 4: Synthesis of N-[3-(6-amino-4-methylpyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 34)



[0287] To a solution of tert-butyl N-[5-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methylpyridin-2-yl]carbamate (78.0 mg, 0.14 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (5.0 mL) and $NH_3.H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue washed with CH_2Cl_2 and then filtered. The solid was collected and dried to afford N-[3-(6-amino-4-methylpyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (10.0 mg, 22%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =308.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.82 (s, 1H), 10.72 (s, 1H), 8.02 - 7.90 (m, 3H), 7.64 - 7.53 (m, 3H), 6.93 (s, 1H), 2.37 (s, 3H), 2.13 - 2.07 (m, 1H), 0.93 - 0.85 (m, 4H).

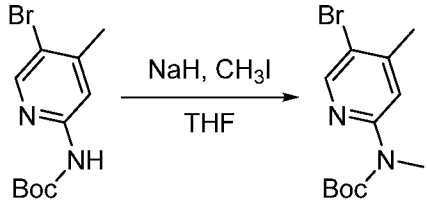
Example S35. Compound 35

Step 1: Synthesis of tert-butyl N-(5-bromo-4-methylpyridin-2-yl)carbamate.



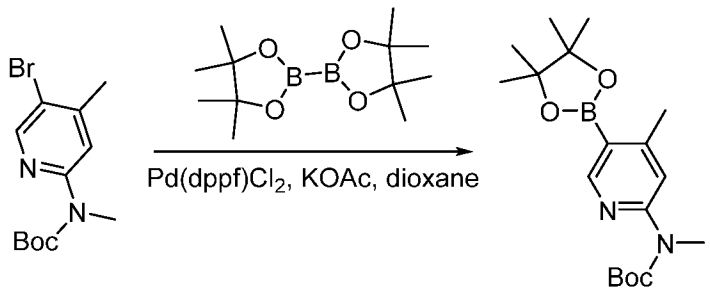
[0288] To a solution of 5-bromo-4-methylpyridin-2-amine (5.0 g, 26.72 mmol) in THF (100.0 mL) was added di-tert-butyl dicarbonate (5.8 g, 26.72 mmol) and DMAP (3.7 g, 26.72 mmol) at room temperature under N_2. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (6/1, v/v) to afford tert-butyl N-(5-bromo-4-methylpyridin-2-yl)carbamate (2.7 g, 35%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =287.0

Step 2: Synthesis of tert-butyl N-(5-bromo-4-methylpyridin-2-yl)-N-methylcarbamate.



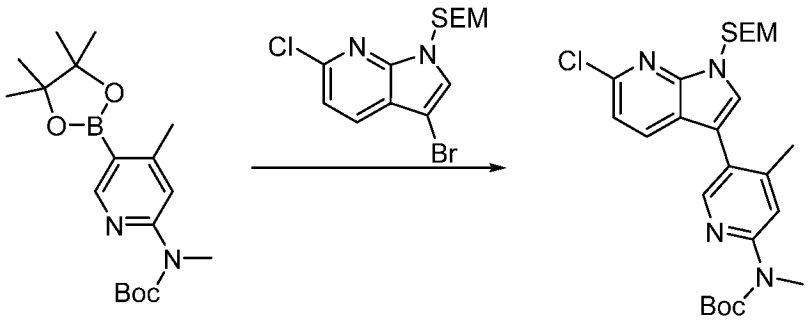
[0289] To a solution of tert-butyl N-(5-bromo-4-methylpyridin-2-yl)carbamate (700.0 mg, 2.48 mmol) in THF (10.0 mL) was added NaH (117.0 mg, 60%) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. Then CH_3I (692.0 mg, 4.88 mmol) was added to the mixture. The resulting mixture was stirred at 0 °C for another 1 h. After the reaction was completed, the resulting mixture was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford tert-butyl N-(5-bromo-4-methylpyridin-2-yl)-N-methylcarbamate (600.0 mg, 95%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =301.0.

Step 3: Synthesis of tert-butyl methyl(4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate:



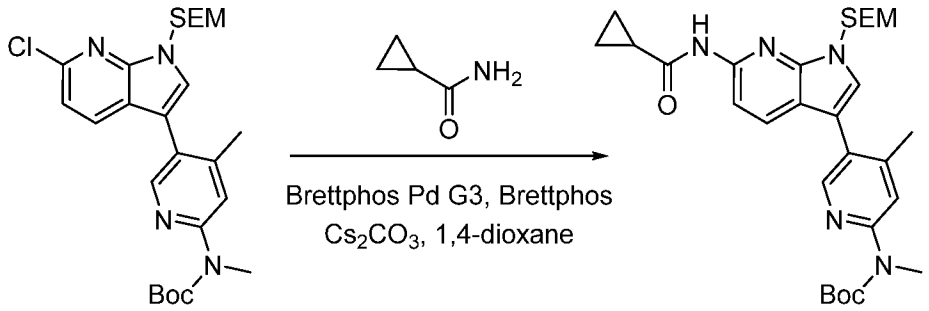
[0290] To a solution of tert-butyl N-(5-bromo-4-methylpyridin-2-yl)-N-methylcarbamate (600.0 mg, 1.92 mmol) in dioxane (10.0 mL, 510.75 mmol) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.5 g, 5.98 mmol), $Pd(dppf)Cl_2$ (145.7 mg, 0.19 mmol) and KOAc (586.5 mg, 5.97 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (7/1, v/v) to afford tert-butyl methyl(4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (500.0 mg, 72%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =349.2.

Step 4: Synthesis of tert-butyl N-[5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methylpyridin-2-yl]-N-methylcarbamate:



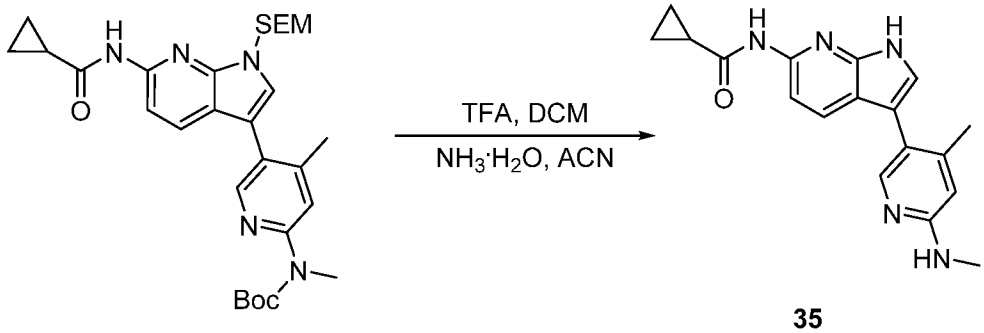
[0291] To a solution of tert-butyl methyl(4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (400.0 mg, 1.50 mmol) in dioxane/H_2O (10.0/1.0 mL) was added 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (1.1 g, 3.06 mmol), $Pd(dppf)Cl_2$ (109.9 mg, 0.15 mmol) and K_2CO_3 (623.5 mg, 4.50 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford tert-butyl N-[5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methylpyridin-2-yl]-N-methylcarbamate (400.0 mg, 53%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =503.2.

Step 5: Synthesis of tert-butyl N-[5-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methylpyridin-2-yl]-N-methylcarbamate:



[0292] To a solution of tert-butyl N-[5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methylpyridin-2-yl]-N-methylcarbamate (380.0 mg, 0.75 mmol) in dioxane (10.0 mL) was added cyclopropanecarboxamide (192.8 mg, 2.26 mmol), BrettPhos Pd G3 (68.7 mg, 0.07 mmol), BrettPhos (81.0 mg, 0.15 mmol) and Cs_2CO_3 (738.6 mg, 2.26 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford tert-butyl N-[5-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methylpyridin-2-yl]-N-methylcarbamate (300.0 mg, 72%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =552.3.

Step 6: Synthesis of N-[3-[4-methyl-6-(methylamino)pyridin-3-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 35):



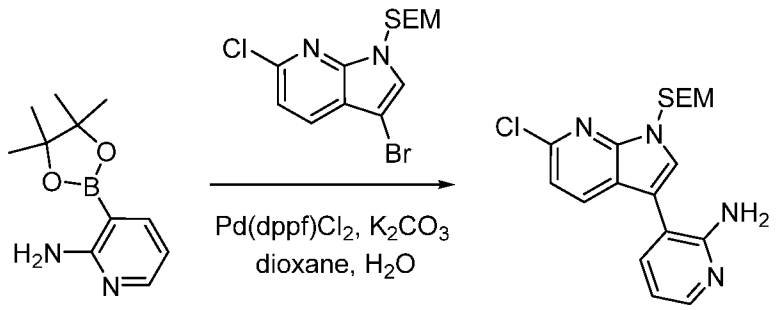
35

[0293] To a solution of tert-butyl N-[5-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methylpyridin-2-yl]-N-methylcarbamate (150.0 mg, 0.27 mmol) in DCM (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (5.0 mL) and $NH_3 \cdot H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L

NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 16% B to 46% B in 10 min; 254 nm) to afford N-[3-[4-methyl-6-(methylamino)pyridin-3-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (17.4 mg, 20%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =322.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.47 (s, 1H), 10.56 (s, 1H), 7.92 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 2.1 Hz, 1H), 6.39 (s, 1H), 6.32 - 6.28 (m, 1H), 2.79 (d, J = 4.8 Hz, 3H), 2.14 (s, 3H), 2.05 - 2.01 (m, 1H), 0.85 - 0.77 (m, 4H).

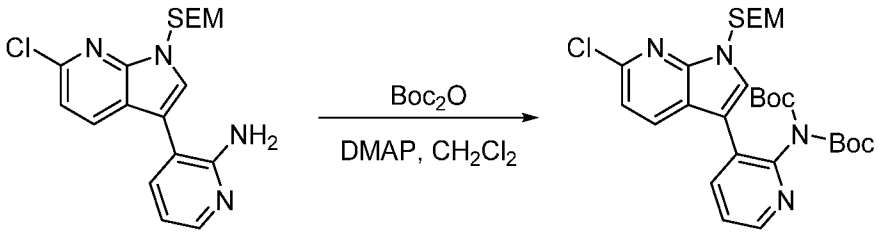
Example S36. Compound 36

Step 1: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-amine:



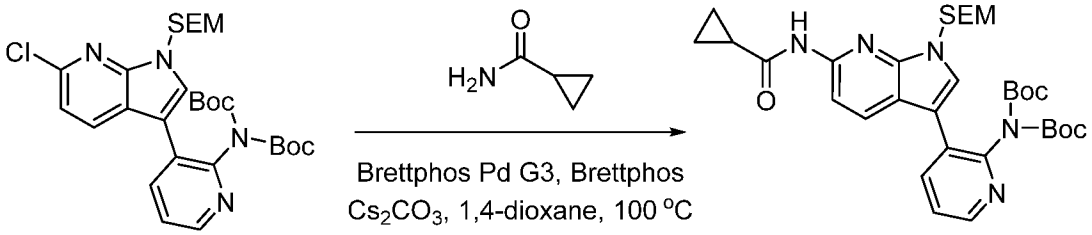
[0294] To a solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (500.0 mg, 2.27 mmol) in dioxane/H_2O (5.0/0.5 mL) was added 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (986.2 mg, 2.72 mmol), $Pd(dppf)Cl_2$ (332.4 mg, 0.45 mmol) and K_2CO_3 (941.9 mg, 6.81 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (62/38, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-amine (150.0 mg, 44%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$=375.1.

Step 2: Synthesis of tert-butyl N-[3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl]carbamate:



[0295] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-amine (330.0 mg, 0.88 mmol) in DCM (5.0 mL) was added di-tert-butyl dicarbonate (768.3 mg, 3.52 mmol), TEA (267.1 mg, 2.64 mmol) and DMAP (21.5 mg, 0.17 mmol) at room temperature. The resulting mixture was stirred at room temperature for 5 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford tert-butyl N-[3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl]carbamate (460.0 mg, 72%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$=575.2.

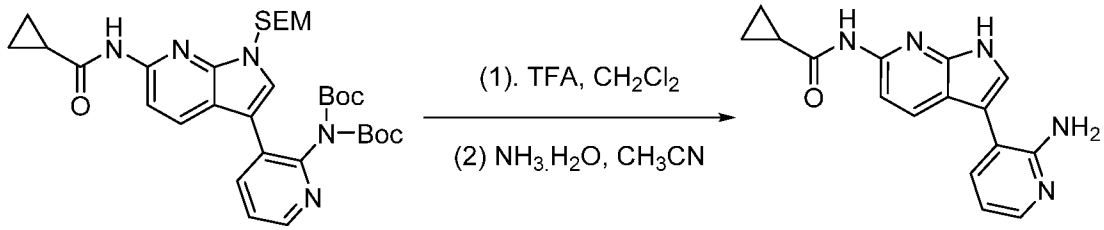
Step 3: Synthesis of tert-butyl N-(tert-butoxycarbonyl)-N-[3-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl]carbamate:



[0296] To a solution of tert-butyl N-(tert-butoxycarbonyl)-N-[3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl]carbamate (440.0 mg, 0.76 mmol) in dioxane (5.0 mL) was added cyclopropanecarboxamide (325.5 mg, 3.82 mmol), BrettPhos (164. mg, 0.30 mmol), BrettPhos Pd G_3 (138.6 mg, 0.15 mmol) and Cs_2CO_3 (747.7 mg, 2.29 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 5 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (76/24, v/v) to afford tert-butyl N-(tert-butoxycarbonyl)-N-[3-(6-

cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl]carbamate (360.0 mg, 75%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$=624.3.

Step 4: Synthesis of N-[3-(2-aminopyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 36):

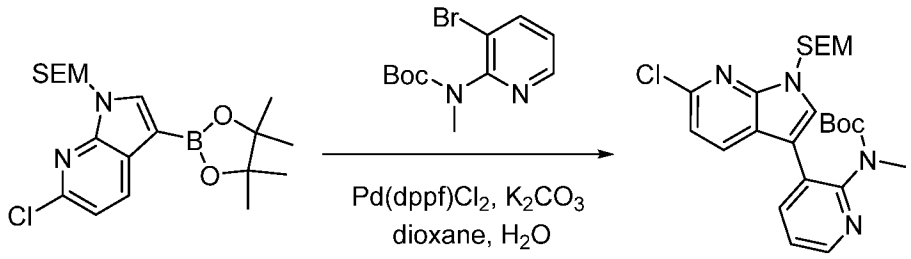


36

[0297] To a solution of tert-butyl N-(tert-butoxycarbonyl)-N-[3-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl]carbamate (310.0 mg, 0.49 mmol) in DCM (2.0 mL) was added TFA (2.0 mL). The mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in ACN (2.0 mL) and $NH_3.H_2O$ (2.0 mL). The mixture was stirred at room temperature for another 5 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30×250 mm, 5 um; 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; 254 nm) to afford N-[3-(2-aminopyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (48.4 mg, 33%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$=294.1. ^1H NMR (300 MHz, DMSO-d_6): δ 10.62 (s, 1H), 7.94 - 7.83 (m, 3H), 7.53 - 7.47 (m, 2H), 6.68 - 6.64 (m, 1H), 6.04 (s, 1H), 5.56 (s, 2H), 2.08 - 2.00 (m, 1H), 0.86 - 0.81 (m, 4H).

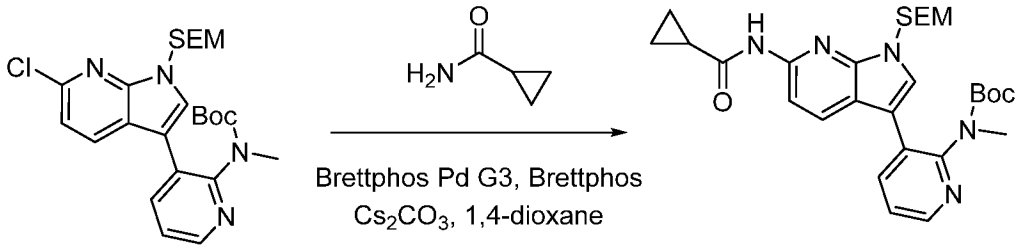
Example S37. Compound 37

Step 1: Synthesis of tert-butyl N-[3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl]-N-methylcarbamate:



[0298] To a solution of 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (220.0 mg, 0.53 mmol) in 1,4-dioxane/H_2O (4.0/0.4 mL) was added tert-butyl N-(3-bromopyridin-2-yl)-N-methylcarbamate (154.5 mg, 0.53 mmol), $Pd(dppf)Cl_2$ (78.7 mg, 0.10 mmol) and K_2CO_3 (223.1 mg, 1.61 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (70/30, v/v) to afford tert-butyl N-[3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl]-N-methylcarbamate (140.0 mg, 53%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =489.2

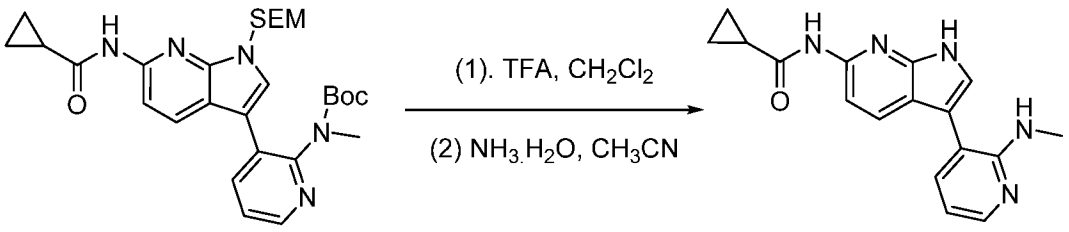
Step 2: Synthesis of tert-butyl N-[3-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl]-N-methylcarbamate:



[0299] To a solution of tert-butyl N-[3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl]-N-methylcarbamate (140.0 mg, 0.28 mmol) in dioxane (4.0 mL) was added cyclopropanecarboxamide (121.8 mg, 1.43 mmol), BrettPhos (61.5 mg, 0.11 mmol), BrettPhos Pd G_3 (51.9 mg, 0.11 mmol) and Cs_2CO_3 (279.8 mg, 0.56 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 5 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with

brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (70/30, v/v) to afford tert-butyl N-[3-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl]-N-methylcarbamate (120.0 mg, 77%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =538.3.

Step 3: Synthesis of N-[3-[2-(methylamino)pyridin-3-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 37):

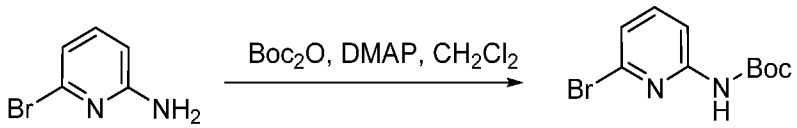


37

[0300] To a solution of tert-butyl N-[3-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl]-N-methylcarbamate (200.0 mg, 0.37 mmol) in DCM (2.0 mL) was added TFA (0.5 mL). The mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in $NH_3.H_2O$ (0.5 mL) and CH_3CN (2.0 mL). The mixture was stirred at room temperature for another 6 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (75/25, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 57% B in 7 min; 254 nm) to afford N-[3-[2-(methylamino)pyridin-3-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (10.7 mg, 98%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =308.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.65 (s, 1H), 10.59 (s, 1H), 8.02 - 8.00 (m, 1H), 7.90 - 7.84 (m, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.50 (s, 1H), 7.41 - 7.38 (m, 1H), 6.62 - 6.58 (m, 1H), 5.76 - 5.73 (m, 1H), 2.79 (d, J = 4.5 Hz, 3H), 2.05 - 1.99 (m, 1H), 0.92 - 0.75 (m, 4H).

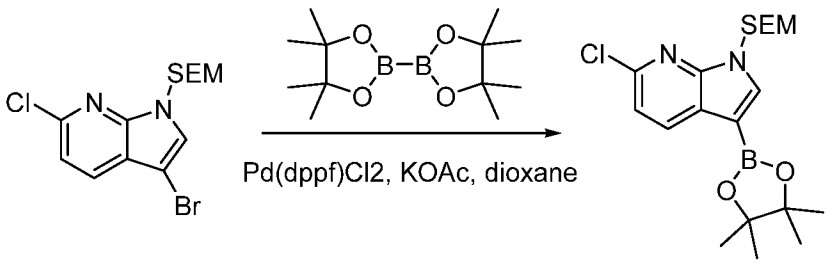
Example S38. Compound 38

Step 1: Synthesis of tert-butyl (6-bromopyridin-2-yl)carbamate:



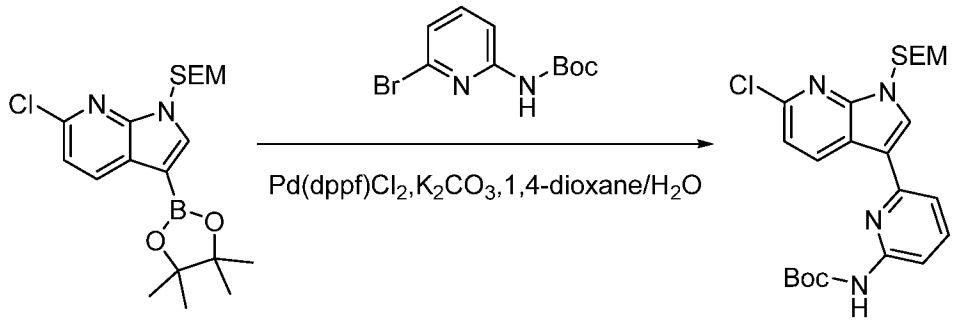
[0301] To a solution of 6-bromopyridin-2-amine (5.0 g, 28.90 mmol) in CH_2Cl_2 (100.0 mL) was added Boc_2O (6.3 g, 28.90 mmol) and DMAP (3.5 g, 28.90 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (88/12, v/v) to afford tert-butyl (6-bromopyridin-2-yl)carbamate (4.3 g, 54%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =273.0.

Step 2: Synthesis of 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine:



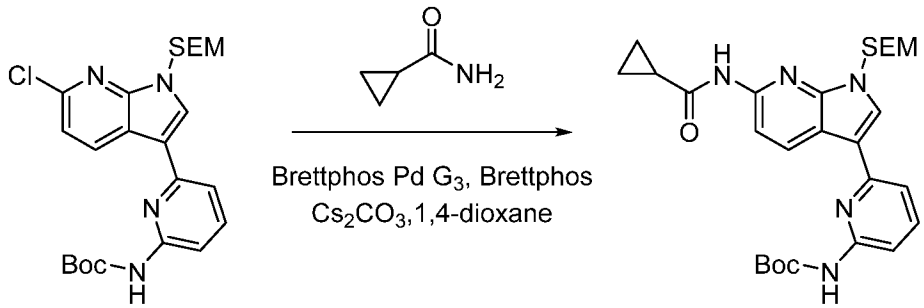
[0302] To a solution of 3-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (1.0 g, 1.55 mmol) in 1,4-dioxane (15.0 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.2 g, 4.65 mmol), KOAc (460.0 mg, 4.65 mmol) and $Pd(dppf)Cl_2$ (113.3 mg, 0.16 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (92/8, v/v) to afford 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (330.0 mg, 52%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =409.2.

Step 3: Synthesis of tert-butyl (6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl)carbamate:



[0303] To a solution of 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (300.0 mg, 0.73 mmol) in 1,4-dioxane/H_2O (10.0/2.0 mL) was added tert-butyl (6-bromopyridin-2-yl)carbamate (200.4 mg, 0.73 mmol), K_2CO_3 (304.3 mg, 2.20 mmol) and $Pd(dppf)Cl_2$ (53.7 mg, 0.07 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (92/8, v/v) to afford tert-butyl (6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl)carbamate (150.0 mg, 43%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =475.2.

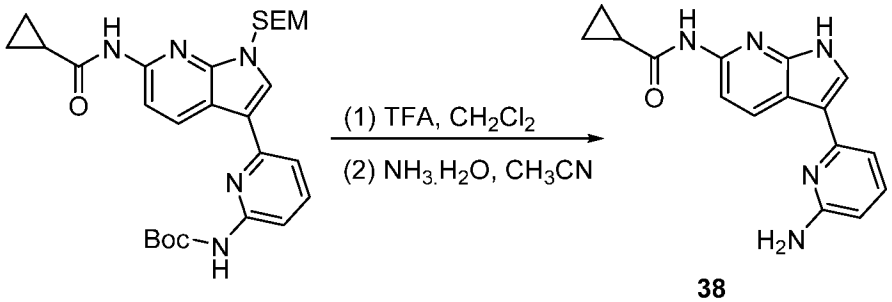
Step 4: Synthesis of tert-butyl (6-(6-(cyclopropanecarboxamido)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl)carbamate:



[0304] To a solution of tert-butyl (6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl)carbamate (130.0 mg, 0.27 mmol) in 1,4-dioxane (10.0 mL) was added cyclopropanecarboxamide (116.5 mg, 1.37 mmol), Cs_2CO_3 (267.5 mg, 0.82 mmol), BrettPhos (29.4 mg, 0.06 mmol) and BrettPhos Pd G3 (24.8 mg, 0.03 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl

acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (75/25, v/v) to afford tert-butyl (6-(6-(cyclopropanecarboxamido)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl)carbamate (140.0 mg, 97%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =524.3.

Step 5: Synthesis of N-(3-(6-aminopyridin-2-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (Compound 38):

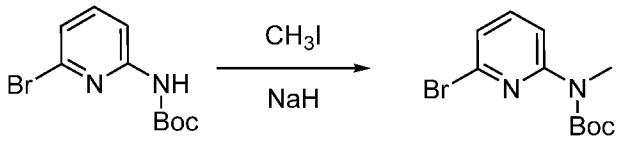


38

[0305] To a solution of tert-butyl (6-(6-(cyclopropanecarboxamido)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl)carbamate (120.0 mg, 0.23 mmol) in CH_2Cl_2 (6.0 mL) was added TFA (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in CH_3CN (6.0 mL) was added $NH_3.H_2O$ (6.0 mL). The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The solid was washed with CH_2Cl_2 and H_2O to afford N-(3-(6-aminopyridin-2-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (31.1 mg, 46%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =294.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.60 (s, 1H), 10.58 (s, 1H), 8.77 (d, J = 8.7 Hz, 1H), 7.95 - 7.91 (m, 2H), 7.39 - 7.34 (m, 1H), 6.99 (d, J = 7.5 Hz, 1H), 6.25 (d, J = 8.1 Hz, 1H), 5.86 (s, 2H), 2.08 - 2.00 (m, 1H), 0.83 - 0.79 (m, 4H).

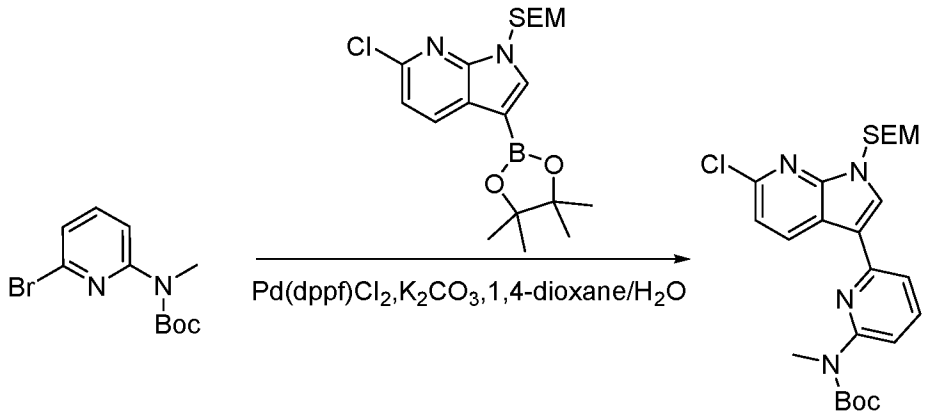
Example S39. Compound 39

Step 1: Synthesis of tert-butyl (6-bromopyridin-2-yl)(methyl)carbamate:



[0306] To a solution of tert-butyl (6-bromopyridin-2-yl)carbamate (1.0 g, 3.67 mmol) in DMF (30.0 mL) was added NaH (439.3 mg, 60%) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. Then CH_3I (2.6 g, 18.31 mmol) was added dropwise to the mixture at 0 °C. The resulting mixture was stirred at 0 °C for another 1 h. After the reaction was completed, the resulting mixture was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (91/9, v/v) to afford tert-butyl (6-bromopyridin-2-yl)(methyl)carbamate (1.0 g, 95%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =287.0.

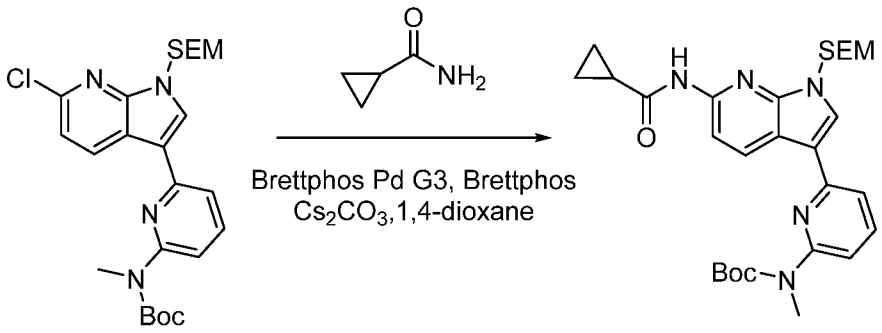
Step 2: Synthesis of tert-butyl (6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl)(methyl)carbamate:



[0307] To a solution of 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (440.0 mg, 1.07 mmol) in 1,4-dioxane/H_2O (10.0/2.0 mL) was added tert-butyl (6-bromopyridin-2-yl)(methyl)carbamate (309.0 mg, 1.07 mmol), K_2CO_3 (448.1 mg, 3.21 mmol) and $Pd(dppf)Cl_2$ (78.6 mg, 0.11 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (92/8, v/v)

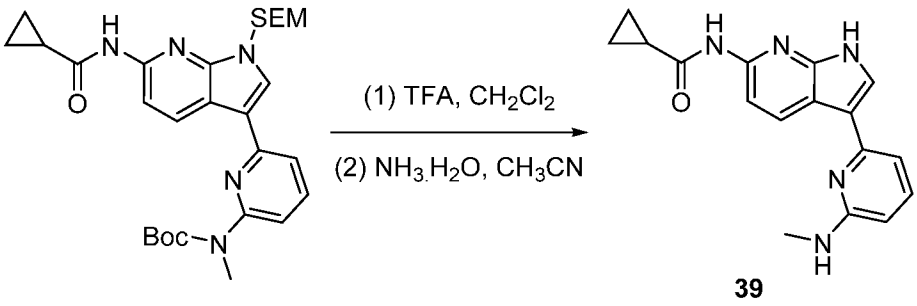
to afford tert-butyl (6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl)(methyl)carbamate (270.0 mg, 53%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =489.2.

Step 3: Synthesis of tert-butyl (6-(6-(cyclopropanecarboxamido)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl)(methyl)carbamate:



[0308] To a solution of tert-butyl (6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl)(methyl)carbamate (250.0 mg, 0.51 mmol) in 1,4-dioxane (10.0 mL) was added cyclopropanecarboxamide (217.5 mg, 2.56 mmol), Cs_2CO_3 (499.6 mg, 1.53 mmol), BrettPhos (54.9 mg, 0.10 mmol) and BrettPhos Pd G3 (46.3 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (75/25, v/v) to afford tert-butyl (6-(6-(cyclopropanecarboxamido)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl)(methyl)carbamate (240.0 mg, 87%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =538.3.

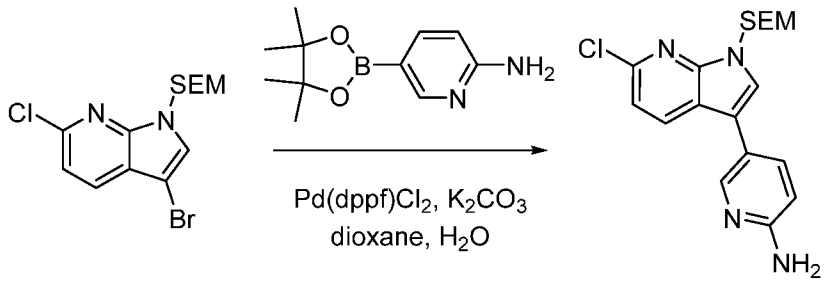
Step 4: Synthesis of N-(3-(6-(methylamino)pyridin-2-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (Compound 39):



[0309] To a solution of tert-butyl (6-(6-(cyclopropanecarboxamido)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-yl)(methyl)carbamate (200.0 mg, 0.37 mmol) in CH_2Cl_2 (6.0 mL) was added TFA (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in CH_3CN (6.0 mL) was added $NH_3.H_2O$ (6.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The solid was washed with CH_2Cl_2 and H_2O. The solid was collected and dried to afford N-(3-(6-(methylamino)pyridin-2-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (47.0 mg, 41%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =308.2. ^1H NMR (300 MHz, DMSO-d_6) δ 11.61 (s, 1H), 10.58 (s, 1H), 8.77 (d, J = 8.7 Hz, 1H), 7.94 - 7.92 (m, 2H), 7.40 - 7.35 (m, 1H), 6.99 (d, J = 7.2 Hz, 1H), 6.40 - 6.39 (m, 1H), 6.24 (d, J = 8.1 Hz, 1H), 2.89 (d, J = 4.2 Hz, 3H), 2.08 - 2.00 (m, 1H), 0.83 - 0.79 (m, 4H).

Example S40. Compound 40

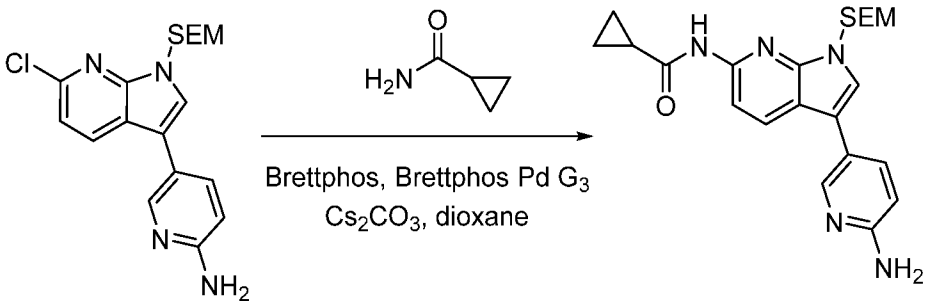
Step 1: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-amine:



[0310] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (1.0 g, 2.76 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (0.7

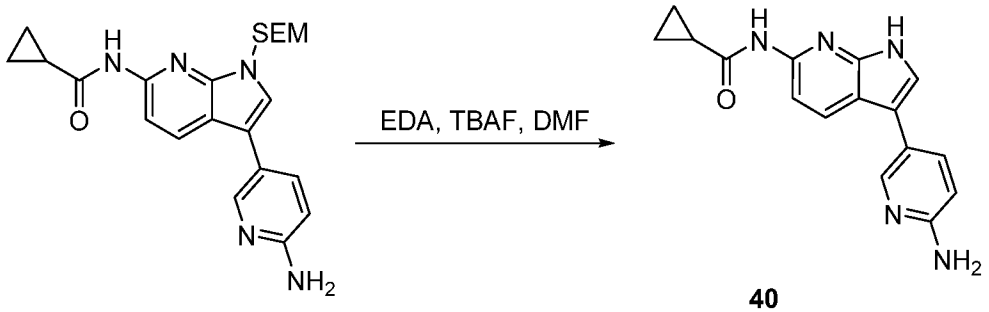
g, 3.31 mmol), K_2CO_3 (1.2 g, 8.29 mmol) and $Pd(dppf)Cl_2$ (0.5 g, 0.55 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (93/7, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-amine (300.0 mg, 29%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =375.1.

[0311] Step 2: Synthesis of N-[3-(6-aminopyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide:



[0312] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)pyridin-2-amine (300.0 mg, 0.85 mmol) in dioxane (3.0 mL) was added cyclopropanecarboxamide (363.2 mg, 4.27 mmol), BrettPhos (183.3 mg, 0.34 mmol), Cs_2CO_3 (834.2 mg, 2.56 mmol) and BrettPhos Pd G3 (154.7 mg, 0.17 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with petroleum ether/ethyl acetate (40/60, v/v) to afford N-[3-(6-aminopyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (38.0 mg, 10%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =424.2.

Step 3: Synthesis of N-[3-(6-aminopyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 40):

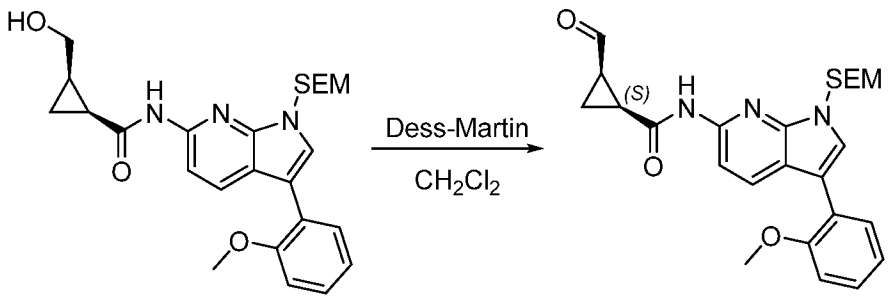


40

[0313] To a solution of N-[3-(6-aminopyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (38.0 mg, 0.09 mmol) in DMF (2.0 mL) was added ethylenediamine (2.0 mL) and TBAF (2.0 mL) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 49% B in 9 min; 254 nm to afford N-[3-(6-aminopyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (2.3 mg, 9%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =294.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.64 (s, 1H), 10.61 (s, 1H), 8.24 (s, 1H), 8.18 - 8.13 (m, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.67 (s, 1H), 7.09 - 6.68 (m, 3H), 2.07 - 1.99 (m, 1H), 0.82 - 0.78 (m, 4H).

Example S41. Compound 41

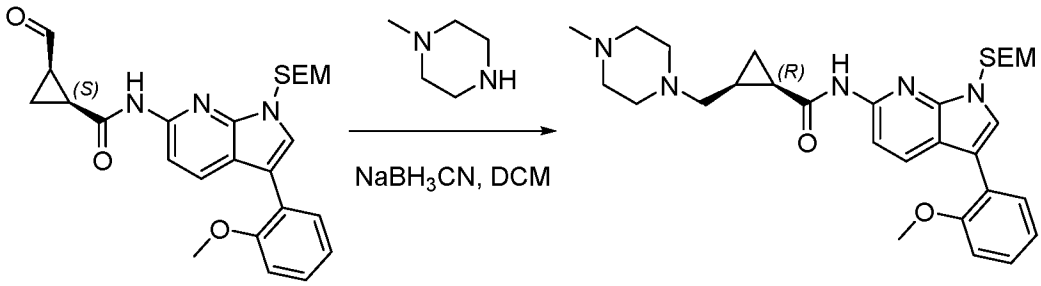
Step 1: Synthesis of cis-(1S,2R)-2-formyl-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0314] To a solution of cis-2-(hydroxymethyl)-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide

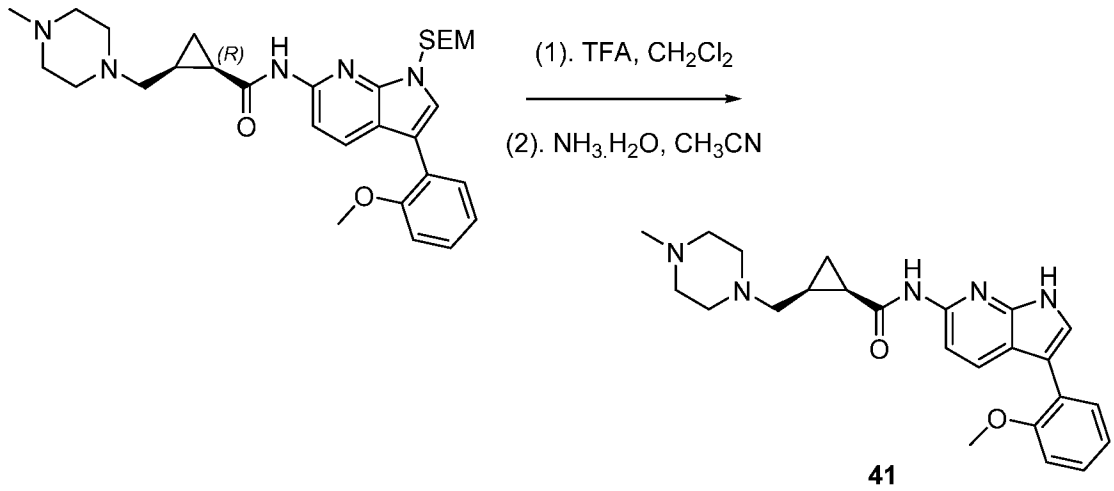
(290.0 mg, 0.62 mmol) in DCM (10.0 mL) was added Dess-Martin (394.5 mg, 0.93 mmol). The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford cis-2-formyl-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (280.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 466.2.

Step 2: Synthesis of cis-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide:



[0315] To a solution of cis-2-formyl-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (300.0 mg, crude) in CH_2Cl_2 (10.0 mL) was added 1-methylpiperazine (129.1 mg, 1.29 mmol) and $NaBH_3CN$ (81.0 mg, 1.29 mmol). The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography with CH_3OH/H_2O (60/40, v/v) to afford cis-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (280.0 mg, 79%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =550.3.

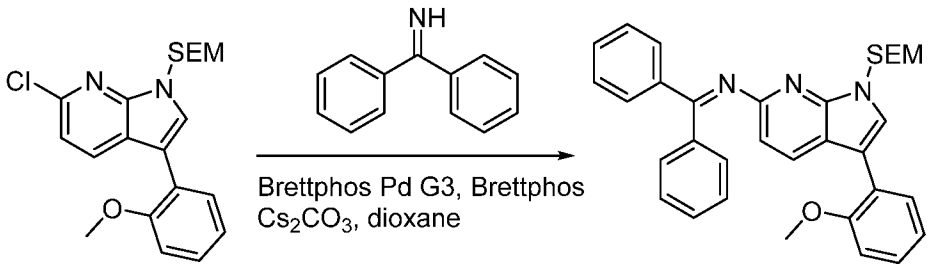
Step 3: Synthesis of cis-N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (Compound 41)



[0316] To a solution of cis-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (280.0 mg, 0.51 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL). The mixture was stirred at room temperature for 2 h. The mixture was concentrated under vacuum. The residue was dissolved in CH_3CN (3.0 mL) and $NH_3.H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient:17% B to 47% B in 10 min; 254 nm) to afford cis-N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (40.7 mg, 19%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 420.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.53 (s, 1H), 10.51 (s, 1H), 7.97 (d, J = 8.7 Hz, 1H), 7.88 (d, J =8.7 Hz, 1H), 7.56 - 7.52 (m, 2H), 7.30 - 7.25 (m, 1H), 7.11 (d, J =7.5 Hz, 1H), 7.05 - 7.00 (m, 1H), 3.82 (s, 3H), 2.60 - 2.52 (m, 1H), 2.49 - 2.40 (m, 5H), 2.28 - 2.20 (m, 4H), 2.15 - 2.09 (m, 4H), 1.35 - 1.30 (m, 1H), 1.02 - 0.98 (m, 1H), 0.90 - 0.87 (m, 1H).

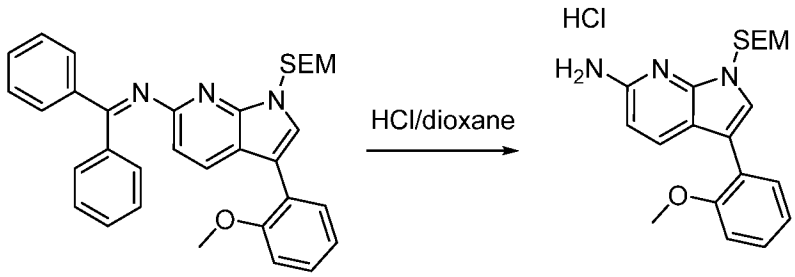
Example S42. Compound 42

Step 1: Synthesis of N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1,1-diphenylmethanimine:



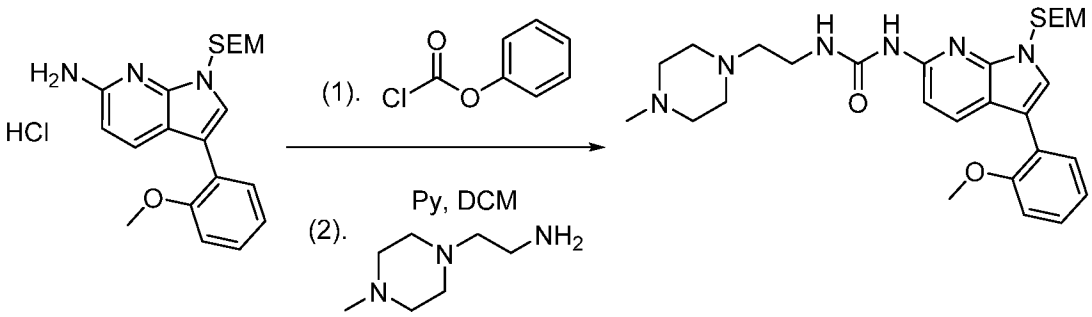
[0317] To a solution of 6-chloro-3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (1.9 g, 4.89 mmol) in 1,4-dioxane (20.0 mL) was added diphenylmethanimine (2.7 g, 14.65 mmol), Cs_2CO_3 (4.8 g, 14.65 mmol), BrettPhos (0.5 g, 0.98 mmol) and BrettPhos Pd G3 (0.4 g, 0.49 mmol). The resulting mixture was stirred at 100 °C for 2 h under N_2. After the reaction was completed, the mixture was concentrated under vacuum. The residue was purified by flash column chromatography with ether/ethyl acetate (20/80, v/v) to afford N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1,1-diphenylmethanimine (900.0 mg, 34%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ = 534.2.

Step 2: Synthesis of 3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine hydrochloride:



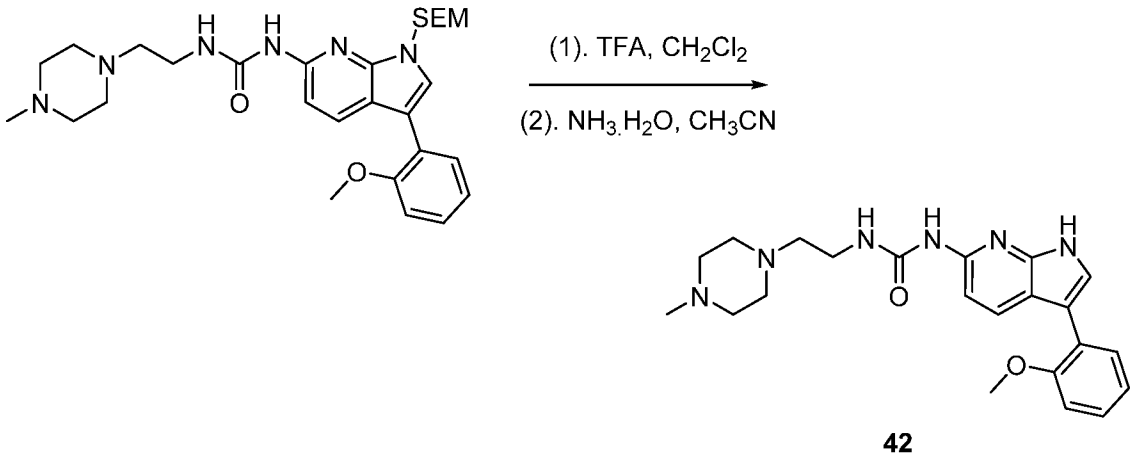
[0318] The solution of N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1,1-diphenylmethanimine (900.0 mg, 1.69 mmol) in HCl/1,4-dioxane (3.0 mL, 4 mol/L) was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was washed with Et_2O to afford 3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine hydrochloride (400.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =370.2.

Step 3: Synthesis of 3-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea:



[0319] To a solution of 3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine hydrochloride (282.6 mg, 3.57 mmol) in CH_2Cl_2 (3.0 mL) was added pyridine (282.6 mg, 3.57 mmol) and phenyl chloroformate (167.8 mg, 1.07 mmol) at 0 °C. The mixture was stirred at room temperature for 16 h. The mixture was concentrated under vacuum. Then pyridine (2.5 mL) and 2-(4-methylpiperazin-1-yl)ethanamine (255.8 mg, 1.79 mmol) were added to the residue. The resulting mixture was stirred at 60 °C for another 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (20/80, v/v) to afford 3-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (200.0 mg, 42%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =539.3.

Step 4: Synthesis of 3-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (Compound 42):



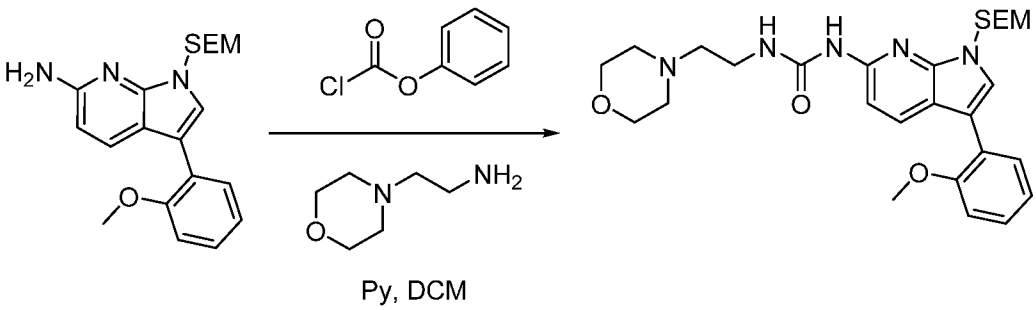
42

[0320] To a solution of 1-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(4-methylpiperazin-1-yl)ethyl)urea (180.0 mg, 0.33 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL). The mixture was stirred at room temperature

for 2 h. The mixture was concentrated under vacuum. Then ACN (2.0 mL) and $NH_3.H_2O$ (2.0 mL) were added to the residue. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 Column, 20×250 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 57% B in 10 min; 254 nm) to afford 3-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (18.8 mg, 14%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 409.2. ^1H NMR (300 MHz, $CDCl_3$): δ 10.07 (s, 1H), 9.73 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.55 - 7.52 (m, 1H), 7.45 - 7.42 (m, 2H), 7.35 - 7.28 (m, 1H), 7.10 - 7.04 (m, 2H), 6.48 (d, J = 8.4 Hz, 1H), 3.90 (s, 3H), 3.67 - 3.61 (m, 2H), 2.88 - 2.83 (m, 6H), 2.62 - 2.59 (m, 4H), 2.40 (s, 3H).

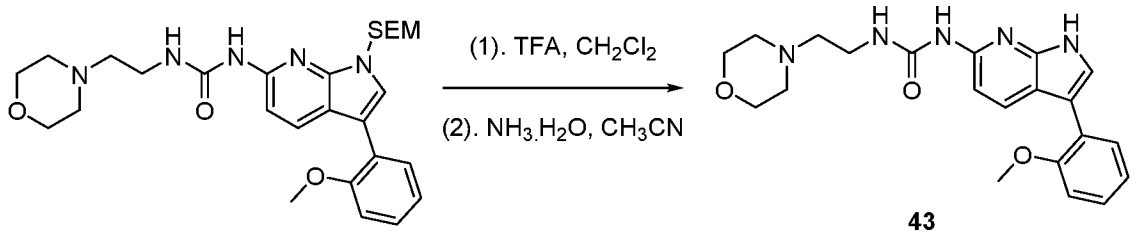
Example S43. Compound 43

Step 1: Synthesis of 1-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-morpholinoethyl)urea:



[0321] To a solution of 3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (250.0 mg, 0.68 mmol) in CH_2Cl_2 (5.0 mL) was added Pyridine (107.0 mg, 1.35 mmol) and phenyl chloroformate (127.1 mg, 0.81 mmol) at 0 °C. The mixture was stirred at room temperature for 16 h. The mixture was concentrated under vacuum. Then pyridine (2.5 mL) and 2-morpholinoethanamine (264.2 mg, 2.03 mmol) were added to the residue. The resulting mixture was stirred at 60 °C for another 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (20/80, v/v) to afford 1-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-morpholinoethyl)urea (200.0 mg, 42%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =526.3.

Step 2: Synthesis of 3-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(morpholin-4-yl)ethyl]urea (Compound 43):



43

[0322] To a solution of 3-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(morpholin-4-yl)ethyl]urea (120.0 mg, 0.23 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (1.0 mL). The mixture was stirred at room temperature for 2 h. The mixture was concentrated under vacuum. Then ACN (2.0 mL) and $NH_3.H_2O$ (2.0 mL) were added to the mixture. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column, 20×250 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 42% B in 10 min; 254 nm) to afford 3-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(morpholin-4-yl)ethyl]urea (31.5 mg, 35%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 396.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.40 (s, 1H), 9.19 (s, 1H), 8.37 (s, 1H), 7.91 (d, J = 8.7 Hz, 1H), 7.53 - 7.46 (m, 2H), 7.29 - 7.23 (m, 1H), 7.12 - 6.99 (m, 3H), 3.81 (s, 3H), 3.61 - 3.58 (m, 4H), 3.38 - 3.34 (m, 2H), 2.47 - 2.42 (m, 6H).

Example S44. Compound 44

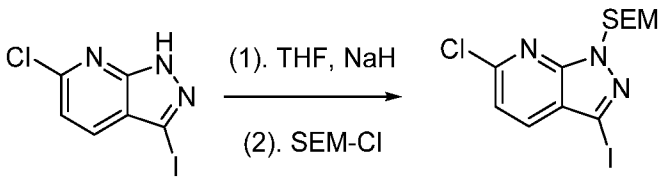
Step 1: Synthesis of 6-chloro-3-iodo-1H-pyrazolo[3,4-b]pyridine:



[0323] A mixture of 6-chloro-1H-pyrazolo[3,4-b]pyridine (1.0 g, 6.51 mmol) and NIS (2.3 g, 0.01 mmol) in DMF (20.0 mL) was stirred at 110 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and

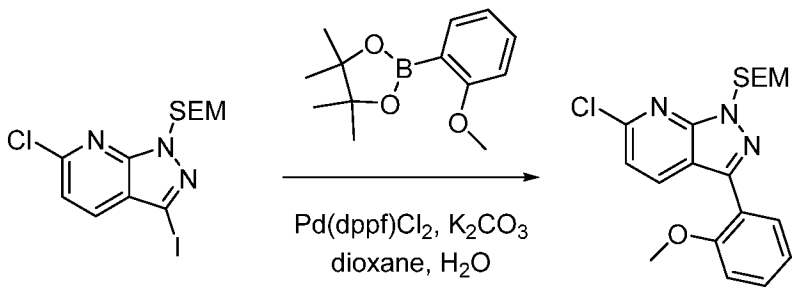
filtered. The filtrate was concentrated under vacuum to afford 6-chloro-3-iodo-1H-pyrazolo[3,4-b]pyridine (1.7 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =279.9.

Step 2: Synthesis of 6-chloro-3-iodo-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine:



[0324] To a solution of 6-chloro-3-iodo-1H-pyrazolo[3,4-b]pyridine (2.7 g, 9.63 mmol) in THF (20.0 mL) was added NaH (0.7 g, 60%) at 0 °C under N_2. The mixture was stirred at 0 °C for 1 h under N_2. Then SEM-Cl (2.4 g, 14.44 mmol) was added to the mixture. The mixture was stirred at room temperature for another 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (14/86, v/v) to afford 6-chloro-3-iodo-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (750.0 mg, 46%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =410.0.

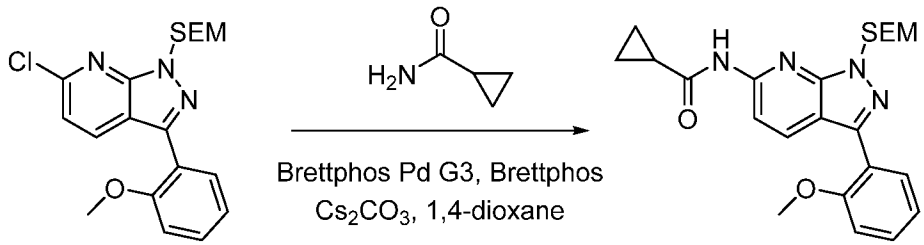
Step 3: Synthesis of 6-chloro-3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine:



[0325] A mixture of 6-chloro-3-iodo-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (700.0 mg, 1.71 mmol), 2-methoxyphenylboronic acid (259.6 mg, 1.71 mmol), K_2CO_3 (708.4 mg, 5.13 mmol) and $Pd(dppf)Cl_2$ (125.0 mg, 0.17 mmol) in dioxane (10.0 mL) and H_2O (2.0 mL) was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined

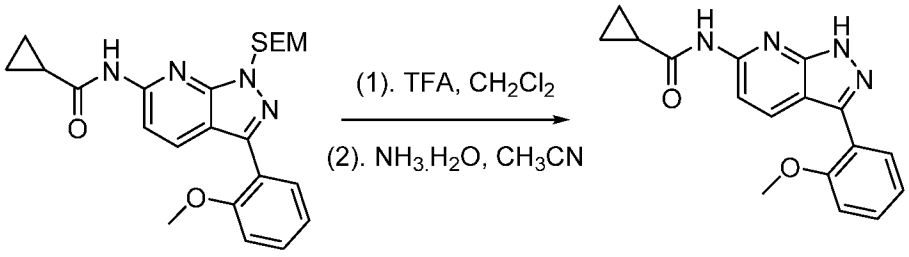
organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (87/13, v/v) to afford 6-chloro-3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (444.0 mg, 67%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 390.1.

Step 4: Synthesis of N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropanecarboxamide:



[0326] A mixture of 6-chloro-3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (440.0 mg, 1.13 mmol), cyclopropanecarboxamide (288.1 mg, 3.39 mmol), Cs_2CO_3 (1102.9 mg, 3.39 mmol), BrettPhos (121.1 mg, 0.23 mmol) and BrettPhos Pd G3 (102.3 mg, 0.11 mmol) in dioxane (20.0 mL) was stirred at 100 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (84/16, v/v) to afford N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropanecarboxamide (483.0 mg, 97%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 439.2.

Step 5: Synthesis of N-[3-(2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 44):

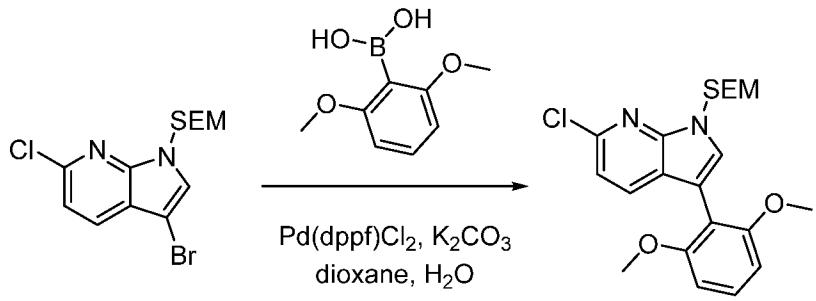


44

[0327] A mixture of N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropanecarboxamide (550.0 mg, 1.25 mmol) and TFA (5.0 mL, 43.85 mmol) in CH_2Cl_2 (2.0 mL) was stirred at room temperature for 2 h. The mixture was evaporated in vacuo. The residue was dissolved in $NH_3.H_2O$ (2.0 mL) and CH_3CN (5.0 mL). The mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (94/6, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 53% B in 10 min; 254 nm) to afford N-[3-(2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropanecarboxamide (56.8 mg, 15%) as a white solid. LCMS (ESI, m/z): $[M+H]^+ = 309.0$. ^1H NMR (300 MHz, DMSO-d_6): δ 13.42 (s, 1H), 10.89 (s, 1H), 8.08 (d, $J = 9.0$ Hz, 1H), 7.98 (d, $J = 9.0$ Hz, 1H), 7.63 - 7.60 (m, 1H), 7.46 - 7.40 (m, 1H), 7.18 (d, $J = 7.8$ Hz, 1H), 7.09 - 7.04 (m, 1H), 3.83 (s, 3H), 2.08 - 2.04 (m, 1H), 0.85 - 0.82 (m, 4H).

Example S45. Compound 45

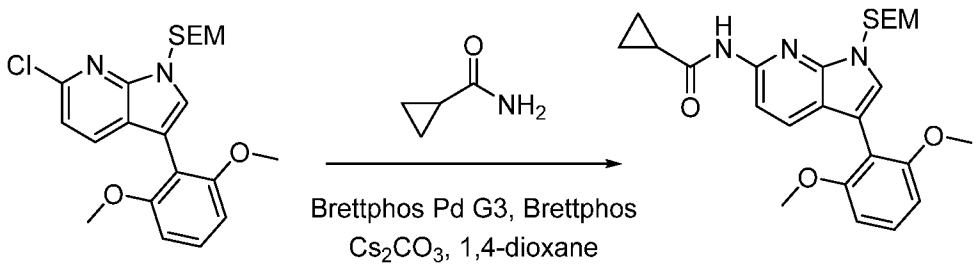
Step 1: Synthesis of 6-chloro-3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



[0328] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (600.0 mg, 1.66 mmol) in 1,4-dioxane/H_2O (10.0/2.0 mL) was added 2,6-dimethoxyphenylboronic acid (362.2 mg, 1.99 mmol), K_2CO_3 (458.5 mg, 3.32 mmol) and $Pd(dppf)Cl_2$ (121.4 mg, 0.17 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h under N_2. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl

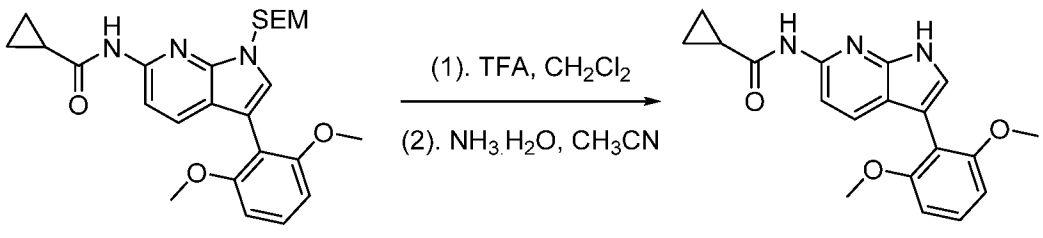
acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford 6-chloro-3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (93.0 mg, 13%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =419.1.

Step 2: Synthesis of N-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide:



[0329] To a solution of 6-chloro-3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (93.0 mg, 0.22 mmol) in 1,4-dioxane (4.0 mL) was added cyclopropanecarboxamide (94.5 mg, 1.11 mmol), Cs_2CO_3 (217.0 mg, 0.67 mmol), BrettPhos (23.8 mg, 0.04 mmol) and BrettPhos Pd G3 (20.1 mg, 0.02 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford N-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (100.0 mg, 96%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =468.2.

Step 3: Synthesis of N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 45)

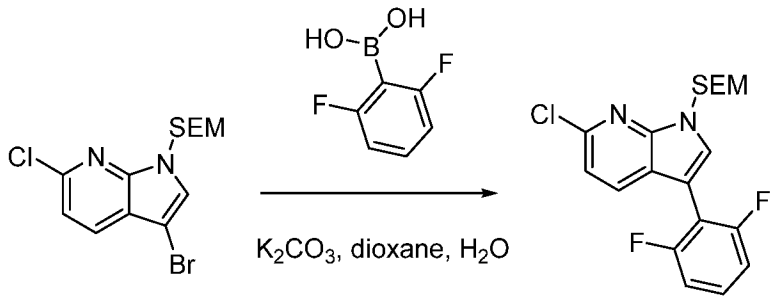


45

[0330] To a solution of N-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (260.0 mg, 0.56 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (3.0 mL) and $NH_3.H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 19x250 mm, 10 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B:MeOH----- Preparative; Flow rate: 25 mL/min; Gradient: 50% B to 65% B in 9 min; 254 nm) to afford N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (11.9 mg, 6%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =338.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.40 (s, 1H), 10.52 (s, 1H), 7.81 (d, J = 8.7 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.27 - 7.25 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 3.69 (s, 6H), 2.06 - 1.99 (m, 1H), 0.82 - 0.80 (m, 4H).

Example S46. Compound 46

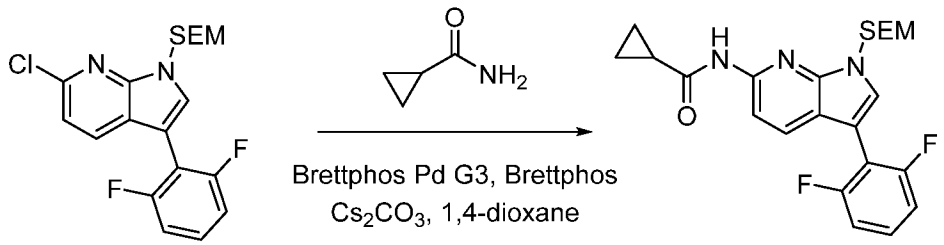
Step 1: Synthesis of 6-chloro-3-(2,6-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine:



[0331] To a solution of 3-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (1.0 g, 2.76 mmol) in 1,4-dioxane/H_2O (20.0/4.0 mL) was added (2,6-difluorophenyl)boronic acid (436.5 mg, 2.76 mmol), K_2CO_3 (1.1 g, 8.29 mmol) and Pd(dppf)Cl_2 (202.3 mg, 0.28 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum

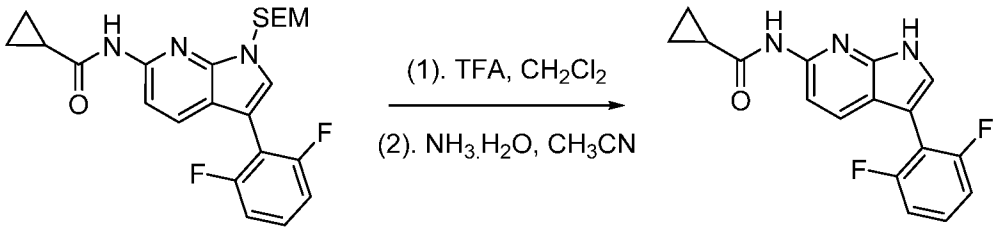
ether/ethyl acetate (88/12, v/v) to afford 6-chloro-3-(2,6-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (160.0 mg, 12%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =395.1.

Step 2: Synthesis of N-(3-(2,6-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide:



[0332] To a solution of 6-chloro-3-(2,6-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (250.0 mg, 0.63 mmol) in 1,4-dioxane (10.0 mL) was added cyclopropanecarboxamide (269.4 mg, 3.17 mmol), Cs_2CO_3 (618.8 mg, 1.90 mmol), BrettPhos (68.0 mg, 0.13 mmol) and BrettPhos Pd G3 (57.4 mg, 0.06 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (83/17, v/v) to afford N-(3-(2,6-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (50.0 mg, 18%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =444.2.

Step 3: Synthesis of N-(3-(2,6-difluorophenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (Compound 46):

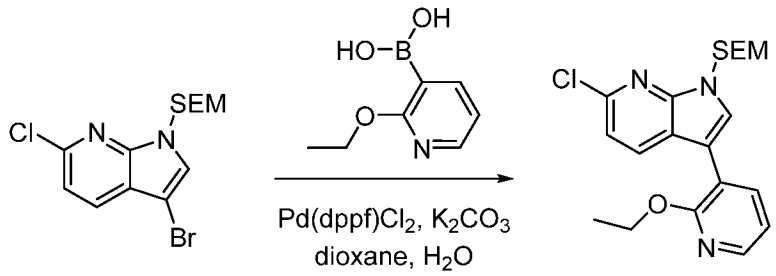


46

[0333] To a solution of N-(3-(2,6-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (50.0 mg, 0.11 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (2.0 mL) and $NH_3.H_2O$ (2.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge BEH C18 OBD Prep Column, 5 μm, 19 mm 250 mm ; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 47% B to 51% B in 12 min; 254 nm) to afford N-(3-(2,6-difluorophenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (11.2 mg, 32%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =314.1. ^1H NMR (400 MHz, DMSO-d_6): δ 11.86 (s, 1H), 10.61 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 1.2 Hz, 1H), 7.46 - 7.34 (m, 1H), 7.22 - 7.18 (m, 2H), 2.10 - 1.98 (m, 1H), 0.82 - 0.76 (m, 4H).

Example S47. Compound 47

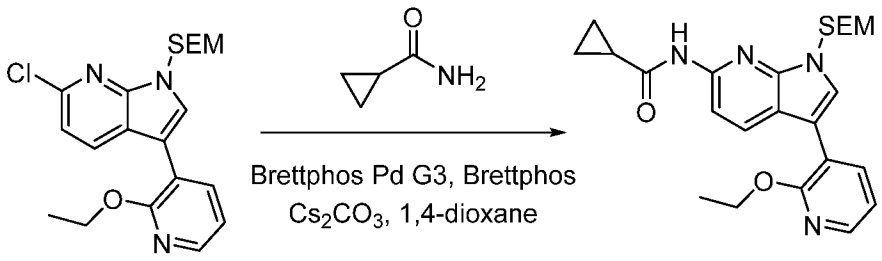
Step 1: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-ethoxypyridine :



[0334] To a mixture of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 0.82 mmol) and 2-ethoxypyridin-3-ylboronic acid (207.7 mg, 1.24 mmol) in dioxane/H_2O (5.0/0.5 mL) was added Pd(dppf)Cl_2 (60.6 mg, 0.08 mmol) and K_2CO_3 (343.8 mg, 2.48 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by

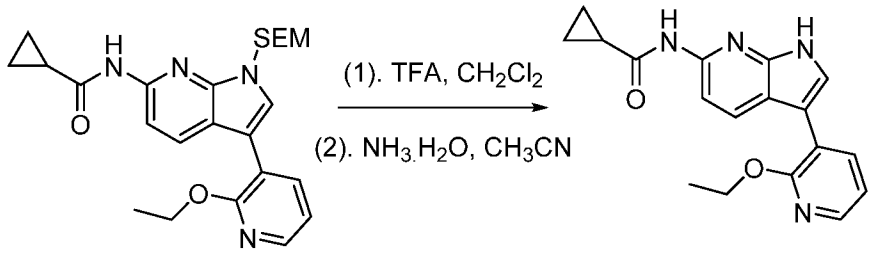
flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-ethoxypyridine (230.0 mg, 69%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =404.1.

Step 2: Synthesis of N-(3-(2-ethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide.



[0335] To a mixture of 6-chloro-3-(2-ethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (260.0 mg, 0.62 mmol) and cyclopropanecarboxamide (211.2 mg, 2.48 mmol) in dioxane (4.0 mL) was added Brettphos Pd G3 (56.2 mg, 0.06 mmol), BrettPhos (66.6 mg, 0.12 mmol) and Cs_2CO_3 (606.5 mg, 1.82 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford N-(3-(2-ethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (260.0 mg, 89%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =453.2

Step 3: Synthesis of N-[3-(2-ethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 47):

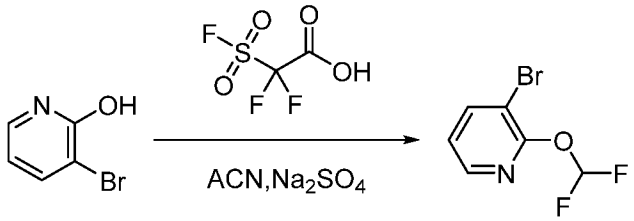


47

[0336] To a solution of N-[3-(2-ethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b] pyridin-6-yl]cyclopropanecarboxamide (270.0 mg, 0.59 mmol) in DCM (4.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the above mixture was added $NH_3 \cdot H_2O$ (4.0 mL) and ACN (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30x250 mm, 5 um; Mobile Phase A:Water (10 mmol NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 62% B in 10 min; 254 nm) to afford N-[3-(2-ethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (46.7 mg, 24%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =323.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.68 (s, 1H), 10.62 (s, 1H), 8.13 (d, J = 9.0 Hz, 1H), 8.07 - 8.04 (m, 1H), 8.01 - 7.92 (m, 2H), 7.74 (d, J = 2.7 Hz, 1H), 7.08 - 7.04 (m, 1H), 4.45 - 4.38 (m, 2H), 2.07 - 2.03 (m, 1H), 1.38 - 1.33 (m, 3H), 0.84 - 0.79 (m, 4H).

Example S48. Compound 48

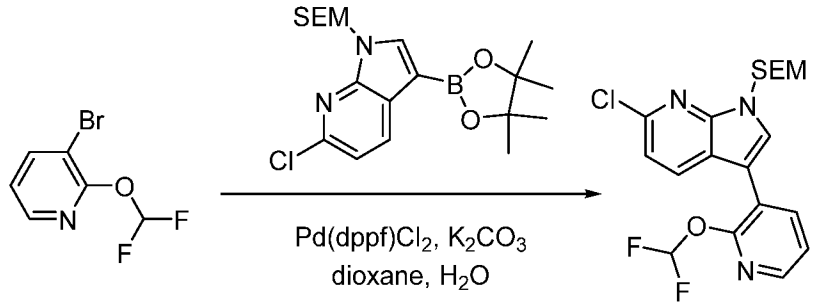
Step 1: Synthesis of 3-bromo-2-(difluoromethoxy)pyridine:



[0337] To a solution of 3-bromopyridin-2-ol (5.0 g, 28.73 mmol) in ACN (10.0 mL) was added 2,2-difluoro-2-(fluorosulfonyl)acetic acid (6.1 g, 34.48 mmol) and Na_2SO_4 (4.9 g, 34.48 mmol) at room temperature under N_2. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum

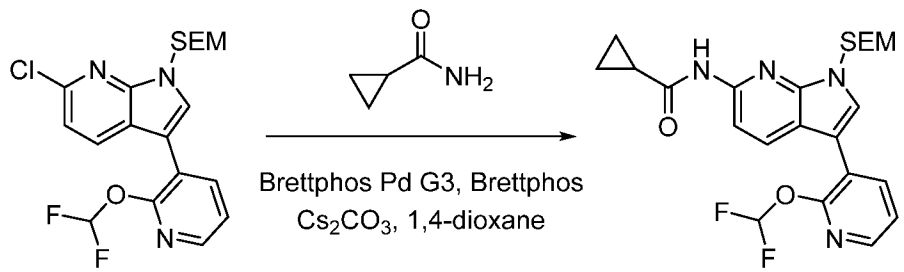
ether/ethyl acetate (94/6, v/v) to afford 3-bromo-2-(difluoromethoxy)pyridine (3.2 g, 50%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =223.9.

Step 2: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-(difluoromethoxy)pyridine:



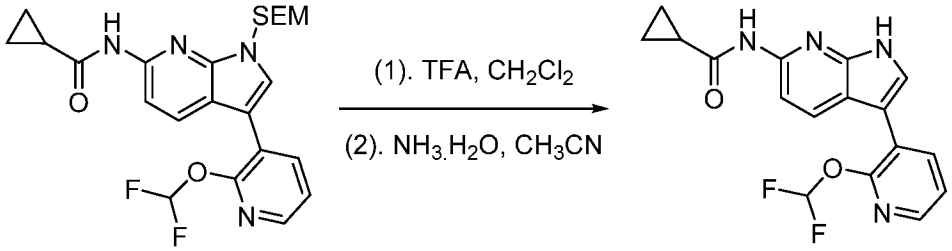
[0338] To a solution of 3-bromo-2-(difluoromethoxy)pyridine (200.0 mg, 0.89 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (574.5 mg, 1.34 mmol), K_2CO_3 (370.2 mg, 2.68 mmol) and $Pd(dppf)Cl_2$ (145.8 mg, 0.18 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (83/17, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-(difluoromethoxy)pyridine (200.0 mg, 52%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =426.1.

Step 3: Synthesis of N-[3-[2-(difluoromethoxy)pyridin-3-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide:



[0339] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-(difluoromethoxy)pyridine (200.0 mg, 0.47 mmol) in dioxane (3.0 mL) was added cyclopropanecarboxamide (119.9 mg, 1.41 mmol), BrettPhos (50.4 mg, 0.09 mmol), Cs_2CO_3 (459.0 mg, 1.41 mmol) and BrettPhos Pd G3 (42.6 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (88/12, v/v) to afford N-[3-[2-(difluoromethoxy)pyridin-3-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (200.0 mg, 89%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =475.2.

Step 4: Synthesis of N-[3-[2-(difluoromethoxy)pyridin-3-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 48):



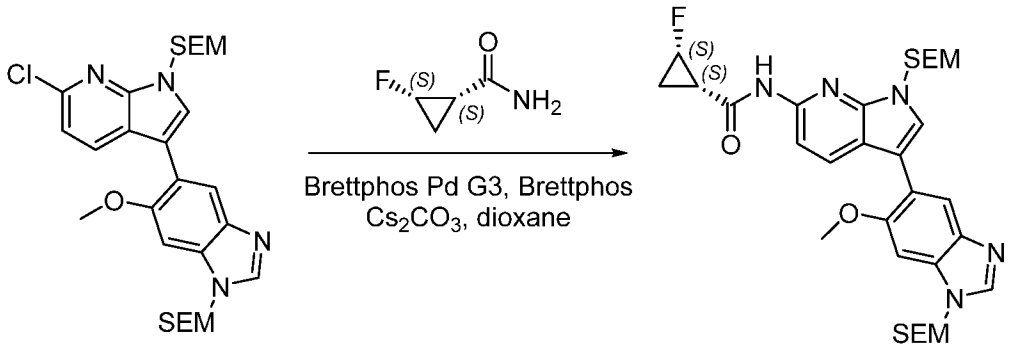
48

[0340] To a solution of N-[3-[2-(difluoromethoxy)pyridin-3-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (190.0 mg, 0.40 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (2.0 mL) and $NH_3 \cdot H_2O$ (2.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30x250 mm, 5 um; 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 10 min; 254 nm) to afford N-[3-[2-(difluoromethoxy)pyridin-3-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (45.2 mg, 28%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$

=345.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.83 (s, 1H), 10.64 (s, 1H), 8.16 (d, J = 6.0 Hz, 2H), 8.10 (d, J = 8.8 Hz, 1H), 7.99 - 7.63 (m, 3H), 7.37 - 7.34 (m, 1H), 2.09 - 1.99 (m, 1H), 0.83 - 0.79 (m, 4H).

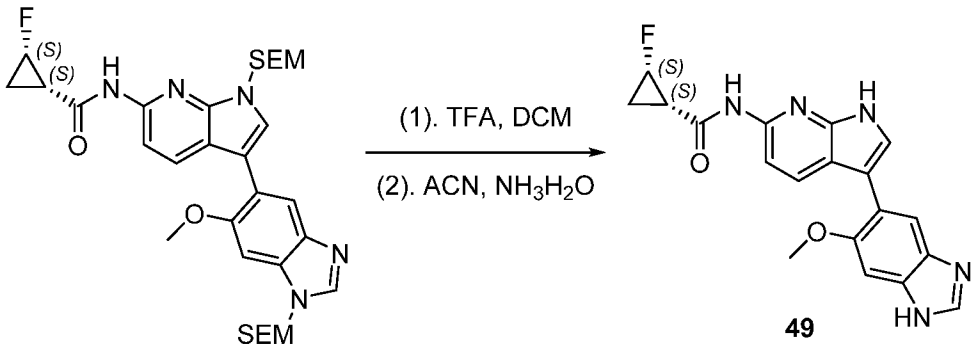
Example S49. Compound 49

Step 1: Synthesis of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0341] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (200.0 mg, 0.18 mmol) in 1,4-dioxane (8.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (92.2 mg, 0.89 mmol), BrettPhos (19.2 mg, 0.04 mmol), Cs_2CO_3 (174.8 mg, 0.54 mmol) and BrettPhos Pd G3 (16.2 mg, 0.02 mmol) at room temperature under N_2. The resulting mixture was stirred with microwave at 100 °C for 2 h under N_2. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/9, v/v) to afford (1S,2S)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (50.0 mg, 45%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =626.3.

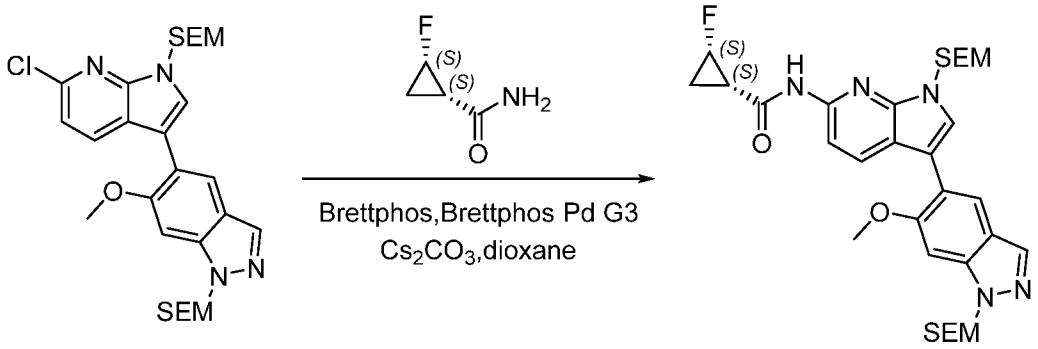
Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1H-1,3-benzodiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide: (Compound 49)



[0342] To a solution of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (215.0 mg, 0.34 mmol) in DCM (6.0 mL) was added TFA (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (2.0 mL) and $NH_3.H_2O$ (2.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 53% B to 43% B in 7 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(6-methoxy-1H-1,3-benzodiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (6.9 mg, 6%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =366.1. ^1H NMR (300 MHz, DMSO-d_6): δ 12.35 - 12.26 (br, 1H), 11.50 (s, 1H), 10.61 (s, 1H), 8.16 (s, 1H), 7.96 - 7.87 (m, 2H), 7.64 (s, 1H), 7.52 (d, J = 2.1 Hz, 1H), 7.24 (s, 1H), 5.06 - 4.78 (m, 1H), 3.82 (s, 3H), 2.27 - 2.21 (m, 1H), 1.71 - 1.61 (m, 1H), 1.19 - 1.15 (m, 1H).

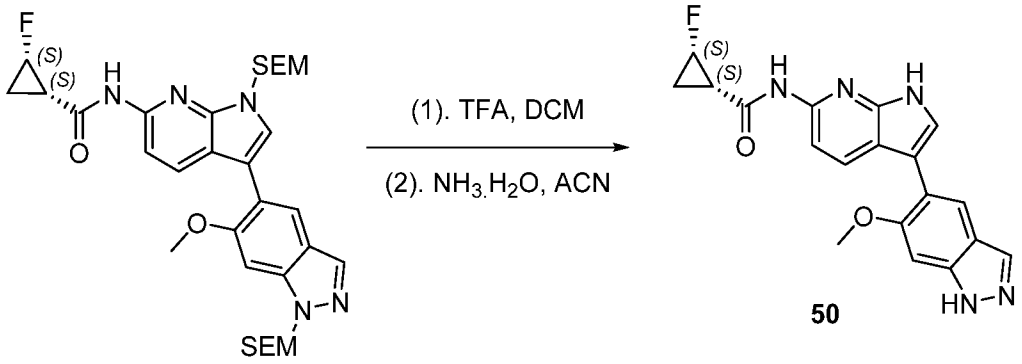
Example S50. Compound 50

Step 1: Synthesis of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0343] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole (300.0 mg, 0.54 mmol) in 1,4-dioxane (12.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (276.5 mg, 2.68 mmol), BrettPhos (57.6 mg, 0.11 mmol), Cs_2CO_3 (524.3 mg, 1.61 mmol) and BrettPhos Pd G3 (48.6 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred with microwave at 120 °C for 1.5 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1S,2S)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (100.0 mg, 30%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =626.3.

Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 50):

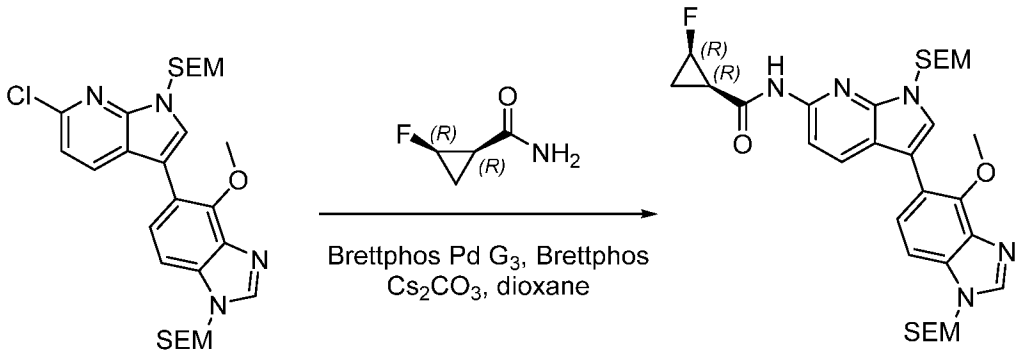


[0344] To a solution of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (100.0 mg, 0.16 mmol) in DCM (4.0 mL) was

added TFA (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (2.0 mL) and $NH_3.H_2O$ (2.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 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 56% B in 7 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(6-methoxy-1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (12.3 mg, 21%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =366.2. ^1H NMR (300 MHz, DMSO-d_6): δ 12.82 (s, 1H), 11.50 (s, 1H), 10.61 (s, 1H), 7.98 - 7.80 (m, 4H), 7.52 (d, J = 2.7 Hz, 1H), 7.06 (s, 1H), 5.17 - 4.73 (m, 1H), 3.87 (s, 3H), 2.32 - 2.18 (m, 1H), 1.78 - 1.52 (m, 1H), 1.29 - 1.01 (m, 1H).

Example S51. Compound 51

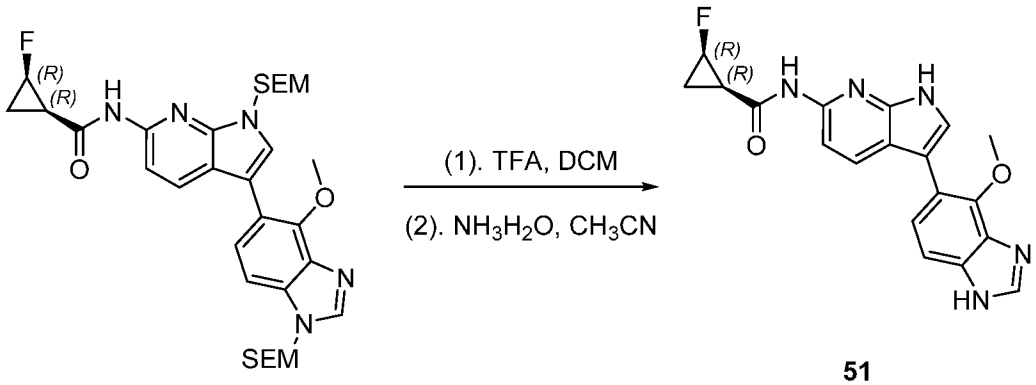
Step 1: Synthesis of (1R,2R)-2-fluoro-N-[3-(4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0345] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (200.0 mg, 0.36 mmol) in 1,4-dioxane (6.0 mL) was added (1R,2R)-2-fluorocyclopropane-1-carboxamide (184.4 mg, 1.79 mmol), BrettPhos (38.4 mg, 0.07 mmol), Cs_2CO_3 (349.6 mg, 1.07 mmol) and BrettPhos Pd G3 (32.4 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was irradiated with microwave radiation at 120 °C for 1.5 h. After the

reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with ether/ethyl acetate (2/1, v/v) to afford (1R,2R)-2-fluoro-N-[3-(4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (92.0 mg, 41%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =626.3.

Step 2: Synthesis of (1R,2R)-2-fluoro-N-[3-(4-methoxy-1H-1,3-benzodiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 51):



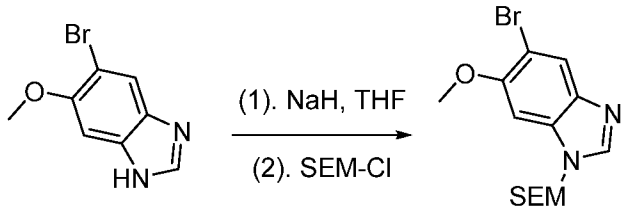
51

[0346] To a solution of (1R,2R)-2-fluoro-N-[3-(4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (40.0 mg, 0.06 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (3.0 mL) and $NH_3.H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 20x250 mm, 5 um, 12 nm; 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; 254 nm) to afford (1R,2R)-2-fluoro-N-[3-(4-methoxy-1H-1,3-benzodiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (5.2 mg, 22%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =366.2. ^1H NMR (300 MHz, DMSO-d_6): δ 12.60 (s, 1H), 11.60 (s, 1H), 10.74 (s, 1H), 8.28 (s, 1H), 8.12 - 7.98 (m, 2H), 7.58 (s, 1H), 7.45 (d, J = 8.4 Hz,

1H), 7.35 (d, J = 8.1 Hz, 1H), 5.15 - 4.91 (m, 1H), 4.32 (s, 2H), 3.75 (s, 1H), 2.38 - 2.31 (m, 1H), 1.81 - 1.71 (m, 1H), 1.34 - 1.20 (m, 1H).

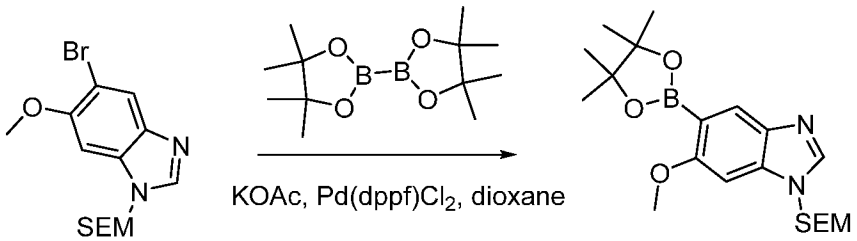
Example S52. Compound 52

Step 1: Synthesis of 5-bromo-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole:



[0347] To a solution of 5-bromo-6-methoxy-1H-1,3-benzodiazole (1.0 g, 4.40 mmol) in THF (20.0 mL) was added NaH (0.2 g, 60%) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. Then SEM-Cl (0.9 g, 5.28 mmol) was added to the mixture. The resulting mixture was stirred at 0 °C for another 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/EtOAc (1/1, v/v) to afford 5-bromo-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (1.5 g, 95%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =357.1.

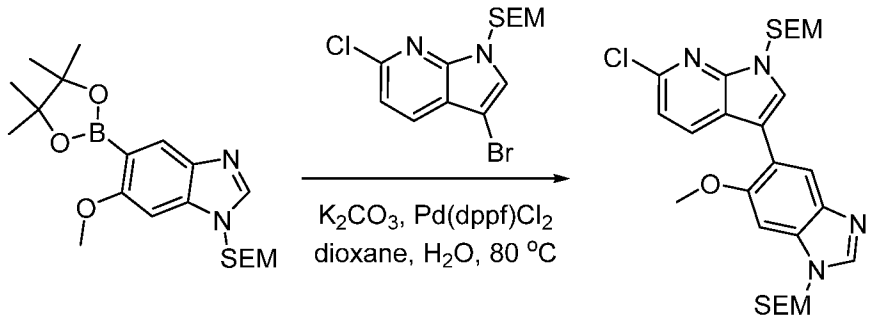
Step 2: Synthesis of 6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole:



[0348] To a solution of 5-bromo-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (750.0 mg, 2.10 mmol) in 1,4-dioxane (20.0 mL) was added bis(pinacolato)diboron (639.6 mg, 2.52 mmol), KOAc (618.0 mg, 6.30 mmol) and $Pd(dppf)Cl_2$ (153.6 mg, 0.21 mmol) at room temperature under N_2. The resulting mixture was

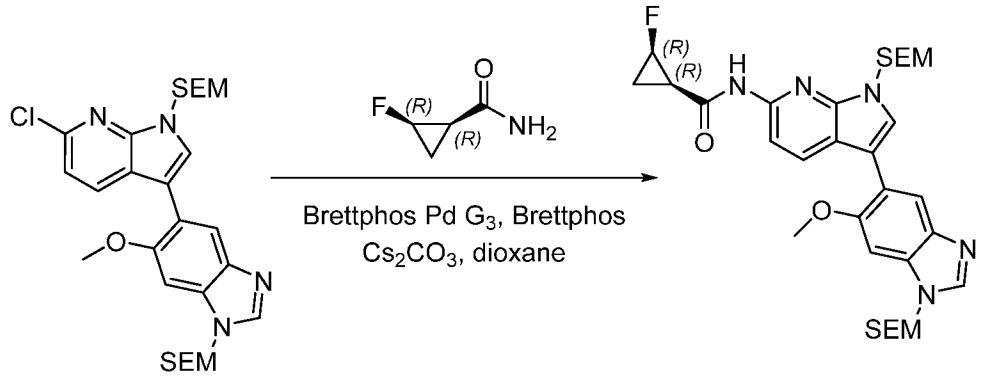
stirred at 80 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (6/1, v/v) to afford 6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (420.0 mg, 49%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =405.2.

Step 3: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole:



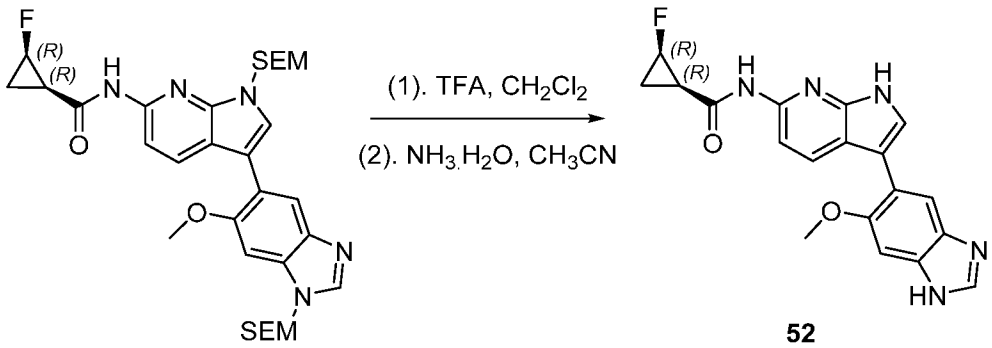
[0349] To a solution of 6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (870.0 mg, 2.15 mmol) in 1,4-dioxane/H_2O (15.0/3.0 mL) was added 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (778.2 mg, 2.15 mmol), K_2CO_3 (892.0 mg, 6.45 mmol) and Pd(dppf)Cl_2 (314.8 mg, 0.43 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (590.0 mg, 49%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =559.2.

Step 4: Synthesis of (1R,2R)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0350] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (540.0 mg, 0.97 mmol) in 1,4-dioxane (10.0 mL) was added (1R,2R)-2-fluorocyclopropane-1-carboxamide (497.7 mg, 4.83 mmol), Cs_2CO_3 (943.8 mg, 2.90 mmol), BrettPhos (103.7 mg, 0.19 mmol) and BrettPhos Pd G3 (87.5 mg, 0.10 mmol) at room temperature under N_2. The reaction mixture was irradiated with microwave radiation at 100 °C for 2 h. After the reaction was completed, the mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1R,2R)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (180.0 mg, 29%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =626.3.

Step 5: Synthesis of (1R,2R)-2-fluoro-N-[3-(6-methoxy-1H-1,3-benzodiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 52):



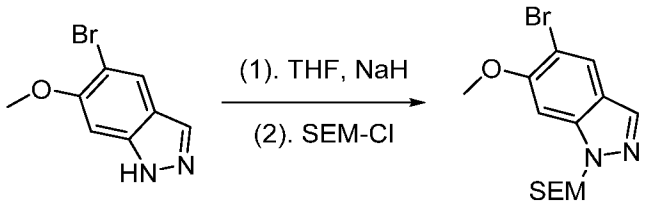
52

[0351] To a solution of (1R,2R)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide

(180.0 mg, 0.29 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (3.0 mL) and $NH_3.H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, 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, 5 um; 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; 254 nm) to afford (1R,2R)-2-fluoro-N-[3-(6-methoxy-1H-1,3-benzodiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (20.1 mg, 19%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =366.1. ^1H NMR (300 MHz, DMSO-d_6): δ 12.25 (s, 1H), 11.50 (s, 1H), 10.62 (s, 1H), 8.11 (s, 1H), 7.97 - 7.88 (m, 2H), 7.72 - 7.57 (m, 1H), 7.53 (s, 1H), 7.41 - 7.10 (m, 1H), 5.03 - 4.81 (m, 1H), 3.83 (s, 3H), 2.29 - 2.18 (m, 1H), 1.71 - 1.60 (m, 1H), 1.19 - 1.12 (m, 1H).

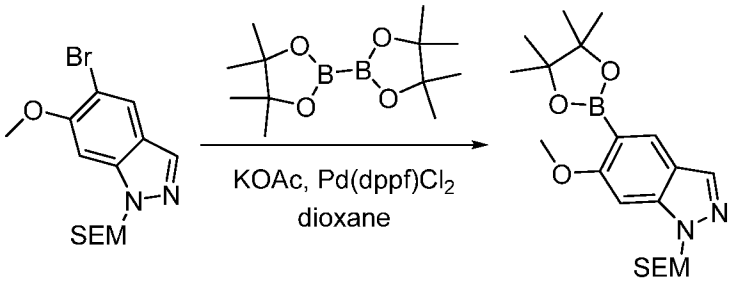
Example S53. Compound 53

Step 1: Synthesis of 5-bromo-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole:



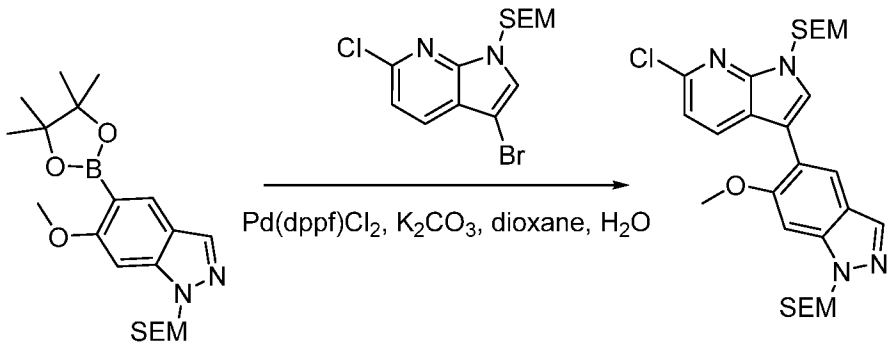
[0352] To a solution of 5-bromo-6-methoxy-1H-indazole (3.0 g, 6.60 mmol) in THF (45.0 mL) was added NaH (475.6 mg, 60%) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. Then SEM-Cl (4.4 g, 26.43 mmol) was added dropwise to the mixture at 0 °C under N_2. The resulting mixture was stirred at 0 °C for another 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/2, v/v) to afford 5-bromo-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole (3.0 g, 64%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =357.1.

Step 2: Synthesis of 6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole:



[0353] To a solution of 5-bromo-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole (2.5 g, 6.99 mmol) in dioxane (40.0 mL) was added bis(pinacolato)diboron (2.6 g, 10.54 mmol), KOAc (2.0 g, 20.99 mmol) and $Pd(dppf)Cl_2$ (511.9 mg, 0.70 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole (1.1 g, 39%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =405.2.

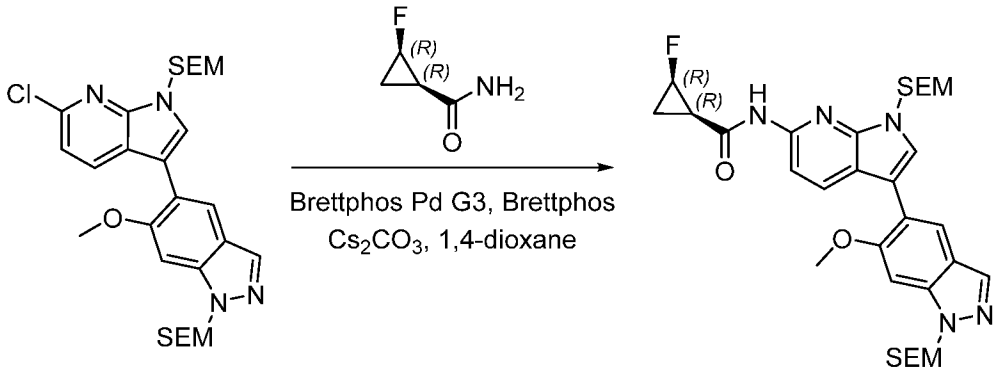
Step 3: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole:



[0354] To a solution of 6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole (1.0 g, 2.47 mmol) in dioxane/H_2O (10.0/1.0 mL) was added $Pd(dppf)Cl_2$ (180.9 mg, 0.27 mmol), 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (894.5 mg, 2.47 mmol) and K_2CO_3 (1025.9 mg, 7.49 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O

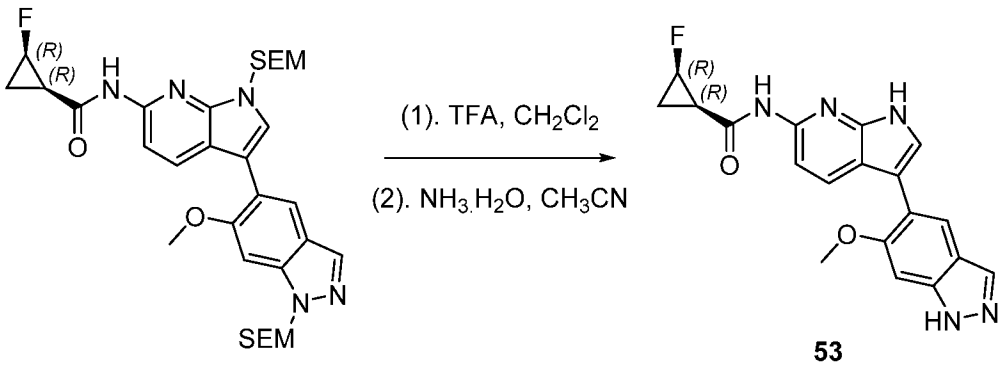
and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole (500.0 mg, 48%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =559.2.

Step 4: Synthesis of (1R,2R)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0355] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole (250.0 mg, 0.47 mmol) in dioxane (10.0 mL) was added Cs_2CO_3 (436.9 mg, 1.31 mmol), (1R,2R)-2-fluorocyclopropane-1-carboxamide (138.6 mg, 1.34 mmol), Brettphos Pd G3 (81.0 mg, 0.09 mmol) and BrettPhos (23.9 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1R,2R)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (100.0 mg, 36%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =626.3.

Step 5: Synthesis of (1R,2R)-2-fluoro-N-[3-(6-methoxy-1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 53):

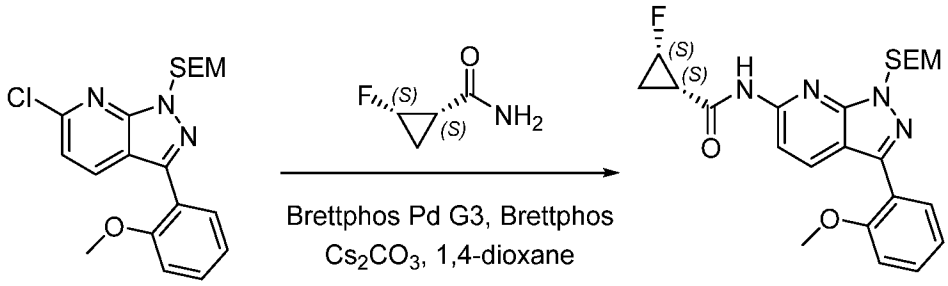


53

[0356] To a solution of (1R,2R)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (100.0 mg, 0.16 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (5.0 mL) and $NH_3.H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 9% B to 26% B in 8 min; 254 nm) to afford (1R,2R)-2-fluoro-N-[3-(6-methoxy-1H-indazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (4.5 mg, 8%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =366.1. ^1H NMR (400 MHz, DMSO-d_6): δ 12.82 (s, 1H), 11.49 (s, 1H), 10.60 (s, 1H), 7.97 - 7.94 (m, 2H), 7.91 - 7.85 (m, 1H), 7.80 (s, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.06 (s, 1H), 5.01 - 4.83 (m, 1H), 3.86 (s, 3H), 2.29 - 2.18 (m, 1H), 1.69 - 1.62 (m, 1H) , 1.18 - 1.15 (m, 1H).

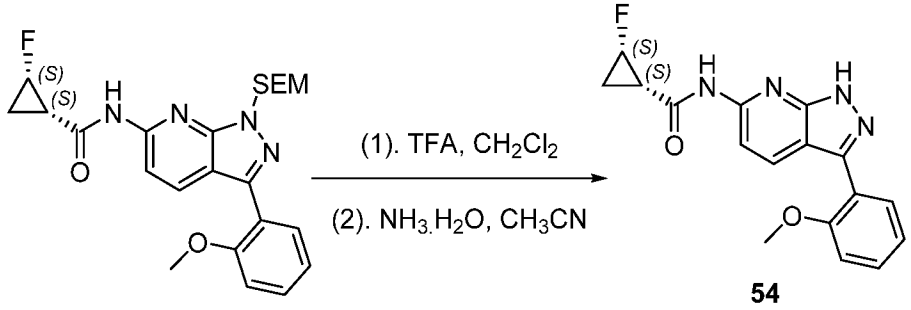
Example S54. Compound 54

Step 1: Synthesis of (1S,2S)-2-fluoro-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0357] A solution of 6-chloro-3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (300.0 mg, 0.77 mmol), (1S,2S)-2-fluorocyclopropane-1-carboxamide (396.6 mg, 3.85 mmol,), Cs_2CO_3 (752.0 mg, 2.31 mmol), BrettPhos (82.6 mg, 0.15 mmol) and BrettPhos Pd G3 (69.7 mg, 0.08 mmol) in dioxane (10.0 mL) was irradiated with microwave radiation at 120 °C for 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (94/6, v/v) to afford (1S,2S)-2-fluoro-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (250.0 mg, 71%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 457.2.

Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-(2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 54):

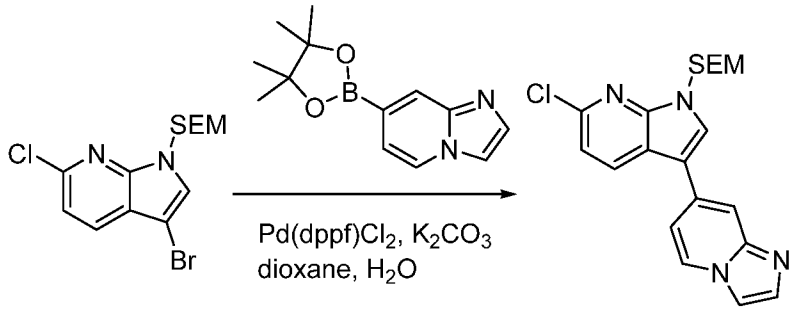


[0358] A mixture of (1S,2S)-2-fluoro-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (250.0 mg, 0.55 mmol) and TFA (5.0 mL) in CH_2Cl_2 (5.0 mL) was stirred at room temperature for 3 h. The resulting mixture was concentrated under vacuum. The residue was dissolved in $NH_3.H_2O$ (5.0 mL) and ACN (5.0 mL). The mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was

diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with Water/ACN (54/46, v/v) and then purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 20×250 mm, 5 um, 12 nm; 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 10 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (82.4 mg, 46%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 327.2 ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.45 (s, 1H), 10.94 (s, 1H), 8.11 (d, J = 9.0 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.64 - 7.60 (m, 1H), 7.47 - 7.41 (m, 1H), 7.19 (d, J = 7.8 Hz, 1H), 7.09 - 7.04 (m, 1H), 5.07 - 4.83 (m, 1H), 3.83 (s, 3H), 2.29 - 2.24 (m, 1H), 1.72 - 1.63 (m, 1H), 1.23 - 1.11 (m, 1H).

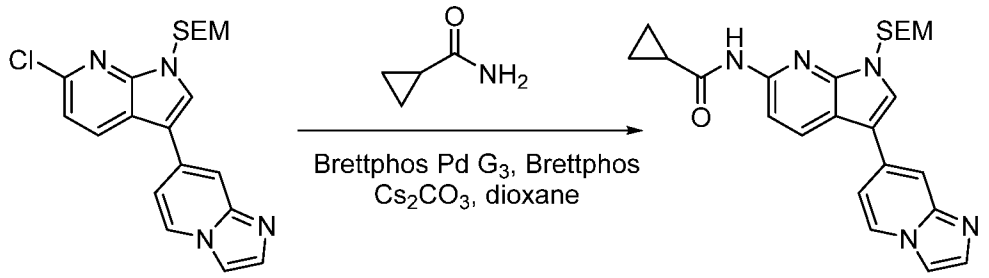
Example S55. Compound 55

Step 1: Synthesis of 6-chloro-3-[imidazo[1,2-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



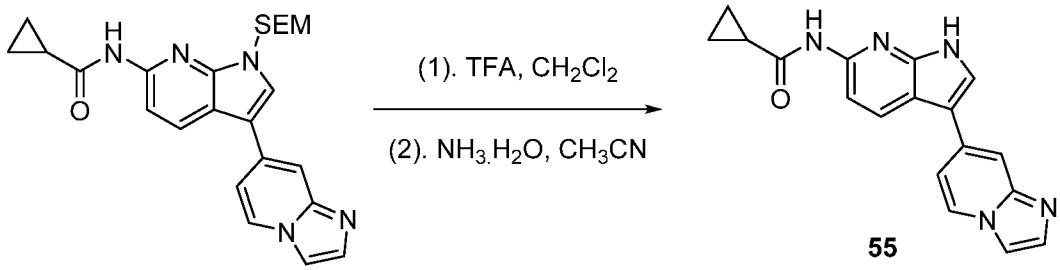
[0359] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (500.0 mg, 1.38 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyridine (337.4 mg, 1.38 mmol), K_2CO_3 (573.1 mg, 4.15 mmol) and $Pd(dppf)Cl_2$ (101.1 mg, 0.07 mmol). The resulting mixture was stirred at 80 °C for 3 h under N_2. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (80/20, v/v) to afford 6-chloro-3-[imidazo[1,2-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (470.0 mg, 85%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 399.1.

Step 2: Synthesis of N-(3-[imidazo[1,2-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide:



[0360] To a solution of 6-chloro-3-[imidazo[1,2-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (440.0 mg, 1.10 mmol) in 1,4-dioxane (10.0 mL) was added cyclopropanecarboxamide (469.3 mg, 5.51 mmol), BrettPhos (118.4 mg, 0.22 mmol), Cs_2CO_3 (1.1 g, 3.31 mmol) and BrettPhos Pd G3 (100.0 mg, 0.11 mmol). The resulting mixture was stirred at 100 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (95/5, v/v) to afford N-(3-[imidazo[1,2-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (450.0 mg, 91%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 448.2.

Step 3: Synthesis of N-(3-[imidazo[1,2-a]pyridin-7-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (Compound 55):

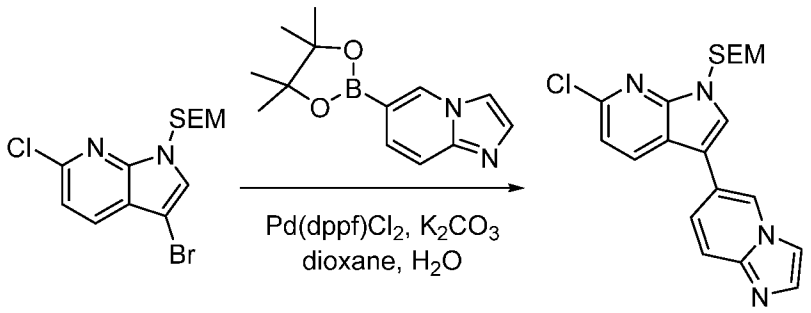


[0361] To a solution of N-(3-[imidazo[1,2-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (400.0 mg, 0.89 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL). The mixture was stirred at room temperature for 1 h. The mixture was concentrated under vacuum. The residue was dissolved in ACN (3.0 mL) and $NH_3.H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for additional 16 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following

conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 47% B in 10 min; 254 nm) to afford N-(3-[imidazo[1,2-a]pyridin-7-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (16.4 mg, 5%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =318.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.83 (s, 1H), 10.66 (s, 1H), 8.55 (d, J = 7.2 Hz, 1H), 8.40 (d, J = 8.8 Hz, 1H), 8.00 - 7.99 (m, 2H), 7.89 (s, 1H), 7.82 (s, 1H), 7.53 (s, 1H), 7.35 - 7.33 (m, 1H), 2.08 - 2.03 (m, 1H), 0.86 - 0.81 (m, 4H).

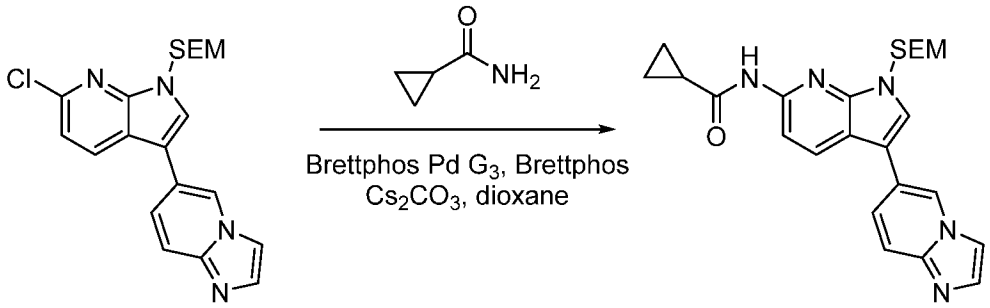
Example S56. Compound 56

Step 1: Synthesis of 6-chloro-3-[imidazo[1,2-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



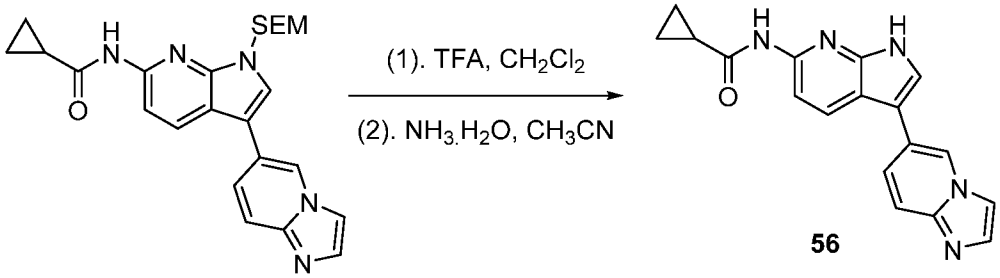
[0362] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (500.0 mg, 1.38 mmol) in dioxane/H_2O (15.0 / 3.0 mL) was added 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyridine (337.4 mg, 1.38 mmol), K_2CO_3 (573.9 mg, 4.17 mmol) and $Pd(dppf)Cl_2$ (101.4 mg, 0.18 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (95/5, v/v) to afford 6-chloro-3-[imidazo[1,2-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (200.0 mg, 82%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =399.1.

Step 2: Synthesis of N-(3-[imidazo[1,2-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide:



[0363] To a solution of 6-chloro-3-[imidazo[1,2-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (430.0 mg, 1.08 mmol) in dioxane (10.0 mL) was added cyclopropanecarboxamide (275.8 mg, 3.23 mmol), BrettPhos (115.7 mg, 0.26 mmol), Brettphos Pd G3 (97.7 mg, 0.32 mmol) and Cs_2CO_3 (1053.8 mg, 3.23 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford N-(3-[imidazo[1,2-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (450.0 mg, 93%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =448.2.

Step 3: Synthesis of N-(3-(imidazo[1,2-a]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (Compound 56):

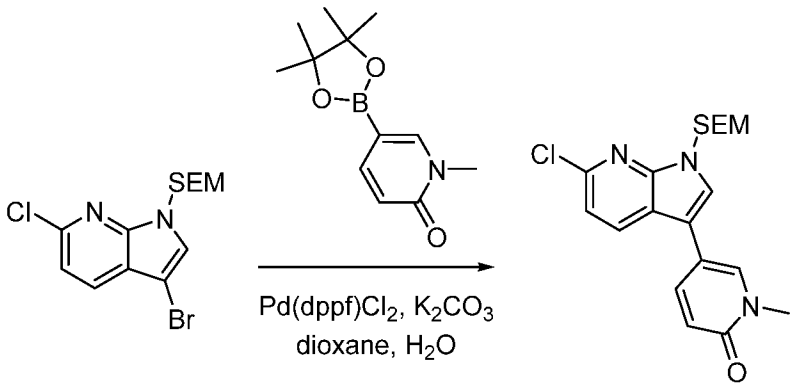


[0364] To a solution of N-(3-[imidazo[1,2-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (400.0 mg, 0.89 mmol) in CH_2Cl_2 (10.0 mL) was added TFA (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (10.0 mL) and $NH_3.H_2O$ (10.0 mL) at room temperature. The resulting mixture was stirred at room

temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; 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 8 min; 254 nm) to afford N-(3-(imidazo[1,2-a]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (21.7 mg, 7%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =318.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.72 (s, 1H), 10.65 (s, 1H), 8.94 (s, 1H), 8.37 (d, J = 8.7 Hz, 1H), 7.99 - 7.97 (m, 2H), 7.84 (d, J = 2.7 Hz, 1H), 7.64 - 7.55 (m, 3H), 2.06 - 1.99 (m, 1H), 0.84 - 0.79 (m, 4H).

Example S57. Compound 57

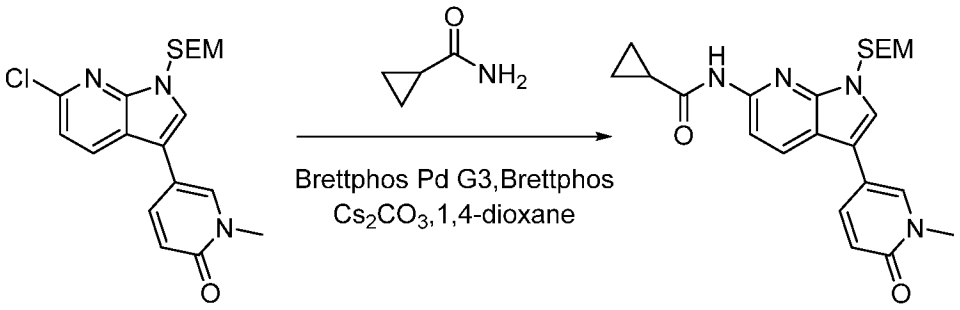
Step 1: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-1-methylpyridin-2-one:



[0365] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (500.0 mg, 1.38 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one (121.3 mg, 0.99 mmol), K_2CO_3 (389.9 mg, 1.65 mmol) and $Pd(dppf)Cl_2$ (121.8 mg, 0.14 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (98/2, v/v) to afford 5-(6-chloro-1-[[2-

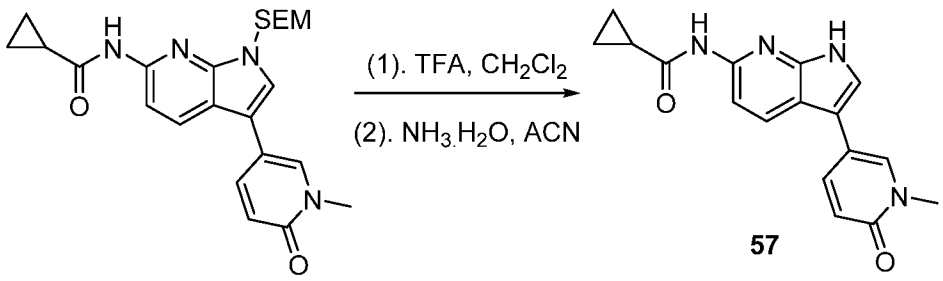
(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-1-methylpyridin-2-one (360.0 mg, 67%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =390.1.

Step 2: Synthesis of N-[3-(1-methyl-6-oxopyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide:



[0366] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-1-methylpyridin-2-one (310.0 mg, 0.79 mmol) in dioxane (4.0 mL) was added cyclopropanecarboxamide (338.3 mg, 3.97 mmol), BrettPhos (85.3 mg, 0.16 mmol), Cs_2CO_3 (777.0 mg, 2.38 mmol) and BrettPhos Pd G3 (72.0 mg, 0.08 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (69/31, v/v) to afford N-[3-(1-methyl-6-oxopyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (340.0 mg, 97%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =439.2.

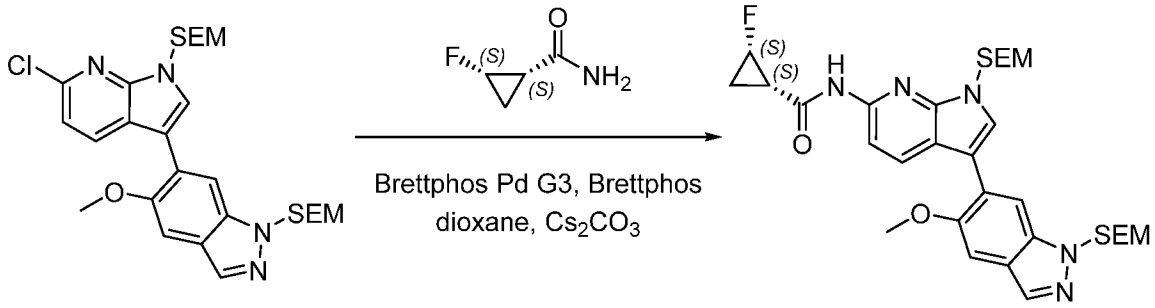
Step 3: Synthesis of N-[3-(1-methyl-6-oxopyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 57):



[0367] To a solution of N-[3-(1-methyl-6-oxopyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (300.0 mg, 0.68 mmol) in DCM (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in ACN (2.0 mL) and $NH_3 \cdot H_2O$ (2.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 19% B to 49% B in 7 min; 254 nm) to afford N-[3-(1-methyl-6-oxopyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (71.6 mg, 34%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =309.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.53 (s, 1H), 10.58 (s, 1H), 8.20 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 2.4 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.82 - 7.80 (m, 1H), 7.59 (d, J = 2.0 Hz, 1H), 6.46 (d, J = 9.6 Hz, 1H), 3.51 (s, 3H), 2.05 - 1.98 (m, 1H), 0.83 - 0.77 (m, 4H).

Example S58. Compound 58

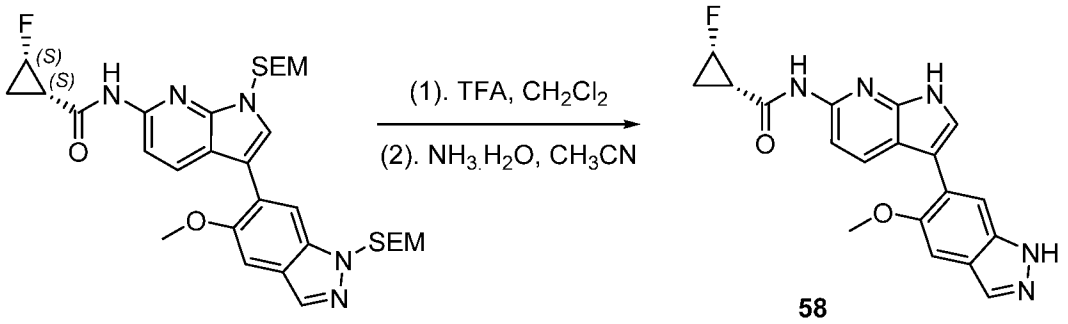
Step 1: Synthesis of (1S,2S)-2-fluoro-N-[3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0368] To a solution of 6-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole (450.0 mg, 0.81 mmol) in 1,4-dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (414.8 mg, 4.02 mmol), BrettPhos (86.4 mg, 0.16 mmol), Cs_2CO_3 (786.5 mg, 2.41 mmol) and BrettPhos Pd G3 (72.9 mg, 0.08 mmol) at room temperature under N_2. The resulting mixture was irradiated with microwave radiation at 120 °C for 1.5 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined

organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford (1S,2S)-2-fluoro-N-[3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (70.0 mg, 14%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =626.3.

Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-(5-methoxy-1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 58):

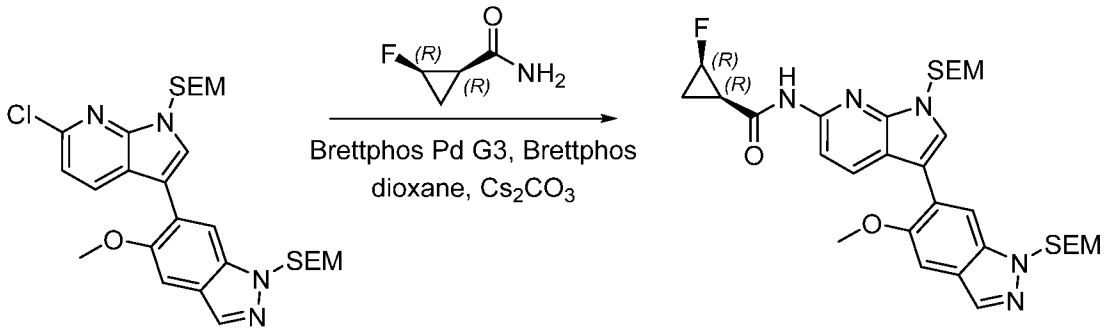


58

[0369] To a solution of (1S,2S)-2-fluoro-N-[3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (70.0 mg, 0.11 mmol) in DCM (4.0 mL) was added TFA (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (2.0 mL) and $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions Column: (YMC-Actus Triart C18, 20x250 mm, 5 um, 12 nm; 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; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(5-methoxy-1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (9.2 mg, 23%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =366.2. ^1H NMR (300 MHz, DMSO-d_6): δ 12.81 (s, 1H), 11.60 (s, 1H), 10.62 (s, 1H), 8.02 - 7.92 (m, 3H), 7.63 - 7.61 (m, 2H), 7.30 (s, 1H), 5.14 - 4.82 (m, 1H), 3.83 (s, 3H), 2.29 - 2.16 (m, 1H), 1.79 - 1.52 (m, 1H), 1.34 - 1.05 (m, 1H).

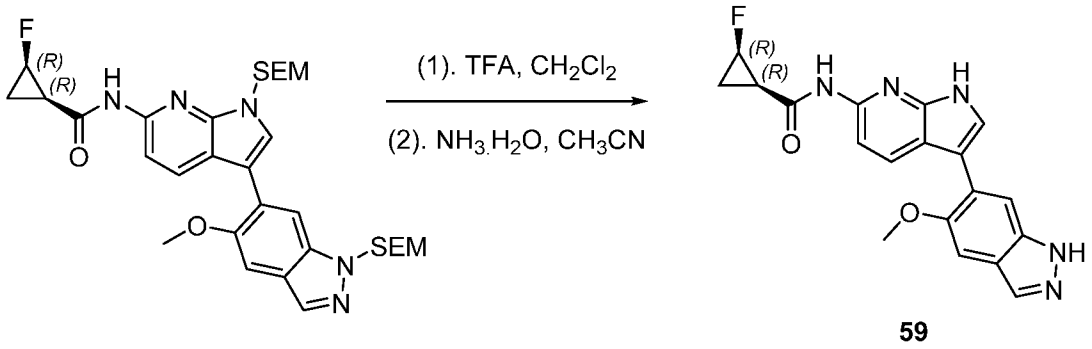
Example S59. Compound 59

Step 1: Synthesis of (1R,2R)-2-fluoro-N-[3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0370] To a solution of 6-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole (250.0 mg, 0.45 mmol) in 1,4-dioxane (4.0 mL) was added (1R,2R)-2-fluorocyclopropane-1-carboxamide (230.4 mg, 2.24 mmol), BrettPhos (48.0 mg, 0.09 mmol), Cs_2CO_3 (349.6 mg, 1.07 mmol) and BrettPhos Pd G3 (40.5 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was irradiated with microwave radiation at 120 °C for 1.5 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with ether/ethyl acetate (3/2, v/v) to afford (1R,2R)-2-fluoro-N-[3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (200.0 mg, 71%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =626.3.

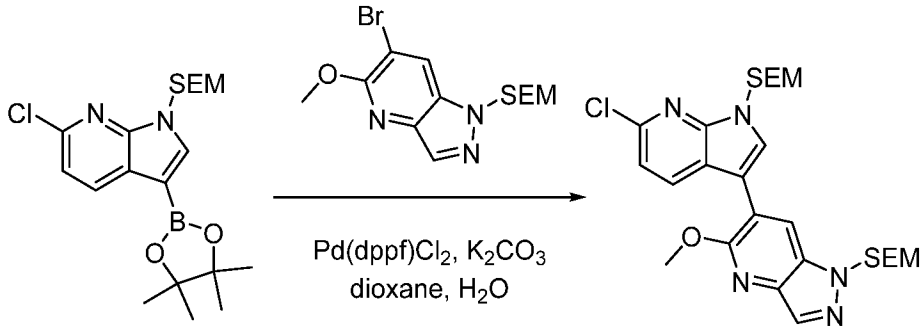
Step 2: Synthesis of (1R,2R)-2-fluoro-N-[3-(5-methoxy-1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 59):



[0371] To a solution of (1R,2R)-2-fluoro-N-[3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (200.0 mg, 0.32 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (3.0 mL) and $NH_3.H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another16 h. After the reaction was completed, 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 53% B in 7 min; 254 nm) to afford (1R,2R)-2-fluoro-N-[3-(5-methoxy-1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (30.7 mg, 26%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =366.2. ^1H NMR (300 MHz, DMSO-d_6): δ 12.78 (s, 1H), 11.57 (s, 1H), 10.60 (s, 1H), 7.96 - 7.84 (m, 3H), 7.57 - 7.54 (m, 2H), 7.24 (s, 1H), 5.00 - 4.73 (m, 1H), 3.76 (s, 3H), 2.20 - 2.15 (m, 1H), 1.66 - 1.54 (m, 1H), 1.20 - 1.00 (m, 1H).

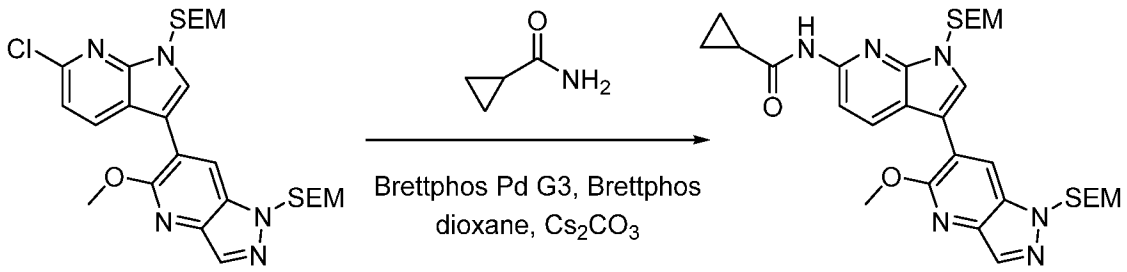
Example S60. Compound 60

Step 1: Synthesis of 6-chloro-3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[4,3-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



[0372] To a solution of 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (400.0 mg, 0.98 mmol) in dioxane (15.0 mL) and H_2O (1.0 mL) was added 6-bromo-5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[4,3-b]pyridine (140.4 mg, 0.78 mmol), $Pd(dppf)Cl_2$ (35.8 mg, 0.08 mmol) and K_2CO_3 (202.8 mg, 2.98 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methyl alcohol (10/1, v/v) to afford 6-chloro-3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[4,3-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (170.0 mg, 58%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =560.2.

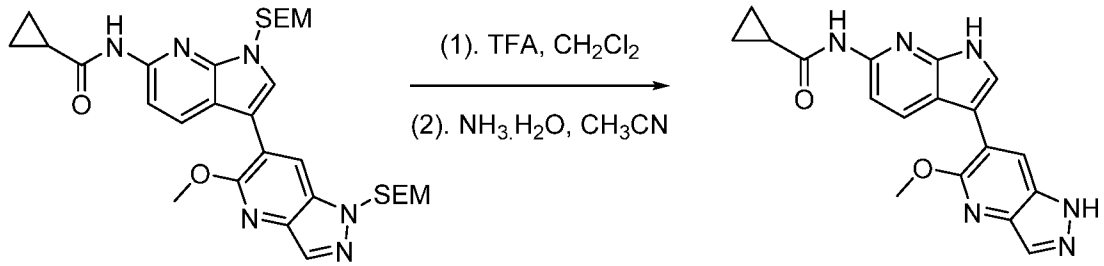
Step 2: Synthesis of N-[3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[4,3-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide:



[0373] To a solution of 6-chloro-3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[4,3-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (120.0 mg, 0.24 mmol) in dioxane (5.0 mL) was added cyclopropanecarboxamide (54.9 mg, 0.63 mmol), Brettphos Pd G3 (19.4 mg,

0.01 mmol), BrettPhos (22.9 mg, 0.04 mmol) and Cs_2CO_3 (209.7 mg, 0.63 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford N-[3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[4,3-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (100.0 mg, 60%) as a red oil. LCMS (ESI, m/z): $[M+H]^+$ =609.3.

Step 3: Synthesis of N-(3-[5-methoxy-1H-pyrazolo[4,3-b]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (Compound 60):



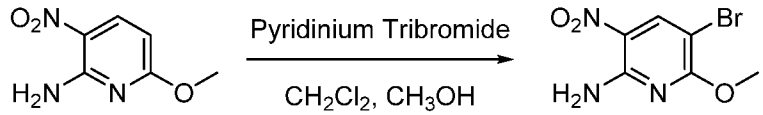
60

[0374] To a solution of N-[3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[4,3-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (100.0 mg, 0.16 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (5.0 mL) and $NH_3.H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 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 56% B in 7 min; 254 nm) to afford N-(3-[5-methoxy-1H-pyrazolo[4,3-b]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (2.4 mg, 4%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$

=349.1. ^{1}H NMR (300 MHz, Methanol-d_4): δ 8.17 - 8.11 (m, 2H), 8.02 (s, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.75 (s, 1H), 4.08 (s, 3H), 1.99 - 1.89 (m, 1H), 1.03 - 1.00 (m, 2H), 0.94 - 0.89 (m, 2H).

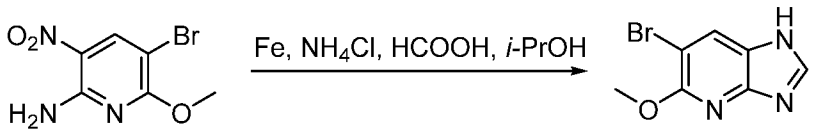
Example S61. Compound 61

Step 1: Synthesis of 5-bromo-6-methoxy-3-nitropyridin-2-amine:



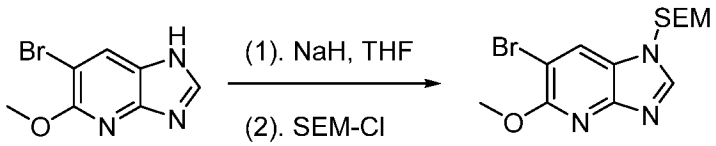
[0375] To a solution of 6-methoxy-3-nitropyridin-2-amine (10.0 g, 59.12 mmol) in CH_2Cl_2/MeOH (40.0 mL/10.0 mL) was added pyridinium Tribromide (28.3 g, 88.68 mmol). The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (70/30, v/v) to afford 5-bromo-6-methoxy-3-nitropyridin-2-amine (7.0 g, 48%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 248.0.

Step 2: Synthesis of 6-bromo-5-methoxy-1H-imidazo[4,5-b]pyridine:



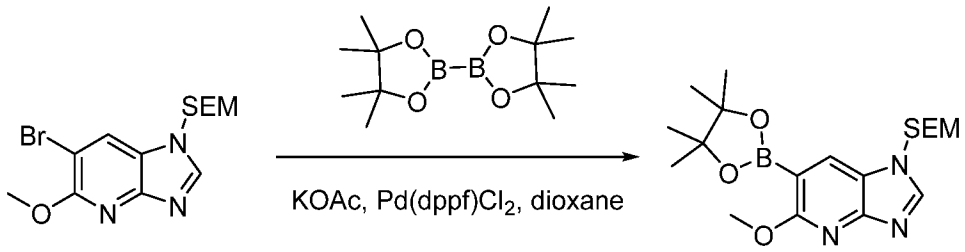
[0376] To a solution of 5-bromo-6-methoxy-3-nitropyridin-2-amine (5.0 g, 20.16 mmol) in HCOOH/i-PrOH (50.0 mL/50.0 mL) was added Fe (11.3 g, 201.58 mmol) and NH_4Cl (10.8 g, 201.58 mmol). The resulting mixture was stirred at 80 °C for 5 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/90, v/v) to afford 6-bromo-5-methoxy-1H-imidazo[4,5-b]pyridine (3.0 g, 65%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =228.0.

Step 3: Synthesis of 6-bromo-5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridine:



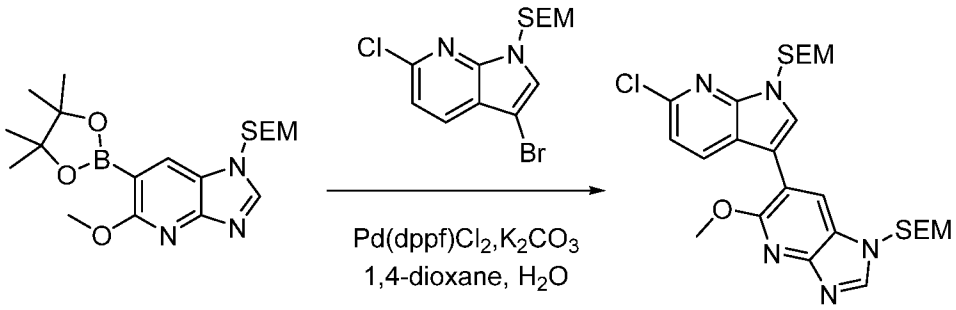
[0377] To a solution of 6-bromo-5-methoxy-1H-imidazo[4,5-b]pyridine (3.0 g, 13.16 mmol) in THF (30.0 mL) was added sodium hydride (631.4 mg, 15.79 mmol) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min. Then SEM-Cl (2.2 g, 13.16 mmol) was added to the mixture at 0 °C under N_2. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the mixture was quenched with MeOH at 0 °C. The resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (60/40, v/v) to afford 6-bromo-5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridine (1.4 g, 30%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =358.1.

Step 4: Synthesis of 5-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridine:



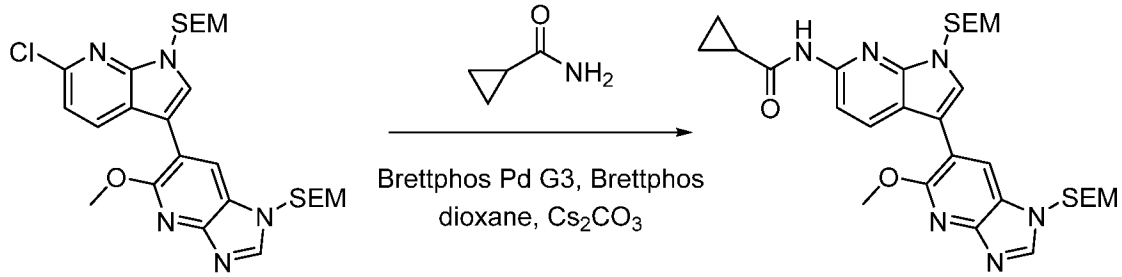
[0378] To a solution of 6-bromo-5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridine (1.3 g, 3.77 mmol) in 1,4-dioxane (10.0 mL) was added bis(pinacolato)diboron (1.9 g, 7.54 mmol), KOAc (1.1 g, 11.30 mmol) and $Pd(dppf)Cl_2$ (275.7 mg, 0.38 mmol). The mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography with H_2O/ACN (30/70, v/v) to afford 5-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridine (820.0 mg, 53%) as a yellow solid. LCMS (ESI, m/z): [M+H]+ = 406.2.

Step 5: Synthesis of 6-chloro-3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



[0379] To a solution of 5-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridine (220.0 mg, 0.54 mmol) in 1,4-dioxane/H_2O (3.0 mL/1.0 mL) was added 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (196.32 mg, 0.54 mmol), K_2CO_3 (225.0 mg, 1.63 mmol) and $Pd(dppf)Cl_2$ (39.7 mg, 0.05 mmol). The mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (12/88, v/v) to afford 6-chloro-3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (140.0 mg, 46%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 560.2.

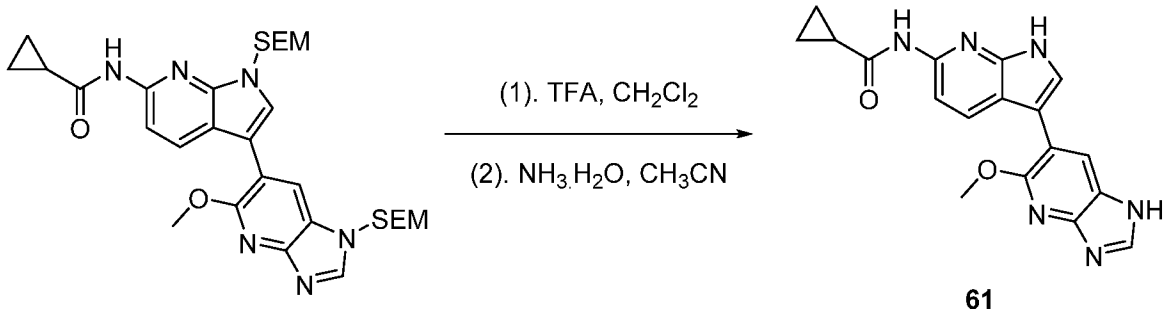
Step 6: Synthesis of N-[3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide:



[0380] To a solution of 6-chloro-3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (120.0 mg, 0.21 mmol) in 1,4-dioxane (3.0 mL) was added cyclopropanecarboxamide (54.7 mg, 0.64 mmol), Cs_2CO_3 (209.4 mg, 0.64 mmol), BrettPhos (23.0 mg, 0.043 mmol) and BrettPhos Pd G3 (19.4 mg, 0.02 mmol). The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the

resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (20/80, v/v) to afford N-[3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (100.0 mg, 76%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 609.3.

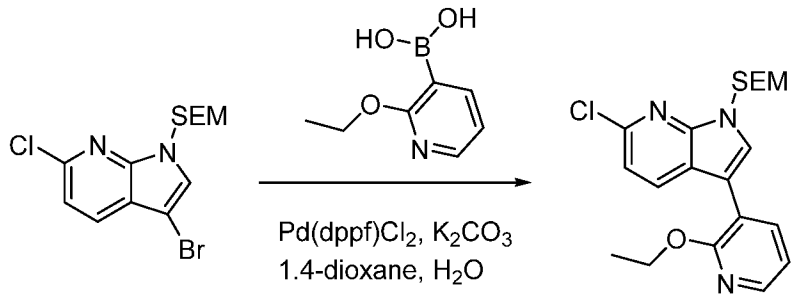
Step 7: Synthesis of N-(3-[5-methoxy-1H-imidazo[4,5-b]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (Compound 61):



[0381] To a solution of N-[3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (80.0 mg, 0.13 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL). The mixture was stirred at room temperature for 2 h. The mixture was concentrated under vacuum. The residue was dissolved in ACN (2.0 mL) and $NH_3.H_2O$ (2.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 Column, 30×250 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 13% B to 43% B in 10 min; 254 nm) to afford N-(3-[5-methoxy-1H-imidazo[4,5-b]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (14.6 mg, 32%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 349.2. ^1H NMR (300 MHz, DMSO-d_6): δ 12.32 (s, 1H), 11.60 (s, 1H), 10.59 (s, 1H), 8.22 (s, 1H), 8.08 (s, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.63 (s, 1H), 3.96 (s, 3H), 2.09 - 2.01 (m, 1H), 0.86 - 0.79 (m, 4H).

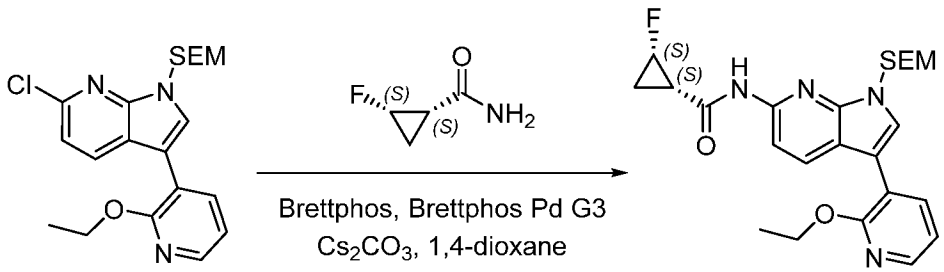
Example S62. Compound 62

Step 1: Synthesis of 6-chloro-3-(2-ethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine:



[0382] To a solution of 3-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (1.0 g, 2.76 mmol) in 1,4-dioxane/H_2O (20.0/4.0 mL) was added (2-ethoxypyridin-3-yl)boronic acid (461.6 mg, 2.76 mmol), K_2CO_3 (1.1g, 8.29 mmol) and $Pd(dppf)Cl_2$ (202.3 mg, 0.28 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (96/4, v/v) to afford 6-chloro-3-(2-ethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (710.0 mg, 63%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =404.1.

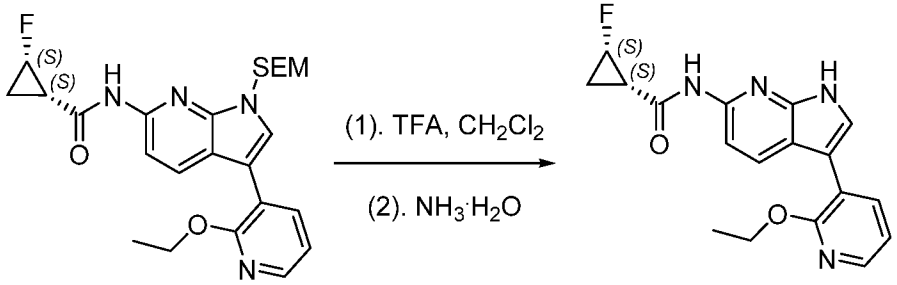
Step 2: Synthesis of (1S,2S)-N-(3-(2-ethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide:



[0383] To a solution of 6-chloro-3-(2-ethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (300.0 mg, 0.74 mmol) in 1,4-dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (382.8 mg, 3.71 mmol), Cs_2CO_3 (725.9 mg, 2.23 mmol), BrettPhos (79.7 mg, 0.15 mmol) and BrettPhos Pd G3 (67.3 mg, 0.07 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried

over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (70/30, v/v) to afford (1S,2S)-N-(3-(2-ethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (190.0 mg, 54%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =471.2.

Step 3: Synthesis of (1S,2S)-N-(3-(2-ethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (Compound 62):

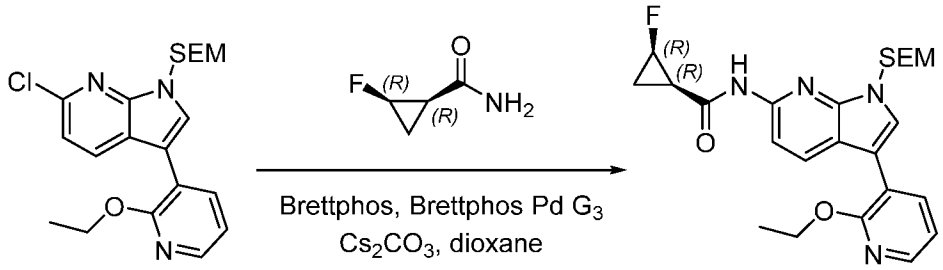


62

[0384] To a solution of (1S,2S)-N-(3-(2-ethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (190.0 mg, 0.40 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (5.0 mL) and $NH_3.H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, 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, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 47% B in 10 min; 254 nm) to afford (1S,2S)-N-(3-(2-ethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (42.2 mg, 30%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =341.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.69 (s, 1H), 10.66 (s, 1H), 8.15 (d, J = 8.8 Hz, 1H), 8.06 - 7.92 (m, 3H), 7.75 (s, 1H), 7.07 - 7.04 (m, 1H), 5.01 - 4.84 (m, 1H), 4.44 - 4.39 (m, 2H), 2.29 - 2.22 (m, 1H), 1.69 - 1.63 (m, 1H), 1.37 - 1.34 (m, 3H), 1.20 - 1.13 (m, 1H).

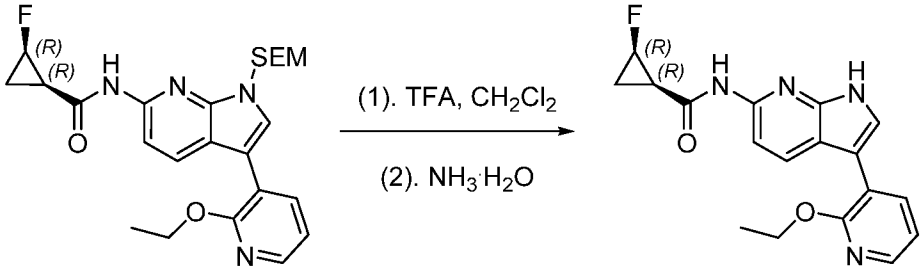
Example S63. Compound 63

Step 1: Synthesis of (1R,2R)-N-(3-(2-ethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide:



[0385] To a solution of 6-chloro-3-(2-ethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (300.0 mg, 0.74 mmol) in 1,4-dioxane (10.0 mL) was added (1R,2R)-2-fluorocyclopropane-1-carboxamide (382.8 mg, 3.71 mmol), Cs_2CO_3 (725.9 mg, 2.23 mmol), BrettPhos (79.7 mg, 0.15 mmol) and BrettPhos Pd G3 (67.3 mg, 0.07 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford (1R,2R)-N-(3-(2-ethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (160.0 mg, 45%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =471.2.

Step 2: Synthesis of (1R,2R)-N-(3-(2-ethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (Compound 63):



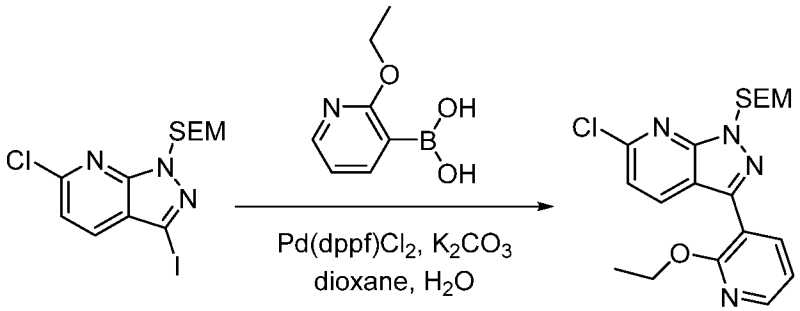
63

[0386] To a solution of (1R,2R)-N-(3-(2-ethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-

carboxamide (110.0 mg, 0.23 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (3.0 mL) and $NH_3.H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 20x250 mm, 5 um, 12 nm; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 10 min; 254 nm) to afford (1R,2R)-N-(3-(2-ethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (31.2 mg, 39%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =341.2. ^1H NMR(300 MHz, DMSO-d_6): δ 11.70 (s, 1H), 10.68 (s, 1H), 8.15 (d, J = 8.7 Hz, 1H), 8.07 - 8.05 (m, 1H), 8.01 - 7.98 (m, 1H), 7.95 - 7.92 (m, 1H), 7.75 (s, 1H), 7.08 - 7.04 (m, 1H), 5.06 - 4.81 (m, 1H), 4.45 - 4.38 (m, 2H), 2.26 - 2.22 (m, 1H), 1.70 - 1.59 (m, 1H), 1.38 - 1.33 (m, 3H), 1.20 - 1.13 (m, 1H).

Example S64. Compound 64

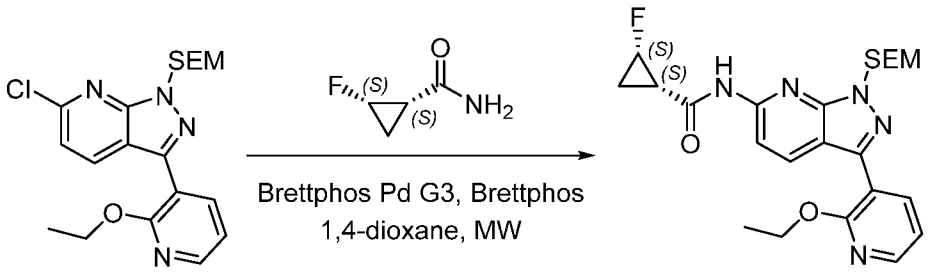
Step 1: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-2-ethoxypyridine:



[0387] A mixture of 6-chloro-3-iodo-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (1.4 g, 3.42 mmol), 2-ethoxypyridin-3-ylboronic acid (0.6 g, 3.42 mmol), K_2CO_3 (1.4 g, 10.25 mmol) and $Pd(dppf)Cl_2$ (0.3 g, 0.34 mmol) in dioxane (20.0 mL) and H_2O (4.0 mL) was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (92/8, v/v) to afford 3-(6-chloro-1-[[2-

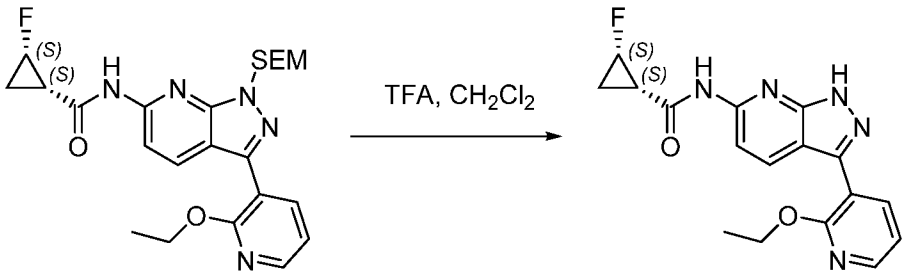
(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-2-ethoxypyridine (960.0 mg, 69%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ = 405.1.

Step 2: Synthesis of (1S,2S)-N-[3-(2-ethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide:



[0388] A mixture of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-2-ethoxypyridine (300.0 mg, 0.74 mmol), (1S,2S)-2-fluorocyclopropane-1-carboxamide (381.9 mg, 3.70 mmol), K_2CO_3 (307.2 mg, 2.22 mmol), BrettPhos (79.5 mg, 0.15 mmol) and BrettPhos Pd G3 (67.15 mg, 0.07 mmol) in dioxane (15.0 mL) was irradiated with microwave radiation (MW) at 120 °C for 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (94/6, v/v) to afford (1S,2S)-N-[3-(2-ethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (330.0 mg, 94%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =472.2.

Step 3: Synthesis of (1S,2S)-N-[3-(2-ethoxypyridin-3-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 64):

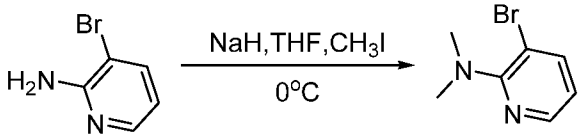


64

[0389] A mixture of (1S,2S)-N-[3-(2-ethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (330.0 mg, 0.70 mmol) and TFA (5.0 mL) in CH_2Cl_2 (5.0 mL) was stirred at room temperature for 16. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (94/6, v/v) and then purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 19×250 mm, 10 um; Mobile Phase A:Water(0.1% FA), Mobile Phase B:MeOH-----Preparative; Flow rate: 25 mL/min; Gradient: 50% B to 58% B in 10 min; 220/254 nm) to afford (1S,2S)-N-[3-(2-ethoxypyridin-3-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (3.7 mg, 1%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 342.2. ^1H NMR (300 MHz, DMSO-d_6): δ 13.59 (s, 1H), 10.97 (s, 1H), 8.28 - 8.23 (m, 2H), 8.06 - 8.00 (m, 2H), 7.14 - 7.10 (m, 1H), 5.07 - 4.83 (m, 1H), 4.48 - 4.41 (m, 2H), 2.30 - 2.25 (m, 1H), 1.73 - 1.63 (m, 1H), 1.32 - 1.21 (m, 4H).

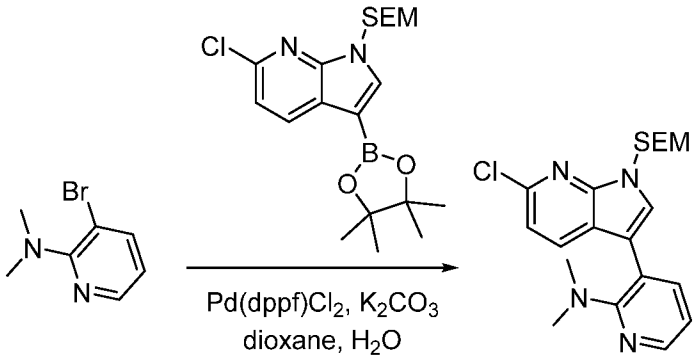
Example S65. Compound 65

Step 1: Synthesis of 3-bromo-N,N-dimethylpyridin-2-amine:



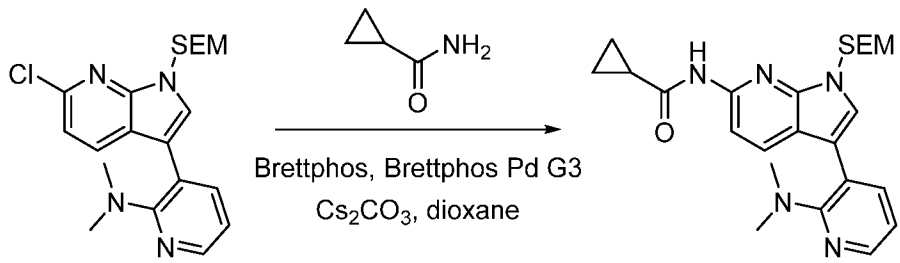
[0390] To a solution of 3-bromopyridin-2-amine (5.0 g, 28.90 mmol) in THF (40.0 mL) was added NaH (5.8 g, 60%) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. Then CH_3I (8.2 g, 57.80 mmol) was added dropwise to the mixture at 0 °C under N_2. The resulting mixture was stirred at 0 °C for another 1 h. After the reaction was completed, the reaction mixture was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (4/1, v/v) to afford 3-bromo-N,N-dimethylpyridin-2-amine (4.6 g, 79%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =201.0.

Step 2: Synthesis of 3-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-N,N-dimethylpyridin-2-amine:



[0391] To a solution of 3-bromo-N,N-dimethylpyridin-2-amine (123.0 mg, 0.61 mmol) in dioxane/H_2O (16.0/4.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (250.0 mg, 0.61 mmol), K_2CO_3 (253.6 mg, 1.84 mmol) and $Pd(dppf)Cl_2$ (44.8 mg, 0.06 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford 3-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-N,N-dimethylpyridin-2-amine (150.0 mg, 60%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =403.2.

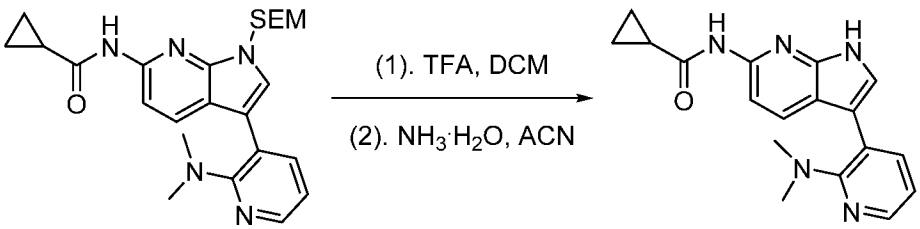
Step 3: Synthesis of N-(3-(2-(dimethylamino)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide:



[0392] To a solution of 3-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-N,N-dimethylpyridin-2-amine (130.0 mg, 0.32 mmol) in dioxane (4.0 mL)

was added cyclopropanecarboxamide (164.7 mg, 1.94 mmol), Cs_2CO_3 (315.3 mg, 0.97 mmol), Brettphos (34.6 mg, 0.07 mmol) and BrettPhos Pd G3 (29.2 mg, 0.03 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford N-(3-(2-(dimethylamino)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (120.0 mg, 82%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =452.2.

Step 4: Synthesis of N-(3-(2-(dimethylamino)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (Compound 65):



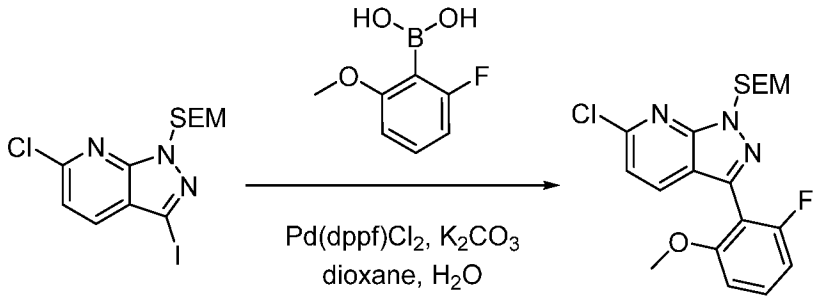
65

[0393] To a solution of N-(3-(2-(dimethylamino)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (100.0 mg, 0.22 mmol) in DCM (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in ACN (5.0 mL) and $NH_3 \cdot H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 2% to 21% in 7 min; 254 nm) to afford N-(3-(2-(dimethylamino)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (32.0 mg, 44%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =322.1. ^1H NMR (400 MHz, CD_3OD): δ 8.09 - 8.08 (m, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.71 - 7.68

(m, 1H), 7.47 (s, 1H), 6.94 - 6.91 (m, 1H), 2.72 (s, 6H), 1.91 - 1.89 (m, 1H), 1.02 - 0.99 (m, 2H), 0.92 - 0.88 (m, 2H).

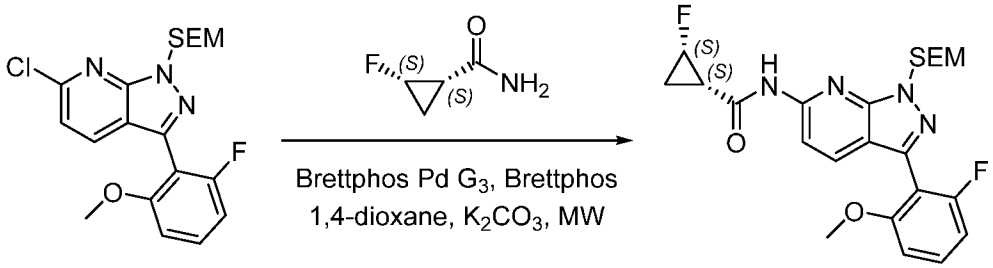
Example S66. Compound 66

Step 1: Synthesis of 6-chloro-3-(2-fluoro-6-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine:



[0394] A mixture of 6-chloro-3-iodo-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (800.0 mg, 1.95 mmol), 2-fluoro-6-methoxyphenylboronic acid (331.8 mg, 1.95 mmol), K_2CO_3 (809.5 mg, 5.86 mmol) and $Pd(dppf)Cl_2$ (142.9 mg, 0.20 mmol) in dioxane (20.0 mL) and H_2O (2.0 mL) was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (95/5, v/v) to afford 6-chloro-3-(2-fluoro-6-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (500.0 mg, 63%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ = 408.1.

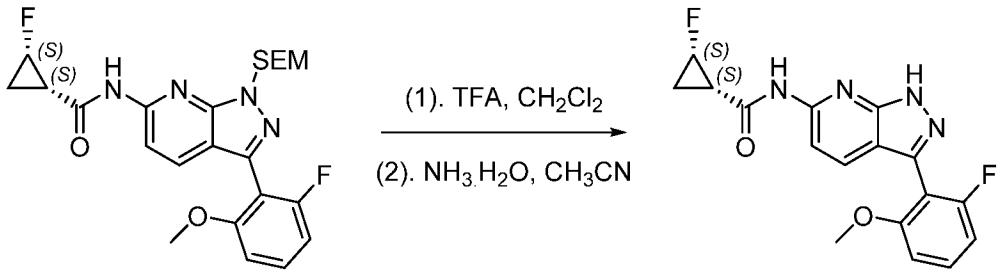
Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-(2-fluoro-6-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0395] A mixture of 6-chloro-3-(2-fluoro-6-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (500.0 mg, 1.23 mmol), (1S,2S)-2-

fluorocyclopropane-1-carboxamide (631.8 mg, 6.13 mmol), K_2CO_3 (508.2 mg, 3.68 mmol), BrettPhos (131.6 mg, 0.25 mmol) and BrettPhos Pd G3 (111.1 mg, 0.12 mmol) in dioxane (12.0 mL) was irradiated with microwave radiation (MW) at 120 °C for 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (94/6, v/v) to afford (1S,2S)-2-fluoro-N-[3-(2-fluoro-6-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (254.0 mg, 44%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 475.2.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-[3-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 66):



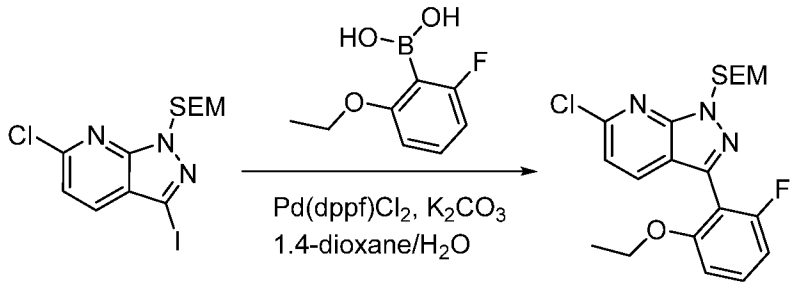
66

[0396] A mixture of (1S,2S)-2-fluoro-N-[3-(2-fluoro-6-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (200.0 mg, 0.42 mmol) and TFA (5.0 mL) in CH_2Cl_2 (5.0 mL) was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in $NH_3.H_2O$ (5.0 mL) and CAN (5.0 mL). The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (94/6, v/v) and then purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A:Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 39% B in 10 min; 254/220 nm) to afford (1S,2S)-2-fluoro-N-[3-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (24.1 mg, 17%). LCMS (ESI, m/z): $[M+H]^+$ = 345.1. ^1H

NMR (300 MHz, DMSO-d_6): δ 13.54 (s, 1H), 10.97 (s, 1H), 8.00 - 7.89 (m, 2H), 7.50 - 7.47 (m, 1H), 7.05 - 6.93 (m, 2H), 5.05 - 4.81 (m, 1H), 3.76 (s, 3H), 2.29 - 2.24 (m, 1H), 1.77 - 1.63 (m, 1H), 1.22 - 1.17 (m, 1H).

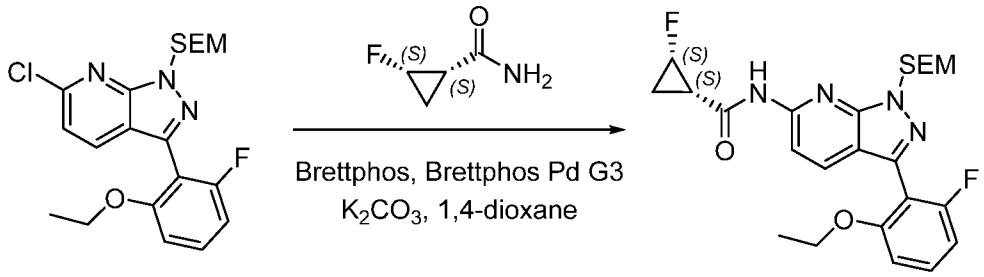
Example S67. Compound 67

Step 1: Synthesis of 6-chloro-3-(2-ethoxy-6-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine:



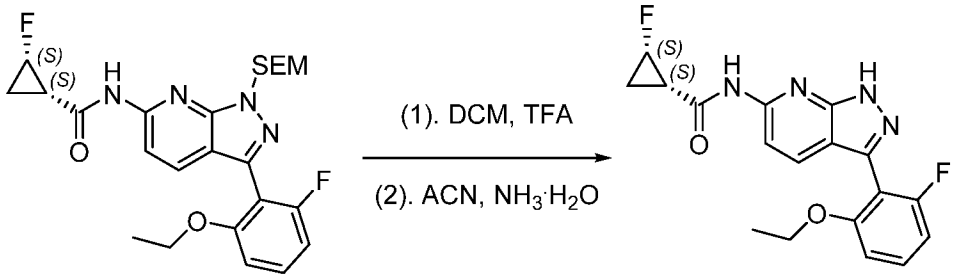
[0397] To a solution of 6-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (500.0 mg, 1.22 mmol) in 1,4-dioxane/H_2O (10.0/2.0 mL) was added (2-ethoxy-6-fluorophenyl)boronic acid (224.5 mg, 1.22 mmol), K_2CO_3 (505.9 mg, 3.66 mmol) and $Pd(dppf)Cl_2$ (89.2 mg, 0.12 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (75/25, v/v) to afford 6-chloro-3-(2-ethoxy-6-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (220.0 mg, 42%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =422.1.

Step 2: Synthesis of (1S,2S)-N-(3-(2-ethoxy-6-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide:



[0398] To a solution of 6-chloro-3-(2-ethoxy-6-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (200.0 mg, 0.47 mmol) in 1,4-dioxane (6.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (244.3 mg, 2.37 mmol), K_2CO_3 (196.5 mg, 1.42 mmol), BrettPhos (50.9 mg, 0.10 mmol) and BrettPhos Pd G3 (43.0 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (75/25, v/v) to afford (1S,2S)-N-(3-(2-ethoxy-6-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (140.0 mg, 60%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =489.2.

Step 3: Synthesis of (1S,2S)-N-(3-(2-ethoxy-6-fluorophenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (Compound 67):



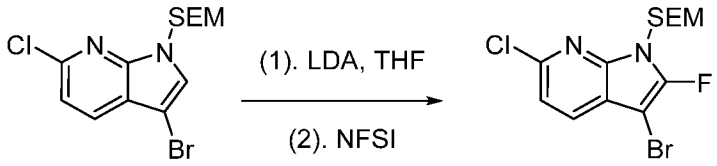
67

[0399] To a solution of (1S,2S)-N-(3-(2-ethoxy-6-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (140.0 mg, 0.29 mmol) in DCM (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in ACN (5.0 mL) and $NH_3.H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, 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, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 10 min; 254 nm) to afford (1S,2S)-N-(3-(2-ethoxy-6-fluorophenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (26.4 mg, 25%) as a light yellow solid.

LCMS (ESI, m/z): $[M+H]^+$ =359.1. ^1H NMR (400 MHz, DMSO-d_6): δ 13.55 (s, 1H), 11.00 (s, 1H), 8.00 - 7.95 (m, 2H), 7.49 - 7.43 (m, 1H), 7.03 - 6.92 (m, 2H), 5.06 - 4.85 (m, 1H), 4.11 - 4.05 (m, 2H), 2.29 - 2.25 (m, 1H), 1.71 - 1.63 (m, 1H), 1.23 - 1.12 (m, 4H).

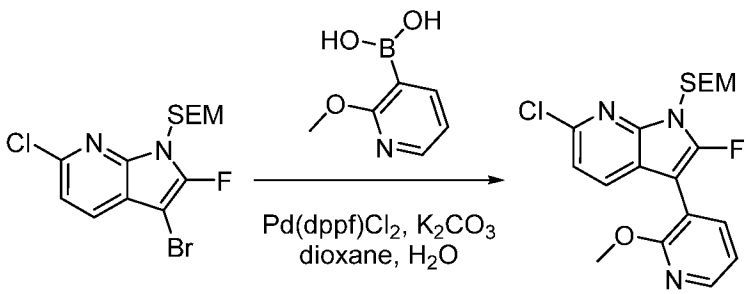
Example S68. Compound 68

Step 1: Synthesis of 3-bromo-6-chloro-2-fluoro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



[0400] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (1.0 g, 2.78 mmol) in THF (10.0 mL) was added LDA (4.4 mL, 2 mol/L) at -70 °C under N_2. The mixture was stirred at -70 °C for 2 h. Then a solution of NFSI (2.3 g, 7.14 mmol) in THF (8.0 mL) was added dropwise to the mixture at -70 °C. The mixture was stirred at -70 °C for another 3 h. After the reaction was completed, the mixture was quenched with aq.NH_4Cl and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/CH_2Cl_2 (76/24, v/v) to afford 3-bromo-6-chloro-2-fluoro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (550.0 mg, 80%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 379.0.

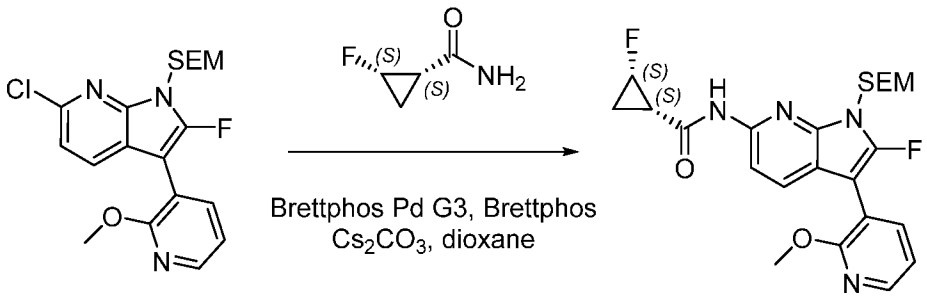
[0401] Step 2: Synthesis of 3-(6-chloro-2-fluoro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-methoxypyridine:



[0402] To a solution of 3-bromo-6-chloro-2-fluoro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (530.0 mg, 1.40 mmol) in 1,4-

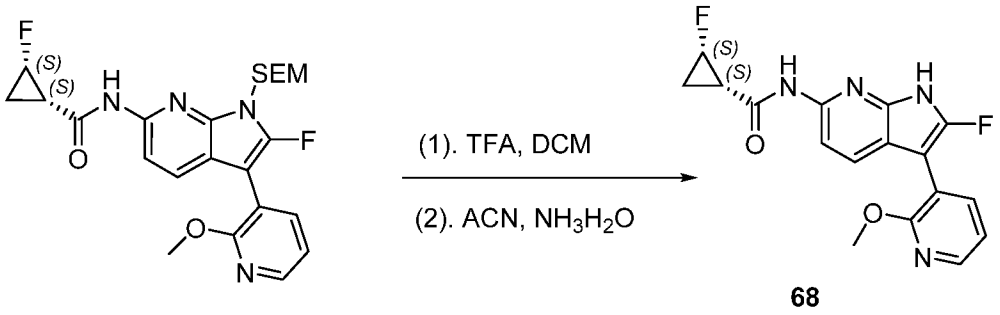
dioxane/H_2O (5.0 mL/1.0 mL) was added 2-methoxypyridin-3-ylboronic acid (213.5 mg, 1.40 mmol), K_2CO_3 (578.7 mg, 4.19 mmol) and Pd(dppf)Cl_2 (102.1 mg, 0.14 mmol). The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (80/20, v/v) to afford 3-(6-chloro-2-fluoro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-methoxypyridine (300.0 mg, 52%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 408.1.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-[2-fluoro-3-(2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0403] To a solution of 3-(6-chloro-2-fluoro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-methoxypyridine (240.0 mg, 0.59 mmol) in 1,4-dioxane (3.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (182.0 mg, 1.77 mmol), Cs_2CO_3 (575.1 mg, 1.77 mmol), BrettPhos (63.2 mg, 0.12 mmol) and BrettPhos Pd G3 (53.3 mg, 0.06 mmol). The resulting mixture was stirred at 100 °C for 2 h under N_2. After the reaction was completed, the mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (60/40, v/v) to afford (1S,2S)-2-fluoro-N-[2-fluoro-3-(2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (100.0 mg, 35%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 475.2.

Step 4: Synthesis of (1S,2S)-2-fluoro-N-[2-fluoro-3-(2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 68):

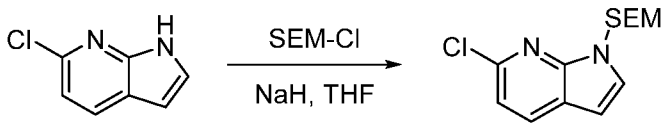


68

[0404] To a solution of (1S,2S)-2-fluoro-N-[2-fluoro-3-(2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (80.0 mg, 0.17 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL). The mixture was stirred at room temperature for 2 h. The mixture was concentrated under vacuum. The residue was dissolved in ACN (2.0 mL) and $NH_3.H_2O$ (2.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 42% B in 8 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[2-fluoro-3-(2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (23.8 mg, 41%) as a white solid. LCMS (ESI, m/z): $[M+H]^+ = 345.1$. ^1H NMR (400 MHz, DMSO-d_6): δ 12.55 (s, 1H), 10.64 (s, 1H), 8.18 - 8.16 (m, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.82 - 7.77 (m, 2H), 7.11 - 7.08 (m, 1H), 5.02 - 4.82 (m, 1H), 3.90 (s, 3H), 2.24 - 2.20 (m, 1H), 1.69 - 1.60 (m, 1H), 1.18 - 1.12 (m, 1H).

Example S69. Compound 69

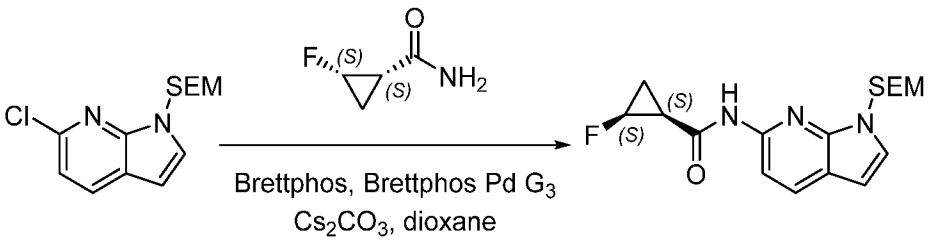
Step 1: Synthesis of 6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine:



[0405] To a solution of 6-chloro-1H-pyrrolo[2,3-b]pyridine (600.0 mg, 3.94 mmol) in THF (5.0 mL) was added NaH (133.6 mg, 60%) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. Then SEM-Cl (786.3 mg, 4.72 mmol) was added to the mixture at 0 °C under N_2. The resulting mixture was stirred at 0 °C for another 1 h under N_2. After the

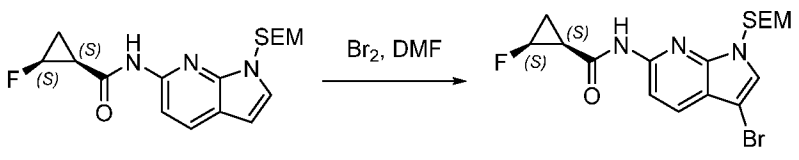
reaction was completed, the reaction was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (8/1, v/v) to afford 6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (440.0 mg, 39%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =283.1.

Step 2: Synthesis of (1S,2S)-2-fluoro-N-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide:



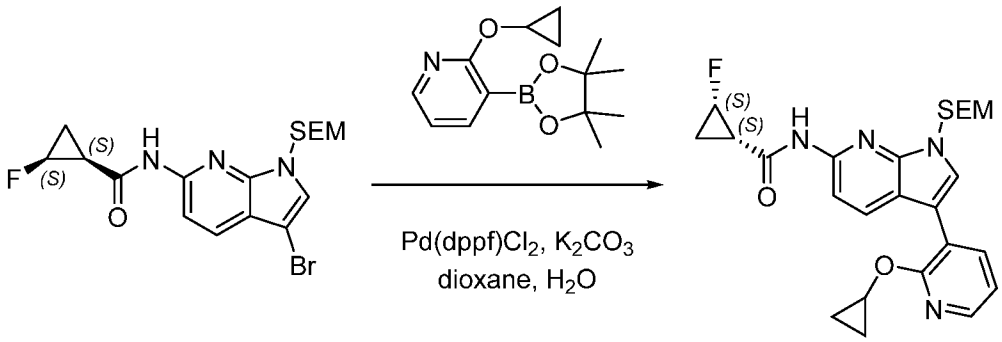
[0406] To a solution of 6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (440.0 mg, 1.56 mmol) in dioxane (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (803.5 mg, 7.80 mmol), Cs_2CO_3 (1.5 g, 4.68 mmol), BrettPhos (167.5 mg, 0.31 mmol) and BrettPhos Pd G3 (141.5 mg, 0.15 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (65/35, v/v) to afford (1S,2S)-2-fluoro-N-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (170.0 mg, 31%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =350.2.

Step 3: Synthesis of (1S,2S)-N-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide:



[0407] To a solution of (1S,2S)-2-fluoro-N-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (170.0 mg, 0.48 mmol) in DMF (5.0 mL) was added Br_2 (93.0 mg, 0.58 mmol) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the mixture was quenched with sat. $NaHSO_3$ at 0 °C. The resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (60/40, v/v) to afford (1S,2S)-N-(3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (70.0 mg, 34%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =428.1.

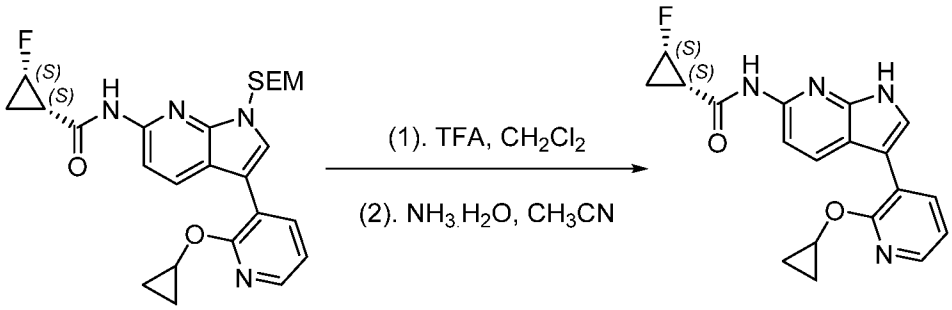
Step 4: Synthesis of (1S,2S)-N-[3-(2-cyclopropoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide:



[0408] To a solution of (1S,2S)-N-(3-bromo-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (70.0 mg, 0.16 mmol) in dioxane/H_2O (5.0/1.0 mL) was added 2-cyclopropoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (51.3 mg, 0.19 mmol), K_2CO_3 (66.2 mg, 0.48 mmol) and $Pd(dppf)Cl_2$ (11.7 mg, 0.02 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (80/20, v/v) to afford (1S,2S)-N-[3-(2-cyclopropoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-

fluorocyclopropane-1-carboxamide (28.0 mg, 29%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =483.2.

Step 5: Synthesis of (1S,2S)-N-[3-(2-cyclopropoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 69):

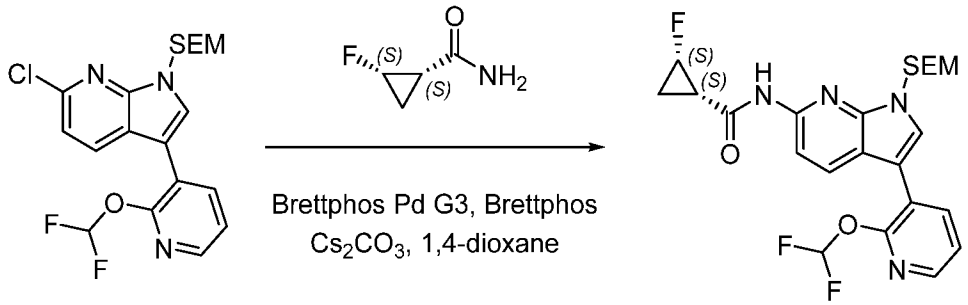


69

[0409] To a solution of (1S,2S)-N-[3-(2-cyclopropoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (28.0 mg, 0.06 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in ACN (3.0 mL) was added $NH_3 \cdot H_2O$ (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32 % B to 47 % B in 7 min; 254 nm) to afford (1S,2S)-N-[3-(2-cyclopropoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (7.2 mg, 35%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =353.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.69 (s, 1H), 10.66 (s, 1H), 8.12 - 8.05 (m, 2H), 7.99 - 7.86 (m, 2H), 7.64 (d, J = 2.4 Hz, 1H), 7.12 - 7.09 (m, 1H), 5.03 - 4.82 (m, 1H), 4.38 - 4.34 (m, 1H), 2.27 - 2.20 (m, 1H), 1.70 - 1.61 (m, 1H), 1.21 - 1.11 (m, 1H), 0.82 - 0.74 (m, 2H), 0.71 - 0.67 (m, 2H).

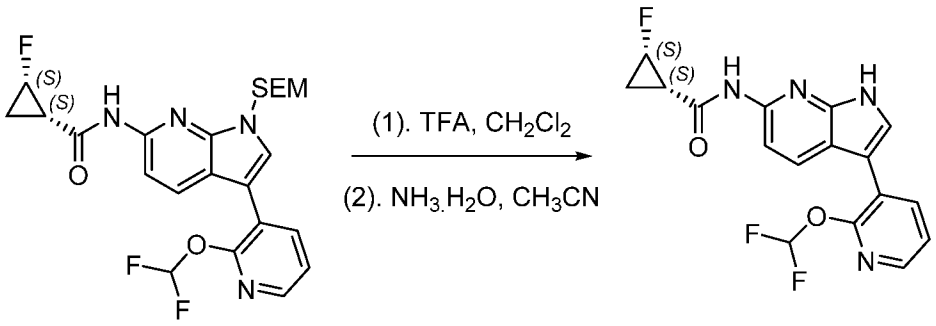
Example S70. Compound 70

Step 1: Synthesis of (1S,2S)-N-[3-[2-(difluoromethoxy)pyridin-3-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide:



[0410] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-(difluoromethoxy)pyridine (140.0 mg, 0.33 mmol) in dioxane (3.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (169.4 mg, 1.64 mmol), BrettPhos (35.3 mg, 0.06 mmol), Cs_2CO_3 (321.3 mg, 0.99 mmol) and BrettPhos Pd G3 (29.8 mg, 0.03 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (80/20, v/v) to afford (1S,2S)-N-[3-[2-(difluoromethoxy)pyridin-3-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (45.0 mg, 28%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =493.2.

Step 2: Synthesis of (1S,2S)-N-[3-[2-(difluoromethoxy)pyridin-3-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 70):

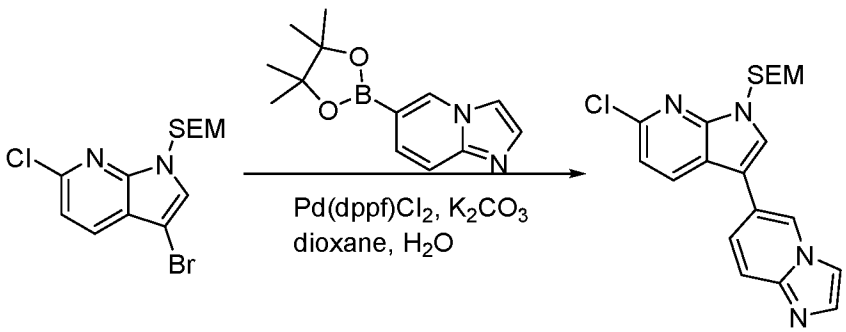


70

[0411] To a solution of (1S,2S)-N-[3-[2-(difluoromethoxy)pyridin-3-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (45.0 mg, 0.09 mmol) in CH_2Cl_2 (1.0 mL) was added TFA (1.0 mL). The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (1.0 mL) and $NH_3 \cdot H_2O$ (1.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31% B to 61% B in 10 min; 254 nm) to afford (1S,2S)-N-[3-[2-(difluoromethoxy)pyridin-3-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (6.4 mg, 19%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =363.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.82 (s, 1H), 10.66 (s, 1H), 8.15 - 8.09 (m, 3H), 7.97 - 7.61 (m, 3H), 7.36 - 7.32 (m, 1H), 5.00 - 4.81 (m, 1H), 2.24 - 2.20 (m, 1H), 1.68 - 1.60 (m, 1H), 1.17 - 1.14 (m, 1H).

Example S71. Compound 71

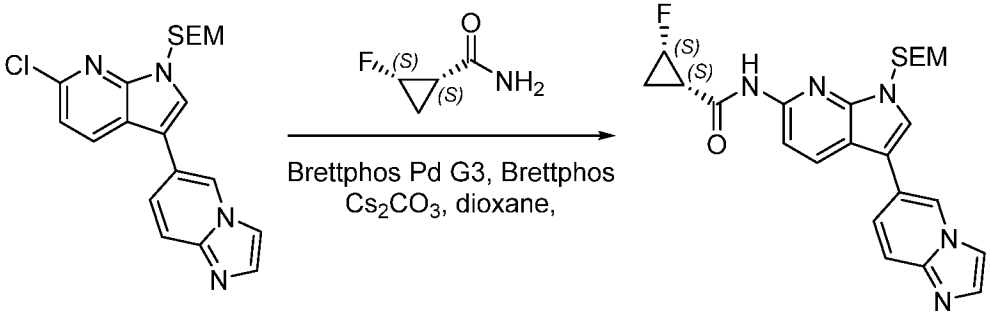
Step 1: Synthesis of 6-chloro-3-[imidazo[1,2-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



[0412] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 0.83 mmol) in 1,4-dioxane/H_2O (10.0/2.0 mL) was added 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyridine (202.4 mg, 0.83 mmol), K_2CO_3 (343.9 mg, 2.49 mmol) and $Pd(dppf)Cl_2$ (60.7 mg, 0.08 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried

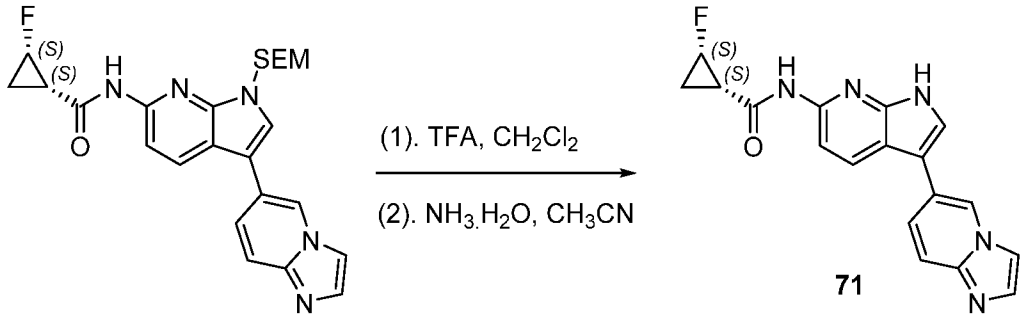
over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (10/1, v/v) to afford 6-chloro-3-[imidazo[1,2-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (270.0 mg, 81%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =399.1.

Step 2: Synthesis of (1S,2S)-2-fluoro-N-(3-[imidazo[1,2-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0413] To a solution of 6-chloro-3-[imidazo[1,2-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (250.0 mg, 0.63 mmol) in 1,4-dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (323.0 mg, 3.13 mmol), BrettPhos (67.3 mg, 0.13 mmol), Cs_2CO_3 (612.5 mg, 1.88 mmol) and BrettPhos Pd G3 (56.8 mg, 0.06 mmol) at room temperature under N_2. The resulting mixture was stirred with microwave at 120 °C for 90 min. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (10/1, v/v) to afford (1S,2S)-2-fluoro-N-(3-[imidazo[1,2-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (160.0 mg, 55%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =466.2.

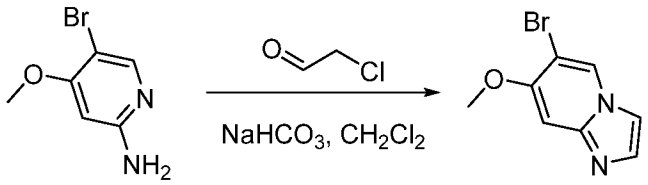
Step 3: Synthesis of (1S,2S)-2-fluoro-N-(3-[imidazo[1,2-a]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 71):



[0414] To a solution of (1S,2S)-2-fluoro-N-(3-[imidazo[1,2-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (160.0 mg, 0.34 mmol) in DCM (6.0 mL) was added TFA (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. he residue was dissolved in CH_3CN (6.0 mL) and $NH_3.H_2O$ (6.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions Column: YMC-Actus Triart C18, 30x250 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 47% B in 10 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-[imidazo[1,2-a]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (5.5 mg, 5%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =336.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.73 (s, 1H), 10.58 (s, 1H), 8.94 (s, 1H), 8.39 (d, J = 8.7 Hz, 1H), 7.98 (d, J = 6.0 Hz, 2H), 7.86 (s, 1H), 7.67 - 7.56 (m, 3H), 5.05 - 4.82 (m, 1H), 2.30 - 2.21 (m, 1H), 1.71 - 1.63 (m, 1H), 1.22 - 1.13 (m, 1H).

Example S72. Compound 72

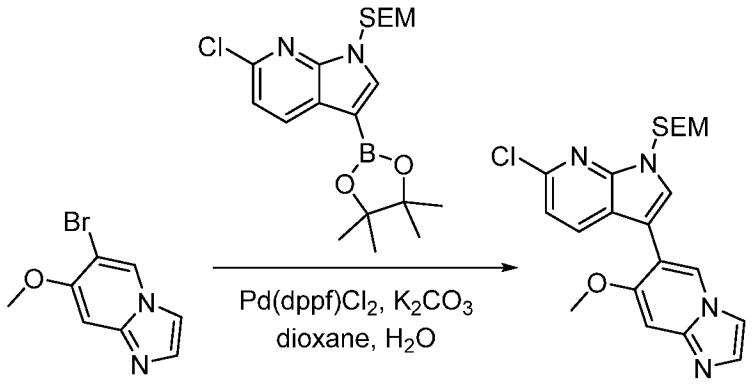
Step 1: Synthesis of 6-bromo-7-methoxyimidazo[1,2-a]pyridine :



[0415] To a solution of 5-bromo-4-methoxypyridin-2-amine (1.0 g, 4.93 mmol) in CH_2Cl_2 (5.0 mL) was added 2-chloroacetaldehyde (2.1 g, 10.84 mmol) and saturated

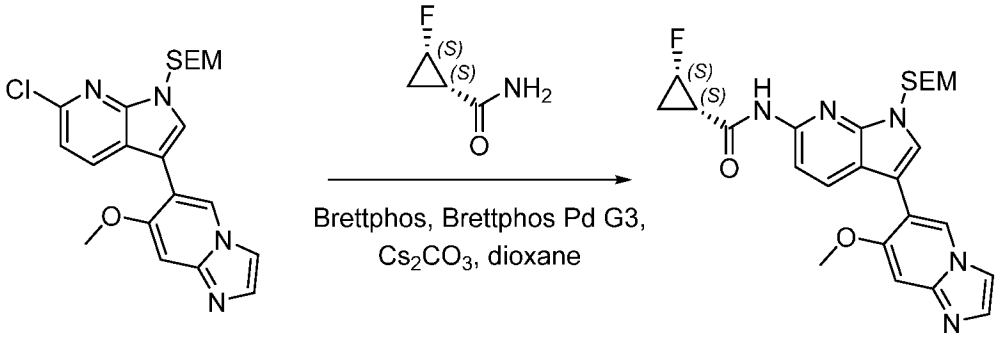
$NaHCO_3$ solution (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (10/1, v/v) to afford 6-bromo-7-methoxyimidazo[1,2-a]pyridine (380.0 mg, 33%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =227.0.

Step 2: Synthesis of 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-methoxyimidazo[1,2-a]pyridine :



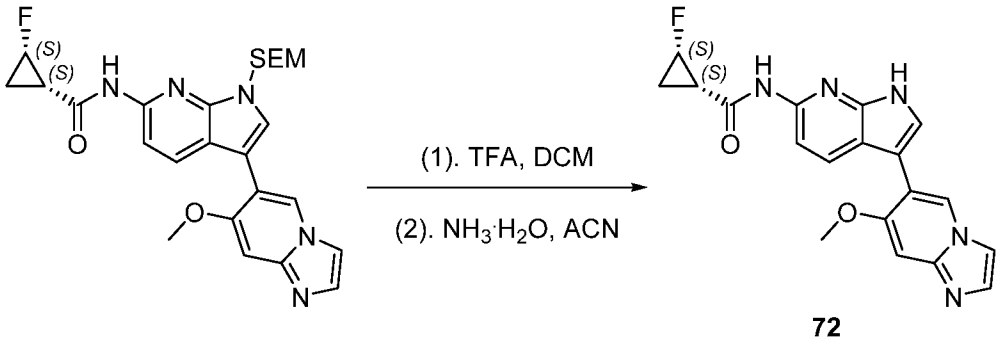
[0416] To a solution of 6-bromo-7-methoxyimidazo[1,2-a]pyridine (140.0 mg, 0.62 mmol) in dioxane/H_2O (16.0/4.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (252.0 mg, 0.62 mmol), K_2CO_3 (255.6 mg, 1.85 mmol) and $Pd(dppf)Cl_2$ (45.1 mg, 0.06 mmol) at room temperature under N_2. The resulting mixture was stirred at 80°C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (10/1, v/v) to afford 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-methoxyimidazo[1,2-a]pyridine (200.0 mg, 75%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =429.1.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-(3-(7-methoxyimidazo[1,2-a]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide :



[0417] To a solution of 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-methoxyimidazo[1,2-a]pyridine (180.0 mg, 0.42 mmol) in dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (216.3 mg, 2.10 mmol), Cs_2CO_3 (401.1 mg, 1.26 mmol), Brettphos (45.0 mg, 0.08 mmol) and BrettPhos Pd G3 (38.0 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (10/1, v/v) to afford (1S,2S)-2-fluoro-N-(3-(7-methoxyimidazo[1,2-a]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (160.0 mg, 76%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =496.2.

Step 4: Synthesis of (1S,2S)-2-fluoro-N-(3-(7-methoxyimidazo[1,2-a]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 72):



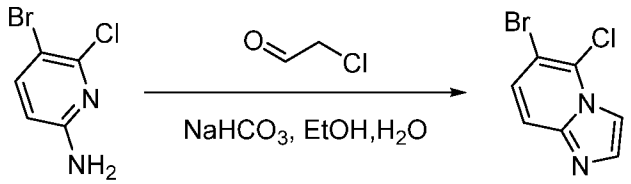
72

[0418] To a solution of (1S,2S)-2-fluoro-N-(3-(7-methoxyimidazo[1,2-a]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (140.0 mg, 0.28 mmol) in DCM (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in ACN (5.0

mL) and $NH_3 \cdot H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with MeOH/H_2O (56/44, v/v) to afford to afford (1S,2S)-2-fluoro-N-(3-(7-methoxyimidazo[1,2-a]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (9.0 mg, 8%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =366.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.64 (s, 1H), 8.61 (s, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.78 (s, 1H), 7.60 (s, 1H), 7.40 - 7.37 (m, 1H), 7.03 (s, 1H), 5.02 - 4.81 (m, 1H), 3.87 (s, 3H), 2.25 - 2.19 (m, 1H), 1.70 - 1.61 (m, 1H), 1.35 - 1.04 (m, 1H).

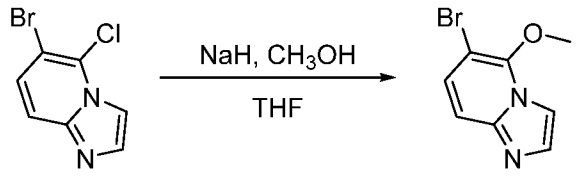
Example S73. Compound 73

Step 1: Synthesis of 6-bromo-5-chloroimidazo[1,2-a]pyridine:



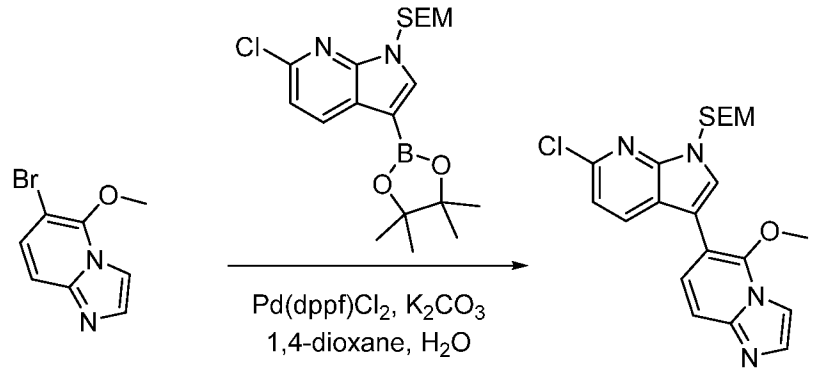
[0419] To a solution of 5-bromo-6-chloropyridin-2-amine (6.0 g, 28.92 mmol) in EtOH/H_2O (48.0/12.0 mL) was added $NaHCO_3$ (2.9 g, 34.71 mmol) and 2-chloroacetaldehyde (6.8 g, 34.71 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (97/3, v/v) to afford 6-bromo-5-chloroimidazo[1,2-a]pyridine (2.4 g, 35%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =230.9.

[0420] **Step 2: Synthesis of 6-bromo-5-methoxyimidazo[1,2-a]pyridine:**



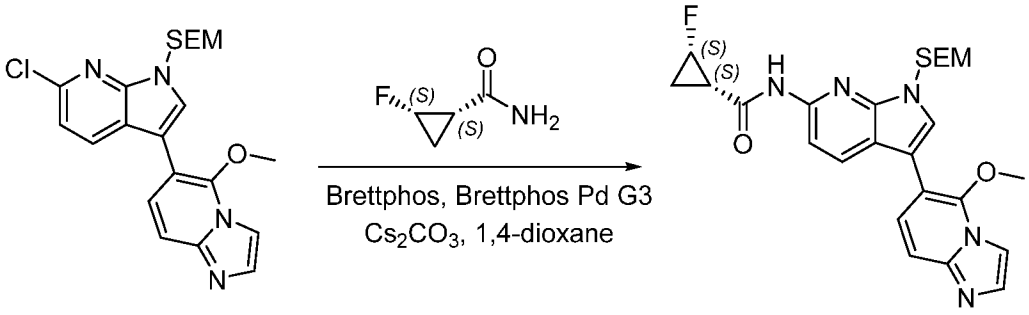
[0421] To a solution of 6-bromo-5-chloroimidazo[1,2-a]pyridine (1.0 g, 4.32 mmol) in THF (15.0 mL) was added CH_3OH (207.6 mg, 6.48 mmol) and NaH (345.6 mg, 60%) at room temperature under N_2. The resulting mixture was stirred at 60 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (96/4, v/v) to afford 6-bromo-5-methoxyimidazo[1,2-a]pyridine (550.0 mg, 56%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =227.0.

Step 3: Synthesis of 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-5-methoxyimidazo[1,2-a]pyridine:



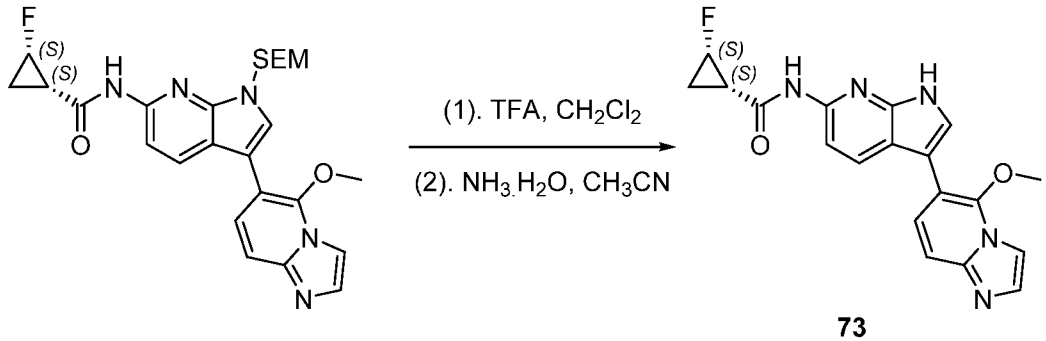
[0422] To a solution of 6-bromo-5-methoxyimidazo[1,2-a]pyridine (155.0 mg, 0.68 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (279.1 mg, 0.68 mmol), K_2CO_3 (283.0 mg, 2.05 mmol) and $Pd(dppf)Cl_2$ (50.0 mg, 0.07 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (90/10, v/v) to afford 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-5-methoxyimidazo[1,2-a]pyridine (162.0 mg, 52%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =429.1.

Step 4: Synthesis of (1S,2S)-2-fluoro-N-(3-(5-methoxyimidazo[1,2-a]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0423] To a solution of 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-5-methoxyimidazo[1,2-a]pyridine (160.0 mg, 0.37 mmol) in 1,4-dioxane (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (192.3 mg, 1.87 mmol), Cs_2CO_3 (364.6 mg, 1.12 mmol), BrettPhos (40.0 mg, 0.08 mmol) and BrettPhos Pd G3 (33.8 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (90/10, v/v) to afford (1S,2S)-2-fluoro-N-(3-(5-methoxyimidazo[1,2-a]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (140.0 mg, 47%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =496.2.

Step 5: Synthesis of (1S,2S)-2-fluoro-N-(3-(5-methoxyimidazo[1,2-a]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 73):



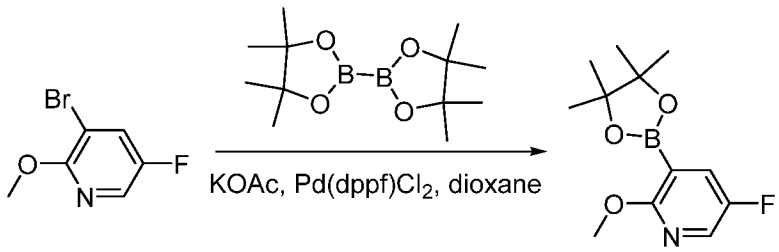
73

[0424] To a solution of (1S,2S)-2-fluoro-N-(3-(5-methoxyimidazo[1,2-a]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (140.0 mg, 0.28 mmol) in DCM (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in ACN (3.0

mL) and $NH_3 \cdot H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30×250 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 21% B to 30% B in 8 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-(5-methoxyimidazo[1,2-a]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl) cyclopropane-1-carboxamide (6.3 mg, 6%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =366.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.33 (s, 1H), 10.61 (s, 1H), 8.26 (d, J = 8.7 Hz, 1H), 8.02 - 7.97 (m, 2H), 7.92 - 7.84 (m, 1H), 7.79 (d, J = 2.1 Hz, 1H), 7.62 (d, J = 2.1 Hz, 1H), 6.38 (d, J = 8.4 Hz, 1H), 5.11 - 4.78 (m, 1H), 3.75 (s, 3H), 2.23 - 2.13 (m, 1H), 1.78 - 1.53 (m, 1H), 1.24 - 1.08 (m, 1H).

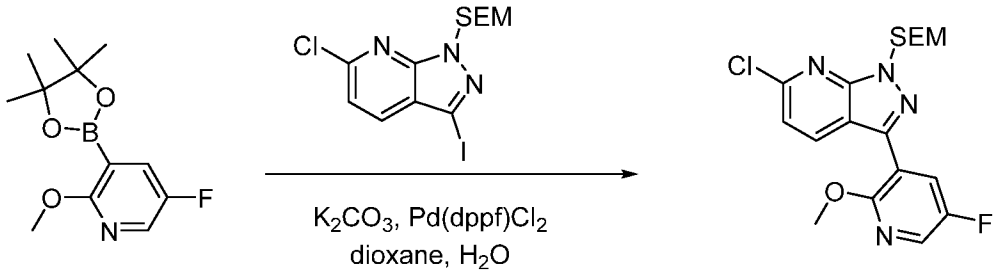
Example S74. Compound 74

Step 1: Synthesis of 5-fluoro-2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine:



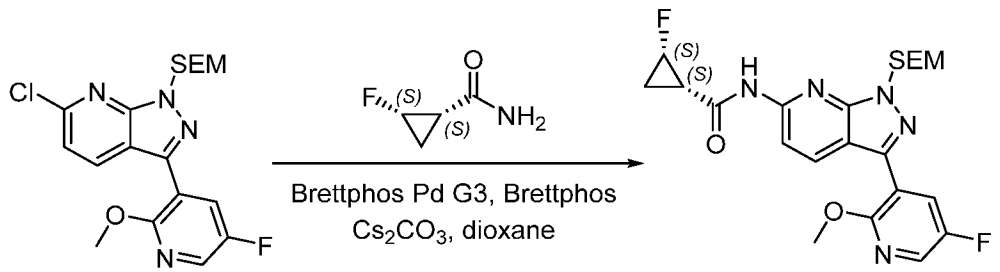
[0425] To a solution of 3-bromo-5-fluoro-2-methoxypyridine (1.0 g, 4.85 mmol) in dioxane (30.0 mL) was added bis(pinacolato)diboron (3.7 g, 14.56 mmol), KOAc (1.43 g, 14.56 mmol) and $Pd(dppf)Cl_2$ (0.4 g, 0.49 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with H_2O/ACN (2/1, v/v) to afford 5-fluoro-2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (600.0 mg, 49%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =254.1.

Step 2: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-5-fluoro-2-methoxypyridine:



[0426] To a solution of 5-fluoro-2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (556.0 mg, 2.20 mmol) in dioxane/H_2O (10.0 mL/2.0 mL) was added 6-chloro-3-iodo-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (900.2 mg, 2.20 mmol), K_2CO_3 (910.9 mg, 6.59 mmol) and Pd(dppf)Cl_2 (160.8 mg, 0.22 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-5-fluoro-2-methoxypyridine (890.0 mg, 99%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =409.1.

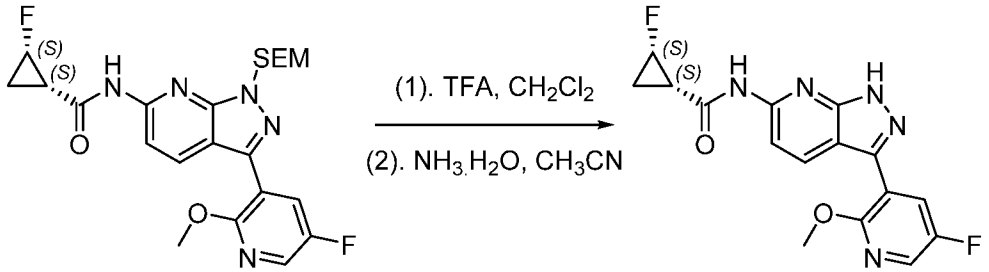
Step 3: Synthesis of (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0427] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-5-fluoro-2-methoxypyridine (170.0 mg, 0.42 mmol) in 1,4-dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (214.3 mg, 2.08 mmol), BrettPhos (44.63 mg, 0.08 mmol), Cs_2CO_3 (406.4 mg, 1.25 mmol) and BrettPhos Pd G3 (37.7 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted

with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (40.0 mg, 20%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =476.2.

Step 4: Synthesis of (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxypyridin-3-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 74):

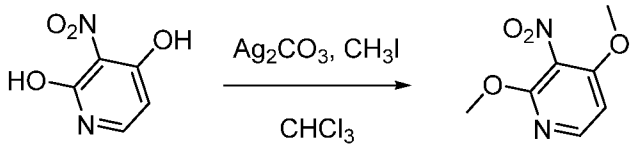


74

[0428] To a solution of (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (120.0 mg, 0.25 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (5.0 mL) was added $NH_3.H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions Column: (Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 51% B in 7 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxypyridin-3-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (19.1 mg, 22%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =346.2. ^1H NMR (400 MHz, DMSO-d_6): δ 13.74 (s, 1H), 10.99 (s, 1H), 8.27 - 8.24 (m, 2H), 8.04 - 7.97 (m, 2H), 5.05 - 4.85 (m, 1H), 3.96 (s, 3H), 2.30 - 2.23 (m, 1H), 1.72 - 1.65 (m, 1H), 1.25 - 1.12 (m, 1H).

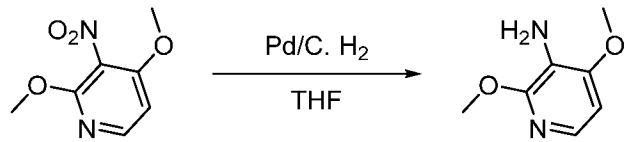
Example S75. Compound 75

Step 1: Synthesis of 2,4-dimethoxy-3-nitropyridine:



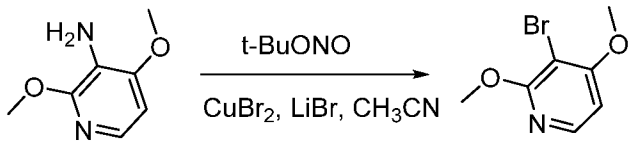
[0429] To a solution of 3-nitropyridine-2,4-diol (5.0 g, 32.03 mmol) in $CHCl_3$ (50.0 mL) was added CH_3I (30.5 g, 256.21 mmol) and Ag_2CO_3 (35.3 g, 128.12 mmol). The resulting mixture was stirred at room temperature for 12 h. After the reaction was completed, the resulting mixture was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (63/37, v/v) to afford 2,4-dimethoxy-3-nitropyridine (3.8 g, 64%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ =185.0.

Step 2: Synthesis of 2,4-dimethoxypyridin-3-amine:



[0430] To a solution of 2,4-dimethoxy-3-nitropyridine (3.7 g, 20.92 mmol) in THF (50.0 mL) was added Pd/C (1.1 g, dry) at room temperature. The resulting mixture was stirred at room temperature for 16 h under H_2. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure to afford 2,4-dimethoxypyridin-3-amine (3.0 g, crude) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ =155.1.

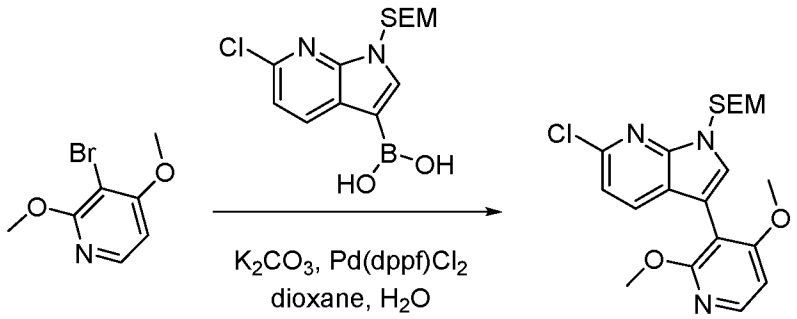
Step 3: Synthesis of 3-bromo-2,4-dimethoxypyridine:



[0431] To a solution of 2,4-dimethoxypyridin-3-amine (1.4 g, 9.08 mmol) in CH_3CN (30.0 mL) was added LiBr (2.7 g, 27.23 mmol), t-BuONO (1.7 g, 16.36 mmol) and $CuBr_2$

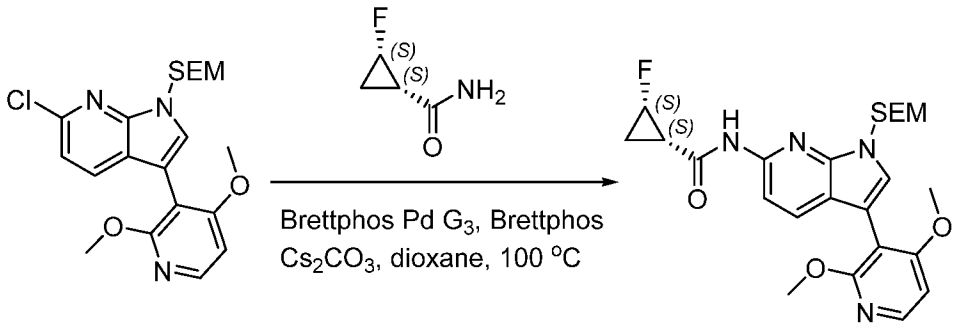
(1.6 g, 10.89 mmol). The resulting mixture was stirred at 60 °C for 3 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with H_2O/ACN (36/64, v/v) to afford 3-bromo-2,4-dimethoxypyridine (1.0 g, 51%) as a red solid. LCMS (ESI, m/z): $[M+H]^+$ =218.0.

Step 4: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2,4-dimethoxypyridine:



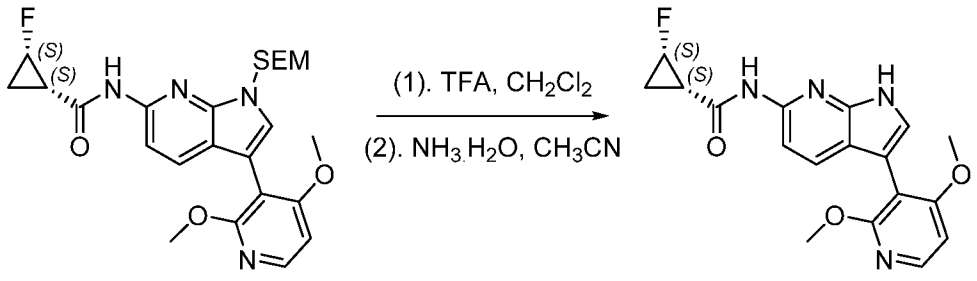
[0432] To a solution of 3-bromo-2,4-dimethoxypyridine (500.0 mg, 2.29 mmol) in H_2O (1.0 mL) and dioxane (10.0 mL) was added K_2CO_3 (950.4 mg, 6.89 mmol), 6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-ylboronic acid (898.8 mg, 2.75 mmol) and Pd(dppf)Cl_2 (167.7 mg, 0.29 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2,4-dimethoxypyridine (230.0 mg, 24%) as a red oil. LCMS (ESI, m/z): $[M+H]^+$ =420.1.

Step 5: Synthesis of (1S,2S)-N-[3-(2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide:



[0433] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2,4-dimethoxypyridine (200.0 mg, 0.47 mmol) in dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (245.8 mg, 2.31 mmol), Brettphos Pd G3 (43.7 mg, 0.08 mmol), BrettPhos (51.2 mg, 0.09 mmol) and Cs_2CO_3 (465.8 mg, 1.49 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 3 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1S,2S)-N-[3-(2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (110.0 mg, 48%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =487.2.

Step 6: Synthesis of (1S,2S)-N-[3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 75):



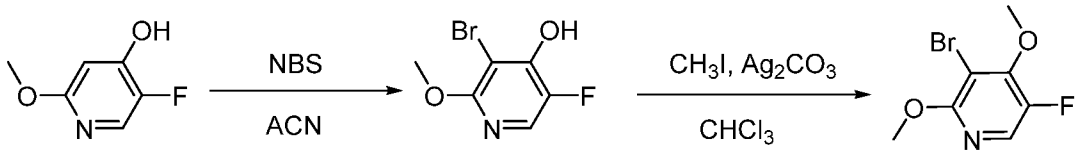
75

[0434] To a solution of (1S,2S)-N-[3-(2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (100.0 mg, 0.19mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was

added $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 39% B in 9 min; 254 nm) to afford (1S,2S)-N-[3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (28.2 mg, 43%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =357.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.53 (s, 1H), 10.58 (s, 1H), 8.06 (d, J = 6.0 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 5.7 Hz, 1H), 5.04 - 4.80 (m, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 2.27 - 2.18 (m, 1H), 1.72 - 1.61 (m, 1H), 1.28 - 1.08 (m, 1H).

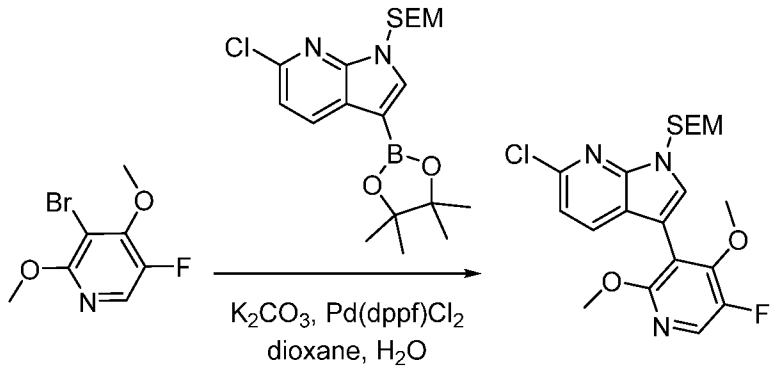
Example S76. Compound 76

Step 1: Synthesis of 3-bromo-5-fluoro-2,4-dimethoxypyridine:



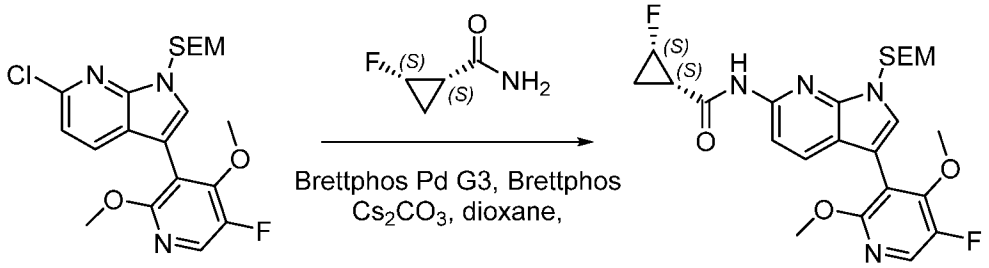
[0435] To a solution of 5-fluoro-2-methoxypyridin-4-ol (3.0 g, 20.96 mmol) in ACN (125.0 mL) was added NBS (3.5 g, 19.91 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (250.0 mL). Then Ag_2CO_3 (15.4 g, 55.85 mmol) and CH_3I (7.9 g, 55.87 mmol) were added to the mixture at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford 3-bromo-5-fluoro-2,4-dimethoxypyridine (3.1 g, 94%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =236.0.

Step 2: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-fluoro-2,4-dimethoxypyridine:



[0436] To a solution of 3-bromo-5-fluoro-2,4-dimethoxypyridine (173.0 mg, 0.73 mmol) in dioxane/H_2O (10.0 mL/2.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (299.6 mg, 0.73 mmol), K_2CO_3 (303.8 mg, 2.20 mmol) and $Pd(dppf)Cl_2$ (53.6 mg, 0.07 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-fluoro-2,4-dimethoxypyridine (220.0 mg, 68%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =438.1.

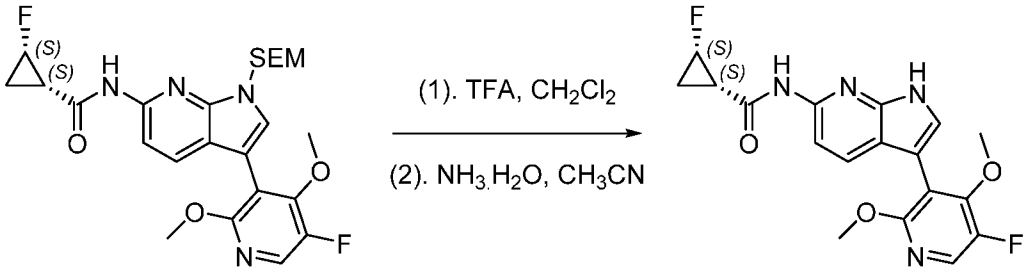
Step 3: Synthesis of (1S,2S)-2-fluoro-N-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0437] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-fluoro-2,4-dimethoxypyridine (200.0 mg, 0.46 mmol) in 1,4-dioxane (15.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (235.4 mg, 2.28 mmol), BrettPhos (49.0 mg, 0.09 mmol), Cs_2CO_3 (446.4 mg, 1.37 mmol) and BrettPhos Pd G3 (41.4 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h. After the reaction was completed, the reaction mixture was diluted with H_2O and

extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford (1S,2S)-2-fluoro-N-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (90.0 mg, 39%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =505.2.

Step 4: Synthesis of (1S,2S)-2-fluoro-N-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 76):

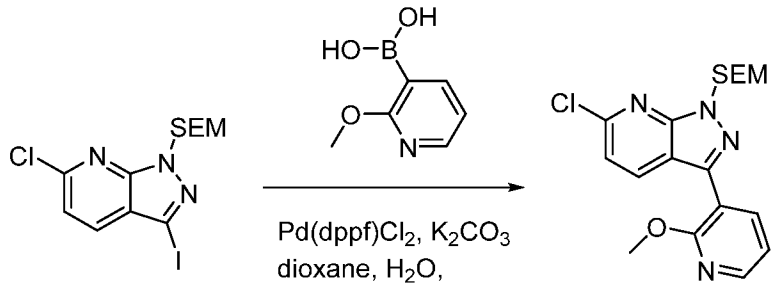


76

[0438] To a solution of (1S,2S)-2-fluoro-N-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (90.0 mg, 0.18 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (5.0 mL) and $NH_3.H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the reaction was diluted with H_2 and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions Column: (YMC-Actus Triart C18, 30x250 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 38% B to 47% B in 8 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (19.3 mg, 29%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =375.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.70 (s, 1H), 10.63 (s, 1H), 8.12 (d, J = 3.2 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 2.4 Hz, 1H), 5.02 - 4.82 (m, 1H), 3.81 - 3.80 (m, 6H), 2.25 - 2.22 (m, 1H), 1.70 - 1.63 (m, 1H), 1.25 - 1.04 (m, 1H).

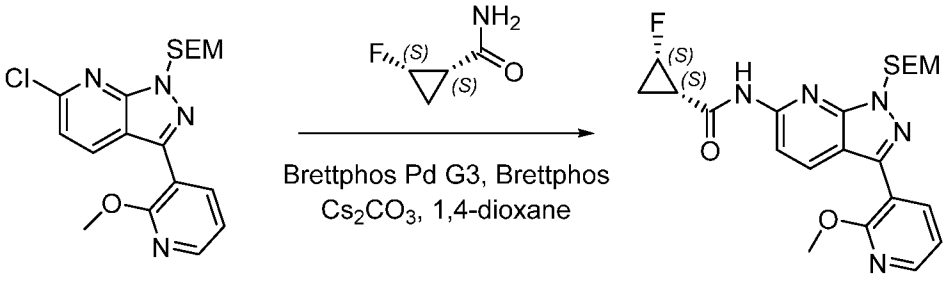
Example S77. Compound 77

Step 1: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-2-methoxypyridine:



[0439] To a solution of 6-chloro-3-iodo-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (300.3 mg, 0.73 mmol) in dioxane/H_2O (10.0 mL/2.0 mL) was added 2-methoxypyridin-3-ylboronic acid (112.0 mg, 0.73 mmol), K_2CO_3 (303.6 mg, 2.20 mmol) and $Pd(dppf)Cl_2$ (53.6 mg, 0.07 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-2-methoxypyridine (227.0 mg, 79%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =391.1.

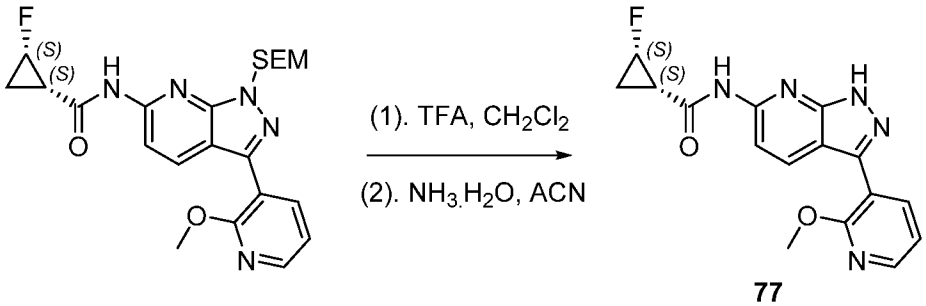
Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-(2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0440] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-2-methoxypyridine (170.0 mg, 0.44 mmol) in 1,4-dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (224.2 mg, 2.17 mmol), BrettPhos (46.7 mg, 0.09 mmol), Cs_2CO_3 (425.1 mg, 1.31 mmol) and BrettPhos Pd G3 (39.4 mg, 0.04 mmol)

at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford (1S,2S)-2-fluoro-N-[3-(2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (138.0 mg, 70%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =458.2.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-[3-(2-methoxypyridin-3-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 77):



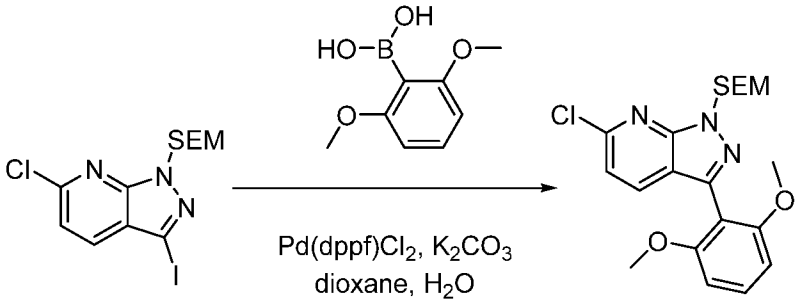
77

[0441] To a solution of (1S,2S)-2-fluoro-N-[3-(2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (138.0 mg, 0.30 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (5.0 mL) and $NH_3.H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; 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 10 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(2-methoxypyridin-3-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (17.3 mg, 18%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =328.2. ^1H NMR (300 MHz, DMSO-d_6): δ 13.60 (s, 1H), 10.96 (s, 1H), 8.29 - 8.20 (m, 2H),

8.08 - 8.00 (m, 2H), 7.16 - 7.12 (m, 1H), 5.07 - 4.84 (m, 1H), 3.96 (s, 3H), 2.29 - 2.25 (m, 1H), 1.73 - 1.60 (m, 1H), 1.23 - 1.18 (m, 1H).

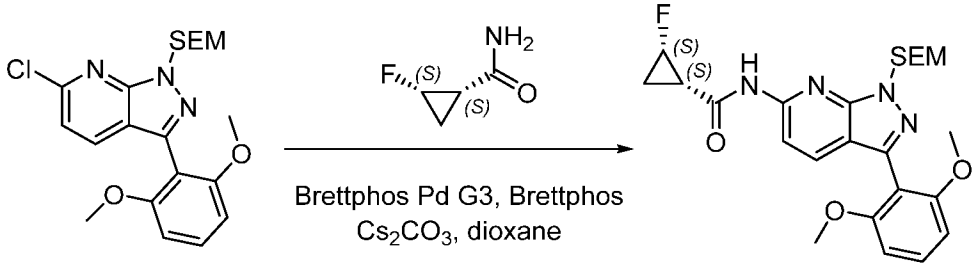
Example S78. Compound 78

Step 1: Synthesis of 6-chloro-3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine :



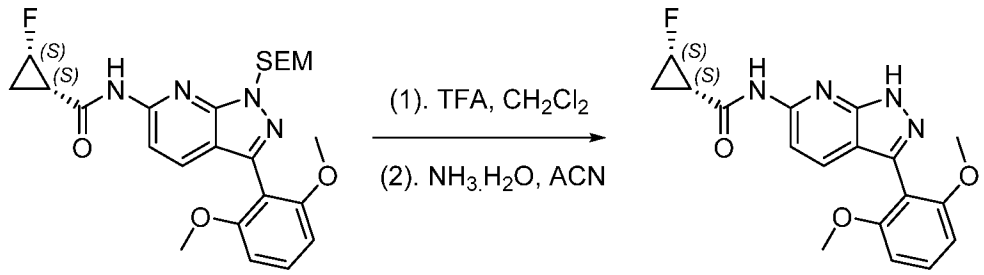
[0442] To a solution of 6-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (562.9 mg, 1.37 mmol) in dioxane/H_2O (16.0/4.0 mL) was added (2,6-dimethoxyphenyl)boronic acid (250.0 mg, 1.37 mmol), K_2CO_3 (569.6 mg, 4.12 mmol) and $Pd(dppf)Cl_2$ (100.5 mg, 0.14 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 6-chloro-3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (200.0 mg, 34%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =420.1.

Step 2: Synthesis of (1S,2S)-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide :



[0443] To a solution of 6-chloro-3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (180.0 mg, 0.43 mmol) in dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (220.9 mg, 2.14 mmol), Cs_2CO_3 (418.9 mg, 1.29 mmol), Brettphos (46.0 mg, 0.09 mmol) and BrettPhos Pd G3 (38.9 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (10/1, v/v) to afford (1S,2S)-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (60.0 mg, 19%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =487.2.

Step 3: Synthesis of (1S,2S)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (Compound 78):



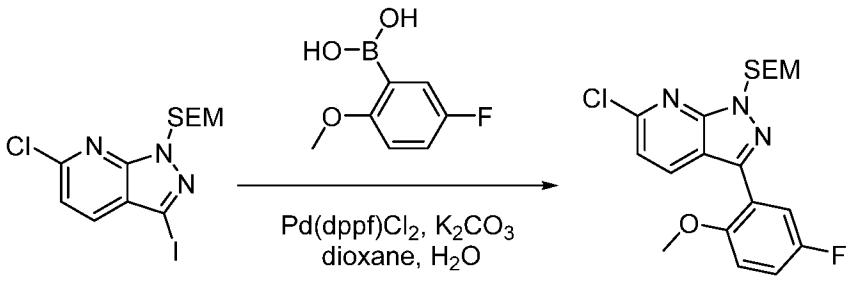
78

[0444] To a solution of (1S,2S)-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (100.0 mg, 0.21 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in ACN (5.0 mL) and $NH_3 \cdot H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 21% to 51% in 7 min; 254 nm) to afford

(1S,2S)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (22.1 mg, 30%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =357.2. ^1H NMR (400 MHz, DMSO-d_6): δ 13.31 (s, 1H), 10.92 (s, 1H), 7.92 - 7.90 (m, 1H), 7.76 - 7.74 (m, 1H), 7.43 - 7.39 (m, 1H), 6.80 - 6.78 (m, 2H), 5.07 - 4.84 (m, 1H), 3.66 (s, 6H), 2.32 - 2.21 (m, 1H), 1.75 - 1.61 (m, 1H), 1.22 - 1.13 (m, 1H).

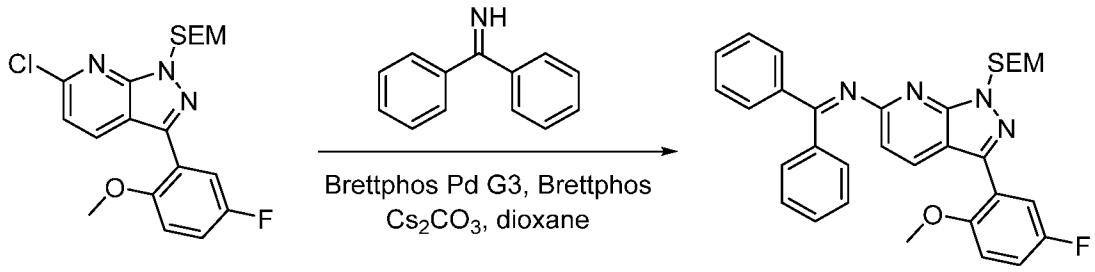
Example S79. Compound 79

Step 1: Synthesis of 6-chloro-3-(5-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine:



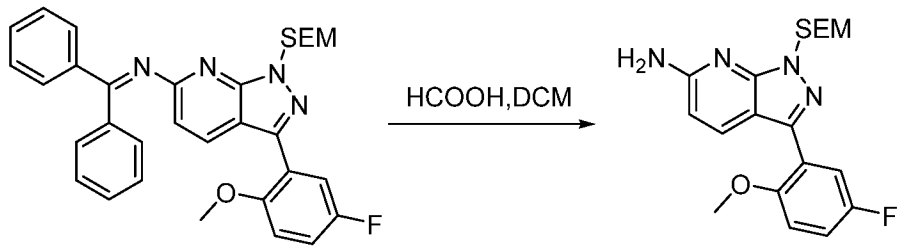
[0445] To a solution of 6-chloro-3-iodo-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (1.5 g, 3.66 mmol) in dioxane/H_2O (5.0/1.0 mL) was added 5-fluoro-2-methoxyphenylboronic acid (750.0 mg, 4.39 mmol), K_2CO_3 (1.5 g, 10.9 mmol) and Pd(dppf)Cl_2 (270.0 mg, 0.36 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (90/10, v/v) to afford 6-chloro-3-(5-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (1.0 g, 67%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =408.1.

Step 2: Synthesis of N-[3-(5-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]-1,1-diphenylmethanimine:



[0446] To a solution of 6-chloro-3-(5-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (980.0 mg, 2.44 mmol) in dioxane (5.0 mL) was added diphenylmethanimine (1.3 g, 7.21 mmol), BrettPhos (257.9 mg, 0.48 mmol), Cs_2CO_3 (2.3 g, 7.21 mmol) and BrettPhos Pd G3 (217.7 mg, 0.24 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (85/15, v/v) to afford N-[3-(5-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]-1,1-diphenylmethanimine (500.0 mg, 36%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =553.2.

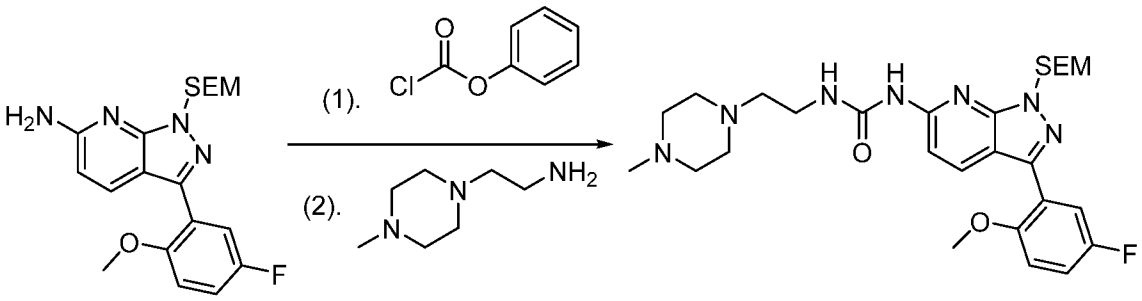
Step 3: Synthesis of 3-(5-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-amine:



[0447] To a solution of N-[3-(5-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]-1,1-diphenylmethanimine (420.0 mg, 0.76 mmol) in DCM (5.0 mL) was added HCOOH (0.03 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (65/35, v/v) to afford 3-(5-fluoro-2-

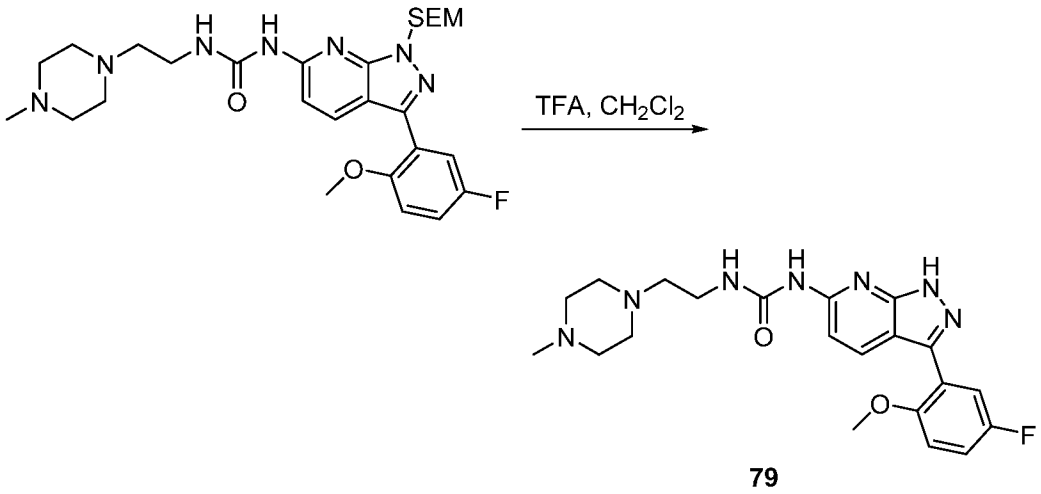
methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-amine (256.0 mg, 87%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =389.2.

Step 4: Synthesis of 3-[3-(5-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea:



[0448] To a solution of 3-(5-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-amine (140.0 mg, 0.36 mmol) in DCM (5.0 mL) was added pyridine (112.0 mg, 1.41 mmol) and phenyl chloroformate (67.7 mg, 0.43 mmol) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. The resulting mixture was concentrated under reduced pressure. Then 2-(4-methylpiperazin-1-yl)ethanamine (206.4 mg, 1.44 mmol) and pyridine (5.0 ml) were added to the residue at 0 °C under N_2. The resulting mixture was stirred at 60 °C for another 1 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (92/8, v/v) to afford 3-[3-(5-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (200.0 mg, 99%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =558.3.

[0449] Step 5: Synthesis of 3-[3-(5-fluoro-2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (Compound 79):

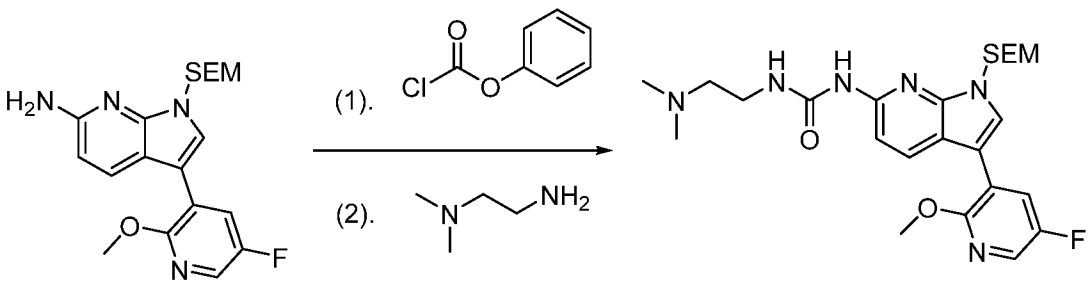


79

[0450] To a solution of 1-(3-(5-fluoro-2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-3-(2-(4-methylpiperazin-1-yl)ethyl)urea (130.0 mg, 0.25 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, 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, 5 um; 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 10 min; 254 nm) to afford 3-[3-(5-fluoro-2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (9.7 mg, 6%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =428.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.37 (s, 1H), 9.64 (s, 1H), 8.43 (s, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.42 - 7.39 (m, 1H), 7.28 - 7.13 (m, 3H), 3.82 (s, 3H), 3.30 (s, 3H), 3.05 - 2.83 (m, 4H), 2.79 - 2.59 (m, 8H).

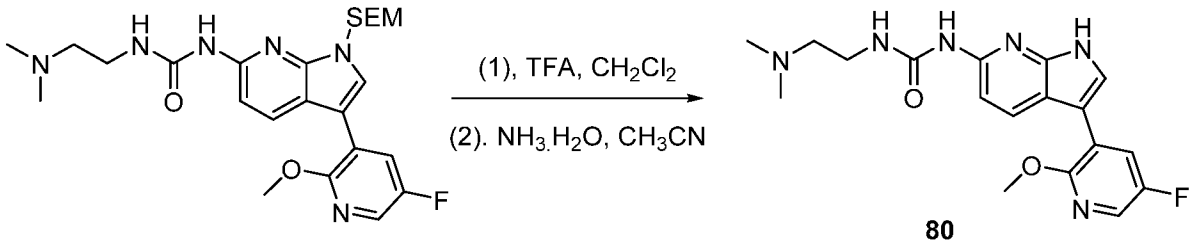
Example S80. Compound 80

Step 1: Synthesis of 3-[2-(dimethylamino)ethyl]-1-[3-(5-fluoro-2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea:



[0451] To a solution of 3-(5-fluoro-2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (180.0 mg, 0.46 mmol) in DCM (5.0 mL) was added pyridine (144.0 mg, 1.82 mmol) and phenyl chloroformate (89.9 mg, 0.57 mmol) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. The resulting mixture was concentrated under reduced pressure. Then (2-aminoethyl)dimethylamine (162.1 mg, 1.84 mmol) and pyridine (5.0 mL) were added to the residue. The resulting mixture was stirred at 60 °C for another 1 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (92/8, v/v) to afford 3-[2-(dimethylamino)ethyl]-1-[3-(5-fluoro-2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (110.0 mg, 47%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =503.3.

Step 2: Synthesis of 3-[2-(dimethylamino)ethyl]-1-[3-(5-fluoro-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (Compound 80):



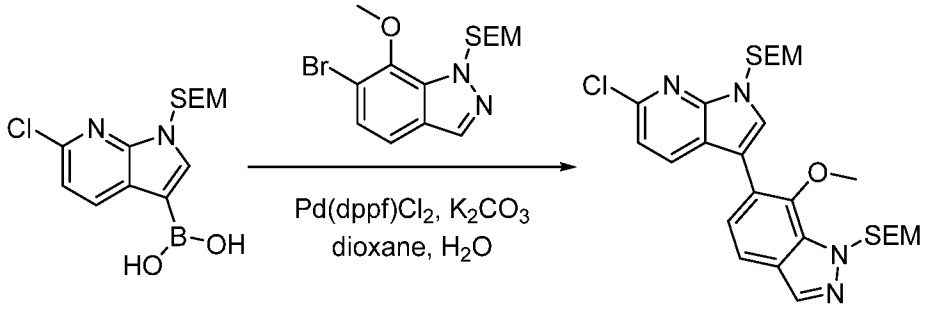
80

[0452] To a solution of 3-[2-(dimethylamino)ethyl]-1-[3-(5-fluoro-2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (110.0 mg, 0.22 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in CH_3CN (3.0 mL) and $NH_3 \cdot H_2O$ (3 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27 % B to 57 % B in 7 min; 254 nm) to afford 3-[2-(dimethylamino)ethyl]-1-[3-(5-fluoro-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (24.0 mg, 29%) as a white

solid. LCMS (ESI, m/z): $[M+H]^+$ =373.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.68 (d, J = 2.0 Hz, 1H), 9.21 (s, 1H), 8.27 (s, 1H), 8.09 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 2.8 Hz, 1H), 7.91 - 7.88 (m, 1H), 7.72 (d, J = 2.8 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 3.94 (s, 3H), 3.33 - 3.28 (m, 2H), 2.41 - 2.38 (m, 2H), 2.20 (s, 6H).

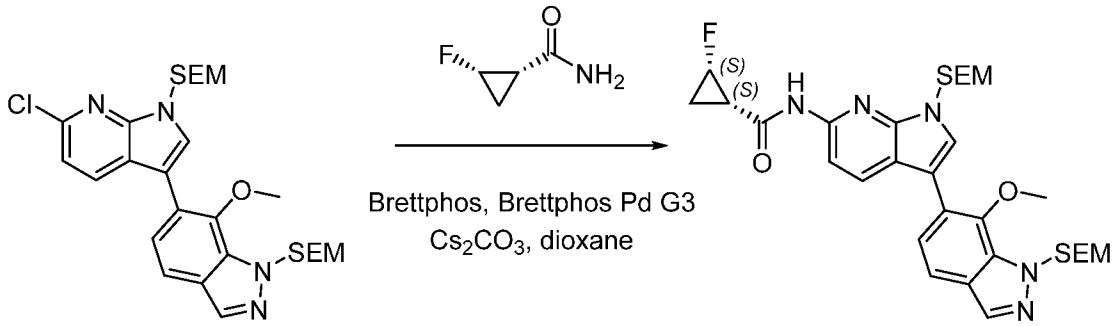
Example S81. Compound 81

Step 1: Synthesis of 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole:



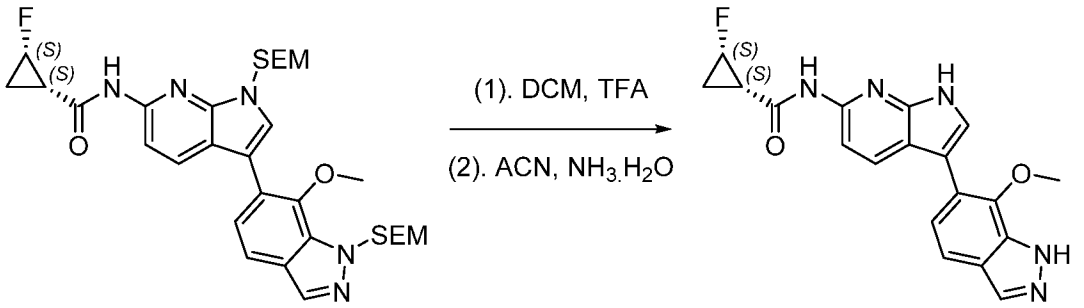
[0453] To a solution of (6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)boronic acid (300.0 mg, 0.92 mmol) in dioxane/H_2O (16.0/4.0 mL) was added 6-bromo-7-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (328.2 mg, 0.92 mmol), K_2CO_3 (380.8 mg, 2.76 mmol) and $Pd(dppf)Cl_2$ (67.2 mg, 0.09 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (300.0 mg, 58%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =559.2.

Step 2: Synthesis of (1S,2S)-2-fluoro-N-(3-(7-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0454] To a solution of 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (280.0 mg, 0.50 mmol) in dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (258.1 mg, 2.50 mmol), Cs_2CO_3 (489.4 mg, 1.50 mmol), Brettphos (53.8 mg, 0.10 mmol) and BrettPhos Pd G3 (45.4 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1S,2S)-2-fluoro-N-(3-(7-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (110.0 mg, 35%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =626.3.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-(3-(7-methoxy-1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 81):



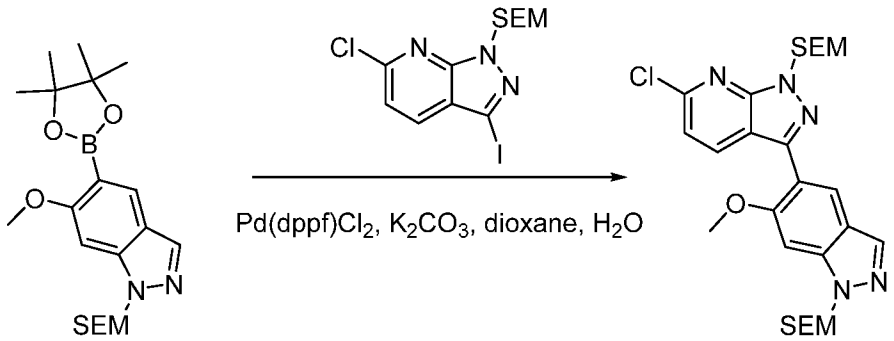
81

[0455] To a solution of (1S,2S)-2-fluoro-N-(3-(7-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (100.0 mg, 0.16 mmol) in DCM (5.0

mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in ACN (5.0 mL) and $NH_3.H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 21% to 43% in 7 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-(7-methoxy-1H-indazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (10.8 mg, 18%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =366.2. ^1H NMR (300 MHz, DMSO-d_6): δ 13.32 - 13.29 (m, 1H), 11.71 (s, 1H), 10.67 (s, 1H), 8.10 - 8.06 (m, 2H), 7.93 (d, J = 8.4 Hz, 1H), 7.67 (s, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 5.07 - 4.81 (m, 1H), 3.68 (s, 3H), 2.28 - 2.21 (m, 1H), 1.71 - 1.62 (m, 1H), 1.24 - 1.19 (m, 1H).

Example S82. Compound 82

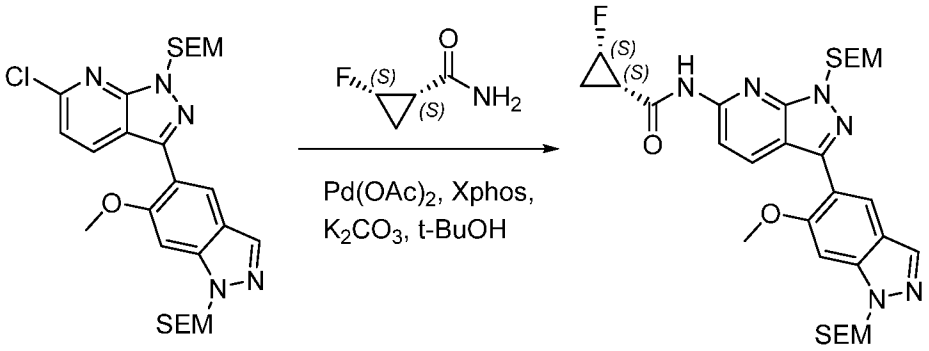
Step 1: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole :



[0456] To a mixture of 6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl) ethoxy]methyl]indazole (800.0 mg, 1.97 mmol) and 6-chloro-3-iodo-1-[[2-(trimethylsilyl)ethoxy]methyl] pyrazolo[3,4-b]pyridine (810.5 mg, 1.97 mmol) in dioxane/H_2O (10.0 mL/2.0 mL) was added K_2CO_3 (820.2 mg, 5.93 mmol) and $Pd(dppf)Cl_2$ (144.7 mg, 0.19 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the reaction was diluted with water at room temperature, extracted with ethyl acetate. The combined organic layer was

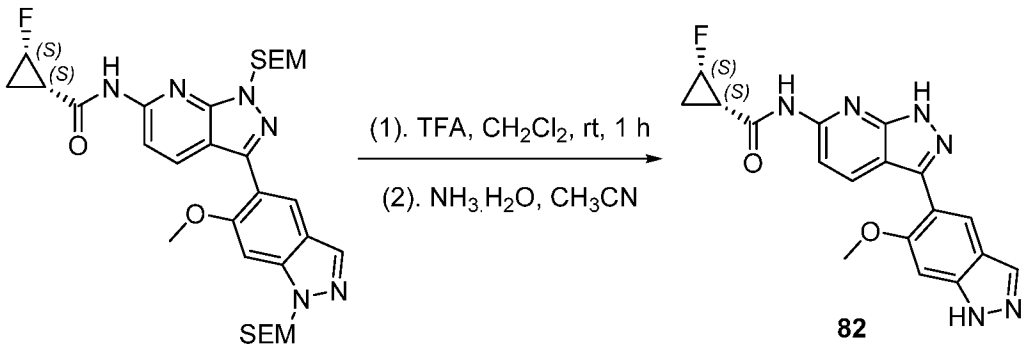
washed with brine, dried over anhydrous sodium sulfate and filtered. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/EtOAc (3/1, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-6-methoxy-1-[[2-(trimethylsilyl) ethoxy]methyl]indazole (520.0 mg, 47%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =560.2

Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0457] To a mixture of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazole (260.0 mg, 0.46 mmol) and (1S,2S)-2-fluorocyclopropane-1-carboxamide (239.2 mg, 2.32 mmol) in t-BuOH (5.0 mL) was added $Pd(OAc)_2$ (10.4 mg, 0.04 mmol), K_2CO_3 (192.4 mg, 1.39 mmol) and Xphos (25.5 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h under N_2. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/EtOAc (3/1, v/v) to afford (1S,2S)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl] indazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (220.0 mg, 75%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =627.3.

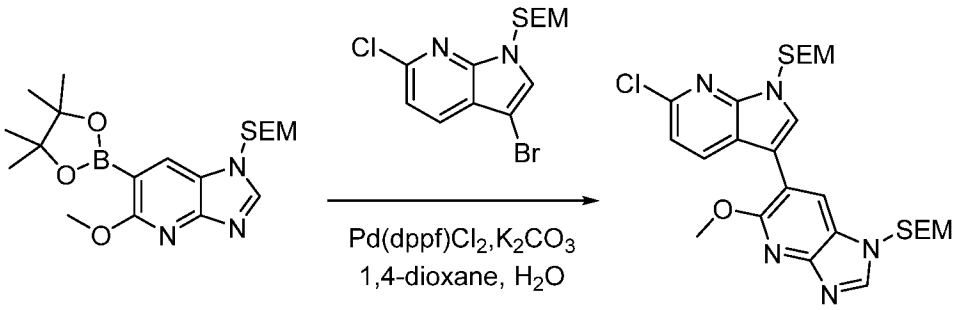
Step 3: Synthesis of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 82):



[0458] To a solution of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]indazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (200.0 mg, 0.31 mmol) in DCM (3.0 mL) was added TFA (3.0 mL). The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added ACN (1.0 mL) and $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 33% B in 9 min; 254/220 nm) to afford (1S,2S)-2-fluoro-N-[3-(6-methoxy-1H-indazol-5-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (12.2 mg, 10%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$=367.1. ^1H NMR (300 MHz, DMSO-d_6): δ 13.38 (s, 1H), 12.94 (s, 1H), 10.95 (s, 1H), 8.08 - 7.91 (m, 4H), 7.11 (s, 1H), 5.07 - 4.83 (m, 1H), 3.87 (s, 3H), 2.27 - 2.20 (m, 1H), 1.74 - 1.63 (m, 1H), 1.24 - 1.18 (m, 1H).

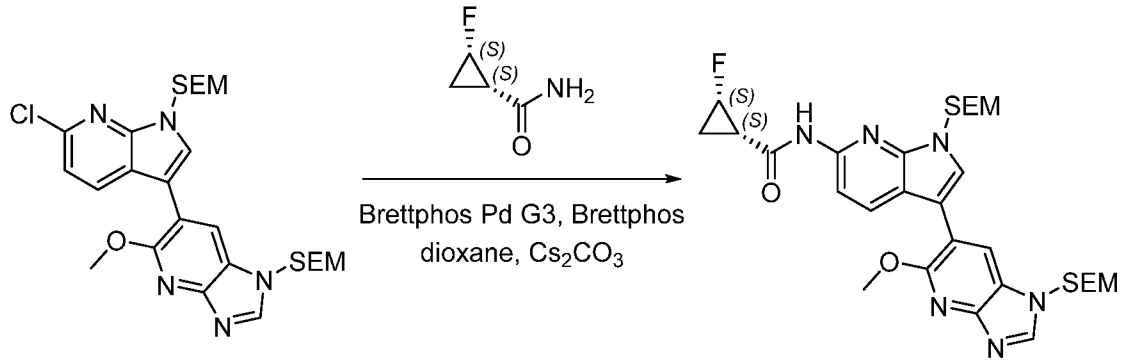
Example S83. Compound 83

Step 1: Synthesis of 6-chloro-3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



[0459] To a solution of 5-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridine (500.0 mg, 1.23 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (446.1 mg, 1.23 mmol), K_2CO_3 (511.4 mg, 3.70 mmol) and Pd(dppf)Cl_2 (180.5 mg, 0.25 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (90/10, v/v) to afford 6-chloro-3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 43%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =560.2.

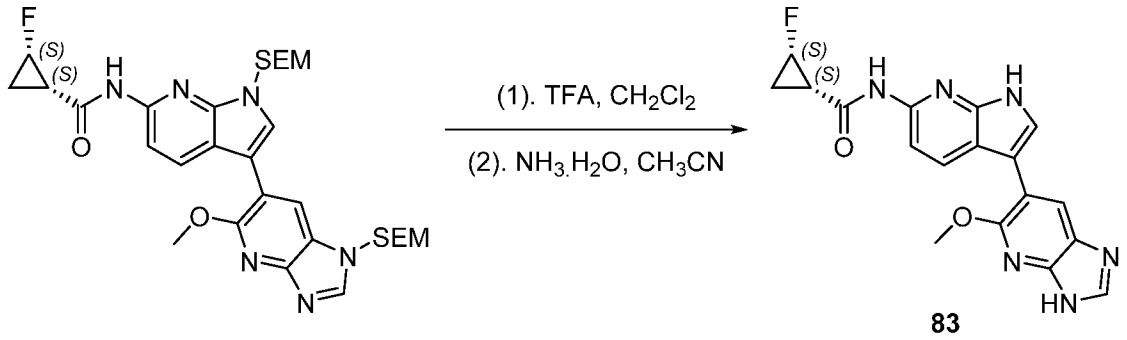
Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0460] To a solution of 6-chloro-3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 0.50 mmol) in dioxane (4.0

mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (154.8 mg, 1.49 mmol), BrettPhos (53.6 mg, 0.10 mmol), Cs_2CO_3 (488.5 mg, 1.49 mmol) and BrettPhos Pd G3 (45.3 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (39/61, v/v) to afford (1S,2S)-2-fluoro-N-[3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (300.0 mg, 76%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =627.3.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-(3-[5-methoxy-3H-imidazo[4,5-b]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 83):



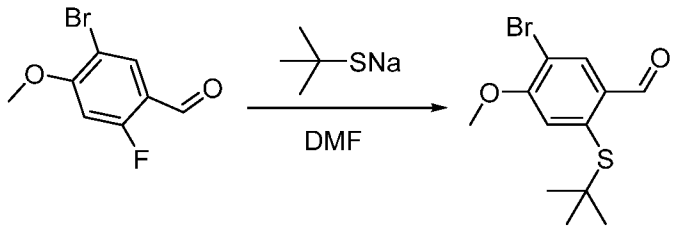
83

[0461] To a solution of (1S,2S)-2-fluoro-N-[3-(5-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazo[4,5-b]pyridin-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (280.0 mg, 0.44 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in CH_3CN (2.0 mL) and $NH_3 \cdot H_2O$ (2.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure, then the was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30x250 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 21 % B to 29 % B in 10 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-[5-methoxy-3H-imidazo[4,5-b]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (8.1 mg, 5%) as a white solid.

LCMS (ESI, m/z): $[M+H]^+$ =367.1. ^1H NMR (400 MHz, DMSO-d_6): δ 13.18 - 12.18 (m, 1H), 11.60 (s, 1H), 10.61 (s, 1H), 8.35 - 7.75 (m, 4H), 7.70 - 7.55 (m, 1H), 5.05 - 4.70 (m, 1H), 3.95 (s, 3H), 2.29 - 2.15 (m, 1H), 1.71 - 1.50 (m, 1H), 1.21 - 1.08 (m, 1H).

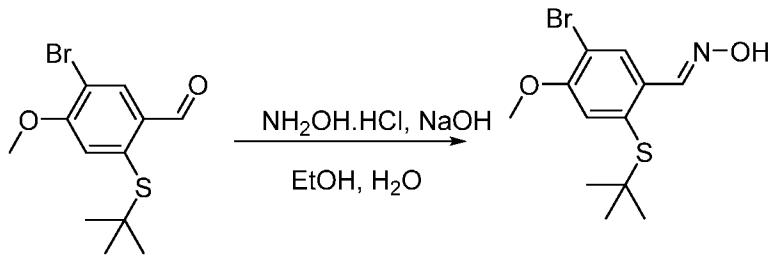
Example S84. Compound 84

Step 1: Synthesis of 5-bromo-2-(tert-butylsulfanyl)-4-methoxybenzaldehyde:



[0462] To a solution of 5-bromo-2-fluoro-4-methoxybenzaldehyde (500.0 mg, 2.14 mmol) in DMF (10.0 mL) was added (tert-butylsulfanyl)sodium (361.0 mg, 3.21 mmol) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 5-bromo-2-(tert-butylsulfanyl)-4-methoxybenzaldehyde (600.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =303.0.

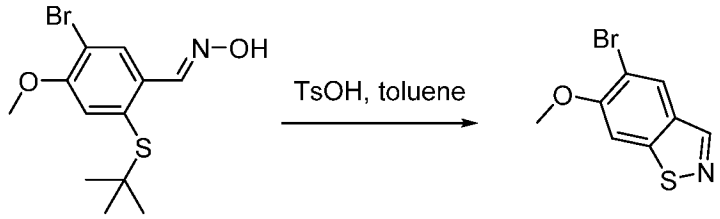
Step 2: Synthesis of (E)-N-[[5-bromo-2-(tert-butylsulfanyl)-4-methoxyphenyl]methylidene]hydroxylamine:



[0463] To a solution of 5-bromo-2-(tert-butylsulfanyl)-4-methoxybenzaldehyde (600.0 mg, 1.98 mmol) in EtOH/H_2O (3.0/9.0 mL) was added $NH_2OH \cdot HCl$ (206.2 mg, 2.96 mmol) and NaOH (237.4 mg, 5.93 mmol) at 0 °C under N_2. The resulting mixture was stirred at 60 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried

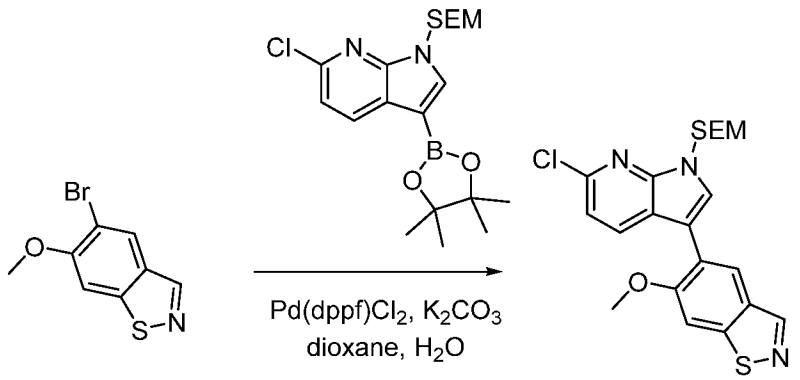
over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford (E)-N-[[5-bromo-2-(tert-butylsulfanyl)-4-methoxyphenyl]methylidene]hydroxylamine (510.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =318.0.

Step 3: Synthesis of 5-bromo-6-methoxy-1,2-benzothiazole:



[0464] To a solution of (E)-N-[[5-bromo-2-(tert-butylsulfanyl)-4-methoxyphenyl]methylidene]hydroxylamine (500.0 mg, 1.57 mmol) in toluene (5.0 mL) was added TsOH (54.1 mg, 0.31 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (65/35, v/v) to afford 5-bromo-6-methoxy-1,2-benzothiazole (150.0 mg, 39%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =243.9.

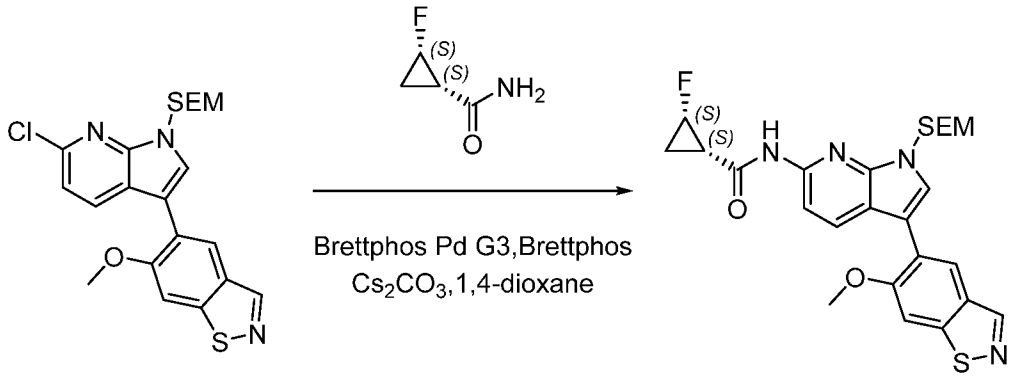
Step 4: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1,2-benzothiazole:



[0465] To a solution of 5-bromo-6-methoxy-1,2-benzothiazole (130.0 mg, 0.53 mmol) in dioxane/H_2O (5.0/1.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (261.2 mg, 0.64 mmol),

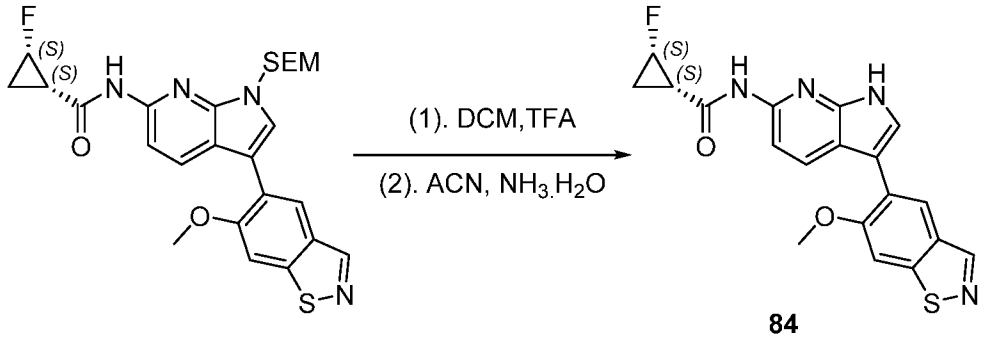
K_2CO_3 (220.8 mg, 1.60 mmol) and $Pd(dppf)Cl_2$ (40.0 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (90/10, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1,2-benzothiazole (220.0 mg, 92%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =446.1.

Step 5: Synthesis of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1,2-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0466] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1,2-benzothiazole (200.0 mg, 0.44 mmol) in 1,4-dioxane (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (230.0 mg, 2.24 mmol), Cs_2CO_3 (438.2 mg, 1.34 mmol), BrettPhos (48.1 mg, 0.09 mmol) and BrettPhos Pd G3 (40.6 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (65/35, v/v) to afford (1S,2S)-2-fluoro-N-[3-(6-methoxy-1,2-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (83.0 mg, 36%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =513.2.

Step 6: Synthesis of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1,2-benzothiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 84):

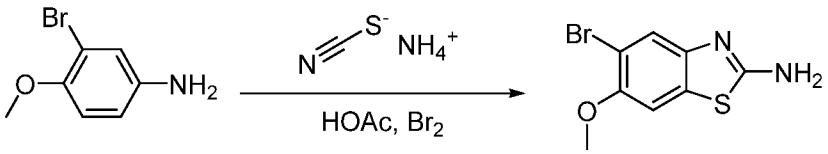


84

[0467] To a solution of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1,2-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (83.0 mg, 0.16 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in ACN (3.0 mL) was added $NH_3 \cdot H_2O$ (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 24 % B to 54 % B in 10 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(6-methoxy-1,2-benzothiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (4.0 mg, 6%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =383.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.68 (d, J = 2.0 Hz, 1H), 10.66 (s, 1H), 9.00 (d, J = 0.8 Hz, 1H), 8.31 (s, 1H), 8.10 (d, J = 8.8 Hz, 1H), 7.94 - 7.89 (m, 2H), 7.68 (d, J = 2.0 Hz, 1H), 5.01 - 4.84 (m, 1H), 3.94 (s, 3H), 2.30 - 2.23 (m, 1H), 1.69 - 1.63 (m, 1H), 1.20 - 1.10 (m, 1H).

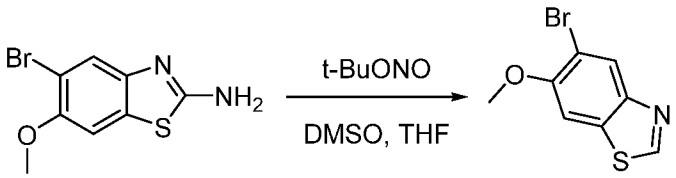
Example S85. Compound 85

Step 1: Synthesis of 5-bromo-6-methoxy-1,3-benzothiazol-2-amine:



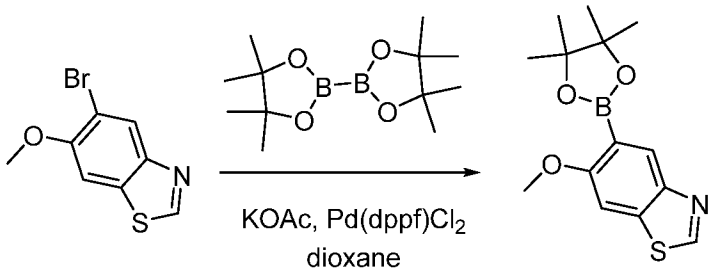
[0468] To a solution of 3-bromo-4-methoxyaniline (4.0 g, 19.80 mmol) in HOAc (30.0 mL) was added ammonium thiocyanate (7.6 g, 99.84 mmol) at room temperature under N_2. The resulting mixture was stirred at room temperature for 1 h. Then Br_2 (1.2 mL) was added dropwise to the mixture at 0 °C. The resulting mixture was stirred at 0 °C for another 2 h. After the reaction was completed, the reaction mixture was quenched with sat. NH_4Cl (aq.) at 0 °C. The pH value of the mixture was adjusted to 12 with $NH_3.H_2O$ (aq.). The resulting mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (20/80, v/v) to afford 5-bromo-6-methoxy-1,3-benzothiazol-2-amine (3.2 g, 62%) as an off white solid. LCMS (ESI, m/z): $[M+H]^+$ =258.9.

Step 2: Synthesis of 5-bromo-6-methoxy-1,3-benzothiazole:



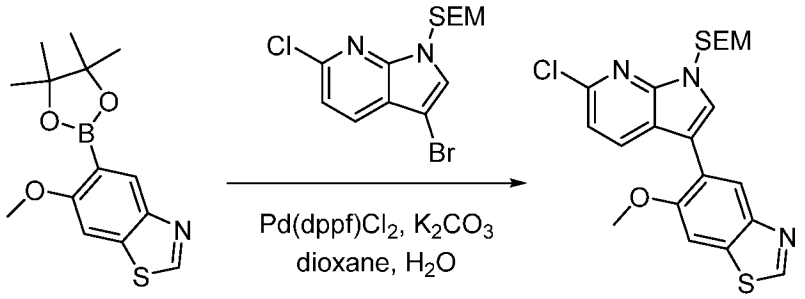
[0469] To a solution of 5-bromo-6-methoxy-1,3-benzothiazol-2-amine (2.7 g, 10.42 mmol) in THF (10.0 mL) was added DMSO (90.0 mg, 1.15 mmol) and t-BuONO (1.8 g, 17.45 mmol) at room temperature. The resulting mixture was stirred at 30 °C for 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (88/12, v/v) to afford 5-bromo-6-methoxy-1,3-benzothiazole (2.3 g, 90%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =243.9.

Step 3: Synthesis of 6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-benzo[d]thiazole:



[0470] To a solution of 5-bromo-6-methoxy-1,3-benzothiazole (500.0 mg, 2.04 mmol) in dioxane (5.0 mL) was added bis(pinacolato)diboron (1.04 g, 4.09 mmol), KOAc (603.1 mg, 6.14 mmol) and $Pd(dppf)Cl_2$ (149.8 mg, 0.20 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with MeOH/H_2O (1/1, v/v) to afford 6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-benzothiazole (300.0 mg, 50%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =292.1.

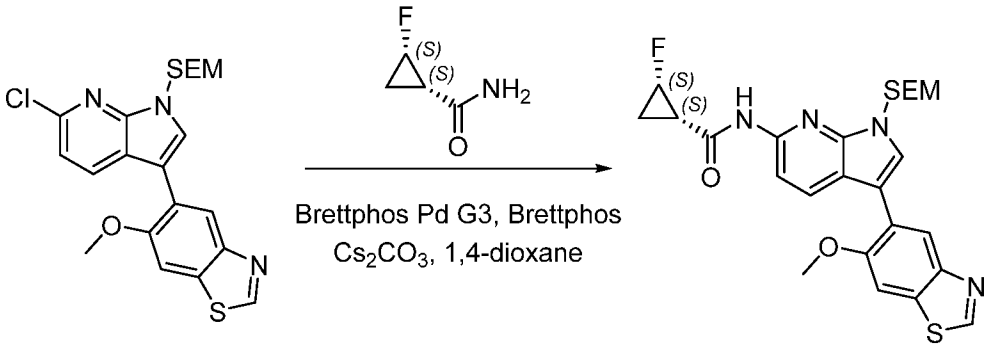
Step 4: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1,3-benzothiazole:



[0471] To a solution of 6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzothiazole (300.0 mg, 1.03 mmol) in dioxane/H_2O (5.0/1.0 mL) was added 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (447.2 mg, 1.23 mmol), K_2CO_3 (599.5 mg, 4.33 mmol) and $Pd(dppf)Cl_2$ (105.5 mg, 0.14 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (88/12, v/v) to afford 5-(6-

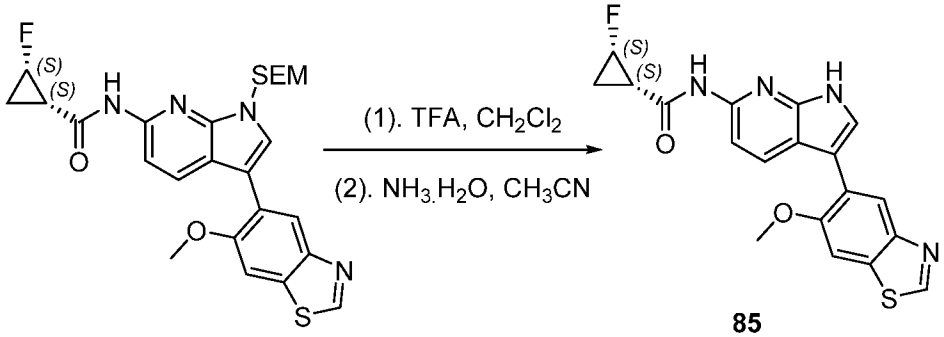
chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1,3-benzothiazole (240.0 mg, 52%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =446.1.

Step 5: Synthesis of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1,3-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0472] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1,3-benzothiazole (200.0 mg, 0.44 mmol) in 1,4-dioxane (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (140.0 mg, 1.35 mmol), BrettPhos (48.1 mg, 0.09 mmol), Cs_2CO_3 (438.2 mg, 1.34 mmol) and BrettPhos Pd G3 (40.6 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford (1S,2S)-2-fluoro-N-[3-(6-methoxy-1,3-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (150.0 mg, 65%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =513.2.

Step 6: Synthesis of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1,3-benzothiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 85):

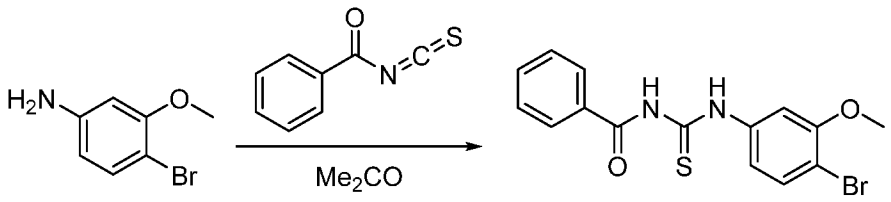


85

[0473] To a solution of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1,3-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (130.0 mg, 0.25 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in CH_3CN (3.0 mL) and $NH_3 \cdot H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, 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, 5 um; 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 10 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(6-methoxy-1,3-benzothiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (36.4 mg, 38%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =383.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.66 (s, 1H), 10.64 (s, 1H), 9.22 (s, 1H), 8.14 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.93 - 7.87 (m, 2H), 7.66 (d, J = 2.7 Hz, 1H), 5.06 - 4.79 (m, 1H), 3.90 (s, 3H), 2.26 - 2.20 (m, 1H), 1.73 - 1.63 (m, 1H), 1.29 - 1.09 (m, 1H).

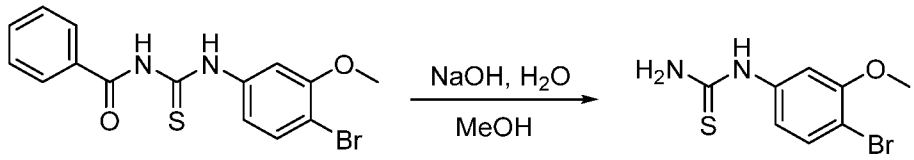
Example S86. Compound 86

Step 1: Synthesis of N-((4-bromo-3-methoxyphenyl)carbamothioyl)benzamide:



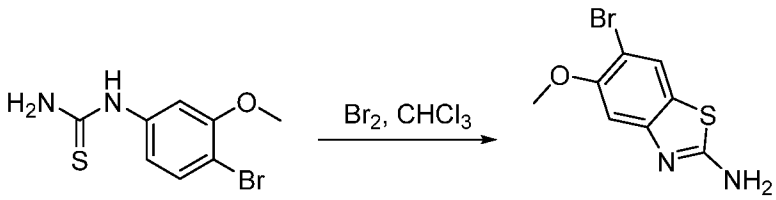
[0474] To a solution of 4-bromo-3-methoxyaniline (2.0 g, 9.90 mmol) in Me_2CO (50.0 mL) was added benzoyl isothiocyanate (1.6 g, 9.90 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 30 min. After the reaction was completed, the reaction mixture was cooled to room temperature and filtered. The solid was collected and dried to afford N-((4-bromo-3-methoxyphenyl)carbamothioyl)benzamide (3.1 g, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =365.0.

Step 2: Synthesis of 1-(4-bromo-3-methoxyphenyl)thiourea:



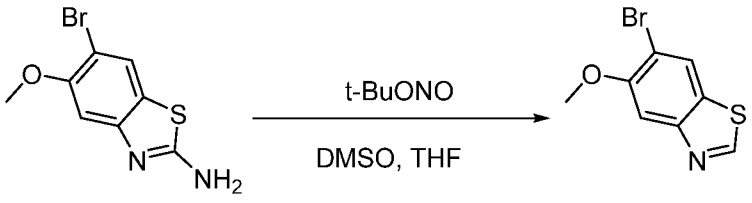
[0475] To a solution of N-((4-bromo-3-methoxyphenyl)carbamothioyl)benzamide (3.1 g, 8.49 mmol) in MeOH/H_2O (30.0/30.0 mL) was added NaOH (0.4 g, 9.34 mmol) at room temperature. The resulting mixture was stirred at 65 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 1-(4-bromo-3-methoxyphenyl)thiourea (1.9 g, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =261.0.

Step 3: Synthesis of 6-bromo-5-methoxybenzo[d]thiazol-2-amine:



[0476] To a solution of 1-(4-bromo-3-methoxyphenyl)thiourea (1.9 g, 7.28 mmol) in $CHCl_3$ (30.0 mL) was added Br_2 (1.4 g, 8.73 mmol) dropwise at 0 °C. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the mixture was filtered. The solid was collected and dried to afford 6-bromo-5-methoxybenzo[d]thiazol-2-amine (1.8 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =258.9.

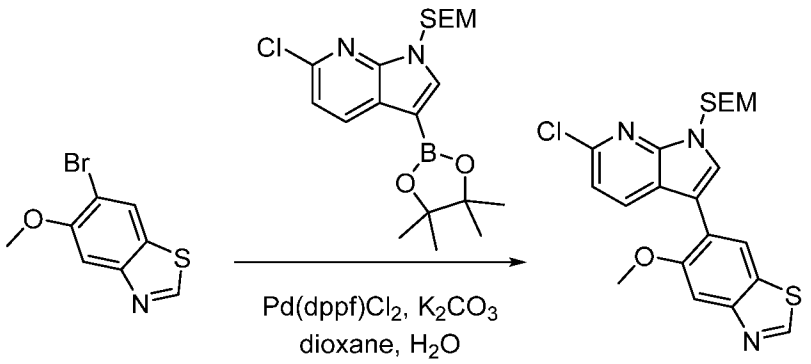
Step 4: Synthesis of 6-bromo-5-methoxybenzo[d]thiazole:



[0477] To a solution of 6-bromo-5-methoxybenzo[d]thiazol-2-amine (1.8 g, 6.95 mmol) in THF (30.0 mL) was added t-BuONO (1.1 g, 10.42 mmol) and DMSO (43.4 mg, 0.56 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum

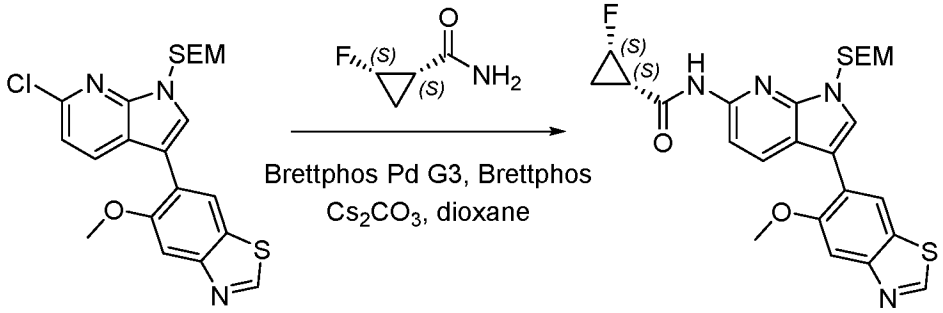
ether/ethyl acetate (1/1, v/v) to afford 6-bromo-5-methoxybenzo[d]thiazole (470.0 mg, 27%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =243.9.

Step 5: Synthesis of 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-5-methoxybenzo[d]thiazole:



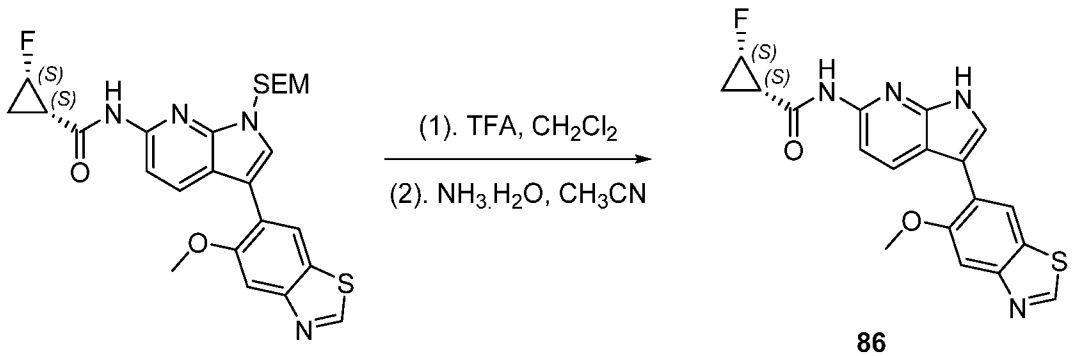
[0478] To a solution of 6-bromo-5-methoxybenzo[d]thiazole (200.0 mg, 0.82 mmol) in dioxane/H_2O (10.0/2.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (334.9 mg, 0.82 mmol), K_2CO_3 (339.7 mg, 2.46 mmol) and $Pd(dppf)Cl_2$ (60.0 mg, 0.08 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-5-methoxybenzo[d]thiazole (210.0 mg, 57%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =446.1.

Step 6: Synthesis of (1S,2S)-2-fluoro-N-(3-(5-methoxybenzo[d]thiazol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0479] To a solution of 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-5-methoxybenzo[d]thiazole (190.0 mg, 0.43 mmol) in dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (219.6 mg, 2.13 mmol), Cs_2CO_3 (416.4 mg, 1.28 mmol), Brettphos (45.7 mg, 0.09 mmol) and BrettPhos Pd G3 (38.6 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h under N_2. After the reaction was completed, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1S,2S)-2-fluoro-N-(3-(5-methoxybenzo[d]thiazol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (80.0 mg, 36%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =513.2.

Step 7: Synthesis of (1S,2S)-2-fluoro-N-(3-(5-methoxybenzo[d]thiazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 86):



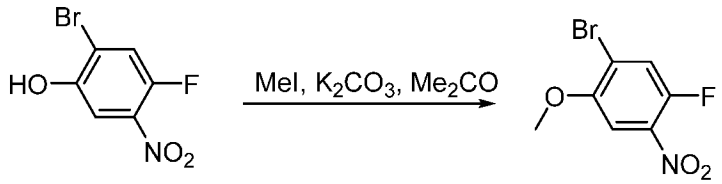
86

[0480] To a solution of (1S,2S)-2-fluoro-N-(3-(5-methoxybenzo[d]thiazol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (60.0 mg, 0.12 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (5.0 mL) and $NH_3.H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for 16 h.

After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% to 40% in 9 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-(5-methoxybenzo[d]thiazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (22.1 mg, 49%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =383.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.67 (s, 1H), 10.66 (s, 1H), 9.33 (s, 1H), 8.28 (s, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.76 (s, 1H), 7.69 (d, J = 2.1 Hz, 1H), 5.07 - 4.80 (m, 1H), 3.94 (s, 3H), 2.29 - 2.20 (m, 1H), 1.73 - 1.62 (m, 1H), 1.22 - 1.15 (m, 1H).

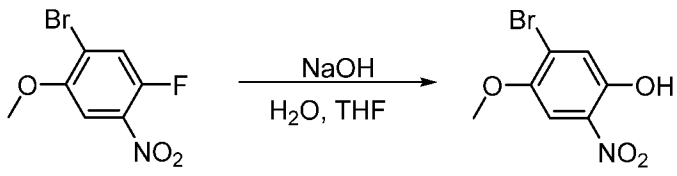
Example S87. Compound 87

Step 1: Synthesis of 1-bromo-5-fluoro-2-methoxy-4-nitrobenzene:



[0481] A mixture of 2-bromo-4-fluoro-5-nitrophenol (3.0 g, 12.71 mmol), K_2CO_3 (3.5 g, 25.42 mmol) and MeI (3.6 g, 25.42 mmol) in acetone (20.0 mL) was stirred at 50 °C for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure to afford 1-bromo-5-fluoro-2-methoxy-4-nitrobenzene (6.0 g, crude) as a yellow solid.

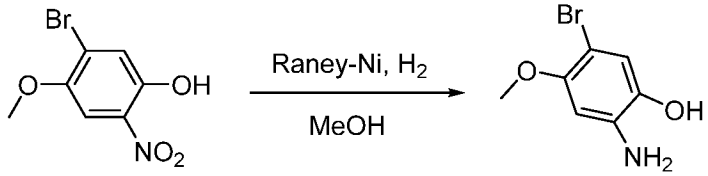
Step 2: Synthesis of 5-bromo-4-methoxy-2-nitrophenol:



[0482] To a solution of 1-bromo-5-fluoro-2-methoxy-4-nitrobenzene (3.2 g, 12.79 mmol) in THF/H_2O (10.0/10.0 mL) was added NaOH (767.8 mg, 19.19 mmol). The resulting mixture was stirred at 60 °C for 16 h. After the reaction was completed, the PH value of the mixture was adjusted to 6 with HCl (aq.). The resulting mixture was extracted with

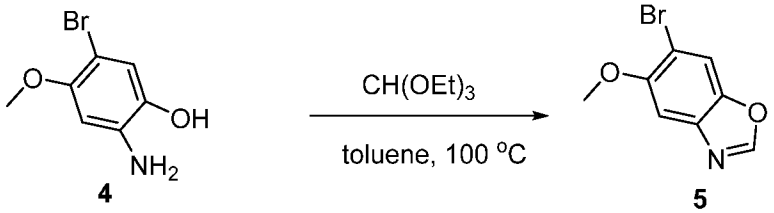
dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford 5-bromo-4-methoxy-2-nitrophenol (2.5 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =247.9.

Step 3: Synthesis of 2-amino-5-bromo-4-methoxyphenol:



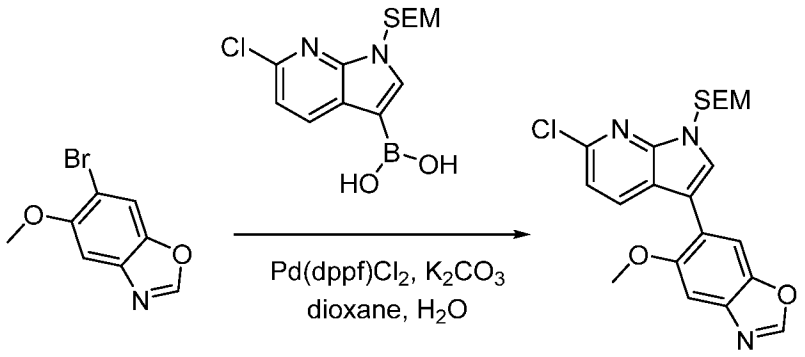
[0483] To a solution of 4-bromo-5-methoxy-2-nitrophenol (400.0 mg, 1.61 mmol) in MeOH (10.0 mL) was added Raney Ni (400.6 mg, 4.67 mmol). The mixture was stirred at room temperature for 2 h under H_2. After the reaction was completed, the reaction mixture was filtered. The filtrate was concentrated under vacuum to afford 2-amino-5-bromo-4-methoxyphenol (400.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =218.0.

Step 4: Synthesis of 6-bromo-5-methoxy-1,3-benzoxazole:



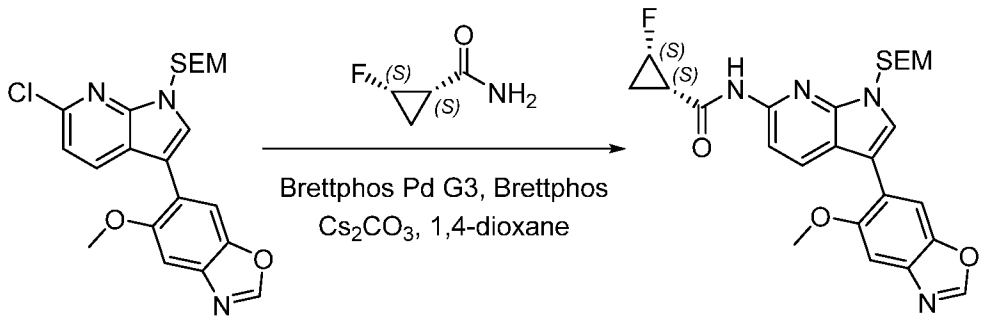
[0484] A mixture of 2-amino-4-bromo-5-methoxyphenol (400.0 mg, 1.83 mmol) and triethyl orthoformate (399.6 mg, 2.69 mmol) in toluene (5.0 mL) was stirred at 100 °C for 16 h. The resulting mixture was concentrated under vacuum. The residue was diluted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (70/30, v/v) to afford 6-bromo-5-methoxybenzo[d]oxazole (300.0 mg, 72%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =228.0.

Step 5: Synthesis of 6-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-methoxy-1,3-benzoxazole:



[0485] To a mixture of 6-bromo-5-methoxy-1,3-benzoxazole (200.0 mg, 0.87 mmol) and 6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-ylboronic acid (315.1 mg, 0.96 mmol) in dioxane/H_2O (5.0/0.5 mL) was added $Pd(dppf)Cl_2$ (71.6 mg, 0.09 mmol) and K_2CO_3 (363.6 mg, 2.63 mmol). The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with H_2O/ACN (50/50, v/v) to afford 6-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-methoxy-1,3-benzoxazole (180.0 mg, 47%) as a brown yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =430.1.

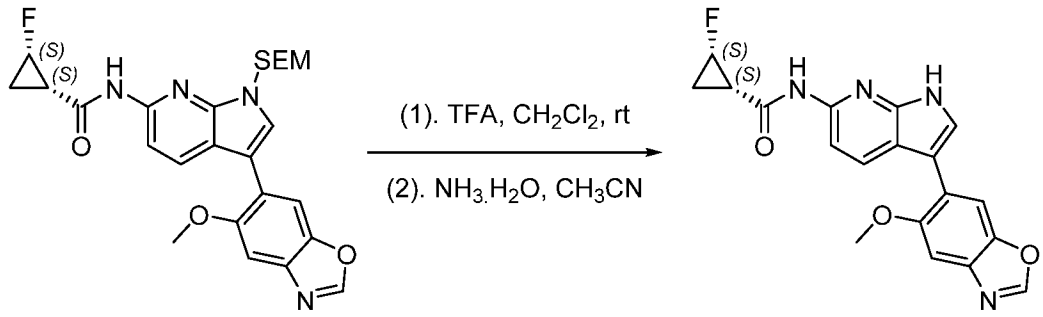
Step 6: Synthesis of (1S,2S)-2-fluoro-N-[3-(5-methoxy-1,3-benzoxazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0486] To a mixture of 6-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-methoxy-1,3-benzoxazole (90.0 mg, 0.21 mmol) and (1S,2S)-2-fluorocyclopropane-1-carboxamide (107.9 mg, 1.05 mmol) in 1,4-dioxane (5.0 mL) was added BrettPhos Pd G3 (37.9 mg, 0.04 mmol), Cs_2CO_3 (204.6 mg, 0.63 mmol) and BrettPhos (44.9 mg, 0.08 mmol). The resulting mixture was stirred at 100 °C for 16 h under N_2. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined

organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with H_2O/ACN (36/64, v/v) to afford (1S,2S)-2-fluoro-N-[3-(5-methoxy-1,3-benzoxazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (35.0 mg, 33%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =497.2.

Step 7: Synthesis of (1S,2S)-2-fluoro-N-(3-(5-methoxybenzo[d]oxazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 87):

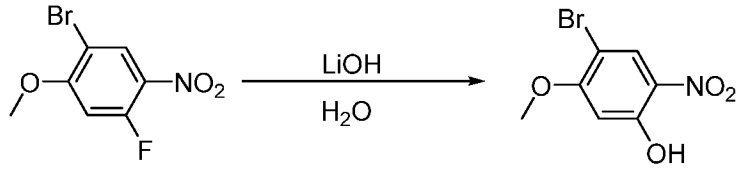


87

[0487] A mixture of (1S,2S)-2-fluoro-N-[3-(5-methoxy-1,3-benzoxazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy] methyl]pyrrolo [2,3-b]pyridin-6-yl] cyclopropane-1-carboxamide (35.0 mg, 0.07 mmol) and TFA (2.0 mL) in DCM (2.0 mL) was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added ACN (2.0 mL) and $NH_3.H_2O$ (2.0 mL). The resulting mixture was stirred at room temperature for another 4 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A: Water, Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 80% B in 7 min; 254/220 nm to afford (1S,2S)-2-fluoro-N-(3-(5-methoxybenzo[d]oxazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (3.9 mg, 15%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =367.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.64 (s, 1H), 10.63 (s, 1H), 8.67 (s, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.93 - 7.88 (m, 1H), 7.84 (s, 1H), 7.62 (d, J = 2.4 Hz, 1H), 7.48 (s, 1H), 5.05 - 4.77 (m, 1H), 3.86 (s, 3H), 2.29 - 2.20 (m, 1H), 1.71 - 1.57 (m, 1H), 1.22 - 1.08 (m, 1H).

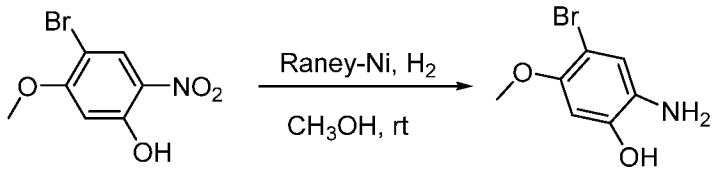
Example S88. Compound 88

Step 1: Synthesis of 4-bromo-5-methoxy-2-nitrophenol:



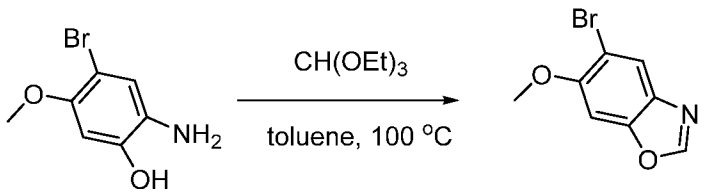
[0488] To a solution of 1-bromo-4-fluoro-2-methoxy-5-nitrobenzene (500.0 mg, 2.00 mmol) in H_2O (20.0 mL) was added lithium hydroxide (239.4 mg, 9.99 mmol). The resulting mixture was stirred at 100 °C for 15 min. After the reaction was completed, the resulting mixture was diluted with water. The pH value of the mixture was adjusted to 5 with 1N HCl. The mixture was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford 4-bromo-5-methoxy-2-nitrophenol (480.0 mg, crude) as a yellow solid.

Step 2: Synthesis of 2-amino-4-bromo-5-methoxyphenol:



[0489] To a solution of 4-bromo-5-methoxy-2-nitrophenol (400.0 mg, 1.61 mmol) in MeOH (10.0 mL) was added Raney Ni (400.6 mg, 4.67 mmol). The resulting mixture was stirred at room temperature for 2 h under H_2. After the reaction was completed, the reaction mixture was filtered. The filtrate was concentrated under vacuum to afford 2-amino-4-bromo-5-methoxyphenol (400.0 mg, crude) as a brown yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =218.0.

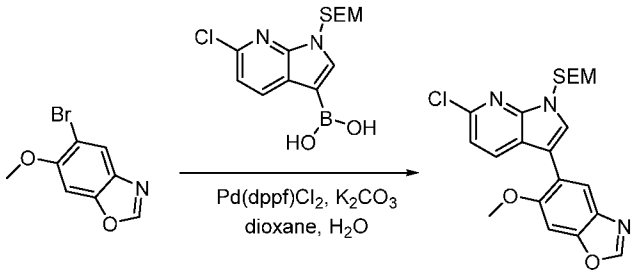
Step 3: Synthesis of 5-bromo-6-methoxybenzo[d]oxazole:



[0490] A mixture of 2-amino-4-bromo-5-methoxyphenol (400.0 mg, 1.83 mmol) and triethyl orthoformate (399.6 mg, 2.69 mmol) in toluene (5.0 mL) was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under vacuum.

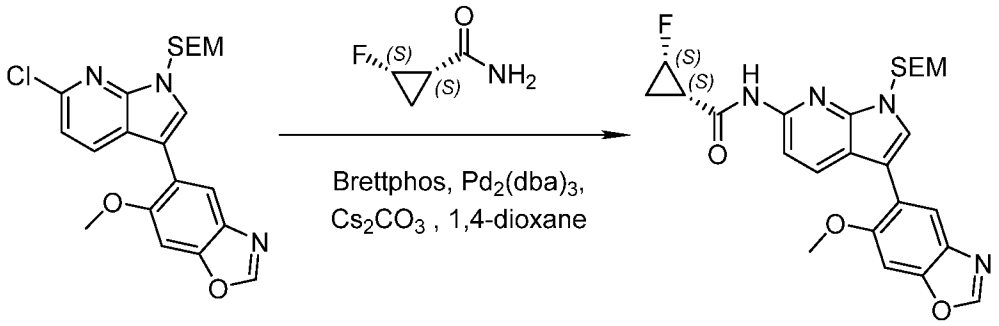
The residue was diluted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (70/30, v/v) to afford 5-bromo-6-methoxybenzo[d]oxazole (300.0 mg, 72%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =228.0.

Step 4: Synthesis of 5-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-6-methoxybenzo[d]oxazole:



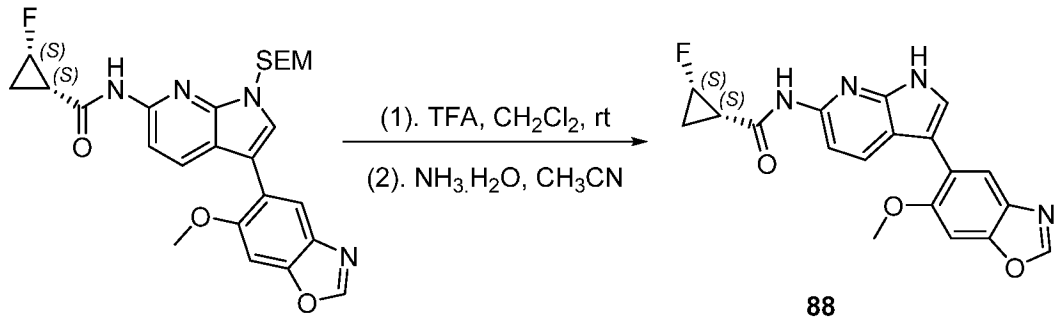
[0491] To a mixture of 5-bromo-6-methoxy-1,3-benzoxazole (300.0 mg, 1.31 mmol) and 6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-ylboronic acid (537.8 mg, 1.31 mmol) in 1,4-dioxane (5.0 mL) and H_2O (0.5 mL) was added $Pd(dppf)Cl_2$ (192.5 mg, 0.26 mmol) and K_2CO_3 (545.4 mg, 3.94 mmol). The mixture was stirred at 80 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1,3-benzoxazole (280.0 mg, 49%) as a brown yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =430.1.

Step 5: Synthesis of (1S,2S)-2-fluoro-N-(3-(6-methoxybenzo[d]oxazol-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0492] To a mixture of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1,3-benzoxazole (240.0 mg, 0.55 mmol) and (1S,2S)-2-fluorocyclopropane-1-carboxamide (575.4 mg, 5.58 mmol) in 1,4-dioxane (5.0 mL) was added BrettPhos (119.8 mg, 0.22 mmol), $Pd_2(dba)_3$ (102.2 mg, 0.11 mmol) and Cs_2CO_3 (545.5 mg, 1.67 mmol). The mixture was stirred at 100 °C for 16 h under N_2. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by reverse phase flash chromatography with ACN/water (30/70, v/v) to afford (1S,2S)-2-fluoro-N-[3-(6-methoxy-1,3-benzoxazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (77.0 mg, 27%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =497.2

Step 6: Synthesis of (1S,2S)-2-fluoro-N-(3-(6-methoxybenzo[d]oxazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 88):



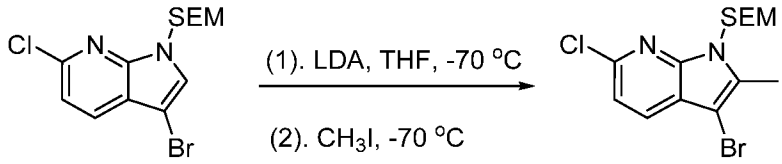
88

[0493] A mixture of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1,3-benzoxazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (67.0 mg, 0.14 mmol) and TFA (1.0 mL) in DCM (1.0 mL) was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added ACN (1.00 mL) and $NH_3.H_2O$ (1.00 mL). The resulting mixture was stirred at room

temperature for another 4 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: Xselect CSH OBD Column 30x150 mm 5 um; Mobile Phase A:Water, Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 80% B in 7 min; 254/220 nm to afford (1S,2S)-2-fluoro-N-[3-(6-methoxy-1,3-benzoxazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (14.7 mg, 29%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =367.1 ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.59 (s, 1H), 10.62 (s, 1H), 8.62 (s, 1H), 7.94 - 7.89 (m, 2H), 7.80 (s, 1H), 7.56 - 7.54 (m, 2H), 5.01 - 4.80 (m, 1H), 3.86 (s, 3H), 2.28 - 2.17 (m, 1H), 1.86 - 1.62 (m, 1H), 1.18 - 0.83 (m, 1H).

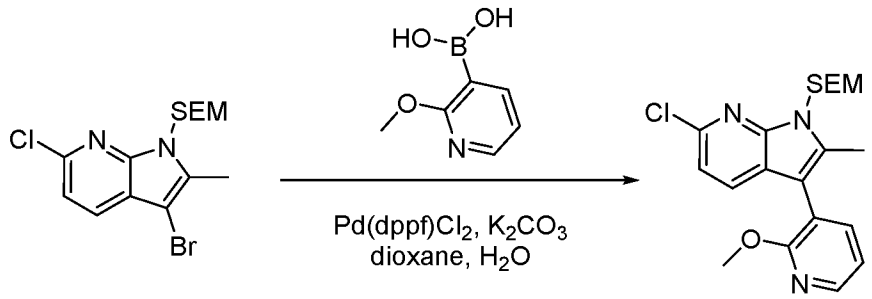
Example S89. Compound 89

Step 1: Synthesis of 3-bromo-6-chloro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine:



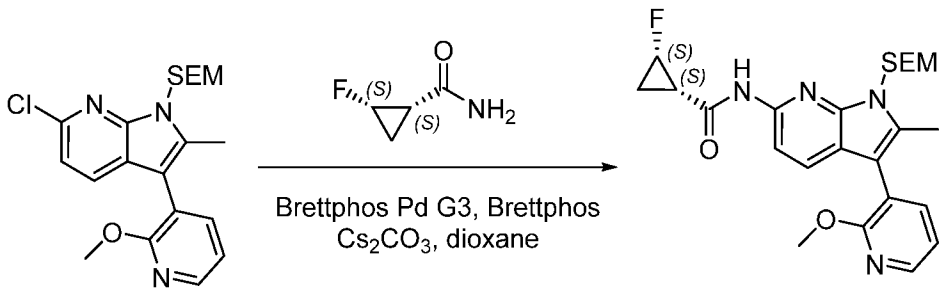
[0494] To a solution of 3-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (500.0 mg, 1.38 mmol) in THF (10.0 mL) was added dropwise LDA (2.1 mL) at -70 °C under N_2. The resulting mixture was stirred at -70 °C for 2 h. Then CH_3I (588.6 mg, 4.15 mmol) was added dropwise to the mixture at -70 °C under N_2. The resulting mixture was stirred at -70 °C for another 2 h. After the reaction was completed, the reaction was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford 3-bromo-6-chloro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (320.0 mg, 61%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =375.0.

Step 2: Synthesis of 6-chloro-3-(2-methoxypyridin-3-yl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine:



[0495] To a solution of 3-bromo-6-chloro-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (300.0 mg, 0.80 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added (2-methoxypyridin-3-yl)boronic acid (122.1 mg, 0.80 mmol), K_2CO_3 (331.0 mg, 2.40 mmol) and $Pd(dppf)Cl_2$ (64.3 mg, 0.09 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (80/20, v/v) to afford 6-chloro-3-(2-methoxypyridin-3-yl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (190.0 mg, 38%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =404.1.

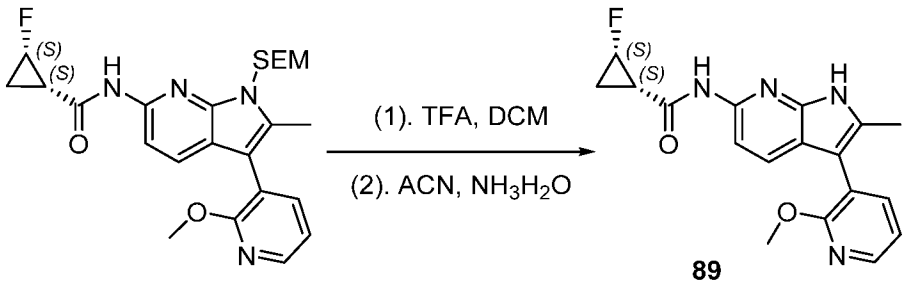
Step 3: Synthesis of (1S,2S)-2-fluoro-N-(3-(2-methoxypyridin-3-yl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0496] To a solution of 6-chloro-3-(2-methoxypyridin-3-yl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (170.0 mg, 0.42 mmol) in dioxane (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (216.9 mg, 2.10 mmol), Cs_2CO_3 (411.9 mg, 1.26 mmol), Brettphos (45.2 mg, 0.08 mmol) and Brettphos Pd G3 (38.2 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and

extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (77/23, v/v) to afford (1S,2S)-2-fluoro-N-(3-(2-methoxypyridin-3-yl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (80.0 mg, 12%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ =471.2.

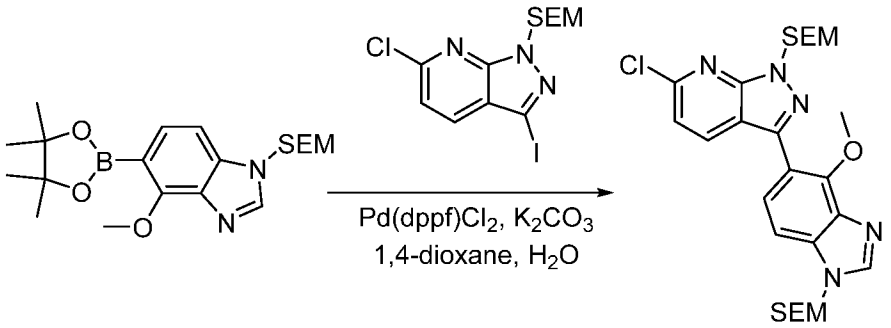
Step 4: Synthesis of (1S,2S)-2-fluoro-N-(3-(2-methoxypyridin-3-yl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 89):



[0497] To a solution of (1S,2S)-2-fluoro-N-(3-(2-methoxypyridin-3-yl)-2-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (80.0 mg, 0.17 mmol) in DCM (1.5 mL) was added TFA (1.5 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in ACN (1.5 mL) was added $NH_3 \cdot H_2O$ (1.5 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30x250 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 40% B in 13 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-(2-methoxypyridin-3-yl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (5.6 mg, 9%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =341.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.45 (s, 1H), 10.56 (s, 1H), 8.17 - 8.15 (m, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.71 - 7.68 (m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.11 - 7.07 (m, 1H), 5.03 - 4.78 (m, 1H), 3.86 (s, 3H), 2.32 (s, 3H), 2.26 - 2.15 (m, 1H), 1.71 - 1.58 (m, 1H), 1.18 - 1.09 (m, 1H).

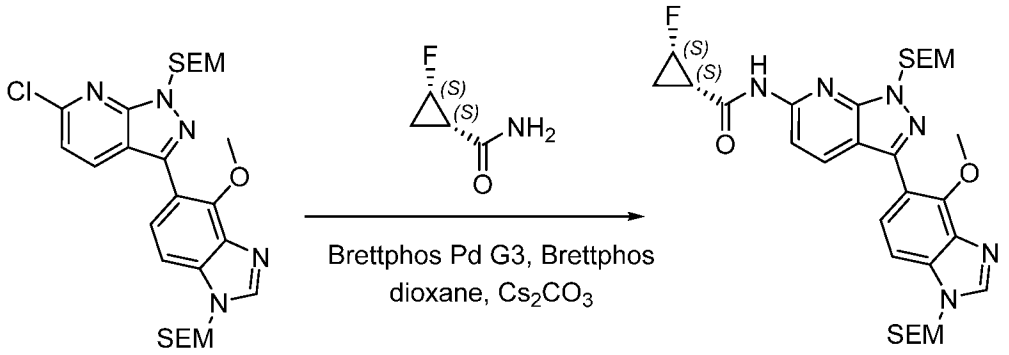
Example S90. Compound 90

Step 1: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole:



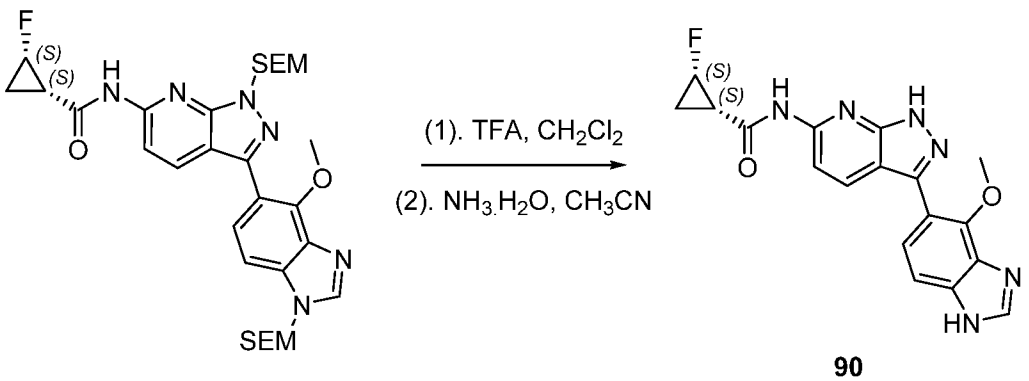
[0498] To a solution of 7-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (500.0 mg, 0.62 mmol) in 1,4-dioxane/H_2O (10.0 mL/2.0 mL) was added 6-chloro-3-iodo-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (211.1 mg, 0.52 mmol), K_2CO_3 (213.6 mg, 1.55 mmol) and $Pd(dppf)Cl_2$ (37.7 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with ACN/H_2O (9/1, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (200.0 mg, 69%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =560.2.

Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-(4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0499] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (150.0 mg, 0.27 mmol) in 1,4-dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (138.0 mg, 1.34 mmol), BrettPhos (28.7 mg, 0.05 mmol), Cs_2CO_3 (261.7 mg, 0.80 mmol) and BrettPhos Pd G3 (24.3 mg, 0.03 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/12, v/v) to afford (1S,2S)-2-fluoro-N-[3-(4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (79.0 mg, 47%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =627.3.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-[3-(4-methoxy-1H-1,3-benzodiazol-5-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 90):



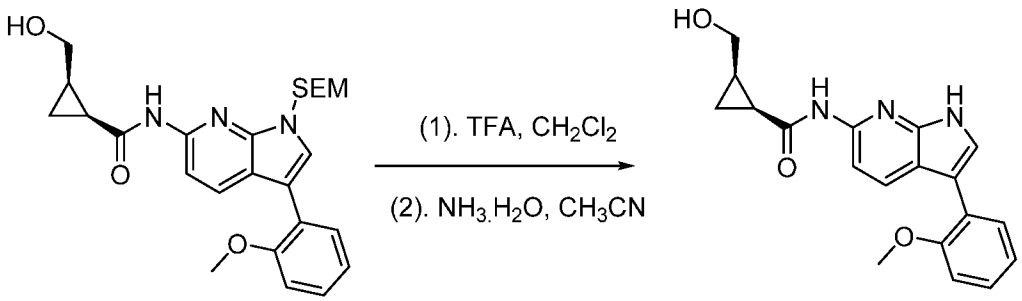
90

[0500] To a solution of (1S,2S)-2-fluoro-N-[3-(4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide

(110.0 mg, 0.18 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (5.0 mL) was added $NH_3.H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions Column: (Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 11% B to 32% B in 7 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(4-methoxy-1H-1,3-benzodiazol-5-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (8.8 mg, 14%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =367.2. ^1H NMR (400 MHz, DMSO-d_6): δ 13.36 (s, 1H), 12.61 (s, 1H), 10.96 (s, 1H), 8.28 - 8.23 (m, 1H), 8.15 (d, J = 8.8 Hz, 1H), 7.99 - 7.96 (m, 1H), 7.50 - 7.44 (m, 1H), 7.27 (d, J = 8.4 Hz, 1H), 5.04 - 4.85 (m, 1H), 4.29 (s, 3H), 2.33 - 2.23 (m, 1H), 1.73 - 1.62 (m, 1H), 1.23 - 1.15 (m, 1H).

Example S91. Compound 91

Step 1: Synthesis of (1S,2R)-2-(hydroxymethyl)-N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 91):



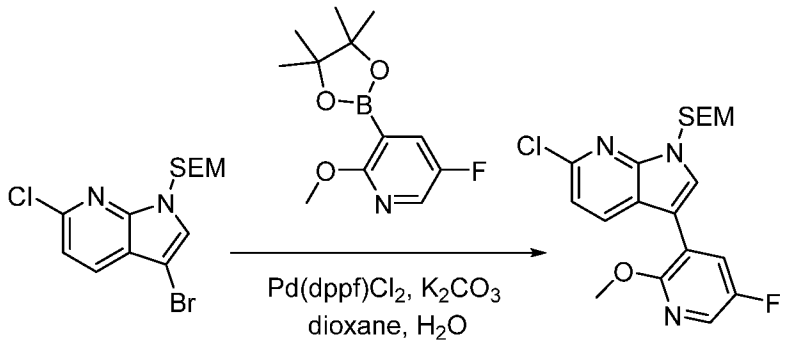
91

[0501] To a solution of (1S,2R)-2-(hydroxymethyl)-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (34.0 mg, 0.07 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in CH_3CN (2.0 mL) and $NH_3 \cdot H_2O$ (2.0 mL).. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure, then the was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD

C18 Column, 19x250 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 31% B to 40% B in 10 min; 254 nm) to afford (1S,2R)-2-(hydroxymethyl)-N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (2.7 mg, 11%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =338.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.50 (s, 1H), 10.44 (s, 1H), 7.96 - 7.87 (m, 2H), 7.54 - 7.51 (m, 2H), 7.28 - 7.24 (m, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.03 - 6.99 (m, 1H), 4.45 - 4.42 (m, 1H), 3.80 (s, 3H), 3.67 - 3.61 (m, 1H), 3.55 - 3.49 (m, 1H), 2.12 - 2.07 (m, 1H), 1.45 - 1.39 (m, 1H), 0.99 - 0.85 (m, 2H).

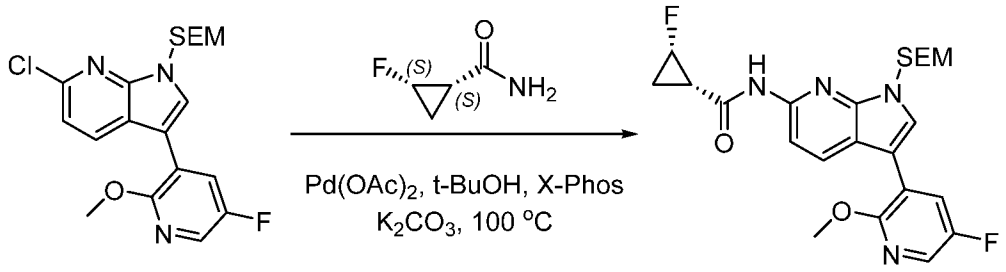
Example S92. Compound 92

Step 1: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-fluoro-2-methoxypyridine:



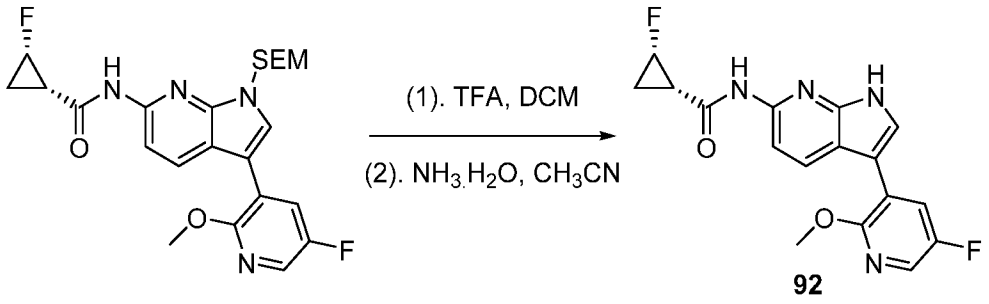
[0502] To a mixture of 5-fluoro-2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (300.0 mg, 1.75 mmol) and 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (634.8 mg, 1.75 mmol) in dioxane/H_2O (10.0 mL/1.0 mL) was added $Pd(dppf)Cl_2$ (128.4 mg, 0.17 mmol) and K_2CO_3 (727.7 mg, 5.26 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (20/1, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-fluoro-2-methoxypyridine (380.0 mg, 53%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =408.1

Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0503] To a mixture of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-fluoro-2-methoxypyridine (280.0 mg, 0.68 mmol) and (1S,2S)-2-fluorocyclopropane-1-carboxamide (353.8 mg, 3.43 mmol) in BuOH (5.0 mL) was added $Pd(OAc)_2$ (30.8 mg, 0.13 mmol), K_2CO_3 (284.5 mg, 2.05 mmol) and X-Phos (65.4 mg, 0.13 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) afford (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (170.0 mg, 52%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =475.2

Step 3: Synthesis of (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 92):

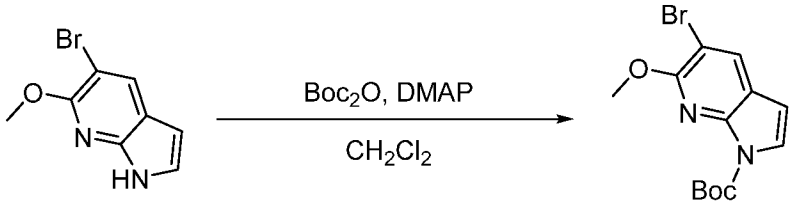


[0504] To a solution of (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (170.0 mg, 0.35 mmol) in DCM (3.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added $NH_3.H_2O$ (2.0 mL) and ACN (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with

H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 30x250 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 41% B to 50% B in 8 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (37.0 mg, 30%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$=345.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.83 (s, 1H), 10.66 (s, 1H), 8.18 (d, J = 8.7 Hz, 1H), 8.04 (d, J = 3.0 Hz, 1H), 7.96 - 7.90 (m, 2H), 7.83 (d, J = 2.7 Hz, 1H), 5.06 - 4.79 (m, 1H), 3.95 (s, 3H), 2.26 - 2.21 (m, 1H), 1.73 - 1.59 (m, 1H), 1.21 - 1.12 (m, 1H).

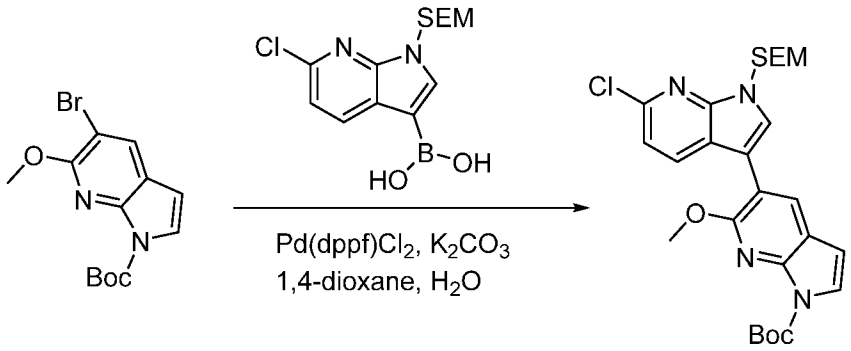
Example S93. Compound 93

Step 1: Synthesis of tert-butyl 5-bromo-6-methoxy-1H-pyrrolo[2,3-b]pyridine-1-carboxylate:



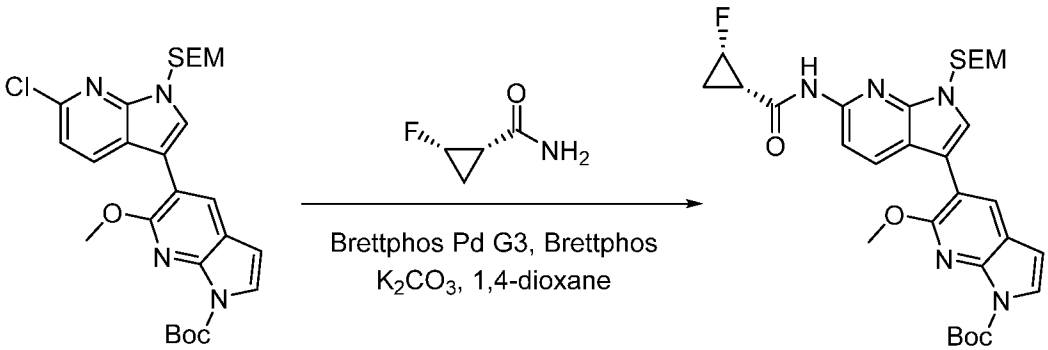
[0505] To a solution of 5-bromo-6-methoxy-1H-pyrrolo[2,3-b]pyridine (300.0 mg, 1.32 mmol) in CH_2Cl_2 (10.0 mL) was added Boc_2O (285.8 mg, 1.32 mmol) and DMAP (160.0 mg, 1.32 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (92/8, v/v) to afford tert-butyl 5-bromo-6-methoxy-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (350.0 mg, 81%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =327.0.

Step 2: Synthesis of tert-butyl 6-chloro-6'-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H,1'H-[3,5'-bipyrrolo[2,3-b]pyridine]-1'-carboxylate:



[0506] To a solution of tert-butyl 5-bromo-6-methoxy-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (320.0 mg, 0.98 mmol) in 1,4-dioxane/H_2O (10.0/2.0 mL) was added (6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)boronic acid (319.5 mg, 0.98 mmol), K_2CO_3 (405.5 mg, 2.93 mmol) and $Pd(dppf)Cl_2$ (71.5 mg, 0.10 mmol) at room temperature under N_2. The resulting mixture was stirred at 80°C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (94/6, v/v) to afford tert-butyl 6-chloro-6'-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H,1'H-[3,5'-bipyrrolo[2,3-b]pyridine]-1'-carboxylate (310.0 mg, 59%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =529.2.

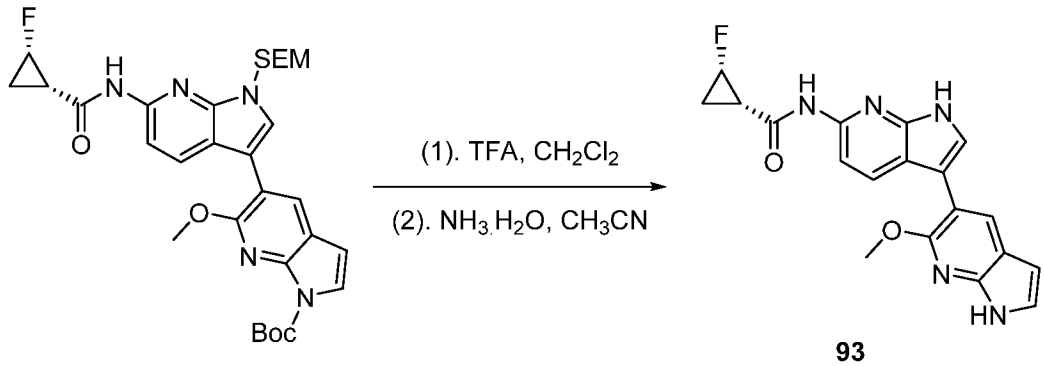
[0507] Step 3: Synthesis of tert-butyl 6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-6'-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H,1'H-[3,5'-bipyrrolo[2,3-b]pyridine]-1'-carboxylate:



[0508] To a solution of tert-butyl 6-chloro-6'-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H,1'H-[3,5'-bipyrrolo[2,3-b]pyridine]-1'-carboxylate (160.0 mg, 0.30 mmol) in 1,4-dioxane (6.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-

carboxamide (155.9 mg, 1.51 mmol), K_2CO_3 (125.4 mg, 0.91 mmol), BrettPhos (32.5 mg, 0.06 mmol) and BrettPhos Pd G3 (27.4 mg, 0.03 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (78/22, v/v) to afford tert-butyl 6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-6'-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H,1'H-[3,5'-bipyrrolo[2,3-b]pyridine]-1'-carboxylate (180.0 mg, 99%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =596.3.

Step 4: Synthesis of (1S,2S)-2-fluoro-N-(6'-methoxy-1H,1'H-[3,5'-bipyrrolo[2,3-b]pyridin]-6-yl)cyclopropane-1-carboxamide (Compound 93):



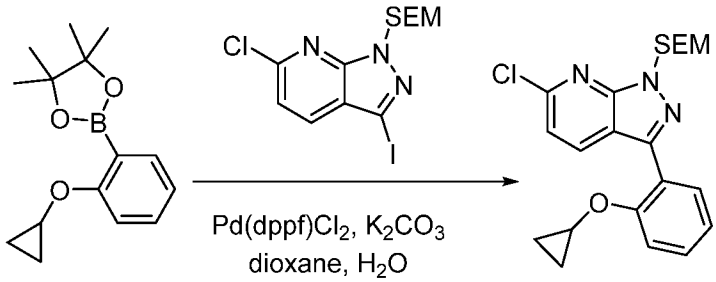
93

[0509] To a solution of tert-butyl 6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-6'-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H,1'H-[3,5'-bipyrrolo[2,3-b]pyridine]-1'-carboxylate (160.0 mg, 0.27 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (5.0 mL) and $NH_3 \cdot H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xcelect CSH F-pheny OBD Column, 19x250 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B:MeOH-----Preparative; Flow rate: 25 mL/min; Gradient: 46% B to 61% B in 9 min; 254 nm) to afford (1S,2S)-2-

fluoro-N-(6'-methoxy-1H,1'H-[3,5'-bipyrrolo[2,3-b]pyridin]-6-yl)cyclopropane-1-carboxamide (18.8 mg, 19%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =366.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.52 - 11.46 (m, 2H), 10.62 (s, 1H), 8.05 - 8.01 (m, 2H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 2.4 Hz, 1H), 7.21 - 7.20 (m, 1H), 6.40 - 6.39 (m, 1H), 5.03 - 4.82 (m, 1H), 3.94 (s, 3H), 2.24 - 2.22 (m, 1H), 1.71 - 1.61 (m, 1H), 1.18 - 1.16 (m, 1H).

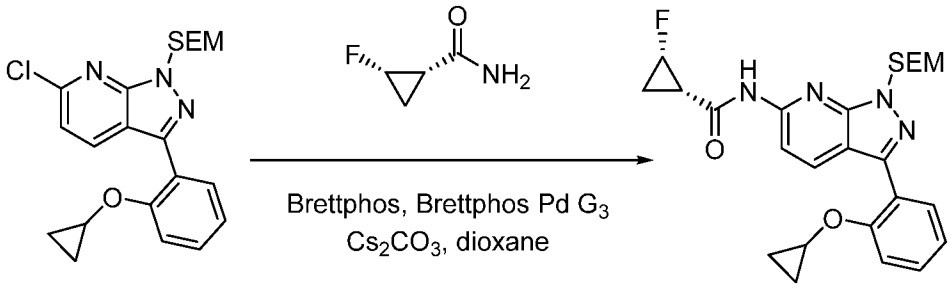
Example S94. Compound 94

Step 1: Synthesis of 6-chloro-3-(2-cyclopropoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine :



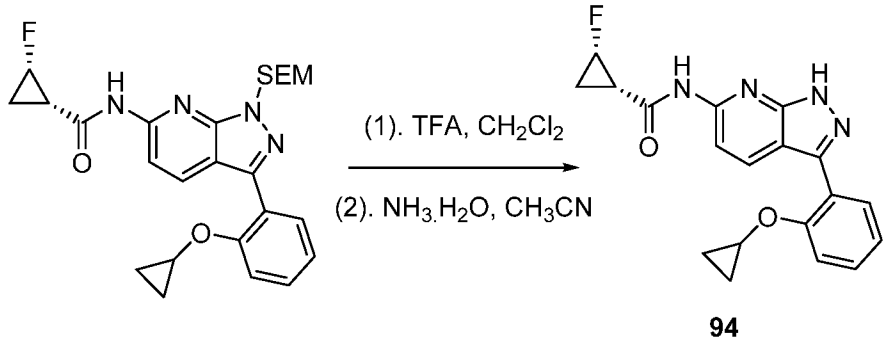
[0510] To a solution of 2-(2-cyclopropoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (320.0 mg, 1.23 mmol) in dioxane/H_2O (16.0/4.0 mL) was added 6-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (504.0 mg, 1.23 mmol), K_2CO_3 (510.0 mg, 3.69 mmol) and $Pd(dppf)Cl_2$ (90.0 mg, 0.12 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford 6-chloro-3-(2-cyclopropoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (300.0 mg, 58%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =416.1.

[0511] Step 2: Synthesis of (1S,2S)-N-(3-(2-cyclopropoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide :



[0512] To a solution of 6-chloro-3-(2-cyclopropoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (260.0 mg, 0.63 mmol) in dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (322.2 mg, 3.13 mmol), Cs_2CO_3 (610.9 mg, 1.88 mmol), Brettphos (67.1 mg, 0.13 mmol) and BrettPhos Pd G3 (56.7 mg, 0.06 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford (1S,2S)-N-(3-(2-cyclopropoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (110.0 mg, 36%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =483.2.

Step 3: Synthesis of (1S,2S)-N-(3-(2-cyclopropoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (Compound 94):



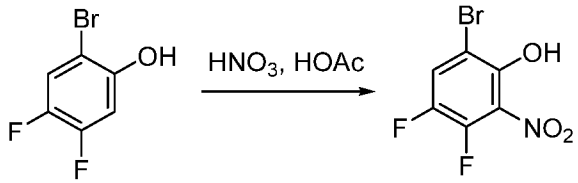
94

[0513] To a solution of (1S,2S)-N-(3-(2-cyclopropoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (90.0 mg, 0.18 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in CH_3CN

(5.0 mL) and $NH_3 \cdot H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column 19×250 mm, 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: MeOH; Flow rate: 25 mL/min; Gradient: 57% to 69% in 12 min; 254 nm) to afford (1S,2S)-N-(3-(2-cyclopropoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (14.0 mg, 21%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =353.2. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.48 (s, 1H), 10.98 (s, 1H), 8.06 - 7.96 (m, 2H), 7.63 - 7.60 (m, 1H), 7.50 - 7.46 (m, 2H), 7.12 - 7.07 (m, 1H), 5.08 - 4.84 (m, 1H), 3.93 - 3.89 (m, 1H), 2.29 - 2.25 (m, 1H), 1.72 - 1.63 (m, 1H), 1.23 - 1.16 (m, 1H), 0.83 - 0.66 (m, 4H).

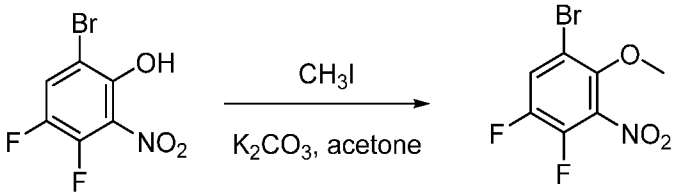
Example S95. Compound 95

Step 1: Synthesis of 6-bromo-3,4-difluoro-2-nitrophenol:



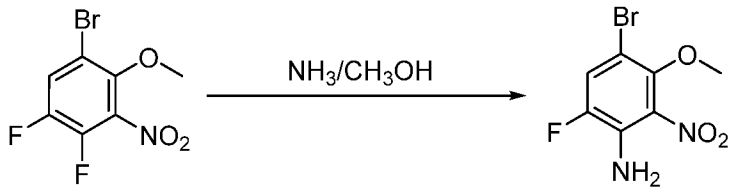
[0514] To a solution of 2-bromo-4,5-difluorophenol (3.7 g, 17.94 mmol) in HOAc (20.0 mL) was added HNO_3 (1.4 g, 21.5 mmol). The mixture was stirred at room temperature for 2 h. After the reaction was completed, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford 6-bromo-3,4-difluoro-2-nitrophenol (3.0 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =253.9.

Step 2: Synthesis of 1-bromo-4,5-difluoro-2-methoxy-3-nitrobenzene:



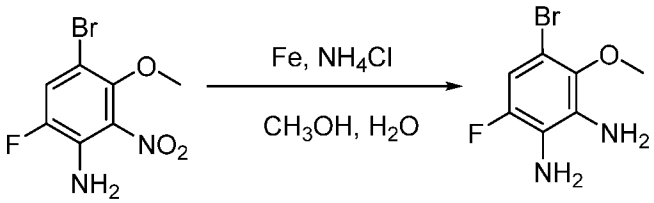
[0515] To a mixture of 6-bromo-3,4-difluoro-2-nitrophenol (2.0 g, 7.87 mmol) and K_2CO_3 (2.2 g, 15.75 mmol) in acetone (40.0 mL) was added methyl iodide (2.2 g, 15.75 mmol). The mixture was stirred at 70 °C for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure to afford 1-bromo-4,5-difluoro-2-methoxy-3-nitrobenzene (2.0 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =267.9.

Step 3: Synthesis of 4-bromo-6-fluoro-3-methoxy-2-nitroaniline:



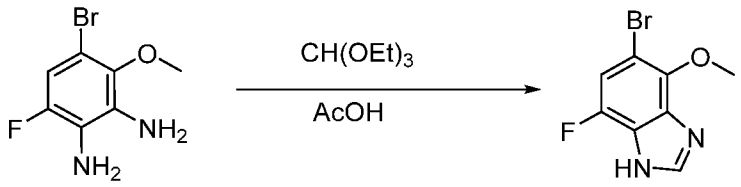
[0516] A mixture of 1-bromo-4,5-difluoro-2-methoxy-3-nitrobenzene (2.0 g, 7.46 mmol) in NH_3/MeOH (16.0 mL, 7 mol/L) was stirred at 60 °C for 2 h. After the reaction was completed, the mixture was concentrated under reduced pressure to afford 4-bromo-6-fluoro-3-methoxy-2-nitroaniline (1.8 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =265.0.

Step 4: Synthesis of 4-bromo-6-fluoro-3-methoxybenzene-1,2-diamine:



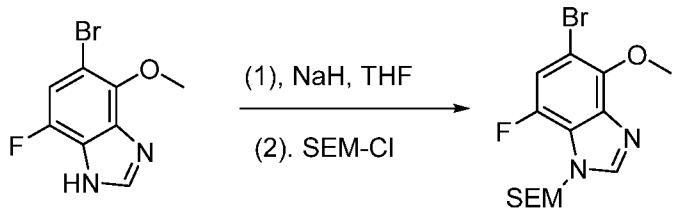
[0517] To a mixture of 4-bromo-6-fluoro-3-methoxy-2-nitroaniline (1.0 g, 3.77 mmol) and NH_4Cl (1.0 g, 18.86 mmol) in MeOH (50.0 mL) and H_2O (5.0 mL) was added Fe (2.1 g, 37.73 mmol). The mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford 4-bromo-6-fluoro-3-methoxybenzene-1,2-diamine (500.0 mg, 56%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =235.0.

Step 5: Synthesis of 5-bromo-7-fluoro-4-methoxy-1H-1,3-benzodiazole:



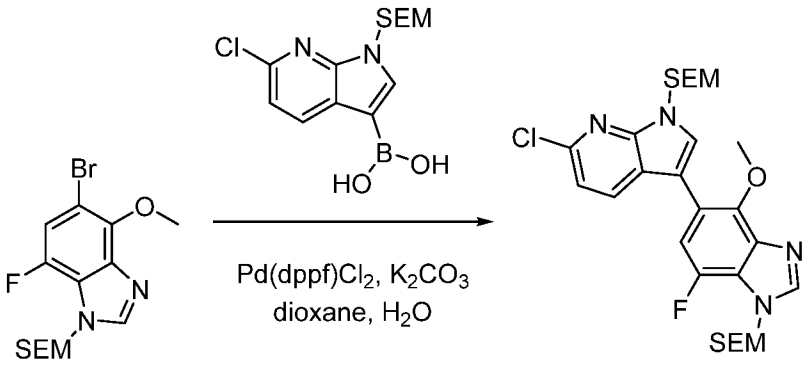
[0518] A mixture of 4-bromo-6-fluoro-3-methoxybenzene-1,2-diamine (400.0 mg, 8.51 mmol) and triethyl orthoformate (5.0 mL) in acetic Acid (5.0 mL) was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford 5-bromo-7-fluoro-4-methoxy-1H-1,3-benzodiazole (400.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =245.0.

Step 6: Synthesis of 5-bromo-7-fluoro-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole:



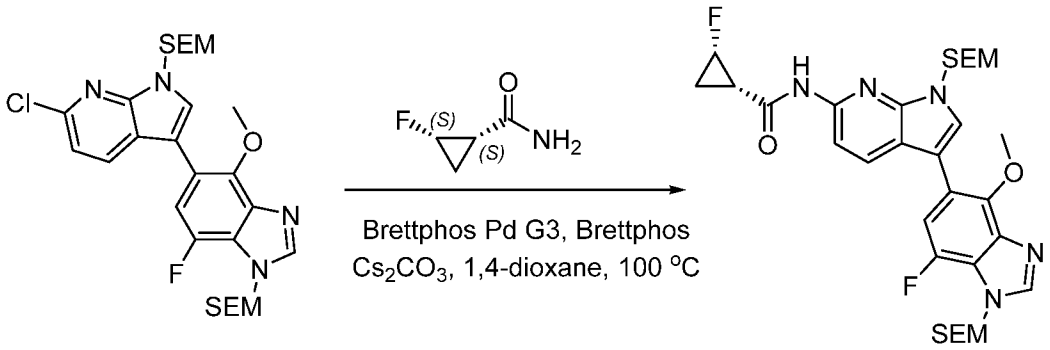
[0519] To a solution of 5-bromo-7-fluoro-4-methoxy-1H-1,3-benzodiazole (510.0 mg, 2.08 mmol) in THF (5.0 mL) was added sodium hydride (100.0 mg, 60%) at 0 °C. The mixture was stirred at 0 °C for 15 min. Then SEM-Cl (381.8 mg, 2.29 mmol) was added to the mixture. The mixture was stirred at room temperature for another 2 h. After the reaction was completed, the reaction mixture was quenched with water and extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford 5-bromo-7-fluoro-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (510.0 mg, 65%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =375.0.

Step 7: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-7-fluoro-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole:



[0520] To a solution of 5-bromo-7-fluoro-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (400.0 mg, 1.06 mmol) in dioxane/H_2O (10.0 mL/1.0 mL) was added 6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-ylboronic acid (382.9 mg, 1.17 mmol), K_2CO_3 (441.9 mg, 3.20 mmol) and $Pd(dppf)Cl_2$ (77.9 mg, 0.11 mmol). The mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (94/6, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-7-fluoro-4-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (330.0 mg, 54%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =577.2.

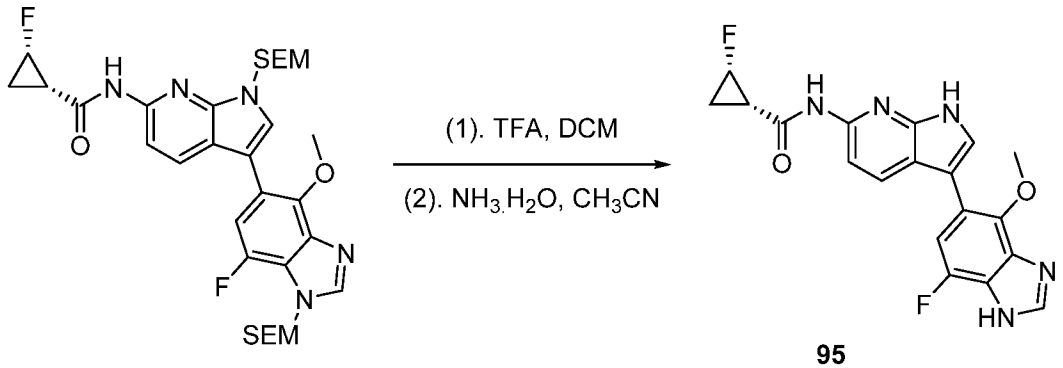
Step 8: Synthesis of (1S,2S)-2-fluoro-N-(3-(7-fluoro-4-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide:



[0521] To a stirred mixture of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-7-fluoro-4-methoxy-1-[[2-

(trimethylsilyl)ethoxy]methyl]-1,3-benzodiazole (250.0 mg, 0.43 mmol) and (1S,2S)-2-fluorocyclopropane-1-carboxamide (89.3 mg, 0.86 mmol) in 1,4-dioxane (5.0 mL) was added BrettPhos (92.9 mg, 0.17 mmol), BrettPhos Pd G3 (78.5 mg, 0.08 mmol) and Cs_2CO_3 (423.3 mg, 1.29 mmol). The resulting mixture was stirred at 100 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (94/6, v/v) to afford (1S,2S)-2-fluoro-N-(3-(7-fluoro-4-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (100.0 mg, 45%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =644.3.

Step 9: Synthesis of (1S,2S)-2-fluoro-N-(3-(7-fluoro-4-methoxy-1H-benzo[d]imidazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (Compound 95):



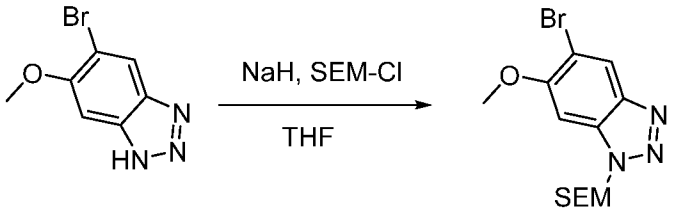
95

[0522] A mixture of (1S,2S)-2-fluoro-N-(3-(7-fluoro-4-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (100.0 mg, 0.19 mmol) and TFA (2.0 mL) in DCM (2.0 mL) was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added ACN (2.0 mL) and $NH_3.H_2O$ (2.0 mL). The resulting mixture was stirred at room temperature for another 4 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A: Water, Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 80% B in 7 min; 254/220 nm to afford (1S,2S)-2-fluoro-N-(3-(7-fluoro-4-methoxy-1H-benzo[d]imidazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (3.9 mg, 5%) as a white solid. LCMS

(ESI, m/z): $[M+H]^+$ =384.1. ^1H NMR (300 MHz, DMSO-d_6): δ 13.09 (s, 1H), 11.67 (s, 1H), 10.64 (s, 1H), 8.25 (s, 1H), 8.09 - 8.02 (m, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.69 - 7.46 (m, 1H), 7.16 - 7.13 (m, 1H), 5.05 - 4.77 (m, 1H), 4.09 (s, 1H), 3.58 (s, 2H), 2.29 - 2.18 (m, 1H), 1.71 - 1.57 (m, 1H), 1.22 - 1.08 (m, 1H).

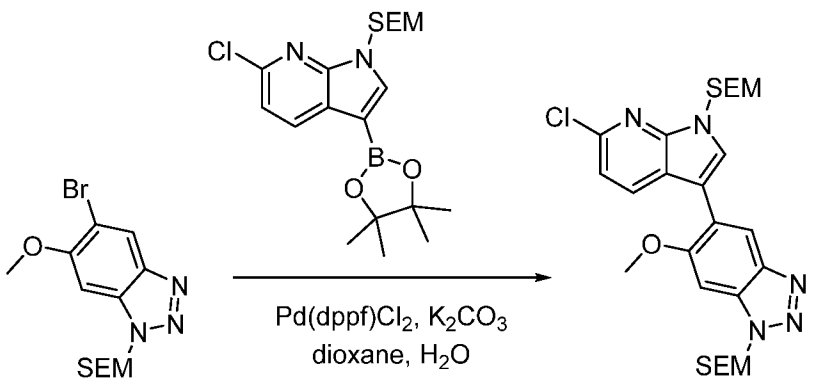
Example S96. Compound 96

Step 1: Synthesis of 5-bromo-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,2,3-benzotriazole:



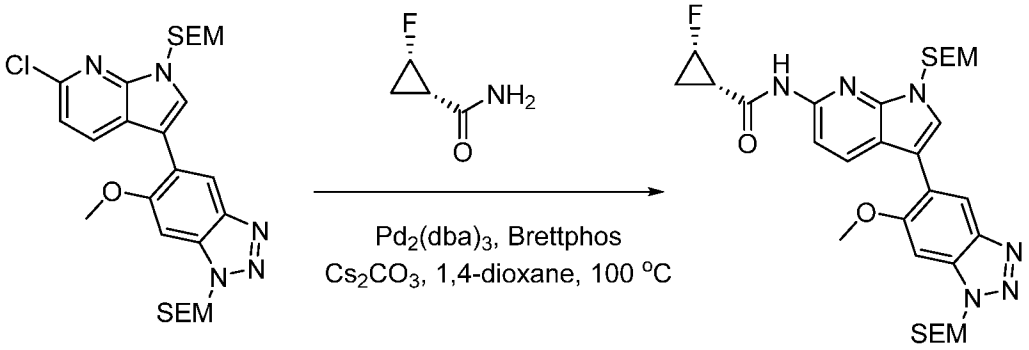
[0523] To a solution of 5-bromo-6-methoxy-1H-1,2,3-benzotriazole (200.0 mg, 0.87 mmol) in THF (10.0 mmL) was added NaH (52.6 mg, 60%) at 0 °C. The mixture was stirred at 0 °C for 15 min. Then SEM-Cl (160.8 mg, 0.96 mmol) was added to the mixture. The mixture was stirred at room temperature for another 2 h. After the reaction was completed, the reaction mixture was quenched with water and extracted with DCM. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (75/25, v/v) to afford 5-bromo-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,2,3-benzotriazole (220.0 mg, 70%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =358.1.

Step 2: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,2,3-benzotriazole:



[0524] To a mixture of 5-bromo-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,2,3-benzotriazole (205.0 mg, 0.57 mmol) and 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (257.2 mg, 0.62 mmol) in dioxane (5.0 mL) and H_2O (0.50 mL) was added $Pd(dppf)Cl_2$ (83.7 mg, 0.11 mmol) and K_2CO_3 (237.2 mg, 1.71 mmol). The mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,2,3-benzotriazole (250.0 mg, 78%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =560.2.

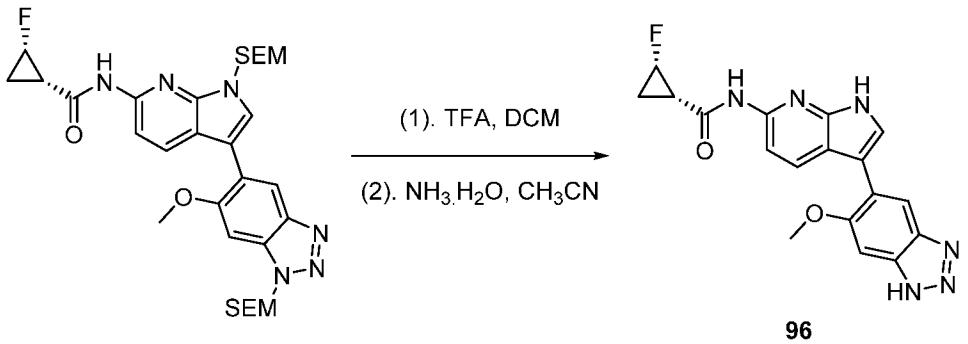
Step 3: Synthesis of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,2,3-benzotriazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0525] To a mixture of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,2,3-benzotriazole (250.0 mg, 0.44 mmol) and (1S,2S)-2-fluorocyclopropane-1-carboxamide (230.0 mg, 2.23 mmol) in 1,4-dioxane (5.0 mL) was added BrettPhos (47.9 mg, 0.09 mmol), $Pd_2(dba)_3$ (163.4 mg, 0.18 mmol) and Cs_2CO_3 (436.1 mg, 1.33 mmol). The mixture was stirred at 100 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with ACN/H_2O (30/70, v/v) to afford (1S,2S)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,2,3-benzotriazol-5-

yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (160.0 mg, 57%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =627.3.

Step 4: Synthesis of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1H-1,2,3-benzotriazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 96):

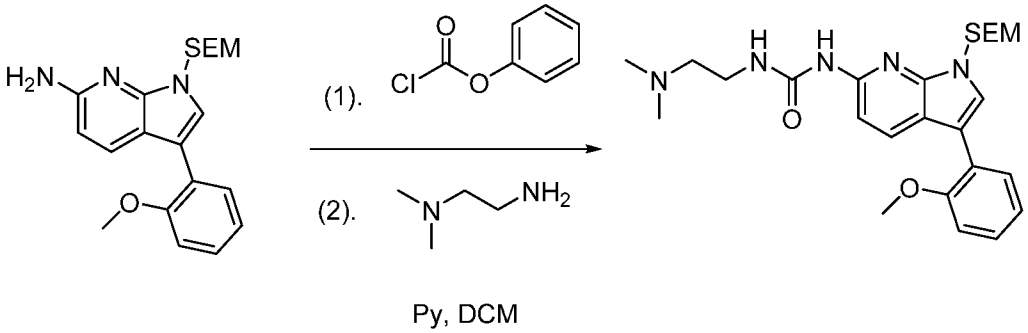


96

[0526] A mixture of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]-1,2,3-benzotriazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (150.0 mg, 0.24 mmol) and TFA (5.0 mL) in DCM (5.0 mL) was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added ACN (5.0 mL) and $NH_3.H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 4 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A: Water, Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 80% B in 7 min; 254/220 to afford (1S,2S)-2-fluoro-N-[3-(6-methoxy-1H-1,2,3-benzotriazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (10.9 mg, 24%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =367.1. ^1H NMR (300 MHz, DMSO-d_6): δ 15.33 (s, 1H), 11.63 (d, J = 1.8 Hz, 1H), 10.63 (s, 1H), 7.99 - 7.88 (m, 3H), 7.61 (d, J = 2.7 Hz, 1H), 7.35 (s, 1H), 5.05 - 4.77 (m, 1H), 3.89 (s, 3H), 2.26 - 2.20 (m, 1H), 1.74 - 1.54 (m, 1H), 1.22 - 1.05 (m, 1H).

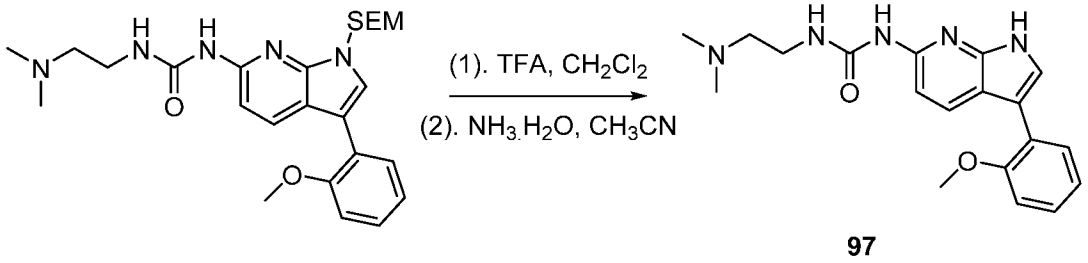
Example S97. Compound 97

Step 1: Synthesis of 1-(2-(dimethylamino)ethyl)-3-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)urea:



[0527] To a solution of 3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (100.0 mg, 0.27 mmol) in DCM (5.0 mL) was added Pyridine (85.6 mg, 1.08 mmol) and phenyl carbonochloridate (50.8 mg, 0.32 mmol) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in pyridine (5.0 mL). Then (2-aminoethyl)dimethylamine (95.4 mg, 1.08 mmol) was added to the mixture at 0 °C under N_2. The resulting mixture was stirred at 60 °C for another 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (92/8, v/v) to afford 1-(2-(dimethylamino)ethyl)-3-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)urea (100.0 mg, 77%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =484.3.

Step 2: Synthesis of 3-[2-(dimethylamino)ethyl]-1-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (Compound 97):



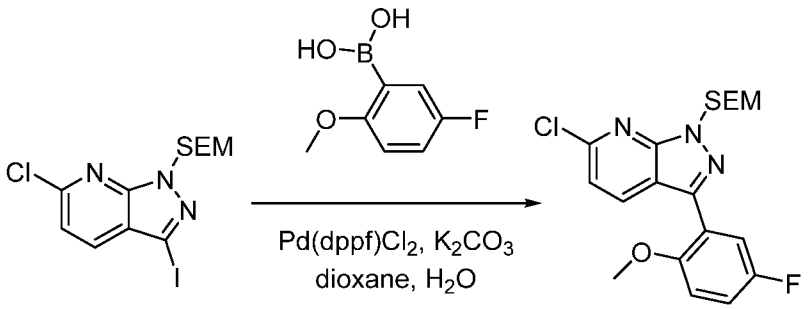
97

[0528] To a solution of 1-(2-(dimethylamino)ethyl)-3-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)urea (100.0 mg, 0.21 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in ACN (3.0 mL) was added $NH_3 \cdot H_2O$ (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After

the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH F-Phenyl OBD column, 19x250 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH-----Preparative; Flow rate: 25 mL/min; Gradient: 70 % B to 90 % B in 7 min; 254 nm) to afford 3-[2-(dimethylamino)ethyl]-1-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (19.7 mg, 27%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =354.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.41 (s, 1H), 9.16 (s, 1H), 8.37 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.51 - 7.49 (m, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.28 - 7.23 (m, 1H), 7.11 - 7.07 (m, 2H), 7.03 - 6.99 (m, 1H), 3.80 (s, 3H), 3.32 - 3.28 (m, 2H), 2.41 - 2.38 (m, 2H), 2.20 (s, 6H).

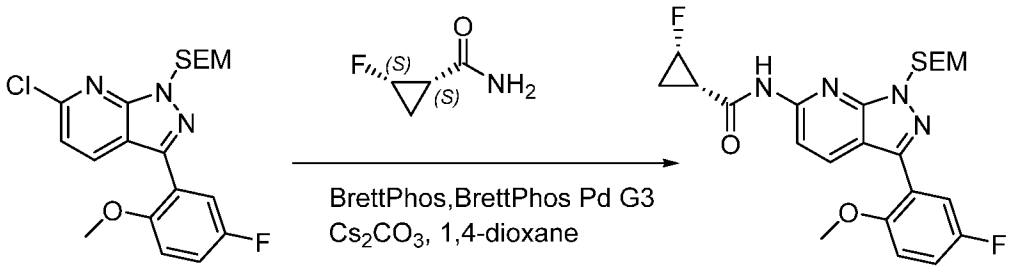
Example S98. Compound 98

Step 1: Synthesis of 6-chloro-3-(5-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine:



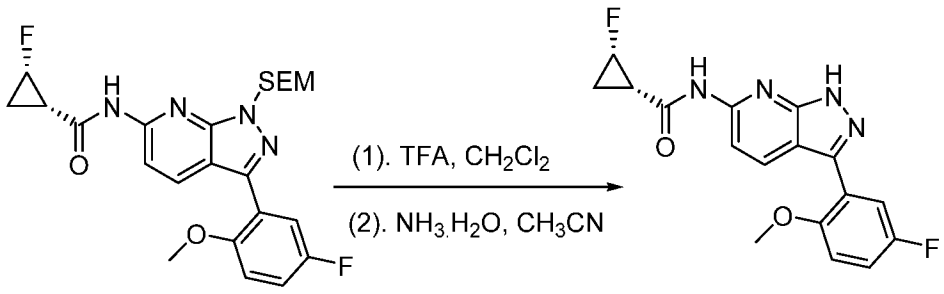
[0529] To a solution of 6-chloro-3-iodo-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (300.0 mg, 0.73 mmol) in dioxane/H_2O (5.0/1.0 mL) was added 5-fluoro-2-methoxyphenylboronic acid (149.3 mg, 0.88 mmol), K_2CO_3 (303.5 mg, 2.19 mmol) and $Pd(dppf)Cl_2$ (53.5 mg, 0.07 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (80/20, v/v) to afford 6-chloro-3-(5-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (220.0 mg, 74%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =408.1.

Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0530] To a solution of 6-chloro-3-(5-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (160.0 mg, 0.38 mmol) in 1,4-dioxane (4.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (202.1 mg, 1.96 mmol), BrettPhos (42.1 mg, 0.08 mmol), Cs_2CO_3 (383.3 mg, 1.17 mmol) and BrettPhos Pd G3 (35.5 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (75/25, v/v) to afford (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (90.0 mg, 48%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =475.2.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 98):



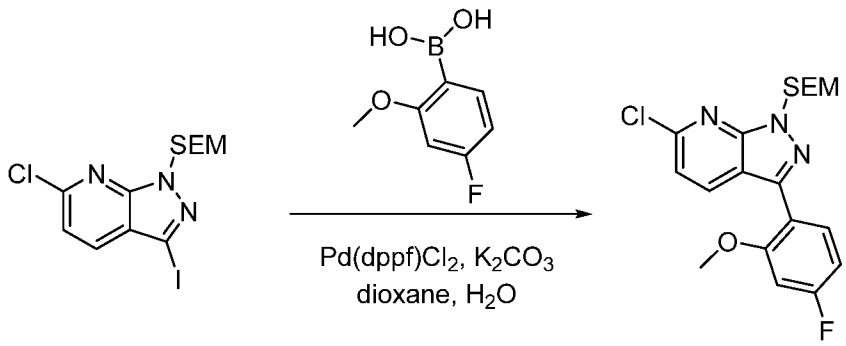
98

[0531] To a solution of (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (90.0 mg, 0.19 mmol) in CH_3Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature.

The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in ACN (2.0 mL) and $NH_3 \cdot H_2O$ (2.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, 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, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 34% B to 44% B in 8 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (12.1 mg, 18%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =345.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.58 (s, 1H), 10.97 (s, 1H), 8.15 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.30 - 7.21 (m, 2H), 5.10 - 4.83 (m, 1H), 3.83 (s, 3H), 2.37 - 2.23 (m, 1H), 1.78 - 1.67 (m, 1H), 1.26 - 1.13 (m, 1H).

Example S99. Compound 99

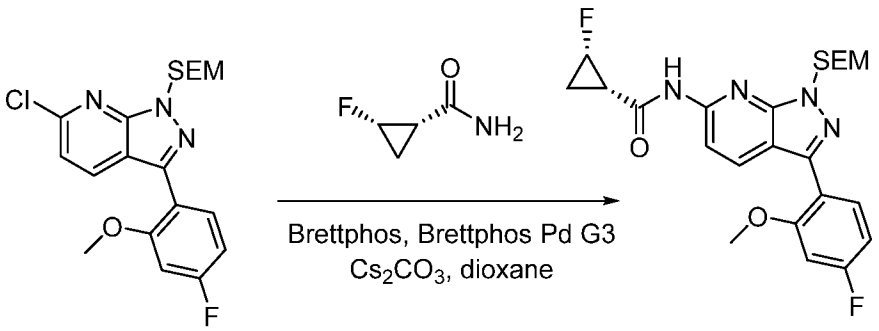
Step 1: Synthesis of 6-chloro-3-(4-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine:



[0532] To a solution of 6-chloro-3-iodo-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (500.0 mg, 1.22 mmol) in 1,4-dioxane/H_2O (25.0 mL/5.0 mL) was added 4-fluoro-2-methoxyphenylboronic acid (207.4 mg, 1.22 mmol), K_2CO_3 (337.3 mg, 2.44 mmol) and $Pd(dppf)Cl_2$ (89.3 mg, 0.12 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to

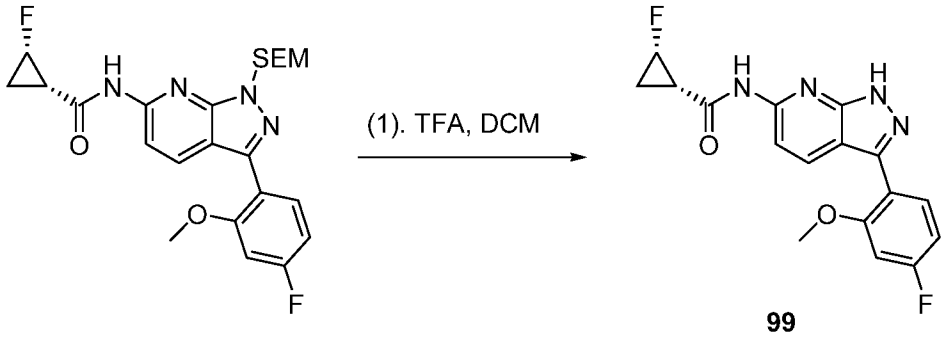
afford 6-chloro-3-(4-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (347.0 mg, 70%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =408.1.

Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-(4-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0533] To a solution of 6-chloro-3-(4-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (347.0 mg, 0.85 mmol) in 1,4-dioxane (20.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (438.5 mg, 4.26 mmol), BrettPhos (91.3 mg, 0.17 mmol), Cs_2CO_3 (831.4 mg, 2.55 mmol) and BrettPhos Pd G3 (77.1 mg, 0.09 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford (1S,2S)-2-fluoro-N-[3-(4-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (56.5 mg, 14%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =475.2.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-[3-(4-fluoro-2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 99):

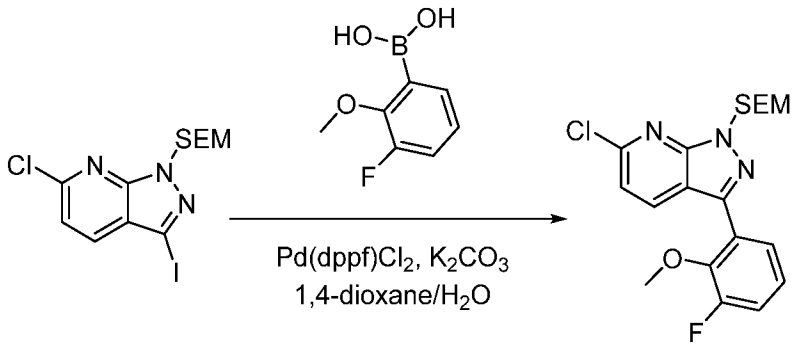


99

[0534] To a solution of (1S,2S)-2-fluoro-N-[3-(4-fluoro-2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (56.6 mg, 0.12 mmol) in DCM (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O. The pH value of the mixture was adjusted to 7 with aq.$NaHCO_3$. The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30x250 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 36% B to 54% B in 8 min; 254/220 nm) to afford (1S,2S)-2-fluoro-N-[3-(4-fluoro-2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (6.8 mg, 16%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =345.3. ^1H NMR (400 MHz, DMSO-d_6): δ 13.50 (s, 1H), 10.96 (s, 1H), 8.10 (d, J = 8.8 Hz, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.65 - 7.61 (m, 1H), 7.12 - 7.08 (m, 1H), 6.92 - 6.87 (m, 1H), 5.04 - 4.86 (m, 1H), 3.85 (s, 3H), 2.35 - 2.25 (m, 1H), 1.70 - 1.64 (m, 1H), 1.22 - 1.16 (m, 1H).

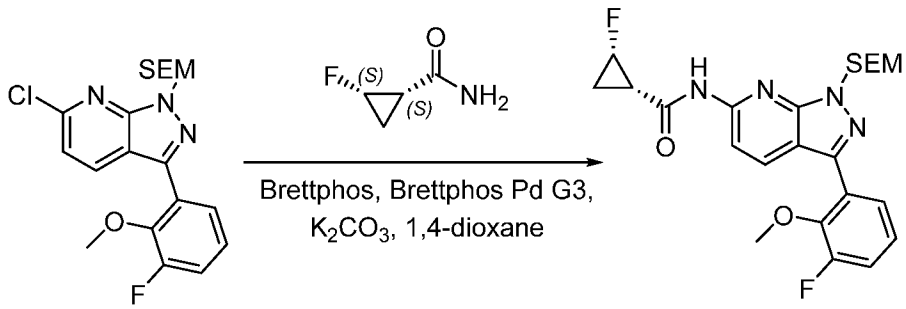
Example S100. Compound 100

Step 1: Synthesis of 6-chloro-3-(3-fluoro-2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine:



[0535] To a solution of 6-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (400.0 mg, 0.98 mmol) in 1,4-dioxane/H_2O (8.0/2.0 mL) was added (3-fluoro-2-methoxyphenyl)boronic acid (165.9 mg, 0.98 mmol), K_2CO_3 (404.8 mg, 2.93 mmol) and $Pd(dppf)Cl_2$ (71.4 mg, 0.10 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (80/20, v/v) to afford 6-chloro-3-(3-fluoro-2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (370.0 mg, 88%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =408.1.

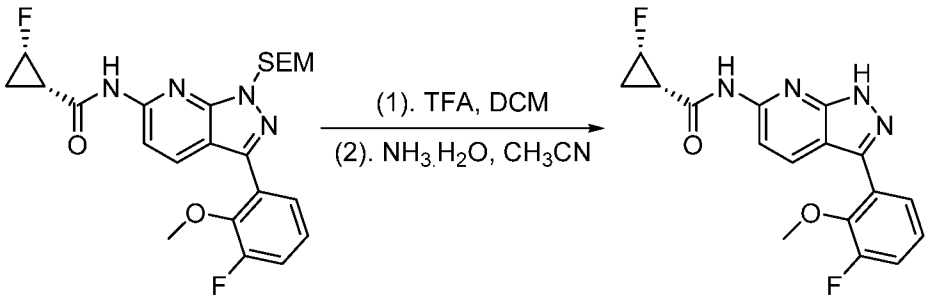
Step 2: Synthesis of (1S,2S)-2-fluoro-N-(3-(3-fluoro-2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0536] To a solution of 6-chloro-3-(3-fluoro-2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (310.0 mg, 0.76 mmol) in 1,4-dioxane (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (391.7 mg, 3.80 mmol), K_2CO_3 (315.1 mg, 2.28 mmol), Brettphos (81.6 mg, 0.15 mmol) and Brettphos Pd G3 (68.9 mg, 0.08 mmol) at room temperature under N_2. The resulting mixture was stirred at

100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (83/17, v/v) to afford (1S,2S)-2-fluoro-N-(3-(3-fluoro-2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)cyclopropane-1-carboxamide (106.0 mg, 28%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =475.2.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-(3-(3-fluoro-2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 100):



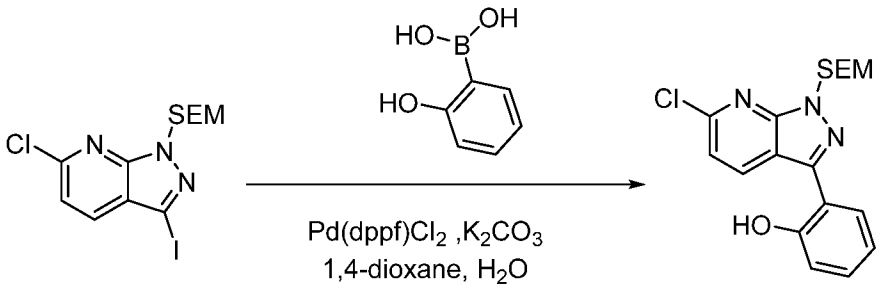
100

[0537] To a solution of (1S,2S)-2-fluoro-N-(3-(3-fluoro-2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)cyclopropane-1-carboxamide (86.0 mg, 0.18 mmol) in DCM (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3 \cdot H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 34% B to 51% B in 7 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-(3-fluoro-2-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)cyclopropane-1-carboxamide (12.2 mg, 19%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =345.2. ^1H NMR (300 MHz, DMSO-d_6): δ 13.67 (s, 1H), 11.02 (s, 1H), 8.21 (d, J = 9.0 Hz, 1H), 8.03 (d, J = 9.0 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.42 - 7.35 (m,

1H), 7.28 - 7.21 (m, 1H), 5.09 - 4.83 (m, 1H), 3.70 (d, J = 1.2 Hz, 3H), 2.47 - 2.32 (m, 1H), 1.74 - 1.61 (m, 1H), 1.26 - 1.16 (m, 1H).

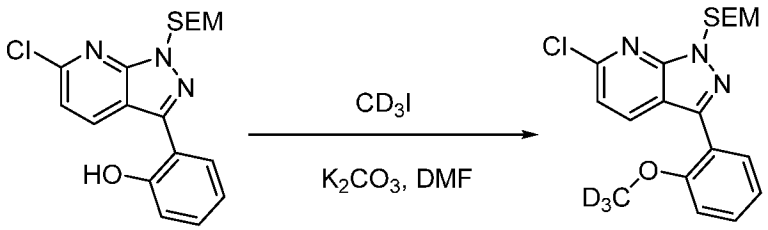
Example S101. Compound 101

Step 1: Synthesis of 2-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)phenol:



[0538] To a solution of 6-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (400.0 mg, 0.97 mmol) in 1,4-dioxane/H_2O (10.0 mL/2.0 mL) was added (2-hydroxyphenyl)boronic acid (134.7 mg, 0.97 mmol), K_2CO_3 (404.8 mg, 2.93 mmol) and $Pd(dppf)Cl_2$ (71.4 mg, 0.10 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (75/25, v/v) to afford 2-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)phenol (270.0 mg, 74%) as a light green solid. LCMS (ESI, m/z): $[M+H]^+$ =376.1.

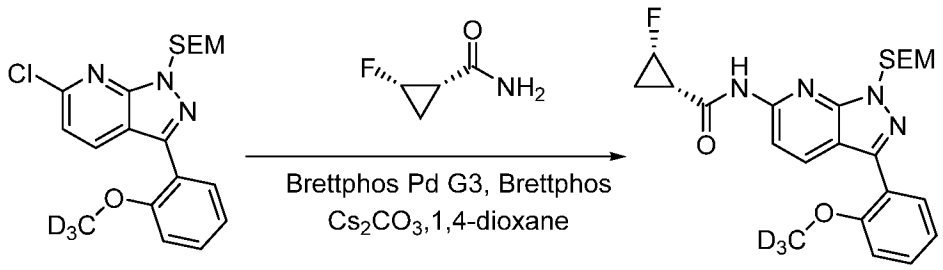
Step 2: Synthesis of 6-chloro-3-(2-(methoxy-d3)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine:



[0539] To a solution of 2-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)phenol (220.0 mg, 0.59 mmol) in DMF (5.0 mL) was added

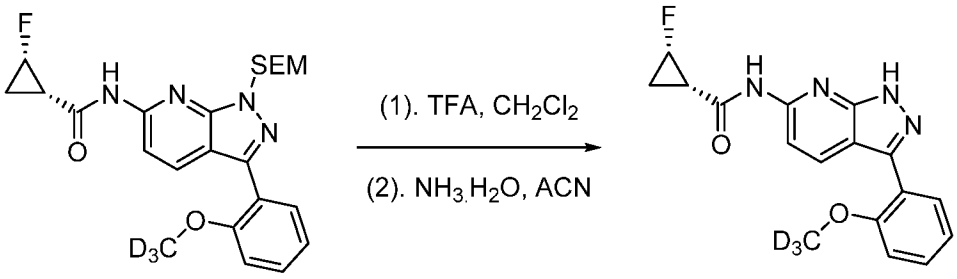
K_2CO_3 (242.6 mg, 1.76 mmol) and iodomethane-*d*3 (127.3 mg, 0.88 mmol) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (99/1, v/v) to afford 6-chloro-3-(2-(methoxy-d3)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (210.0 mg, 91%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =393.2.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-(3-(2-(methoxy-d3)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0540] To a solution of 6-chloro-3-(2-(methoxy-d3)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (120.0 mg, 0.31 mmol) in 1,4-dioxane (6.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (157.4 mg, 1.53 mmol), Cs_2CO_3 (298.5 mg, 0.92 mmol), BrettPhos (32.8 mg, 0.06 mmol) and BrettPhos Pd G3 (27.7 mg, 0.03 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (75/25, v/v) to afford (1S,2S)-2-fluoro-N-(3-(2-(methoxy-d3)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)cyclopropane-1-carboxamide (75.0 mg, 53%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =460.2.

Step 4: Synthesis of (1S,2S)-2-fluoro-N-(3-(2-(methoxy-d3)phenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 101):

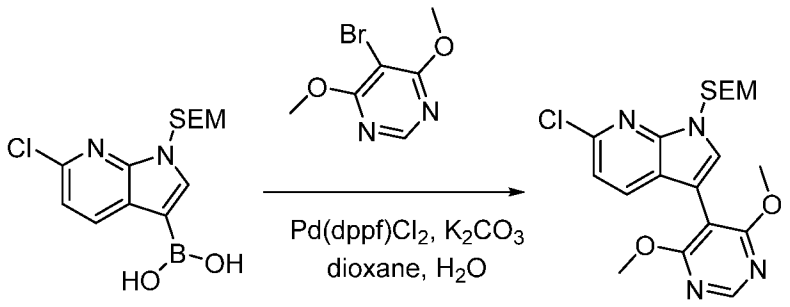


101

[0541] To a solution of (1S,2S)-2-fluoro-N-(3-(2-(methoxy-d3)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)cyclopropane-1-carboxamide (75.0 mg, 0.16 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in ACN (5.0 mL) was added $NH_3.H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 19×250 mm, 10 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 39% B to 49% B in 10 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-(2-(methoxy-d3)phenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)cyclopropane-1-carboxamide (10.9 mg, 20%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =330.1. ^1H NMR (300 MHz, DMSO-d_6): δ 13.47 (s, 1H), 10.97 (s, 1H), 8.12 (d, J = 9.0 Hz, 1H), 7.99 (d, J = 9.0 Hz, 1H), 7.64 - 7.61 (m, 1H), 7.47 - 7.41 (m, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.10 - 7.05 (m, 1H), 5.08 - 4.82 (m, 1H), 2.30 - 2.25 (m, 1H), 1.73 - 1.62 (m, 1H), 1.23 - 1.16 (m, 1H).

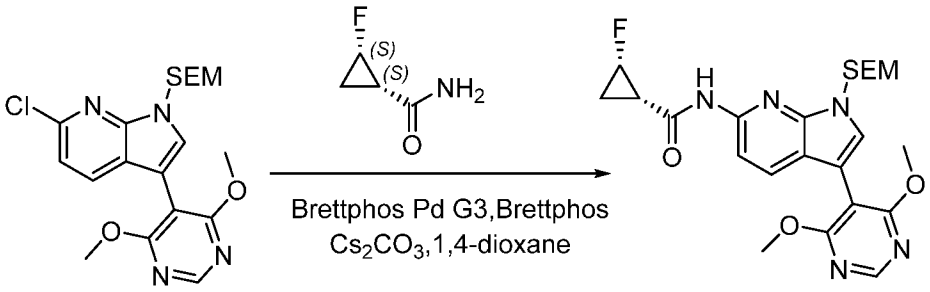
Example S102. Compound 102

Step 1: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4,6-dimethoxypyrimidine:



[0542] To a solution of 6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-ylboronic acid (350.0 mg, 1.07 mmol) in dioxane/H_2O (5.0/1.0 mL) was added 5-bromo-4,6-dimethoxypyrimidine (187.7 mg, 0.85 mmol), K_2CO_3 (444.2 mg, 3.20 mmol) and $Pd(dppf)Cl_2$ (78.4 mg, 0.10 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (90/10, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4,6-dimethoxypyrimidine (180.0 mg, 40%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =421.1.

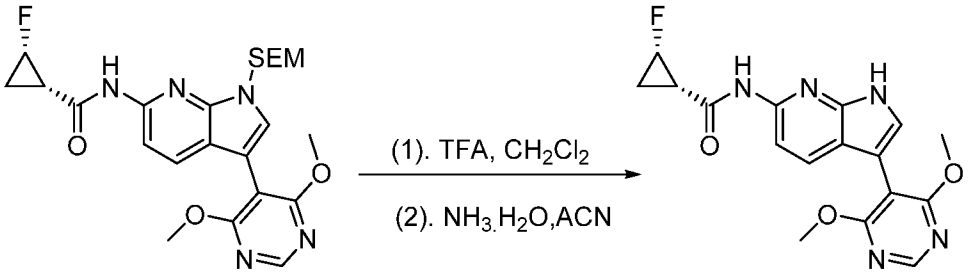
Step 2: Synthesis of (1S,2S)-N-[3-(4,6-dimethoxypyrimidin-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide:



[0543] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4,6-dimethoxypyrimidine (160.0 mg, 0.38 mmol) in 1,4-dioxane (4.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (195.9 mg, 1.90 mmol), Cs_2CO_3 (371.5 mg, 1.14 mmol), BrettPhos (40.8 mg, 0.07 mmol) and BrettPhos Pd G3 (34.4 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted

with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (70/30, v/v) to afford (1S,2S)-N-[3-(4,6-dimethoxypyrimidin-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (160.0 mg, 86%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =488.2.

Step 3: Synthesis of (1S,2S)-N-[3-(4,6-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 102):

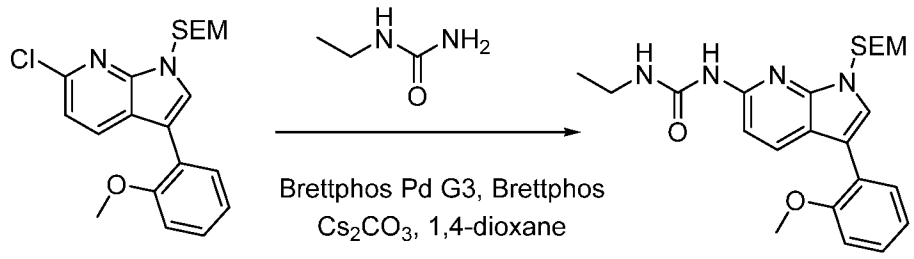


102

[0544] To a solution of (1S,2S)-N-[3-(4,6-dimethoxypyrimidin-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (280.0 mg, 0.44 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in ACN (2.0 mL) was added $NH_3 \cdot H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18, 30x250 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31 % B to 40 % B in 9 min; 254 nm) to afford (1S,2S)-N-[3-(4,6-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (29.5 mg, 25%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =358.1. ^1H NMR (400 MHz, DMSO-d_6): δ 11.66 (s, 1H), 10.62 (s, 1H), 8.47 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 1.6 Hz, 1H), 5.01 - 4.82 (m, 1H), 3.91 (s, 6H), 2.27 - 2.19 (m, 1H), 1.69 - 1.61 (m, 1H), 1.17 - 1.14 (m, 1H).

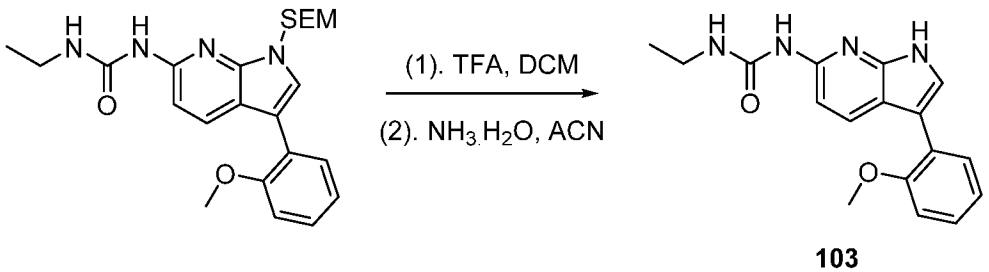
Example S103. Compound 103

Step 1: Synthesis of 3-ethyl-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea :



[0545] To a mixture of 6-chloro-3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 0.77 mmol) and ethylurea (206.0 mg, 0.23 mmol) in dioxane (5.0 mL) was added Brettphos Pd G3 (69.9 mg, 0.07 mmol), Cs_2CO_3 (753.8 mg, 2.31 mmol) and BrettPhos (84.0 mg, 0.14 mmol) at room temperature under N_2. The resulting mixture was stirred at 60 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 3-ethyl-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl) ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (300.0 mg, 88%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =441.2

Step 2: Synthesis of 3-ethyl-1-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (Compound 103):



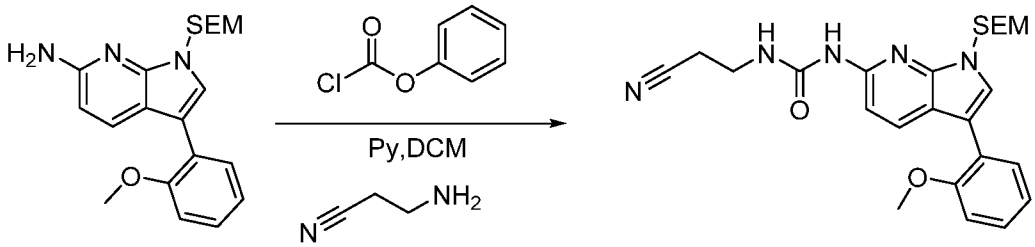
103

[0546] To a solution of 3-ethyl-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl] pyrrolo[2,3-b]pyridin-6-yl]urea (170.0 mg, 0.38 mmol) in DCM (2.0 mL) was added TFA (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated under reduced

pressure. To the above residue was added ACN (1.0 mL) and $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 30x250 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 41% B to 50% B in 9 min; 254 nm) to afford 3-ethyl-1-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (43.9 mg, 36%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =311.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.51 (s, 1H), 9.15 (s, 1H), 8.59 - 8.56 (m, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.52 - 7.46 (m, 2H), 7.29 - 7.23 (m, 1H), 7.10 (d, J = 7.5 Hz, 1H), 7.04 - 6.99 (m, 2H), 3.81 (s, 3H), 3.30 - 3.21 (m, 2H) , 1.19 - 1.14 (m, 3H).

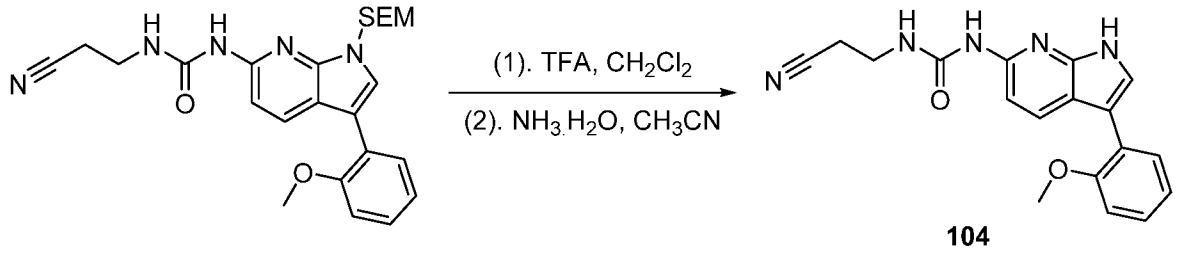
Example S104. Compound 104

Step 1: Synthesis of 3-(2-cyanoethyl)-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea:



[0547] To a solution of 3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (100.0 mg, 0.27 mmol) in CH_2Cl_2 (2.0 mL) was added Pyridine (85.6 mg, 1.08 mmol) and phenyl chloroformate (50.8 mg, 0.33 mmol) at 0 °C. The mixture was stirred at room temperature for 16 h. The mixture was concentrated under vacuum. To the residue was added pyridine (2.0 mL) and 3-aminopropanenitrile (56.9 mg, 0.81 mmol). The resulting mixture was stirred at 60 °C for another 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (20/80, v/v) to afford 3-(2-cyanoethyl)-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (70.0 mg, 55%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =466.2.

Step 2: Synthesis of 3-(2-cyanoethyl)-1-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (Compound 104):

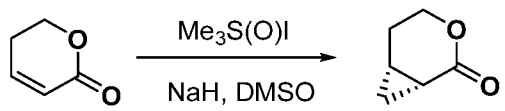


104

[0548] To a solution of 3-(2-cyanoethyl)-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (60.0 mg, 0.13 mmol) in CH_2Cl_2 (1.0 mL) was added TFA (1.0 mL). The mixture was stirred at room temperature for 2 h. The mixture was concentrated under vacuum. The residue was dissolved in ACN (1.0 mL) and $NH_3.H_2O$ (1.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 47% B in 7 min; 254 nm) to afford 3-(2-cyanoethyl)-1-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (24.5 mg, 56%) as a white solid. LCMS (ESI, m/z): $[M+H]^+ = 336.1$. ^1H NMR (300 MHz, DMSO-d_6): δ 11.48 (s, 1H), 9.33 (s, 1H), 8.70 (s, 1H), 7.93 (d, $J = 8.4$ Hz, 1H), 7.53 - 7.48 (m, 2H), 7.29 - 7.24 (m, 1H), 7.12 - 7.08 (m, 2H), 7.04 - 6.99 (m, 1H), 3.81 (s, 3H), 3.51 - 3.46 (m, 2H), 2.80 - 2.73 (m, 2H).

Example S105. Compound 105

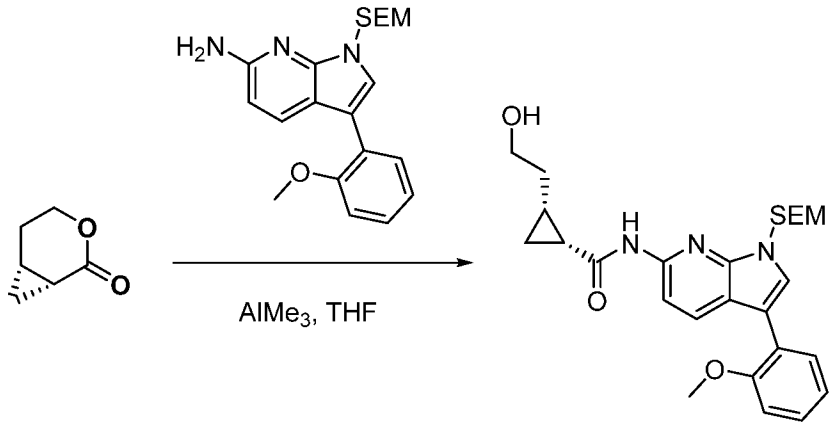
Step 1: Synthesis of cis-3-oxa-bicyclo[4.1.0]heptan-2-one:



[0549] To a solution of trimethylsulfoxonium iodide (1.2 g, 5.61 mmol) in DMSO (10.0 mL) was added NaH (224.6 mg, 60%) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. Then 5,6-dihydropyran-2-one (500.0 mg, 5.10 mmol) was added dropwise to the mixture at 0 °C. The resulting mixture was stirred at room temperature for another 16 h under N_2. After the reaction was completed, the resulting mixture was quenched with water and

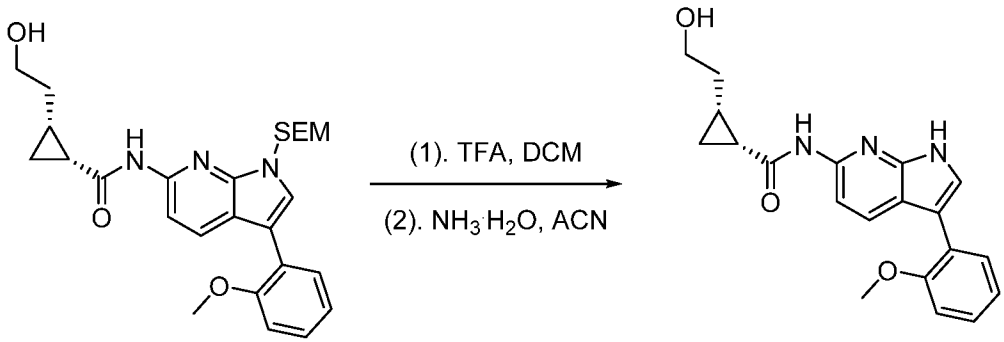
extracted with Et_2O. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford cis-3-oxa-bicyclo[4.1.0]heptan-2-one (80.0 mg, crude) as a yellow oil.

Step 2: Synthesis of cis-2-(2-hydroxyethyl)-N-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide:



[0550] To a mixture of 3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (70.0 mg, 0.19 mmol) and cis-3-oxa-bicyclo[4.1.0]heptan-2-one (63.7 mg, crude) in THF (10.0 mL) was added $AlMe_3$ (0.47 mL, 2 mol/L) at 0 °C under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (30/70, v/v) to afford cis-2-(2-hydroxyethyl)-N-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (40.0 mg, 44%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =482.2.

Step 3: Synthesis of cis-2-(2-hydroxyethyl)-N-(3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (Compound 105):

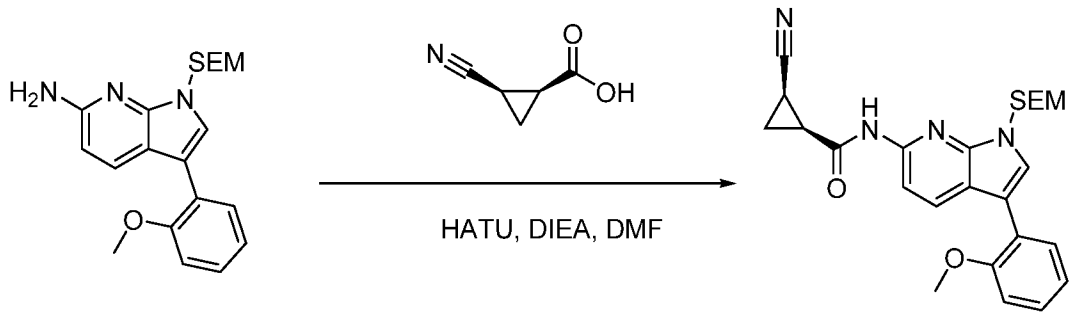


105

[0551] To a solution of cis-2-(2-hydroxyethyl)-N-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (35.0 mg, 0.07 mmol) in CH_2Cl_2 (1.0 mL) was added TFA (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in ACN (1.0 mL) and $NH_3.H_2O$ (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with petroleum MeOH/H_2O (70/30, v/v) to afford cis-2-(2-hydroxyethyl)-N-(3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropanecarboxamide (10.3 mg, 40%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =352.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.53 (d, J = 1.8 Hz, 1H), 10.47 (s, 1H), 7.98 - 7.88 (m, 2H), 7.56 - 7.52 (m, 2H), 7.30 - 7.24 (m, 1H), 7.13 - 7.05 (m, 1H), 7.03 - 7.00 (m, 1H), 4.44 - 4.40 (m, 1H), 3.82 (s, 3H), 3.43 - 3.37 (m, 2H), 2.07 - 2.01 (m, 1H), 1.72 - 1.63 (m, 2H), 1.33 - 1.25 (m, 1H), 0.99 - 0.85 (m, 2H).

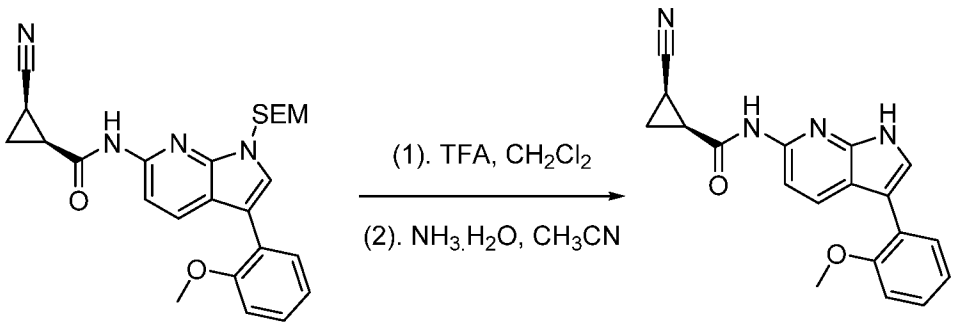
Example S106. Compound 106

Step 1: Synthesis of cis-2-cyano-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0552] To a solution of 3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (300.0 mg, 0.82 mmol) in DMF (10.0 mL) was added cis-2-cyanocyclopropane-1-carboxylic acid (90.9 mg, 0.81 mmol), HATU (463.2 mg, 1.21 mmol) and DIEA (157.3 mg, 1.28 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford cis-2-cyano-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (300.0 mg, 80%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =463.2.

Step 2: Synthesis of cis-2-cyano-N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 106):



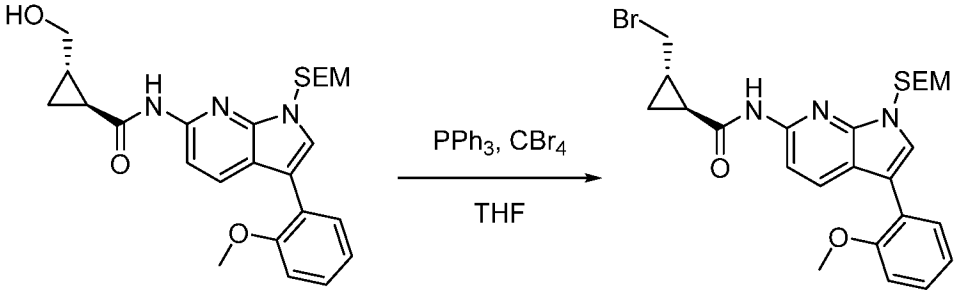
106

[0553] To a solution of cis-2-cyano-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (150.0 mg, 0.43 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (3.0 mL) and

$NH_3.H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 55% B to 75% B in 10 min; 254 nm) to afford cis-2-cyano-N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (3.7 mg, 3%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =333.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.66 (s, 1H), 10.93 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.55 - 7.52 (m, 1H), 7.31 - 7.25 (m, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.05 - 7.00 (m, 1H), 3.82 (s, 3H), 2.77 - 2.71 (m, 1H), 2.16 - 2.10 (m, 1H), 1.63 - 1.54 (m, 1H), 1.45 - 1.38 (m, 1H).

Example S107. Compound 107

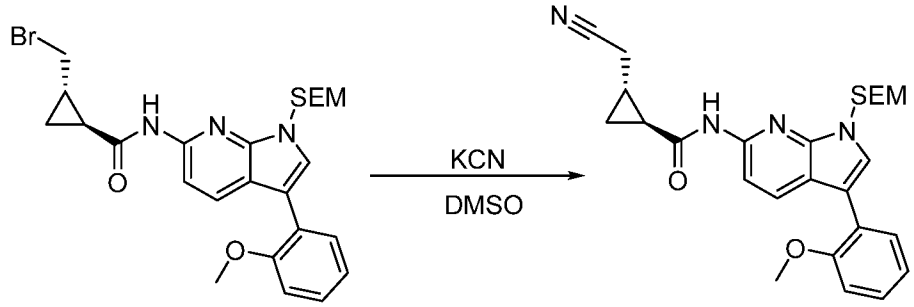
Step 1: Synthesis of trans-2-(bromomethyl)-N-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0554] To a solution of trans-2-(hydroxymethyl)-N-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (300.0 mg, 0.64 mmol) in THF (10.0 mL) was added PPh_3 (185.0 mg, 0.70 mmol) and CBr_4 (319.2 mg, 0.96 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (83/17, v/v) to afford trans-2-(bromomethyl)-N-(3-(2-methoxyphenyl)-1-

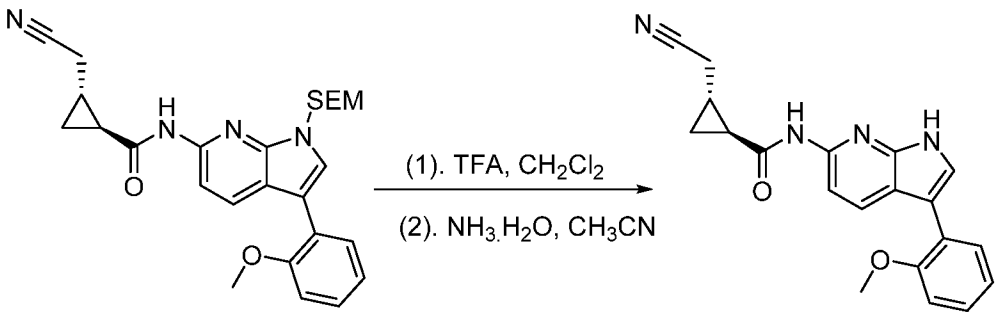
((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (250.0 mg, 40%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =530.1.

Step 2: Synthesis of trans-2-(cyanomethyl)-N-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0555] To a solution of trans-2-(bromomethyl)-N-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (200.0 mg, 0.39 mmol) in DMSO (10.0 mL) was added KCN (37.7 mg, 0.58 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 3 h. After the reaction was completed, the resulting mixture was quenched with aq. $NaHCO_3$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (72/28, v/v) to afford trans-2-(cyanomethyl)-N-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (150.0 mg, 81%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =477.2.

[0556] Step 3: Synthesis of trans-2-(cyanomethyl)-N-(3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 107):

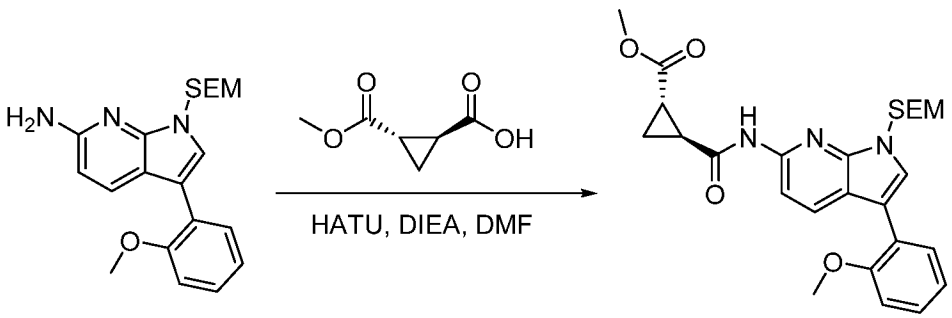


107

[0557] To a solution of trans-2-(cyanomethyl)-N-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (130.0 mg, 0.27 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (5.0 mL) and $NH_3 \cdot H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 42% B to 52% B in 8 min; 254 nm) to afford trans-2-(cyanomethyl)-N-(3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (37.2 mg, 39%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =347.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.58 (s, 1H), 10.70 (s, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.58 - 7.52 (m, 2H), 7.30 - 7.25 (m, 1H), 7.11 (d, J = 8.1 Hz, 1H), 7.05 - 7.00 (m, 1H), 3.82 (s, 3H), 2.73 (d, J = 6.6 Hz, 2H), 2.10 - 2.05 (m, 1H), 1.59 - 1.52 (m, 1H), 1.14 - 1.08 (m, 1H), 0.95 - 0.83 (m, 1H).

Example S108. Compound 108

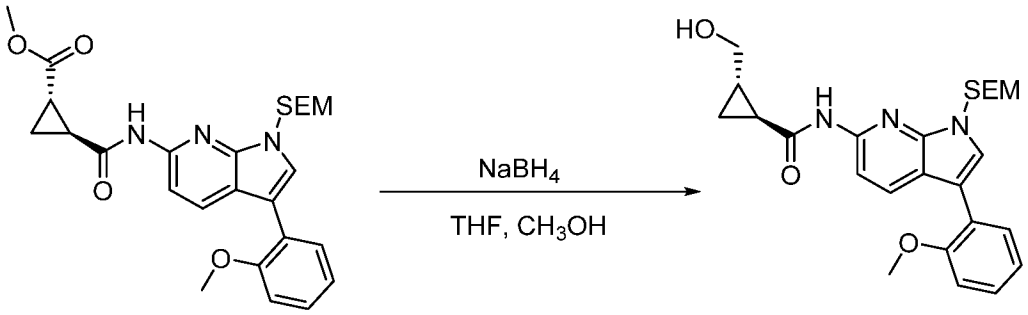
Step 1: Synthesis of trans-methyl 2-((3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamoyl)cyclopropane-1-carboxylate:



[0558] To a solution of 3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy] methyl] pyrrolo[2,3-b] pyridin-6-amine (600.0 mg, 1.62 mmol) in DMF (10.0 mL) was added DIEA (1049.2 mg, 8.12 mmol), trans-2-(methoxycarbonyl) cyclopropane-1-carboxylic acid (280.8

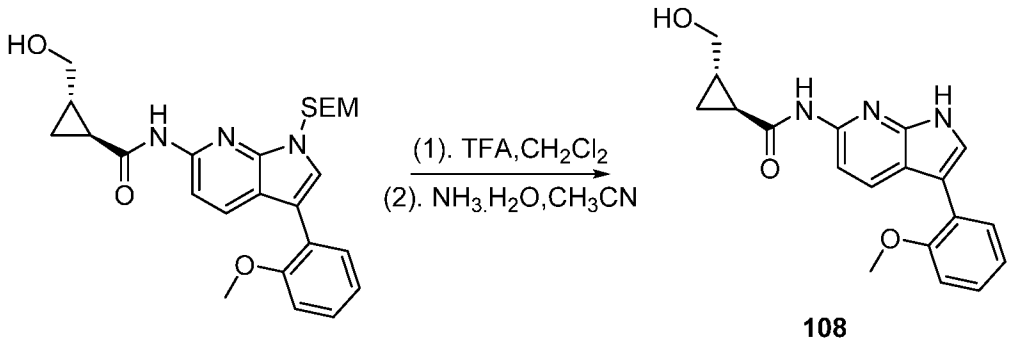
mg, 1.95 mmol) and HATU (926.0 mg, 2.44 mmol) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford trans-methyl 2-[[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]cyclopropane-1-carboxylate (660.0 mg, 82%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 496.2.

[0559] Step 2: Synthesis of trans-2-(hydroxylmethyl)-N-(3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b] pyridin-6-yl) cyclopropane-1-carboxamide:



[0560] To a solution of trans-methyl 2-[[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl) ethoxy] methyl] pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]cyclopropane-1-carboxylate (640.0 mg, 1.29 mmol) in THF/CH_3OH (8.0/2.0 mL) was added $NaBH_4$ (488.5 mg, 12.91 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the reaction mixture was quenched with CH_3OH and concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford trans-2-(hydroxymethyl)-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl) ethoxy]methyl]pyrrolo[2,3-b] pyridin-6-yl] cyclopropane-1-carboxamide (500.0 mg, 82%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 468.2.

Step 3: Synthesis of trans-2-(hydroxymethyl)-N-(3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 108):

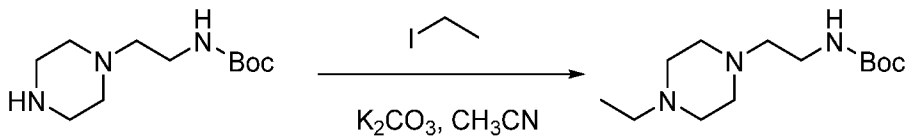


108

[0561] To a solution of trans-2-(hydroxymethyl)-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy] methyl]pyrrolo [2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (130.0 mg, 0.28 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (3.0 mL) and $NH_3 \cdot H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; 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; 254 nm) to afford trans-2-(hydroxymethyl)-N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b] pyridin-6-yl] cyclopropane-1-carboxamide (20.3 mg, 21%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =338.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.54 (s, 1H), 10.46 (s, 1H), 7.96 (d, J = 8.7 Hz, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.55 - 7.52 (m, 2H), 7.29 - 7.23 (m, 1H), 7.10 (d, J = 7.5 Hz, 1H), 7.04 - 6.99 (m, 1H), 4.66 - 4.62 (m, 1H), 3.81 (s, 3H), 3.49 - 3.42 (m, 1H), 3.31 - 3.27 (m, 1H), 1.97 - 1.93 (m, 1H), 1.49 - 1.43 (m, 1H), 1.01 - 0.95 (m, 1H), 0.80 - 0.75 (m, 1H).

[0562] ***Example S109. Compound 109***

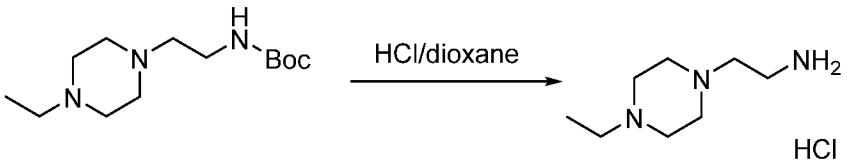
[0563] **Step 1: Synthesis of tert-butyl N-[2-(4-ethylpiperazin-1-yl)ethyl]carbamate:**



[0564] To a solution of tert-butyl N-[2-(piperazin-1-yl)ethyl]carbamate (2.0 g, 8.72 mmol) in CH_3CN (20.0 mL) was added K_2CO_3 (2.4 g, 17.44 mmol) and ethyl iodide (2.0 g,

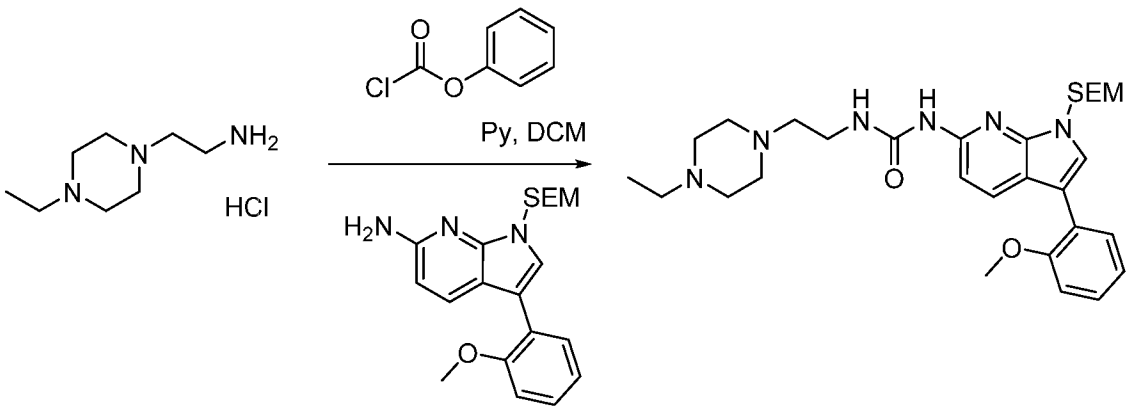
13.08 mmol). The mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (88/12, v/v) to afford tert-butyl N-[2-(4-ethylpiperazin-1-yl)ethyl]carbamate (400.0 mg, 17%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =258.2.

[0565] Step 2: Synthesis of 2-(4-ethylpiperazin-1-yl)ethanamine hydrochloride:



[0566] The solution of tert-butyl N-[2-(4-ethylpiperazin-1-yl)ethyl]carbamate (400.0 mg, 1.55 mmol) in HCl/dioxane (3.0 mL, 4 mol/L) was stirred at room temperature for 2 h. After the reaction was completed, the mixture was filtered. The solid was washed with Et_2O and dried to afford 2-(4-ethylpiperazin-1-yl)ethanamine hydrochloride (200.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =158.2.

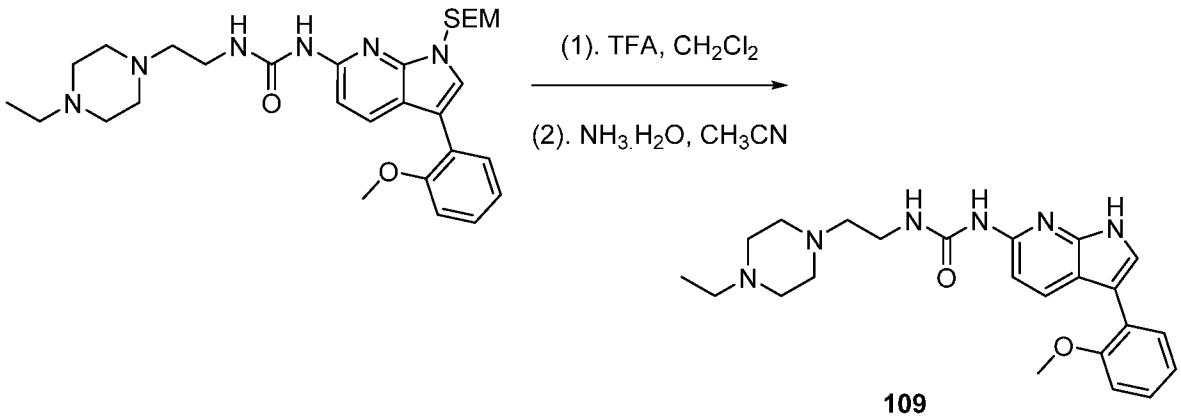
Step 3: Synthesis of 1-[2-(4-ethylpiperazin-1-yl)ethyl]-3-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea:



[0567] To a solution of 3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (150.0 mg, 0.41 mmol) in CH_2Cl_2 (3.0 mL) was added pyridine (128.4 mg, 1.62 mmol) and phenyl chloroformate (76.3 mg, 0.49 mmol) at 0 °C. The mixture was stirred at room temperature for 16 h. The mixture was concentrated under vacuum. To the above residue was added pyridine (3.0 mL) and 2-(4-ethylpiperazin-1-yl)ethanamine hydrochloride (236.7 mg, crude). The resulting mixture was

stirred at 60 °C for another 5 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/95, v/v) to afford 1-[2-(4-ethylpiperazin-1-yl)ethyl]-3-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (200.0 mg, 89%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =553.3

Step 4: Synthesis of 1-[2-(4-ethylpiperazin-1-yl)ethyl]-3-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (Compound 109):

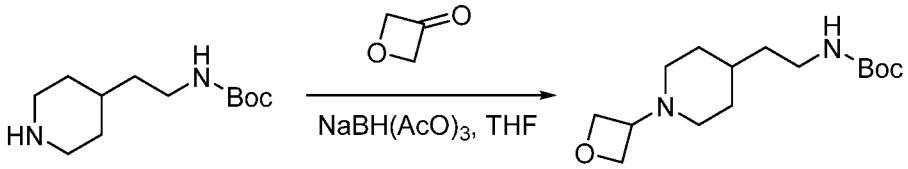


109

[0568] To a solution of 1-[2-(4-ethylpiperazin-1-yl)ethyl]-3-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (180.0 mg, 0.33 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL). The mixture was stirred at room temperature for 2 h. The mixture was concentrated under vacuum. To the above residue was added ACN (3.0 mL) and $NH_3.H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 37% B to 47% B in 8 min; 254 nm) to afford 1-[2-(4-ethylpiperazin-1-yl)ethyl]-3-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (24.6 mg, 17%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 423.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H), 9.18 (s, 1H), 8.30 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.51 - 7.49 (m, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.28 - 7.23 (m, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.03 - 6.99 (m, 1H), 3.81 (s, 3H), 2.47 - 2.44 (m, 6H), 2.36 - 2.26 (m, 6H), 0.99 - 0.96 (m, 3H).

Example S110. Compound 110

Step 1: Synthesis of tert-butyl N-[2-[1-(oxetan-3-yl)piperidin-4-yl]ethyl]carbamate:



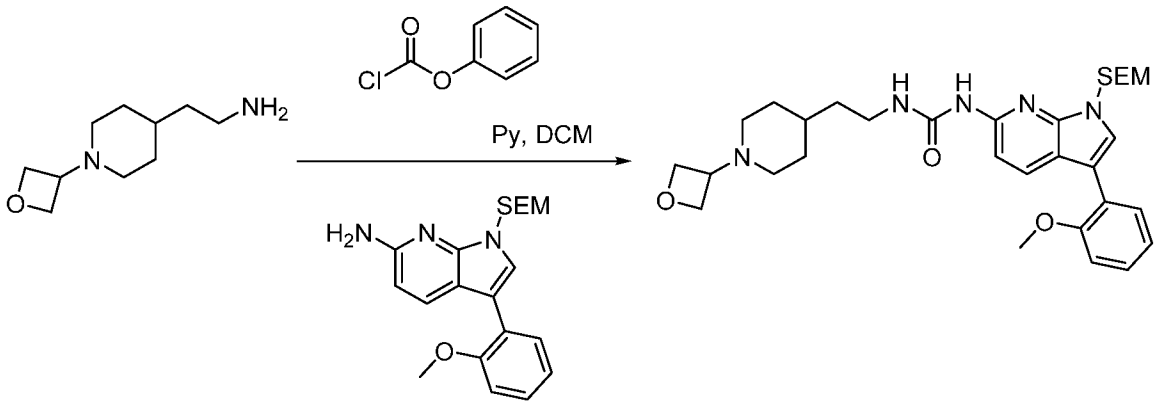
[0569] To a solution of tert-butyl N-[2-(piperidin-4-yl)ethyl]carbamate (1.0 g, 4.38 mmol) in THF (50.0 mL) was added 3-oxetanone (0.4 g, 5.26 mmol) and $NaBH(OAc)_3$ (1.4 g, 6.57 mmol at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (10/1, v/v) to afford tert-butyl N-[2-[1-(oxetan-3-yl)piperidin-4-yl]ethyl]carbamate (900.0 mg, 72%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =285.0.

Step 2: Synthesis of 2-[1-(oxetan-3-yl)piperidin-4-yl]ethanamine:



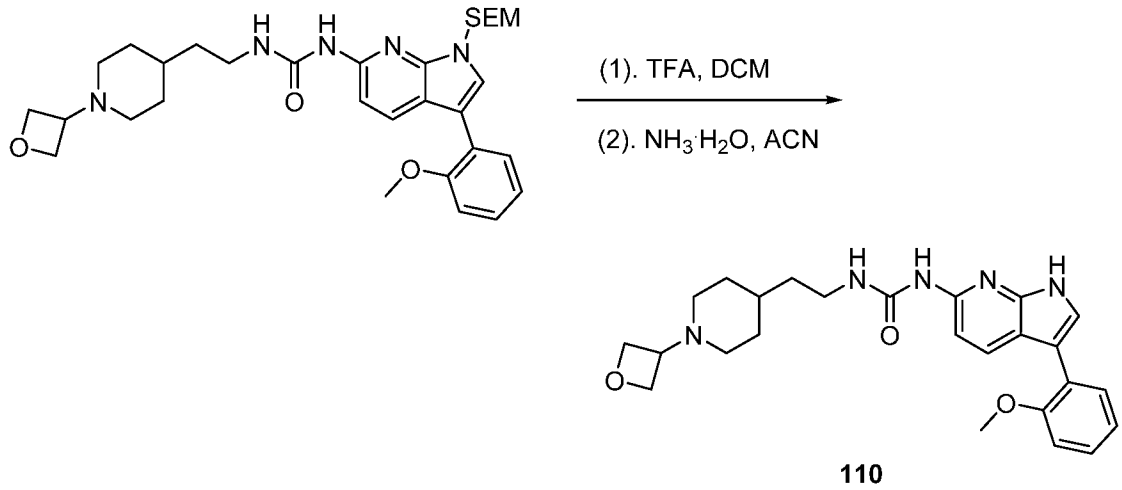
[0570] To a solution of tert-butyl N-[2-[1-(oxetan-3-yl)piperidin-4-yl]ethyl]carbamate (800.0 mg, 2.81 mmol) in DCM (6.0 mL) was added TFA (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the mixture was basified to pH=8 with saturated $NaHCO_3$ (aq.). The mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 2-[1-(oxetan-3-yl)piperidin-4-yl]ethanamine (500.0 mg, crude) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =185.2.

Step 3: Synthesis of 3-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-[4-(oxetan-3-yl)piperazin-1-yl]ethyl]urea:



[0571] To a solution of 3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (130.0 mg, 0.35 mmol) in DCM (5.0 mL) was added pyridine (112.7 mg, 1.41 mmol) and phenyl chloroformate (66.1 mg, 0.42 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added pyridine (6.0 mL) and 2-[1-(oxetan-3-yl)piperidin-4-yl]ethanamine (129.7 mg, 0.70 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 16 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (5/1, v/v) to afford 3-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-[4-(oxetan-3-yl)piperazin-1-yl]ethyl]urea (100.0 mg, 49%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =581.3.

Step 4: Synthesis of 3-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-[1-(oxetan-3-yl)piperidin-4-yl]ethyl]urea (Compound 110):

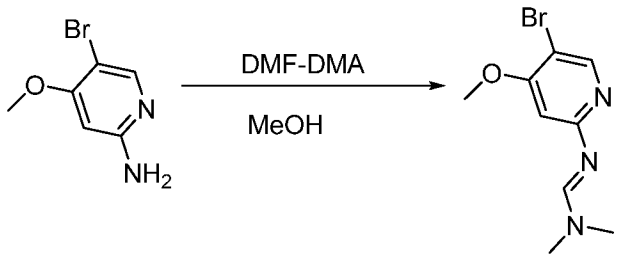


110

[0572] To a solution of 3-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-[4-(oxetan-3-yl)piperazin-1-yl]ethyl]urea (90.0 mg, 0.16 mmol) in CH_2Cl_2 (4.0 mL) was added TFA (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (4.0 mL) and $NH_3.H_2O$ (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; 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 9 min; 254 nm) to afford 3-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-[1-(oxetan-3-yl)piperidin-4-yl]ethyl]urea (2.2 mg, 3%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =450.3. ^1H NMR (400 MHz, DMSO-d_6): δ 11.49 (s, 1H), 9.13 (s, 1H), 8.55 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.53 (s, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.26 - 7.22 (m, 1H), 7.11 - 7.08 (m, 1H), 7.02 - 6.95 (m, 2H), 4.52 - 4.49 (m, 2H), 4.42 - 4.39 (m, 2H), 3.80 (s, 3H), 3.30 - 3.25 (m, 2H), 2.68 - 2.64 (m, 2H), 1.79 - 1.69 (m, 4H), 1.49 - 1.44 (m, 2H), 1.37 - 1.28 (m, 1H), 1.24 - 1.17 (m, 2H).

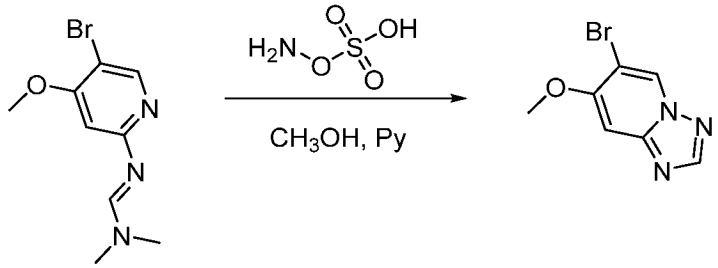
Example S111. Compound 111

Step 1: Synthesis of (E)-N'-(5-bromo-4-methoxypyridin-2-yl)-N,N-dimethylformimidamide:



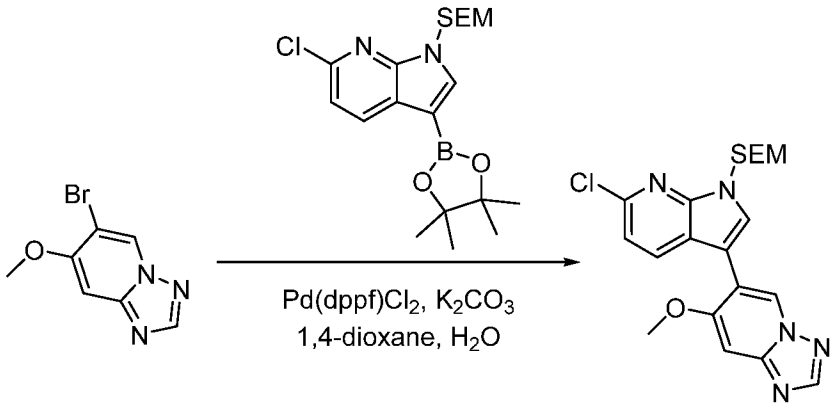
[0573] To a solution of 5-bromo-4-methoxypyridin-2-amine (1.0 g, 4.93 mmol) in MeOH (10.0 mL) was added DMF-DMA (704.2 mg, 5.91 mmol) at room temperature. The resulting mixture was stirred at 75 °C for 3 h. After the reaction was completed, the resulting mixture concentrated under reduced pressure to afford (E)-N'-(5-bromo-4-methoxypyridin-2-yl)-N,N-dimethylformimidamide (870.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =258.0.

Step 2: Synthesis of 6-bromo-7-methoxy-[1,2,4]triazolo[1,5-a]pyridine:



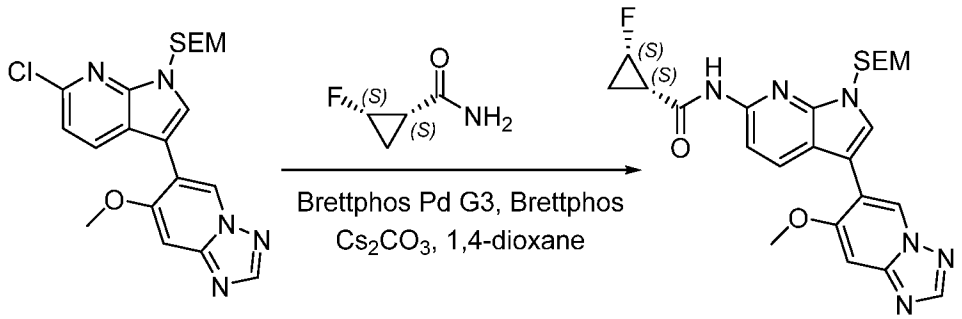
[0574] To a solution of (E)-N'-(5-bromo-4-methoxypyridin-2-yl)-N,N-dimethylformimidamide (550.0 mg, 2.13 mmol) in CH_3OH/Pyridine (5.0/0.5 mL) was added (aminooxy)sulfonic acid (361.5 mg, 3.20 mmol) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was quenched with aq. $NaHCO_3$ and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (1/1, v/v) to afford 6-bromo-7-methoxy-[1,2,4]triazolo[1,5-a]pyridine (100.0 mg, 20%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =228.0.

Step 3: Synthesis of 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-methoxy-[1,2,4]triazolo[1,5-a]pyridine:



[0575] To a solution of 6-bromo-7-methoxy-[1,2,4]triazolo[1,5-a]pyridine (150.0 mg, 0.66 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (268.9 mg, 0.66 mmol), K_2CO_3 (272.7 mg, 1.97 mmol) and $Pd(dppf)Cl_2$ (48.1 mg, 0.07 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/90, v/v) to afford 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-methoxy-[1,2,4]triazolo[1,5-a]pyridine (100.0 mg, 35%) as a light brown solid. LCMS (ESI, m/z): $[M+H]^+$ =430.1.

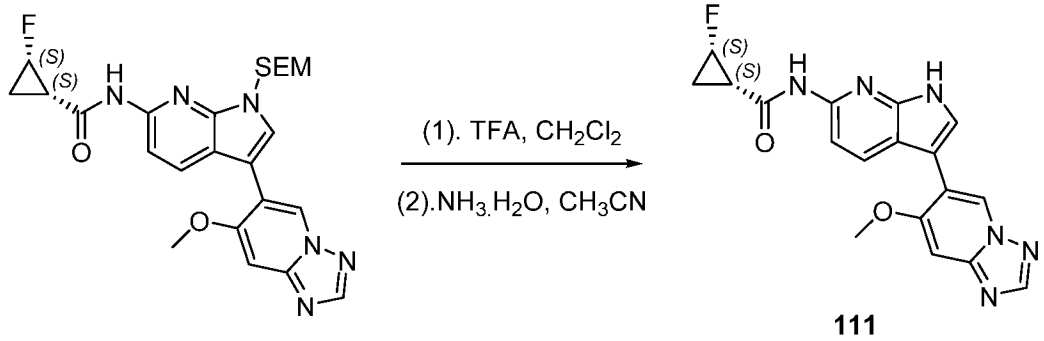
Step 4: Synthesis of (1S,2S)-2-fluoro-N-(3-(7-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0576] To a solution of 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-methoxy-[1,2,4]triazolo[1,5-a]pyridine (80.0 mg, 0.19 mmol) in 1,4-dioxane (4.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (95.9 mg, 0.93

mmol), Cs_2CO_3 (181.9 mg, 0.56 mmol), BrettPhos (20.0 mg, 0.04 mmol) and BrettPhos Pd G3 (16.9 mg, 0.02 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (30/70, v/v) to afford (1S,2S)-2-fluoro-N-(3-(7-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (70.0 mg, 76%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =497.2.

Step 5: Synthesis of (1S,2S)-2-fluoro-N-(3-(7-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 111):



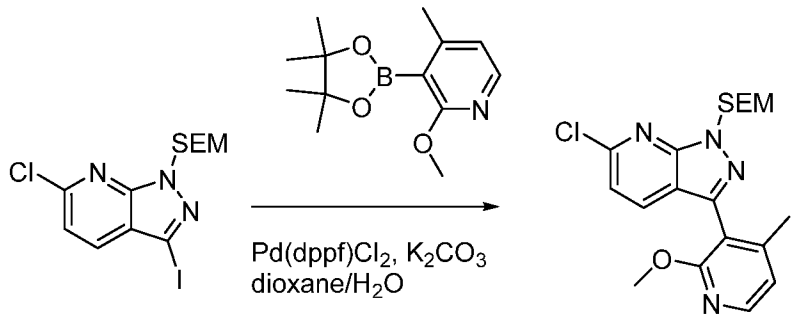
111

[0577] To a solution of (1S,2S)-2-fluoro-N-(3-(7-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (70.0 mg, 0.14 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (3.0 mL) and $NH_3 \cdot H_2O$ (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 33% B in 8 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-(7-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-

carboxamide (14.3 mg, 27%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =367.2. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.77 (s, 1H), 10.68 (s, 1H), 8.90 (s, 1H), 8.35 (s, 1H), 8.02 - 7.91 (m, 2H), 7.68 (d, J = 2.4 Hz, 1H), 7.36 (s, 1H), 5.08 - 4.72 (m, 1H), 3.96 (s, 3H), 2.30 - 2.13 (m, 1H), 1.78 - 1.55 (m, 1H), 1.23 - 1.04 (m, 1H).

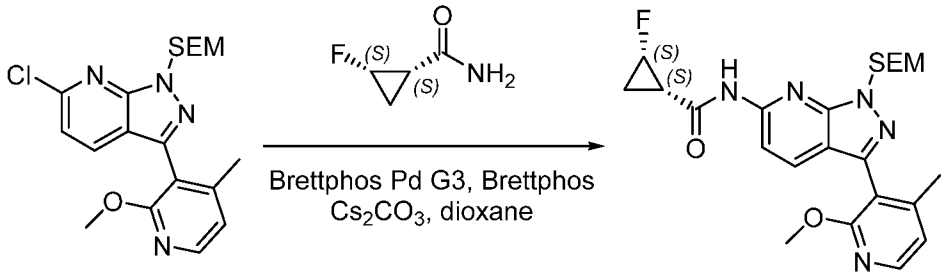
Example S112. Compound 112

Step 1: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-2-methoxy-4-methylpyridine:



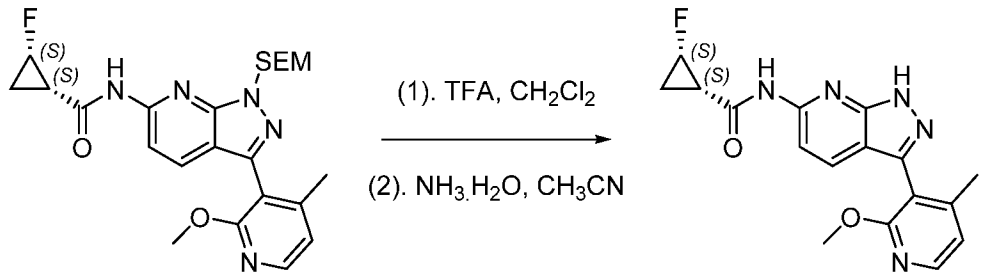
[0578] To a solution of 6-chloro-3-iodo-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (400.0 mg, 0.98 mmol) in dioxane/H_2O (10.0 mL/2.0 mL) was added 2-methoxy-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (243.2 mg, 0.98 mmol), K_2CO_3 (404.8 mg, 2.93 mmol) and $Pd(dppf)Cl_2$ (71.4 mg, 0.10 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-2-methoxy-4-methylpyridine (100.0 mg, 25%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =405.1.

Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-(2-methoxy-4-methylpyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0579] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-3-yl)-2-methoxy-4-methylpyridine (160.0 mg, 0.40 mmol) in 1,4-dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (203.7 mg, 1.98 mmol), BrettPhos (42.4 mg, 0.08 mmol), Cs_2CO_3 (386.2 mg, 1.19 mmol) and BrettPhos Pd G3 (35.8 mg, 0.04 mmol) at room temperature under N_2. The reaction mixture was stirred with microwave at 120 °C for 1.5 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1S,2S)-2-fluoro-N-[3-(2-methoxy-4-methylpyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (57.0 mg, 31%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =472.2.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-[3-(2-methoxy-4-methylpyridin-3-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 112):



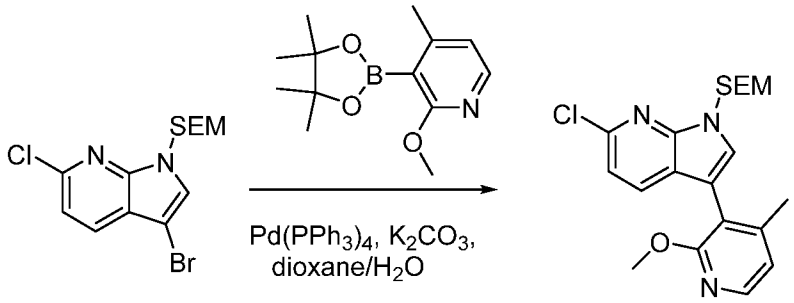
112

[0580] To a solution of (1S,2S)-2-fluoro-N-[3-(2-methoxy-4-methylpyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (57.0 mg, 0.12 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (3.0 mL) and

$NH_3.H_2O$ (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions Column: (Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 38% B in 8 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(2-methoxy-4-methylpyridin-3-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (10.9 mg, 26%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =342.1. ^1H NMR (400 MHz, DMSO-d_6): δ 13.53 (s, 1H), 10.99 (s, 1H), 8.13 (s, 1H), 7.98 - 7.90 (m, 2H), 7.02 (s, 1H), 5.03 - 4.87 (m, 1H), 3.79 (s, 3H), 2.27 - 2.20 (m, 4H), 1.70 - 1.64 (m, 1H), 1.30 - 1.15 (m, 1H).

Example S113. Compound 113

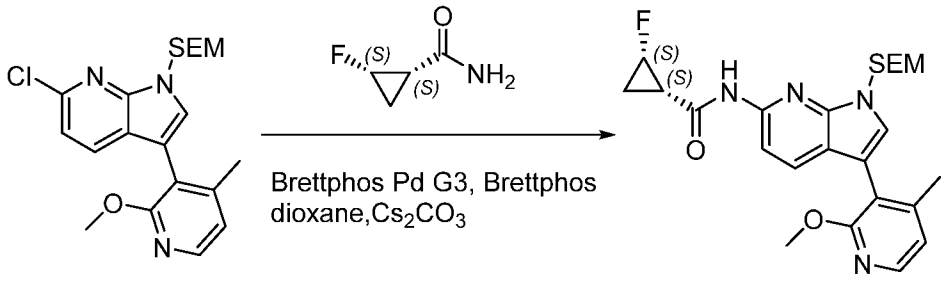
Step 1: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-methoxy-4-methylpyridine:



[0581] To a solution of 3-bromo-6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (500.0 mg, 1.38 mmol) in 1,4-dioxane/H_2O (25.0 mL/5.0 mL) was added 2-methoxy-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (413.2 mg, 1.66 mmol), K_2CO_3 (382.1 mg, 2.76 mmol) and $Pd(PPh_3)_4$ (159.7 mg, 0.14 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (90/10, v/v) to afford 3-(6-chloro-1-[[2-

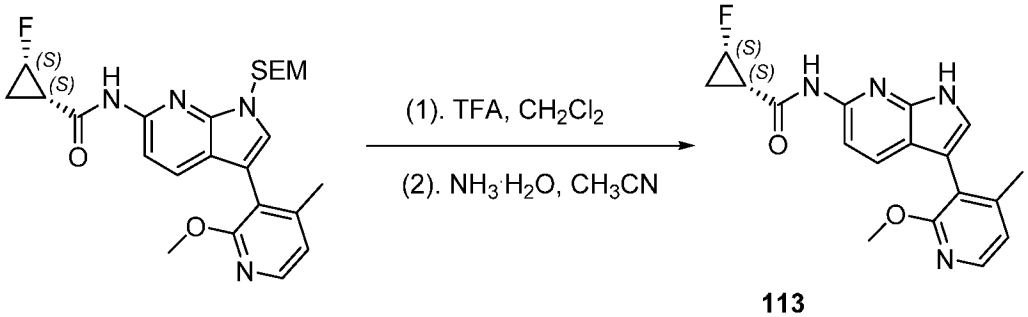
(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-methoxy-4-methylpyridine (160.0 mg, 28%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =404.1.

Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-(2-methoxy-4-methylpyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0582] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-methoxy-4-methylpyridine (140.0 mg, 0.35 mmol) in 1,4-dioxane (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (178.6 mg, 1.73 mmol), BrettPhos (37.2 mg, 0.07 mmol), Cs_2CO_3 (338.7 mg, 1.04 mmol) and BrettPhos Pd G3 (31.4 mg, 0.04 mmol) at room temperature under N_2. The reaction mixture was stirred with microwave at 120 °C for 1.5 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (80/20, v/v) to afford (1S,2S)-2-fluoro-N-[3-(2-methoxy-4-methylpyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (80.0 mg, 49%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =471.2.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-[3-(2-methoxy-4-methylpyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 113):

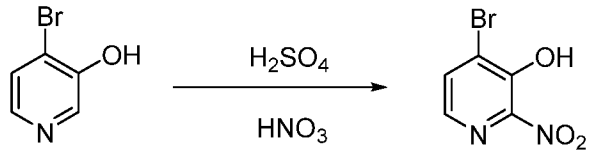


113

[0583] To a solution of (1S,2S)-2-fluoro-N-[3-(2-methoxy-4-methylpyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (80.0 mg, 0.17 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (3.0 mL) and $NH_3 \cdot H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another 3 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 34 % B to 44 % B in 8 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(2-methoxy-4-methylpyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (6.9 mg, 11%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =341.0. ^1H NMR (400 MHz, DMSO-d_6): δ 11.59 (s, 1H), 10.62 (s, 1H), 8.02 (d, J = 4.8 Hz, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 5.2 Hz, 1H), 5.02 - 4.81 (m, 1H), 3.75 (s, 3H), 2.23 - 2.18 (m, 4H), 1.68 - 1.61 (m, 1H), 1.19 - 1.14 (m, 1H).

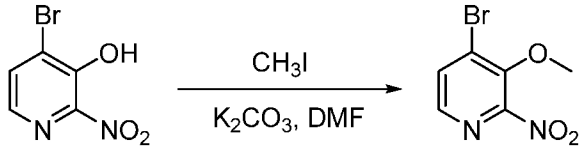
Example S114. Compound 114

Step 1: Synthesis of 4-bromo-2-nitropyridin-3-ol:



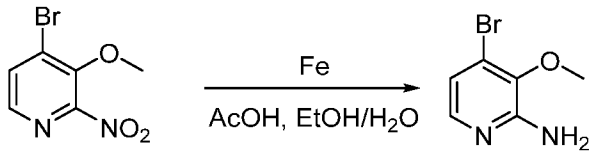
[0584] To a solution of 4-bromopyridin-3-ol (5.0 g, 28.74 mmol) in sulfuric acid (25.0 mL) was added nitric acid (5.4 g, 86.21 mmol) at room temperature under N_2. The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (9/1, v/v) to afford 4-bromo-2-nitropyridin-3-ol (2.3 g, 19 %) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =218.9.

Step 2: Synthesis of 4-bromo-3-methoxy-2-nitropyridine:



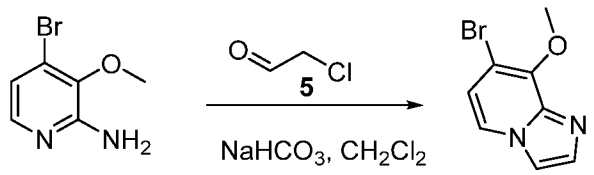
[0585] To a solution of 4-bromo-2-nitropyridin-3-ol (2.3 g, 10.50 mmol) in DMF (115.0 mL) was added K_2CO_3 (2.9 g, 21.01 mmol) at room temperature. The resulting mixture was stirred at room temperature for 10 min. Then CH_3I (3.0 g, 21.11 mmol) was added to the mixture at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (9/1, v/v) to afford 4-bromo-3-methoxy-2-nitropyridine (1.8 g, 73 %) as a white solid LCMS (ESI, m/z): $[M+H]^+$ =232.9.

Step 3: Synthesis of 4-bromo-3-methoxypyridin-2-amine:



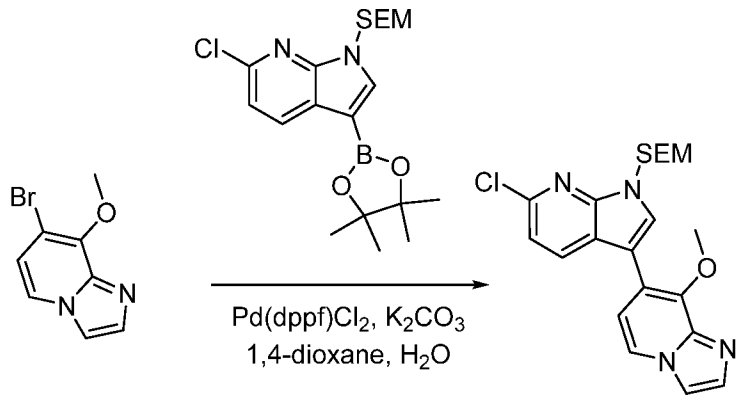
[0586] To a solution of 4-bromo-3-methoxy-2-nitropyridine (1.8 g, 7.73 mmol) in AcOH (10.0 mL)/EtOH (10.0 mL)/H_2O (5.0 mL) was added Fe (2.2 g, 38.68 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography petroleum ether/ethyl acetate (1/1, v/v) to afford 4-bromo-3-methoxypyridin-2-amine (1.3 g, 83 %) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =203.1.

Step 4: Synthesis of 7-bromo-8-methoxyimidazo[1,2-a]pyridine:



[0587] To a solution of 4-bromo-3-methoxypyridin-2-amine (650.0 mg, 3.20 mmol) in sat $NaHCO_3$ (25.0 mL)/DCM (25.0 mL) was added chloroacetaldehyde (1.6 g, 8.00 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 7-bromo-8-methoxyimidazo[1,2-a]pyridine (450.0 mg, 62%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =227.0.

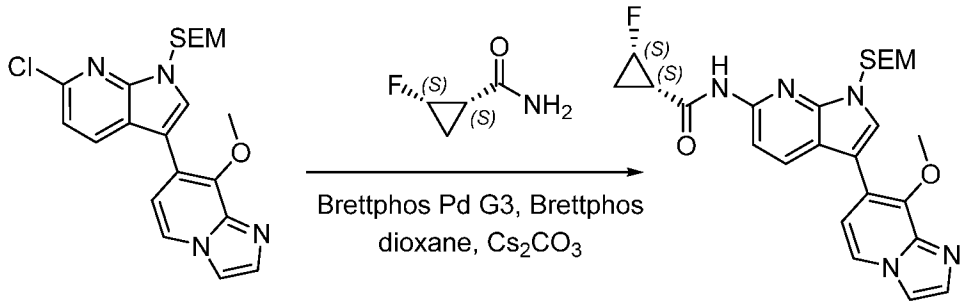
Step 5: Synthesis of 6-chloro-3-[8-methoxyimidazo[1,2-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



[0588] To a solution of 7-bromo-8-methoxyimidazo[1,2-a]pyridine (500.0 mg, 2.20 mmol) in dioxane/H_2O (20.0 mL/4.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (900.2 mg, 2.20 mmol), K_2CO_3 (913.0 mg, 6.61 mmol), $Pd(dppf)Cl_2$ (161.1 mg, 0.22 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 6-chloro-3-[8-methoxyimidazo[1,2-a]pyridin-7-yl]-1-[[2-

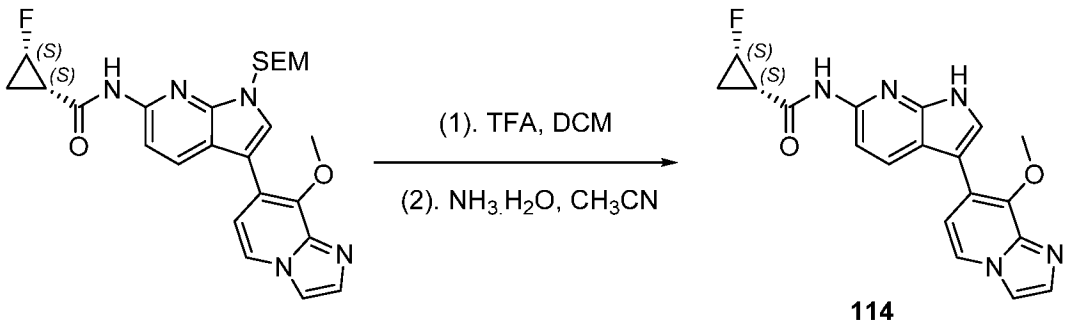
(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (140.0 mg, 15%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =429.1.

Step 6: Synthesis of (1S,2S)-2-fluoro-N-(3-[8-methoxyimidazo[1,2-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0589] To a solution of 6-chloro-3-[8-methoxyimidazo[1,2-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (120.0 mg, 0.28 mmol) in 1,4-dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (144.2 mg, 1.40 mmol), BrettPhos (30.0 mg, 0.06 mmol), Cs_2CO_3 (273.4 mg, 0.84 mmol) and BrettPhos Pd G3 (25.4 mg, 0.03 mmol) at room temperature under N_2. The resulting mixture was stirred with microwave at 120 °C for 90 min. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/2, v/v) to afford (1S,2S)-2-fluoro-N-(3-[8-methoxyimidazo[1,2-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (70.0 mg, 50%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =496.2.

Step 7: Synthesis of (1S,2S)-2-fluoro-N-(3-[8-methoxyimidazo[1,2-a]pyridin-7-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 114):

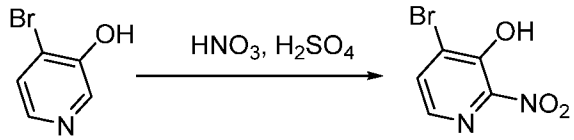


114

[0590] To a solution of (1S,2S)-2-fluoro-N-(3-[8-methoxyimidazo[1,2-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (70.0 mg, 0.14 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (5.0 mL) was added $NH_3.H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions Column: (Xselect CSH OBD Column 30x150 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 35% B in 8 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-[8-methoxyimidazo[1,2-a]pyridin-7-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (11.7 mg, 23%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =366.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.78 (s, 1H), 10.67 (s, 1H), 8.35 (d, J = 6.4 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.98 - 7.92 (m, 2H), 7.74 (s, 1H), 7.56 (s, 1H), 7.15 (d, J = 6.4 Hz, 1H), 5.02 - 4.85 (m, 1H), 4.12 (s, 3H), 2.25 - 2.20 (m, 1H), 1.69 - 1.64 (m, 1H), 1.22 - 1.10 (m, 1H).

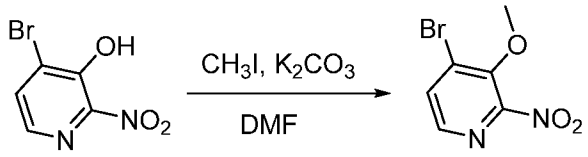
Example S115. Compound 115

Step 1: Synthesis of 4-bromo-2-nitropyridin-3-ol:



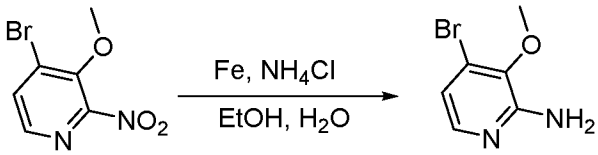
[0591] To a solution of 4-bromopyridin-3-ol (10.0 g, 57.47 mmol) in H_2SO_4 (30.0 mL) was added HNO_3 (10.0 mL) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 4-bromo-2-nitropyridin-3-ol (6.3 g, 35%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ =218.9.

Step 2: Synthesis of 4-bromo-3-methoxy-2-nitropyridine:



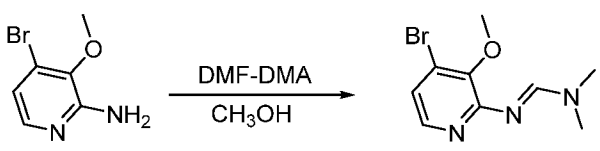
[0592] To a solution of 4-bromo-2-nitropyridin-3-ol (6.3 g, 28.77 mmol) in DMF (20.0 mL) was added K_2CO_3 (7.9 g, 56.94 mmol) and CH_3I (4.0 g, 28.77 mmol) at room temperature under N_2. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (93/7, v/v) to afford 4-bromo-3-methoxy-2-nitropyridine (3.2 g, 48%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =232.9.

Step 3: Synthesis of 4-bromo-3-methoxypyridin-2-amine:



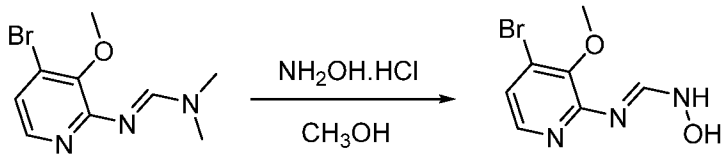
[0593] To a solution of 4-bromo-3-methoxy-2-nitropyridine (3.2 g, 13.73 mmol) in EtOH/H_2O (25.0/5.0 mL) was added Fe (3.8 g, 68.66 mmol) and NH_4Cl (3.6 g, 68.66 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with DCM/MeOH (95/5, v/v) to afford 4-bromo-3-methoxypyridin-2-amine (2.6 g, 93%) as a purple solid. LCMS (ESI, m/z): $[M+H]^+$ =203.0.

Step 4: Synthesis of (E)-N'-(4-bromo-3-methoxypyridin-2-yl)-N,N-dimethylmethanimidamide:



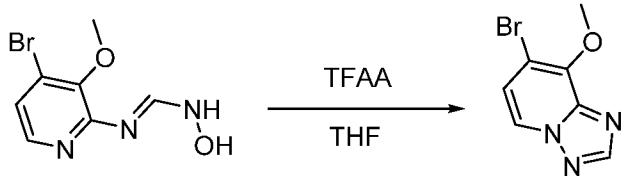
[0594] To a solution of 4-bromo-3-methoxypyridin-2-amine (2.5 g, 12.31 mmol) in CH_3OH (40.0 mL) was added DMF-DMA (1.8 g, 14.94 mmol) at room temperature under N_2. The resulting mixture was stirred at 70 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (45/55, v/v) to afford (E)-N'-(4-bromo-3-methoxypyridin-2-yl)-N,N-dimethylmethanimidamide (2.4 g, 75%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =258.0.

Step 5: Synthesis of (E)-N'-(4-bromo-3-methoxypyridin-2-yl)-N-hydroxymethanimidamide:



[0595] To a solution of (E)-N'-(4-bromo-3-methoxypyridin-2-yl)-N,N-dimethylmethanimidamide (2.4 g, 9.30 mmol) in CH_3OH (20.0 mL) was added $NH_2OH \cdot HCl$ (2.4 g, 34.51 mmol) at room temperature under N_2. The resulting mixture was stirred at 70 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (77/23, v/v) to afford (E)-N'-(4-bromo-3-methoxypyridin-2-yl)-N-hydroxymethanimidamide (2.1 g, 92%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =246.0.

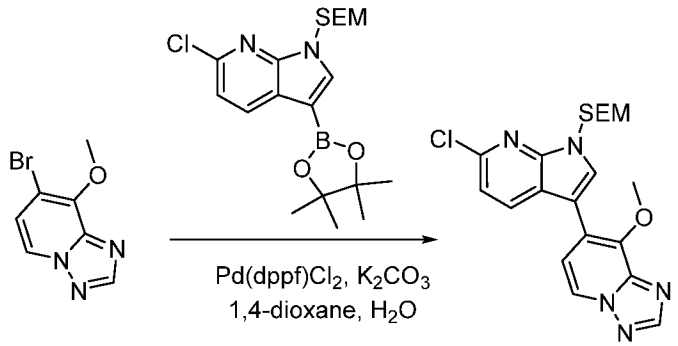
Step 6: Synthesis of 7-bromo-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine:



[0596] To a solution of (E)-N'-(4-bromo-3-methoxypyridin-2-yl)-N-hydroxymethanimidamide (1.0 g, 4.06 mmol) in THF (5.0 mL) was added TFAA (938.9 mg, 4.47 mmol) at room temperature under N_2. The resulting mixture was stirred at room

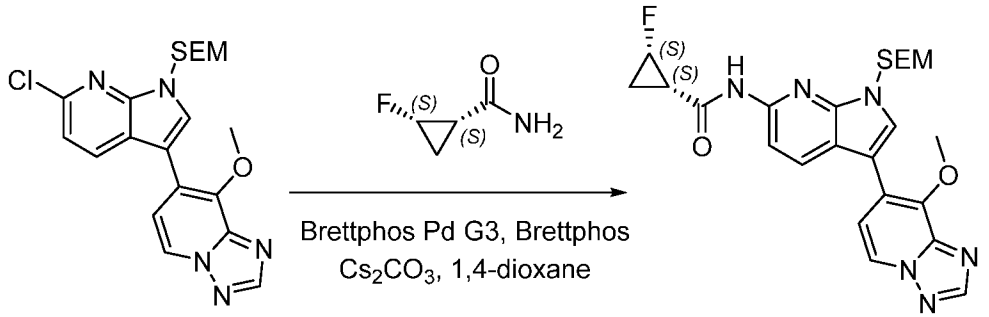
temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 7-bromo-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (1.2 g, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =228.0.

Step 7: Synthesis of 6-chloro-3-[8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



[0597] To a solution of 7-bromo-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (1.2 g, 5.26 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (2.4 g, 5.87 mmol), K_2CO_3 (2.1 g, 15.19 mmol) and $Pd(dppf)Cl_2$ (420.0 mg, 0.54 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (80/20, v/v) to afford 6-chloro-3-[8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (1.2 g, 52%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =430.1.

Step 8: Synthesis of (1S,2S)-2-fluoro-N-(3-[8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0598] To a solution of 6-chloro-3-[8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 0.68 mmol) in 1,4-dioxane (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (360.0 mg, 3.49 mmol), Cs_2CO_3 (681.9 mg, 2.01 mmol), Brettphos (75.0 mg, 0.14 mmol) and Brettphos Pd G3 (63.2 mg, 0.07 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (68/32, v/v) to afford (1S,2S)-2-fluoro-N-(3-[8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (122.0 mg, 36%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ =497.2.

Step 9: Synthesis of (1S,2S)-2-fluoro-N-(3-[8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 115):



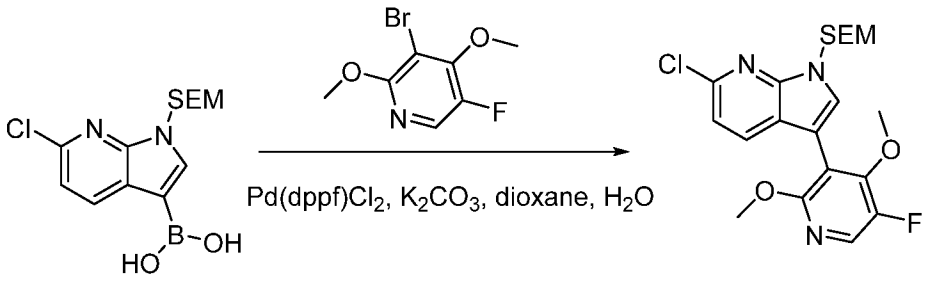
115

[0599] To a solution of (1S,2S)-2-fluoro-N-(3-[8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (60.0 mg, 0.12 mmol) in DCM (3.0 mL) was added TFA (3.0 mL) at room

temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in ACN (3.0 mL) and $NH_3 \cdot H_2O$ (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient:11% B to 41% B in 9 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-[8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (14.4 mg, 32%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =367.0. ^1H NMR (400 MHz, DMSO-d_6): δ 11.93 (s, 1H), 10.71 (s, 1H), 8.72 (d, J = 7.2 Hz, 1H), 8.48 (s, 1H), 8.16 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.86 (s, 1H), 7.45 (d, J = 7.2 Hz, 1H), 5.04 - 4.83 (m, 1H), 4.20 (s, 3H), 2.26 - 2.23 (m, 1H), 1.71 - 1.64 (m, 1H), 1.26 - 1.10 (m, 1H).

Example S116. Compound 116

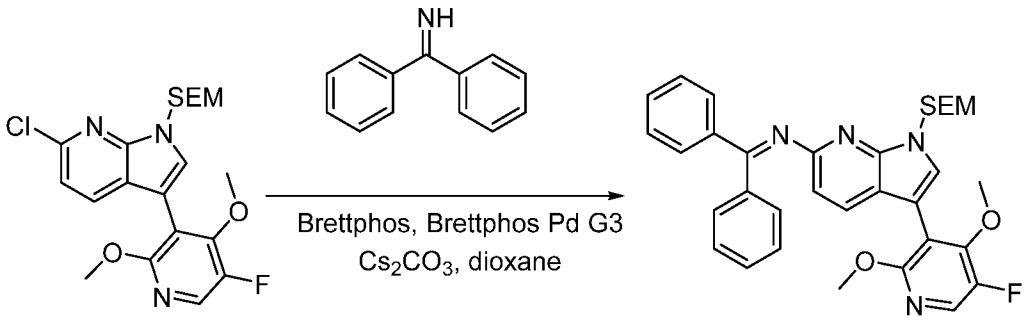
Step 1: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-fluoro-2,4-dimethoxypyridine:



[0600] To a solution of 6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-ylboronic acid (300.0 mg, 0.92 mmol) in 1,4-dioxane/H_2O (15.0 mL/3.0 mL) was added 3-bromo-5-fluoro-2,4-dimethoxypyridine (216.8 mg, 0.92 mmol), K_2CO_3 (253.9 mg, 1.84 mmol) and $Pd(dppf)Cl_2$ (67.2 mg, 0.09 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column

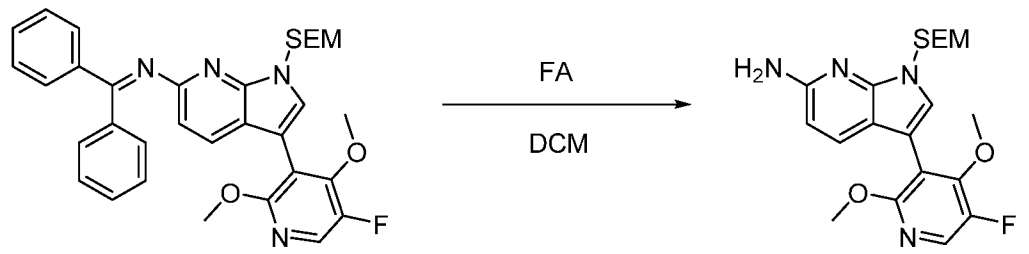
chromatography with petroleum ether/ethyl acetate (80/20, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-fluoro-2,4-dimethoxypyridine (277.9 mg, 69%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =438.1.

Step 2: Synthesis of N-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1,1-diphenylmethanimine:



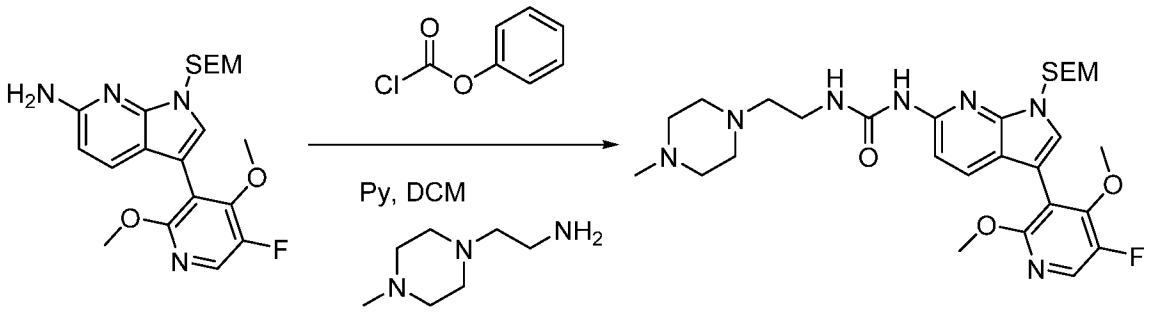
[0601] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-fluoro-2,4-dimethoxypyridine (213.0 mg, 0.49 mmol) in 1,4-dioxane (16.0 mL) was added diphenylmethanimine (440.7 mg, 2.43 mmol), BrettPhos (52.2 mg, 0.10 mmol), Cs_2CO_3 (475.4 mg, 1.46 mmol) and BrettPhos Pd G3 (44.1 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (90/10, v/v) to afford N-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1,1-diphenylmethanimine (146.9 mg, 51%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =583.2.

Step 3: Synthesis of 3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine:



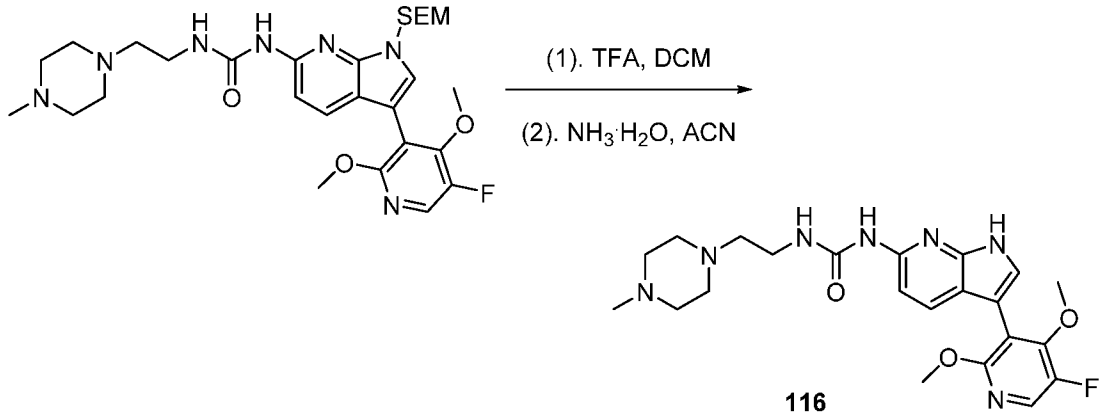
[0602] To a solution of N-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1,1-diphenylmethanimine (123.5 mg, 0.21 mmol) in CH_2Cl_2 (6.0 mL) was added FA (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, The pH value of the mixture was adjusted to 8 with aq.$NaHCO_3$. The resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (80/20, v/v) to afford 3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (46.3 mg, 52%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =419.2.

Step 4: Synthesis of 3-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea:



[0603] To a solution of 3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (209.0 mg, 0.50 mmol) in DCM (9.0 mL) was added pyridine (158.0 mg, 2.00 mmol) and phenyl chloroformate (93.8 mg, 0.60 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was concentrated under reduced pressure. To the above mixture was added 2-(4-methylpiperazin-1-yl)ethanamine (214.6 mg, 1.50 mmol) and pyridine (9.0 mL) at room temperature. The resulting mixture was stirred at 60 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with methylene chloride/methanol (90/10, v/v) to afford 3-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (99.1 mg, 33%) as a light brown oil. LCMS (ESI, m/z): $[M+H]^+$ =588.3.

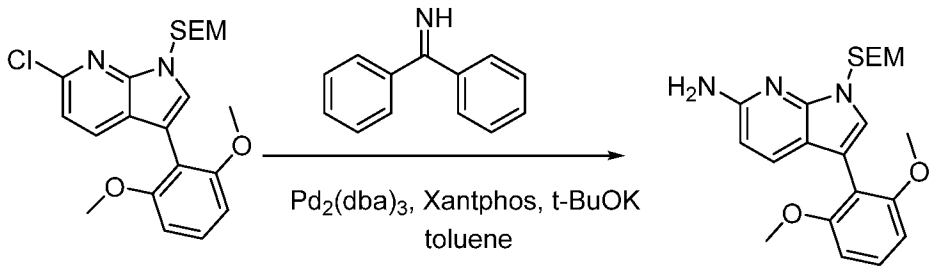
Step 5: Synthesis of 3-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (Compound 116):



[0604] To a solution of 3-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (99.1 mg, 0.169 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (3.0 mL) and $NH_3 \cdot H_2O$ (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; 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; 254 nm) to afford 3-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (10.6 mg, 13%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =458.3. ^1H NMR (400 MHz, DMSO-d_6): δ 11.55 (s, 1H), 9.19 (s, 1H), 8.27 (s, 1H), 8.10 (d, J = 2.8 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.35 (s, 1H), 7.08 (d, J = 8.8 Hz, 1H), 3.79 - 3.78 (m, 6H), 2.54 - 2.44 (m, 6H), 2.32 (s, 4H), 2.15 (s, 3H).

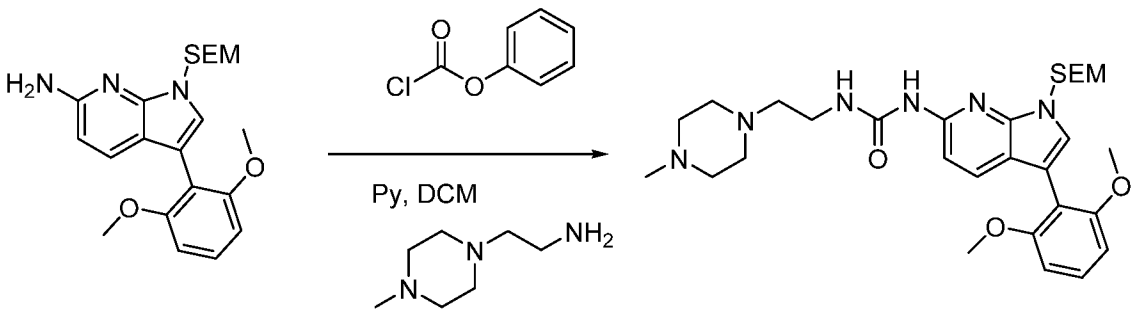
Example S117. Compound 117

Step 1: Synthesis of 3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine:



[0605] To a solution of 6-chloro-3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (270.0 mg, 0.64 mmol) in toluene (12.0 mL) was added diphenylmethanimine (350.4 mg, 1.93 mmol), XantPhos (74.6 mg, 0.13 mmol), t-BuOK (216.9 mg, 1.93 mmol) and $Pd_2(dba)_3$ (118.0 mg, 0.13 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford 3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (135.5 mg, 53%) as a light brown oil. LCMS (ESI, m/z): $[M+H]^+$ =400.2.

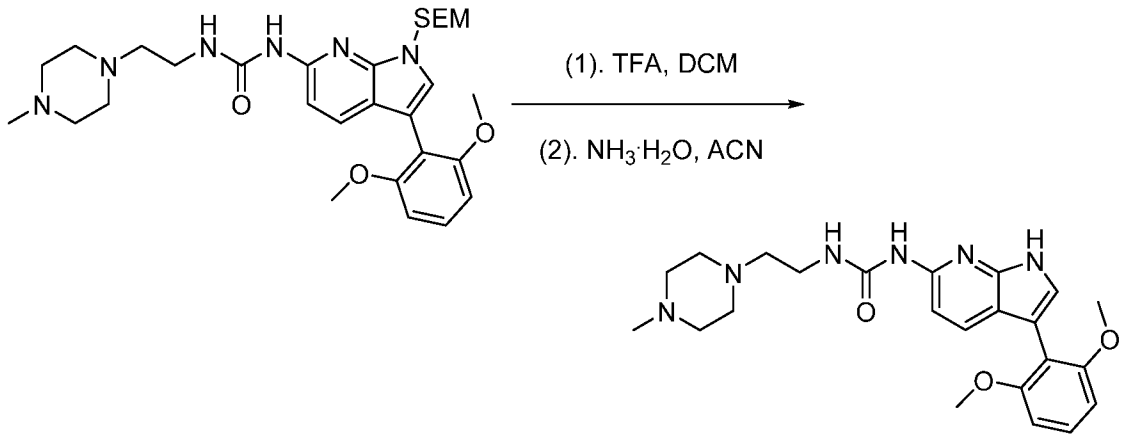
Step 2: Synthesis of 3-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea:



[0606] To a solution of 3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (180.0 mg, 0.45 mmol) in DCM (8.0 mL) was added Pyridine (142.5 mg, 1.80 mmol) and phenyl chloroformate (84.6 mg, 0.54 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added 2-(4-methylpiperazin-1-yl)ethanamine (193.6 mg, 1.35 mmol) and pyridine (8.0

mL) at room temperature. The resulting mixture was stirred at 60 °C for another 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with methylene chloride/methanol (9/1, v/v) to afford 3-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (209.2 mg, 82%) as a light brown oil. LCMS (ESI, m/z): $[M+H]^+$ =569.3.

Step 3: Synthesis of 3-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (Compound 117):



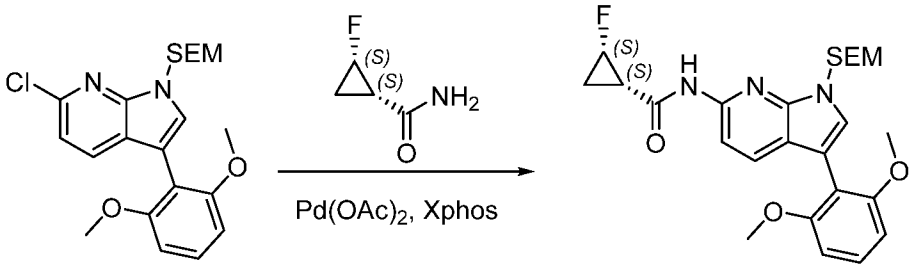
117

[0607] To a solution of 3-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (209.2 mg, 0.37 mmol) in CH_2Cl_2 (6.0 mL) was added TFA (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (6.0 mL) was added $NH_3.H_2O$ (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 3 h. After the reaction was completed, 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, 5 um; Mobile Phase A:Water (10.0 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17 % B to 47 % B in 7 min; 254 nm) to afford 3-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (14.3 mg, 8%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =439.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.28 (s, 1H), 9.13 (s, 1H), 8.37(s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.28 - 7.24 (m, 1H), 7.16 (d, J = 2.0 Hz,

1H), 6.99 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 2H), 3.68 (s, 6H), 2.50 - 2.44 (m, 6H), 2.32 (s, 4H), 2.15 (s, 3H).

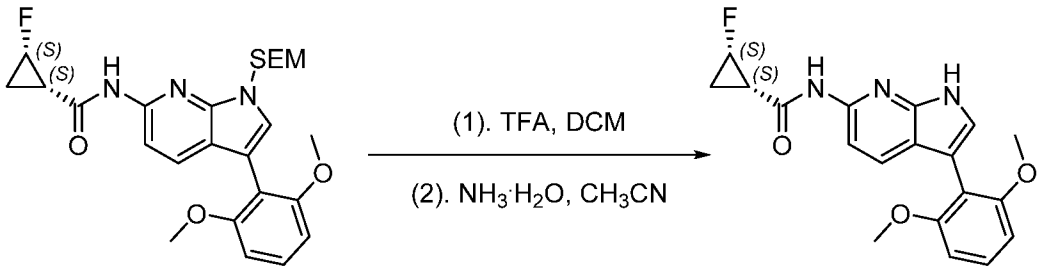
Example S118. Compound 118

Step 1: Synthesis of (1S,2S)-N-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide:



[0608] To a solution of 6-chloro-3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (280.0 mg, 0.67 mmol) in dioxane (7.5 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (344.5 mg, 3.34 mmol), K_2CO_3 (277.1 mg, 2.0 mmol), XPhos (63.7 mg, 0.13 mmol) and $Pd(OAc)_2$ (15.0 mg, 0.07 mmol) under N_2. The mixture was stirred at 100 °C for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/EtOAc (2/1, v/v) to afford (1S,2S)-N-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (129.0 mg, 39%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 486.2.

Step 2: Synthesis of (1S,2S)-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 118):

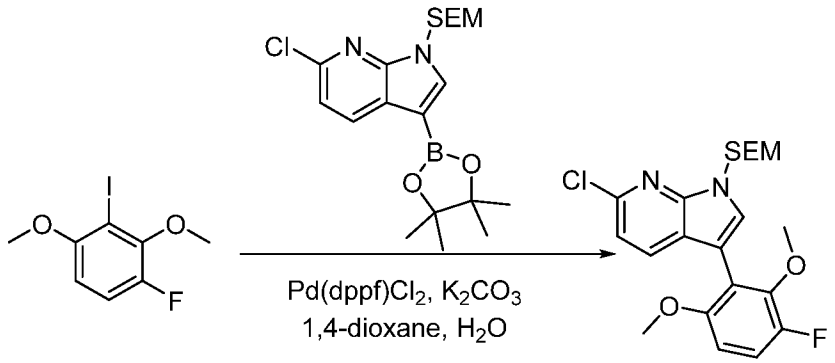


118

[0609] To a solution of (1S,2S)-N-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (109.0 mg, 0.22 mmol) in CH_2Cl_2 (6.0 mL) was added TFA (3.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under vacuum. The residue was dissolved in CH_3CN (5.0 mL) and $NH_3{\cdot}H_2O$ (5.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; 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; 254 nm, RT1: 6.5 min to afford (1S,2S)-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (24.9 mg, 30%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 356.0. ^1H NMR (300 MHz, DMSO-d_6): δ 11.43 (s, 1H), 10.58 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.31 - 7.25 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 5.04 - 4.80 (m, 1H), 3.70 (s, 6H), 2.25 - 2.20 (m, 1H), 1.70 - 1.60 (m, 1H), 1.18 - 1.11 (m, 1H).

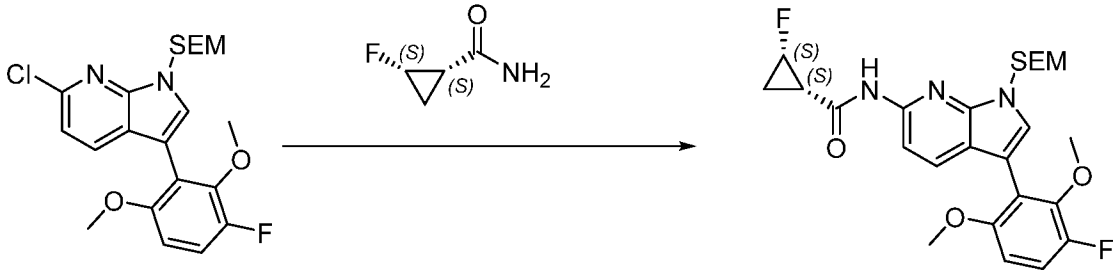
Example S119. Compound 119

Step 1: Synthesis of 6-chloro-3-(3-fluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



[0610] To a solution of 1-fluoro-3-iodo-2,4-dimethoxybenzene (1.0 g, 3.55 mmol) in 1,4-dioxane (18.0 mL) and H_2O (3.6 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (1.5 g, 3.55 mmol), K_2CO_3 (1.0 g, 0.01 mmol) and $Pd(dppf)Cl_2$ (0.3 g, 0.36 mmol) under N_2. The mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ EtOAc (10/1, v/v) to afford 6-chloro-3-(3-fluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (1.0 g, 64%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+ = 437.1$.

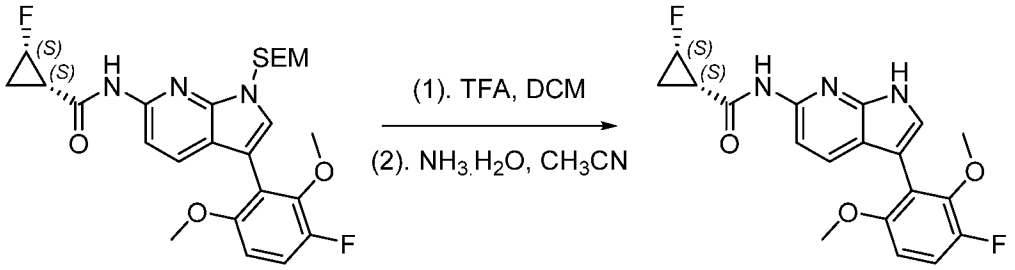
Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-(3-fluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0611] To a solution of 6-chloro-3-(3-fluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 0.69 mmol) in *t*-BuOH (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (353.9 mg, 3.43 mmol), K_2CO_3 (284.7 mg, 2.06 mmol), XPhos (65.5 mg, 0.14 mmol) and $Pd(OAc)_2$ (15.4 mg, 0.07 mmol) under N_2. The mixture was stirred at 100 °C for 4 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The

combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/EtOAc (2/1, v/v) to afford (1S,2S)-2-fluoro-N-[3-(3-fluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (279.0 mg, 55%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 504.2.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-[3-(3-fluoro-2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 119):

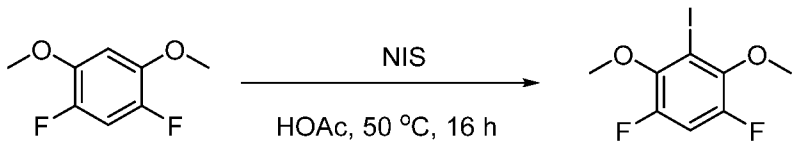


119

[0612] To a solution of (1S,2S)-2-fluoro-N-[3-(3-fluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (279.0 mg, 0.56 mmol) in CH_2Cl_2 (14.0 mL) was added TFA (14.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under vacuum. The residue was dissolved in CH_3CN (15.0 mL) and $NH_3{\cdot}H_2O$ (15.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 41% B to 51% B in 9 min; 254/220 nm; to afford (1S,2S)-2-fluoro-N-[3-(3-fluoro-2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (78.0 mg, 37%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 374.0. ^1H NMR (300 MHz, DMSO-d_6): δ 11.60 (d, J =1.8 Hz, 1H), 10.62 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.24 - 7.17 (m, 1H), 6.85 - 6.80 (m, 1H), 5.06 - 4.78 (m, 1H), 3.68 (s, 3H), 3.53 (s, 3H), 2.25 - 2.20 (m, 1H), 1.70 - 1.59 (m, 1H), 1.18 - 1.11 (m, 1H)

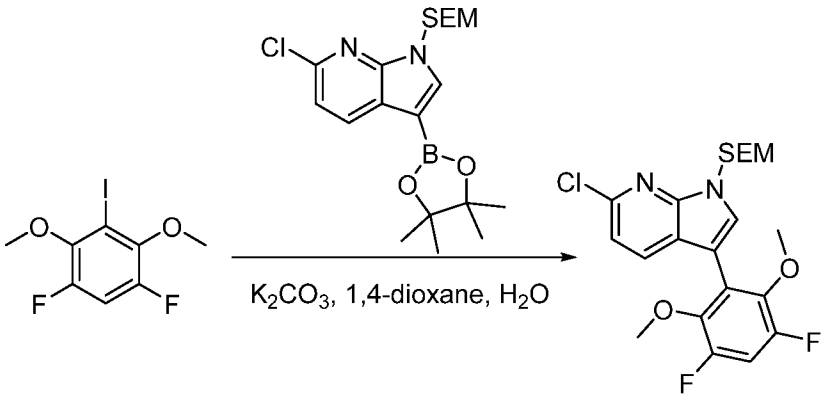
Example S120. Compound 120

Step 1: Synthesis of 1,5-difluoro-3-iodo-2,4-dimethoxybenzene:



[0613] To a solution of 1,5-difluoro-2,4-dimethoxybenzene (500.0 mg, 2.87 mmol) in HOAc (10.0 mL) was added NIS (1.3 g, 5.74 mmol) at room temperature. The mixture was stirred at 50 °C for 16 h. After the reaction was completed, the mixture was concentrated under vacuum. The residue was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/EtOAc (5/1, v/v) to afford 1,5-difluoro-3-iodo-2,4-dimethoxybenzene (386.0 mg, 44%) as a white solid.

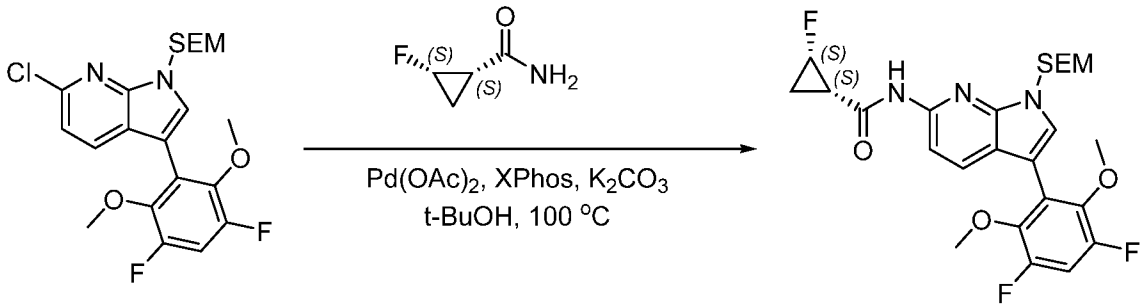
Step 2: Synthesis of 6-chloro-3-(3,5-difluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



[0614] To a solution of 1,5-difluoro-3-iodo-2,4-dimethoxybenzene (500.0 mg, 1.67 mmol) in 1,4-dioxane (10.0 mL) and H_2O (2.0 mL) were added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (681.2 mg, 1.67 mmol), $Pd(PPh_3)_4$ (385.1 mg, 0.33 mmol) and K_2CO_3 (460.6 mg, 3.33 mmol) at room temperature under N_2. The mixture was stirred at 100 °C for 12 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue

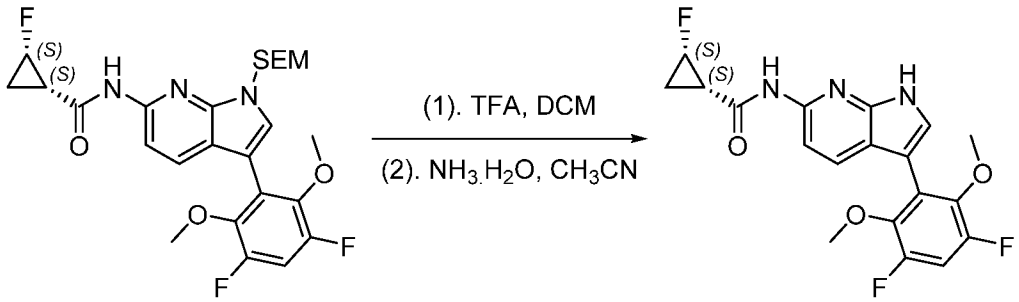
was purified by flash column chromatography with petroleum ether/EtOAc (10/1, v/v) to afford 6-chloro-3-(3,5-difluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (321.0 mg, 42%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 455.1.

Step 3: Synthesis of (1S,2S)-N-[3-(3,5-difluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide:



[0615] To a solution of 6-chloro-3-(3,5-difluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (260.0 mg, 0.57 mmol) in t-BuOH (5.5 mL) were added (1S,2S)-2-fluorocyclopropane-1-carboxamide (294.6 mg, 2.86 mmol), K_2CO_3 (236.9 mg, 1.71 mmol), $Pd(OAc)_2$ (12.8 mg, 0.06 mmol) and XPhos (54.5 mg, 0.11 mmol) at room temperature under N_2. The mixture was stirred at 100 °C for 12 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/EtOAc (2/1, v/v) to afford (1S,2S)-N-[3-(3,5-difluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (70.0 mg, 23%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 522.2.

Step 4: Synthesis of (1S,2S)-N-[3-(3,5-difluoro-2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 120):

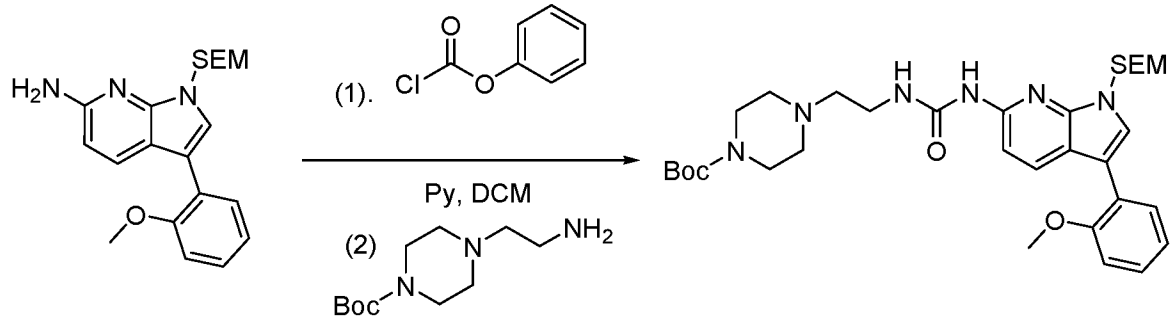


120

[0616] To a solution of (1S,2S)-N-[3-(3,5-difluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (60.0 mg, 0.12 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under vacuum. The residue was dissolved in CH_3CN (4.0 mL) and $NH_3{\cdot}H_2O$ (4.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 42% B to 52% B in 9 min to afford (1S,2S)-N-[3-(3,5-difluoro-2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (14.9 mg, 32%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 392.0. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.77 (s, 1H), 10.66 (s, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 2.4 Hz, 1H), 7.46 - 7.38 (m, 1H), 5.07 - 4.79 (m, 1H), 3.50 (s, 6H), 2.29 - 2.20 (m, 1H), 1.72 - 1.59 (m, 1H), 1.21 - 1.10 (m, 1H).

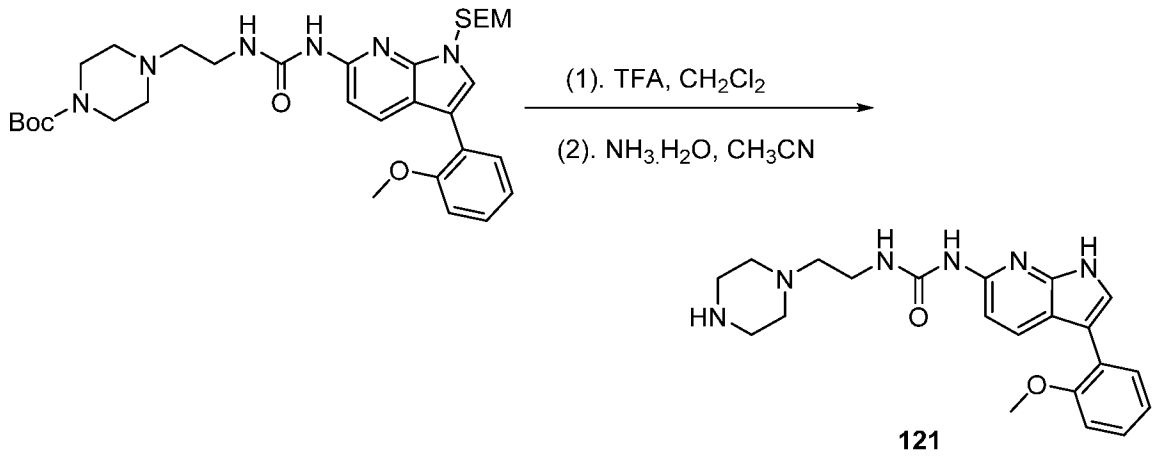
Example S121. Compound 121

Step 1: Synthesis of tert-butyl 4-[2-([[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate:



[0617] To a solution of 3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (150.0 mg, 0.41 mmol) in CH_2Cl_2 (3.0 mL) was added pyridine (128.4 mg, 1.62 mmol) and phenyl chloroformate (76.3 mg, 0.49 mmol) at 0 °C. The mixture was stirred at room temperature for 16 h. The mixture was concentrated under vacuum. To the above residue was added pyridine (3.0 mL) and tert-butyl 4-(2-aminoethyl)piperazine-1-carboxylate (279.3 mg, 1.22 mmol). The resulting mixture was stirred at 60 °C for another 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/95, v/v) to afford tert-butyl 4-[2-([[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate (190.0 mg, 74%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =625.3.

Step 2: Synthesis of 3-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(piperazin-1-yl)ethyl]urea (Compound 121):



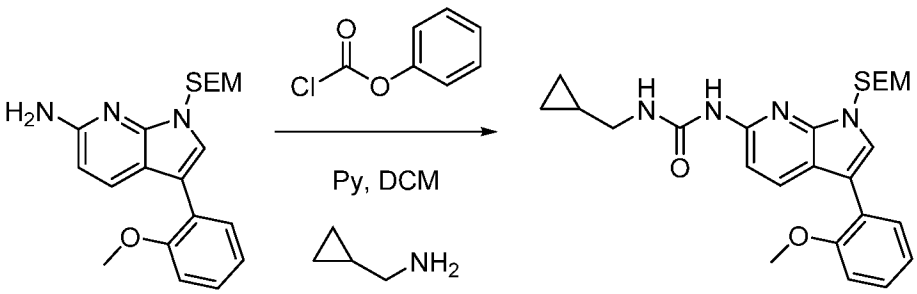
121

[0618] To a solution of tert-butyl 4-[2-([[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate (160.0 mg, 0.26 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL). The

mixture was stirred at room temperature for 2 h. The mixture was concentrated under vacuum. To the above residue was added ACN (3.0 mL) and $NH_3.H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column, 30×150 mm, 5 um; 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; 254 nm) to afford 3-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(piperazin-1-yl)ethyl]urea (48.0 mg, 47%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 395.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.43 (s, 1H), 9.19 (s, 1H), 8.32 (s, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.52 - 7.45 (m, 2H), 7.28 - 7.23 (m, 1H), 7.11 - 6.99 (m, 3H), 3.81 (s, 3H), 2.51 - 2.36 (m, 12H).

Example S122. Compound 122

Step 1: Synthesis of 3-(cyclopropylmethyl)-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea:



[0619] To a solution of 3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (130.0 mg, 0.35 mmol) in DCM (10.0 mL) was added pyridine (111.3 mg, 1.41 mmol) and phenyl chloroformate (66.1 mg, 0.42 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the above mixture was added 1-cyclopropylmethanamine (75.1 mg, 1.06 mmol) and pyridine (10.0 mL) at room temperature. The resulting mixture was stirred at 70 °C for another 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford 3-(cyclopropylmethyl)-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (160.0 mg, 97%) as a light brown oil. LCMS (ESI, m/z): $[M+H]^+$ =467.2.

Step 2: Synthesis of 3-(cyclopropylmethyl)-1-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (Compound 122):

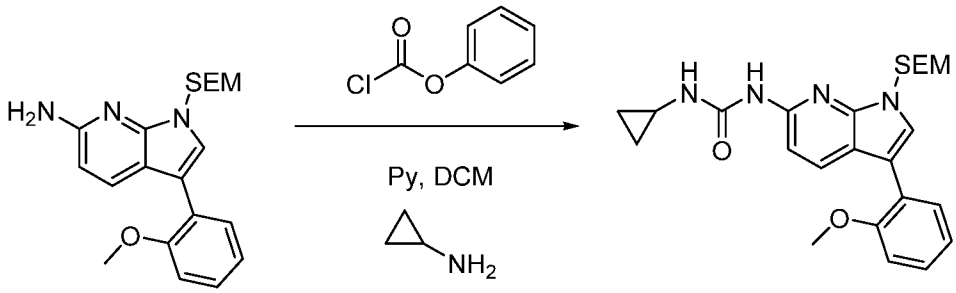


122

[0620] To a solution of 3-(cyclopropylmethyl)-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (165.0 mg, 0.35 mmol) in CH_2Cl_2 (6.0 mL) was added TFA (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (6.0 mL) and $NH_3 \cdot H_2O$ (6.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 45 % B to 53 % B in 9 min; 254 nm) to afford 3-(cyclopropylmethyl)-1-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (13.5 mg, 11%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =337.3. ^1H NMR (400 MHz, DMSO-d_6): δ 11.49 (s, 1H), 9.14 (s, 1H), 8.56 (s, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.52 - 7.46 (m, 2H), 7.28 - 7.24 (m, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.05 - 6.99 (m, 2H), 3.81 (s, 3H), 3.15 - 3.12 (m, 2H), 1.06 - 0.99 (m, 1H), 0.50 - 0.45 (m, 2H), 0.24 - 0.19 (m, 2H).

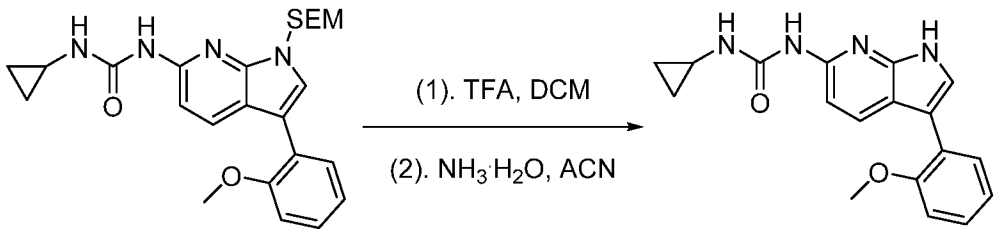
Example S123. Compound 123

Step 1: Synthesis of 3-cyclopropyl-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea:



[0621] To a solution of 3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (130.0 mg, 0.35 mmol) in DCM (10.0 mL) was added pyridine (111.3 mg, 1.41 mmol) and phenyl chloroformate (66.1 mg, 0.42 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was concentrated under reduced pressure. To the above mixture was added aminocyclopropane (60.3 mg, 1.06 mmol) and pyridine (10.0 mL) at room temperature. The resulting mixture was stirred at 70 °C for another 3 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford 3-cyclopropyl-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (120.0 mg, 75%) as a light brown oil. LCMS (ESI, m/z): $[M+H]^+$ =453.2.

Step 2: Synthesis of 3-cyclopropyl-1-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (Compound 123):



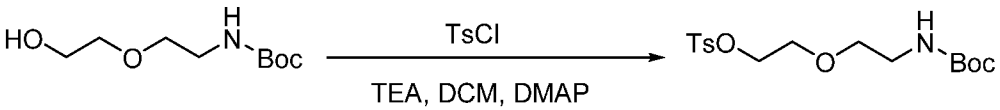
123

[0622] To a solution of 3-cyclopropyl-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (120.0 mg, 0.27 mmol) in CH_2Cl_2 (6.0 mL) was added TFA (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (6.0 mL) and $NH_3 \cdot H_2O$ (6.0 mL). The resulting mixture was stirred at room temperature for another 3 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The

combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 41 % B to 51 % B in 8 min; 254 nm) to afford 3-cyclopropyl-1-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (35.8 mg, 41%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =323.3. ^1H NMR (400 MHz, DMSO-d_6): δ 11.53 (s, 1H), 9.13 (s, 1H), 8.73 (s, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.51 - 7.46 (m, 2H), 7.28 - 7.23 (m, 1H), 7.10 (d, J = 7.6 Hz, 1H), 7.02 - 6.98 (m, 2H), 3.80 (s, 3H), 2.68 - 2.65 (m, 1H), 0.72 - 0.69 (m, 2H), 0.53 - 0.50 (m, 2H).

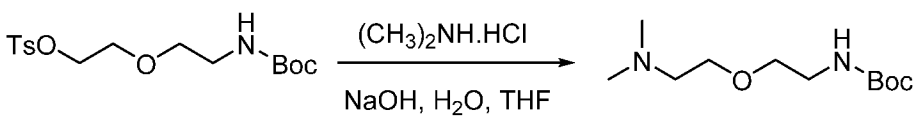
Example S124. Compound 124

Step 1: Synthesis of tert-butyl N-(2-[2-[(4-methylbenzenesulfonyl)oxy]ethoxy]ethyl)carbamate:



[0623] To a solution of tert-butyl N-[2-(2-hydroxyethoxy)ethyl]carbamate (2.0 g, 9.74 mmol) in CH_2Cl_2 (15.0 mL) were added p-toluenesulfonyl chloride (3.7 g, 19.49 mmol), TEA (4.9 g, 48.72 mmol) and DMAP (119.0 mg, 0.97 mmol). The mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (45/55, v/v) to afford tert-butyl N-(2-[2-[(4-methylbenzenesulfonyl)oxy]ethoxy]ethyl)carbamate (2.3 g, 65%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =360.1.

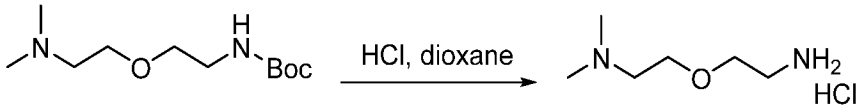
Step 2: Synthesis of tert-butyl N-[2-[2-(dimethylamino)ethoxy]ethyl]carbamate:



[0624] To a solution of tert-butyl N-(2-[2-[(4-methylbenzenesulfonyl)oxy]ethoxy]ethyl)carbamate (2.2 g, 6.12 mmol) in THF/H_2O (20.0 mL/3.0 mL) was added dimethylamine hydrochloride (2.0 g, 24.48 mmol) and NaOH (0.9 g,

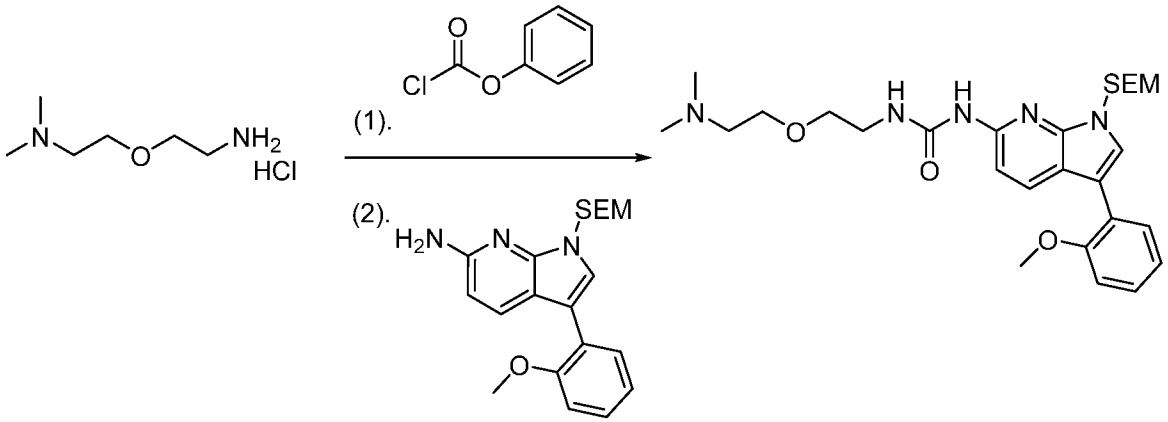
24.48 mmol). The mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (95/5, v/v) to afford tert-butyl N-[2-[2-(dimethylamino)ethoxy]ethyl]carbamate (1.2 g, 84%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =233.2.

Step 3: Synthesis of 2-(2-aminoethoxy)-N,N-dimethylethan-1-amine hydrochloride:



[0625] A solution of tert-butyl N-[2-[2-(dimethylamino)ethoxy]ethyl]carbamate (1.2 g, 5.16 mmol) in HCl/1,4-dioxane (10.0 mL, 4 mol/L) was stirred at room temperature for 2 h. The mixture was concentrated under vacuum to afford 2-(2-aminoethoxy)-N,N-dimethylethan-1-amine hydrochloride (700.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =133.1.

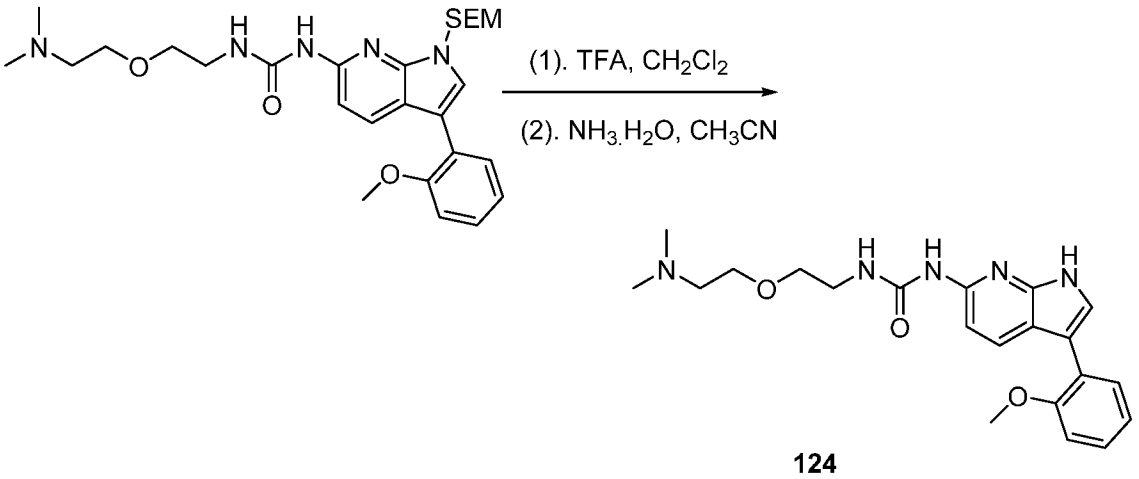
Step 4: Synthesis of 3-[2-[2-(dimethylamino)ethoxy]ethyl]-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea:



[0626] To a solution of 3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (150.0 mg, 0.41 mmol) in CH_2Cl_2 (3.0 mL) was added pyridine (128.4 mg, 1.62 mmol) and phenyl chloroformate (76.3 mg, 0.49 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was concentrated under vacuum. To the above mixture was added pyridine (3.0 mL) and 2-(2-aminoethoxy)-N,N-dimethylethan-1-amine hydrochloride (176.8 mg, crude). The resulting mixture was stirred at 60 °C for another 2 h. After the reaction was completed, the resulting

mixture was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (96/4, v/v) to afford 3-[2-[2-(dimethylamino)ethoxy]ethyl]-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (180.0 mg, 84%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =528.3.

Step 5: Synthesis of 3-[2-[2-(dimethylamino)ethoxy]ethyl]-1-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (Compound 124):

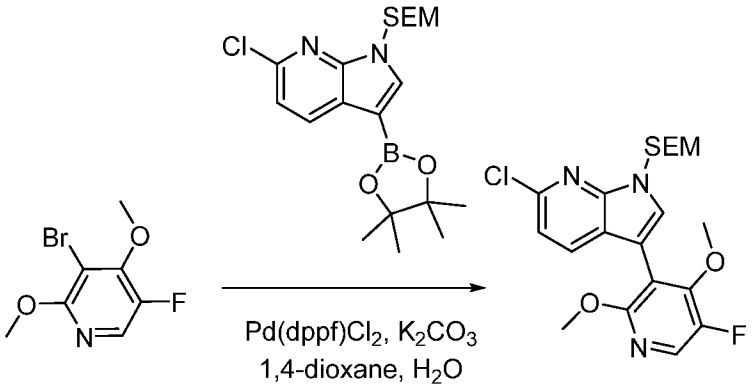


124

[0627] To a solution of 3-[2-[2-(dimethylamino)ethoxy]ethyl]-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (150.0 mg, 0.28 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL). The mixture was stirred at room temperature for 2 h. The mixture was concentrated under vacuum. To the above mixture were added ACN (3.0 mL) and $NH_3.H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 39% B to 49% B in 7 min; 254 nm) to afford 3-[2-[2-(dimethylamino)ethoxy]ethyl]-1-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (41.0 mg, 36%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 398.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.63 (s, 1H), 9.23 (s, 1H), 8.72 (s, 1H), 7.91 (d, J = 8.7 Hz, 1H), 7.53 - 7.47 (m, 2H), 7.29 - 7.23 (m, 1H), 7.10 (d, J = 7.5 Hz, 1H), 7.04 - 6.99 (m, 2H), 3.81 (s, 3H), 3.58 - 3.51 (m, 4H), 3.41 - 3.34 (m, 2H), 2.52 - 2.44 (m, 2H), 2.16 (s, 6H).

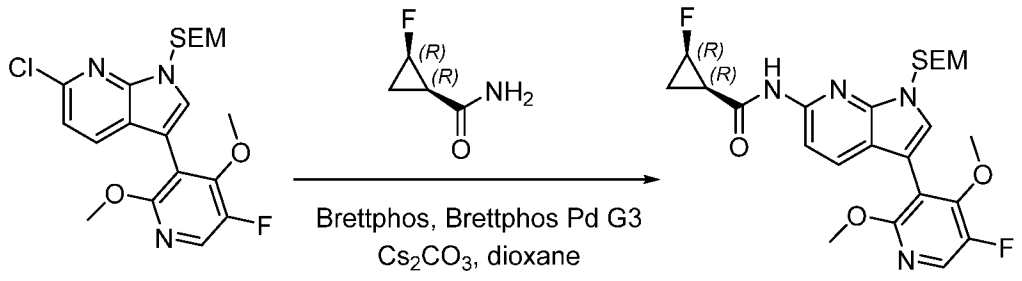
Example S125. Compound 125

Step 1: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-fluoro-2,4-dimethoxypyridine:



[0628] To a solution of 3-bromo-5-fluoro-2,4-dimethoxypyridine (345.0 mg, 1.46 mmol) in 1,4-dioxane (7.0 mL) and H_2O (1.4 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (597.5 mg, 1.46 mmol), K_2CO_3 (404.0 mg, 2.92 mmol) and $Pd(dppf)Cl_2$ (107.0 mg, 0.15 mmol) at room temperature under N_2. The mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/EtOAc (10/1, v/v) to 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-fluoro-2,4-dimethoxypyridine (350.0 mg, 57%) as an orange solid. LCMS (ESI, m/z): $[M+H]^+$ =438.1.

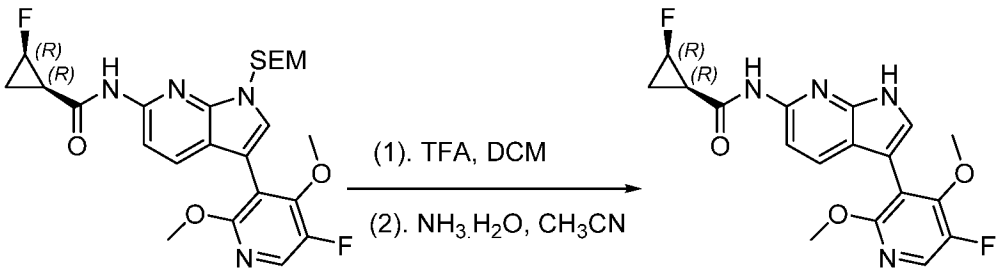
Step 2: Synthesis of (1R,2R)-2-fluoro-N-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0629] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-fluoro-2,4-dimethoxypyridine (300.0 mg, 0.69 mmol) in t-BuOH (10.0 mL) was added (1R,2R)-2-fluorocyclopropane-1-carboxamide (353.1 mg, 3.43 mmol), K_2CO_3

(284.0 mg, 2.06 mmol), XPhos (65.3 mg, 0.14 mmol) and $Pd(OAc)_2$ (15.4 mg, 0.07 mmol) at room temperature under N_2. The mixture was stirred at 100 °C for 4 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/EtOAc (2/1, v/v) to afford (1R,2R)-2-fluoro-N-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (196.0 mg, 64%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 505.2.

Step 3: Synthesis of (1R,2R)-2-fluoro-N-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 125):



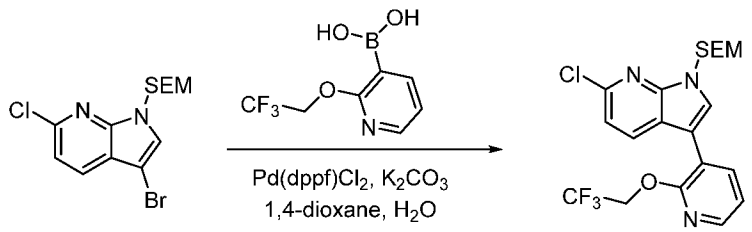
125

[0630] To a solution of (1R,2R)-2-fluoro-N-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (196.0 mg, 0.39 mmol) in CH_2Cl_2 (6.0 mL) was added TFA (3.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under vacuum. The residue was dissolved in CH_3CN (10.0 mL) and $NH_3.H_2O$ (10.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 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 56% B in 9 min; 254 nm; RT1:8.5 min to afford (1R,2R)-2-fluoro-N-[3-(5-fluoro-2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (42.0 mg, 29%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 375.0. ^1H NMR (300 MHz, DMSO-d_6): δ 11.70 (d, J = 1.8 Hz, 1H), 10.64 (s, 1H), 8.12 (d,

J = 3.0 Hz, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.47 (d, J = 2.4 Hz, 1H), 5.05 - 4.80 (m, 1H), 3.81 - 3.80 (m, 6H), 2.25 - 2.21 (m, 1H), 1.70 - 1.60 (m, 1H), 1.19 - 1.14 (m, 1H).

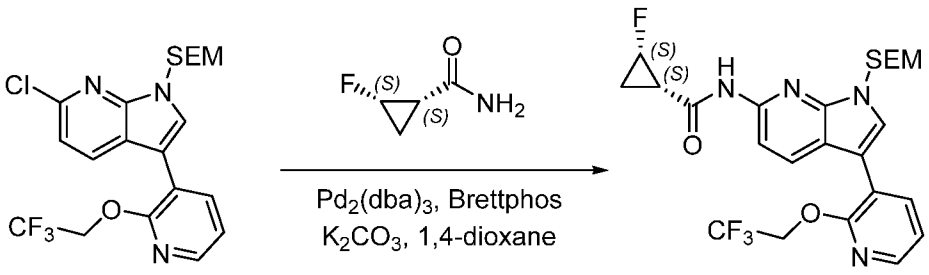
Example S126. Compound 126

Step 1: Synthesis of 6-chloro-3-(2-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine:



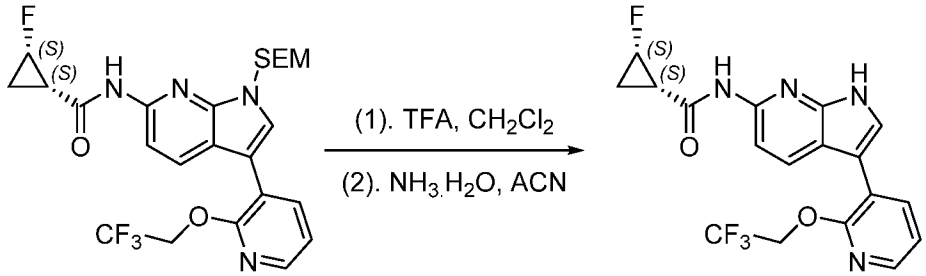
[0631] To a solution of 3-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (500.0 mg, 1.38 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added (2-(2,2,2-trifluoroethoxy)pyridin-3-yl)boronic acid (305.4 mg, 1.38 mmol), K_2CO_3 (573.1 mg, 4.15 mmol) and $Pd(dppf)Cl_2$ (101.1 mg, 0.14 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (90/10, v/v) to 6-chloro-3-(2-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (270.0 mg, 42%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =458.1.

Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-[2-(2,2,2-trifluoroethoxy)pyridin-3-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0632] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-(2,2,2-trifluoroethoxy)pyridine (126.0 mg, 0.28 mmol) in 1,4-dioxane (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (141.8 mg, 1.38 mmol), K_2CO_3 (268.8 mg, 1.95 mmol), BrettPhos (29.5 mg, 0.06 mmol) and $Pd_2(dba)_3$ (25.2 mg, 0.03 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (80/20, v/v) to afford (1S,2S)-2-fluoro-N-[3-[2-(2,2,2-trifluoroethoxy)pyridin-3-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (115.0 mg, 79%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 525.2.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-(3-(2-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 126):



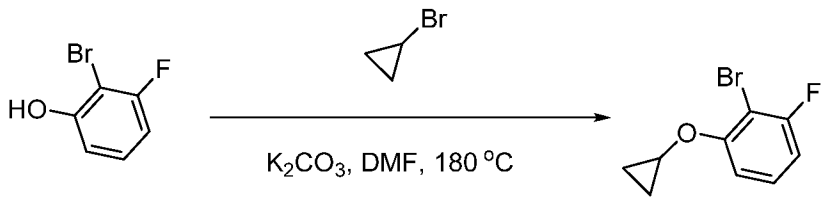
126

[0633] To a solution of (1S,2S)-2-fluoro-N-[3-[2-(2,2,2-trifluoroethoxy)pyridin-3-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (110.0 mg, 0.21 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature under N_2. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in ACN (2.0 mL) and $NH_3 \cdot H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 46% B to

53% B in 8 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-(2-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (12.8 mg, 15%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 395.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.80 (s, 1H), 10.71 (s, 1H), 8.18 (d, J = 8.8 Hz, 1H), 8.14 - 8.10 (m, 2H), 7.94 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 2.8 Hz, 1H), 7.23 - 7.20 (m, 1H), 5.10 - 5.05 (m, 2H), 5.02 - 4.84 (m, 1H), 2.25 - 2.19 (m, 1H), 1.69 - 1.62 (m, 1H), 1.19 - 1.16 (m, 1H).

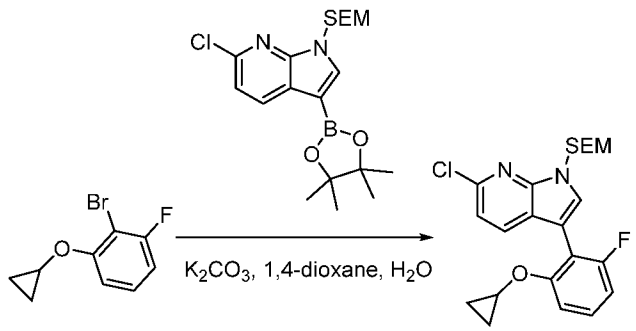
Example S127. Compound 127

Step 1: Synthesis of 2-bromo-1-cyclopropoxy-3-fluorobenzene:



[0634] To a solution of 2-bromo-3-fluorophenol (2.5 g, 13.09 mmol) in DMF (50.0 mL) was added bromocyclopropane (9.2 g, 75.89 mmol) and K_2CO_3 (8.7 g, 62.83 mmol) at room temperature. The mixture was stirred at 180 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether to afford 2-bromo-1-cyclopropoxy-3-fluorobenzene (1.4 g, 46%) as a yellow oil.

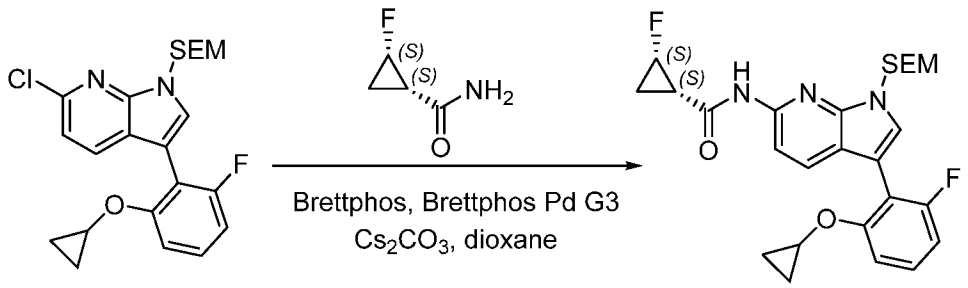
Step 2: Synthesis of 6-chloro-3-(2-cyclopropoxy-6-fluorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



[0635] To a solution of 2-bromo-1-cyclopropoxy-3-fluorobenzene (850.0 mg, 3.68 mmol) in dioxane (17.0 mL) and H_2O (3.4 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-

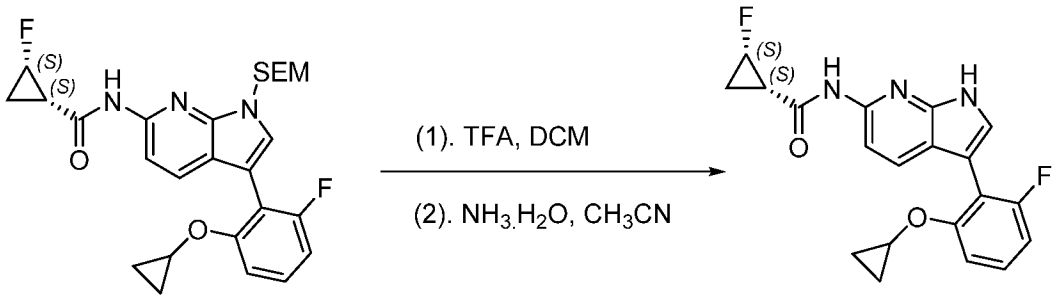
1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (1503.8 mg, 3.68 mmol), K_2CO_3 (1016.8 mg, 7.36 mmol), XPhos (350.7 mg, 0.74 mmol) and XPhos Pd G3 (311.4 mg, 0.37 mmol) at room temperature under N_2. The mixture was stirred at 70 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/EtOAc (10/1, v/v) to afford 6-chloro-3-(2-cyclopropoxy-6-fluorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (453.0 mg, 28%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ = 433.1.

Step 3: Synthesis of (1S,2S)-N-[3-(2-cyclopropoxy-6-fluorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide:



[0636] To a solution of 6-chloro-3-(2-cyclopropoxy-6-fluorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (390.0 mg, 0.90 mmol) in t-BuOH (8.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (464.3 mg, 4.50 mmol), K_2CO_3 (311.2 mg, 2.25 mmol), $Pd(OAc)_2$ (20.2 mg, 0.09 mmol) and XPhos (85.9 mg, 0.18 mmol) at room temperature under N_2. The mixture was stirred at 100 °C for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/EtOAc (2/1, v/v) to afford (1S,2S)-N-[3-(2-cyclopropoxy-6-fluorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (76.0 mg, 16%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 500.2.

Step 4: Synthesis of (1S,2S)-N-[3-(2-cyclopropoxy-6-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 127):

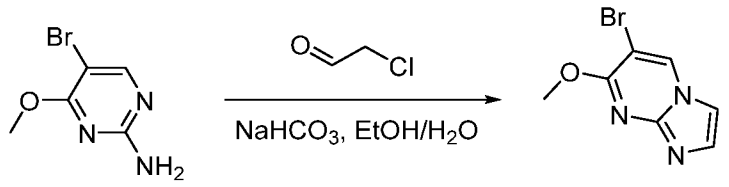


127

[0637] To a solution of (1S,2S)-N-[3-(2-cyclopropoxy-6-fluorophenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (76.0 mg, 0.15 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under vacuum. The residue was dissolved in CH_3CN (4.0 mL) and $NH_3{\cdot}H_2O$ (4.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 46% B to 56% B in 8 min, 254/220 nm to afford (1S,2S)-N-[3-(2-cyclopropoxy-6-fluorophenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (8.3 mg, 14%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 370.0. ^1H NMR (300 MHz, DMSO-d_6): δ 11.66 (s, 1H), 10.64 (s, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.67 - 7.63 (m, 1H), 7.43 - 7.25 (m, 3H), 6.97 - 6.93 (m, 1H), 5.06 - 4.79 (m, 1H), 3.90 - 3.83 (m, 1H), 2.27 - 2.19 (m, 1H), 1.72 - 1.61 (m, 1H), 1.21 - 1.10 (m, 1H), 0.80 - 0.76 (m, 2H), 0.65 - 0.60 (m, 2H).

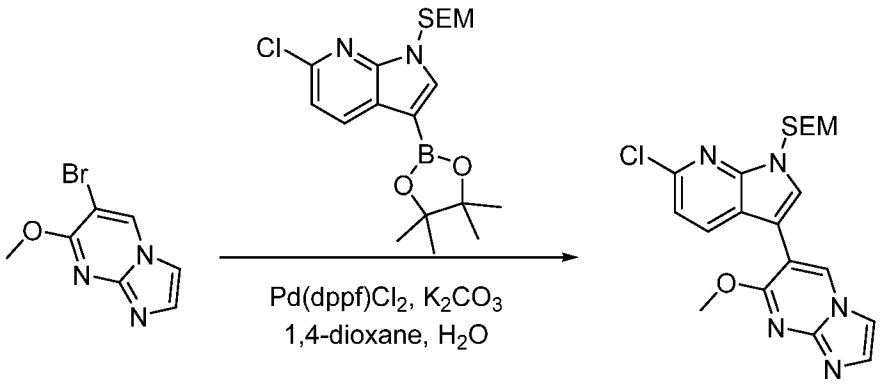
Example S128. Compound 128

Step 1: Synthesis of 6-bromo-7-methoxyimidazo[1,2-a]pyrimidine:



[0638] To a solution of 5-bromo-4-methoxypyrimidin-2-amine (500.0 mg, 2.45mmol) in EtOH/H_2O (10.0 mL/2.5 mL) was added 2-chloroacetaldehyde (1.9 g, 9.80 mmol) and $NaHCO_3$ (247.1 mg, 2.94 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (84/16, v/v) to afford 6-bromo-7-methoxyimidazo[1,2-a]pyrimidine (80.0 mg, 14%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =228.0.

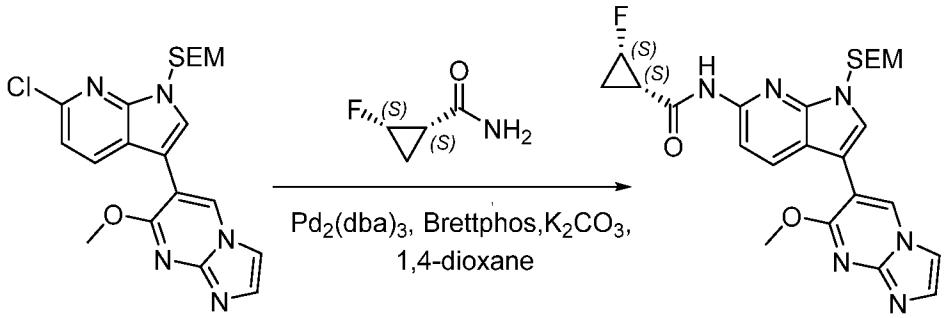
Step 2: Synthesis of 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-methoxyimidazo[1,2-a]pyrimidine:



[0639] To a solution of 6-bromo-7-methoxyimidazo[1,2-a]pyrimidine (140.0 mg, 0.61 mmol) in 1,4-dioxane/H_2O (10.0 mL/2.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (200.5 mg, 0.61 mmol), K_2CO_3 (254.5 mg, 1.84 mmol) and $Pd(dppf)Cl_2$ (44.9 mg, 0.06 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (9/91, v/v) to afford 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-

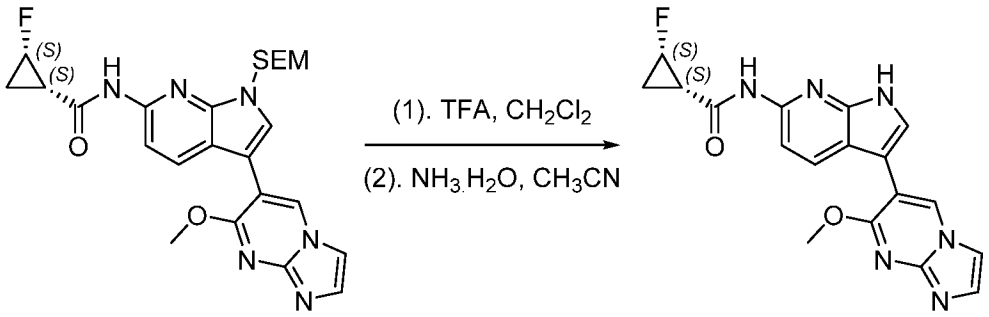
b]pyridin-3-yl)-7-methoxyimidazo[1,2-a]pyrimidine (200.0 mg, 76%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =430.1.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-(3-(7-methoxyimidazo[1,2-a]pyrimidin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0640] To a solution of 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-methoxyimidazo[1,2-a]pyrimidine (160.0 mg, 0.37 mmol) in 1,4-dioxane (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (191.8 mg, 1.86 mmol), K_2CO_3 (154.3 mg, 1.12 mmol), BrettPhos (40.0 mg, 0.07 mmol) and $Pd_2(dba)_3$ (34.1 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 3 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (30/70, v/v) to afford (1S,2S)-2-fluoro-N-(3-(7-methoxyimidazo[1,2-a]pyrimidin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (238.0 mg, 90%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =497.2.

Step 4: Synthesis of (1S,2S)-2-fluoro-N-(3-(7-methoxyimidazo[1,2-a]pyrimidin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 128):

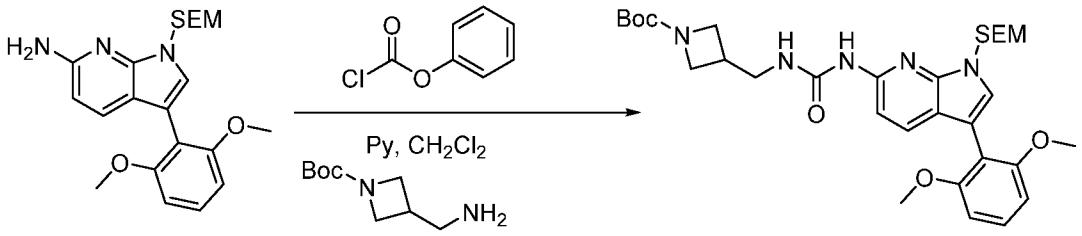


128

[0641] To a solution of (1S,2S)-2-fluoro-N-(3-(7-methoxyimidazo[1,2-a]pyrimidin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (238.0 mg, 0.48 mmol) in CH_2Cl_2 (10.0 mL) was added TFA (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (10.0 mL) was added $NH_3.H_2O$ (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 21% B to 31% B in 9 min, 254 nm) to afford (1S,2S)-2-fluoro-N-(3-(7-methoxyimidazo[1,2-a]pyrimidin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (4.2 mg, 1%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =367.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.80 (s, 1H), 10.70 (s, 1H), 9.03 (s, 1H), 8.19 (d, J = 8.7 Hz, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.72 (d, J = 1.5 Hz, 2H), 7.43 (d, J = 1.5 Hz, 1H), 5.06 - 4.80 (m, 1H), 4.03 (s, 3H), 2.27 - 2.22 (m, 1H), 1.73 - 1.60 (m, 1H), 1.24 - 1.11 (m, 1H).

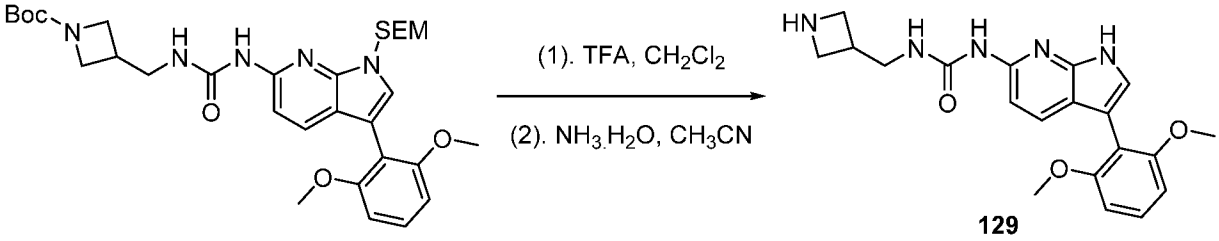
Example S129. Compound 129

Step 1: Synthesis of tert-butyl 3-((3-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)ureido)methyl)azetidine-1-carboxylate:



[0642] To a solution of 3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (100.0 mg, 0.25 mmol) in CH_2Cl_2 (5.0 mL) was added phenyl chloroformate (58.8 mg, 0.38 mmol) and pyridine (80.0 mg, 1.01 mmol) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. The resulting mixture was concentrated under reduced pressure. To the above mixture in pyridine (5.0 mL) was added tert-butyl 3-(aminomethyl)azetidine-1-carboxylate (186.5 mg, 1.00 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (90/10, v/v) to afford tert-butyl 3-((3-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)ureido)methyl)azetidine-1-carboxylate (97.0 mg, 63%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =612.3.

Step 2: Synthesis of 1-(azetidin-3-ylmethyl)-3-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)urea (Compound 129):

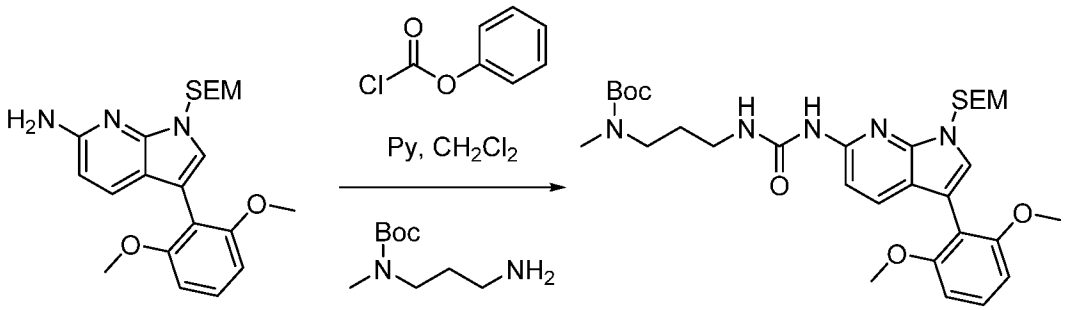


[0643] To a solution of tert-butyl 3-((3-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)ureido)methyl)azetidine-1-carboxylate (120.0 mg, 0.20 mmol) in CH_2Cl_2 (1.0 mL) was added TFA (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (1.0 mL) was added $NH_3 \cdot H_2O$ (1.0 mL) at room temperature. The resulting mixture was stirred at room

temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 35% B in 8 min; 254 nm) to afford 1-(azetidin-3-ylmethyl)-3-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)urea (13.0 mg, 17.4%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =382.4. ^1H NMR (400 MHz, DMSO-d_6 +D_2O): δ 7.46 (d, J = 8.4 Hz, 1H), 7.27 - 7.21 (m, 1H), 7.17 (s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 2H), 3.86 - 3.74 (m, 2H), 3.68 - 3.57 (m, 2H), 3.49 - 3.39 (m, 2H), 2.95 - 2.92 (m, 1H).

Example S130. Compound 130

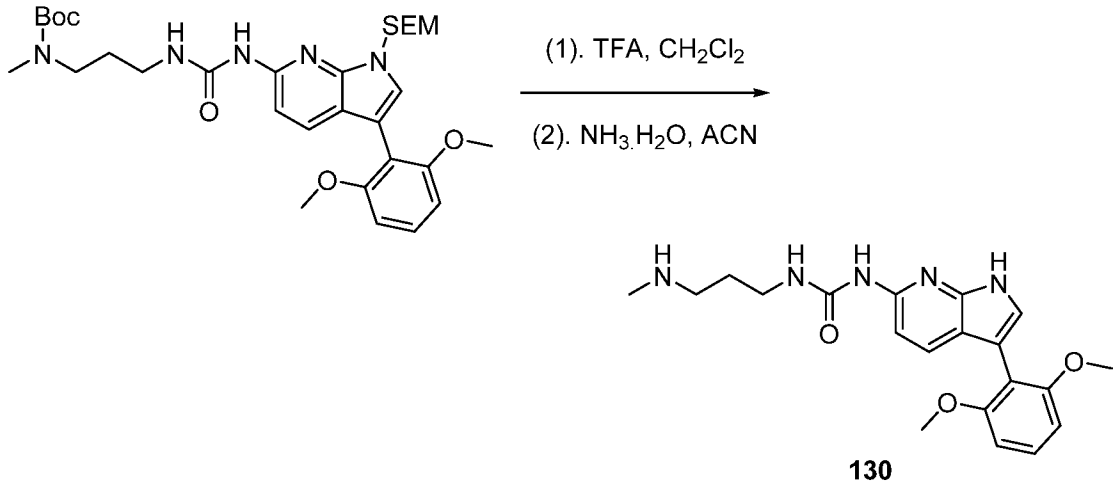
Step 1: Synthesis of tert-butyl N-[3-([[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)propyl]-N-methylcarbamate:



[0644] To a solution of 3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (130.0 mg, 0.33 mmol) in DCM (5.0 mL) was added pyridine (104.23 mg, 1.30 mmol) and phenyl chloroformate (61.1 mg, 0.39 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the above mixture was added tert-butyl N-(3-aminopropyl)-N-methylcarbamate (183.8 mg, 0.98 mmol) and pyridine (5.0 mL) at room temperature. The resulting mixture was stirred at 60 °C for another 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (90/10, v/v) to afford tert-butyl N-[3-([[3-(2,6-dimethoxyphenyl)-1-[[2-

(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)propyl]-N-methylcarbamate (180.0 mg, 90%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =614.3.

Step 2: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(methylamino)propyl]urea (Compound 130):

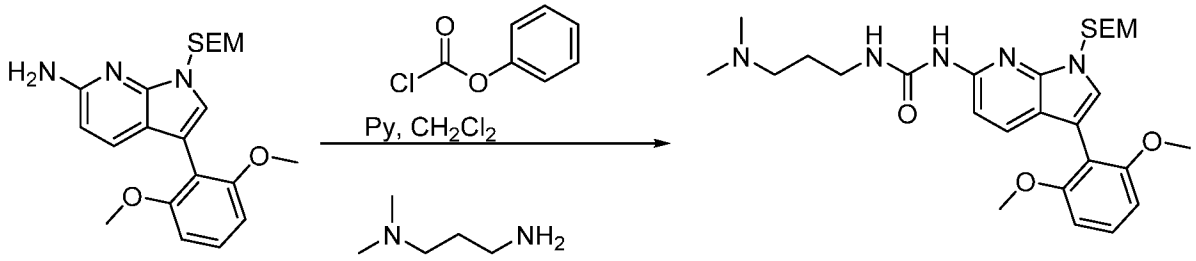


130

[0645] To a solution of tert-butyl N-[3-([[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)propyl]-N-methylcarbamate (160.0 mg, 0.26 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (3.0 mL) and $NH_3 \cdot H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another 3 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 45% B in 9 min; 254 nm) to afford 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(methylamino)propyl]urea (29.9 mg, 29%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =384.3. ^1H NMR (300 MHz, DMSO-d_6): δ 11.39 (s, 1H), 9.13 (s, 1H), 8.67 (s, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.29 - 7.24 (m, 1H), 7.17 (s, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 8.4 Hz, 2H), 3.68 (s, 6H), 3.34 - 3.24 (m, 3H), 2.58 - 2.50 (m, 2H), 2.30 (s, 3H), 1.71 - 1.62 (m, 2H).

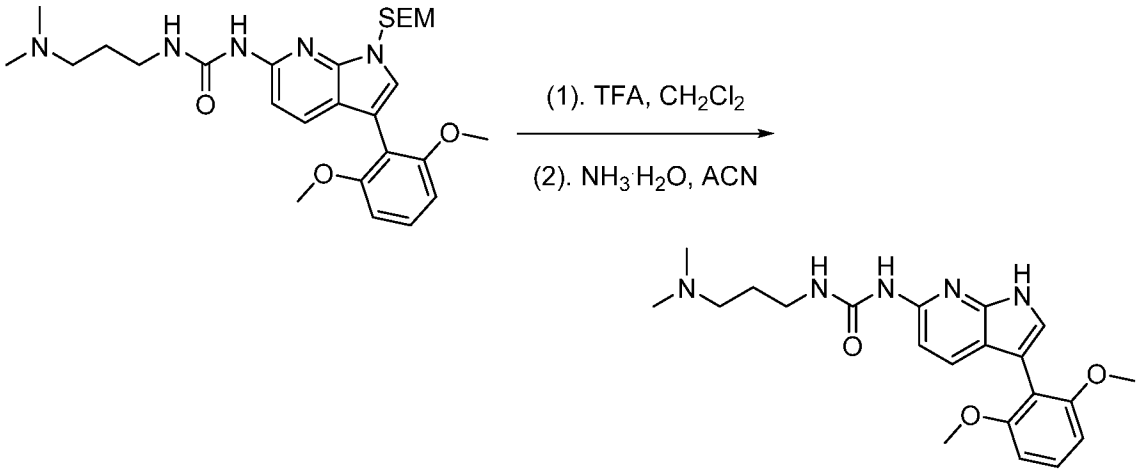
Example S131. Compound 131

Step 1: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea:



[0646] To a solution of 3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (130.0 mg, 0.33 mmol) in DCM (6.0 mL) was added pyridine (102.9 mg, 1.30 mmol) and phenyl chloroformate (61.1 mg, 0.39 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the above mixture was added dimethylaminopropylamine (99.7 mg, 0.98 mmol) and pyridine (6.0 mL) at room temperature. The resulting mixture was stirred at 60 °C for another 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (9/1, v/v) to afford 1-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea (166.0 mg, 96%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =528.3.

Step 2: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea (Compound 131):

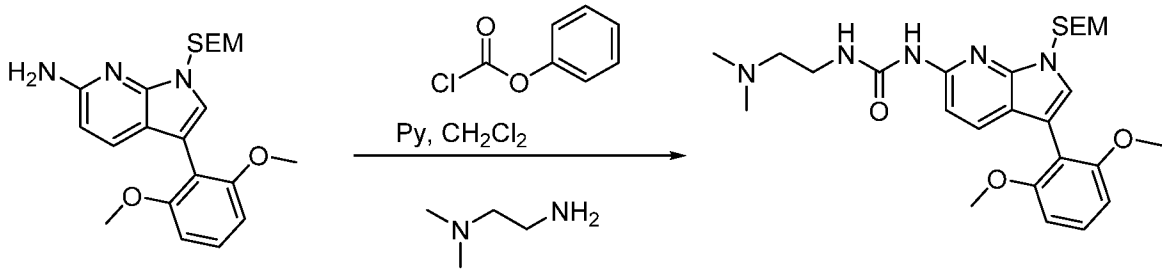


131

[0647] To a solution of 1-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea (172.0 mg, 0.33 mmol) in CH_2Cl_2 (6.0 mL) was added TFA (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (6.0 mL) was added $NH_3 \cdot H_2O$ (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 57% B in 7 min; 254 nm) to afford 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea (25.8 mg, 19%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =398.3. ^1H NMR (400 MHz, DMSO-d_6): δ 11.35 (s, 1H), 9.11 (s, 1H), 8.60 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.28 - 7.24 (m, 1H), 7.15 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 8.4 Hz, 2H), 3.68 (s, 6H), 3.26 - 3.21 (m, 2H), 2.29 - 2.25 (m, 2H), 2.14 (s, 6H), 1.68 - 1.61 (m, 2H).

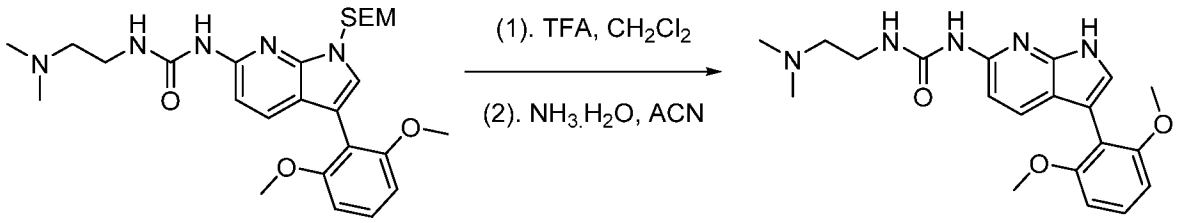
Example S132. Compound 132

Step 1: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-3-[2-(dimethylamino)ethyl]urea:



[0648] To a solution of 3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (130.0 mg, 0.33 mmol) in DCM (13.0 mL) was added pyridine (104.2 mg, 1.30 mmol) and phenyl chloroformate (61.1 mg, 0.39 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was concentrated under reduced pressure. To the residue in pyridine (10.0 mL) was added (2-aminoethyl)dimethylamine (143.4 mg, 1.63 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 4 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (10/1, v/v) to afford 1-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-3-[2-(dimethylamino)ethyl]urea (127.0 mg, 76%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =514.3.

Step 2: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[2-(dimethylamino)ethyl]urea (Compound 132):



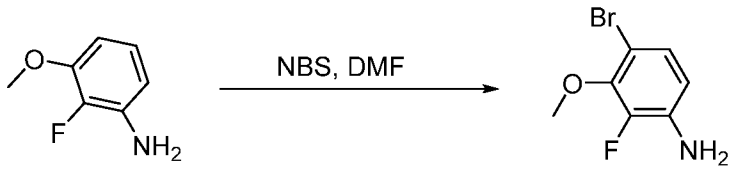
132

[0649] To a solution of 1-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-3-[2-(dimethylamino)ethyl]urea (107.0 mg, 0.21 mmol) in CH_2Cl_2 (8.0 mL) was added TFA (8.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (8.0 mL) was added $NH_3.H_2O$ (8.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16

h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions Column: (Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 43% B in 8 min; 254 nm) to afford 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[2-(dimethylamino)ethyl]urea (26.4 mg, 33%) as a light green solid. LCMS (ESI, m/z): $[M+H]^+$ =384.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.28 (d, J = 1.6 Hz, 1H), 9.11 (s, 1H), 8.46 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.28 - 7.24 (m, 1H), 7.15 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 2H), 3.68 (s, 6H), 3.33 - 3.28 (m, 2H), 2.41 - 2.38 (m, 2H), 2.21 (s, 6H).

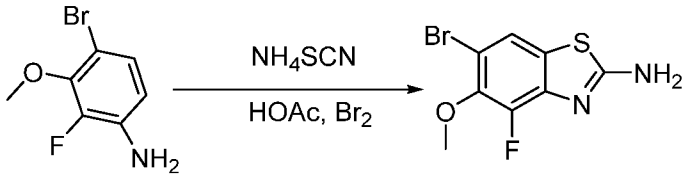
Example S133. Compound 133

Step 1: Synthesis of 4-bromo-2-fluoro-3-methoxyaniline:



[0650] To a solution of 2-fluoro-3-methoxyaniline (2.0 g, 14.17 mmol) in DMF (20.0 mL) was added NBS (2.5 g, 14.17 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the reaction mixture was quenched with Na_2SO_3 (aq.). The resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 4-bromo-2-fluoro-3-methoxyaniline (2.1 g, 67%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =220.0.

Step 2: Synthesis of 6-bromo-4-fluoro-5-methoxy-1,3-benzothiazol-2-amine:



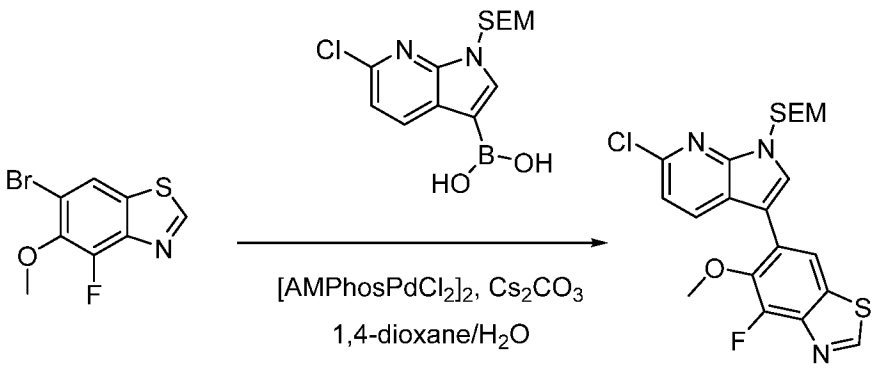
[0651] To a mixture of 4-bromo-2-fluoro-3-methoxyaniline (1.0 g, 4.54 mmol) and NH_4SCN (380.5 mg, 5.00 mmol) in acetic acid (40.0 mL) was added dropwise Br_2 (871.5 mg, 5.45 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the mixture was basified to pH=8 with saturated Na_2CO_3 (aq.). The resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 6-bromo-4-fluoro-5-methoxy-1,3-benzothiazol-2-amine (750.0 mg, 59%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ =276.9.

Step 3: Synthesis of 6-bromo-4-fluoro-5-methoxy-1,3-benzothiazole:



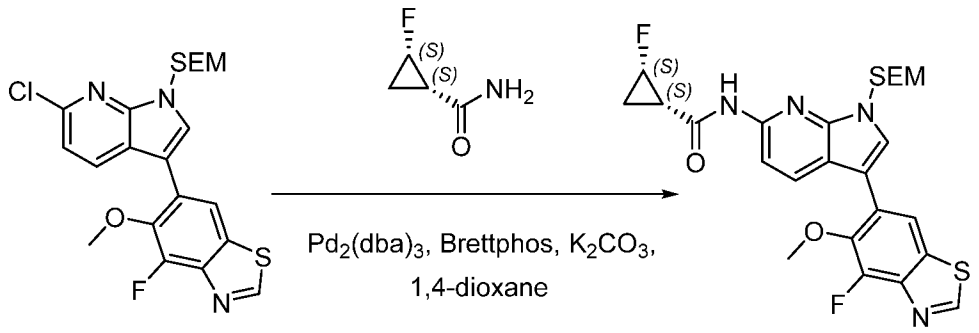
[0652] To a mixture of 6-bromo-4-fluoro-5-methoxy-1,3-benzothiazol-2-amine (380.0 mg, 1.37 mmol) and 2-methyl-2-propylnitrite (212.1 mg, 2.05 mmol) in THF (10.0 mL) was added dropwise DMSO (10.7 mg, 0.14 mmol). The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford 6-bromo-4-fluoro-5-methoxy-1,3-benzothiazole (200.0 mg, 55%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =261.9.

Step 4: Synthesis of 6-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-fluoro-5-methoxy-1,3-benzothiazole:



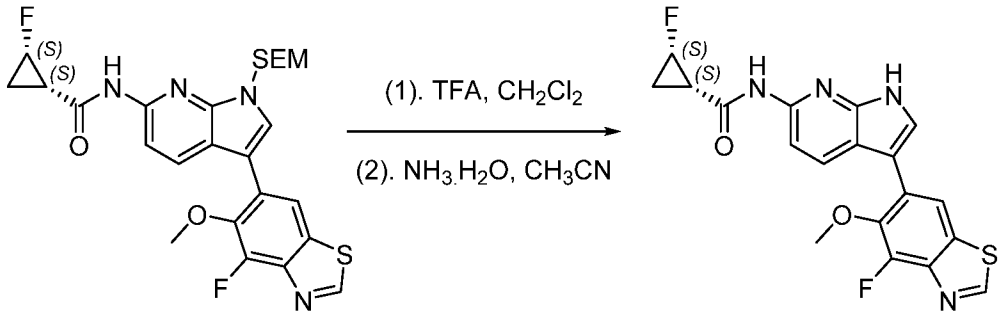
[0653] To a mixture of 6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-ylboronic acid (548.4 mg, 1.68 mmol) and 6-bromo-4-fluoro-5-methoxy-1,3-benzothiazole (400.0 mg, 1.52 mmol) in dioxane (10.0 mL) were added $[AMPhosPdCl_2]_2$ (216.1 mg, 0.31 mmol), Cs_2CO_3 (1491.7 mg, 4.58 mmol) and H_2O (1.0 mL) at room temperature. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 6-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-fluoro-5-methoxy-1,3-benzothiazole (400.0 mg, 56%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =464.1.

Step 5: Synthesis of (1S,2S)-2-fluoro-N-[3-(4-fluoro-5-methoxy-1,3-benzothiazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0654] To a mixture of 6-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-fluoro-5-methoxy-1,3-benzothiazole (300.0 mg, 0.68 mmol) and (1S,2S)-2-fluorocyclopropane-1-carboxamide (333.3 mg, 3.23 mmol) in 1,4-dioxane (5.0 mL) was added $Pd_2(dba)_3$ (118.4 mg, 0.13 mmol), BrettPhos (138.8 mg, 0.26 mmol) and K_2CO_3 (268.0 mg, 1.94 mmol). The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1S,2S)-2-fluoro-N-[3-(4-fluoro-5-methoxy-1,3-benzothiazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (50.0 mg, 14%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =531.2.

Step 6: Synthesis of (1S,2S)-2-fluoro-N-[3-(4-fluoro-5-methoxy-1,3-benzothiazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 133):

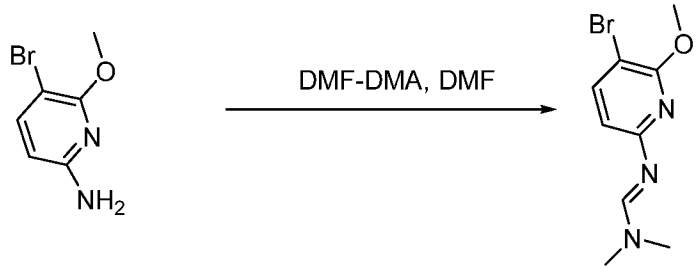


133

[0655] To a solution of (1S,2S)-2-fluoro-N-[3-(4-fluoro-5-methoxy-1,3-benzothiazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (45.0 mg, 0.09 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A:Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 35% B in 7 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(4-fluoro-5-methoxy-1,3-benzothiazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (11.6 mg, 34%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =401.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.80 (s, 1H), 10.68 (s, 1H), 9.36 (s, 1H), 8.19 - 8.17 (m, 2H), 7.93 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 2.7 Hz, 1H), 5.05 - 4.78 (m, 1H), 3.74 (s, 3H), 2.25 - 2.18 (m, 1H), 1.88 - 1.58 (m, 1H), 1.22 - 1.07 (m, 1H).

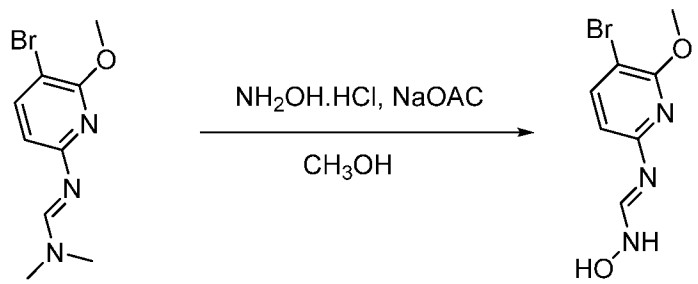
Example S134. Compound 134

Step 1: Synthesis of (E)-N'-(5-bromo-6-methoxypyridin-2-yl)-N,N-dimethylformimidamide:



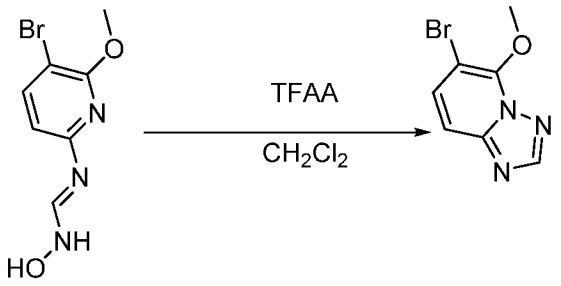
[0656] To a solution of 5-bromo-6-methoxypyridin-2-amine (1.5 g, 7.42 mmol) in DMF (10.0 mL) was added DMF-DMA (972.0 mg, 8.17 mmol). The resulting mixture was stirred at 70 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (E)-N'-(5-bromo-6-methoxypyridin-2-yl)-N,N-dimethylformimidamide (1.5 g, 79%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ =258.0.

Step 2: Synthesis of (E)-N'-(5-bromo-6-methoxypyridin-2-yl)-N-hydroxymethanimidamide:



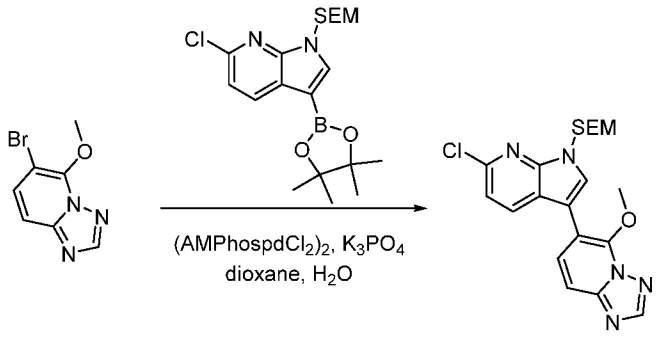
[0657] To a solution of (E)-N'-(5-bromo-6-methoxypyridin-2-yl)-N,N-dimethylformimidamide (1.5 g, 5.81 mmol) in methanol (10.0 mL) was added hydroxylamine hydrochloride (1.5 g, 21.44 mmol) and NaOAc (1.5 g, 18.85 mmol). The resulting mixture was stirred at 70 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (E)-N'-(5-bromo-6-methoxypyridin-2-yl)-N-hydroxymethanimidamide (1.4 g, 98%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ =246.0.

Step 3: Synthesis of 6-bromo-5-methoxy-[1,2,4]triazolo[1,5-a]pyridine:



[0658] To a solution of (E)-N'-(5-bromo-6-methoxypyridin-2-yl)-N-hydroxymethanimidamide (1.4 g, 5.69 mmol) in DCM (10.0 mL) was added TFAA (1.3 g, 6.27 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 6-bromo-5-methoxy-[1,2,4]triazolo[1,5-a]pyridine (600.0 mg, 46%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =228.0.

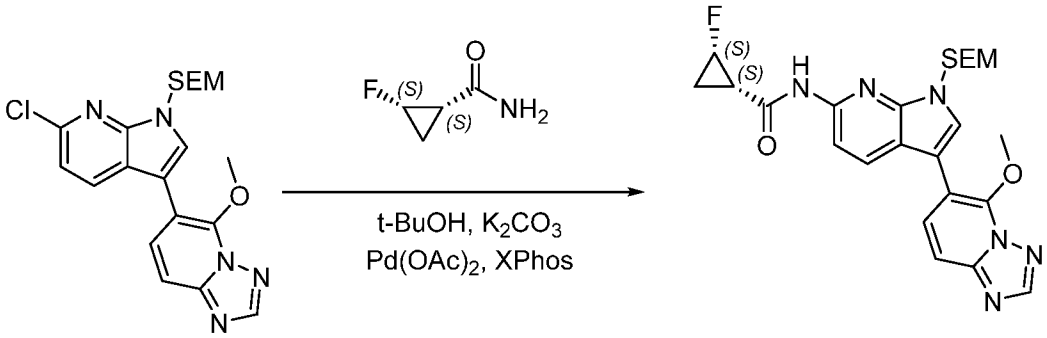
Step 4: Synthesis of 6-chloro-3-[5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



[0659] To a solution of 6-bromo-5-methoxy-[1,2,4]triazolo[1,5-a]pyridine (300.0 mg, 1.36 mmol) in dioxane (5.0 mL) and H_2O (0.5 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (645.5 mg, 1.59 mmol), $(AMPhospdCl_2)_2$ (93.1 mg, 0.12 mmol) and K_3PO_4 (837.7 mg, 3.94 mmol). The resulting mixture was stirred at 80 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium

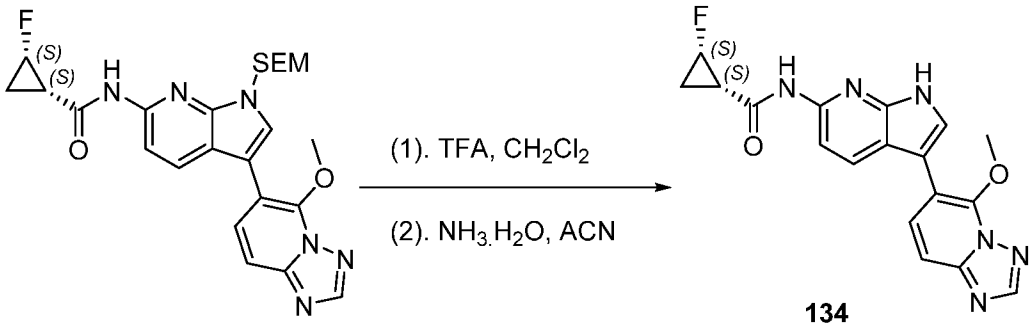
sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 6-chloro-3-[5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (200.0 mg, 35%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =430.1.

Step 5: Synthesis of (1S,2S)-2-fluoro-N-(3-(5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0660] To a solution of 6-chloro-3-[5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (200.0 mg, 0.45 mmol) in t-BuOH (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (479.4 mg, 4.61 mmol), $Pd(OAc)_2$ (20.9 mg, 0.09 mmol), XPhos (22.7 mg, 0.05 mmol) and K_2CO_3 (192.8 mg, 1.39 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1S,2S)-2-fluoro-N-(3-(5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (70.0 mg, 30%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =497.2.

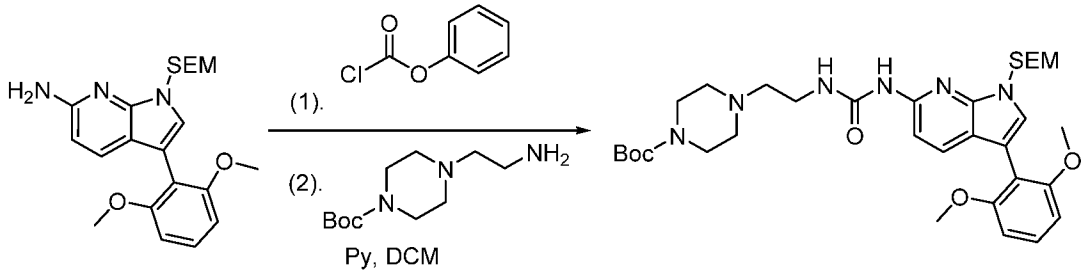
Step 6: Synthesis of (1S,2S)-2-fluoro-N-(3-[5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 134):



[0661] To a solution of (1S,2S)-2-fluoro-N-(3-[5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (70.0 mg, 0.14 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A:Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 24% B to 32% B in 7 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-[5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (1.2 mg, 2%) LCMS (ESI, m/z): $[M+H]^+$ =367.3. ^1H NMR (300 MHz, DMSO-d_6): δ 11.87 (s, 1H), 10.70 (s, 1H), 8.55 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.99 - 7.93 (m, 2H), 7.73 - 7.70 (m, 2H), 5.05 - 4.82 (m, 1H), 4.03 (s, 3H), 2.30 - 2.19 (m, 1H), 1.70 - 1.60 (m, 1H), 1.23 - 1.13 (m, 1H).

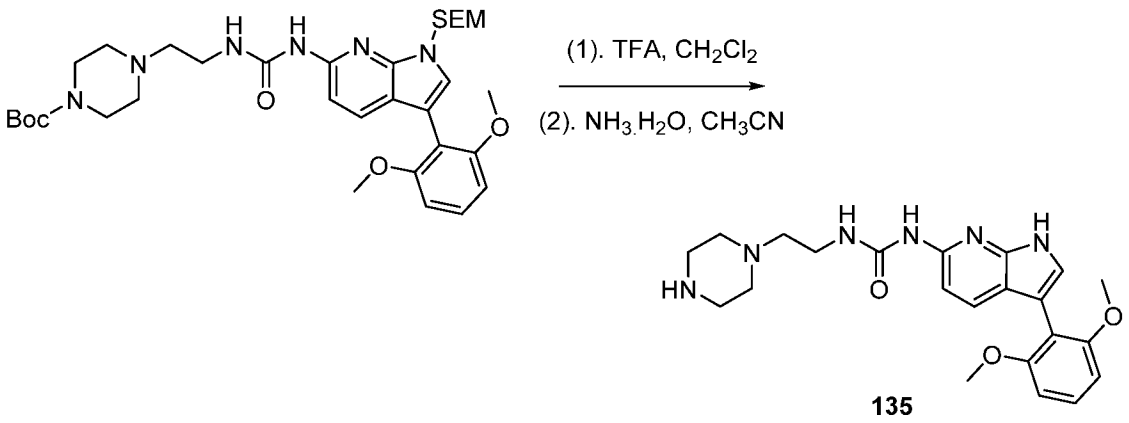
Example S135. Compound 135

Step 1: Synthesis of tert-butyl 4-[2-([[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate:



[0662] To a solution of 3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (110.0 mg, 0.28 mmol) in CH_2Cl_2 (3.0 mL) was added pyridine (87.1 mg, 1.10 mmol) and phenyl chloroformate (51.7 mg, 0.33 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was concentrated under vacuum. To the above mixture was added pyridine (2.0 mL) and tert-butyl 4-(2-aminoethyl)piperazine-1-carboxylate (189.4 mg, 0.83 mmol). The resulting mixture was stirred at 60 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (95/5, v/v) to afford tert-butyl 4-[2-([[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate (110.0 mg, 61%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =655.4.

Step 2: Synthesis of 3-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(piperazin-1-yl)ethyl]urea (Compound 135):

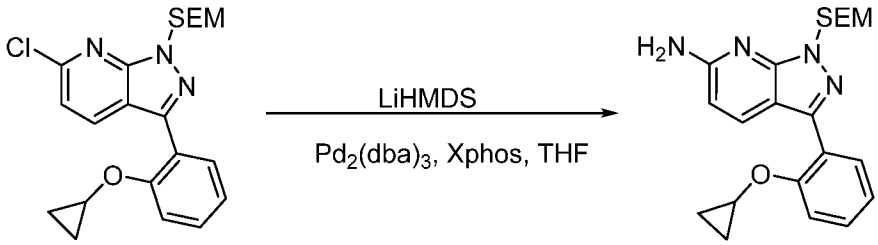


[0663] To a solution of tert-butyl 4-[2-([[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate (120.0 mg, 0.18 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL). The mixture was stirred at room temperature for 4 h. The mixture was concentrated under vacuum. To the above residue were added ACN (3.0 mL) and $NH_3.H_2O$ (3.0 mL). The

resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 42% B in 8 min; 254 nm) to afford 3-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(piperazin-1-yl)ethyl]urea (24.6 mg, 31%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 425.3. ^1H NMR (300 MHz, DMSO-d_6): δ 11.30 (s, 1H), 9.15 (s, 1H), 8.41 (s, 1H), 7.46 (d, J = 8.7 Hz, 1H), 7.29 - 7.24 (m, 1H), 7.17 (d, J = 2.1 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 8.4 Hz, 2H), 3.69 (s, 6H), 2.73 - 2.70 (m, 4H), 2.46 - 2.37 (m, 6H).

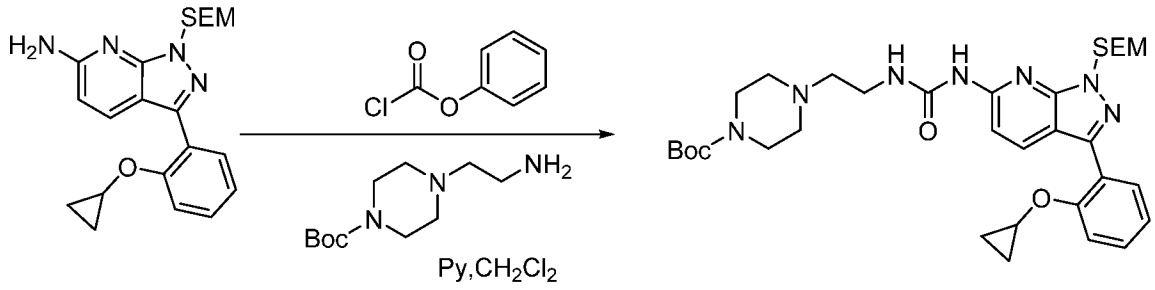
Example S136. Compound 136

Step 1: Synthesis of 3-(2-cyclopropoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-amine:



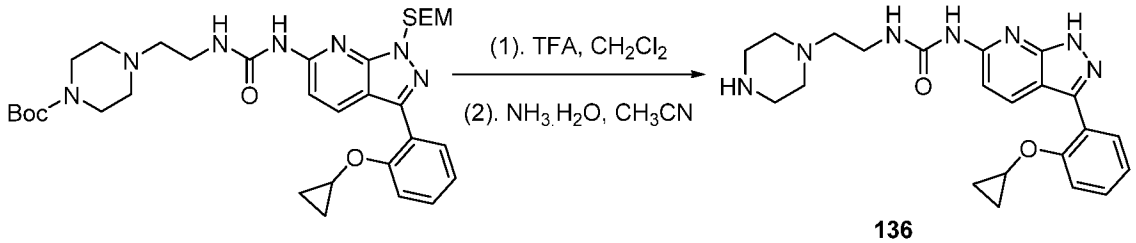
[0664] To a solution of 6-chloro-3-(2-cyclopropoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (320.0 mg, 0.77 mmol) in THF (5.0 mL) was added X-Phos (73.3 mg, 0.15 mmol), $Pd_2(dba)_3$ (70.4 mg, 0.08 mmol) and LiHMDS (1.2 mL, 1 mol/L) at room temperature. The resulting mixture was stirred at 60 °C for 1 h. After the reaction was completed, the reaction was quenched with water. The resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (93/7, v/v) to afford 3-(2-cyclopropoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-amine (120.0 mg, 39%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =397.2.

Step 2: Synthesis of tert-butyl 4-[2-([[3-(2-cyclopropoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate:



[0665] To a solution of 3-(2-cyclopropoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-amine (100.0 mg, 0.25 mmol) in CH_2Cl_2 (3.0 mL) was added pyridine (79.8 mg, 1.01 mmol) and phenyl chloroformate (47.4 mg, 0.30 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was concentrated under vacuum. To the above residue was added pyridine (2.0 mL) and tert-butyl 4-(2-aminoethyl)piperazine-1-carboxylate (173.5 mg, 0.76 mmol). The resulting mixture was stirred at 60 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (94/6, v/v) to afford tert-butyl 4-[2-([[3-(2-cyclopropoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate (100.0 mg, 60%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =652.4.

Step 3: Synthesis of 3-[3-(2-cyclopropoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]-1-[2-(piperazin-1-yl)ethyl]urea (Compound 136):



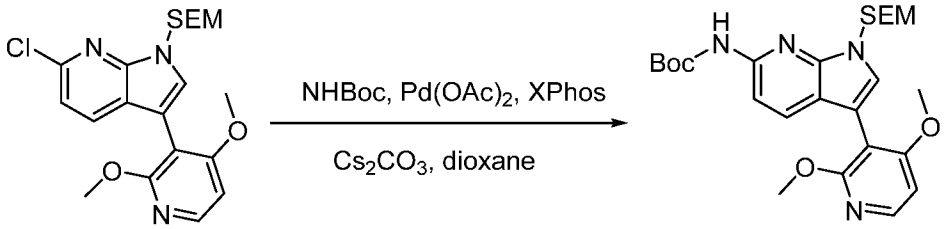
136

[0666] To a solution of tert-butyl 4-[2-([[3-(2-cyclopropoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate (80.0 mg, 0.12 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL). The mixture was stirred at room temperature for 3 h. The mixture was concentrated under vacuum. To the above residue were added ACN (3.0 mL) and $NH_3.H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another 3 h. After the reaction was completed, the resulting mixture was concentrated under vacuum.

The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column, 19×250 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 47% B to 68% B in 9 min; 254 nm) to afford 3-[3-(2-cyclopropoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]-1-[2-(piperazin-1-yl)ethyl]urea (14.0 mg, 27%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 422.3. ^1H NMR (300 MHz, DMSO-d_6): δ 13.30 (s, 1H), 9.61 (s, 1H), 8.43 - 8.39 (m, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.58 (d, J = 1.2 Hz, 1H), 7.49 - 7.41 (m, 2H), 7.16 - 7.06 (m, 2H), 3.93 - 3.87 (m, 1H), 3.37 - 3.23 (s, 3H), 2.78 - 2.75 (m, 4H), 2.47 - 2.39 (m, 6H), 0.83 - 0.73 (m, 2H), 0.68 - 0.63 (m, 2H).

Example S137. Compound 137

Step 1: Synthesis of tert-butyl N-[3-(2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamate:



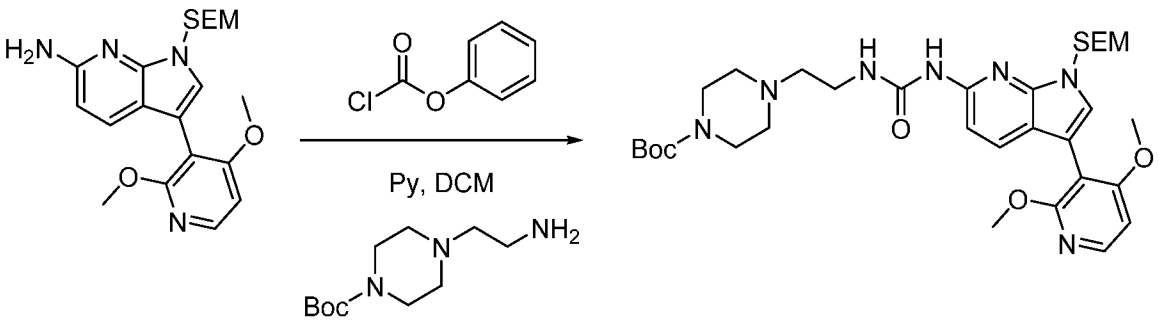
[0667] To a mixture of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2,4-dimethoxypyridine (600.0 mg, 1.43 mmol), Cs_2CO_3 (1.4 g, 4.28 mmol) and $BocNH_2$ (836.8 mg, 7.14 mmol) in dioxane (5.0 mL) were added $Pd(OAc)_2$ (64.1 mg, 0.28 mmol) and X-Phos (272.4 mg, 0.57 mmol). The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford tert-butyl N-[3-(2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamate (550.0 mg, 77%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =501.2.

Step 2: Synthesis of 3-(2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine:



[0668] A mixture of tert-butyl N-[3-(2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamate (250.0 mg, 0.5 mmol) and formic acid (10.0 mL) in DCM (20.0 mL) was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O. The pH value of the mixture was adjusted to 8 with saturated $NaHCO_3$ solution and then extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 3-(2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (200.0 mg, crude) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =401.2.

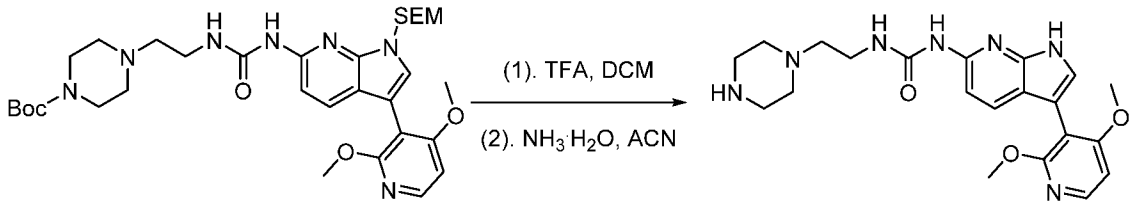
Step 3: Synthesis of tert-butyl 4-[2-([[3-(2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate:



[0669] To a mixture of 3-(2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (100.0 mg, 0.25 mmol) and pyridine (79.9 mg, 1.0 mmol) in DCM (10.0 mL) was added phenyl chloroformate (46.9 mg, 0.30 mmol). The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in pyridine (5.0 mL) was added tert-butyl 4-(2-aminoethyl)piperazine-1-carboxylate (343.5 mg, 1.50 mmol) at room temperature. The resulting mixture was stirred at 60 °C for another 16 h. After the reaction was completed, the mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford tert-butyl

4-[2-([[3-(2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate (100.0 mg, 61%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =656.4.

Step 4: Synthesis of 3-[3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(piperazin-1-yl)ethyl]urea (Compound 137):

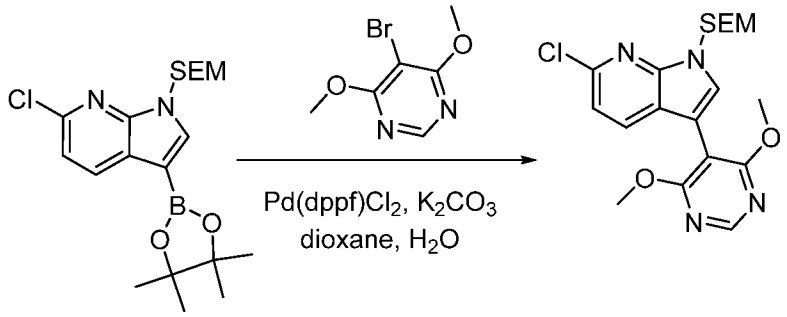


137

[0670] To a solution of tert-butyl 4-[2-([[3-(2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate (170.0 mg, 0.26 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A:Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 24% B to 32% B in 7 min; 254 nm) to afford 3-[3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(piperazin-1-yl)ethyl]urea (13.2 mg, 11%) as a white solid.. LCMS (ESI, m/z): $[M+H]^+$ =426.2. ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H), 9.58 (s, 1H), 8.09 (d, J = 5.7 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.33 (s, 1H), 7.21 (s, 1H), 6.66 (d, J = 5.7 Hz, 1H), 6.48 - 6.44 (m, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 3.61 - 3.56 (m, 2H), 3.07 - 3.02 (m, 4H), 2.76 - 2.64 (m, 6H).

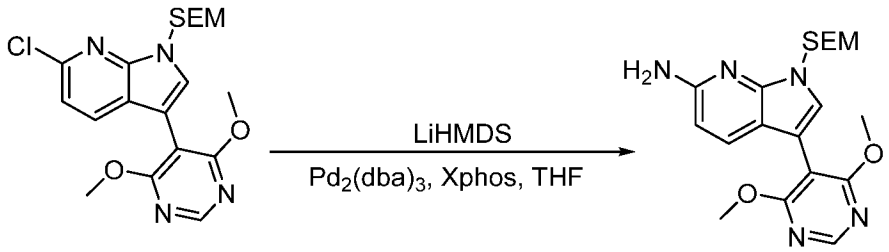
Example S138. Compound 138

Step 1: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4,6-dimethoxypyrimidine:



[0671] To a solution of 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (500.0 mg, 1.22 mmol) in 1,4-dioxane/H_2O (20.0 mL/5.0 mL) was added 5-bromo-4,6-dimethoxypyrimidine (267.9 mg, 1.22 mmol), K_2CO_3 (507.1 mg, 3.67 mmol) and $Pd(dppf)Cl_2$ (89.4 mg, 0.12 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4,6-dimethoxypyrimidine (240.0 mg, 46%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =421.1.

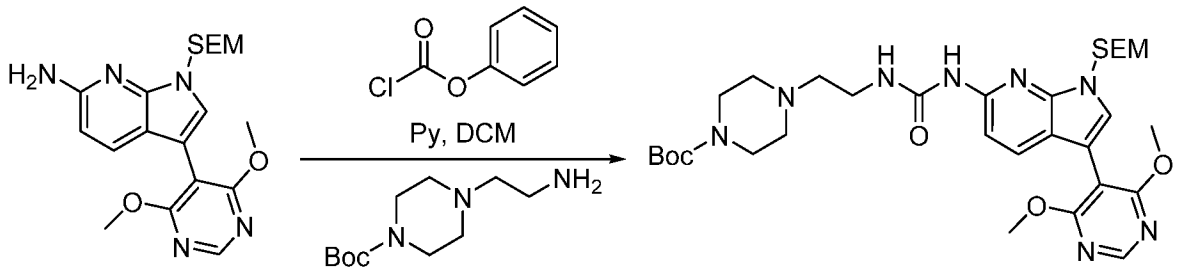
Step 2: Synthesis of 3-(4,6-dimethoxypyrimidin-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine:



[0672] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4,6-dimethoxypyrimidine (110.0 mg, 0.26 mmol) in THF (8.0 mL) was added XPhos (24.9 mg, 0.05 mmol), $Pd_2(dba)_3$ (15.0 mg, 0.03 mmol) and LiHMDS (0.4 mL, 1 mol/L) at room temperature under N_2. The resulting mixture was stirred at 65 °C for 0.5 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford 3-(4,6-dimethoxypyrimidin-5-yl)-1-[[2-

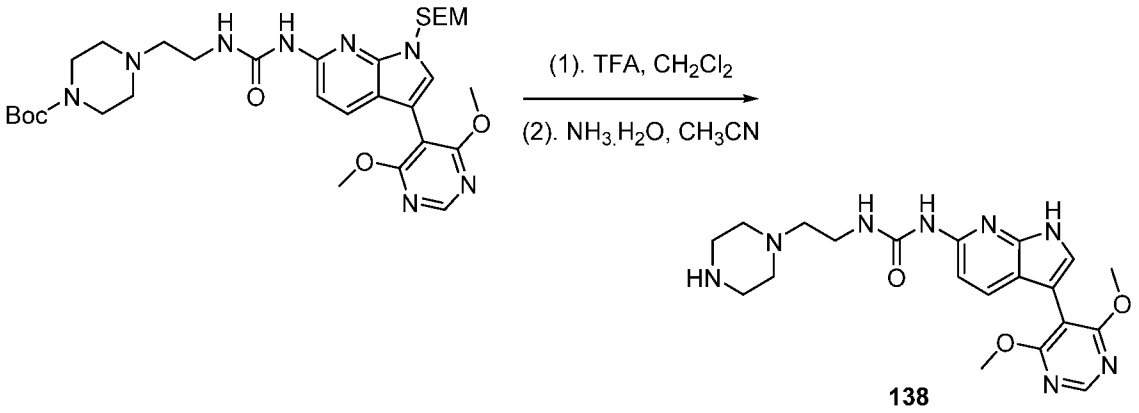
(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (100.0 mg, 95%) as a brown yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =402.2.

Step 3: Synthesis of tert-butyl 4-[2-([[3-(4,6-dimethoxypyrimidin-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate:



[0673] To a solution of 3-(4,6-dimethoxypyrimidin-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (180.0 mg, 0.45 mmol) in DCM (10.0 mL) was added pyridine (143.6 mg, 1.79 mmol) and phenyl chloroformate (84.2 mg, 0.54 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added tert-butyl 4-(2-aminoethyl)piperazine-1-carboxylate (308.4 mg, 1.35 mmol) and pyridine (10.0 mL) at room temperature. The resulting mixture was stirred at 60 °C for another 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with DCM/MeOH (20/1, v/v) to afford tert-butyl 4-[2-([[3-(4,6-dimethoxypyrimidin-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate (200.0 mg, 67%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =657.3.

Step 4: Synthesis of 3-[3-(4,6-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(piperazin-1-yl)ethyl]urea (Compound 138):

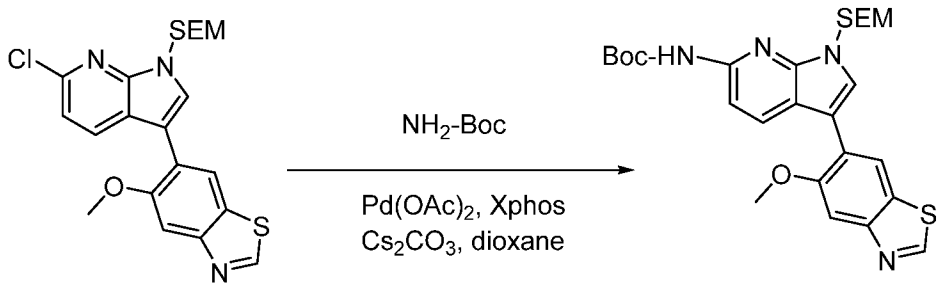


138

[0674] To a solution of tert-butyl 4-[2-([[3-(4,6-dimethoxypyrimidin-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate (180.0 mg, 0.27 mmol) in DCM (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (3.0 mL) was added $NH_3 \cdot H_2O$ (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 3 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 24% B to 34% B in 7 min, 254/220 nm) to afford 3-[3-(4,6-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(piperazin-1-yl)ethyl]urea (33.5 mg, 28%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =427.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.53 (s, 1H), 9.20 (s, 1H), 8.46 (s, 1H), 8.32 (s, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.37 (s, 1H), 7.06 (d, J = 8.8 Hz, 1H), 3.91 (s, 6H), 3.39 - 3.30 (m, 3H), 2.71 (s, 4H), 2.51 - 2.50 (m, 2H), 2.45 - 2.37 (m, 4H).

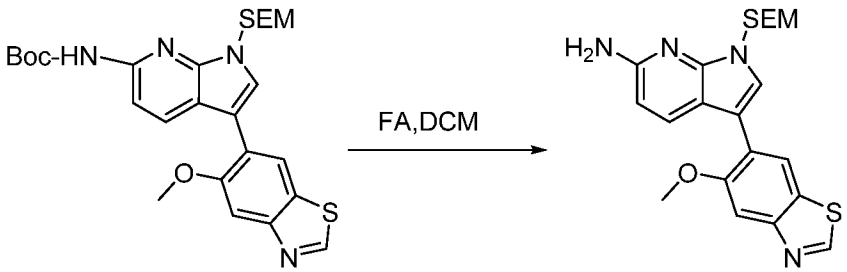
Example S139. Compound 139

Step 1: Synthesis of tert-butyl N-[3-(5-methoxy-1,3-benzothiazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamate:



[0675] To a solution of 6-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-methoxy-1,3-benzothiazole (380.0 mg, 0.85 mmol) in 1.4-dioxane (10.0 mL) was added tert-butyl carbamate (139.7 mg, 1.19 mmol), Xphos (81.2 mg, 0.17 mmol), Cs_2CO_3 (694.0 mg, 2.13 mmol) and $Pd(OAc)_2$ (19.1 mg, 0.09 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (7/3, v/v) to afford tert-butyl N-[3-(5-methoxy-1,3-benzothiazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamate (420.0 mg, 93%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =527.2.

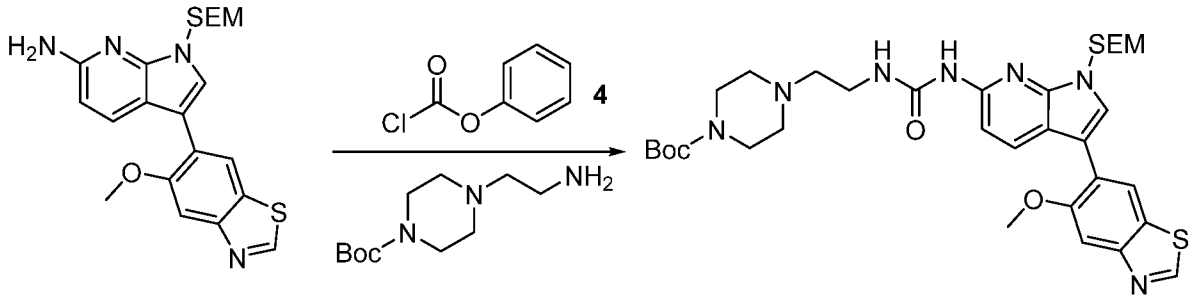
Step 2: Synthesis of 3-(5-methoxy-1,3-benzothiazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine:



[0676] To a solution of tert-butyl N-[3-(5-methoxy-1,3-benzothiazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamate (470.0 mg, 0.89 mmol) in CH_2Cl_2 (10.0 mL) was added formic acid (FA, 10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the pH value of the mixture was adjusted to 8 with $NaHCO_3$ solution. The resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was

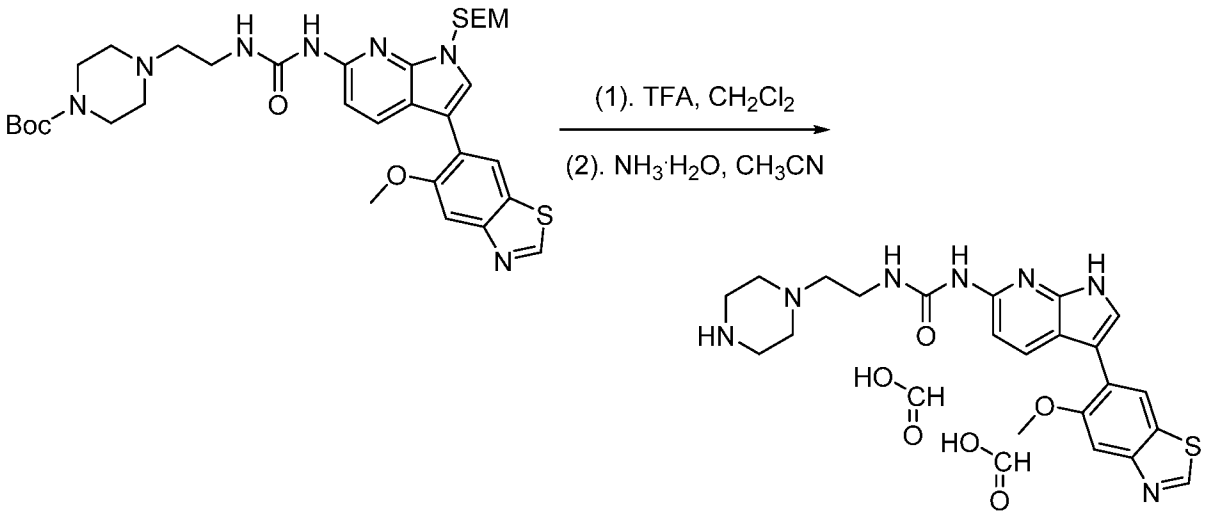
concentrated under reduced pressure to afford 3-(5-methoxy-1,3-benzothiazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (380.0 mg, crude) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =427.2.

Step 3: Synthesis of tert-butyl 4-[2-([[3-(5-methoxy-1,3-benzothiazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate:



[0677] To a solution of 3-(5-methoxy-1,3-benzothiazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (290.0 mg, crude) in DCM (8.0 mL) was added pyridine (215.1 mg, 2.72 mmol) and phenyl chloroformate (255.4 mg, 1.63 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was concentrated under reduced pressure. To the above mixture was added tert-butyl 4-(2-aminoethyl)piperazine-1-carboxylate (935.3 mg, 4.08 mmol) and pyridine (8.0 mL) at room temperature. The resulting mixture was stirred at 60 °C for another 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (15/1, v/v) to afford tert-butyl 4-[2-([[3-(5-methoxy-1,3-benzothiazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate (155.0 mg, 33%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =682.3.

Step 4: Synthesis of 3-[3-(5-methoxy-1,3-benzothiazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(piperazin-1-yl)ethyl]urea; bis(formic acid) (Compound 139):

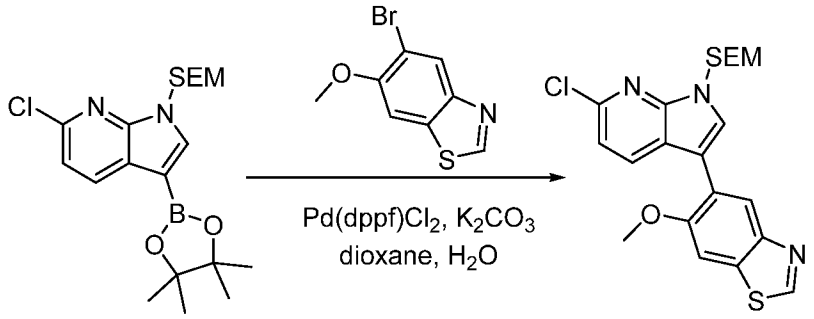


139

[0678] To a solution of tert-butyl 4-[2-([[3-(5-methoxy-1,3-benzothiazol-6-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate (155.0 mg, 0.23 mmol) in CH_2Cl_2 (8.0 mL) was added TFA (8.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (8.0 mL) was added $NH_3 \cdot H_2O$ (8.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 7% B to 20% B in 8 min; 254/220 nm) to afford 3-[3-(5-methoxy-1,3-benzothiazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(piperazin-1-yl)ethyl]urea; bis(formic acid) (12.9 mg, 9%) as a white semi-solid. LCMS (ESI, m/z): $[M+H]^+$ =452.3. ^1H NMR (400 MHz, DMSO-d_6): δ 11.58 (s, 1H), 9.31 (s, 1H), 9.23 (s, 1H), 8.41 (s, 1H), 8.30 (d, J = 3.6 Hz, 2H), 8.24 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.75 (s, 1H), 7.57 (d, J = 2.4 Hz, 1H), 7.11 (d, J = 8.8 Hz, 1H), 3.92 (s, 3H), 3.37 - 3.32 (m, 2H), 3.02 - 2.91 (m, 4H), 2.67 - 2.55 (m, 5H).

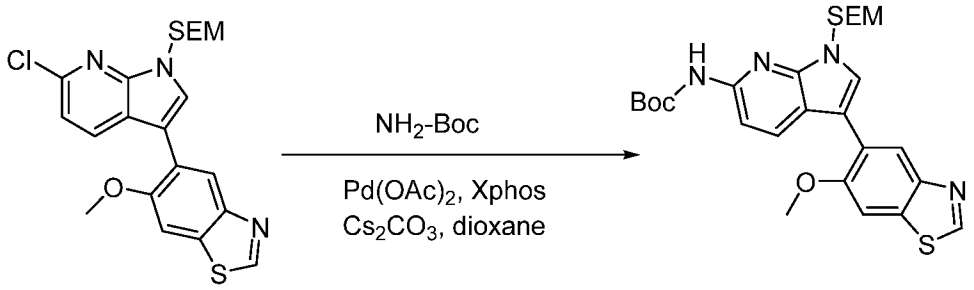
Example S140. Compound 140

Step 1: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1,3-benzothiazole:



[0679] To a solution of 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (500.0 mg, 1.22 mmol) in dioxane/H_2O (20.0 mL/4.0 mL) was added 5-bromo-6-methoxy-1,3-benzothiazole (298.6 mg, 1.22 mmol), K_2CO_3 (507.1 mg, 3.67 mmol) and $Pd(dppf)Cl_2$ (89.5 mg, 0.12 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1,3-benzothiazole (250.0 mg, 48 %) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =446.1.

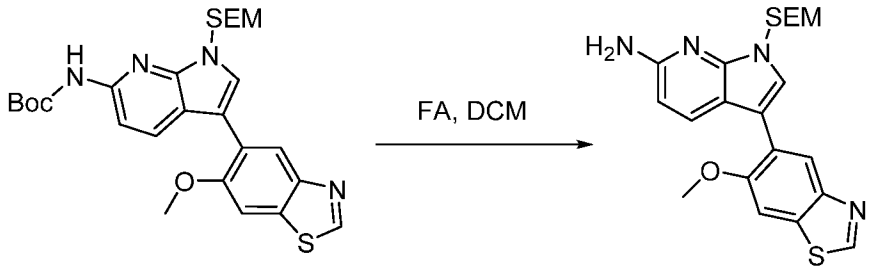
Step 2: Synthesis of tert-butyl N-[3-(6-methoxy-1,3-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamate:



[0680] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-6-methoxy-1,3-benzothiazole (230.0 mg, 0.52 mmol) in 1,4-dioxane (24.0 mL) was added tert-butyl carbamate (84.6 mg, 0.72 mmol), XPhos (49.2 mg, 0.11 mmol), Cs_2CO_3 (420.0 mg, 1.29 mmol) and $Pd(OAc)_2$ (11.6 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and

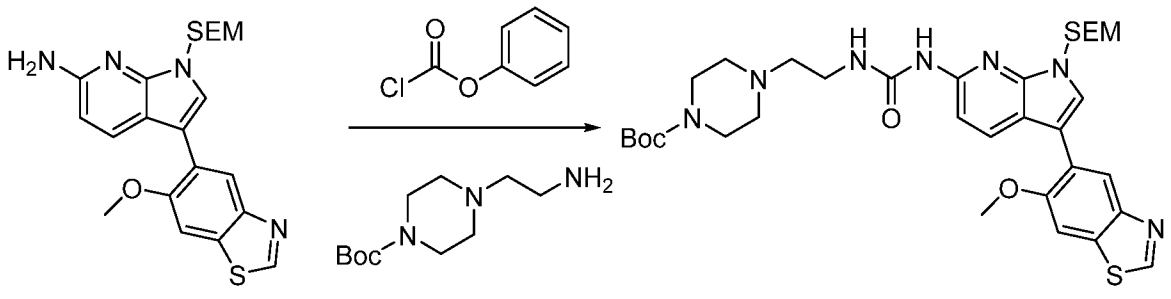
filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with ACN/H_2O (1/3, v/v) to afford tert-butyl N-[3-(6-methoxy-1,3-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamate (160.0 mg, 59%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =527.2.

Step 3: Synthesis of 3-(6-methoxy-1,3-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine:



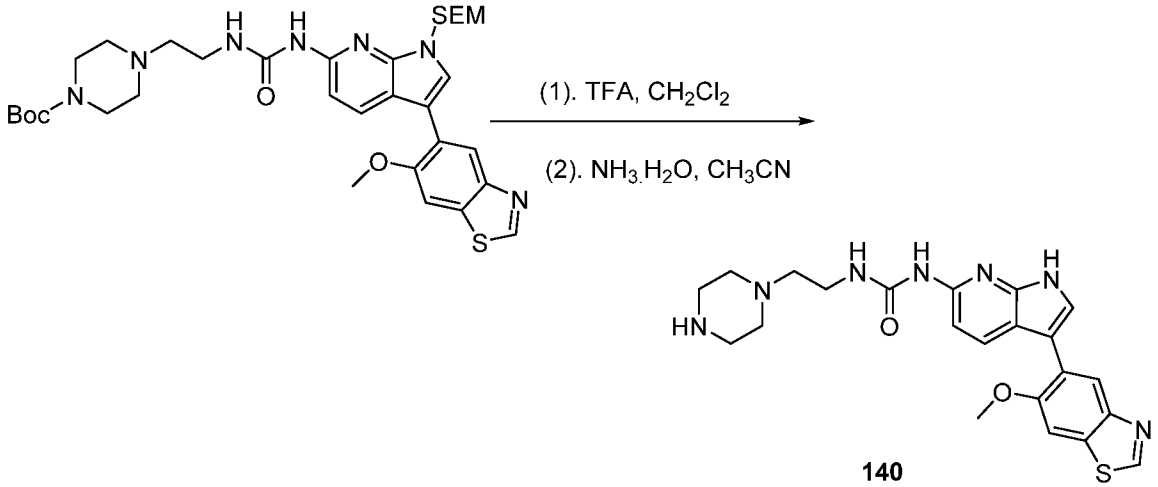
[0681] To a solution of tert-butyl N-[3-(6-methoxy-1,3-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamate (140.0 mg, 0.27 mmol) in DCM (15.0 mL) was added HCOOH (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 30 min. After the reaction was completed, the reaction mixture was diluted with H_2O. The pH value of the mixture was adjusted to 8 with saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated in vacuo to afford 3-(6-methoxy-1,3-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (110.0 mg, crude) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =427.2.

Step 4: Synthesis of tert-butyl 4-[2-([[3-(6-methoxy-1,3-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate:



[0682] To a solution of 3-(6-methoxy-1,3-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (80.0 mg, crude) in DCM (8.0 mL) was added pyridine (60.1 mg, 0.75 mmol) and phenyl chloroformate (35.2 mg, 0.23 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h under N_2. The resulting mixture was concentrated under reduced pressure. To the residue in pyridine (8.0 mL) was added tert-butyl 4-(2-aminoethyl)piperazine-1-carboxylate (215.0 mg, 0.94 mmol) at room temperature. The resulting mixture was stirred at 60 °C for another 4 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (10/1, v/v) to afford tert-butyl 4-[2-([[3-(6-methoxy-1,3-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate (120.0 mg, 94%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =682.3.

Step 5: Synthesis of 3-[3-(6-methoxy-1,3-benzothiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(piperazin-1-yl)ethyl]urea (Compound 140):



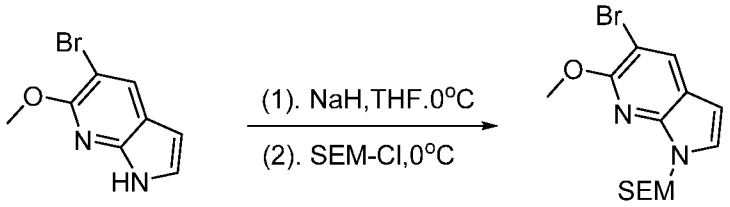
140

[0683] To a solution of tert-butyl 4-[2-([[3-(6-methoxy-1,3-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)ethyl]piperazine-1-carboxylate (120.0 mg, 0.18 mmol) in CH_2Cl_2 (10.0 mL) was added TFA (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (10.0 mL) was added $NH_3.H_2O$ (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 4 h. After the reaction was completed, 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 12% B to 42% B in 9 min; 254 nm) to afford 3-[3-(6-methoxy-1,3-benzothiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(piperazin-1-yl)ethyl]urea (22.4 mg, 28%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =452.3. ^1H NMR (400 MHz, CD_3OD): δ 9.09 (d, *J* = 1.6 Hz, 1H), 8.16 (d, *J* = 1.6 Hz, 1H), 8.02 - 8.00 (m, 1H), 7.74 (d, *J* = 3.6 Hz, 1H), 7.55 (d, *J* = 0.8 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 3.96 (s, 3H), 3.57 - 3.49 (m, 2H), 2.94 - 2.92 (m, 4H), 2.79 - 2.60 (m, 6H).

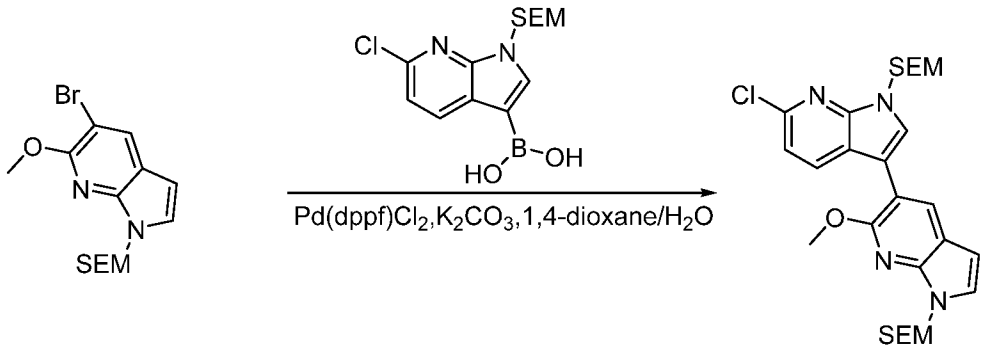
Example S141. Compound 141

Step 1: Synthesis of 5-bromo-6-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine:



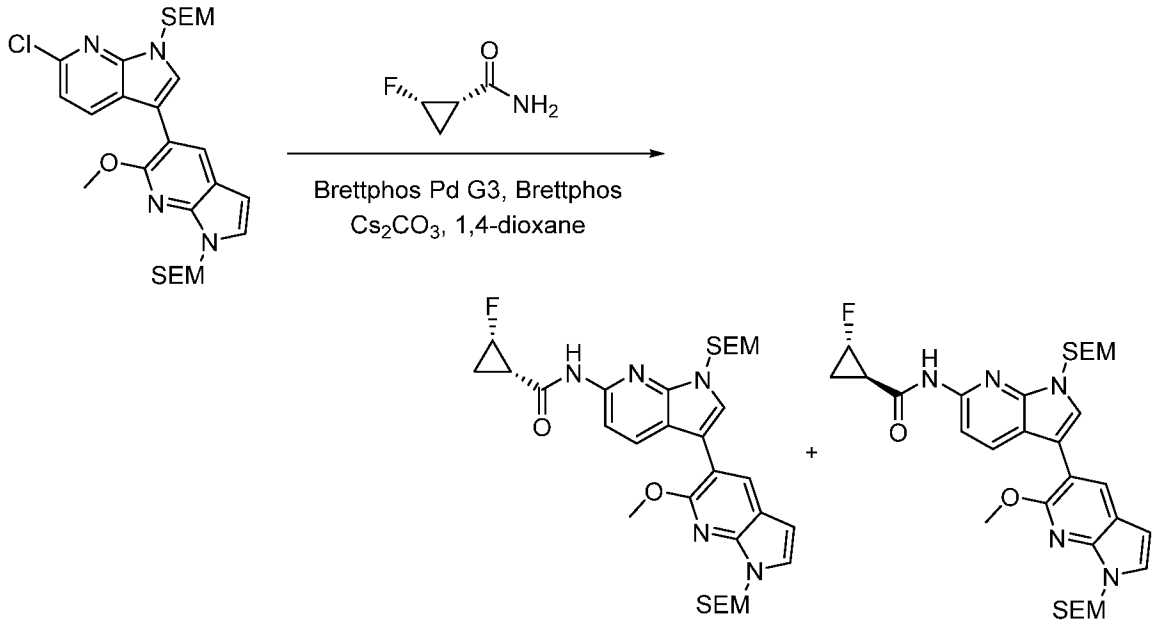
[0684] To a solution of 5-bromo-6-methoxy-1H-pyrrolo[2,3-b]pyridine (500.0 mg, 2.20 mmol) in THF (5.0 mL) was added NaH (158.5 mg, 60%) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h under N_2. Then SEM-Cl (440.5 mg, 2.64 mmol) was added to the mixture at 0 °C under N_2. The resulting mixture was stirred at 0 °C for another 1 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (93/7, v/v) to afford 5-bromo-6-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (620.0 mg, 80%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =357.1.

Step 2: Synthesis of 6-chloro-6'-methoxy-1,1'-bis((2-(trimethylsilyl)ethoxy)methyl)-1H,1'H-3,5'-bipyrrolo[2,3-b]pyridine:



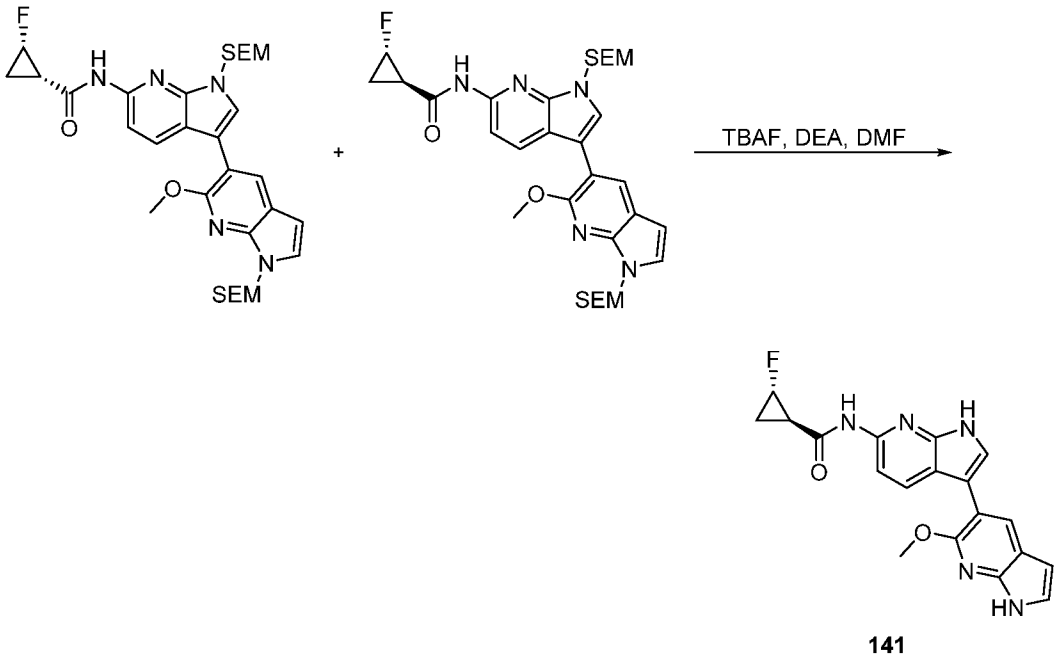
[0685] To a solution of 5-bromo-6-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (320.0 mg, 0.90 mmol) in 1,4-dioxane/H_2O (10.0/2.0 mL) was added (6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)boronic acid (366.1 mg, 0.90 mmol), K_2CO_3 (371.3 mg, 2.69 mmol) and $Pd(dppf)Cl_2$ (65.5 mg, 0.09 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (93/7, v/v) to afford 6-chloro-6'-methoxy-1,1'-bis ((2-(trimethylsilyl)ethoxy)methyl)-1H,1'H-3,5'-bipyrrolo[2,3-b]pyridine (210.0 mg, 41%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =559.2.

Step 3: Synthesis of the mixture of (1S,2S)-2-fluoro-N-(6'-methoxy-1,1'-bis((2-(trimethylsilyl)ethoxy)methyl)-1H,1'H-[3,5'-bipyrrolo[2,3-b]pyridin]-6-yl)cyclopropane-1-carboxamide and (1R,2S)-2-fluoro-N-(6'-methoxy-1,1'-bis((2-(trimethylsilyl)ethoxy)methyl)-1H,1'H-[3,5'-bipyrrolo[2,3-b]pyridin]-6-yl)cyclopropane-1-carboxamide:



[0686] To a solution of 6-chloro-6'-methoxy-1,1'-bis ((2-(trimethylsilyl)ethoxy)methyl)-1H,1'H-3,5'-bipyrrolo[2,3-b]pyridine (210.0 mg, 0.38 mmol) in 1,4-dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (193.6 mg, 1.87 mmol), Cs_2CO_3 (367.0 mg, 1.13 mmol), BrettPhos (40.3 mg, 0.08 mmol) and BrettPhos Pd G3 (34.0 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (83/17, v/v) to afford the mixture of (1S,2S)-2-fluoro-N-(6'-methoxy-1,1'-bis((2-(trimethylsilyl)ethoxy)methyl)-1H,1'H-[3,5'-bipyrrolo[2,3-b]pyridin]-6-yl)cyclopropane-1-carboxamide and (1R,2S)-2-fluoro-N-(6'-methoxy-1,1'-bis((2-(trimethylsilyl)ethoxy)methyl)-1H,1'H-[3,5'-bipyrrolo[2,3-b]pyridin]-6-yl)cyclopropane-1-carboxamide (110.0 mg, 49%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =626.3.

Step 4: Synthesis of (1R,2S)-2-fluoro-N-(6'-methoxy-1H,1'H-[3,5'-bipyrrolo[2,3-b]pyridin]-6-yl)cyclopropane-1-carboxamide (Compound 141):

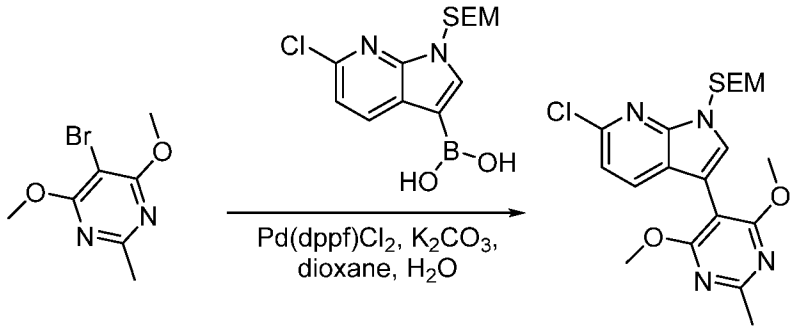


141

[0687] To a solution of the mixture of (1S,2S)-2-fluoro-N-(6'-methoxy-1,1'-bis((2-(trimethylsilyl)ethoxy)methyl)-1H,1'H-[3,5'-bipyrrolo[2,3-b]pyridin]-6-yl)cyclopropane-1-carboxamide and (1R,2S)-2-fluoro-N-(6'-methoxy-1,1'-bis((2-(trimethylsilyl)ethoxy)methyl)-1H,1'H-[3,5'-bipyrrolo[2,3-b]pyridin]-6-yl)cyclopropane-1-carboxamide (50.0 mg, 0.08 mmol) in DMF (2.0 mL) was added TBAF (62.7 mg, 0.24 mmol) and DEA (24.1 mg, 0.40 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) and then Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 40% B in 11 min; 254 nm) to afford (1R,2S)-2-fluoro-N-(6'-methoxy-1H,1'H-[3,5'-bipyrrolo[2,3-b]pyridin]-6-yl)cyclopropane-1-carboxamide (3.1 mg, 10%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =366.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.56 - 11.46 (m, 2H), 10.76 (s, 1H), 8.05 - 8.00 (m, 2H), 7.85 (d, J = 7.8 Hz, 1H), 7.58 (s, 1H), 7.22 - 7.20 (m, 1H), 6.40 (s, 1H), 5.01 - 4.79 (m, 1H), 3.94 (s, 3H), 2.60 - 2.51 (m, 1H), 1.57 - 1.45 (m, 1H), 1.31 - 1.20 (m, 1H).

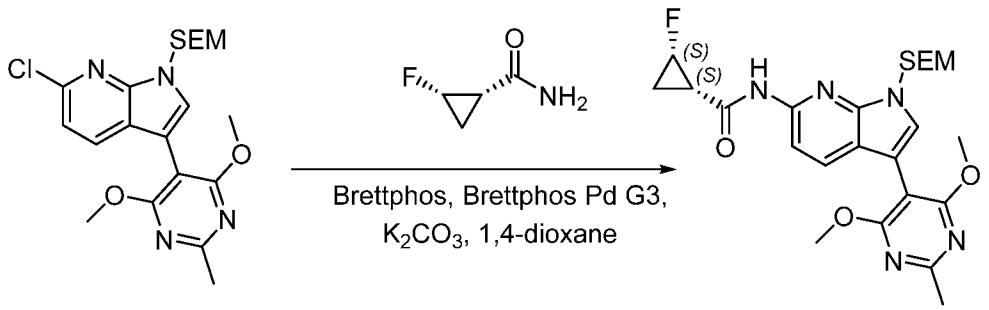
Example S142. Compound 142

Step 1: Synthesis of 6-chloro-3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine:



[0688] To a solution of 5-bromo-4,6-dimethoxy-2-methylpyrimidine (400.0 mg, 1.72 mmol) in dioxane/H_2O (16.0/4.0 mL) was added (6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)boronic acid (560.6 mg, 1.72 mmol), K_2CO_3 (711.6 mg, 5.15 mmol) and $Pd(dppf)Cl_2$ (125.6 mg, 0.17 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford 6-chloro-3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (270.0 mg, 20%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ = 435.2.

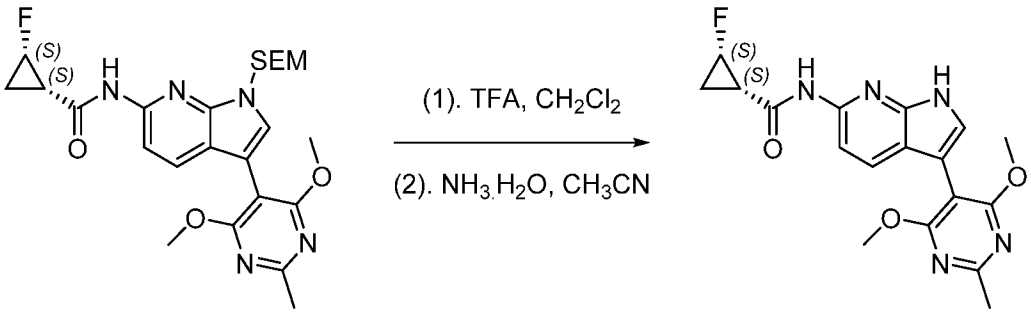
Step 2: Synthesis of (1S,2S)-N-(3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide:



[0689] To a solution of 6-chloro-3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (100.0 mg, 0.23 mmol) in 1,4-

dioxane (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (118.5 mg, 1.15 mmol), K_2CO_3 (95.3 mg, 0.69 mmol), Brettphos (24.7 mg, 0.05 mmol) and BrettPhos Pd G3 (20.8 mg, 0.02 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1S,2S)-N-(3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (60.0 mg, 52%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =502.2.

Step 3: Synthesis of (1S,2S)-N-(3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (Compound 142):



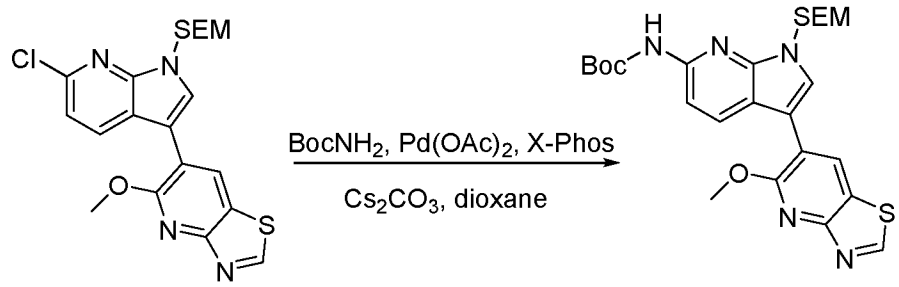
142

[0690] To a solution of (1S,2S)-N-(3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (50.0 mg, 0.10 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3 \cdot H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 36% to 46% in 8 min; 254 nm) to afford (1S,2S)-N-(3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (13.6 mg, 36%) as a white

solid. LCMS (ESI, m/z): $[M+H]^+$ =372.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.59 (s, 1H), 10.59 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 5.05 - 4.78 (m, 1H), 3.88 (s, 6H), 2.52 (s, 3H), 2.27 - 2.20 (m, 1H), 1.72 - 1.60 (m, 1H), 1.25 - 1.08 (m, 1H).

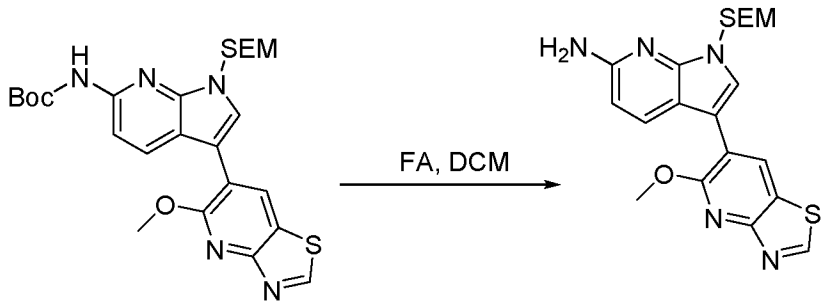
Example S143. Compound 143

Step 1: Synthesis of tert-butyl N-(3-[5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)carbamate:



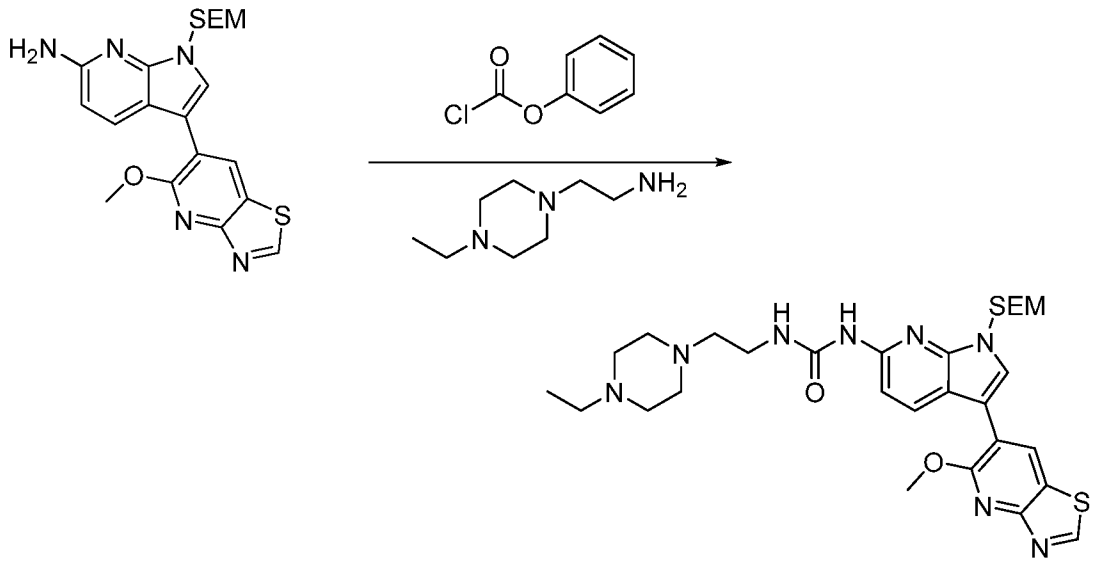
[0691] To a mixture of 6-chloro-3-[5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (300.0 mg, 0.67 mmol), $BocNH_2$ (235.8 mg, 2.01 mmol) and Cs_2CO_3 (655.9 mg, 2.01 mmol) in dioxane (5.0 mL) were added $Pd(OAc)_2$ (15.1 mg, 0.07 mmol) and X-Phos (63.9 mg, 0.14 mmol). The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford tert-butyl N-(3-[5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)carbamate (330.0 mg, 93%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =528.2.

Step 2: Synthesis of 3-(5-methoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine:



[0692] A mixture of tert-butyl N-(3-[5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)carbamate (300.0 mg, 0.57 mmol) and formic acid (10.0 mL) in DCM (20.0 mL) was stirred at room temperature for 16 h. After the reaction was completed, the pH value of the mixture was adjusted to 7 with $NaHCO_3$ solution. The resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 3-(5-methoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (200.0 mg, crude) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =428.1.

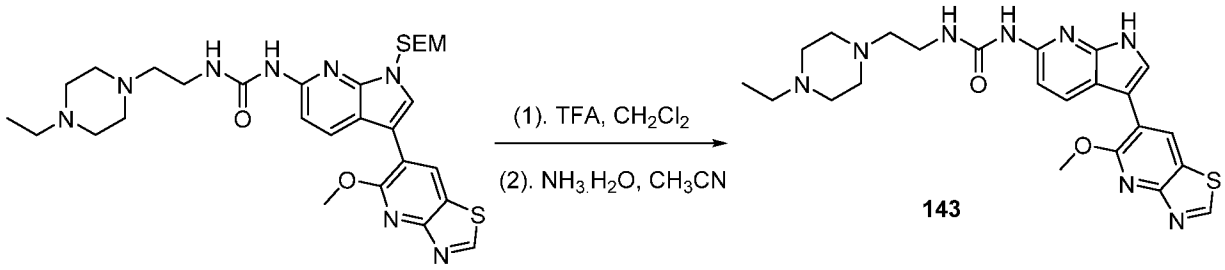
Step 3: Synthesis of 1-(2-(4-ethylpiperazin-1-yl)ethyl)-3-(3-(5-methoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)urea:



[0693] To a mixture of 3-[5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (100.0 mg, 0.23 mmol) and pyridine (74.0 mg, 0.94 mmol) in DCM (2.0 mL) was added phenyl chloroformate (73.2 mg, 0.46 mmol). The resulting mixture was stirred at room temperature for 3 h. The mixture was

evaporated in vacuo. To the above residue was added pyridine (4.0 mL) and 2-(4-ethylpiperazin-1-yl)ethanamine (183.9 mg, 1.17 mmol). The resulting mixture was stirred at 60 °C for another 16 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/5, v/v) to afford 1-(2-(4-ethylpiperazin-1-yl)ethyl)-3-(3-(5-methoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)urea (35.0 mg, 25%) as a yellow solid.. LCMS (ESI, m/z): $[M+H]^+$ =611.3.

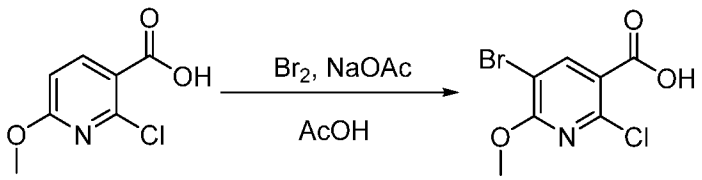
[0694] Step 4: Synthesis of 1-(2-(4-ethylpiperazin-1-yl)ethyl)-3-(3-(5-methoxythiazolo[4,5-b]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)urea (Compound 143):



[0695] To a solution of 1-(2-(4-ethylpiperazin-1-yl)ethyl)-3-(3-(5-methoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)urea (35.0 mg, 0.06 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue was added CH_3CN (2.0 mL) and $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A:Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 35% B in 7 min; 254 nm) to afford 1-(2-(4-ethylpiperazin-1-yl)ethyl)-3-(3-(5-methoxythiazolo[4,5-b]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)urea (3.8 mg, 13%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =481.4. ^1H NMR (400 MHz, CD_3OD): δ 9.38 (s, 1H), 8.61 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 6.83 (d, J = 8.4 Hz, 1H), 4.14 (s, 3H), 3.58 - 3.55 (m, 2H), 2.94 - 2.84 (m, 4H), 2.82 - 2.74 (m, 8H), 1.25 - 1.21 (m, 3H).

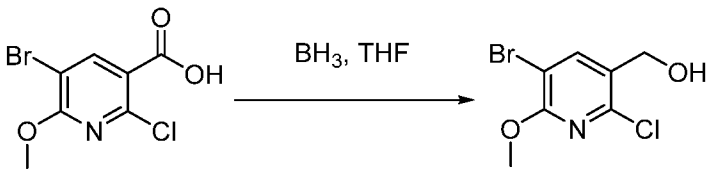
Example S144. Compound 144

Step 1: Synthesis of 5-bromo-2-chloro-6-methoxypyridine-3-carboxylic acid:



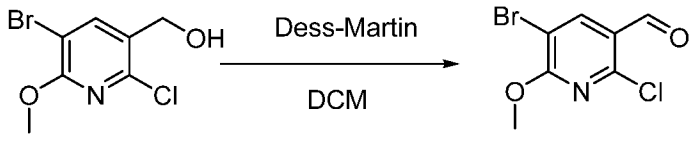
[0696] To a mixture of 2-chloro-6-methoxypyridine-3-carboxylic acid (5.0 g, 26.6 mmol) and NaOAc (4.3 g, 53.27 mmol) in AcOH (50.0 mL) was added dropwises Br_2 (17.04 g, 106.62 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the reaction was quenched with water at room temperature and then filtered. The solid was washed with water and petroleum ether to afford 5-bromo-2-chloro-6-methoxypyridine-3-carboxylic acid (2.0 g, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =265.9

Step 2: Synthesis of (5-bromo-2-chloro-6-methoxypyridin-3-yl)methanol:



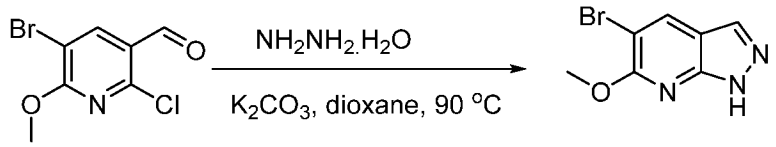
[0697] The solution of 5-bromo-2-chloro-6-methoxypyridine-3-carboxylic acid (2.0 g, 7.50 mmol) in BH_3. THF (30.0 mL, 1 mol/L) was stirred at room temperature for 2 h. After the reaction was completed, the reaction mixture was quenched with MeOH and then concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford (5-bromo-2-chloro-6-methoxypyridin-3-yl)methanol (1.4 g, 73%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =251.9.

[0698] Step 3: Synthesis of 5-bromo-2-chloro-6-methoxypyridine-3-carbaldehyde:



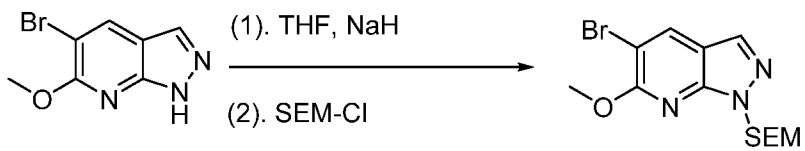
[0699] To a solution of (5-bromo-2-chloro-6-methoxypyridin-3-yl)methanol (1.4 g, 5.54 mmol) in DCM (20.0 mL) was added Dess-Martin reagent (2.3 g, 5.54 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 5-bromo-2-chloro-6-methoxypyridine-3-carbaldehyde (1.2 g, 86 %) as a white solid. LCMS (ESI, m/z): $[M+H]^+$= 249.9.

Step 4: Synthesis of 5-bromo-6-methoxy-1H-pyrazolo[3,4-b]pyridine:



[0700] To a mixture of 5-bromo-2-chloro-6-methoxypyridine-3-carbaldehyde (400.0 mg, 1.59 mmol) and K_2CO_3 (882.8 mg, 6.38 mmol) in dioxane (5.0 mL) was added $NH_2NH_2.H_2O$ (2.3 g, 80%) at room temperature. The resulting mixture was stirred at 90 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 5-bromo-6-methoxy-1H-pyrazolo[3,4-b]pyridine (130.0 mg, 35%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$=228.0.

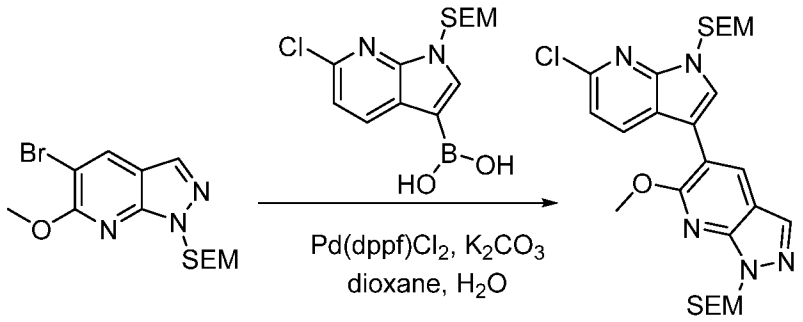
Step 5: Synthesis of 5-bromo-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine:



[0701] To a solution of 5-bromo-6-methoxy-1H-pyrazolo[3,4-b]pyridine (130.0 mg, 0.57 mmol) in THF (2.0 mL) was added NaH (27.3 mg, 60%) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h under N_2. Then SEM-Cl (142.5 mg, 0.85 mmol) was added

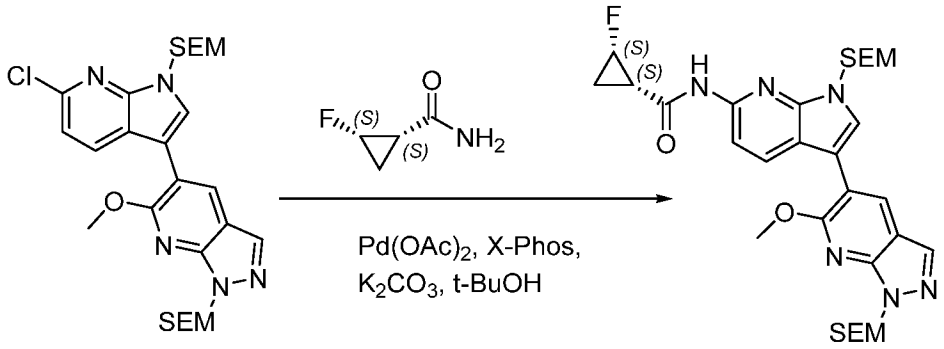
to the mixture at 0 °C. The resulting mixture was stirred at 0 °C for another 2 h. After the reaction was completed, the reaction mixture was quenched with saturated NH_4Cl solution and then concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 5-bromo-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (200.0 mg, 97%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$=358.1.

Step 6: Synthesis of 6-chloro-3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



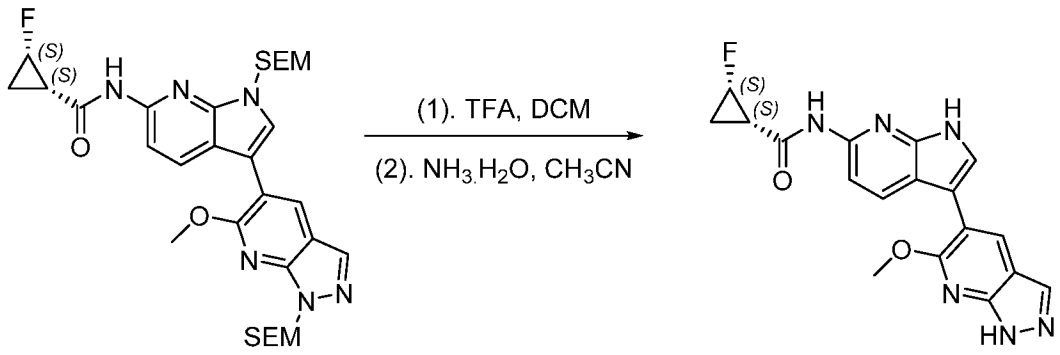
[0702] To a solution of 5-bromo-6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridine (200.0 mg, 0.55 mmol) in dioxane/H_2O (5.0/0.5 mL) were added 6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-ylboronic acid (182.3 mg, 0.55 mmol), $Pd(dppf)Cl_2$ (40.8 mg, 0.05 mmol) and K_2CO_3 (231.4 mg, 1.67 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford 6-chloro-3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (150.0 mg, 47%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$=560.2.

Step 7: Synthesis of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide:



[0703] To a solution of 6-chloro-3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (110.0 mg, 0.19 mmol) in BuOH (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (101.2 mg, 0.98 mmol), $Pd(OAc)_2$ (4.4 mg, 0.02 mmol), K_2CO_3 (81.4 mg, 0.58 mmol) and Xphos (18.7 mg, 0.03 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford (1S,2S)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (65.0 mg, 52%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$=627.3

Step 8: Synthesis of (1S,2S)-2-fluoro-N-(3-[6-methoxy-1H-pyrazolo[3,4-b]pyridin-5-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 144):



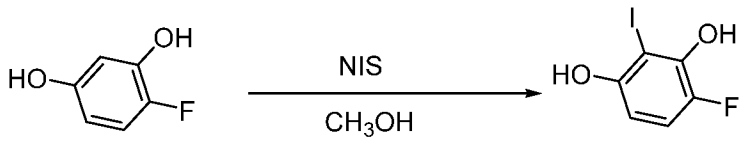
144

[0704] To a solution of (1S,2S)-2-fluoro-N-[3-(6-methoxy-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazolo[3,4-b]pyridin-5-yl)-1-[[2-

(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (110.0 mg, 0.17 mmol) in DCM (3.0 mL) was added TFA (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 30x250 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 24% B to 42% B in 9 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-[6-methoxy-1H-pyrazolo[3,4-b]pyridin-5-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl) cyclopropane-1-carboxamide (6.0 mg, 9%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 367.1. ^1H NMR (300 MHz, DMSO-d_6): δ 13.36 (s, 1H), 11.63 (s, 1H), 10.65 (s, 1H), 8.26 (s, 1H), 8.08 - 7.90 (m, 3H), 7.63 (d, J = 2.4 Hz, 1H), 5.07-4.80 (m, 1H), 4.00 (s, 3H), 2.44 - 2.31 (m, 1H), 1.73 - 1.60 (m, 1H), 1.24 - 1.12 (m, 1H).

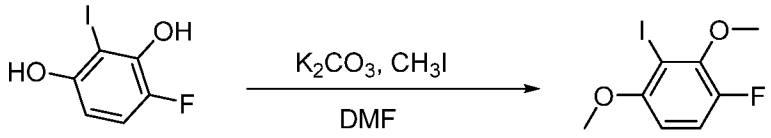
Example S145. Compound 145

Step 1: Synthesis of 4-fluoro-2-iodobenzene-1,3-diol:



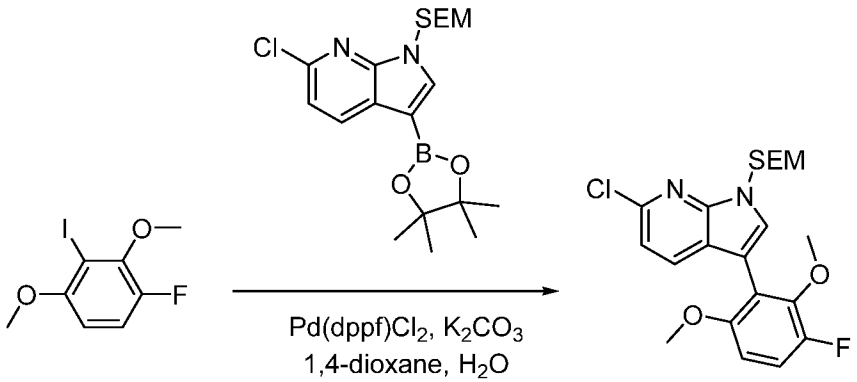
[0705] To a solution of 4-fluorobenzene-1,3-diol (10.0 g, 78.06 mmol) in CH_3OH (100.0 mL) was added NIS (8.8 g, 39.03 mmol) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 16. After the reaction was completed, the reaction was quenched with saturated $Na_2S_2O_3$ solution at 0 °C. The resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (93/7, v/v) to afford 4-fluoro-2-iodobenzene-1,3-diol (9.7 g, 49%) as a white solid.

Step 2: Synthesis of 1-fluoro-3-iodo-2,4-dimethoxybenzene:



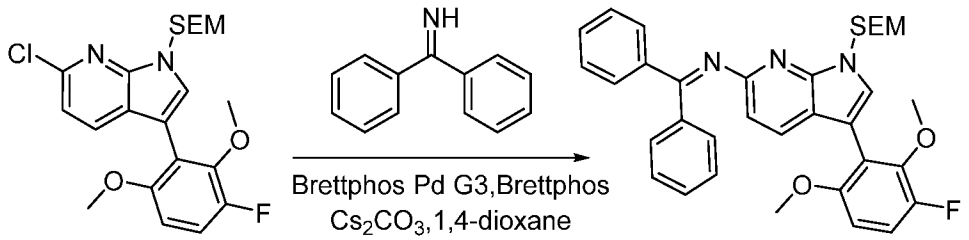
[0706] To a solution of 4-fluoro-2-iodobenzene-1,3-diol (9.7 g, 38.19 mmol) in DMF (20.0 mL) was added K_2CO_3 (15.8 g, 114.32 mmol) and CH_3I (11.9 g, 83.63 mmol) at room temperature under N_2. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (100/0, v/v) to afford 1-fluoro-3-iodo-2,4-dimethoxybenzene (5.8 g, 54%) as a white solid.

Step 3: Synthesis of 6-chloro-3-(3-fluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



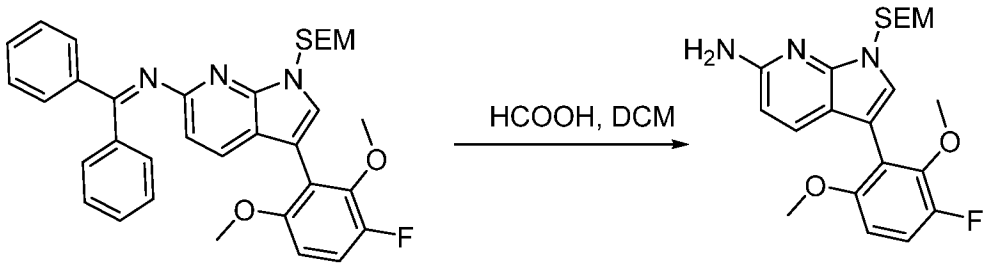
[0707] To a solution of 1-fluoro-3-iodo-2,4-dimethoxybenzene (2.0 g, 7.09 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (3.5 g, 8.51 mmol), K_2CO_3 (2.9 g, 21.27 mmol) and $Pd(dppf)Cl_2$ (518.8 mg, 0.71 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (94/6, v/v) to afford 6-chloro-3-(3-fluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (2.3 g, 74%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =437.1.

Step 4: Synthesis of N-(3-(3-fluoro-2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-1,1-diphenylmethanimine:



[0708] To a solution of 6-chloro-3-(3-fluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (500.0 mg, 1.14 mmol) in 1,4-dioxane (5.0 mL) was added diphenylmethanimine (622.1 mg, 3.43 mmol), Cs_2CO_3 (1.1 g, 3.43 mmol), BrettPhos (122.8 mg, 0.23 mmol) and BrettPhos Pd G3 (103.7 mg, 0.11 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (56/44, v/v) to afford N-(3-(3-fluoro-2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-1,1-diphenylmethanimine (200.0 mg, 30%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =582.3.

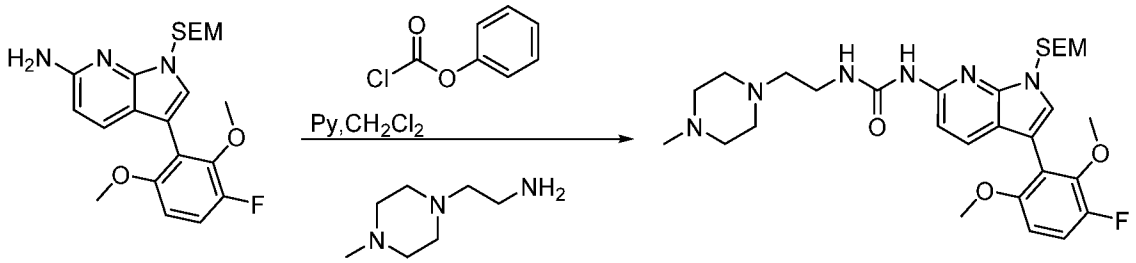
Step 5: Synthesis of 3-(3-fluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine:



[0709] To a solution of N-[3-(3-fluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1,1-diphenylmethanimine (200.0 mg, 0.34 mmol) in DCM (5.0 mL) was added HCOOH (0.5 ml) at room temperature under N_2. The resulting mixture was stirred at room temperature for 2 h. After the reaction was

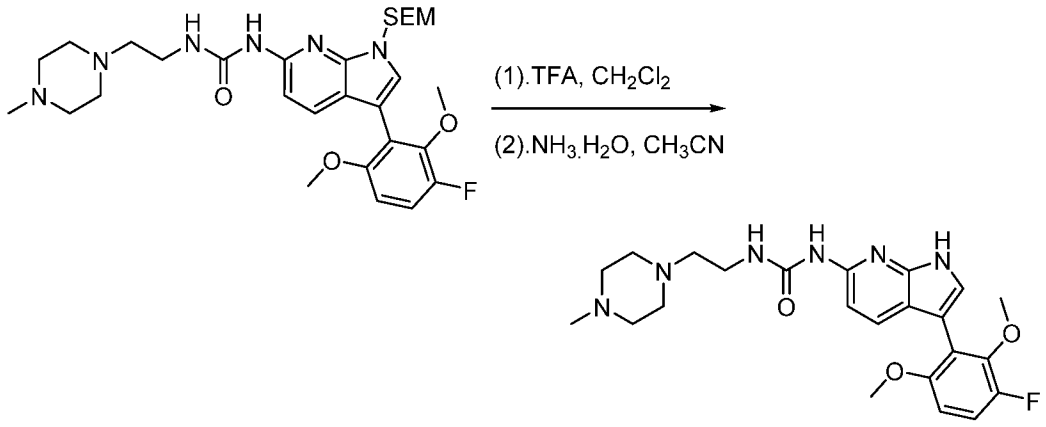
completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (47/53, v/v) to afford 3-(3-fluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (100.0 mg, 69%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =418.2.

Step 6: Synthesis of 3-[3-(3-fluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea:



[0710] To a solution of 3-(3-fluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (100.0 mg, 0.24 mmol) in CH_2Cl_2 (5.0 mL) was added pyridine (75.7 mg, 0.96 mmol) and phenyl chloroformate (37.5 mg, 0.24 mmol) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. The resulting mixture was concentrated under reduced pressure. To the above mixture in pyridine (5.0 mL) was added 2-(4-methylpiperazin-1-yl)ethanamine (137.4 mg, 0.96 mmol) at 0 °C under N_2. The resulting mixture was stirred at 60 °C for another 1 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (88/12, v/v) to afford 3-[3-(3-fluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (100.0 mg, 71%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =587.3.

Step 7: Synthesis of 3-[3-(3-fluoro-2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (Compound 145):

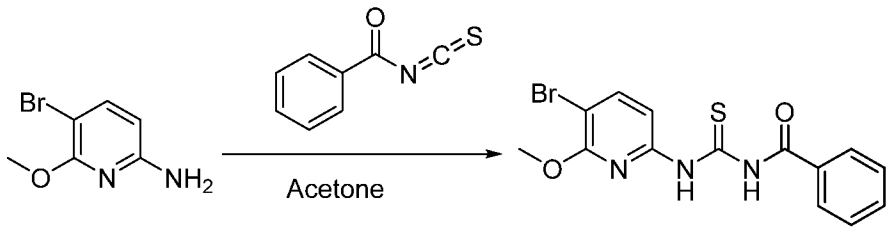


145

[0711] To a solution of 3-[3-(3-fluoro-2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (140.0 mg, 0.24 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3 \cdot H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Fluoro Phenyl, 30×250 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH-----Preparative; Flow rate: 25 mL/min; Gradient: 63% B to 87% B in 7 min; 254 nm) to afford 3-[3-(3-fluoro-2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (27.4 mg, 25%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =457.3. ^1H NMR (400 MHz, $CDCl_3$): δ 10.18 (s, 1H), 9.78 (s, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.28 (s, 1H), 7.08 - 7.03 (m, 1H), 6.69 - 6.66 (m, 1H), 6.43 (d, J = 8.4 Hz, 1H), 3.79 (s, 3H), 3.64 - 3.61 (m, 5H), 2.90 - 2.78 (m, 6H), 2.64 - 2.61 (m, 4H), 2.41 (s, 3H).

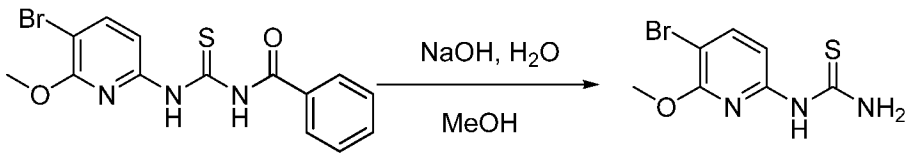
Example S146. Compound 146

Step 1: Synthesis of 1-benzoyl-3-(5-bromo-6-methoxypyridin-2-yl)thiourea:



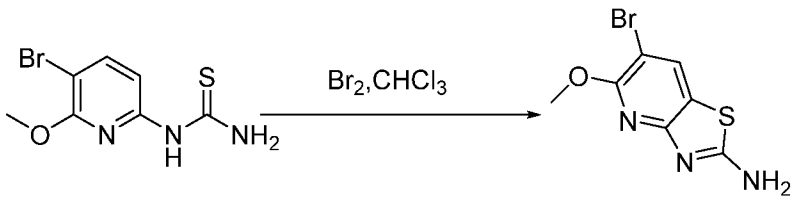
[0712] To a solution of 5-bromo-6-methoxypyridin-2-amine (3.0 g, 14.77 mmol) in acetone (40.0 mL) was added benzoyl isothiocyanate (2.9 g, 17.73 mmol) at room temperature under N_2. The resulting mixture was stirred at 60 °C for 30 min. After the reaction was completed, the resulting mixture was concentrated under reduced pressure to afford 1-benzoyl-3-(5-bromo-6-methoxypyridin-2-yl)thiourea (5.7 g, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =366.0.

Step 2: Synthesis of 5-bromo-6-methoxypyridin-2-ylthiourea:



[0713] To a solution of 1-benzoyl-3-(5-bromo-6-methoxypyridin-2-yl)thiourea (5.2 g, crude) in MeOH/H_2O (20.0/10.0 mL) was added NaOH (1.1 g, 28.54 mmol) at room temperature under N_2. The resulting mixture was stirred at 60 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 5-bromo-6-methoxypyridin-2-ylthiourea (3.5 g, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =262.0.

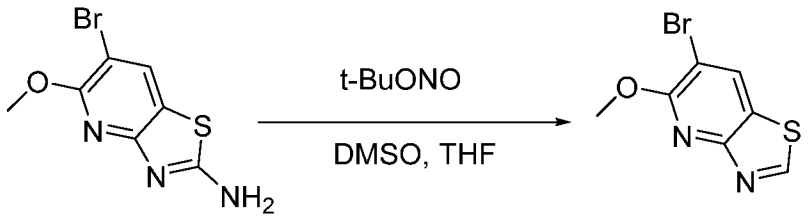
Step 3: Synthesis of 6-bromo-5-methoxy-[1,3]thiazolo[4,5-b]pyridin-2-amine:



[0714] To a solution of 5-bromo-6-methoxypyridin-2-ylthiourea (1.5 g, crude) in $CHCl_3$ (15.0 mL) was added Br_2 (0.9 g, 5.72 mmol) at 0 °C under N_2. The resulting mixture was

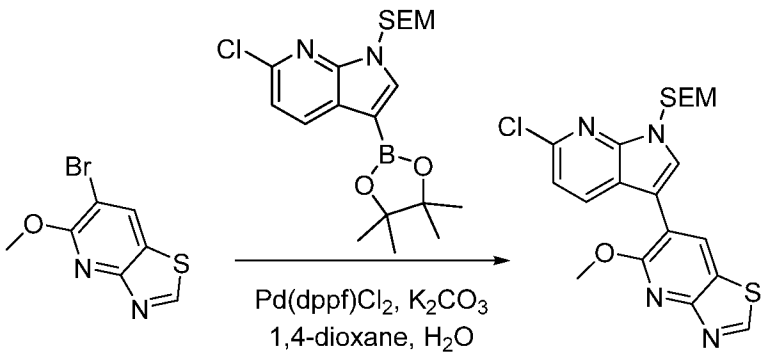
stirred at 60 °C for 16 h. After the reaction was completed, the reaction was quenched with sat. NH_4Cl (aq.) and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (88/12, v/v) to afford 6-bromo-5-methoxy-[1,3]thiazolo[4,5-b]pyridin-2-amine (690.0 mg, 46%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =259.9.

Step 4: Synthesis of 6-bromo-5-methoxy-[1,3]thiazolo[4,5-b]pyridine:



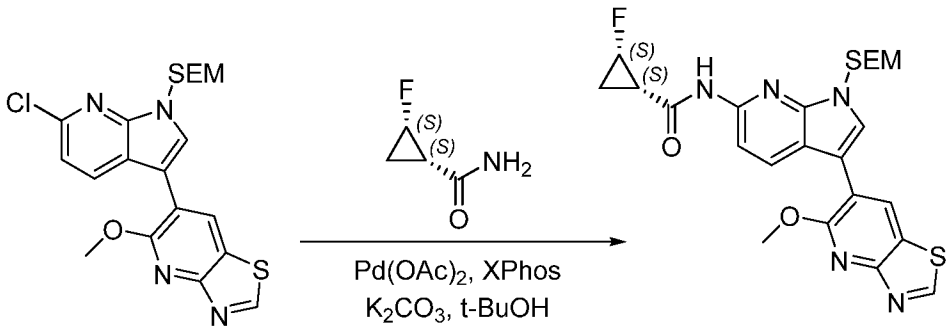
[0715] To a solution of 6-bromo-5-methoxy-[1,3]thiazolo[4,5-b]pyridin-2-amine (690.0 mg, 2.65 mmol) in THF (10.0 mL) was added DMSO (18.6 mg, 0.24 mmol) and t-BuONO (410.3 mg, 3.98 mmol) at room temperature under N_2. The resulting mixture was stirred at 30 °C for 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (92/8, v/v) to afford 6-bromo-5-methoxy-[1,3]thiazolo[4,5-b]pyridine (120.0 mg, 18%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =244.9.

Step 5: Synthesis of 6-chloro-3-[5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine:



[0716] To a solution of 6-bromo-5-methoxy-[1,3]thiazolo[4,5-b]pyridine (120.0 mg, 0.49 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (240.2 mg, 0.58 mmol), K_2CO_3 (203.0 mg, 1.46 mmol) and $Pd(dppf)Cl_2$ (79.5 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (65/35, v/v) to afford 6-chloro-3-[5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (130.0 mg, 32%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =447.1.

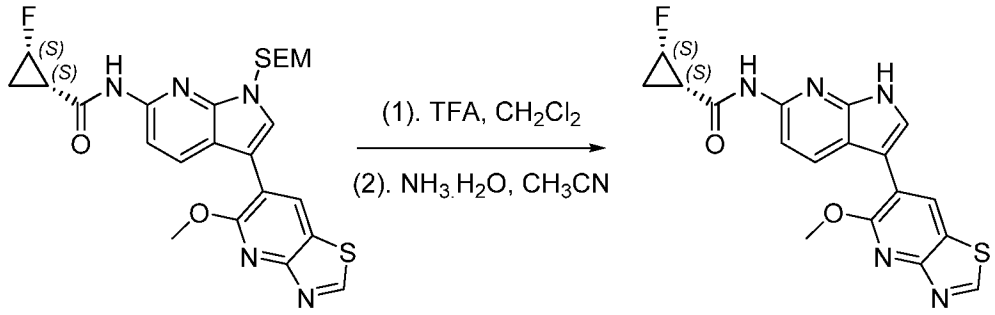
Step 6: Synthesis of (1S,2S)-2-fluoro-N-(3-[5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0717] To a solution of 6-chloro-3-[5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (100.0 mg, 0.22 mmol) in t-BuOH (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (115.3 mg, 1.12 mmol), XPhos (21.3 mg, 0.04 mmol), K_2CO_3 (92.7 mg, 0.61 mmol) and $Pd(OAc)_2$ (5.0 mg, 0.02 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (65/35, v/v) to afford (1S,2S)-2-fluoro-N-(3-[5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl]-1-[[2-

(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (47.0 mg, 41%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =514.2.

Step 7: Synthesis of (1S,2S)-2-fluoro-N-(3-[5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 146):



146

[0718] To a solution of (1S,2S)-2-fluoro-N-(3-[5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (47.0 mg, 0.09 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (3.0 mL) was added $NH_3 \cdot H_2O$ (3 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, 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, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 47% B in 10 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-[5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (5.9 mg, 16%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =384.1. ^1H NMR (400 MHz, DMSO-d_6): δ 11.80 (s, 1H), 10.68 (s, 1H), 9.51 (s, 1H), 8.81 (s, 1H), 8.25 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 1.6 Hz, 1H), 5.04 - 4.83 (m, 1H), 4.06 (s, 3H), 2.26 - 2.23 (m, 1H), 1.72 - 1.63 (m, 1H), 1.24 - 1.12 (m, 1H).

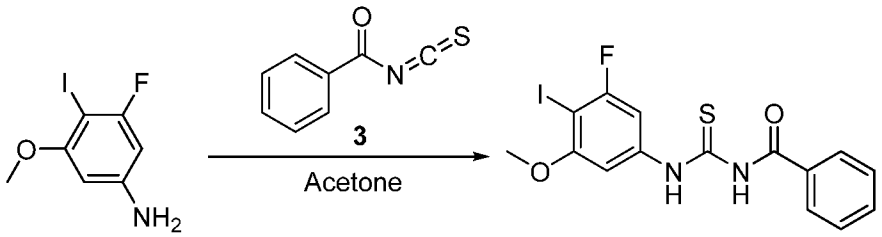
Example S147. Compound 147

Step 1: Synthesis of 3-fluoro-4-iodo-5-methoxyaniline:



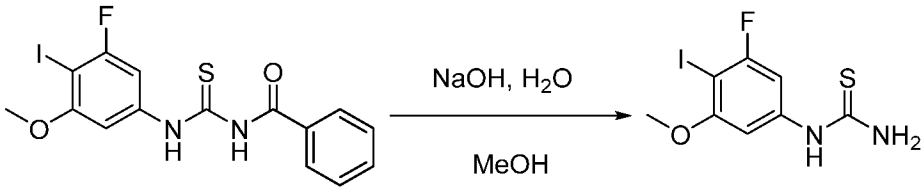
[0719] To a solution of 3-fluoro-5-methoxyaniline (2.0 g, 14.17 mmol) in DMF (20.0 mL) was added NIS (3.2 g, 14.17 mmol) at room temperature. The resulting mixture was stirred at room temperature for 0.5 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 3-fluoro-4-iodo-5-methoxyaniline (2.5 g, 66%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =268.0.

Step 2: Synthesis of N-((3-fluoro-4-iodo-5-methoxyphenyl)carbamothioyl)benzamide:



[0720] To a solution of 3-fluoro-4-iodo-5-methoxyaniline (2.5 g, 9.36 mmol) in acetone (50.0 mL) was added benzoyl isothiocyanate (1.5 g, 9.36 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 30 min. After the reaction was completed, the reaction mixture was cooled to room temperature and filtered. The solid was collected and dried to afford N-((3-fluoro-4-iodo-5-methoxyphenyl)carbamothioyl)benzamide (3.8 g, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =431.0.

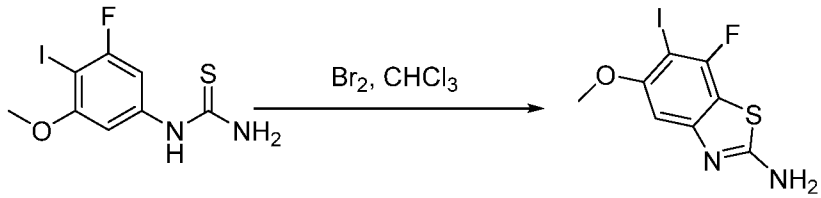
Step 3: Synthesis of 1-(3-fluoro-4-iodo-5-methoxyphenyl)thiourea:



[0721] To a solution of N-((3-fluoro-4-iodo-5-methoxyphenyl)carbamothioyl)benzamide (3.8 g, 8.83 mmol) in MeOH/H_2O (30.0/30.0 mL) was added NaOH (0.4 g, 9.7 mmol) at

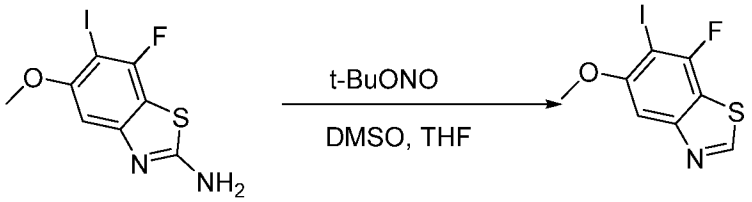
room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 1-(3-fluoro-4-iodo-5-methoxyphenyl)thiourea (1.9 g, 65%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =326.9.

Step 4: Synthesis of 7-fluoro-6-iodo-5-methoxybenzo[d]thiazol-2-amine:



[0722] To a solution of 1-(3-fluoro-4-iodo-5-methoxyphenyl)thiourea (1.9 g, 5.83 mmol) in $CHCl_3$ (30.0 mL) was added dropwise Br_2 (1.0 g, 6.41 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was quenched with aq. $NaHSO_3$ and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 7-fluoro-6-iodo-5-methoxybenzo[d]thiazol-2-amine (1.3 g, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =324.9.

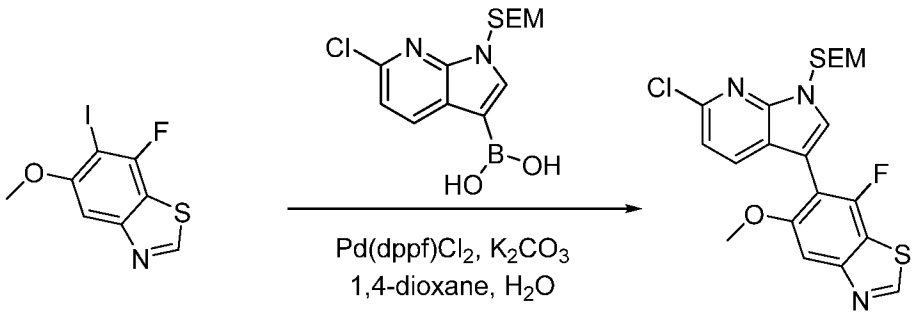
Step 5: Synthesis of 7-fluoro-6-iodo-5-methoxybenzo[d]thiazole:



[0723] To a solution of 7-fluoro-6-iodo-5-methoxybenzo[d]thiazol-2-amine (1.3 g, 4.01 mmol) in THF (30.0 mL) was added t-BuONO (0.6 g, 6.02 mmol) and DMSO (25.1 mg, 0.32 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 7-

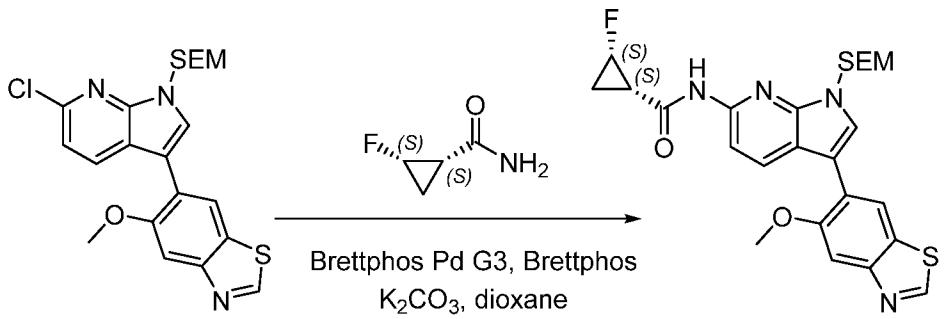
fluoro-6-iodo-5-methoxybenzo[d]thiazole (1.2 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =309.9.

Step 6: Synthesis of 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-fluoro-5-methoxybenzo[d]thiazole:



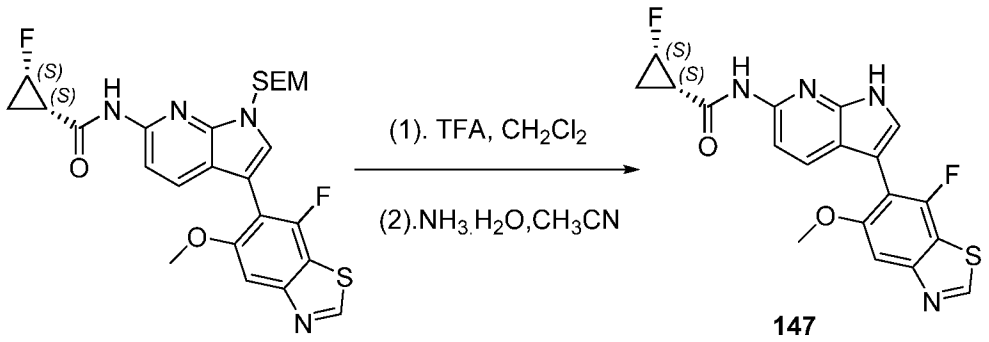
[0724] To a solution of 7-fluoro-6-iodo-5-methoxybenzo[d]thiazole (300.0 mg, 0.97 mmol) in 1,4-dioxane/H_2O (16.0/4.0 mL) was added (6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)boronic acid (317.0 mg, 0.97 mmol), K_2CO_3 (402.4 mg, 2.91 mmol) and $Pd(dppf)Cl_2$ (71.0 mg, 0.10 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-fluoro-5-methoxybenzo[d]thiazole (270.0 mg, 59%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =464.1.

Step 7: Synthesis of (1S,2S)-2-fluoro-N-(3-(7-fluoro-5-methoxybenzo[d]thiazol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide:



[0725] To a solution of 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-7-fluoro-5-methoxybenzo[d]thiazole (210.0 mg, 0.45 mmol) in dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (233.3 mg, 2.27 mmol), K_2CO_3 (187.6 mg, 1.36 mmol), Brettphos (48.6 mg, 0.09 mmol) and BrettPhos Pd G3 (41.0 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h under N_2. After the reaction was completed, the mixture was evaporated in vacuo. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1S,2S)-2-fluoro-N-(3-(7-fluoro-5-methoxybenzo[d]thiazol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (160.0 mg, 66%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =531.2.

Step 8: Synthesis of (1S,2S)-2-fluoro-N-(3-(7-fluoro-5-methoxybenzo[d]thiazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 147):



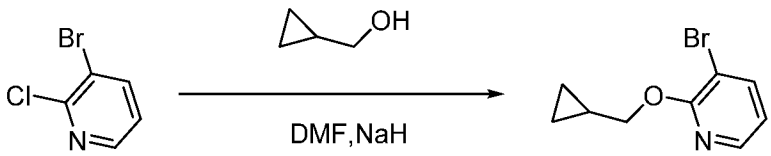
147

[0726] To a solution of (1S,2S)-2-fluoro-N-(3-(7-fluoro-5-methoxybenzo[d]thiazol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (140.0 mg, 0.26 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (5.0 mL) was added $NH_3 \cdot H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% to 53% in 10 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-(7-fluoro-5-methoxybenzo[d]thiazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide

(33.5 mg, 31%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =401.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.80 (s, 1H), 10.68 (s, 1H), 9.45 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.77 - 7.70 (m, 2H), 7.58 (s, 1H), 5.05 - 4.82 (m, 1H), 3.90 (s, 3H), 2.28 - 2.19 (m, 1H), 1.70 - 1.62 (m, 1H), 1.22 - 1.11 (m, 1H).

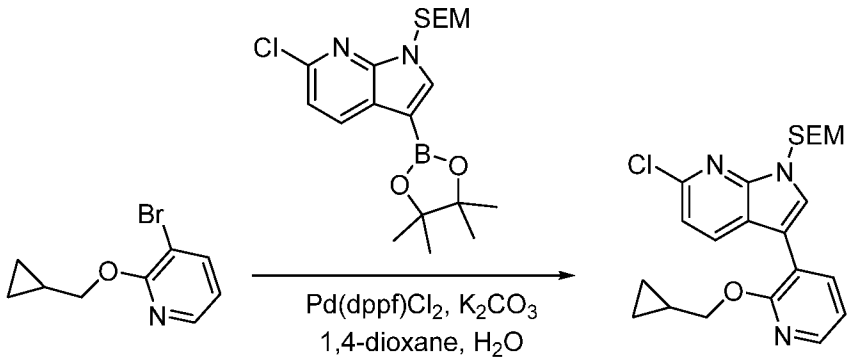
Example S148. Compound 148 and Compound 149

Step 1: Synthesis of 3-bromo-2-(cyclopropylmethoxy)pyridine:



[0727] To a solution of cyclopropylmethanol (2.1 g, 28.58 mmol) in DMF (50.0 mL) was added NaH (1.9 g, 60%) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h under N_2. Then 3-bromo-2-chloropyridine (5.0 g, 25.98 mmol) was added to the mixture at 0 °C under N_2. The resulting mixture was stirred at 70 °C for another 6 h. After the reaction was completed, the reaction mixture was quenched with H_2O at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 3-bromo-2-(cyclopropylmethoxy)pyridine (3.0 g, 50%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =228.0.

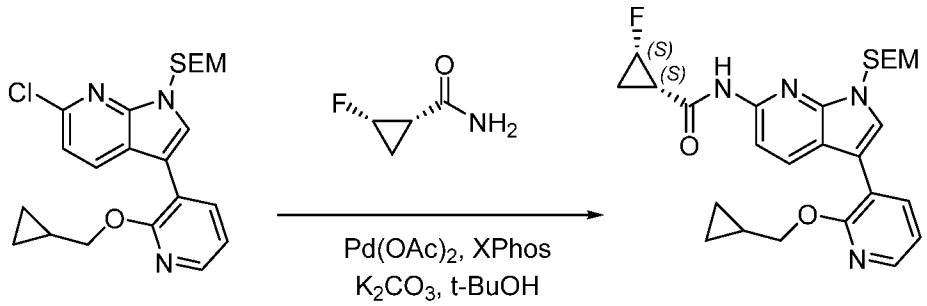
[0728] Step 2: Synthesis of 6-chloro-3-(2-(cyclopropylmethoxy)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine:



[0729] To a solution of 3-bromo-2-(cyclopropylmethoxy)pyridine (500.0 mg, 2.19 mmol) in 1,4-dioxane/H_2O (16.0/4.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-

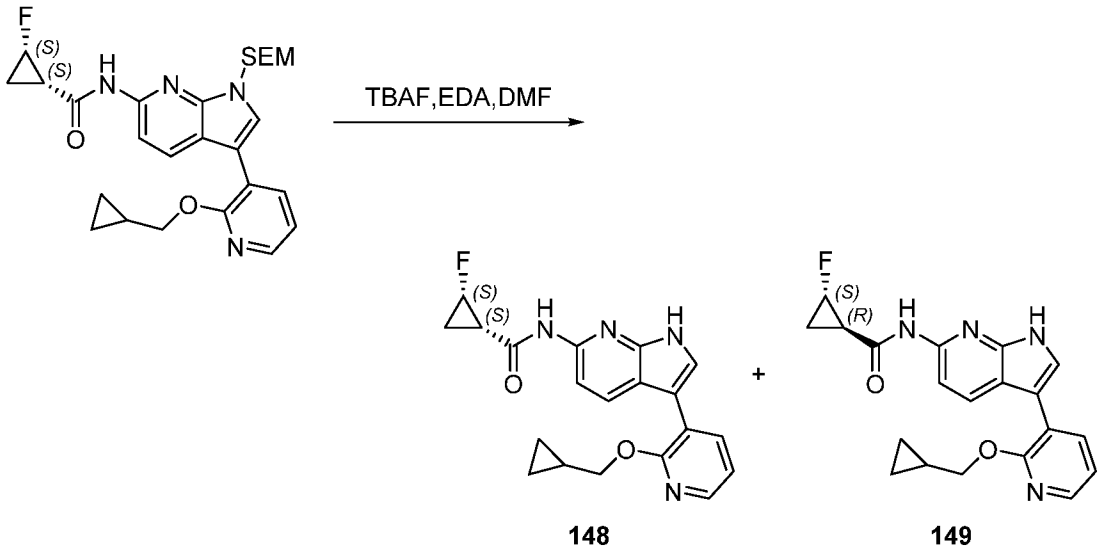
dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (896.2 mg, 2.19 mmol), K_2CO_3 (908.9 mg, 6.58 mmol) and $Pd(dppf)Cl_2$ (160.4 mg, 0.22 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 6-chloro-3-(2-(cyclopropylmethoxy)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (500.0 mg, 53%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =430.2.

Step 3: Synthesis of (1S,2S)-N-(3-(2-(cyclopropylmethoxy)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide:



[0730] To a solution of 6-chloro-3-(2-(cyclopropylmethoxy)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (400.0 mg, 0.93 mmol) in t-BuOH (20.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (479.5 mg, 4.65 mmol), K_2CO_3 (385.7 mg, 2.79 mmol), $Pd(OAc)_2$ (20.9 mg, 0.09 mmol) and XPhos (88.7 mg, 0.19 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford (1S,2S)-N-(3-(2-(cyclopropylmethoxy)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (160.0 mg, 34%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =497.2.

Step 4: Synthesis of (1S,2S)-N-(3-(2-(cyclopropylmethoxy)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide and **(1R,2S)-N-(3-(2-(cyclopropylmethoxy)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (Compound 148 and Compound 149):**



148 149

[0731] To a solution of (1S,2S)-N-(3-(2-(cyclopropylmethoxy)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (150.0 mg, 0.18 mmol) in DMF (5.0 mL) was added ethylenediamine (90.8 mg, 1.51 mmol) and TBAF (236.9 mg, 0.91 mmol) at room temperature. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (10/1, v/v) and then purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 44% to 54% in 8 min; 254 nm) to afford N-(3-(2-(cyclopropylmethoxy)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide Enantiomer 1 (5.2 mg, 4%, retention time: 7.38 minutes) as a white solid and N-(3-(2-(cyclopropylmethoxy)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide Enantiomer 2 (10.2 mg, 9%, retention time, 7.79 minutes) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be

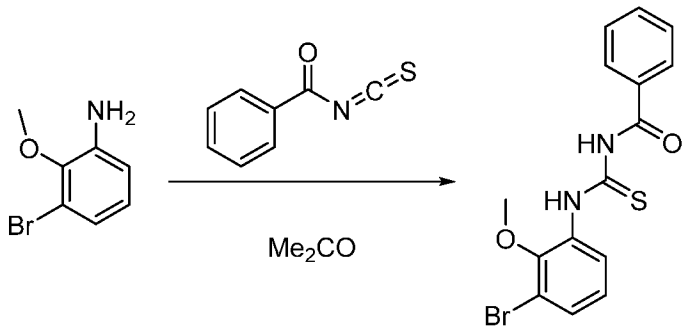
obtained from chiral separation of the enantiomeric mixture as described above are shown as Compounds 148 and 149 in Table 1.

[0732] N-(3-(2-(cyclopropylmethoxy)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide Enantiomer 1: LCMS (ESI, m/z): $[M+H]^+$ =367.2. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.73 (s, 1H), 10.69 (s, 1H), 8.21 (d, J = 8.7 Hz, 1H), 8.05 - 7.92 (m, 3H), 7.80 (s, 1H), 7.08 - 7.04 (m, 1H), 5.04 - 4.82 (m, 1H), 4.22 (d, J = 7.2 Hz, 2H), 2.26 - 2.22 (m, 1H), 1.78 - 1.55 (m, 1H), 1.31 - 1.13 (m, 2H), 0.59 - 0.53 (m, 2H), 0.39 - 0.34 (m, 2H).

[0733] N-(3-(2-(cyclopropylmethoxy)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide Enatiomer 2: LCMS (ESI, m/z): $[M+H]^+$ =367.2. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.75 (s, 1H), 10.81 (s, 1H), 8.20 (d, J = 8.7 Hz, 1H), 8.05 - 7.98 (m, 2H), 7.89 (d, J = 8.7 Hz, 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.07 - 7.03 (m, 1H), 5.02 - 4.78 (m, 1H), 4.21 (d, J = 7.2 Hz, 2H), 2.69 - 2.55 (m, 1H), 1.55 - 1.48 (m, 1H), 1.29 - 1.22 (m, 2H), 0.57 - 0.52 (m, 2H), 0.38 - 0.35 (m, 2H).

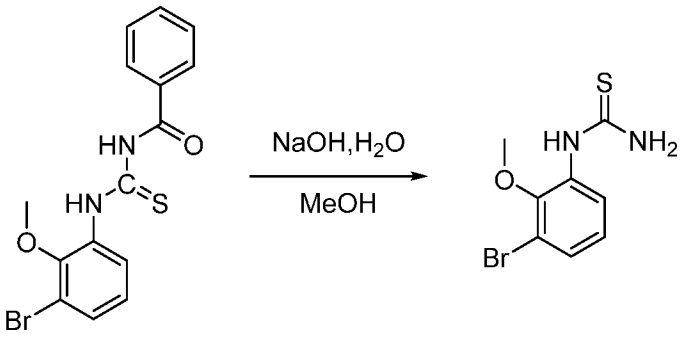
Example S149. Compound 150

Step 1: Synthesis of 1-benzoyl-3-(3-bromo-2-methoxyphenyl)thiourea



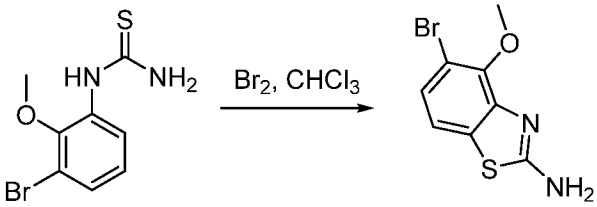
[0734] To a solution of 3-bromo-2-methoxyaniline (5.0 g, 24.75 mmol) in acetone (125.0 mL) was added benzoyl isothiocyanate (4.0 g, 24.76 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 0.5 h. After the reaction was completed. The resulting mixture was concentrated under reduced pressure. The residue were washed with ethyl ether and then filtered. The solid was collected and dried to afford 1-benzoyl-3-(3-bromo-2-methoxyphenyl)thiourea (7.8 g, crude) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =365.0.

Step 2: Synthesis of 3-bromo-2-methoxyphenylthiourea



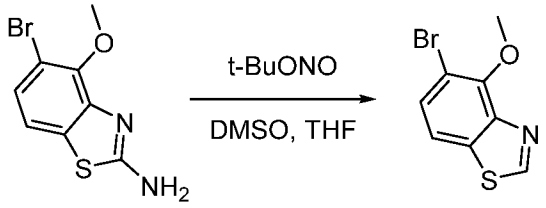
[0735] To a solution of 1-benzoyl-3-(3-bromo-2-methoxyphenyl)thiourea (7.8 g, crude) in MeOH/H_2O (130.0 mL/26.0 mL) was added NaOH (4.3 g, 106.76 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 3-bromo-2-methoxyphenylthiourea (5.0 g, crude) as a light pink solid. LCMS (ESI, m/z): $[M+H]^+$ =261.0

Step 3: Synthesis of 5-bromo-4-methoxy-1,3-benzothiazol-2-amine



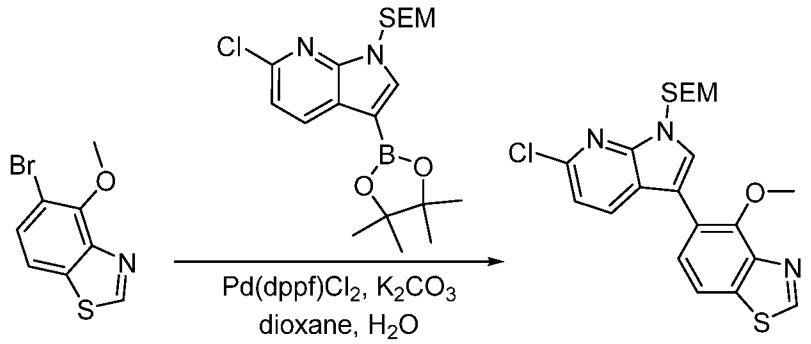
[0736] To a solution of 3-bromo-2-methoxyphenylthiourea (5.0 g, 19.15 mmol) in $CHCl_3$ (300.0 mL) was added dropwise Br_2 (3.7 g, 22.98 mmol) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 8 h. After the reaction was completed, the reaction mixture was quenched with $NaHSO_3$ (aq.) at 0 °C. The resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with acetonitrile/water (1/1, v/v) to afford 5-bromo-4-methoxy-1,3-benzothiazol-2-amine (4.0 g, 80%) as a light brown solid. LCMS (ESI, m/z): $[M+H]^+$ =258.9.

Step 4: Synthesis of 5-bromo-4-methoxy-1,3-benzothiazole



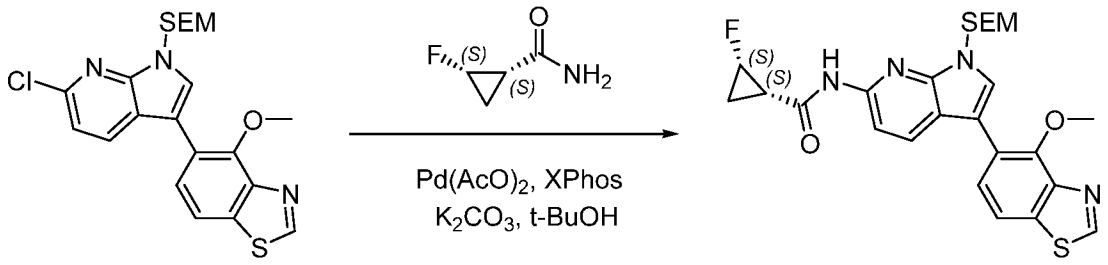
[0737] To a solution of 5-bromo-4-methoxy-1,3-benzothiazol-2-amine (4.0 g, 15.45 mmol) in THF (60.0 mL) was added tert-butyl nitrite (2.4 g, 23.16 mmol) and DMSO (96.5 mg, 1.24 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (7/1, v/v) to afford 5-bromo-4-methoxy-1,3-benzothiazole (1.6 g, 42%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =243.9.

Step 5: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxy-1,3-benzothiazole



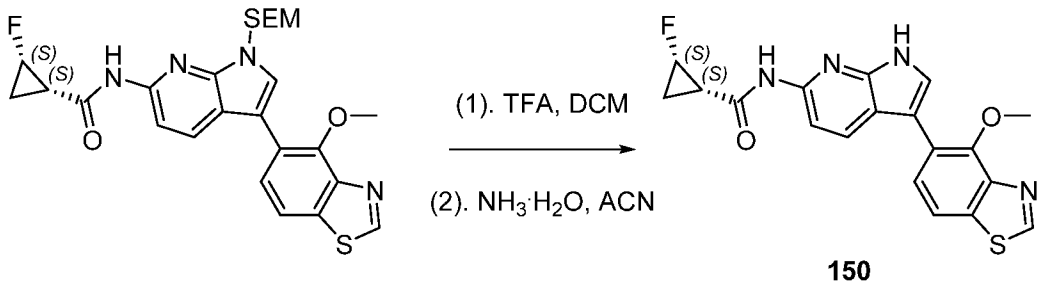
[0738] To a solution of 5-bromo-4-methoxy-1,3-benzothiazole (124.1 mg, 0.51 mmol) in 1,4-dioxane/H_2O (10.0 mL/2.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (250.0 mg, 0.61 mmol), K_2CO_3 (140.5 mg, 1.02 mmol) and $Pd(dppf)Cl_2$ (37.2 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxy-1,3-benzothiazole (220.0 mg, 97%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =446.1.

Step 6: Synthesis of (1S,2S)-2-fluoro-N-[3-(4-methoxy-1,3-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide



[0739] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxy-1,3-benzothiazole (190.0 mg, 0.43 mmol) in t-BuOH (20.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (219.6 mg, 2.13 mmol), XPhos (40.6 mg, 0.09 mmol), K_2CO_3 (176.6 mg, 1.28 mmol) and $Pd(OAc)_2$ (9.6 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100°C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford (1S,2S)-2-fluoro-N-[3-(4-methoxy-1,3-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (114.0 mg, 52%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =513.2.

Step 7: Synthesis of (1S,2S)-2-fluoro-N-[3-(4-methoxy-1,3-benzothiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 150)



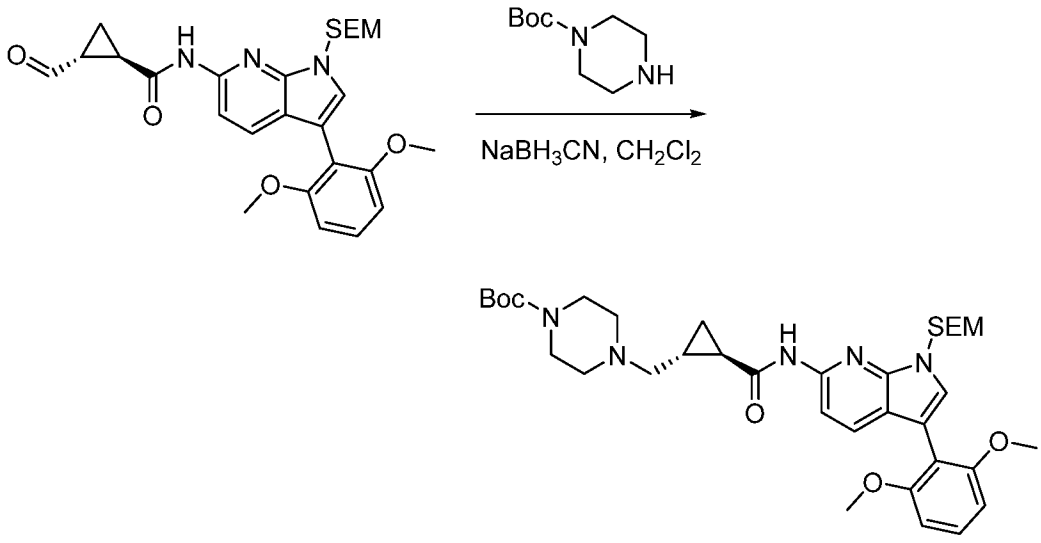
150

[0740] To a solution of (1S,2S)-2-fluoro-N-[3-(4-methoxy-1,3-benzothiazol-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (114.0 mg, 0.22 mmol) in CH_2Cl_2 (6.0 mL) was added TFA (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was

concentrated under reduced pressure. To the residue in CH_3CN (6.0 mL) was added $NH_3 \cdot H_2O$ (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 38% B to 47% B in 8 min; 254/220 nm) to afford (1S,2S)-2-fluoro-N-[3-(4-methoxy-1,3-benzothiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (16.7 mg, 19%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =383.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.69 (s, 1H), 10.65 (s, 1H), 9.37 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.71 - 7.67 (m, 2H), 5.01 - 4.84 (m, 1H), 4.05 (s, 3H), 2.28 - 2.19 (m, 1H), 1.70 - 1.62 (m, 1H), 1.23 - 1.17 (m, 1H).

Example S150. Compound 151 and Compound 152

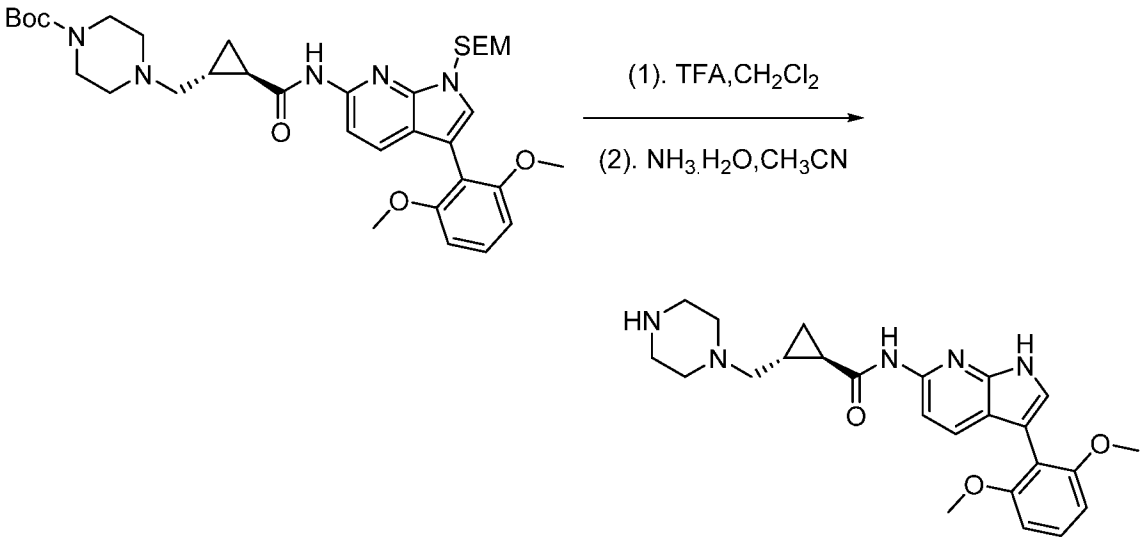
Step 1: Synthesis of tert-butyl 4-[[trans-2-[[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]cyclopropyl]methyl]piperazine-1-carboxylate



[0741] To a solution of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-formylcyclopropanecarboxamide (260.0 mg, 0.53 mmol) in DCM (26.0 mL) were added tert-butyl piperazine-1-carboxylate (293.1 mg, 1.57 mmol) and $NaBH_3CN$ (98.9 mg, 1.57 mmol)

at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford tert-butyl 4-[[trans-2-[[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]cyclopropyl]methyl]piperazine-1-carboxylate (180.0 mg, 52%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =666.4.

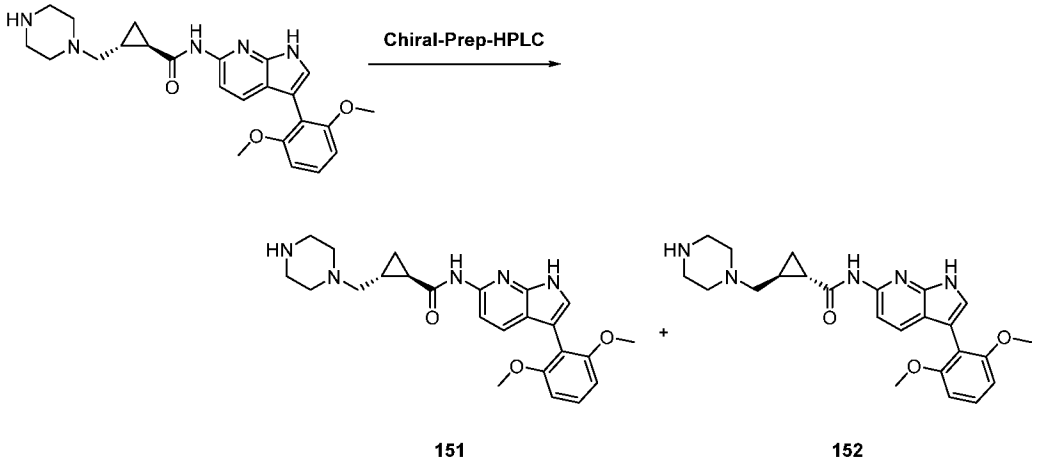
Step 2: Synthesis of trans-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide



[0742] To a solution of tert-butyl 4-[[trans-2-[[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]cyclopropyl]methyl]piperazine-1-carboxylate (350.0 mg, 0.53 mmol) in CH_2Cl_2 (10.0 mL) was added TFA (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (20.0 mL) was added $NH_3 \cdot H_2O$ (20.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 43% B in 9 min; 254 nm) to afford trans-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide (80.0 mg, 39%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =436.2.

Step 3: Synthesis of (1R,2R)-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide and (1S,2S)-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide (Compound 151 and Compound 152)



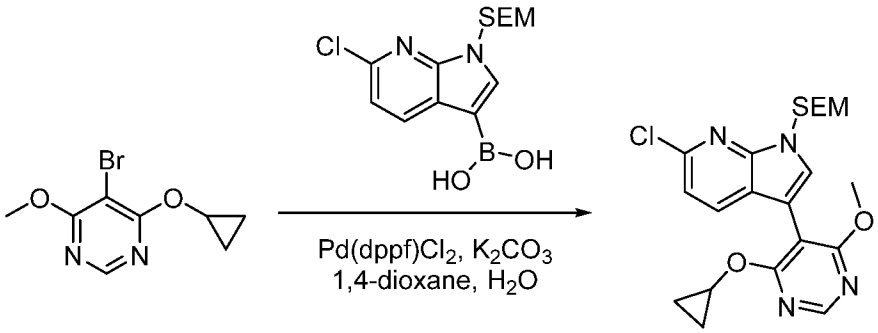
[0743] The racemic trans-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide (80.0 mg, 0.18 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IE, 2x25 cm, 5 um; Mobile Phase A:MTBE (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B:MeOH--HPLC; Flow rate:20 mL/min; Gradient:15% B to 15% B in 13 min; 220/254 nm) to afford N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide Enantiomer 1 (12.4 mg, 15%, Retention time 1: 7.557 min) as a white solid and N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide Enantiomer 2 (12.5 mg, 15%, Retention time 2: 9.866 min) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as Compounds 151 and 152 in Table 1.

[0744] **N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide Enantiomer 1:** LCMS (ESI, m/z): $[M+H]^+$ =436.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.40 (s, 1H), 10.51 (s, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.29 - 7.25 (m, 2H), 6.74 (d, J = 8.4 Hz, 2H), 3.68 (s, 6H), 2.73 - 2.67 (m, 4H), 2.38 - 2.32 (m, 5H), 2.22 - 2.18 (m, 1H), 1.89 - 1.87 (m, 1H), 1.35 - 1.31 (m, 1H), 1.04 - 0.98 (m, 1H), 0.78 - 0.61 (m, 1H).

[0745] **N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide Enatiomer 2:** LCMS (ESI, m/z): $[M+H]^+$ =436.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.40 (s, 1H), 10.51 (s, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.29 - 7.25 (m, 2H), 6.74 (d, J = 8.4 Hz, 2H), 3.68 (s, 6H), 2.73 - 2.67 (m, 4H), 2.38 - 2.32 (m, 5H), 2.22 - 2.18 (m, 1H), 1.89 - 1.87 (m, 1H), 1.35 - 1.31 (m, 1H), 1.04 - 0.98 (m, 1H), 0.78 - 0.61 (m, 1H).

Example S151. Compound 153

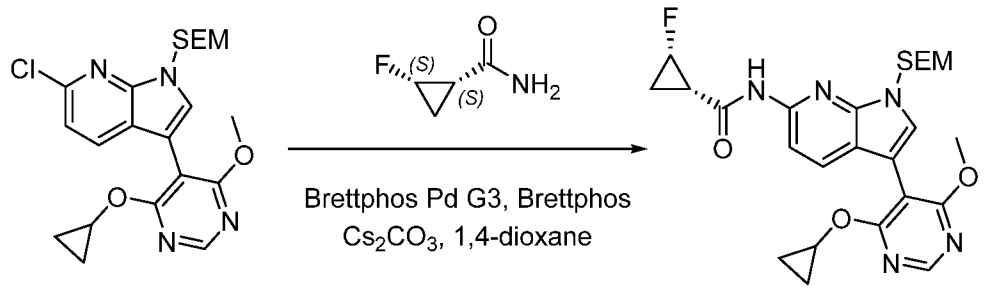
Step 1: Synthesis of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-cyclopropoxy-6-methoxypyrimidine



[0746] To a solution of 5-bromo-4-cyclopropoxy-6-methoxypyrimidine (500.0 mg, 2.04 mmol) in dioxane/H_2O (20.0 mL/4.0 mL) was added 6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-ylboronic acid (666.5 mg, 2.04 mmol), K_2CO_3 (845.9 mg, 6.12 mmol) and $Pd(dppf)Cl_2$ (149.3 mg, 0.20 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford 5-(6-

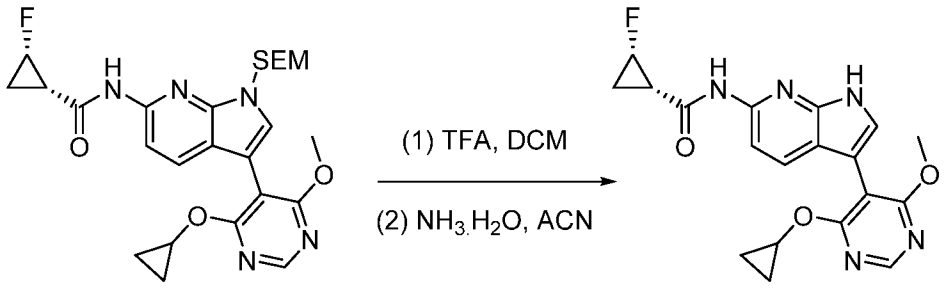
chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-cyclopropoxy-6-methoxypyrimidine (260.0 mg, 29%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =447.2.

Step 2: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide



[0747] To a solution of 5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-cyclopropoxy-6-methoxypyrimidine (240.0 mg, 0.54 mmol) in 1,4-dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (276.8 mg, 2.68 mmol), BrettPhos (57.6 mg, 0.11 mmol), Cs_2CO_3 (524.8 mg, 1.61 mmol) and BrettPhos Pd G3 (48.67 mg, 0.054 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h under N_2. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1S,2S)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (150.0 mg, 54%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =514.2.

Step 3: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 153)

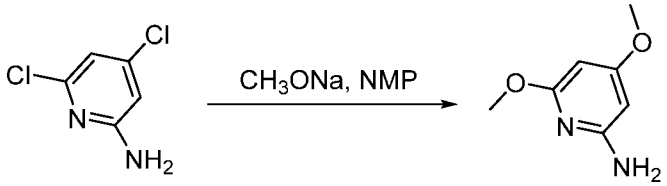


153

[0748] To a solution of (1S,2S)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (150.0 mg, 0.12 mmol) in CH_2Cl_2 (10.0 mL) was added TFA (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The reaction mixture was evaporated in vacuo. To the residue in CH_3CN (10.0 mL) was added $NH_3.H_2O$ (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions Column: (Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31% B to 41% B in 8 min; 254 nm) to afford (1S,2S)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (17.2 mg, 20%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =384.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.65 (s, 1H), 10.63 (s, 1H), 8.49 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 2.8 Hz, 1H), 5.01 - 4.83 (m, 1H), 4.38 - 4.34 (m, 1H), 3.92 (s, 3H), 2.28 - 2.22 (m, 1H), 1.68 - 1.61 (m, 1H), 1.18 - 1.14 (m, 1H), 0.82 - 0.71 (m, 2H), 0.69 - 0.61 (m, 2H).

Example S152. Compound 154

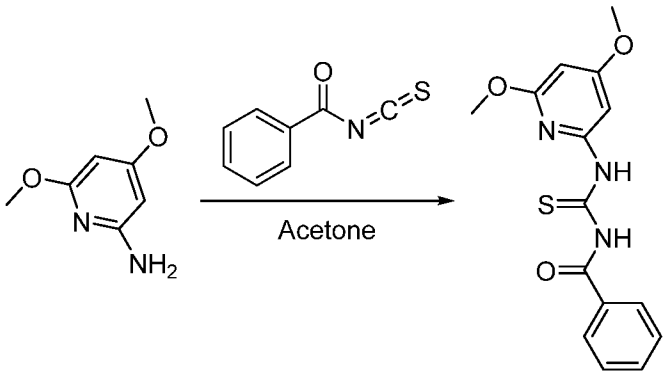
Step 1: Synthesis of 4,6-dimethoxypyridin-2-amine



[0749] To a solution of 4,6-dichloropyridin-2-amine (5.0 g, 30.68 mmol) in NMP (30.0 mL) was added CH_3ONa (8.3 g, 153.38 mmol). The resulting mixture was stirred at 120 °C

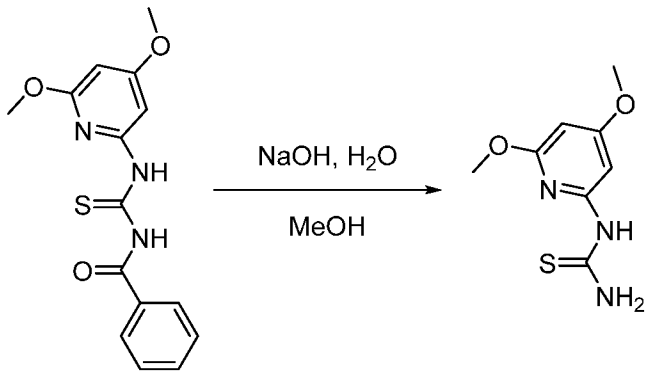
for 16 h. After the reaction was completed, the reaction was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (70/30, v/v) to afford 4,6-dimethoxypyridin-2-amine (2.7 g, 57%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =155.1.

Step 2: Synthesis of 3-benzoyl-1-(4,6-dimethoxypyridin-2-yl)thiourea



[0750] To a solution of 4,6-dimethoxypyridin-2-amine (1.0 g, 6.49 mmol) in acetone (10.0 mL) was added benzoyl isothiocyanate (1.2 g, 7.14 mmol). The mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was filtered. The solid was collected and dried to afford 3-benzoyl-1-(4,6-dimethoxypyridin-2-yl)thiourea (1.8 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =318.1.

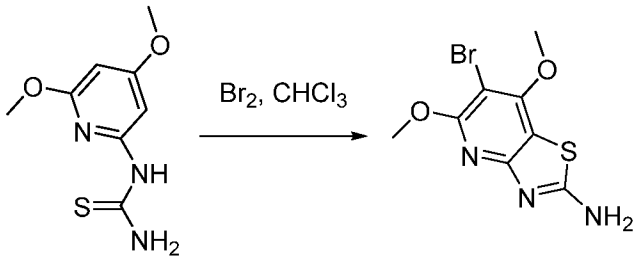
Step 3: Synthesis of 4,6-dimethoxypyridin-2-ylthiourea



[0751] To a solution of 3-benzoyl-1-(4,6-dimethoxypyridin-2-yl)thiourea (1.7 g, 5.36 mmol) in MeOH/H_2O (15.0 mL/3.0 mL) was added NaOH (428.5 mg, 10.71 mmol). The mixture was stirred at room temperature for 2 h. After the reaction was completed, the

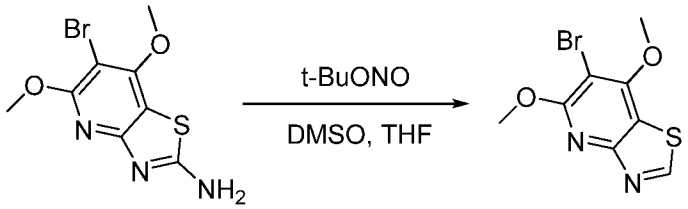
mixture was filtered. The solid was washed with H_2O and dried to afford 4,6-dimethoxypyridin-2-ylthiourea (1.1 g, crude) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =214.1.

Step 4: Synthesis of 6-bromo-5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-2-amine



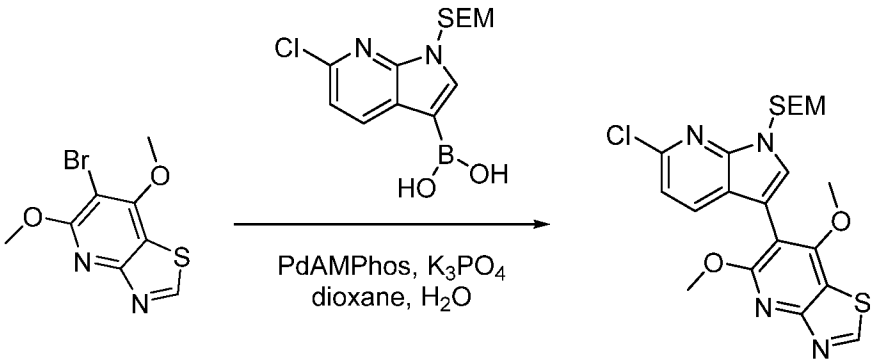
[0752] To a solution of 4,6-dimethoxypyridin-2-ylthiourea (1.0 g, 4.69 mmol) in $CHCl_3$ (10.0 mL) was added dropwise Br_2 (1.5 g, 9.38 mmol) at 0 °C. The mixture was stirred at 60 °C for 1 h. After the reaction was completed, the reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (90/10, v/v) to afford 6-bromo-5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-2-amine (1.2 g, 88%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =290.0.

Step 5: Synthesis of 6-bromo-5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridine



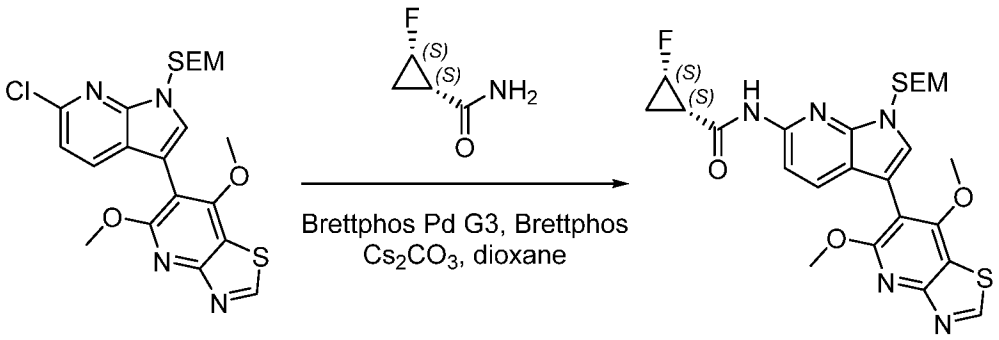
[0753] To a solution of 6-bromo-5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-2-amine (1.1 g, 3.79 mmol) in THF (10.0 mL) was added 2-methyl-2-propylnitrite (469.2 mg, 4.55 mmol) and DMSO (50.0 uL). The mixture was stirred at room temperature for 2 h. After the reaction was completed, the reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (90/10, v/v) to afford 6-bromo-5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridine (320.0 mg, 30%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =274.9.

Step 6: Synthesis of 6-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridine



[0754] To a solution of 6-bromo-5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridine (260.0 mg, 0.95 mmol) in 1,4-dioxane/H_2O (5.0 mL/1.0 mL) was added 6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-ylboronic acid (308.7 mg, 0.95 mmol), K_3PO_4 (601.8 mg, 2.84 mmol) and PdAMPHOS (66.9 mg, 0.10 mmol). The mixture was stirred at 80 °C for 2 h under N_2. After the reaction was completed, the reaction mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (75/25, v/v) to afford 6-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridine (220.0 mg, 48%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =477.1.

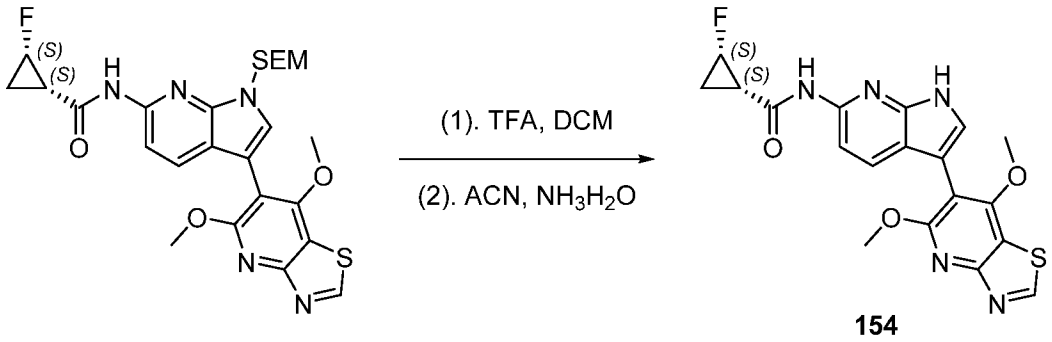
Step 7: Synthesis of (1S,2S)-N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide



[0755] To a solution of 6-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridine (200.0 mg, 0.42 mmol) in 1,4-dioxane (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (216.1 mg, 2.10 mmol), Cs_2CO_3 (409.7 mg, 1.257 mmol), BrettPhos (45.0 mg, 0.08 mmol) and BrettPhos Pd G3 (38.0 mg, 0.04 mmol) under N_2. The mixture was stirred with microwave at 120 °C for 1 h. After the reaction was completed, the reaction was concentrated under vacuum. The

residue was purified by flash column chromatography with CH_2Cl_2/MeOH (90/10, v/v) to afford (1S,2S)-N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (160.0 mg, 70%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =544.2.

Step 8: Synthesis of (1S,2S)-N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (Compound 154)

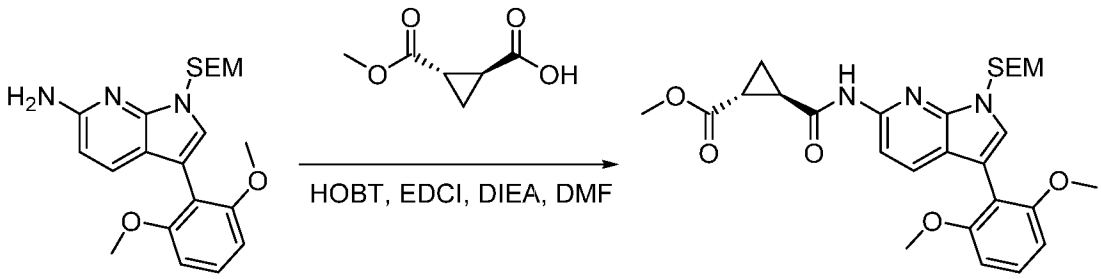


154

[0756] To a solution of (1S,2S)-N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (140.0 mg, 0.26 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL). The mixture was stirred at room temperature for 3 h. The mixture was concentrated under vacuum. To the above mixture were added ACN (3.0 mL) and $NH_3.H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for another 3 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD Column, 30×150 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 35% B in 9 min; 254 nm) to afford (1S,2S)-N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropane-1-carboxamide (31.0 mg, 29%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 414.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.68 (s, 1H), 10.65 (s, 1H), 9.56 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 2.4 Hz, 1H), 5.06 - 4.78 (m, 1H), 3.90 (s, 6H), 2.28 - 2.23 (m, 1H), 1.72 - 1.58 (m, 1H), 1.18 - 1.05 (m, 1H).

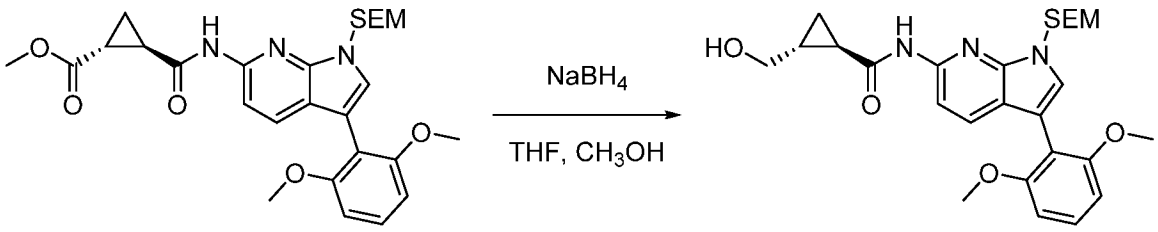
Example S153. Compound 155 and Compound 156

Step 1: Synthesis of trans-methyl 2-[[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]cyclopropane-1-carboxylate



[0757] To a solution of trans-2-(methoxycarbonyl)cyclopropane-1-carboxylic acid (144.3 mg, 1.00 mmol) in DMF (20.0 mL) were added EDCI (287.9 mg, 1.50 mmol) and HOBT (202.9 mg, 1.50 mmol) at room temperature. The resulting mixture was stirred at room temperature for 20 min. Then DIEA (517.5 mg, 4.00 mmol) and 3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (400.0 mg, 1.00 mmol) were added to the mixture at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the mixture was purified by reverse phase flash chromatography with H_2O/CH_3CN (1/1, v/v) to afford trans-methyl 2-[[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]cyclopropane-1-carboxylate (280.0 mg, 53%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =526.2.

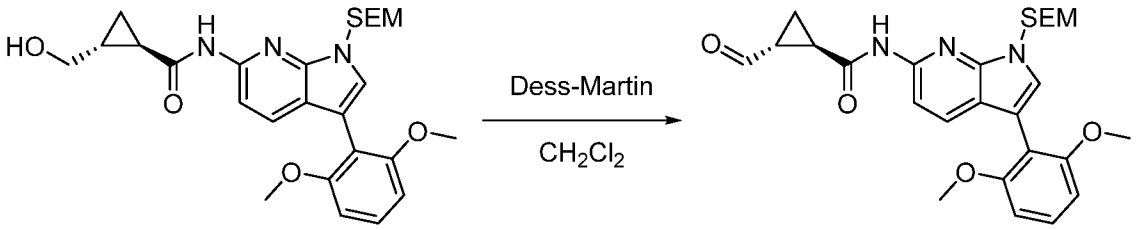
Step 2: Synthesis of trans-N-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide



[0758] To a solution of trans-methyl 2-[[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]cyclopropane-1-carboxylate (330.0 mg, 0.63 mmol) in THF (33.0 mL)/CH_3OH (33.0 mL) was added $NaBH_4$ (712.5 mg, 18.83 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford trans-N-[3-(2,6-dimethoxyphenyl)-1-[[2-

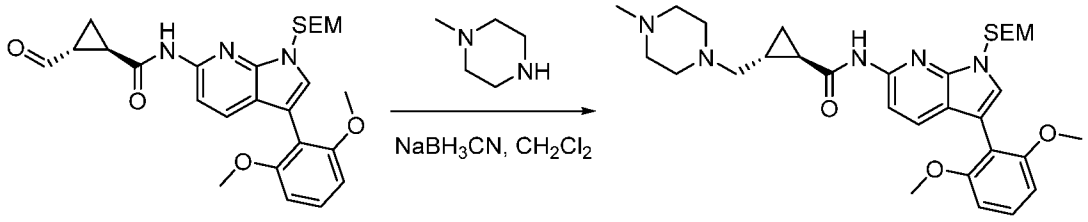
(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide (300.0 mg, 96%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =498.2.

Step 3: Synthesis of trans-N-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide



[0759] To a solution of trans-N-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide (300.0 mg, 0.60 mmol) in CH_2Cl_2 (30.0 mL) was added Dess-Martin (767.0 mg, 1.81 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford trans-N-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (260.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =496.2.

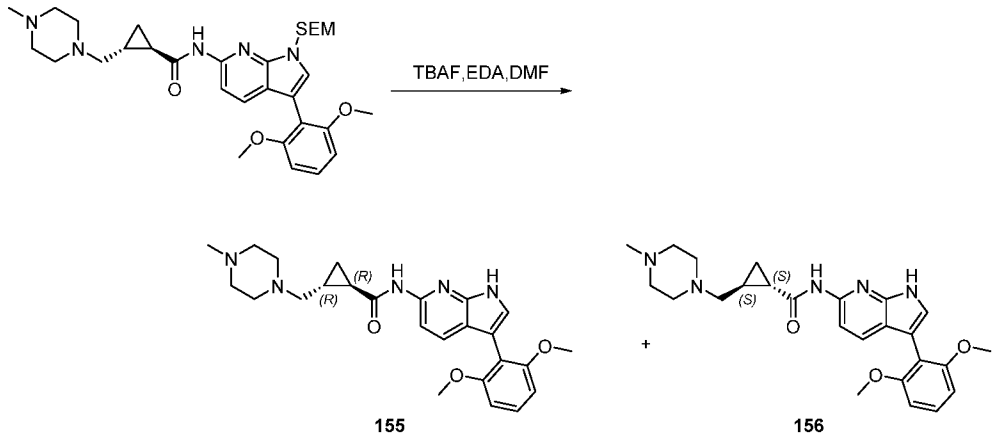
Step 4: Synthesis of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide



[0760] To a solution of trans-N-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (350.0 mg, crude) in CH_2Cl_2 (20.0 mL) was added 1-methylpiperazine (212.2 mg, 2.12 mmol) and $NaBH_3CN$ (133.1 mg, 2.12 mmol) at room temperature. The resulting

mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was quenched with CH_3OH. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (86/14, v/v) to afford trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (180.0 mg, 43%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =580.3.

Step 5: Synthesis of (1R,2R)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide and **(1S,2S)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (Compound 155 and Compound 156)**



[0761] To a solution of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (180.0 mg, 0.31 mmol) in DMF (5.0 mL) was added ethylenediamine (93.3 mg, 1.55mmol) and TBAF (243.5 mg, 0.93 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (75/25, v/v) and then separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IE, 2×25 cm, 5 um; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 10% to 10% in 46 min; 220/254 nm) to afford N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-

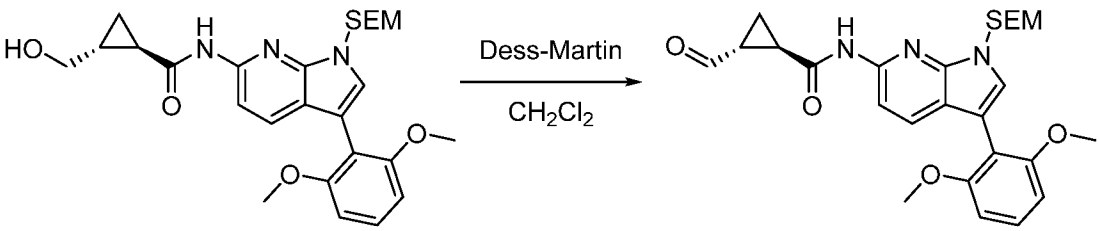
yl)methyl)cyclopropane-1-carboxamide Enantiomer 1 (10.3 mg, 7%, Retention time 1: 16.876 min) as a white solid and N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide Enantiomer 1 (12.3 mg, 8%, Retention time 2: 30.093 min) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as Compounds 155 and 156 in Table 1.

[0762] N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide Enantiomer 1: LCMS (ESI, m/z): $[M+H]^+$ =450.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H), 10.53 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.29 - 7.25 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 3.69 (s, 6H), 2.49 - 2.26 (m, 8H), 2.14 (s, 3H), 1.97 - 1.89 (m, 1H), 1.33 - 1.23 (m, 1H), 1.04 - 1.02 (m, 1H), 0.73 - 0.65 (m, 1H).

[0763] N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide Enantiomer 2: LCMS (ESI, m/z): $[M+H]^+$ =450.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H), 10.53 (s, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.29 - 7.25 (m, 2H), 6.75 (d, J = 8.0 Hz, 2H), 3.69 (s, 6H), 2.49 - 2.24 (m, 8H), 2.14 (s, 3H), 1.97 - 1.89 (m, 1H), 1.33 - 1.23 (m, 1H), 1.04 - 1.02 (m, 1H), 0.73 - 0.65 (m, 1H).

Example S154. Compound 157 and Compound 158

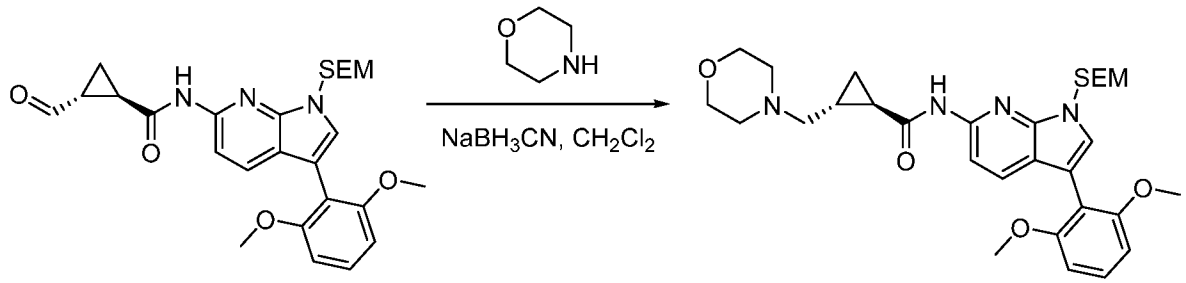
Step 1: Synthesis of trans-N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide



[0764] To a solution of trans-N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide (400.0 mg, 0.80 mmol) in CH_2Cl_2 (5.0 mL) was added Dess-Martin (1022.7

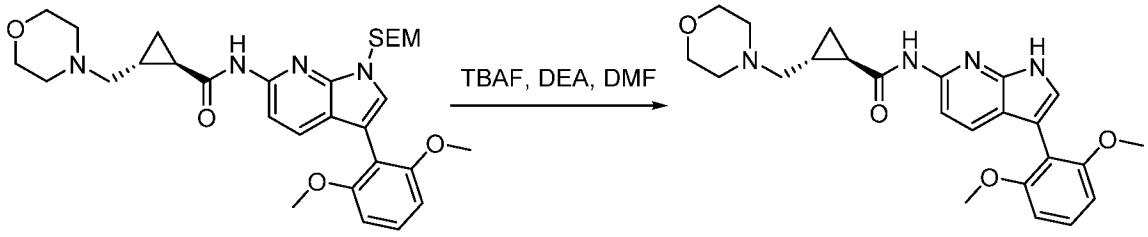
mg, 2.41 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford trans-N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (500.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =496.2.

Step 2: Synthesis of trans-N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(morpholin-4-ylmethyl)cyclopropane-1-carboxamide



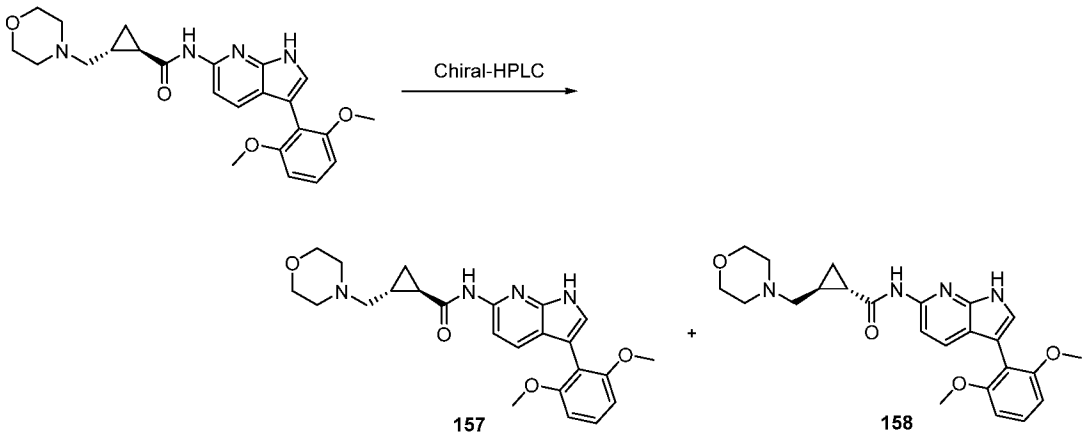
[0765] To a solution of trans-N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (500.0 mg, crude) in CH_2Cl_2 (10.0 mL) was added morpholine (262.6 mg, 3.03 mmol) and $NaBH_3CN$ (189.4 mg, 3.03 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum CH_2Cl_2/MeOH (95/5, v/v) to afford trans-N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(morpholin-4-ylmethyl)cyclopropane-1-carboxamide (410.0 mg, 59%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =567.3.

Step 3: Synthesis of trans-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(morpholinomethyl)cyclopropanecarboxamide



[0766] To a solution of trans-N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(morpholin-4-ylmethyl)cyclopropane-1-carboxamide (390.0 mg, 0.69 mmol) in DMF (5.0 mL) was added TBAF (539.7 mg, 2.06 mmol) and DEA (206.8 mg, 3.44 mmol) at room temperature. The resulting mixture was stirred at 80°C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum CH_2Cl_2/MeOH (90/10, v/v) and then purified by reverse phase flash chromatography with ACN/H_2O (50/50, v/v) to afford trans-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(morpholinomethyl)cyclopropanecarboxamide (100.0 mg, 30%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =437.2.

Step 4: Synthesis of (1R,2R)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(morpholinomethyl)cyclopropanecarboxamide and **(1S,2S)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(morpholinomethyl)cyclopropanecarboxamide (Compound 157 and Compound 158)**



[0767] The racemic trans-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(morpholinomethyl)cyclopropanecarboxamide (100.0 mg, 0.23 mmol) was separated by

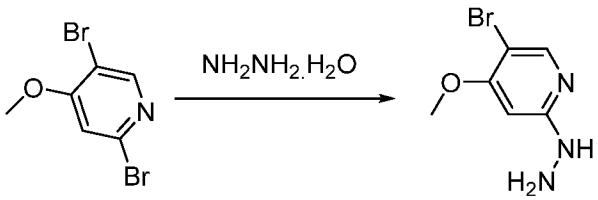
Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IE, 2×25 cm, 5 um; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 18 mL/min; Gradient: 50% B to 50% B in 23 min; 254/220 nm) to afford N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-(morpholin-4-ylmethyl)cyclopropane-1-carboxamide Enantiomer 1 (22.2 mg, 44%, Retention time 1: 11.1 min) as a white solid and (1S,2S)-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-(morpholin-4-ylmethyl)cyclopropane-1-carboxamide Enantiomer 2 (assumed, 28.4 mg, 56%, Retention time 2: 15.904 min) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as Compounds 157 and 158 in Table 1.

[0768] N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-(morpholin-4-ylmethyl)cyclopropane-1-carboxamide Enantiomer 1: LCMS (ESI, m/z): $[M+H]^+$ =437.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H), 10.54 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.30 - 7.25 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 3.69 (s, 6H), 3.59 - 3.57 (m, 4H), 2.50 - 2.43 (m, 4H), 2.38 - 2.33 (m, 1H), 2.27 - 2.25 (m, 1H), 1.95 - 1.86 (m, 1H), 1.41 - 1.32 (m, 1H), 1.11 - 0.99 (m, 1H), 0.77 - 0.65 (m, 1H).

[0769] N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-(morpholin-4-ylmethyl)cyclopropane-1-carboxamide Enantiomer 2: LCMS (ESI, m/z): $[M+H]^+$ =437.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.42 (s, 1H), 10.54 (s, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.30 - 7.25 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 3.69 (s, 6H), 3.59 - 3.57 (m, 4H), 2.50 - 2.43 (m, 4H), 2.38 - 2.33 (m, 1H), 2.27 - 2.25 (m, 1H), 1.95 - 1.86 (m, 1H), 1.41 - 1.32 (m, 1H), 1.11 - 0.99 (m, 1H), 0.77 - 0.65 (m, 1H).

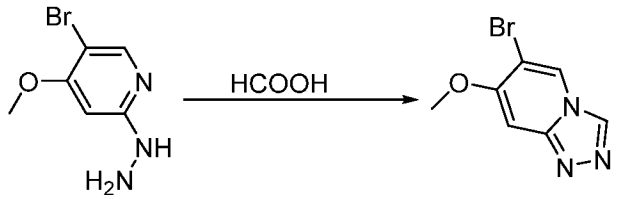
Example S155: Synthesis of (1S,2S)-2-fluoro-N-(3-[7-methoxy-[1,2,4]triazolo[4,3-a]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 159)

Step 1: Synthesis of 5-bromo-2-hydrazinyl-4-methoxypyridine



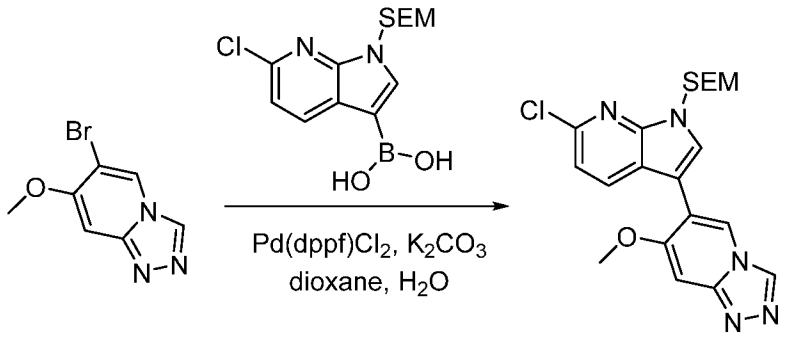
[0770] The solution of 2,5-dibromo-4-methoxypyridine (500.0 mg, 2.24 mmol) in $NH_2NH_2.H_2O$ (50.0 mL, 80%) was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with CH_3CN/H_2O (1/4, v/v) to afford 5-bromo-2-hydrazinyl-4-methoxypyridine (60.0 mg, 12%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =218.0

Step 2: Synthesis of 6-bromo-7-methoxy-[1,2,4]triazolo[4,3-a]pyridine



[0771] The solution of 5-bromo-2-hydrazinyl-4-methoxypyridine (600.0 mg, 2.75 mmol) in formic acid (10.0 mL) was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with $MeOH/H_2O$ (1/10, v/v) to afford 6-bromo-7-methoxy-[1,2,4]triazolo[4,3-a]pyridine (120.0 mg, 19%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =228.0

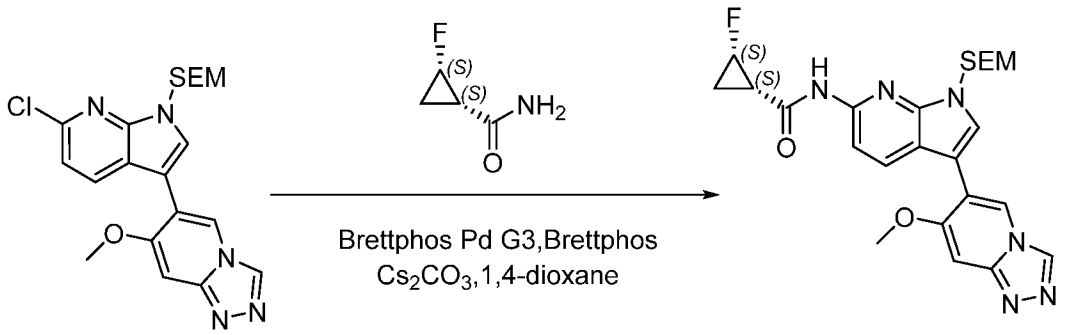
Step 3: Synthesis of 6-chloro-3-[7-methoxy-[1,2,4]triazolo[4,3-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine



[0772] To a mixture of 6-bromo-7-methoxy-[1,2,4]triazolo[4,3-a]pyridine (100.0 mg, 0.43 mmol) and 6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-ylboronic acid (214.8 mg, 0.65 mmol) in dioxane/H_2O (5.0/1.0 mL) were added $Pd(dppf)Cl_2$ (32.0 mg, 0.04 mmol,) and K_2CO_3 (181.8 mg, 1.31 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed,

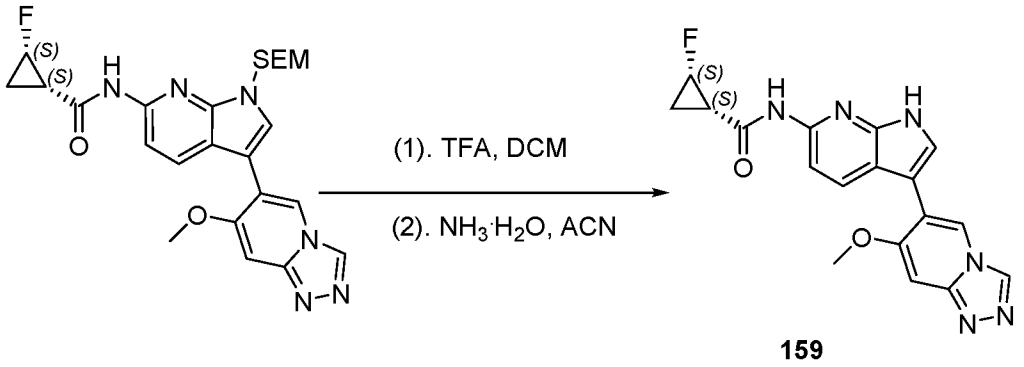
the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was residue was purified by flash column chromatography with MeOH/DCM (1/10,v/v) to afford 6-chloro-3-[7-methoxy-[1,2,4]triazolo[4,3-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (110.0 mg, 58%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =430.1

Step 4: Synthesis of (1S,2S)-2-fluoro-N-(3-[7-methoxy-[1,2,4]triazolo[4,3-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide



[0773] To a mixture of 6-chloro-3-[7-methoxy-[1,2,4]triazolo[4,3-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (90.0 mg, 0.20 mmol) and (1S,2S)-2-fluorocyclopropane-1-carboxamide (107.9 mg, 1.04 mmol) in dioxane (4.0 mL) was added BrettPhos Pd G3 (37.5 mg, 0.04 mmol), BrettPhos (44.9 mg, 0.08 mmol) and Cs_2CO_3 (204.0 mg, 0.62 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with MeOH/DCM (1/10,v/v) to afford (1S,2S)-2-fluoro-N-(3-[7-methoxy-[1,2,4]triazolo[4,3-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (40.0 mg, 38%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =497.2

Step 5: Synthesis of (1S,2S)-2-fluoro-N-(3-[7-methoxy-[1,2,4]triazolo[4,3-a]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 159)

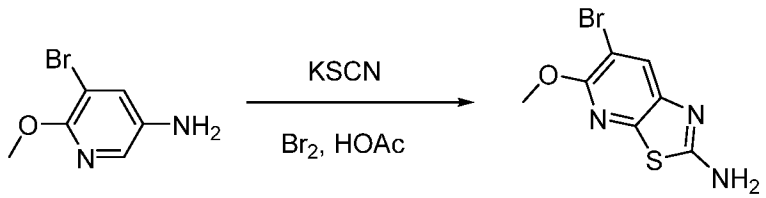


159

[0774] To a solution of (1S,2S)-2-fluoro-N-(3-[7-methoxy-[1,2,4]triazolo[4,3-a]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (30.0 mg, 0.06 mmol) in DCM (1.0 mL) was added TFA (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under vacuum. To the above residue was added ACN (2.0 mL) and $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 16% B to 26% B in 8 min, 254 nm) to afford (1S,2S)-2-fluoro-N-(3-[7-methoxy-[1,2,4]triazolo[4,3-a]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide **(Compound 159)** (5.0 mg, 22%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =367.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.77 (s, 1H), 10.68 (s, 1H), 9.06 (s, 1H), 8.68 (s, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.68 (s, 1H), 7.20 (s, 1H), 5.07 - 4.80 (m, 1H), 3.95 (s, 3H), 2.27 - 2.24 (m, 1H), 1.73 - 1.60 (m, 1H), 1.22 - 1.10 (m, 1H).

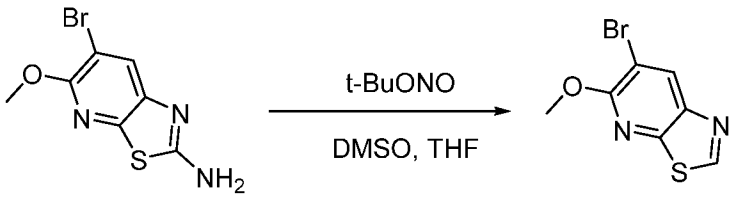
Example S156: Synthesis of (1S,2S)-2-fluoro-N-(3-[5-methoxy-[1,3]thiazolo[5,4-b]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 160)

Step 1: Synthesis of 6-bromo-5-methoxy-[1,3]thiazolo[5,4-b]pyridin-2-amine



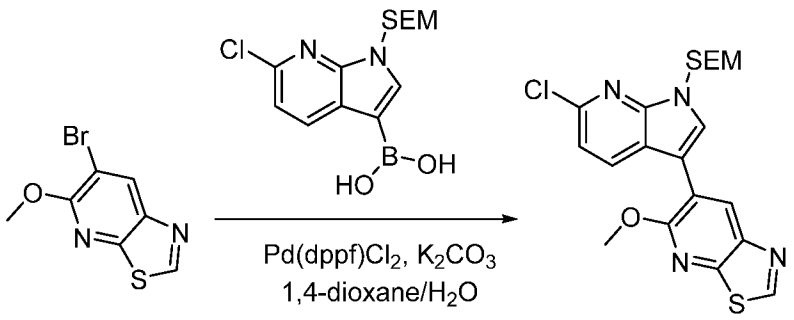
[0775] To a mixture of 5-bromo-6-methoxypyridin-3-amine (1.0 g, 4.92 mmol) and KSCN (238.8 mg, 2.46 mmol) in AcOH (20.0 mL) was added Br_2 (390.0 mg, 2.46 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the pH value of the mixture was adjusted to 9 with aq.$NaHCO_3$. The resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 6-bromo-5-methoxy-[1,3]thiazolo[5,4-b]pyridin-2-amine (2.0 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =259.9

Step 2: Synthesis of 6-bromo-5-methoxy-[1,3]thiazolo[5,4-b]pyridine



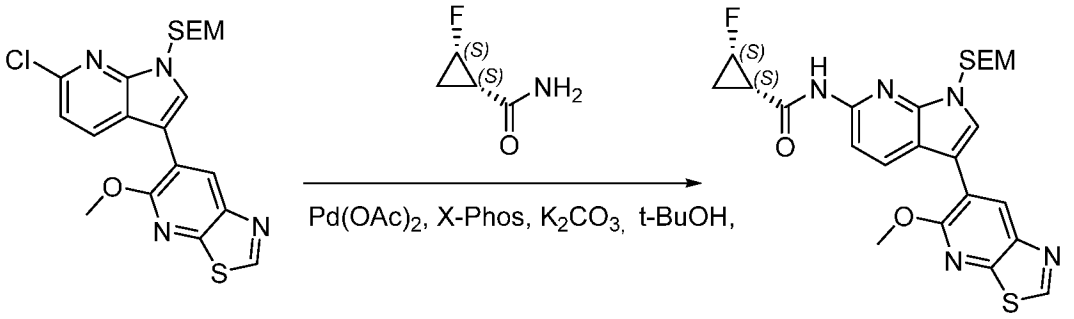
[0776] To a mixture of 6-bromo-5-methoxy-[1,3]thiazolo[5,4-b]pyridin-2-amine (1.3 g, 4.99 mmol) and DMSO (312.4 mg, 3.99 mmol) in THF (20.0 mL) was added dropwise 2-methyl-2-propylnitrite (1.5 g, 15.00 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 6-bromo-5-methoxy-[1,3]thiazolo[5,4-b]pyridine (800.0 mg, 65%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =244.9

Step 3: Synthesis of 6-chloro-3-[5-methoxy-[1,3]thiazolo[5,4-b]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine



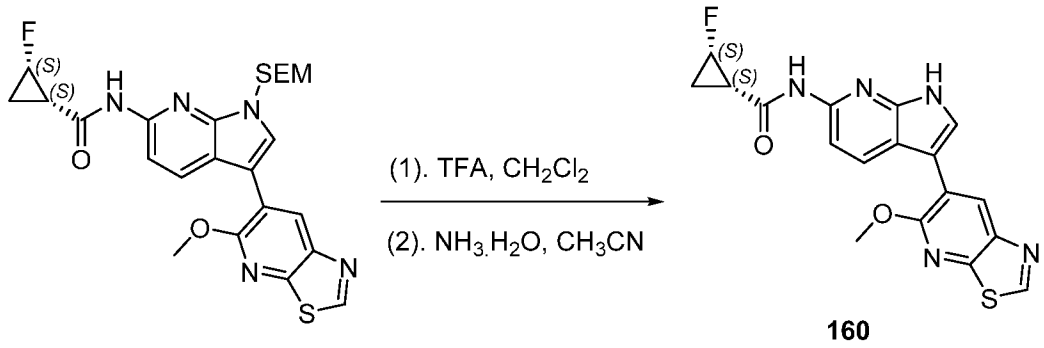
[0777] To a mixture of 6-bromo-5-methoxy-[1,3]thiazolo[5,4-b]pyridine (400.0 mg, 1.63 mmol) and 6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-ylboronic acid (1.0 g, 2.44 mmol) in dioxane/H_2O (10.0/1.0 mL) was added K_2CO_3 (676.6 mg, 4.89 mmol) and $Pd(dppf)Cl_2$ (119.4 mg, 0.16 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (9/1, v/v) to afford 6-chloro-3-[5-methoxy-[1,3]thiazolo[5,4-b]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (370.0 mg, 50%) as a purple solid. LCMS (ESI, m/z): $[M+H]^+$ =447.1

Step 4: Synthesis of (1S,2S)-2-fluoro-N-(3-[5-methoxy-[1,3]thiazolo[5,4-b]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide



[0778] To a mixture of 6-chloro-3-[5-methoxy-[1,3]thiazolo[5,4-b]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy] methyl]pyrrolo[2,3-b]pyridine (350.0 mg, 0.78 mmol) and (1S,2S)-2-fluorocyclopropane-1-carboxamide (403.5 mg, 3.91 mmol) in BuOH (5.0 mL) was added $Pd(OAc)_2$ (35.1 mg, 0.15 mmol), K_2CO_3 (324.6 mg, 2.34 mmol) and X-Phos (37.3 mg, 0.07 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1S,2S)-2-fluoro-N-(3-[5-methoxy-[1,3]thiazolo[5,4-b]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (50.0 mg, 12%) as a green solid. LCMS (ESI, m/z): $[M+H]^+$ =514.2

Step 5: Synthesis of (1S,2S)-2-fluoro-N-(3-[5-methoxy-[1,3]thiazolo[5,4-b]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 160)



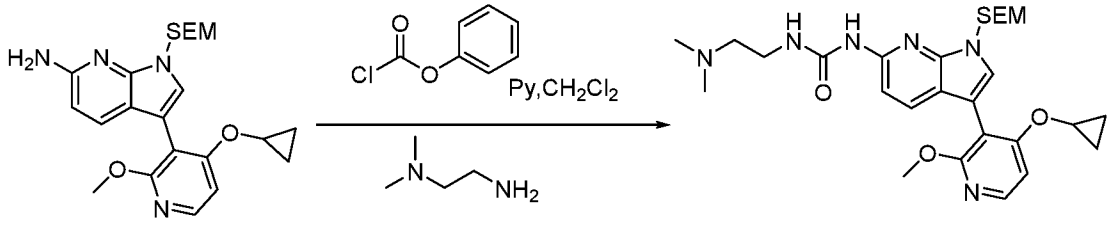
160

[0779] To a solution of (1S,2S)-2-fluoro-N-(3-[5-methoxy-[1,3]thiazolo[5,4-b]pyridin-6-yl]-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (40.0 mg, 0.07 mmol) in DCM (1.0 mL) was added TFA (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added ACN (1.0 mL) and $NH_3.H_2O$ (2.0 mL). The resulting mixture was stirred at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 37% B to 46% B in 8 min, 254 nm) to afford (1S,2S)-2-fluoro-N-(3-[5-methoxy-[1,3]thiazolo[5,4-b]pyridin-6-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide **(Compound 160)** (9.2 mg, 31%) LCMS (ESI, m/z): $[M+H]^+$ =384.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.81 (s, 1H), 10.68 (s, 1H), 9.33 (s, 1H), 8.54 (s, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.80 (d, J = 1.5 Hz, 1H), 5.10 - 4.80 (m, 1H), 4.05 (s, 3H), 2.25 - 2.15 (m, 1H), 1.78 - 1.60 (m, 1H), 1.27 - 1.10 (m, 1H).

Example S157: Synthesis of 1-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(dimethylamino)ethyl)urea (Compound 161)

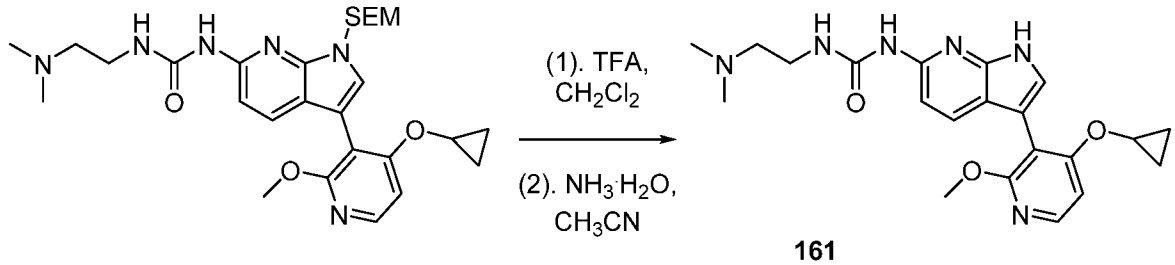
Step 1: Synthesis of 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[2-

(dimethylamino)ethyl]urea



[0780] To a solution of 3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (180.0 mg, 0.42 mmol) in DCM (13.0 mL) was added pyridine (133.5 mg, 1.69 mmol) and phenyl chloroformate ((132.1 mg, 0.84 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in pyridine (13.0 mL) was added (2-aminoethyl)dimethylamine (372.0 mg, 4.22 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (9/1, v/v) to afford 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[2-(dimethylamino)ethyl]urea (180.0 mg, 79%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =541.3.

Step 2: Synthesis of 1-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(dimethylamino)ethyl)urea (Compound 161)



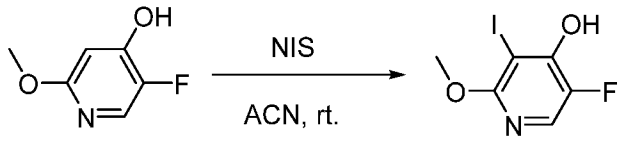
161

[0781] To a solution of 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[2-(dimethylamino)ethyl]urea (180.0 mg, 0.33 mmol) in CH_2Cl_2 (8.0 mL) was added TFA (8.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (8.0 mL) was added $NH_3.H_2O$ (8.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, 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, 30x150 mm, 5 μm; Mobile Phase A:Water (10 mmol/L NH_4HCO_3). Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 36% B in 8 min; 254 nm) to afford 1-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(dimethylamino)ethyl)urea **(Compound 161)** (49.6 mg, 36%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =411.4. ^1H NMR (400 MHz, DMSO-d_6): δ 11.40 (s, 1H), 9.16 (s, 1H), 8.43 (s, 1H), 8.06 (d, J = 6.0 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 7.13 (d, J = 6.0 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 3.94 - 3.90 (m, 1H), 3.81 (s, 3H), 3.34 - 3.28 (m, 2H), 2.42 - 2.34 (m, 2H), 2.21 (s, 6H), 0.81 - 0.76 (m, 2H), 0.65 - 0.61 (m, 2H).

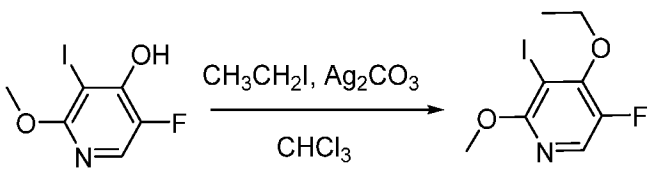
Example S158: Synthesis of (1S,2S)-N-[3-(4-ethoxy-5-fluoro-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 162)

Step 1: Synthesis of 5-fluoro-3-iodo-2-methoxypyridin-4-ol



[0782] To a solution of 5-fluoro-2-methoxypyridin-4-ol (400.0 mg, 2.79 mmol) in MeCN (5.0 mL) was added NIS (628.8 mg, 2.79mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 5-fluoro-3-iodo-2-methoxypyridin-4-ol (450.0 mg, crude) as yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =269.9

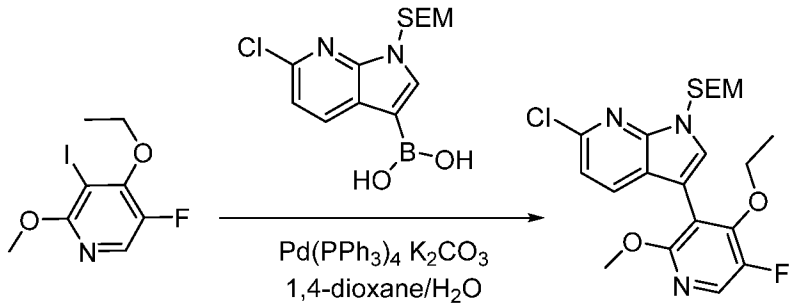
Step 2: Synthesis of 4-ethoxy-5-fluoro-3-iodo-2-methoxypyridine



[0783] To a mixture of 5-fluoro-3-iodo-2-methoxypyridin-4-ol (700.0 mg, crude) and Ag_2CO_3 (2.8 g, 10.40 mmol) in $CHCl_3$ (15.0 mL) was added CH_3CH_2I (1.5 g, 10.40 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the

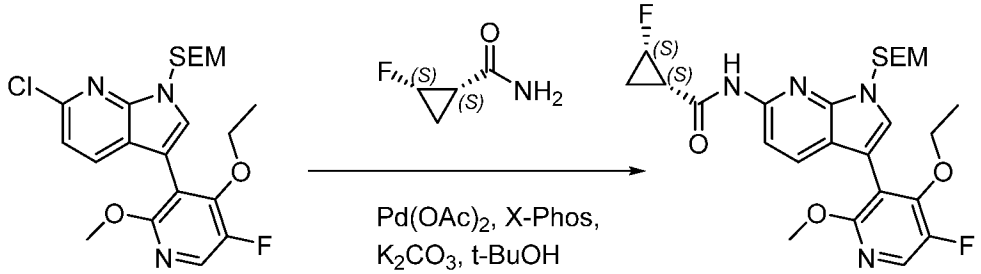
reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford 4-ethoxy-5-fluoro-3-iodo-2-methoxypyridine (700.0 mg, 90%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =298.0.

Step 3: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-ethoxy-5-fluoro-2-methoxypyridine



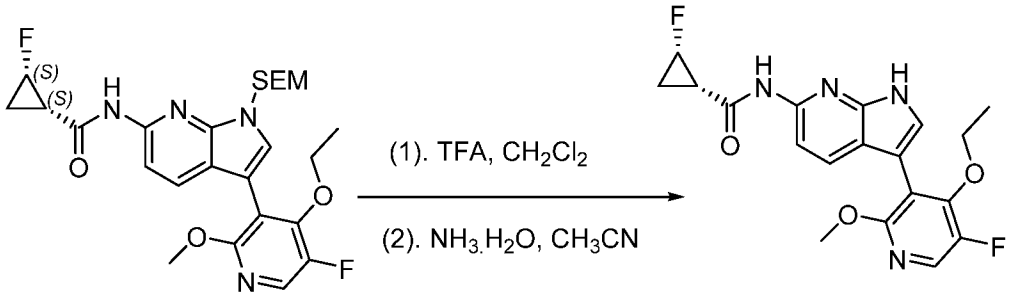
[0784] To a mixture of 4-ethoxy-5-fluoro-3-iodo-2-methoxypyridine (200.0 mg, 0.67 mmol) and 6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-ylboronic acid (263.9 mg, 0.80 mmol) in dioxane/H_2O (5.0/0.5 mL) was added $Pd(PPh_3)_4$ (155.6 mg, 0.13 mmol) and K_2CO_3 (279.1 mg, 2.02 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-ethoxy-5-fluoro-2-methoxypyridine (140.0 mg, 46%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =452.1

Step 4: Synthesis of (1S,2S)-N-[3-(4-ethoxy-5-fluoro-2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide



[0785] To a mixture of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-ethoxy-5-fluoro-2-methoxypyridine (100.0 mg, 0.22 mmol) and (1S,2S)-2-fluorocyclopropane-1-carboxamide (114.0 mg, 1.10 mmol) in t-BuOH (4.0 mL) was added X-Phos (42.1 mg, 0.08 mmol), $Pd(OAc)_2$ (9.93 mg, 0.044 mmol) and K_2CO_3 (91.7 mg, 0.66 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1S,2S)-N-[3-(4-ethoxy-5-fluoro-2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (80.0 mg, 69%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =519.2

Step 5: Synthesis of (1S,2S)-N-[3-(4-ethoxy-5-fluoro-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 162)



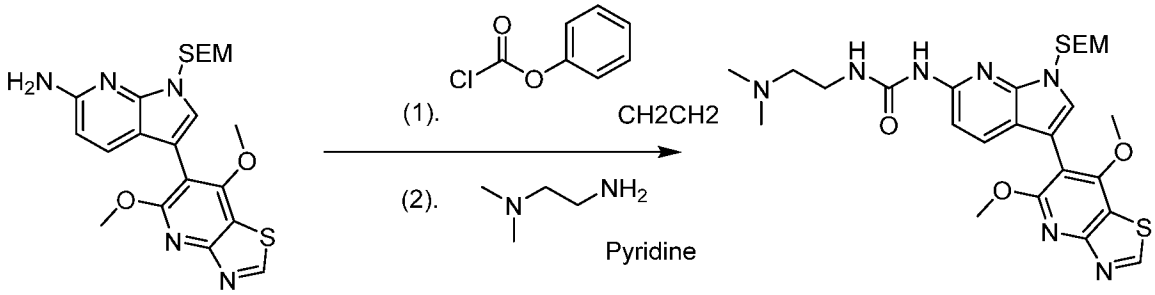
162

[0786] To a solution of (1S,2S)-N-[3-(4-ethoxy-5-fluoro-2-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (70.0 mg, 0.13 mmol) in DCM (2.0 mL) was added TFA (2.0 mL). The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under vacuum. To the above residue was added ACN (2.0 mL) and $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um, Mobile Phase A:Water (10 mmol/L NH_4HCO_3, Mobile Phase B:

ACN; Flow rate: 60 mL/min; Gradient: 39% B to 49% B in 9 min, 254/220 nm) to afford (1S,2S)-N-[3-(4-ethoxy-5-fluoro-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide **(Compound 162)** (5.4 mg, 10%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =389.2. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.71 (s, 1H), 10.65 (s, 1H), 8.11 (d, J = 2.7 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.49 (d, J = 2.7 Hz, 1H), 5.05 - 4.81 (m, 1H), 4.07 - 4.00 (m, 2H), 3.35 (s, 3H), 2.31 - 2.19 (m, 1H), 1.72 - 1.62 (m, 1H), 1.22 - 1.18 (m, 1H), 1.11 - 1.02 (m, 3H).

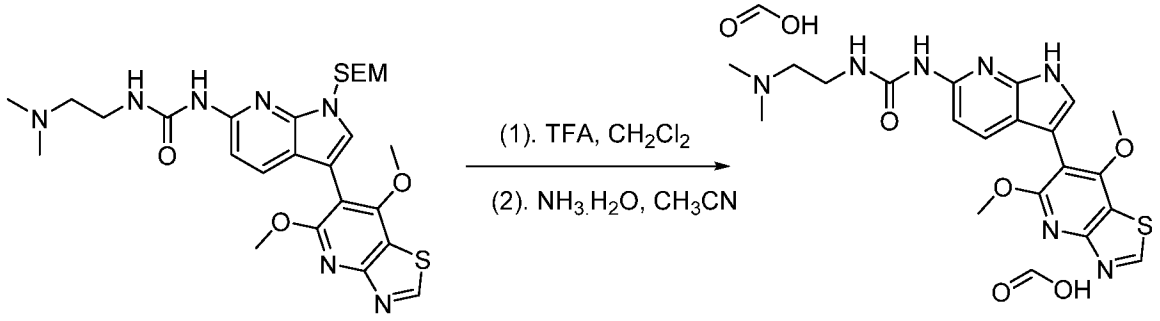
Example S159: Synthesis of 1-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(dimethylamino)ethyl)urea diformate (Compound 163)

Step 1: Synthesis of 1-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(dimethylamino)ethyl)urea



[0787] To a solution of 3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (150.0 mg, 0.33 mmol) in CH_2Cl_2 (2.0 mL) was added phenyl carbonochloridate (77.0 mg, 0.49 mmol) and pyridine (1.0 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. Then a solution of (2-aminoethyl)dimethylamine (260.6 mg, 2.95 mmol) in pyridine (3.0 mL) was added dropwise to the mixture at 0 °C. The resulting mixture was stirred at 60 °C for another 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford 1-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(dimethylamino)ethyl)urea (100.0 mg, 86%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =572.2.

Step 2: Synthesis of 1-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(dimethylamino)ethyl)urea diformate (Compound 163)

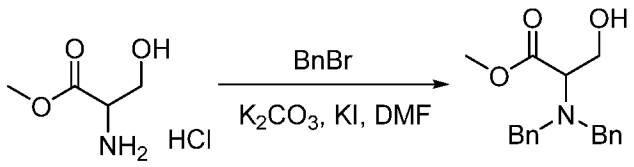


163

[0788] To a solution of 1-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(dimethylamino)ethyl)urea (100.0 mg, 0.21 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L FA), Mobile Phase B: MeOH; Flow rate: 25 mL/min; Gradient: 26% B to 26% B in 15 min; 254 nm) to afford 1-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(dimethylamino)ethyl)urea diformate **(Compound 163)** (16.5 mg, 14%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 442.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.56 (s, 1H), 9.56 (s, 1H), 9.19 (s, 1H), 8.43 (s, 1H), 8.24 (s, 2H), 7.63 (d, J = 8.8 Hz, 1H), 7.36 (s, 1H), 7.06 (d, J = 8.4 Hz, 1H), 3.92 - 3.89 (m, 6H), 3.39 - 3.33 (m, 2H), 2.51 - 2.45 (m, 2H), 2.25 (s, 6H).

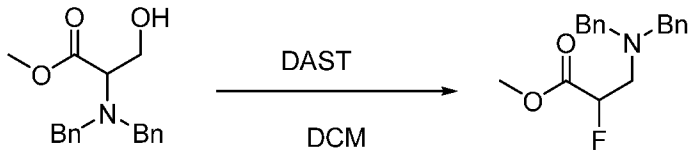
Example S160: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[(2S)-3-(dimethylamino)-2-fluoropropyl]urea and 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[(2R)-3-(dimethylamino)-2-fluoropropyl]urea (Compound 164 and Compound 165)

Step 1: Synthesis of methyl 2-(dibenzylamino)-3-hydroxypropanoate



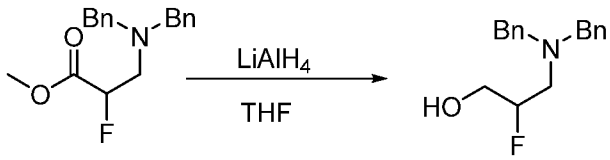
[0789] To a solution of methyl 2-amino-3-hydroxypropanoate hydrochloride (10.0 g, 64.28 mmol) in DMF (600.0 mL) was added KI (5.3 g, 32.14 mmol), K_2CO_3 (26.7 g, 192.83 mmol) and benzyl bromide (23.1 g, 134.98 mmol) dropwise at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (11/4, v/v) to afford methyl 2-(dibenzylamino)-3-hydroxypropanoate (15.1 g, 78%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =300.2.

Step 2: Synthesis of methyl 3-(dibenzylamino)-2-fluoropropanoate



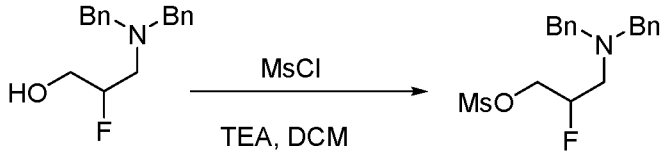
[0790] To a solution of methyl 2-(dibenzylamino)-3-hydroxypropanoate (7.0 g, 23.38 mmol) in DCM (300.0 mL) was added dropwise DAST (9.4 g, 58.46 mmol) at -40 °C under N_2. The reaction mixture was stirred at room temperature for 16 h. After the reaction was completed. The reaction mixture was quenched with sat. NH_4Cl (aq.) at 0 °C. The resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (9/2, v/v) to afford methyl 3-(dibenzylamino)-2-fluoropropanoate (4.9 g, 68%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =302.1.

Step 3: Synthesis of 3-(dibenzylamino)-2-fluoropropan-1-ol



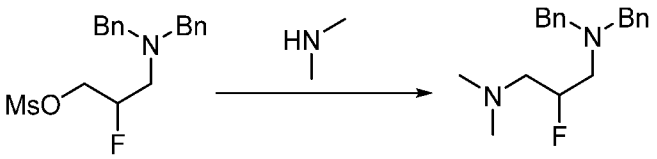
[0791] To a solution of $LiAlH_4$ (1.9 g, 49.77 mmol) in THF (200.0 mL) was added dropwise a solution of methyl 3-(dibenzylamino)-2-fluoropropanoate (5 g, 16.59 mmol) in THF at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h under N_2. After the reaction was completed. The reaction was quenched with water at 0 °C. The pH value of the mixture was adjusted to 5 with HCl (aq.). The resulting mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (7/3, v/v) to afford 3-(dibenzylamino)-2-fluoropropan-1-ol (3.4 g, 74%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =274.2.

Step 4: Synthesis of 3-(dibenzylamino)-2-fluoropropyl methanesulfonate



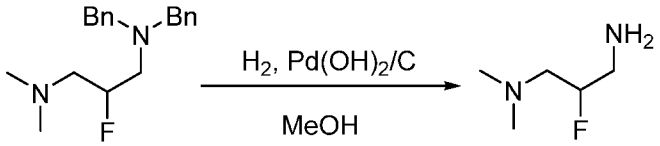
[0792] To a solution of 3-(dibenzylamino)-2-fluoropropan-1-ol (5.2 g, 19.02 mmol) in CH_2Cl_2 (300.0 mL) was added TEA (2.9 g, 28.54 mmol) and methanesulfonyl chloride (2.4 g, 20.93 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 6 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 3-(dibenzylamino)-2-fluoropropyl methanesulfonate (6.6 g, crude) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =352.1.

Step 5: Synthesis of [3-(dibenzylamino)-2-fluoropropyl]dimethylamine



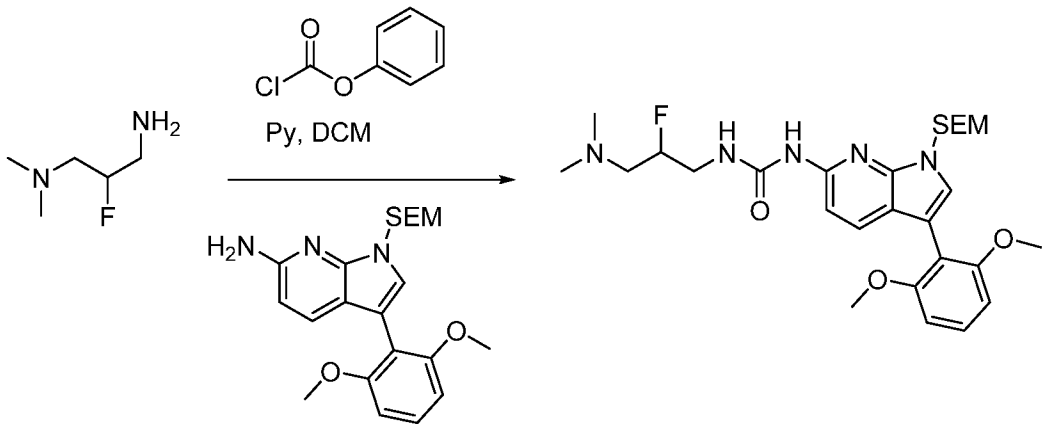
[0793] The mixture of 3-(dibenzylamino)-2-fluoropropyl methanesulfonate (4.0 g, crude) in dimethylamine/water (120.0 mL, 30%) was stirred at 60 °C for 3 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford [3-(dibenzylamino)-2-fluoropropyl]dimethylamine (3.3 g, crude) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =301.2.

Step 6: Synthesis of (3-amino-2-fluoropropyl)dimethylamine



[0794] To a solution of [3-(dibenzylamino)-2-fluoropropyl]dimethylamine (3.8 g, 12.65 mmol) in MeOH (200.0 mL) was added $Pd(OH)_2/C$ (1.1 g, wet) at room temperature. The resulting mixture was stirred at 60 °C for 16 h under H_2. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure to afford (3-amino-2-fluoropropyl)dimethylamine (1.4 g, crude) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =121.1.

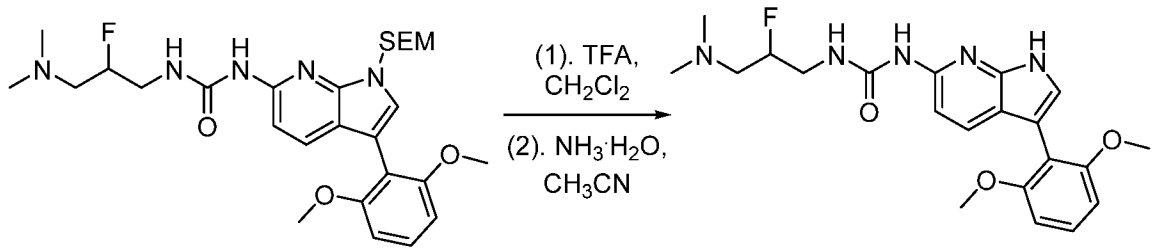
Step 7: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea



[0795] To a solution of 3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (300.0 mg, 0.75 mmol) in

DCM (12.0 mL) was added pyridine (237.6 mg, 3.00 mmol) and phenyl chloroformate (235.1 mg, 1.50 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added (3-amino-2-fluoropropyl)dimethylamine (902.3 mg, 7.51 mmol) and pyridine (20.0 mL) at room temperature. The resulting mixture was stirred at 60 °C for 16 h. After the reaction was completed. the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (13/1, v/v) to afford 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea (336.0 mg, 82%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =546.3.

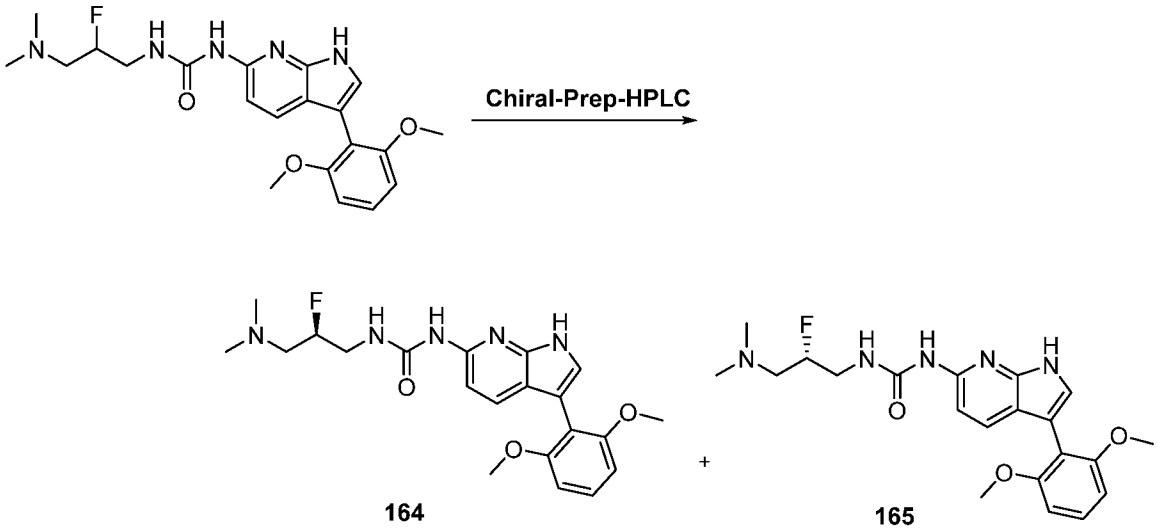
Step 8: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea



[0796] To a solution of 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea (300.0 mg, 0.55 mmol) in CH_2Cl_2 (10.0 mL) was added TFA (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (10.0 mL) was added $NH_3{\cdot}H_2O$ (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with acetonitrile/water (7/4, v/v) to afford 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea (106.0 mg, 46%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =416.2.

Step 9: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[(2S)-3-(dimethylamino)-2-fluoropropyl]urea and 1-[3-(2,6-dimethoxyphenyl)-1H-

pyrrolo[2,3-b]pyridin-6-yl]-3-[(2R)-3-(dimethylamino)-2-fluoropropyl]urea (Compound 164 and Compound 165)



[0797] The racemic 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea (90.0 mg, 0.22 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IA, 2x25 cm, 20 um; Mobile Phase A:Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 14 min; 220/254 nm;) to afford 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea Enantiomer 1 (12.6 mg, 14%) as a white solid and 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea Enantiomer 2 (16.9 mg, 18%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 164 and 165** in Table 1.

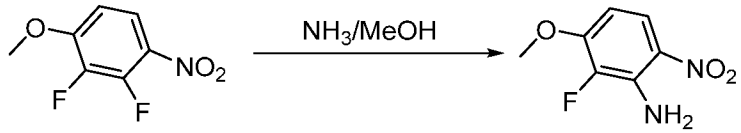
[0798] **1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea Enantiomer 1:** Retention Time 1: 7.811 min; LCMS (ESI, m/z): $[M+H]^+$ =416.1. ^1H NMR (300 MHz, CD_3OD): δ 7.59 (d, J = 8.7 Hz, 1H), 7.31 - 7.26 (m, 1H), 7.21 (s, 1H), 6.75 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 1H), 5.00 - 4.80 (m, 1H), 3.77 - 3.71 (m, 7H), 3.69 - 3.50 (m, 1H), 2.78 - 2.71 (m, 1H), 2.69 - 2.50 (m, 1H), 2.36 (s, 6H).

[0799] **1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea Enantiomer 2:** Retention Time 2: 11.45 min; LCMS (ESI, m/z): $[M+H]^+$ = 416.1. ^1H NMR(300 MHz, CD_3OD): δ 7.59 (d, J = 8.4 Hz, 1H), 7.31 -

7.26 (m, 1H), 7.21 (s, 1H), 6.75 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 1H), 5.00 - 4.80 (m, 1H), 3.77 - 3.71 (m, 6H), 3.69 - 3.50 (m, 2H), 2.79 - 2.71 (m, 1H), 2.69 - 2.50 (m, 1H), 2.36 (s, 6H).

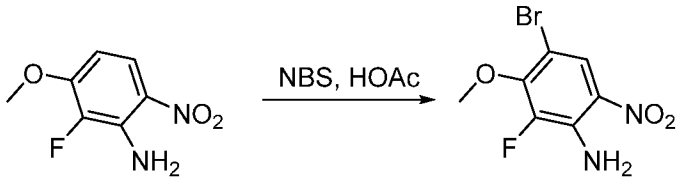
Example S161: Synthesis of (1S,2S)-2-fluoro-N-[3-(7-fluoro-6-methoxy-3H-1,3-benzodiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 166)

Step 1: Synthesis of 2-fluoro-3-methoxy-6-nitroaniline



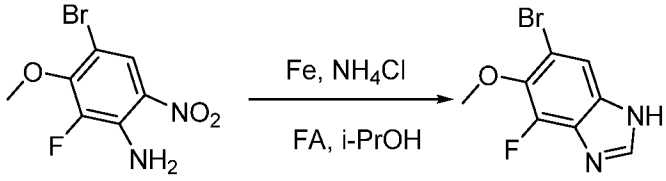
[0800] The solution of 2,3-difluoro-1-methoxy-4-nitrobenzene (2.0 g, 10.57 mmol) in NH_3/MeOH (20.0 mL, 7 mol/L) was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 2-fluoro-3-methoxy-6-nitroaniline (1.8 g, 91%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =187.0

Step 2: Synthesis of 4-bromo-2-fluoro-3-methoxy-6-nitroaniline



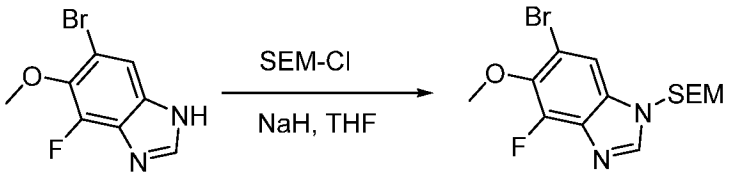
[0801] The mixture of 2-fluoro-3-methoxy-6-nitroaniline (1.5 g, 8.05 mmol) and NBS (2.1 g, 12.08 mmol) in AcOH (20.0 mL) was stirred at 90 °C for 4 h. After the reaction was completed, the reaction mixture was diluted with water and then filtered. The solid was washed with H_2O and then collected to afford 4-bromo-2-fluoro-3-methoxy-6-nitroaniline (2.5 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =265.0

Step 3: Synthesis of 6-bromo-4-fluoro-5-methoxy-1H-1,3-benzodiazole



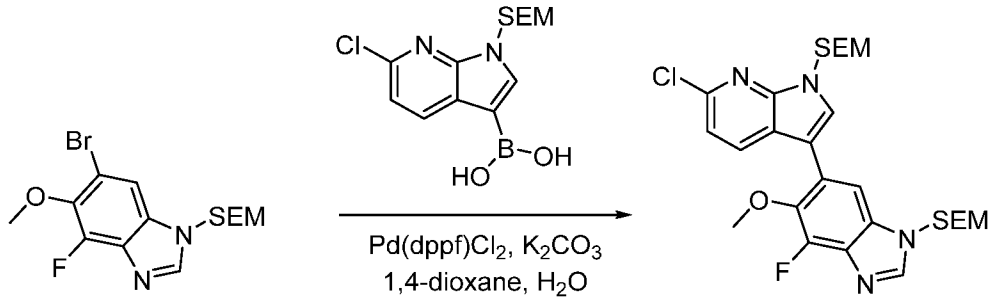
[0802] To a mixture of 4-bromo-2-fluoro-3-methoxy-6-nitroaniline (1.5 g, 5.66 mmol) and Fe (3.1 g, 56.60 mmol) in i-PrOH (10.0 mL) was added NH_4Cl (2.1 g, 39.62 mmol) and formic acid (10.0 mL) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (4/1, v/v) to afford 6-bromo-4-fluoro-5-methoxy-1H-1,3-benzodiazole (620.0 mg, 44%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =245.0.

Step 4: Synthesis of 6-bromo-4-fluoro-5-methoxy-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-benzodiazole



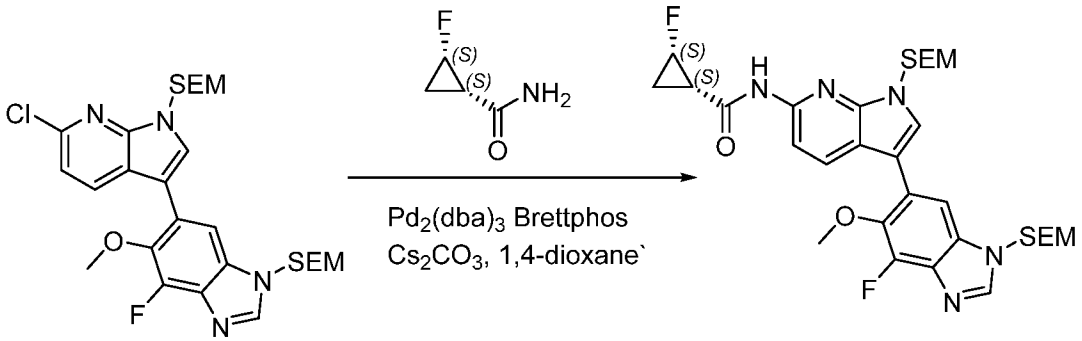
[0803] To a solution of 6-bromo-4-fluoro-5-methoxy-1H-1,3-benzodiazole (500.0 mg, 2.04 mmol) in THF (5.0 mL) was added NaH (146.8 mg, 60%) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 2 h. Then [2-(chloromethoxy)ethyl]trimethylsilane (510.2 mg, 3.06 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred at room temperature for additional 2 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (4/1, v/v) to afford 6-bromo-4-fluoro-5-methoxy-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-benzodiazole (700.0 mg, 91%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =375.0

Step 5: Synthesis of 6-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-fluoro-5-methoxy-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-benzodiazole



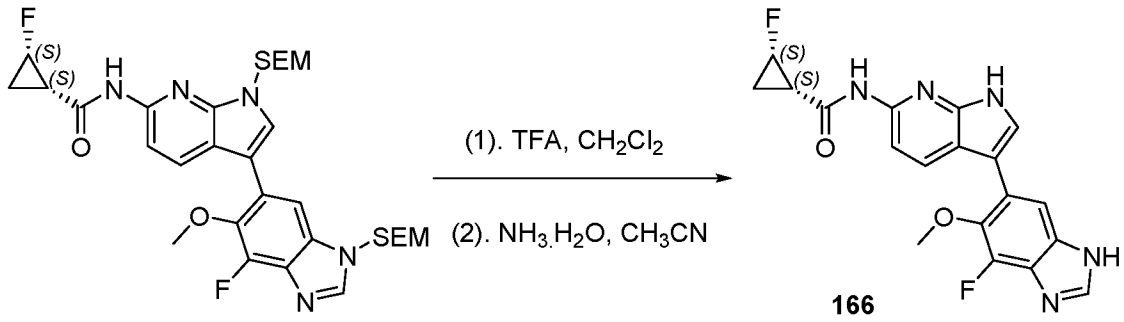
[0804] To a mixture of 6-bromo-4-fluoro-5-methoxy-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-benzodiazole (350.0 mg, 0.93 mmol) and 6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-ylboronic acid (609.2 mg, 1.86 mmol) in 1,4-dioxane/H_2O (5.0/0.5 mL) were added $Pd(dppf)Cl_2$ (136.4 mg, 0.18 mmol) and K_2CO_3 (386.6 mg, 2.79 mmol) at room temperature under N_2. The resulting mixture was stirred at 80°C for 3 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) afford 6-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-fluoro-5-methoxy-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-benzodiazole (200.0 mg, 37%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =577.2.

Step 6: Synthesis of (1S,2S)-2-fluoro-N-[3-(7-fluoro-6-methoxy-3-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-benzodiazol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide



[0805] To a mixture of 6-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-fluoro-5-methoxy-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-benzodiazole (190.0 mg, 0.32 mmol) and (1S,2S)-2-fluorocyclopropane-1-carboxamide (169.6 mg, 1.64 mmol) in 1,4-dioxane (4.0 mL) were added $Pd_2(dba)_3$ (60.2 mg, 0.06 mmol), BrettPhos (70.7 mg, 0.13 mmol) and Cs_2CO_3 (321.7 mg, 0.98 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 3 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/2, v/v) to afford (1S,2S)-2-fluoro-N-[3-(7-fluoro-6-methoxy-3-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-benzodiazol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (100.0 mg, 47%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =644.3.

Step 7: Synthesis of (1S,2S)-2-fluoro-N-[3-(7-fluoro-6-methoxy-3H-1,3-benzodiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 166)



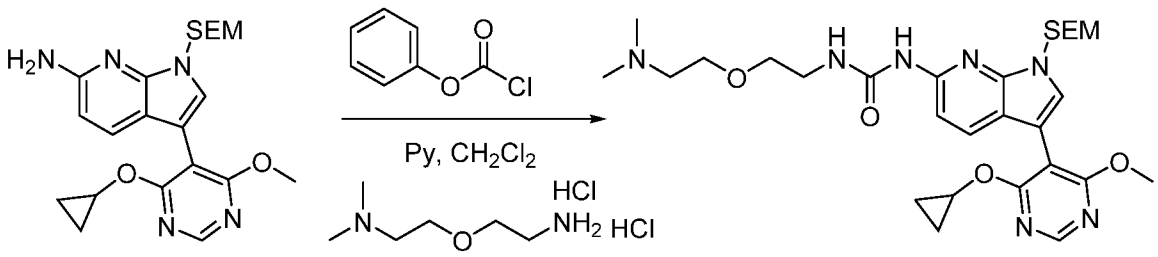
166

[0806] To a solution of (1S,2S)-2-fluoro-N-[3-(7-fluoro-6-methoxy-3-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-benzodiazol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (100.0 mg, 0.15 mmol) in DCM (1.0 mL) was added TFA (1.0 mL). The mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added $NH_3.H_2O$ (2.0 mL) and ACN (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 14% B to 34% B in 9 min, 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(7-fluoro-6-methoxy-3H-1,3-benzodiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide **(Compound 166)** (5.2 mg, 9%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =384.1. ^1H NMR (400 MHz, DMSO-d_6): δ 12.73 - 12.68 (br, 1H), 11.70 (s, 1H), 10.69 (s, 1H), 8.25 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.50 (s, 1H), 5.02 - 4.85 (m, 1H), 3.62 (s, 3H), 2.32 - 2.25 (m, 1H), 1.70 - 1.64 (m, 1H), 1.23 - 1.16 (m, 1H).

Example S162: Synthesis of 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-{2-[2-(dimethylamino)ethoxy]ethyl}urea; formic acid (Compound 167)

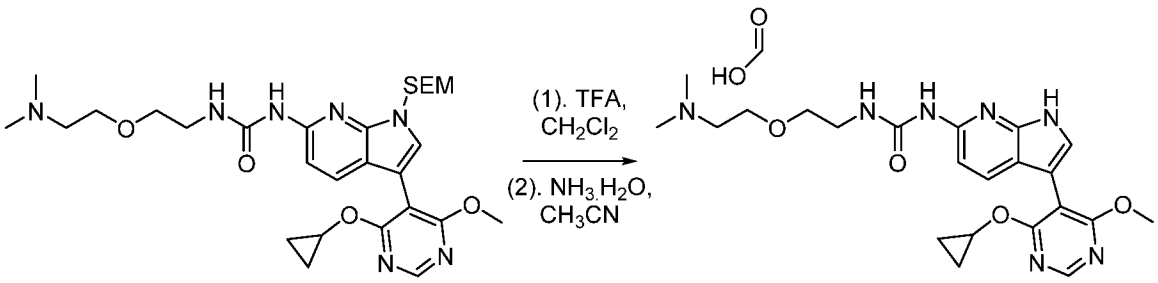
Step 1: Synthesis of 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-{2-[2-(dimethylamino)ethoxy]ethyl}urea



[0807] To a solution of 3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (200.0 mg, 0.47 mmol) in DCM (4.0 mL) was added phenyl chloroformate (87.9 mg, 0.56 mmol) and pyridine (148.0 mg, 1.87 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated under reduced pressure. To the residue in pyridine (4.0 mL) was added [2-(2-aminoethoxy)ethyl]dimethylamine (185.5 mg, 1.40 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with CH_3CN/H_2O (80/20, v/v) to afford 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-

b]pyridin-6-yl]-3-{2-[2-(dimethylamino)ethoxy]ethyl}urea (100.0 mg, 36%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =586.3.

Step 2: Synthesis of 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-{2-[2-(dimethylamino)ethoxy]ethyl}urea; formic acid (Compound 167)



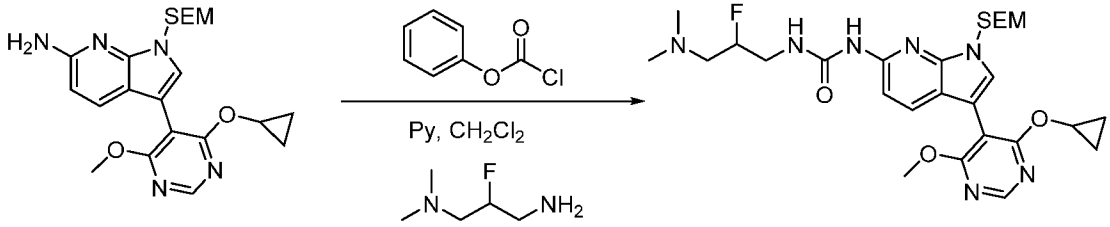
167

[0808] To a solution of 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-{2-[2-(dimethylamino)ethoxy]ethyl}urea (100 mg, 0.17 mmol) in DCM (1.0 mL) was added TFA (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in ACN (1.0 mL) was added $NH_3 \cdot H_2O$ (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A:Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 30% B in 7 min, 254 nm) to afford 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-{2-[2-(dimethylamino)ethoxy]ethyl}urea; formic acid **(Compound 167)** (3.9 mg, 4%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =456.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.74 (s, 1H), 9.25 (s, 1H), 8.70 (d, J = 4.0 Hz, 1H), 8.50 (s, 1H), 8.22 - 8.19 (m, 1H) 7.58 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 4.37 - 4.34 (m, 1H), 3.91 (s, 3H), 3.63 - 3.59 (m, 2H), 3.54 - 3.45 (m, 2H), 3.39 - 3.34 (m, 2H), 2.68 - 2.60 (m, 1H), 2.34 - 2.14 (m, 7H), 0.77 - 0.69 (m, 2H), 0.65 - 0.61 (m, 2H).

Example S163: Synthesis of 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[(2R)-3-(dimethylamino)-2-fluoropropyl]urea and 1-[3-(4-

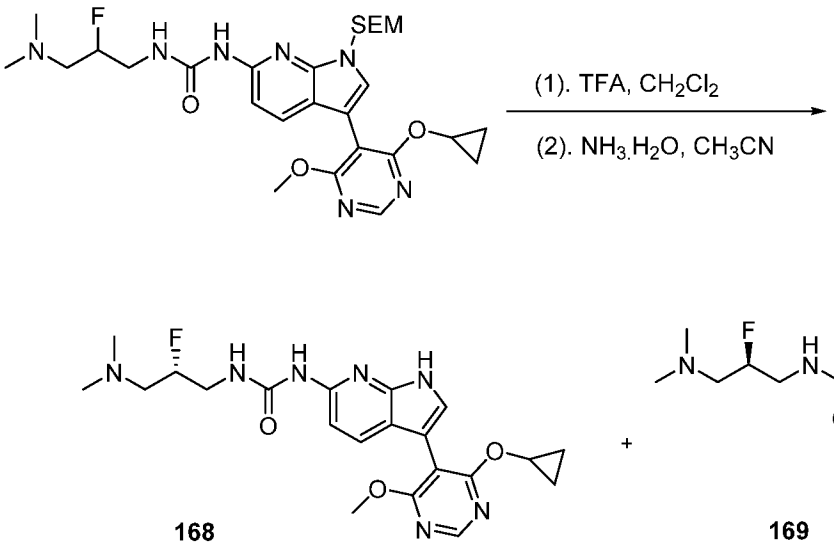
cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[(2S)-3-(dimethylamino)-2-fluoropropyl]urea (Compound 168 and Compound 169)

Step 1: Synthesis of 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea



[0809] To a solution of 3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (190.0 mg, 0.44 mmol) in CH_2Cl_2 (4.0 mL) was added pyridine (140.6 mg, 1.78 mmol) and phenyl chloroformate (83.5 mg, 0.53 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated under reduced pressure. To the residue in pyridine (4.0 mL) was added (3-amino-2-fluoropropyl)dimethylamine (534.0 mg, 4.44 mmol) at room temperature. The resulting mixture was stirred at 60 °C for another 1 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum CH_2Cl_2/CH_3OH (95/5, v/v) to afford 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea (160.0 mg, 62%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =574.3.

Step 2: Synthesis of 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[(2R)-3-(dimethylamino)-2-fluoropropyl]urea and **1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[(2S)-3-(dimethylamino)-2-fluoropropyl]urea (Compound 168 and Compound 169)**



168 + 169

[0810] To a solution of 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea (150.0 mg, 0.26 mmol) in CH_2Cl_2 (4.0 mL) was added TFA (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (4.0 mL) was added $NH_3.H_2O$ (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2×25 cm, 5 um; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) -- HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 10.5 min; 254 nm) to afford 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea Enantiomer 1 (10.2 mg, 8%) as a white solid and 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea Enantiomer 2 (11.0 mg, 9%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 168 and 169** in Table 1.

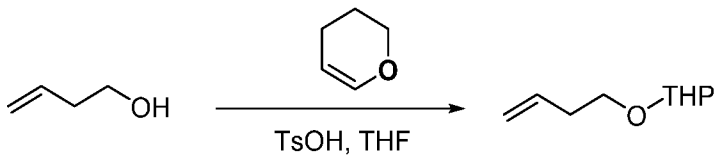
[0811] **1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea Enantiomer 1:** Retention Time 1: 5.876 min; LCMS (ESI, m/z): $[M+H]^+$ = 444.1. ^1H NMR (400 MHz, DMSO-d_6): δ 11.59 (s, 1H), 9.25 (s,

1H), 8.58 (s, 1H), 8.49 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.33 (s, 1H), 7.04 (d, J = 8.4 Hz, 1H), 4.81 - 4.70 (m, 1H), 4.37 - 4.33 (m, 1H), 3.92 (s, 3H), 3.64 - 3.52 (m, 1H), 3.45 - 3.38 (m, 1H), 2.22 (s, 6H), 0.86 - 0.82 (m, 2H), 0.69 - 0.62 (m, 2H) .

[0812] 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea Enantiomer 2: Retention Time 2: 9.106 min; LCMS (ESI, m/z): $[M+H]^+$ =444.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.60 (s, 1H), 9.27 (s, 1H), 8.60 (s, 1H), 8.49 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 4.81 - 4.68 (m, 1H), 4.37 - 4.33 (m, 1H), 3.91 (s, 3H), 3.64 - 3.52 (m, 1H), 3.43 - 3.34 (m, 1H), 2.21 (s, 6H), 0.85 - 0.72 (m, 2H), 0.72 - 0.62 (m, 2H).

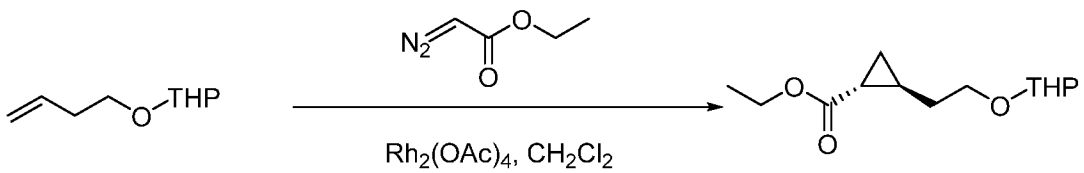
Example S164: Synthesis of trans-2-(2-hydroxyethyl)-N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 170)

Step 1: Synthesis of 2-(but-3-en-1-yloxy)tetrahydro-2H-pyran



[0813] To a solution of 3-buten-1-ol (10.0 g, 138.68 mmol) in tetrahydrofuran (100.0 mL) was added 3,4-dihydro-2H-pyran (2.4 g, 13.88 mmol) and 4-methylbenzenesulfonic acid (17.5 g, 208.01 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford 2-(but-3-en-1-yloxy)tetrahydro-2*H*-pyran (9.3 g, 43%) as a colorless oil.

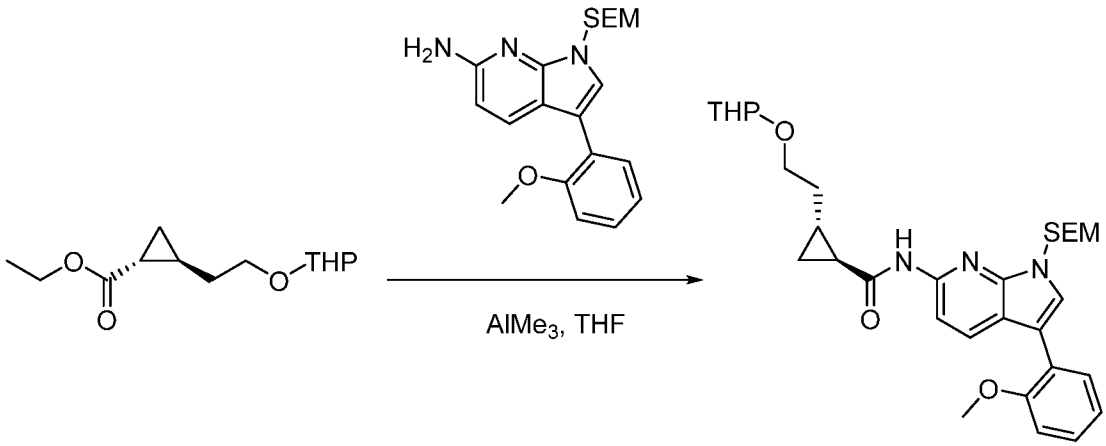
Step 2: Synthesis of Trans-ethyl 2-[2-(oxan-2-yloxy)ethyl]cyclopropane-1-carboxylate



[0814] To a mixture of 2-(but-3-en-1-yloxy)tetrahydro-2*H*-pyran (800.0 mg, 5.11 mmol) and $Rh_2(OAc)_4$ (22.63 mg, 0.05 mmol) in CH2Cl2 (5.0 mL) was added dropwise ethyl

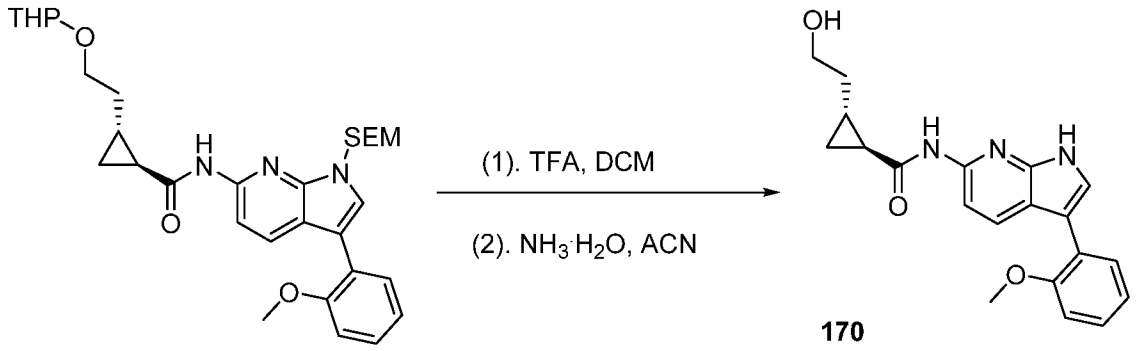
diazoacetate (1.1 g, 10.22 mmol) at room temperature during 8 h under N_2. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford trans-ethyl 2-[2-(oxan-2-yloxy)ethyl]cyclopropane-1-carboxylate (300.0 mg, 24%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =243.2.

Step 3: Synthesis of trans-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-[2-(oxan-2-yloxy)ethyl]cyclopropane-1-carboxamide



[0815] To a solution of trans-ethyl 2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)cyclopropane-1-carboxylate (300.0 mg, 0.82 mmol) in THF (5.0 mL) was added 3-(2-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (590.15 mg, 2.43 mmol) and $AlMe_3$ (0.2 mL, 2 mol/L) at 0 °C. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by reverse flash column chromatography with MeOH/H_2O (5/80, v/v) to afford trans-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-[2-(oxan-2-yloxy)ethyl]cyclopropane-1-carboxamide (100.0 mg, 33%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =566.3.

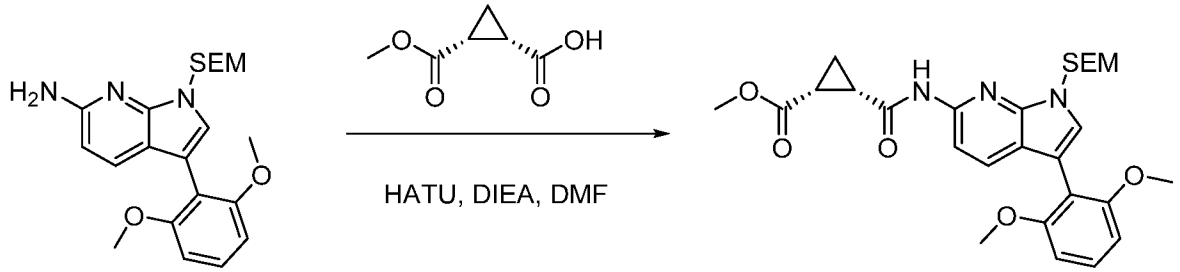
Step 4: Synthesis of trans-2-(2-hydroxyethyl)-N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 170)



[0816] To a solution of trans-N-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-[2-(oxan-2-yloxy)ethyl]cyclopropane-1-carboxamide (100.0 mg, 0.17 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3 \cdot H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 36% B to 46% B in 8 min; 254 nm) to afford trans-2-(2-hydroxyethyl)-N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide **(Compound 170)** (8.7 mg, 14 %) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =352.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.55 (d, J = 2.4 Hz, 1H), 10.50 (s, 1H), 7.99 - 7.89 (m, 2H), 7.57 - 7.53 (m, 2H), 7.29 - 7.24 (m, 1H), 7.11 - 7.00 (m, 2H), 4.55 - 4.52 (m, 1H), 3.81 (s, 3H), 3.54 - 3.48 (m, 2H), 1.86 - 1.84 (m, 1H), 1.48 - 1.42 (m, 2H), 1.34 - 1.28 (m, 1H), 1.04 - 1.01 (m, 1H), 0.71 - 0.68 (m, 1H).

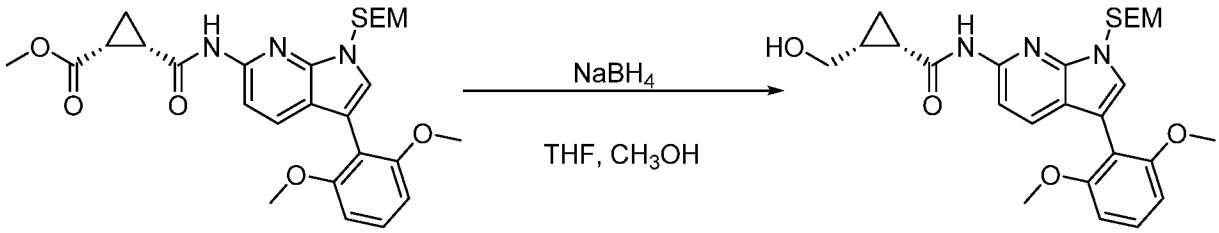
Example S165: Synthesis of (1S,2R)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide and (1R,2S)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide (Compound 171 and Compound 172)

Step 1: Synthesis of Methyl cis-2-((3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamoyl)cyclopropane-1-carboxylate



[0817] To a solution of 3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (500.0 mg, 1.25 mmol) in DMF (10.0 mL) was added cis-2-(methoxycarbonyl)cyclopropane-1-carboxylic acid (180.4 mg, 1.25 mmol), DIEA (808.6 mg, 6.26 mmol) and HATU (570.9 mg, 1.50 mmol) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 2 h under N_2. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (62/38, v/v) to afford methyl cis-2-((3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamoyl)cyclopropane-1-carboxylate (640.0 mg, 97%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =526.2.

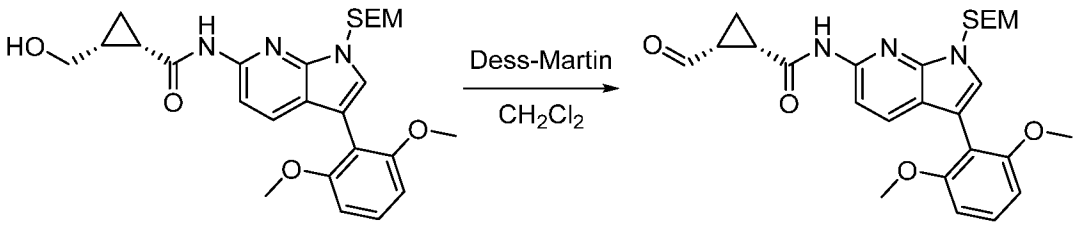
Step 2: Synthesis of Cis-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(hydroxymethyl)cyclopropane-1-carboxamide



[0818] To a solution of methyl cis-2-((3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamoyl)cyclopropane-1-carboxylate (640.0 mg, 1.21 mmol) in THF/CH_3OH (10.0 mL/10.0 mL) was added $NaBH_4$ (460.6 mg, 12.17 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was quenched with H_2O at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated

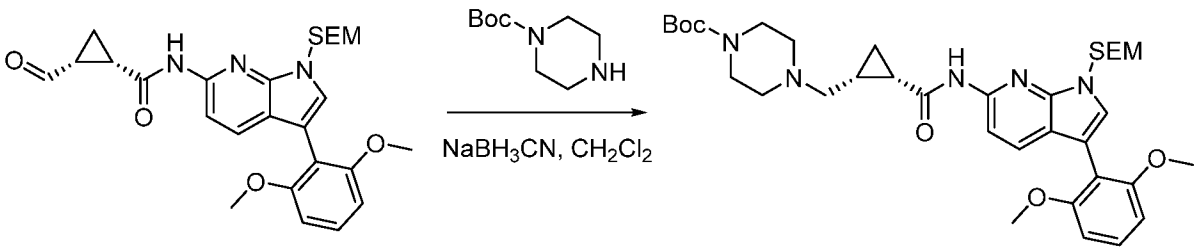
under reduced pressure to afford cis-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(hydroxymethyl)cyclopropane-1-carboxamide (510.0 mg, crude) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =498.2.

Step 3: Synthesis of Cis-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-formylcyclopropane-1-carboxamide



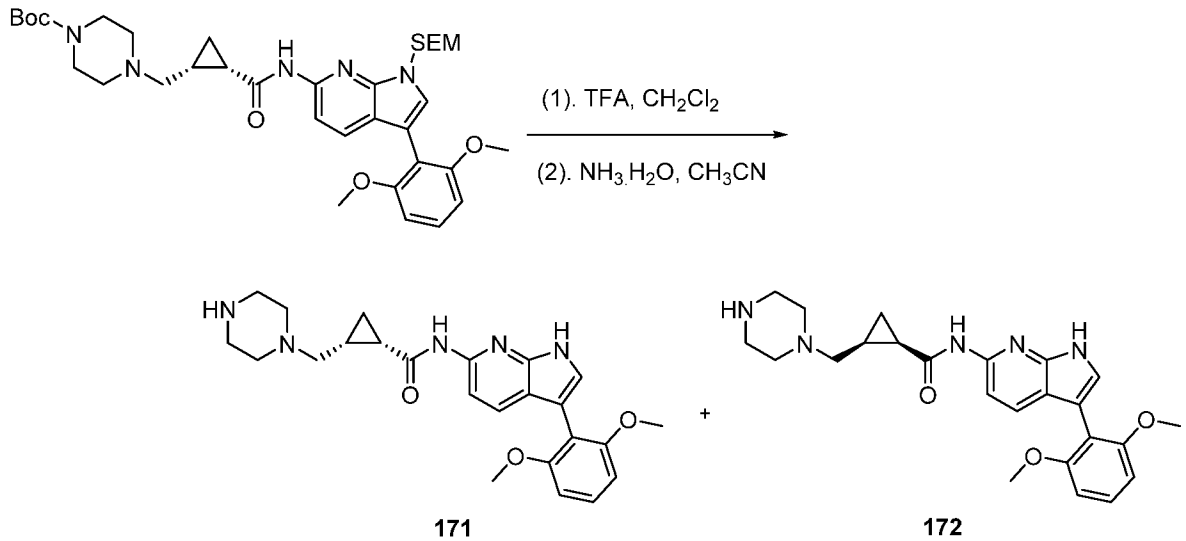
[0819] To a solution of cis-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(hydroxymethyl)cyclopropane-1-carboxamide (510.0 mg, crude) in CH_2Cl_2 (20.0 mL) was added Dess-Martin (869.3 mg, 2.06 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford cis-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-formylcyclopropane-1-carboxamide (840.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =496.2.

Step 4: Synthesis of tert-butyl 4-((cis-2-((3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamoyl)cyclopropyl)methyl)piperazine-1-carboxylate



[0820] To a solution of cis-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-formylcyclopropane-1-carboxamide (840.0 mg, 1.69 mmol) in CH_2Cl_2 (20.0 mL) was added tert-butyl piperazine-1-carboxylate (631.3 mg, 3.39 mmol) and $NaBH_3CN$ (213.0 mg, 3.39 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was quenched with CH_3OH. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (20/80, v/v) to afford tert-butyl 4-((cis-2-((3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamoyl)cyclopropyl)methyl)piperazine-1-carboxylate (660.0 mg, 58%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =666.4.

Step 5: Synthesis of (1S,2R)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide and (1R,2S)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide (Compound 171 and Compound 172)



[0821] To a solution of tert-butyl 4-((cis-2-((3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamoyl)cyclopropyl)methyl)piperazine-1-carboxylate (75.0 mg, 0.16 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in ACN (5.0 mL) was added $NH_3.H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting

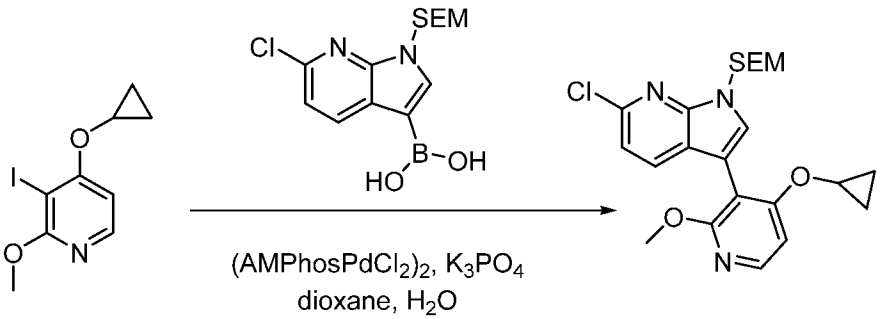
mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was separated by Prep-Chiral-HPLC with the following conditions (Column: Lux 5 um Cellulose-2, 2.12×25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH3-MeOH) -- HPLC, Mobile Phase B:EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 24 min; 254 nm) to afford N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide Enantiomer 1 (5.1 mg, 2%) as a white solid and N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide Enantiomer 2 (3.2 mg, 1%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 171 and 172** in Table 1.

[0822] N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide Enantiomer 1: Retention Time 1: 15.594 min; LCMS (ESI, m/z): $[M+H]^+$ =436.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.39 (s, 1H), 10.46 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.29 - 7.25 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 3.69 (s, 6H), 2.67 - 2.62 (m, 3H), 2.47 - 2.42 (m, 1H), 2.38 - 2.21 (m, 4H), 2.10 - 2.06 (m, 1H), 1.36 - 1.30 (m, 1H), 1.04 - 0.91 (m, 1H), 0.89 - 0.82 (m, 1H).

[0823] N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(piperazin-1-ylmethyl)cyclopropane-1-carboxamide Enantiomer 2: Retention Time 2: 21.022 min; LCMS (ESI, m/z): $[M+H]^+$ =436.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.39 (s, 1H), 10.46 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.27 - 7.25 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 3.69 (s, 6H), 2.67 - 2.61 (m, 3H), 2.47 - 2.30 (m, 4H), 2.10 - 2.06 (m, 1H), 1.35 - 1.32 (m, 1H), 0.98- 0.91 (m, 1H), 0.89 - 0.82 (m, 1H)

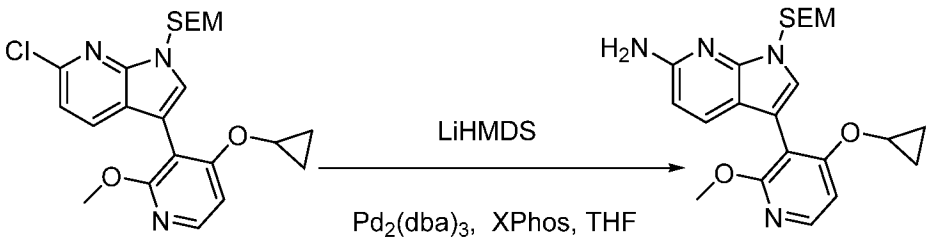
Example S166: Synthesis of 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea (Compound 173)

Step 1: Synthesis of 3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-cyclopropoxy-2-methoxypyridine



[0824] To a solution of 4-cyclopropoxy-3-iodo-2-methoxypyridine (500.0 mg, 1.72 mmol) in 1, 4 - dioxane (20.0 mL)/H_2O (5.0 mL) was added K_3PO_4 (1093.8 mg, 5.15 mmol), 6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-ylboronic acid (561.1 mg, 1.72 mmol) and $(AMPhosPdCl_2)_2$ (243.3 mg, 0.34 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-cyclopropoxy-2-methoxypyridine (650.0 mg, 84%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =446.2.

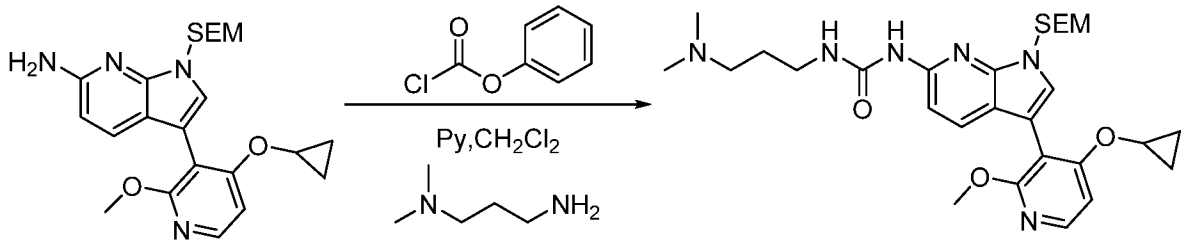
Step 2: Synthesis of 3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine



[0825] To a solution of 3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-cyclopropoxy-2-methoxypyridine (524.0 mg, 1.2 mmol) in THF (20.0 mL) was added $Pd_2(dba)_3$ (107.6 mg, 0.12 mmol), LiHMDS (3.5 mL, 1.0 mol/L) and XPhos (112.0 mg, 0.24 mmol) at room temperature under N_2. The resulting mixture was stirred at 60 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum

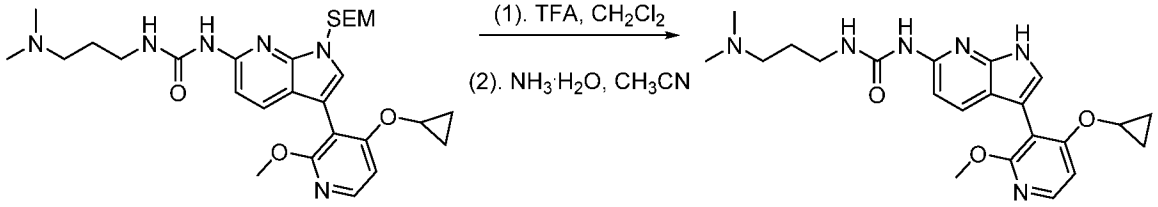
ether/ethyl acetate (3/1, v/v) to afford 3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (440.0 mg, 87%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =427.2.

Step 3: Synthesis of 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea



[0826] To a solution of 3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (200.0 mg, 0.47 mmol) in CH_2Cl_2 (15.0 mL) was added Pyridine (148.3 mg, 1.88 mmol) and phenyl chloroformate (146.8 mg, 0.94 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added N^1, N^1-dimethylpropane-1,3-diamine (335.3 mg, 3.28 mmol) and Pyridine (10.0 mL) at room temperature. The resulting mixture was stirred at 60 C for 3 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (20/1, v/v) to afford 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea (140.0 mg, 53%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =555.3.

Step 4: Synthesis of 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea (Compound 173)

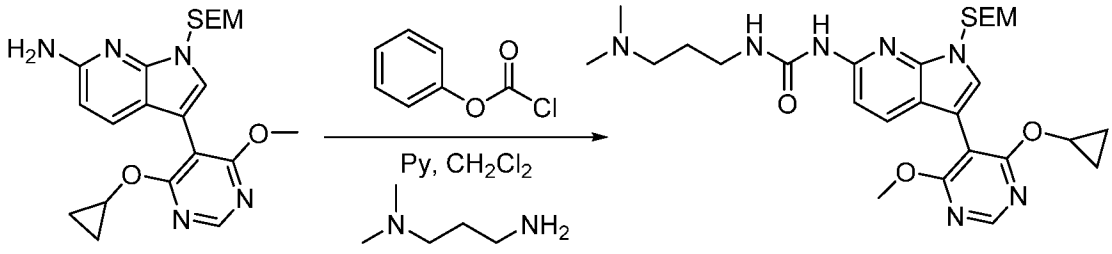


173

[0827] To a solution of 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea (120.0 mg, 0.22 mmol) in CH_2Cl_2 (8.0 mL) was added TFA (8.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added $NH_3.H_2O$ (8.0 mL) and CH_3CN (8.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C_{18} Column, 30x150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60.0 mL/min; Gradient: 18% B to 35% B in 8 min; Wave Length: 254 nm) to afford 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea **(Compound 173)** (37.4 mg, 39%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 425.4. ^1H NMR (400 MHz, DMSO-d_6): δ 11.43 (s, 1H), 9.11 (s, 1H), 8.53 (s, 1H); 8.06 (d, J = 6.0 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 2.4 Hz, 1H), 7.13 (d, J = 5.6 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 3.94 - 3.90 (m, 1H), 3.81 (s, 3H), 3.27 - 3.22 (m, 2H), 2.29 - 2.26 (m, 2H), 2.15 (s, 6H), 1.69 - 1.62 (m, 2H), 0.81 - 0.78 (m, 2H), 0.66 - 0.61 (m, 2H).

Example S167: Synthesis of 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea (Compound 174)

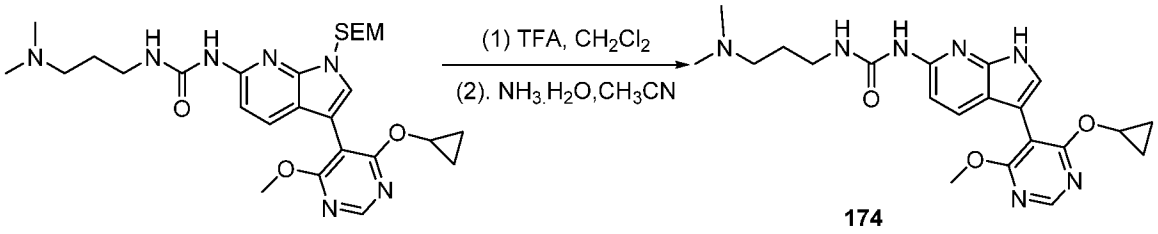
Step 1: Synthesis of 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea



[0828] To a solution of 3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (600.0 mg, 1.40 mmol) in CH_2Cl_2 (6.0 mL) was added phenyl chloroformate (263.7 mg, 1.68 mmol) and pyridine (444.0 mg, 5.61 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated under reduced pressure. To the

residue in pyridine (6.0 mL) was added N^1,N^1-dimethylpropane-1,3-diamine (430.2 mg, 4.21 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with CH_2Cl_2/CH_3OH (90/10, v/v) to afford 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea (390.0 mg, 50%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =556.3.

Step 2: Synthesis of 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea (Compound 174)



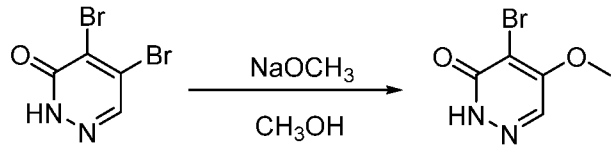
174

[0829] To a solution of 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea (200.0 mg, 0.36 mmol) in CH_2Cl_2 (4.0 mL) was added TFA (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (4.0 mL) was added $NH_3 \cdot H_2O$ (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 18% B to 38% B in 8 min, 38% B; Wave Length: 254 nm) to afford 1-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)propyl]urea **(Compound 174)** (56.7 mg, 36%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =426.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.56 (s, 1H), 9.15 (s, 1H), 8.48 (s, 2H), 7.58 (d, J = 8.4 Hz, 1H), 7.33 (s, 1H), 6.98 (d,

J = 8.8 Hz, 1H), 4.38 - 4.33 (m, 1H), 3.91 (s, 3H), 3.26 - 3.21 (m, 2H), 2.29 - 2.25 (m, 2H), 2.14 (s, 6H), 1.69 - 1.62 (m, 2H), 0.77 - 0.74 (m, 2H), 0.69 - 0.59 (m, 2H).

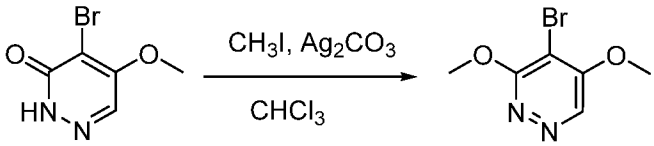
Example S168: Synthesis of (1S,2S)-N-[3-(3,5-dimethoxypyridazin-4-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 175)

Step 1: Synthesis of 4-bromo-5-methoxy-2H-pyridazin-3-one



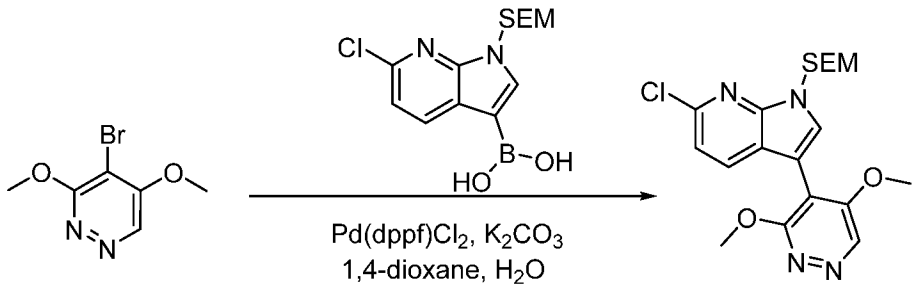
[0830] To a solution of 4,5-dibromo-2H-pyridazin-3-one (5.0 g, 19.69 mmol) in CH_3OH (80.0 mL) was added NaOMe (3.2 g, 59.08 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the reaction solution was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with ACN/H_2O (1/10, v/v) to afford 4-bromo-5-methoxy-2H-pyridazin-3-one (150.0 mg, 4%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =205.0.

Step 2: Synthesis of 4-bromo-3,5-dimethoxypyridazine



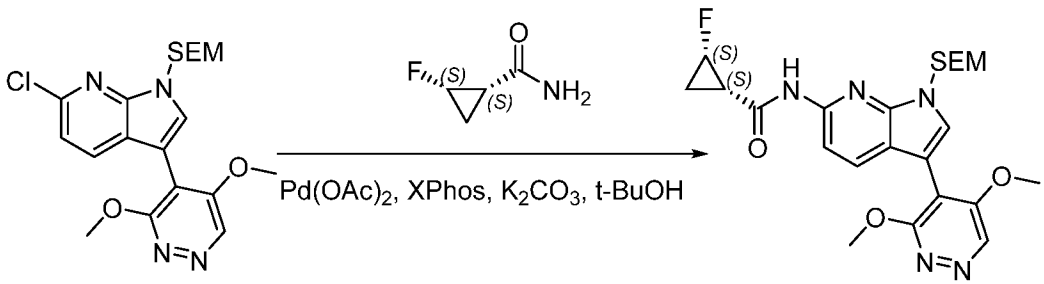
[0831] To a solution of 4-bromo-5-methoxy-2H-pyridazin-3-one (2.0 g, 9.76 mmol) in $CHCl_3$ (30.0 mL) was added Ag_2CO_3 (10.8 g, 39.02 mmol) and CH_3I (11.1 g, 78.04 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with ACN/H_2O (1/2, v/v) to afford 4-bromo-3,5-dimethoxypyridazine (100.0 mg, 4%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =219.0.

Step 3: Synthesis of 4-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-3,5-dimethoxypyridazine



[0832] To a solution of 4-bromo-3,5-dimethoxypyridazine (130.0 mg, 0.59 mmol) in dioxane/H_2O (10.0 mL/2.0 mL) was added 6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-ylboronic acid (193.9 mg, 0.59 mmol), K_2CO_3 (246.1 mg, 1.78 mmol) and $Pd(dppf)Cl_2$ (43.4 mg, 0.06 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 4-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-3,5-dimethoxypyridazine (70.0 mg, 28%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ = 421.1.

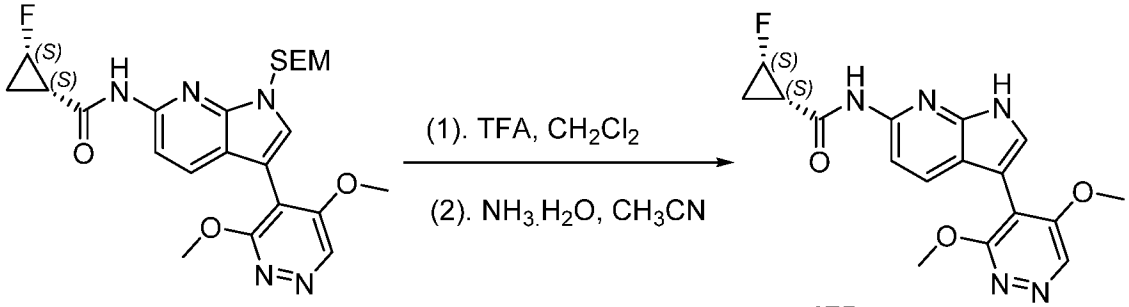
Step 4: Synthesis of (1S,2S)-N-[3-(3,5-dimethoxypyridazin-4-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide



[0833] To a solution of 4-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-3,5-dimethoxypyridazine (80.0 mg, 0.19 mmol) in t-BuOH (6.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (97.9 mg, 0.95 mmol), X-Phos (18.1 mg, 0.04 mmol), K_2CO_3 (78.8 mg, 0.57 mmol) and $Pd(OAc)_2$ (4.3 mg, 0.02 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h under N_2. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous

sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with ACN/ H_2O (1/2, v/v) to afford (1S,2S)-N-[3-(3,5-dimethoxypyridazin-4-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (30.0 mg, 32%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =488.2.

Step 5: Synthesis of (1S,2S)-N-[3-(3,5-dimethoxypyridazin-4-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 175)

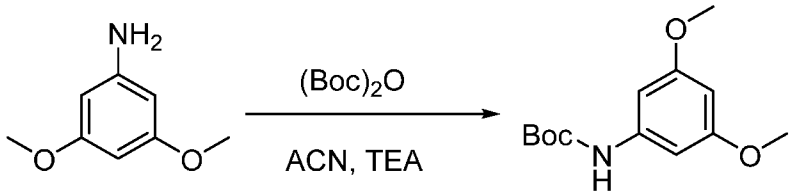


175

[0834] To a solution of (1S,2S)-N-[3-(3,5-dimethoxypyridazin-4-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (50.0 mg, 0.12 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions Column (YMC-Actus Triart C18 ExRS, 30x150 mm, 5 μm; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:15% B to 40% B in 8 min; 254 nm) to afford (1S,2S)-N-[3-(3,5-dimethoxypyridazin-4-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide **(Compound 175)** (6.6 mg, 17 %) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =358.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.84 (s, 1H), 10.64 (s, 1H), 9.01 (s, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.64 (s, 1H), 5.01 - 4.84 (m, 1H), 4.04 (s, 3H), 3.99 (s, 3H), 2.26 - 2.22 (m, 1H), 1.70 - 1.63 (m, 1H), 1.19 - 1.13 (m, 1H).

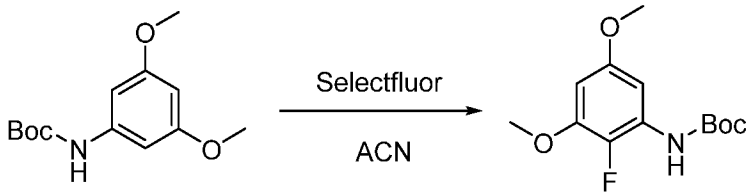
Example S169: Synthesis of (1S,2S)-2-fluoro-N-(3-(4-fluoro-5,7-dimethoxybenzo[d]thiazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 176)

Step 1: Synthesis of tert-butyl N-(3,5-dimethoxyphenyl)carbamate



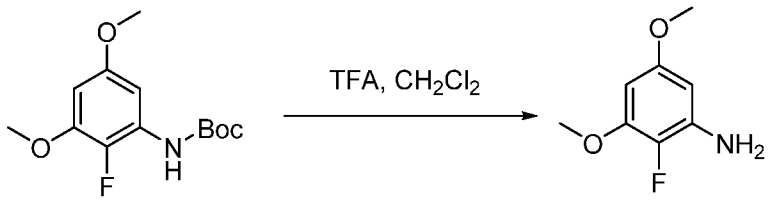
[0835] To a solution of 3,5-dimethoxyaniline (10.0 g, 6.52 mmol) in ACN (10.0 mL) was added Boc_2O (21.3 g, 97.93 mmol) and TEA (19.8 g, 195.84 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford tert-butyl N-(3,5-dimethoxyphenyl)carbamate (5.0 g, 30%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =254.1.

Step 2: Synthesis of tert-butyl N-(2-fluoro-3,5-dimethoxyphenyl)carbamate:



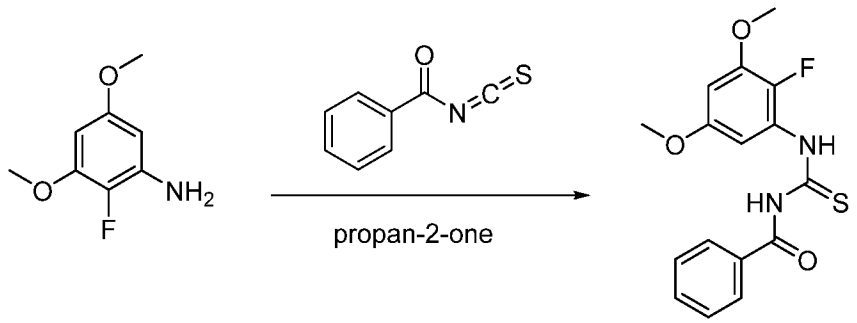
[0836] To a solution of Selectfluor (5.0 g, 15.72 mmol) in ACN (50.0 mL) was added tert-butyl N-(3,5-dimethoxyphenyl)carbamate (4.0 g, 15.72 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h. After the reaction was completed, the resulting mixture was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford tert-butyl N-(2-fluoro-3,5-dimethoxyphenyl)carbamate (1.2 g, 28%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =272.1.

Step 3: Synthesis of 2-fluoro-3,5-dimethoxyaniline



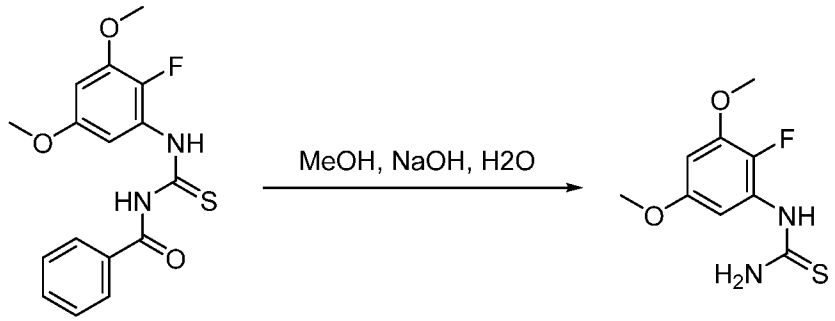
[0837] To a solution of tert-butyl N-(2-fluoro-3,5-dimethoxyphenyl)carbamate (1.0 g, 3.66 mmol) in DCM (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O. The pH value of the mixture was adjusted to 7 with aq. $NaHCO_3$. The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 2-fluoro-3,5-dimethoxyaniline (500.0 mg, 79%) as a red solid. LCMS (ESI, m/z): $[M+H]^+$ =172.1.

Step 4: Synthesis of 1-benzoyl-3-(2-fluoro-3,5-dimethoxyphenyl)thiourea



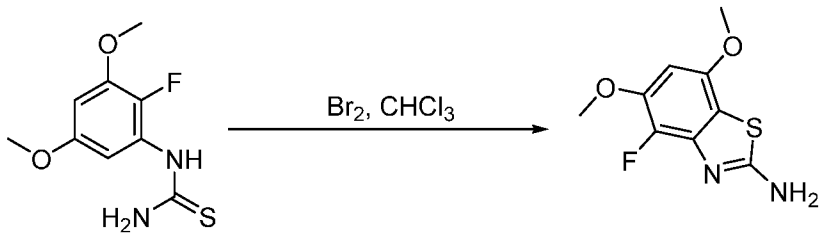
[0838] To a solution of 2-fluoro-3,5-dimethoxyaniline (500.0 mg, 2.91 mmol) in propan-2-one (5.0 mL) was added benzoyl isothiocyanate (441.6 mg, 2.91 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 12 h. After the reaction was completed, the resulting mixture was filtered. The solid was collected and dried to afford 1-benzoyl-3-(2-fluoro-3,5-dimethoxyphenyl)thiourea (500.0 mg, crude) as a red oil. LCMS (ESI, m/z): $[M+H]^+$ =335.1.

Step 5: Synthesis of 2-fluoro-3,5-dimethoxyphenylthiourea



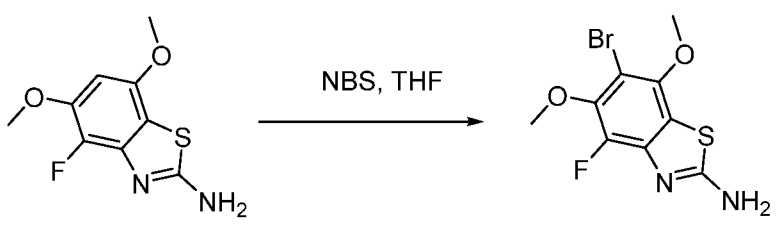
[0839] To a solution of 1-benzoyl-3-(2-fluoro-3,5-dimethoxyphenyl)thiourea (500.0 mg, crude) in MeOH (5.0 mL) and H_2O (5.0 mL) was added NaOH (39.6 mg, 1.65 mmol). The resulting mixture was stirred at 80 °C for 12 h. After the reaction was completed, the resulting mixture was filtered. The solid was washed with CH_3OH and then dried to afford 2-fluoro-3,5-dimethoxyphenylthiourea (300.0 mg, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =231.1.

Step 6: Synthesis of 4-fluoro-5,7-dimethoxy-1,3-benzothiazol-2-amine



[0840] To a solution of 2-fluoro-3,5-dimethoxyphenylthiourea (300.0 mg, 1.34 mmol) in $CHCl_3$ (5.0 mL) was added Br_2 (417.4 mg, 1.5 mmol). The resulting mixture was stirred at 60 °C for 2 h. After the reaction was completed, the resulting mixture was filtered. The solid was collected and dried to afford 4-fluoro-5,7-dimethoxy-1,3-benzothiazol-2-amine (250.0 mg, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =229.0.

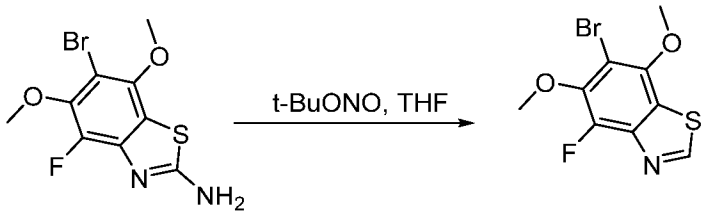
Step 7: Synthesis of 6-bromo-4-fluoro-5,7-dimethoxy-1,3-benzothiazol-2-amine



[0841] To a solution of 4-fluoro-5,7-dimethoxy-1,3-benzothiazol-2-amine (250.0 mg, 1.10 mmol) in THF (5.0 mL) was added NBS (300.0 mg, 1.64 mmol). The resulting mixture

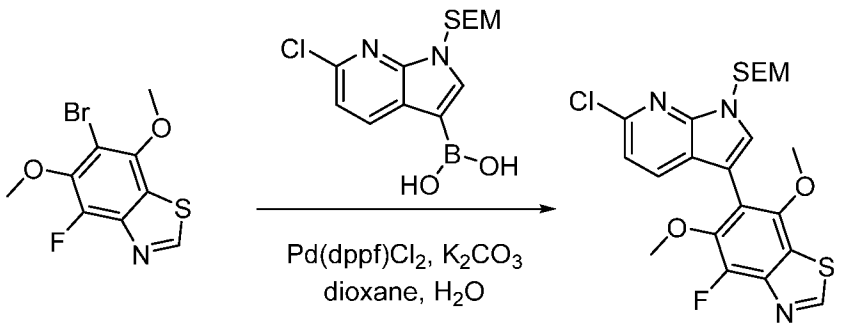
was stirred at 60 °C for 2 h. After the reaction was completed, the resulting mixture was filtered. The solid was collected and dried to afford 6-bromo-4-fluoro-5,7-dimethoxy-1,3-benzothiazol-2-amine (250.0 mg, crude) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ =306.9.

Step 8: Synthesis of 6-bromo-4-fluoro-5,7-dimethoxy-1,3-benzothiazole



[0842] To a solution of 6-bromo-4-fluoro-5,7-dimethoxy-1,3-benzothiazol-2-amine (250.0 mg, crude) in THF (5.0 mL) was added tert-butyl nitrite (125.9 mg, 1.36 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 6-bromo-4-fluoro-5,7-dimethoxy-1,3-benzothiazole (200.0 mg, 84%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =291.9.

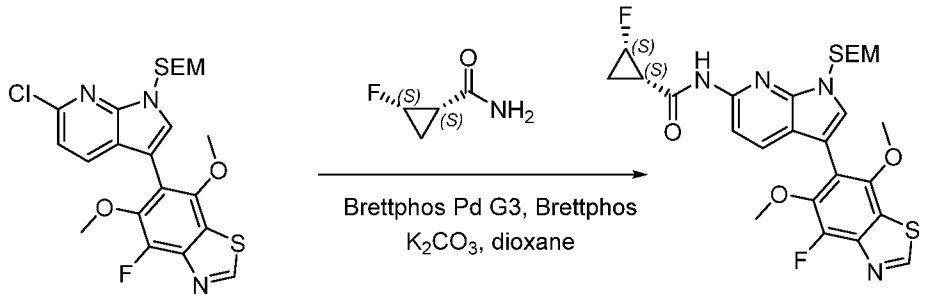
Step 9: Synthesis of 6-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-fluoro-5,7-dimethoxy-1,3-benzothiazole



[0843] To a solution of 6-bromo-4-fluoro-5,7-dimethoxy-1,3-benzothiazole (200.0 mg, 0.69 mmol) in dioxane (5.0 mL) and H_2O (0.5 mL) was added 6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-ylboronic acid (268.4 mg, 0.82 mmol), $Pd(dppf)Cl_2$ (50.2 mg, 0.07 mmol) and K_2CO_3 (283.9 mg, 2.07 mmol) under N_2. The

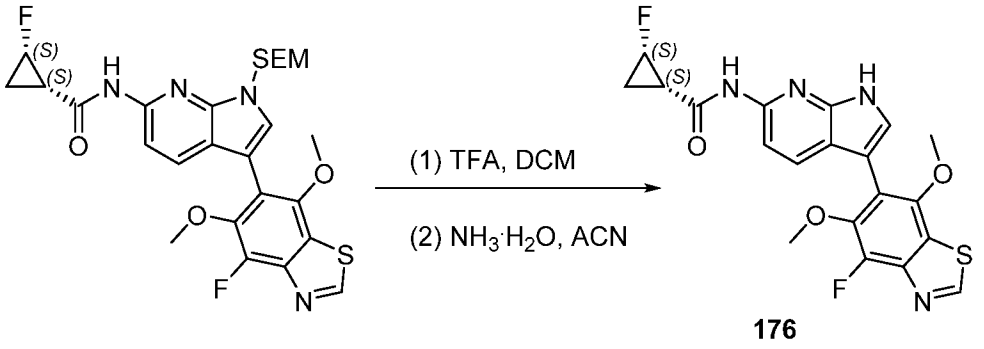
resulting mixture was stirred at 80 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 6-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-fluoro-5,7-dimethoxy-1,3-benzothiazole (200.0 mg, 59%) as a green oil. LCMS (ESI, m/z): $[M+H]^+$ =494.1.

Step 10: Synthesis of (1S,2S)-2-fluoro-N-[3-(4-fluoro-5,7-dimethoxy-1,3-benzothiazol-6-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide



[0844] To a solution of 6-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-fluoro-5,7-dimethoxy-1,3-benzothiazole (200.0 mg, 0.45 mmol) in dioxane (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (125.2 mg, 1.25 mmol), K_2CO_3 (167.8 mg, 1.25 mmol), BrettPhos (43.4 mg, 0.08 mmol) and BrettPhos Pd G3 (36.7 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1S,2S)-2-fluoro-N-[3-(4-fluoro-5,7-dimethoxy-1,3-benzothiazol-6-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (100.0 mg, 44%) as a green oil. LCMS (ESI, m/z): $[M+H]^+$ =561.2.

Step 11: Synthesis of (1S,2S)-2-fluoro-N-(3-(4-fluoro-5,7-dimethoxybenzo[d]thiazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 176)

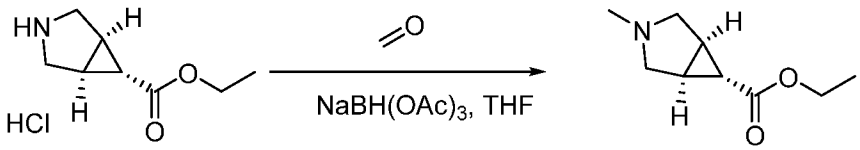


176

[0845] To a solution of (1S,2S)-2-fluoro-N-[3-(4-fluoro-5,7-dimethoxy-1,3-benzothiazol-6-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (100.0 mg, 0.18 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3·H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 49% B to 63% B in 10 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-(4-fluoro-5,7-dimethoxybenzo[d]thiazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide **(Compound 176)** (2.3 mg, 2%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =431.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.79 (s, 1H), 10.67 (s, 1H), 9.42 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.55 (d, J = 2.4 Hz, 1H), 5.03 - 4.79 (m, 1H), 3.61 (s, 3H), 3.47 (s, 3H), 2.26 - 2.20 (m, 1H), 1.68 - 1.59 (m, 1H), 1.17 - 1.08 (m, 1H).

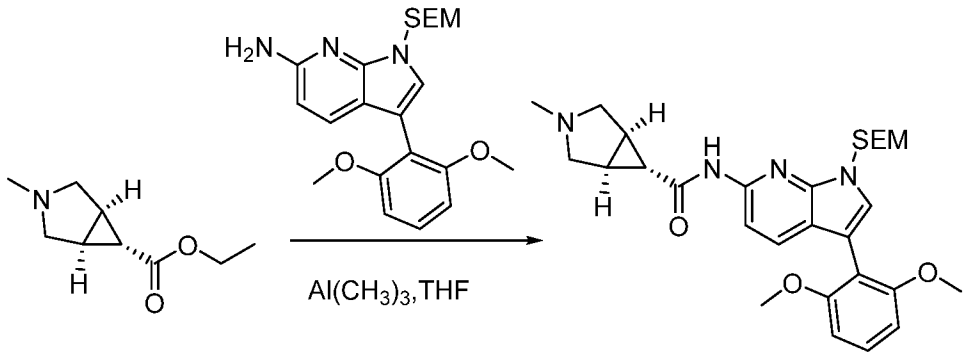
Example S170: Synthesis of (1R,5S,6R)-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-methyl-3-azabicyclo[3.1.0]hexane-6-carboxamide (Compound 177)

Step 1: Synthesis of ethyl (1R,5S,6R)-3-methyl-3-azabicyclo[3.1.0]hexane-6-carboxylate



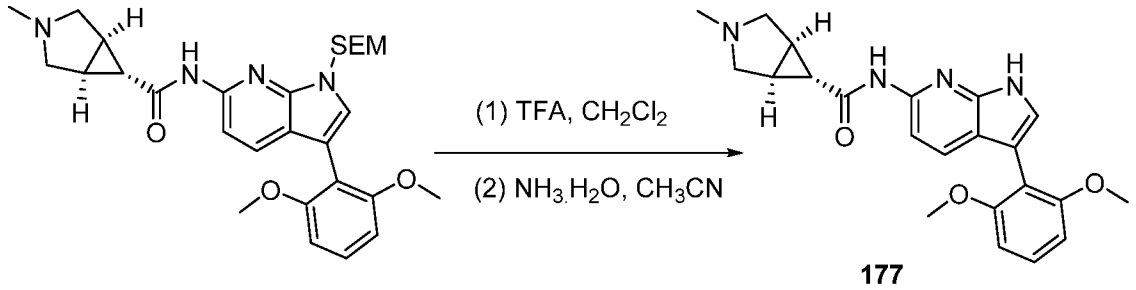
[0846] To a solution of ethyl (1R,5S,6R)-3-azabicyclo[3.1.0]hexane-6-carboxylate hydrochloride (200.0 mg, 1.04 mmol) in THF (5.0 mL) was added formaldehyde (522.2 mg, 5.22 mmol) and $NaBH(OAc)_3$ (442.3 mg, 2.09 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the reaction mixture was quenched with MeOH. The resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (90/10, v/v) to afford ethyl (1R,5S,6R)-3-methyl-3-azabicyclo[3.1.0]hexane-6-carboxylate (140.0 mg, 79%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =170.1.

Step 2: Synthesis of (1R,5S,6R)-N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-methyl-3-azabicyclo[3.1.0]hexane-6-carboxamide



[0847] To a mixture of ethyl (1R,5S,6R)-3-methyl-3-azabicyclo[3.1.0]hexane-6-carboxylate (120.0 mg, 0.71 mmol) and 3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (141.7 mg, 0.35 mmol) in THF (3.0 mL) was added dropwise $AlMe_3$ (1.8 mL, 2 mol/L) at 0 °C. The mixture was stirred at 80 °C for 2 h. After the reaction was completed, the reaction mixture was quenched with water. The resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/ MeOH (90/10, v/v) to afford (1R,5S,6R)-N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-methyl-3-azabicyclo[3.1.0]hexane-6-carboxamide (80.0 mg, 21%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =523.3.

Step 3: Synthesis of (1R,5S,6R)-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-methyl-3-azabicyclo[3.1.0]hexane-6-carboxamide (Compound 177)

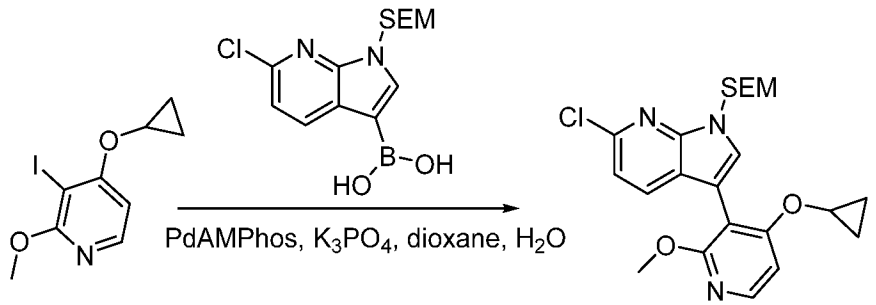


177

[0848] To a solution of (1R,5S,6R)-N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-methyl-3-azabicyclo[3.1.0]hexane-6-carboxamide (60.0 mg, 0.12 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL). The mixture was stirred at room temperature for 1 h. The mixture was concentrated under vacuum. To the aboveresidue were added ACN (2.0 mL) and $NH_3.H_2O$ (2.0 mL). The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 34% B to 48% B in 8 min; 254 nm) to afford (1R,5S,6R)-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-methyl-3-azabicyclo[3.1.0]hexane-6-carboxamide **(Compound 177)** (15.5 mg, 34%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 393.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.42 (s, 1H), 10.35 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.52 - 7.50 (m, 1H), 7.29 - 7.25 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 3.69 (s, 6H), 3.00 - 2.98 (m, 2H), 2.36 - 2.31 (m, 3H), 2.25 (s, 3H), 1.85 (s, 2H).

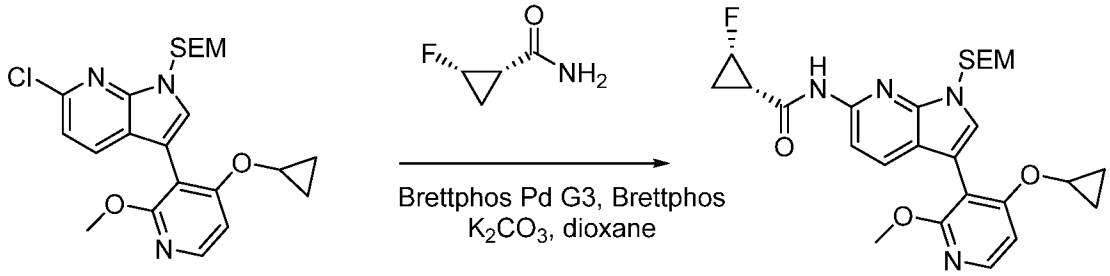
Example S171: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 178)

Step 1: Synthesis of 3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-cyclopropoxy-2-methoxypyridine



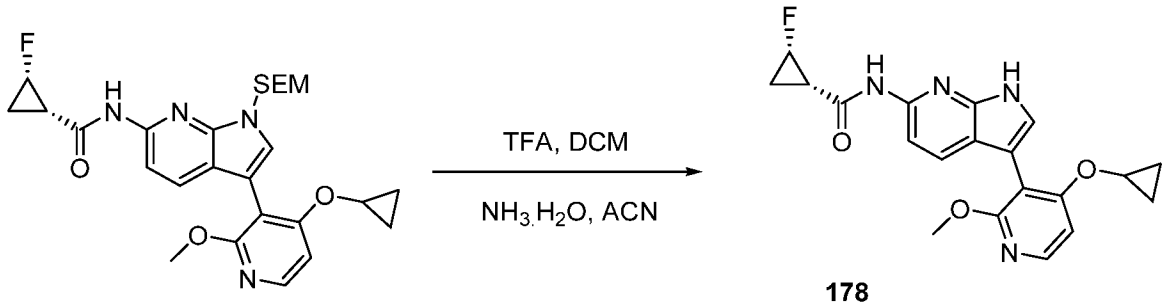
[0849] To a solution of 4-cyclopropoxy-3-iodo-2-methoxypyridine (268.0 mg, 0.92 mmol) in 1,4-dioxane/H_2O (8.0 mL/1.6 mL) was added 6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-ylboronic acid (300.8 mg, 0.92 mmol), K_3PO_4 (390.9 mg, 1.84 mmol) and PdAMPhos (130.4 mg, 0.18 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-cyclopropoxy-2-methoxypyridine (253.0 mg, 61%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =446.2.

Step 2: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide



[0850] To a solution of 3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-cyclopropoxy-2-methoxypyridine (170.0 mg, 0.38 mmol) in dioxane (6.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (117.9 mg, 1.14 mmol), K_2CO_3 (158.0 mg, 1.14 mmol), Brettphos (40.9 mg, 0.08 mmol) and Brettphos Pd G3 (34.6 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether / ethyl acetate (1/1, v/v) to afford (1S,2S)-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (80.0 mg, 41%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =513.2.

Step 3: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 178)

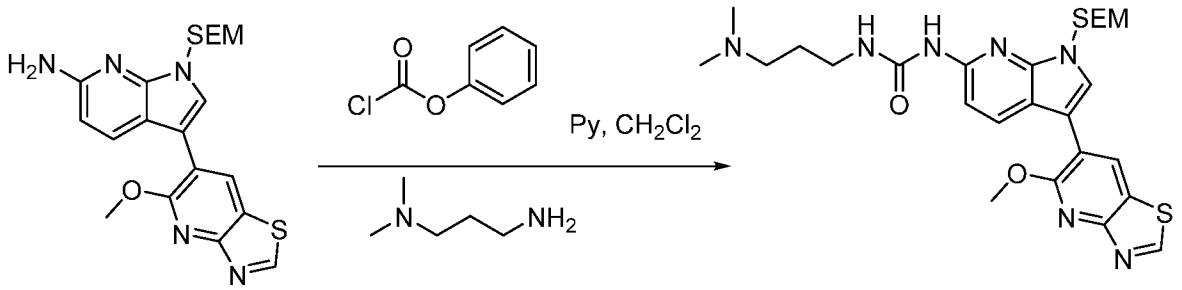


178

[0851] To a solution of (1S,2S)-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (80.0 mg, 0.16 mmol) in DCM (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added $NH_3 \cdot H_2O$ (3.0 mL) and ACN (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for additional 4 h. After the reaction was completed, the mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (4/1, v/v) and then purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 40% B in 8 min, 254 nm) to afford (1S,2S)-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide **(Compound 178)** (10.3 mg, 16%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =383.1. ^1H NMR (400 MHz, DMSO-d_6): δ 11.55 (s, 1H), 10.61 (s, 1H), 8.08 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 5.6 Hz, 1H), 5.02 - 4.83 (m, 1H), 3.95 - 3.92 (m, 1H), 3.82 (s, 3H), 2.28 - 2.19 (m, 1H), 1.72 - 1.55 (m, 1H), 1.16 - 1.13 (m, 1H), 0.80 - 0.76 (m, 2H), 0.66 - 0.61 (m, 2H).

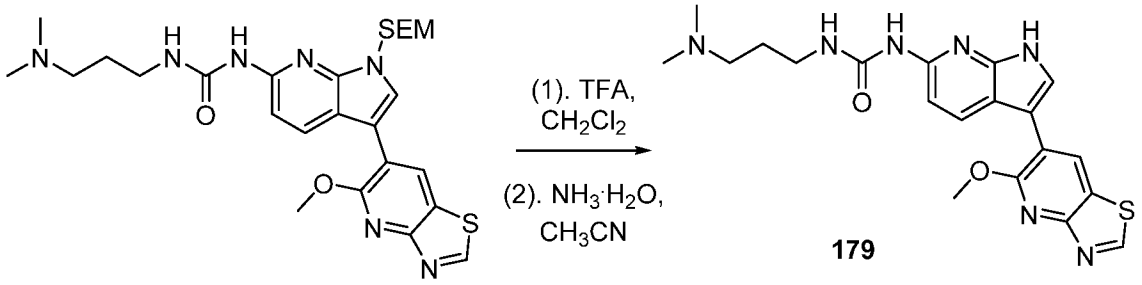
Example S172: Synthesis of 3-[3-(dimethylamino)propyl]-1-(3-{5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)urea (Compound 179)

Step 1: Synthesis of 3-[3-(dimethylamino)propyl]-1-(3-{5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl)urea



[0852] To a solution of 3-{5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (170.0 mg, 0.40 mmol) in CH_2Cl_2 (5.0 mL) was added pyridine (125.8 mg, 1.59 mmol) and phenyl chloroformate (74.7 mg, 0.48 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. The mixture was concentrated under vacuum. To the above residue was added pyridine (3.0 mL) and N1,N1-dimethylpropane-1,3-diamine (121.9 mg, 1.19 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 3 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (85/15, v/v) to afford 3-[3-(dimethylamino)propyl]-1-(3-{5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl)urea (100.0 mg, 45%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =556.2.

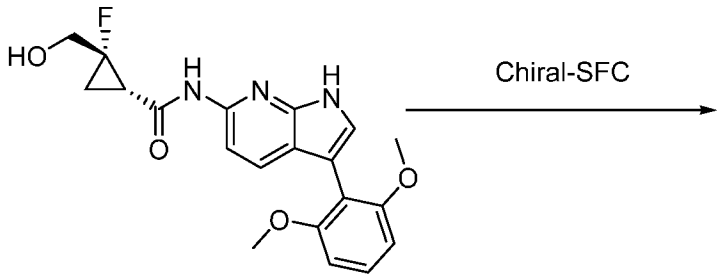
Step 2: Synthesis of 3-[3-(dimethylamino)propyl]-1-(3-{5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)urea (Compound 179)



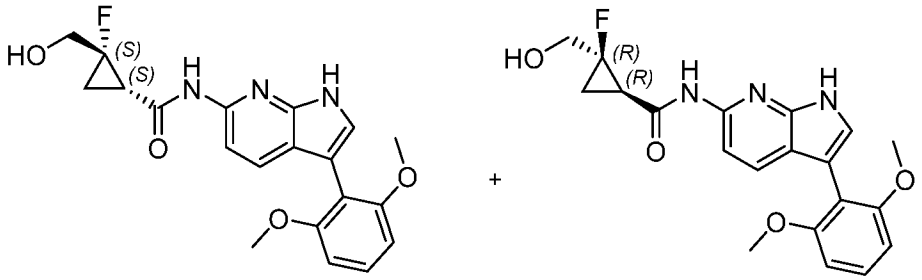
[0853] To a solution of 3-[3-(dimethylamino)propyl]-1-(3-{5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl)urea (80.0 mg, 0.14 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The mixture was stirred at room temperature for 2 h. The mixture was concentrated under vacuum. To the above residue were added ACN (2.0 mL) and $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue

was purified by Prep-HPLC with the following conditions (Column: YMC-Actus Triart C18 ExRS, 30×250 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 30% B in 11 min; 254 nm) to afford 3-[3-(dimethylamino)propyl]-1-(3-{5-methoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)urea **(Compound 179)** (19.8 mg, 32%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 426.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.71 (s, 1H), 9.51 (s, 1H), 9.19 (s, 1H), 8.78 (s, 1H), 8.45 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 4.06 (s, 3H), 3.27 - 3.22 (m, 2H), 2.34 - 2.27 (m, 2H), 2.14 (s, 6H), 1.70 - 1.64 (m, 2H).

Example S173: Synthesis of (1S,2S)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-2-(hydroxymethyl)cyclopropanecarboxamide and (1R,2R)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-2-(hydroxymethyl)cyclopropanecarboxamide (Compound 180 and Compound 181)



188



180 181

[0854] The cis-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-2-(hydroxymethyl)cyclopropanecarboxamide (94.0 mg, 0.24 mmol) was separated by CHIRAL-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2x25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 17 min; Wave Length: 220/254

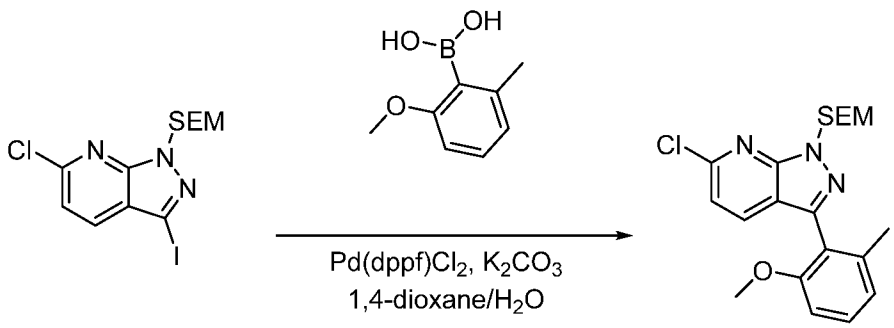
nm) to afford N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-2-(hydroxymethyl)cyclopropanecarboxamide Enantiomer 1 (18.2 mg, 19%) as a white solid and N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-2-(hydroxymethyl)cyclopropanecarboxamide Enantiomer 2 (22.6 mg, 24%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 180 and 181** in Table 1.

[0855] N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-2-(hydroxymethyl)cyclopropanecarboxamide Enantiomer 1: Retention Time 1=7.02 min; LCMS (ESI, m/z): $[M+H]^+ = 386.1$. ^1H NMR (400 MHz, DMSO-d_6): δ 11.43 (d, J = 1.6 Hz, 1H), 10.43 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.30 - 7.26 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 5.15 - 5.12 (m, 1H), 3.72 - 3.66 (m, 8H), 2.33 - 2.29 (m, 1H), 1.76 - 1.68 (m, 1H), 1.25 - 1.22 (m, 1H).

[0856] N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-2-(hydroxymethyl)cyclopropanecarboxamide Enantiomer 2: Retention Time 2=14.64 min; LCMS (ESI, m/z): $[M+H]^+ = 386.3$. ^1H NMR (400 MHz, DMSO-d_6): δ 11.41 (s, 1H), 10.39 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.30 - 7.26 (m, 2H), 6.75 (d, J = 8.0 Hz, 2H), 5.13 - 5.10 (m, 1H), 3.73 - 3.66 (m, 8H), 2.33 - 2.29 (m, 1H), 1.77 - 1.69 (m, 1H), 1.29 - 1.18 (m, 1H).

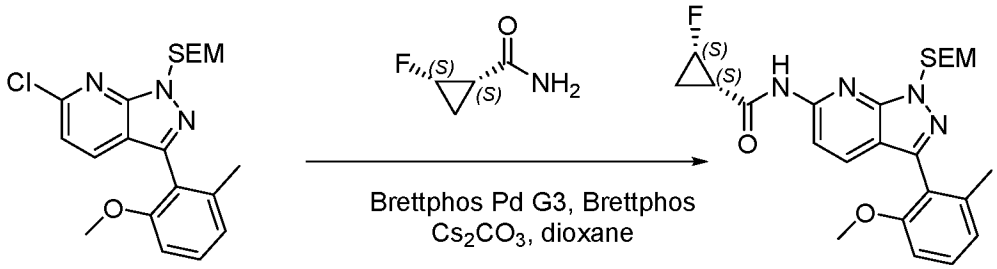
Example S174: Synthesis of (1S,2S)-2-fluoro-N-[3-(2-methoxy-6-methylphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 182)

Step 1: Synthesis of 6-chloro-3-(2-methoxy-6-methylphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridine



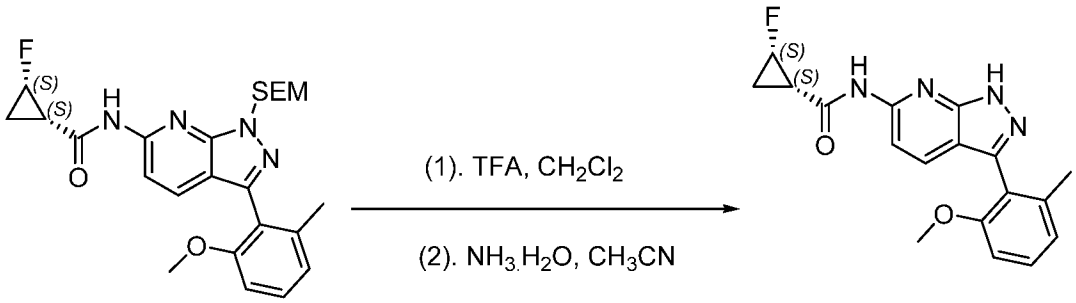
[0857] To a solution of 6-chloro-3-iodo-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridine (400.0 mg, 0.98 mmol) in dioxane/H_2O (10.0 mL/2.0 mL) was added 2-methoxy-6-methylphenylboronic acid (162.0 mg, 0.97 mmol), K_2CO_3 (404.8 mg, 2.93 mmol) and $Pd(dppf)Cl_2$ (71.4 mg, 0.10 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford 6-chloro-3-(2-methoxy-6-methylphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridine (120.0 mg, 30%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =404.1.

Step 2: Synthesis of (1S,2S)-2-fluoro-N-[3-(2-methoxy-6-methylphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide



[0858] To a solution of 6-chloro-3-(2-methoxy-6-methylphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridine (210.0 mg, 0.52 mmol) in 1,4-dioxane (16.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (267.9 mg, 2.60 mmol), BrettPhos (55.8 mg, 0.10 mmol), Cs_2CO_3 (508.1 mg, 1.56 mmol) and BrettPhos Pd G3 (47.1 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h under N_2. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1S,2S)-2-fluoro-N-[3-(2-methoxy-6-methylphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (120.0 mg, 49%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =471.2.

Step 3: Synthesis of (1S,2S)-2-fluoro-N-[3-(2-methoxy-6-methylphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 182)

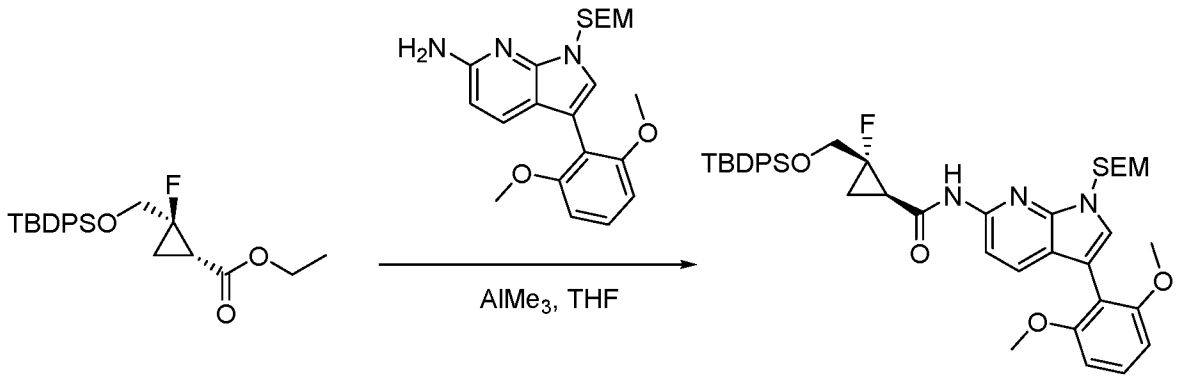


182

[0859] To a solution of (1S,2S)-2-fluoro-N-[3-(2-methoxy-6-methylphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide (120.0 mg 0.12 mmol) in CH_2Cl_2 (10.0 mL) was added TFA (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (8.0 mL) was added $NH_3.H_2O$ (8.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:33% B to 43% B in 8 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(2-methoxy-6-methylphenyl)-1H-pyrazolo[3,4-b]pyridin-6-yl]cyclopropane-1-carboxamide **(Compound 182)** (16.9 mg, 14 %) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =341.2. ^1H NMR (400 MHz, DMSO-d_6): δ 13.39 (s, 1H), 10.96 (s, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.36 - 7.32 (m, 1H), 7.00 - 6.94 (m, 2H), 5.05 - 4.85 (m, 1H), 3.66 (s, 3H), 2.28 - 2.25 (m, 1H), 2.12 (s, 3H), 1.70 - 1.62 (m, 1H), 1.23 - 1.16 (m, 1H).

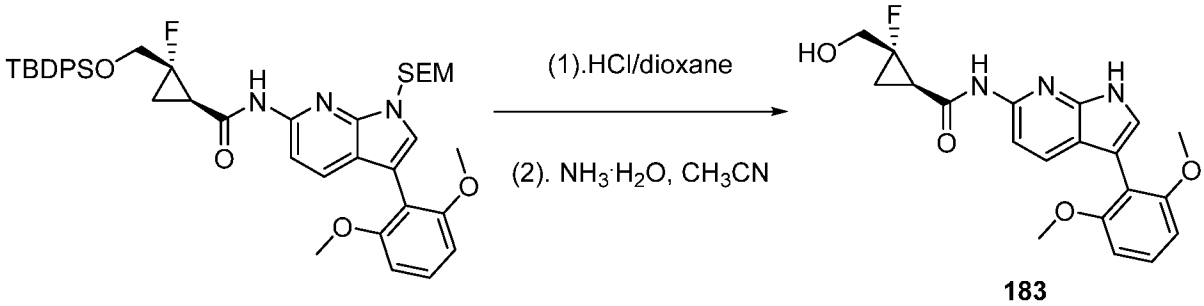
Example S175: Synthesis of trans-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-2-(hydroxymethyl)cyclopropanecarboxamide (Compound 183)

Step 1: Synthesis of trans-2-((tert-butyldiphenylsilyloxy)methyl)-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropanecarboxamide



[0860] To a solution of 3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (300.0 mg, 0.75 mmol) in THF (10.0 mL) was added trans-ethyl 2-((tert-butyldiphenylsilyloxy)methyl)-2-fluorocyclopropanecarboxylate (902 mg, 2.25 mmol) and $AlMe_3$ (1.9 mL, 2 mol/L) at 0 °C under N_2. The resulting mixture was stirred at 80 °C for 5 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (30/70, v/v) to afford trans-2-((tert-butyldiphenylsilyloxy)methyl)-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropanecarboxamide (200.0 mg, 35%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =754.3.

Step 2: Synthesis of trans-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-2-(hydroxymethyl)cyclopropanecarboxamide (Compound 183)



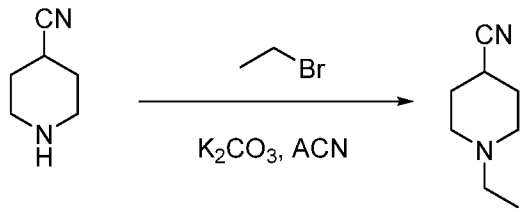
183

[0861] The solution of trans-2-((tert-butyldiphenylsilyloxy)methyl)-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropanecarboxamide (150.0 mg, 0.20 mmol) in HCl/dioxane (5.0 mL, 4 mol/L) was stirred at room temperature for 16 h. The resulting mixture was concentrated under

reduced pressure. To the residue in ACN (5.0 mL) was added $NH_3.H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash column chromatography with petroleum MeOH/H_2O (70/30, v/v) to afford trans-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-2-(hydroxymethyl)cyclopropanecarboxamide **(Compound 183)** (1.2 mg, 2%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =386.3. ^1H NMR (400 MHz, DMSO-d_6): δ 11.47 (s, 1H), 10.64 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.30 - 7.26 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 5.06 - 5.03 (m, 1H), 3.98 - 3.91 (m, 1H), 3.86 - 3.74 (m, 1H) 3.69 (s, 6H) 2.69 - 2.62 (m, 1H), 1.53 - 1.47 (m, 1H), 1.35 - 1.30 (m, 1H).

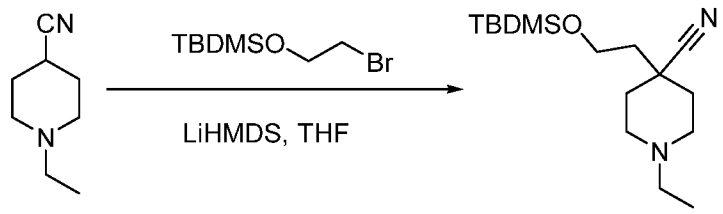
Example S176: Synthesis of 1-[2-(4-cyano-1-ethylpiperidin-4-yl)ethyl]-3-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (Compound 184)

Step 1: Synthesis of 1-ethylpiperidine-4-carbonitrile



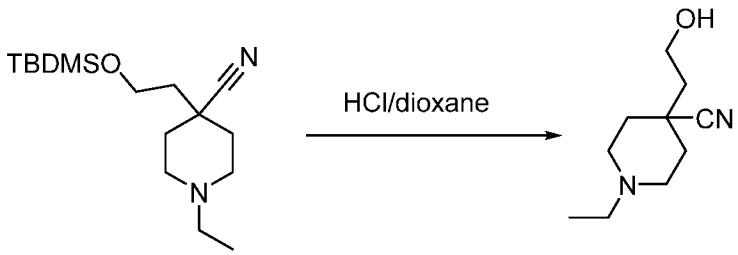
[0862] To a mixture of piperidine-4-carbonitrile (1.0 g, 9.07 mmol) and K_2CO_3 (3.7 g, 27.20 mmol) in MeCN (10.0 mL) was added bromoethane (1.0 g, 9.08 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (5/1, v/v) to afford 1-ethylpiperidine-4-carbonitrile (750.0 mg, 59%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =139.1

Step 2: Synthesis of 4-[2-[(tert-butyldimethylsilyl)oxy]ethyl]-1-ethylpiperidine-4-carbonitrile



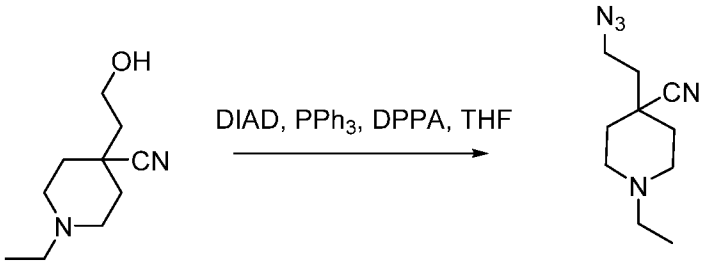
[0863] To a solution of 1-ethylpiperidine-4-carbonitrile (2.2 g, 15.91 mmol) in THF (20.0 mL) was added LiHMDS (31.0 mL, 1 mol/L) at -10 °C under N_2. The resulting mixture was stirred at -10 °C for 1 h under N_2. Then 2-bromoethoxy(tert-butyl)dimethylsilane (7.6 g, 31.85 mmol) was added dropwise to the mixture at -10 °C. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 4-[2-[(tert-butyldimethylsilyl)oxy]ethyl]-1-ethylpiperidine-4-carbonitrile (3.0 g, 63%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ = 297.2

Step 3: Synthesis of 1-ethyl-4-(2-hydroxyethyl)piperidine-4-carbonitrile



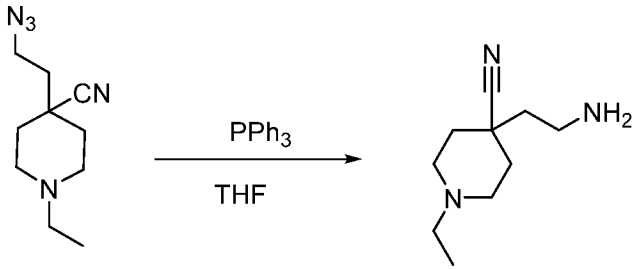
[0864] The solution of 4-[2-[(tert-butyldimethylsilyl)oxy]ethyl]-1-ethylpiperidine-4-carbonitrile (3.0 g, 10.11 mmol) in HCl/1,4-dioxane (20.0 mL, 4 mol/L) was stirred at room temperature for 2 h. After the reaction was completed, the reaction mixture was evaporated in vacuo. The PH of the residue was adjusted to 8 with $NaHCO_3$ (aq) and then extracted with ethyl acetate. The aqueous layer was concentrated under reduced pressure to afford 1-ethyl-4-(2-hydroxyethyl)piperidine-4-carbonitrile (2.3 g, crude) as yellow solid. LCMS (ESI, m/z): $[M+H]^+$=183.1

Step 4: Synthesis of 4-(2-azidoethyl)-1-ethylpiperidine-4-carbonitrile



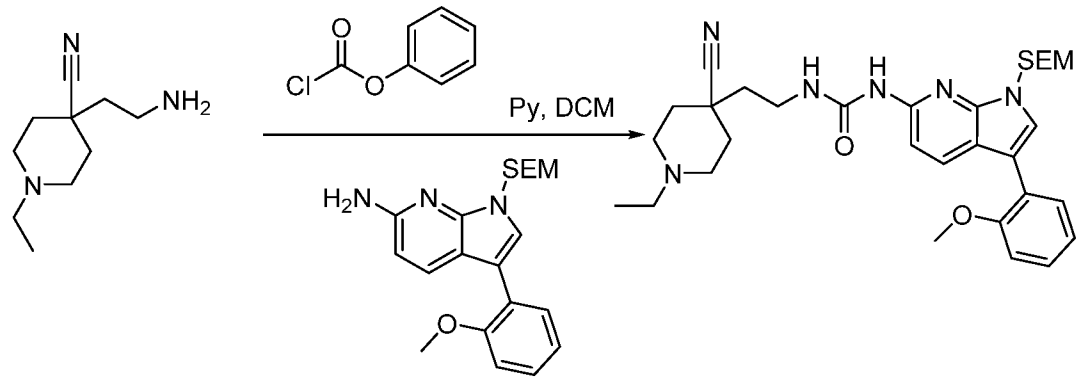
[0865] To a mixture of 1-ethyl-4-(2-hydroxyethyl)piperidine-4-carbonitrile (300.0 mg, 1.64 mmol) and PPh_3 (863.4 mg, 3.29 mmol) in THF (5.0 mL) was added DIAD (665.6 mg, 3.29 mmol) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 15 min under N_2. Then DPPA (905.9 mg, 3.29 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (10/1, v/v) to afford 4-(2-azidoethyl)-1-ethylpiperidine-4-carbonitrile (300.0 mg, 87%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$=208.1

Step 5: Synthesis of 4-(2-aminoethyl)-1-ethylpiperidine-4-carbonitrile



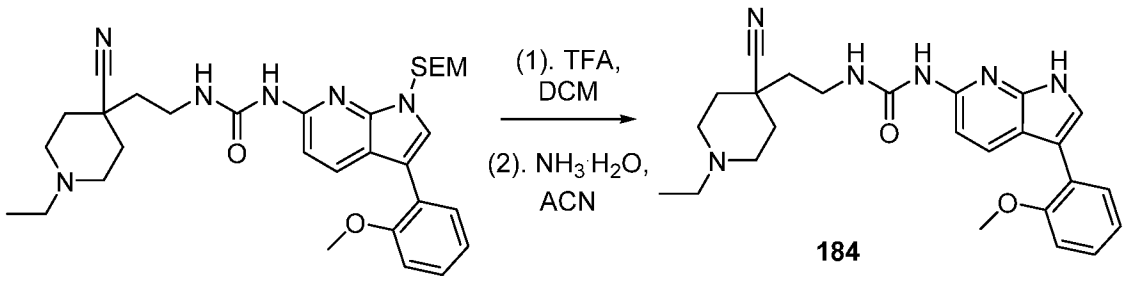
[0866] To a solution of 4-(2-azidoethyl)-1-ethylpiperidine-4-carbonitrile (1.4 g, 6.75 mmol) in THF (20.0 mL) was added triphenylphosphine (2.6 g, 10.13 mmol) at room temperature. The resulting mixture was stirred at 70 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The aqueous layer was concentrated under reduced pressure to afford 4-(2-aminoethyl)-1-ethylpiperidine-4-carbonitrile (1.1 g, crude) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$=182.2

Step 6: Synthesis of 1-[2-(4-cyano-1-ethylpiperidin-4-yl)ethyl]-3-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea



[0867] To a mixture of 3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (1.0 g, 2.75 mmol) and pyridine (872.6 mg, 11.03 mmol) in DCM (10.0 mL) was added phenyl chloroformate (518.2 mg, 3.31 mmol) at 0 °C. The resulting mixture was stirred for at room temperature 2 h. The resulting mixture was concentrated under reduced pressure. To the above mixture was added pyridine (10.0 mL) and 4-(2-aminoethyl)-1-ethylpiperidine-4-carbonitrile (500.0 mg, 2.75 mmol) at room temperature. The resulting mixture was stirred at 70 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (8/1, v/v) to afford 1-[2-(4-cyano-1-ethylpiperidin-4-yl)ethyl]-3-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (450.0 mg, 28%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$=577.3

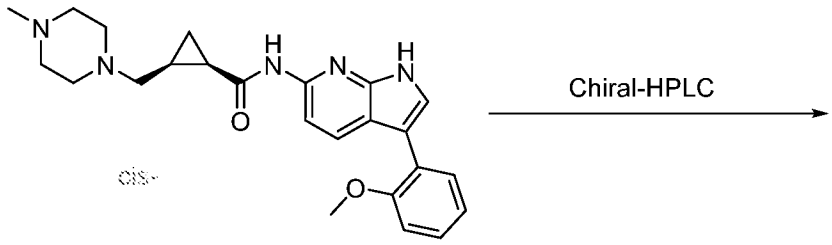
Step 7: Synthesis of 1-[2-(4-cyano-1-ethylpiperidin-4-yl)ethyl]-3-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (Compound 184)



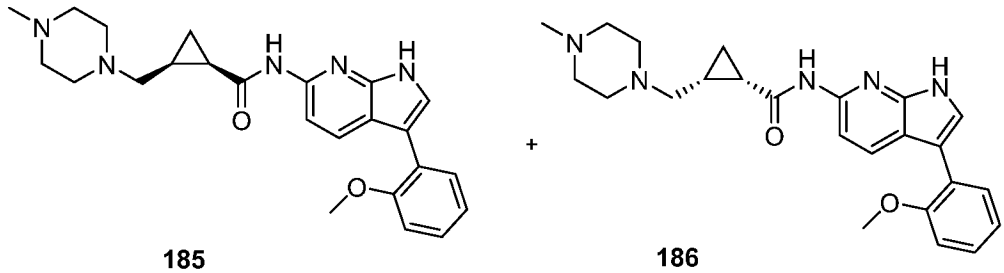
[0868] To a solution of 1-[2-(4-cyano-1-methylpiperidin-4-yl)ethyl]-3-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (450.0 mg, 0.80 mmol) in DCM (5.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was concentrated under reduced pressure. To the above mixture was added $NH_3.H_2O$ (2.0 mL) and ACN (2.0 mL) at room temperature. The resulting mixture was stirred

at room temperature for another 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 11% B to 20% B in 8 min, 254/220 nm) to afford 1-[2-(4-cyano-1-ethylpiperidin-4-yl)ethyl]-3-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea **(Compound 184)** (77.3 mg, 22%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$=447.2. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.41 (s, 1H), 9.42 (s, 1H), 7.99 - 7.89 (m, 2H), 7.56 - 7.52 (m, 2H), 7.30 - 7.24 (m, 1H), 7.11 (d, J = 7.5 Hz, 1H), 7.05 - 7.00 (m, 1H), 3.82 (s, 3H), 3.62 - 3.48 (m, 2H), 3.34 - 2.73 (m, 3H), 2.08 - 1.76 (m, 6H), 1.29 - 1.19 (m, 3H).

Example S177: Synthesis of (1R,2S)-N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide and (1S,2R)-N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (Compound 185 and Compound 186)



41



185 186

[0869] The cis-N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (**Compound 41**) (33.0 mg, 0.08 mmol) was separated by CHIRAL-HPLC with the following conditions (Column: CHIRALPAK IH, 2x25 cm, 5 um; Mobile Phase A: MTBE (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 10% B to 10% B in 22 min;

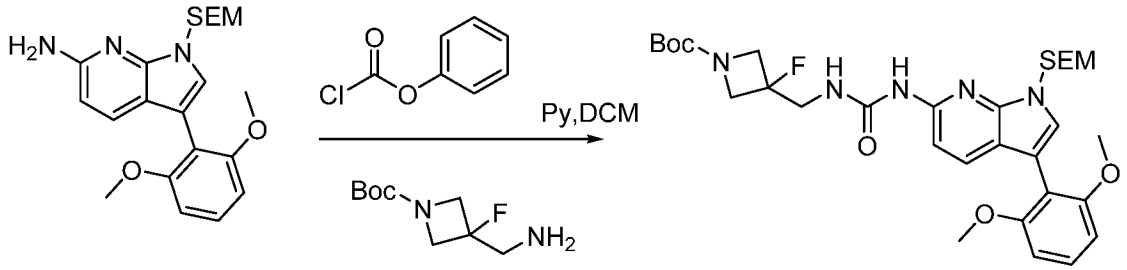
Wave Length: 254/220 nm) to afford N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 1 (10.4 mg, 31%) as a white solid and N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 2 (10.0 mg, 30%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 185 and 186** in Table 1.

[0870] N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 1: Retention Time 1: 7.772 min; LCMS (ESI, m/z): $[M+H]^+ = 420.3$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.53 (d, J = 2.1 Hz, 1H), 10.51 (s, 1H), 7.97 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.56 - 7.52 (m, 2H), 7.30 - 7.25 (m, 1H), 7.11 (d, J = 7.5 Hz, 1H), 7.05 - 7.00 (m, 1H), 3.82 (s, 3H), 2.60 - 2.52 (m, 2H), 2.51 - 2.46 (m, 1H), 2.44 - 2.32 (m, 3H), 2.31 - 2.17 (m, 4H), 2.16 - 2.10 (m, 1H), 2.08 (s, 3H), 1.35 - 1.30 (m, 1H), 1.03 - 0.99 (m, 1H), 0.91 - 0.82 (m, 1H).

[0871] N-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 2: Retention Time 2: 17.229 min; LCMS (ESI, m/z): $[M+H]^+ = 420.3$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.53 (d, J = 1.8 Hz, 1H), 10.51 (s, 1H), 7.97 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.56 - 7.52 (m, 2H), 7.30 - 7.25 (m, 1H), 7.11 (d, J = 7.5 Hz, 1H), 7.05 - 7.00 (m, 1H), 3.82 (s, 3H), 2.60 - 2.52 (m, 2H), 2.51 - 2.46 (m, 1H), 2.44 - 2.32 (m, 3H), 2.31 - 2.17 (m, 4H), 2.16 - 2.10 (m, 1H), 2.08 (s, 3H), 1.38 - 1.31 (m, 1H), 1.03 - 0.99 (m, 1H), 0.91 - 0.82 (m, 1H).

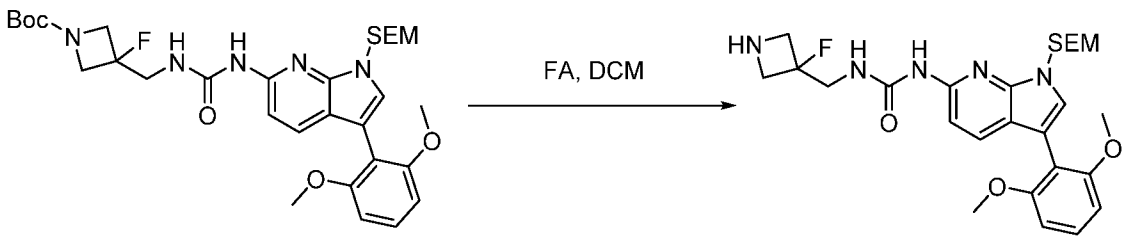
Example S178: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[(3-fluoro-1-methylazetidin-3-yl)methyl]urea (Compound 187)

Step 1: Synthesis of tert-butyl 3-[({[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}amino)methyl]-3-fluoroazetidine-1-carboxylate



[0872] To a solution of 3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (450.0 mg, 1.13 mmol) in DCM (10.0 mL) was added pyridine (356.3 mg, 4.50 mmol) and phenyl chloroformate (211.6 mg, 1.35 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was concentrated under reduced pressure. To the residue in pyridine (10 mL) was added tert-butyl 3-(aminomethyl)-3-fluoroazetidine-1-carboxylate (690.1 mg, 3.38 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 4 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (10/1, v/v) to afford tert-butyl 3-[({[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}amino)methyl]-3-fluoroazetidine-1-carboxylate (600.0 mg, 85%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =630.3.

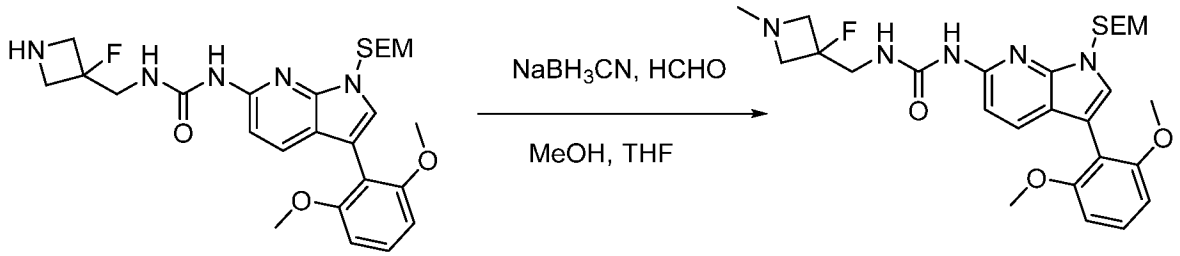
Step 2: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[(3-fluoroazetidin-3-yl)methyl]urea



[0873] To a solution of tert-butyl 3-[({[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}amino)methyl]-3-fluoroazetidine-1-carboxylate (580.0 mL, 0.92 mmol) in DCM (5.0 mL) was added HCOOH (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the pH value of the mixture was adjusted to 8 with

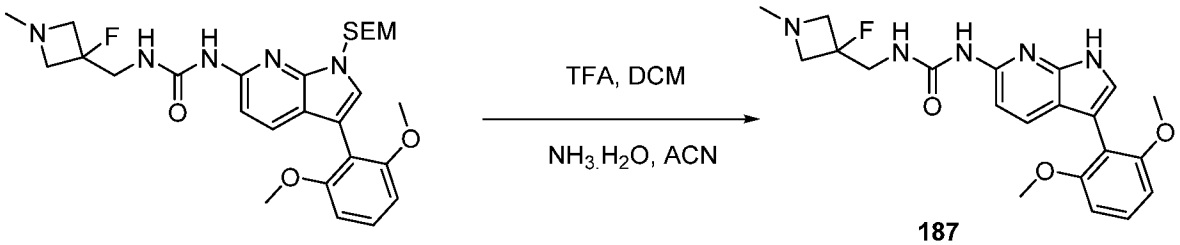
$NaHCO_3$ (aq). The mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[(3-fluoroazetidin-3-yl)methyl]urea (420.0 mg, crude) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =530.3.

Step 3: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[(3-fluoro-1-methylazetidin-3-yl)methyl]urea



[0874] To a solution of 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[(3-fluoroazetidin-3-yl)methyl]urea (420.0 mg, crude) in THF/CH_3OH (20.0 mL/4.0 mL) was added $NaBH_3CN$ (149.5 mg, 2.38 mmol) and HCHO (238.1 mg, 7.93 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[(3-fluoro-1-methylazetidin-3-yl)methyl]urea (400.0 mg, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =544.3.

Step 4: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[(3-fluoro-1-methylazetidin-3-yl)methyl]urea (Compound 187)

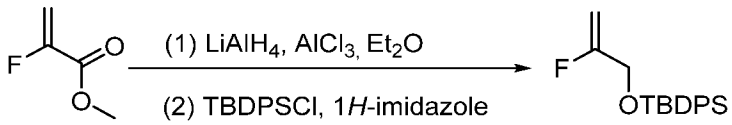


187

[0875] To a solution of 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[(3-fluoro-1-methylazetidin-3-yl)methyl]urea (400.0 mg, crude) in CH_2Cl_2 (20.0 mL) was added TFA (20.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (20.0 mL) was added $NH_3.H_2O$ (20.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate: 60 mL/min; Gradient:23% B to 53% B in 9 min; 254 nm) to afford 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[(3-fluoro-1-methylazetidin-3-yl)methyl]urea **(Compound 187)** (12.9 mg, 4%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =414.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.40 (s, 1H), 9.25 (s, 1H), 8.76 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.28 - 7.24 (m, 1H), 7.17 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 2H), 3.75 - 3.67 (m, 10H), 3.46 - 3.31 (m, 2H), 2.45 (s, 3H).

Example S179: Synthesis of cis-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-2-(hydroxymethyl)cyclopropanecarboxamide (Compound 188)

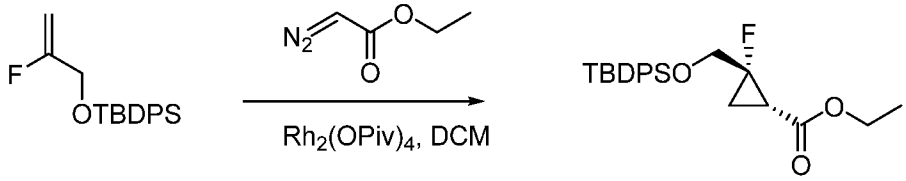
Step 1: Synthesis of tert-butyl(2-fluoroallyloxy)diphenylsilane



[0876] To a solution of $LiAlH_4$ (5.5 g, 114.12 mmol) in Et_2O (100.0 mL) was added $AlCl_3$ (6.4 g, 48.04 mmol) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 30 min. Then methyl 2-fluoroacrylate (5.0 g, 48.04 mmol) was added dropwise to the mixture at 0 °C. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was filtered. To the above filtrate was added TBDPSCl (19.8 g, 72.12 mmol) and 1H-imidazole (11.3 g, 96.15 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column

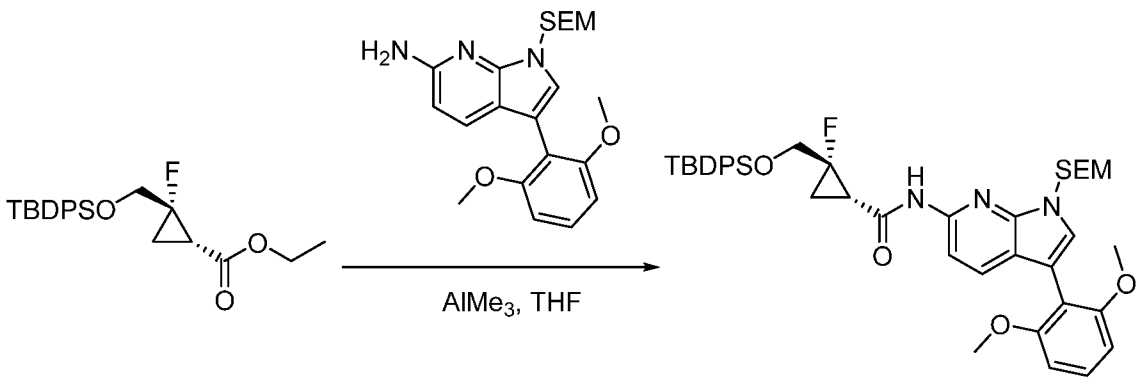
chromatography with petroleum ether/ethyl acetate (95/5, v/v) to afford tert-butyl(2-fluoroallyloxy)diphenylsilane (4.0 g, 19%) as a yellow oil.

Step 2: Synthesis of cis-ethyl 2-((tert-butyldiphenylsilyloxy)methyl)-2-fluorocyclopropanecarboxylate & trans-ethyl 2-((tert-butyldiphenylsilyloxy)methyl)-2-fluorocyclopropanecarboxylate



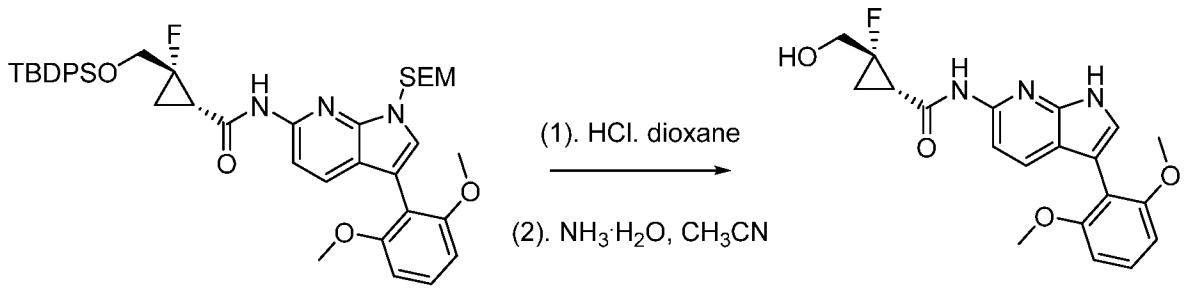
[0877] To a solution of tert-butyl(2-fluoroallyloxy)diphenylsilane (1.0 g, 3.18 mmol) in DCM (5.0 mL) was added dropwise ethyl 2-diazoacetate (1.1 g, 9.54 mmol) at 0 °C for 8 h.. The resulting mixture was stirred at room temperature for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (90/10, v/v) to afford cis-ethyl 2-((tert-butyldiphenylsilyloxy)methyl)-2-fluorocyclopropanecarboxylate (300.0 mg, 24%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =401.2. and trans-ethyl 2-((tert-butyldiphenylsilyloxy)methyl)-2-fluorocyclopropanecarboxylate. (400.0 mg, 31%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =401.2.

Step 3: Synthesis of cis-2-((tert-butyldiphenylsilyloxy)methyl)-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropanecarboxamide



[0878] To a solution of 3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (400.0 mg, 1.00 mmol) in THF (10.0 mL) was added cis-ethyl 2-((tert-butyldiphenylsilyloxy)methyl)-2-fluorocyclopropanecarboxylate (1.2 g, 3.00 mmol) and $AlMe_3$ (2.5 mL, 2 mol/L) at 0 °C under N_2. The resulting mixture was stirred at 80 °C for 5 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (30/70, v/v) to afford cis-2-((tert-butyldiphenylsilyloxy)methyl)-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropanecarboxamide (150.0 mg, 20%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =754.3.

Step 4: Synthesis of cis-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-2-(hydroxymethyl)cyclopropanecarboxamide (Compound 188)



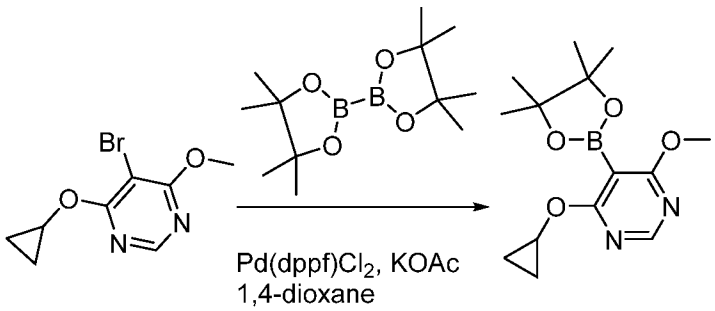
188

[0879] The solution of cis-2-((tert-butyldiphenylsilyloxy)methyl)-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluorocyclopropanecarboxamide (90.0 mg, 0.07 mmol) in HCl/dioxane (5.0 mL, 4 mol/L) was stirred at room temperature for 16 h. The resulting mixture was concentrated under reduced pressure. To the residue in ACN (5.0 mL) was added $NH_3.H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash column chromatography with petroleum MeOH/H_2O (70/30, v/v) to afford cis-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-fluoro-2-(hydroxymethyl)cyclopropanecarboxamide **(Compound 188)** (4.2 mg, 9%) as a white solid.

LCMS (ESI, m/z): $[M+H]^+$ =386.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.41 (d, J = 2.0 Hz, 1H), 10.40 (s, 1H), 7.81 ((d, J = 8.4 Hz, 1H), 7.55 ((d, J = 8.8 Hz, 1H), 7.30 - 7.26 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 5.13 - 5.10 (m, 1H), 3.73 - 3.66 (m, 8H), 2.34 - 2.29 (m, 1H), 1.77 - 1.70 (m, 1H), 1.29 - 1.08 (m, 1H).

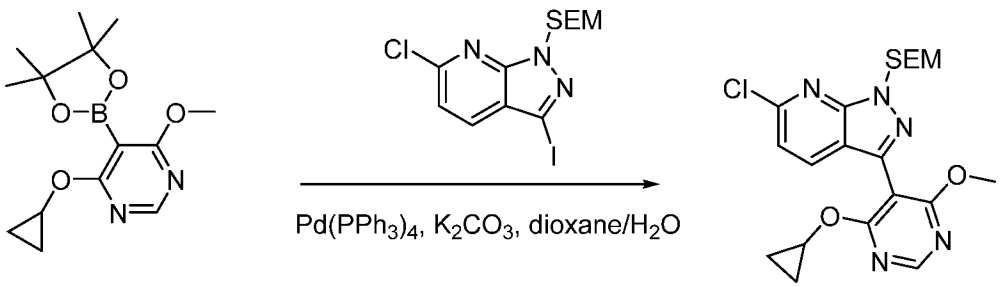
Example S180: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 189)

Step 1: Synthesis of 4-cyclopropoxy-6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine



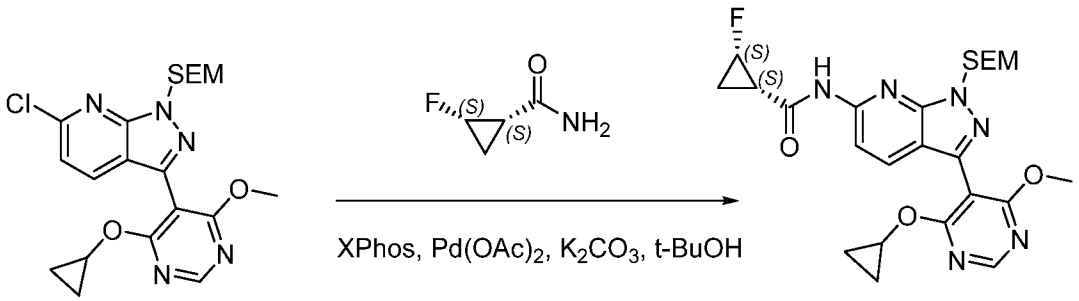
[0880] To a solution of 5-bromo-4-cyclopropoxy-6-methoxypyrimidine (500.0 mg, 2.04 mmol) in 1,4-dioxane (10.0 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.6 g, 6.12 mmol), KOAc (400.5 mg, 4.08 mmol) and $Pd(dppf)Cl_2$ (149.3 mg, 0.20 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford 4-cyclopropoxy-6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (240.0 mg, 40%) as a light brown oil. LCMS (ESI, m/z): $[M+H]^+$ = 293.2.

Step 2: Synthesis of 5-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridin-3-yl)-4-cyclopropoxy-6-methoxypyrimidine



[0881] To a solution of 4-cyclopropoxy-6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (320.0 mg, 1.10 mmol) in 1,4-dioxane/H_2O (30.0 mL/6.0 mL) was add 6-chloro-3-iodo-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridine (372.5 mg, 0.91 mmol), K_2CO_3 (302.8 mg, 2.19 mmol) and $Pd(PPh_3)_4$ (126.6 mg, 0.11 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether / ethyl acetate (7/1, v/v) to afford 5-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridin-3-yl)-4-cyclopropoxy-6-methoxypyrimidine (295.0 mg, 60%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ = 448.1.

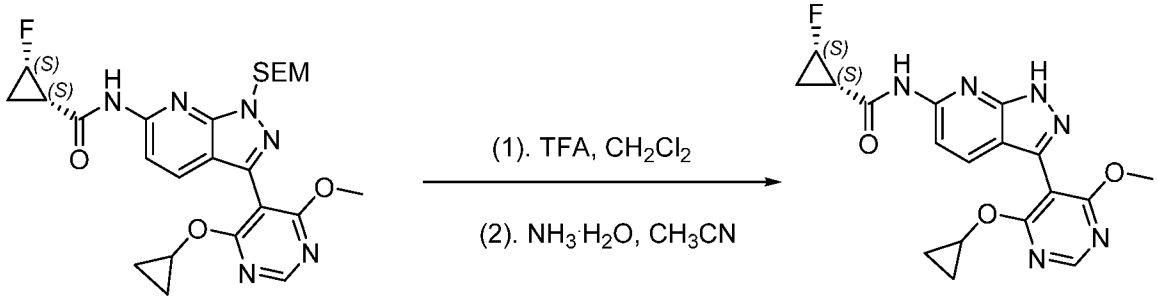
Step 3: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide



[0882] To a solution of 5-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridin-3-yl)-4-cyclopropoxy-6-methoxypyrimidine (255.0 mg, 0.57 mmol) in t-BuOH (25.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (293.4 mg, 2.85 mmol), XPhos (54.3 mg, 0.11 mmol), K_2CO_3 (236.0 mg, 1.71 mmol) and $Pd(OAc)_2$ (12.8 mg, 0.06 mmol) at room temperature under N_2. The final reaction mixture was stirred at 100 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/2, v/v) to afford (1S,2S)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-

(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (85.0 mg, 29%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ = 515.2.

Step 4: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 189)



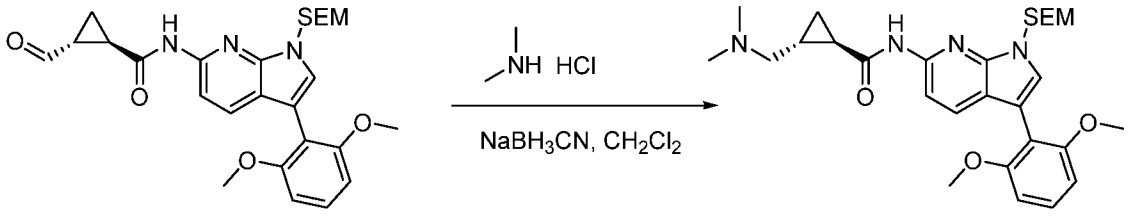
189

[0883] To a solution of (1S,2S)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (85.0 mg, 0.17 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (3.0 mL) was added $NH_3 \cdot H_2O$ (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 35% B in 9 min; 254/220 nm) to afford (1S,2S)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide **(Compound 189)** (13.5 mg, 21%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 385.2. ^1H NMR (400 MHz, DMSO-d_6): δ 13.55 (s, 1H), 11.01 (s, 1H), 8.64 (s, 1H), 7.98 - 7.90 (m, 2H), 5.04 - 4.87 (m, 1H), 4.37 - 4.34 (m, 1H), 3.89 (s, 3H), 2.28 - 2.21 (m, 1H), 1.70 - 1.63 (m, 1H), 1.22 - 1.16 (m, 1H), 0.77 - 0.72 (m, 2H), 0.57 - 0.52 (m, 2H).

Example S181: Synthesis of (1R,2R)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide and (1S,2S)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-

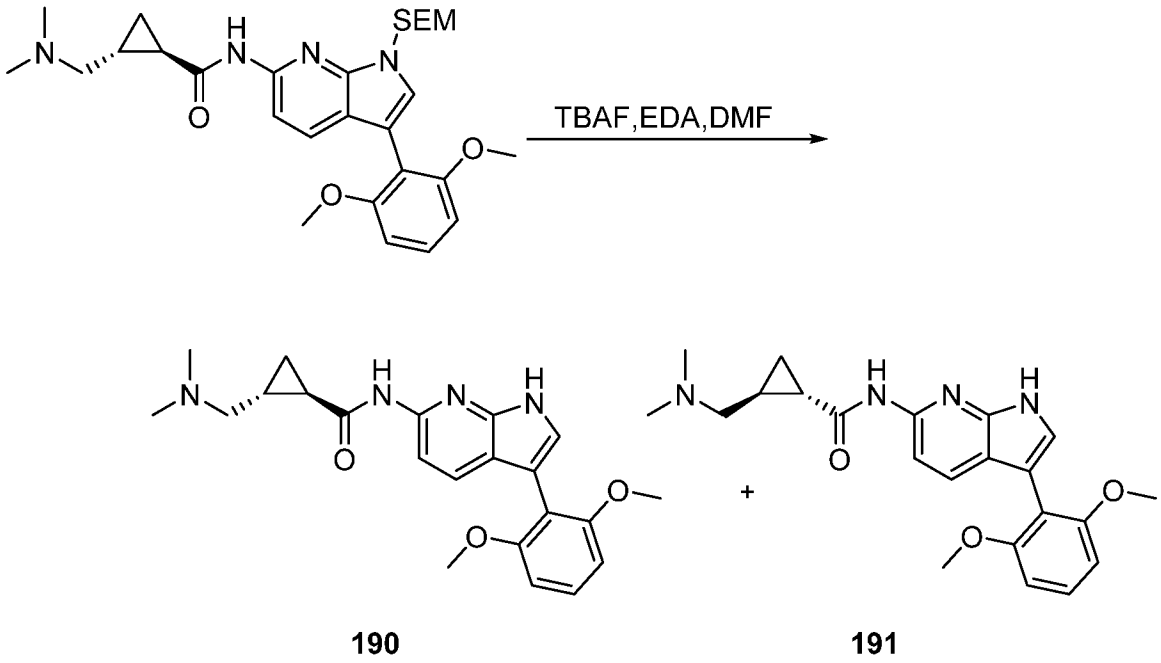
((dimethylamino)methyl)cyclopropane-1-carboxamide (Compound 190 and Compound 191)

Step 1: Synthesis of Trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide



[0884] To a solution of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-formylcyclopropane-1-carboxamide (500.0 mg, 1.01 mmol) in CH_2Cl_2 (20.0 mL) was added dimethylamine hydrochloride (246.8 mg, 3.03 mmol) and $NaBH_3CN$ (190.2 mg, 3.03 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was quenched with CH_3OH. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (80/20, v/v) to afford trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (210.0 mg, 39%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 525.3.

Step 2: Synthesis of (1R,2R)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide and **(1S,2S)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (Compound 190 and Compound 191)**



190 **191**

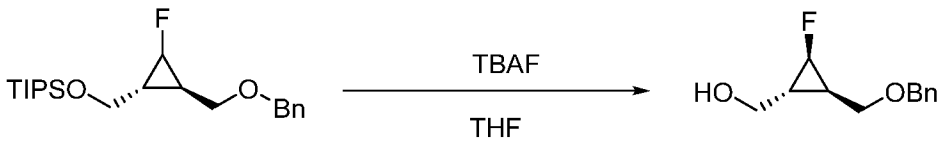
[0885] To a solution of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (210.0 mg, 0.40 mmol) in DMF (5.0 mL) was added ethylenediamine (120.3 mg, 2.00 mmol) and TBAF (313.9 mg, 1.20 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (75/25, v/v) and then separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK ID, 2×25 cm, 5 um; Mobile Phase A: Hex (0.2% IPA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 30% to 30% in 23 min; 220/254 nm) to afford N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide Enantiomer 1 (19.8 mg, 12%) as a white solid and N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide Enantiomer 2 (33.3 mg, 21%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 190 and 191** in Table 1.

[0886] **N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide Enantiomer 1:** Retention Time 1:14.6 min; LCMS (ESI, m/z): $[M+H]^+$ = 395.2. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.42 (s, 1H), 10.52 (s, 1H), 7.81 (d, J = 8.7 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.30 - 7.25 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 3.69 (s, 6H), 2.32 - 2.25 (m, 1H), 2.19 - 2.12 (m, 7H), 1.92 - 1.86 (m, 1H), 1.36 - 1.32 (m, 1H), 1.07 - 1.04 (m, 1H), 0.74 - 0.65 (m, 1H).

[0887] **N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide Enantiomer 2:** Retention Time 2:18.357 min; LCMS (ESI, m/z): $[M+H]^+$ = 395.2. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.41 (s, 1H), 10.52 (s, 1H), 7.81 (d, J = 8.7 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.30 - 7.25 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 3.69 (s, 6H), 2.32 - 2.25 (m, 1H), 2.19 - 2.12 (m, 7H), 1.92 - 1.86 (m, 1H), 1.36 - 1.31 (m, 1H), 1.07 - 1.04 (m, 1H), 0.74 - 0.65 (m, 1H).d

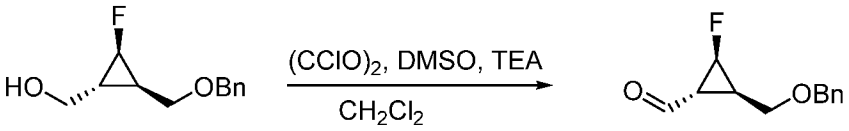
Example S182: Synthesis of trans-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(S)-fluoro-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (Compound 192)

Step 1: Synthesis of trans-(2-((benzyloxy)methyl)-3(R)-fluorocyclopropyl)methanol



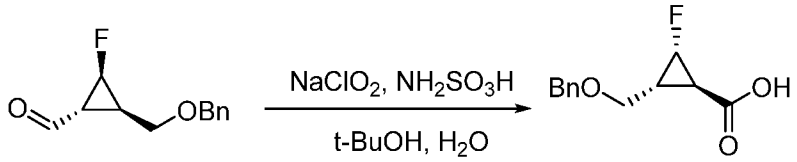
[0888] To a solution of (trans-(2-((benzyloxy)methyl)-3-fluorocyclopropyl)methoxy)triisopropylsilane (23.0 g, 62.74 mmol) in THF (200.0 mL) was added TBAF (19.7 g, 75.39 mmol) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (40/60, v/v) to afford trans-(2-((benzyloxy)methyl)-3(R)-fluorocyclopropyl)methanol (1.6 g, 12%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =211.1.

Step 2: Synthesis of trans-(2-((benzyloxy)methyl)-3(S)-fluorocyclopropyl)-1-carbaldehyde



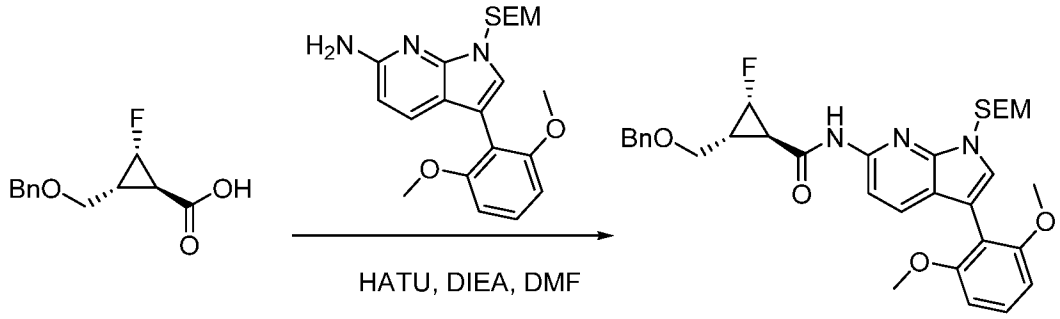
[0889] To a solution of $(CClO)_2$ (1.9 g, 15.22 mmol) in CH_2Cl_2 (20.0 mL) was added dropwise a solution of DMSO (4.8 g, 60.88 mmol) in CH_2Cl_2 (20.0 mL) at -78 °C under N_2. The resulting mixture was stirred at -78 °C for 0.5 h under N_2. Then a solution of trans-(2-((benzyloxy)methyl)-3(R)-fluorocyclopropyl)methanol (1.6 g, 7.61 mmol) in CH_2Cl_2 (20.0 mL) was added dropwise to the mixture at -78 °C under N_2. The resulting mixture was stirred at -78 °C for 1 h. Then TEA (6.2 g, 60.88 mmol) was added dropwise to the mixture at -78 °C under N_2. The resulting mixture was stirred at -78 °C for 0.5 h under N_2. After the reaction was completed, the resulting mixture was quenched with aqueous NH_4Cl at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (90/10, v/v) to afford trans-(2-((benzyloxy)methyl)-3(S)-fluorocyclopropyl)-1-carbaldehyde (1.1 g, 69%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =209.1.

Step 3: Synthesis of trans-(2-((benzyloxy)methyl)-3(S)-fluorocyclopropyl)-1-carboxylic acid



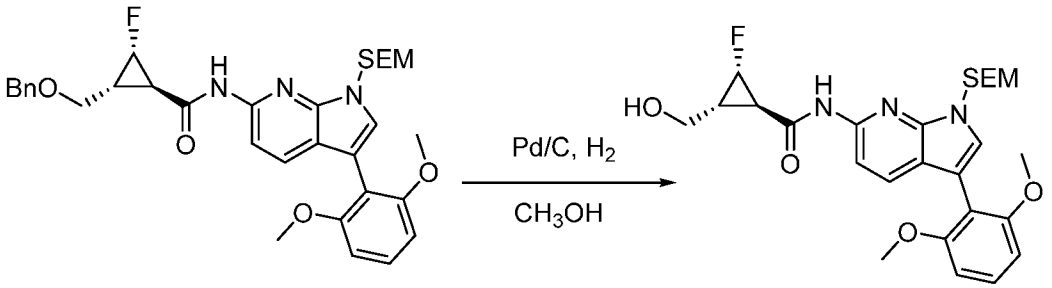
[0890] To a mixture of trans-(2-((benzyloxy)methyl)-3(S)-fluorocyclopropyl)-1-carbaldehyde (1.1 g, 5.28 mmol) and NH_2SO_3H (5.1 g, 52.83 mmol) in t-BuOH/H_2O (2.0/18.0 mL) was added $NaClO_2$ (4.8 g, 52.83 mmol) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 1.5 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (50/50, v/v) to afford trans-(2-((benzyloxy)methyl)-3(S)-fluorocyclopropyl)-1-carboxylic acid (800.0 mg, 67%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =225.1.

Step 4: Synthesis of trans-2-((benzyloxy)methyl)-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(S)-fluorocyclopropane-1-carboxamide



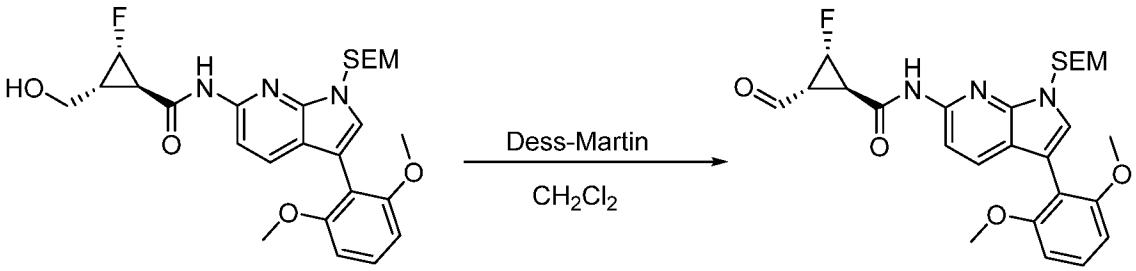
[0891] To a mixture of 3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (1.4 g, 3.57 mmol) and DIEA (1.4 g, 10.70 mmol) in DMF (20.0 mL) was added trans-(2-((benzyloxy)methyl)-3(S)-fluorocyclopropyl)-1-carboxylic acid (800.0 mg, 3.57 mmol) and HATU (1.6 g, 4.28 mmol) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (90/10, v/v) to afford trans-2-((benzyloxy)methyl)-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(S)-fluorocyclopropane-1-carboxamide (1.4 g, 65%) as a white solid . LCMS (ESI, m/z): $[M+H]^+$ =606.3.

Step 5: Synthesis of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(S)-fluoro-2-(hydroxymethyl)cyclopropane-1-carboxamide



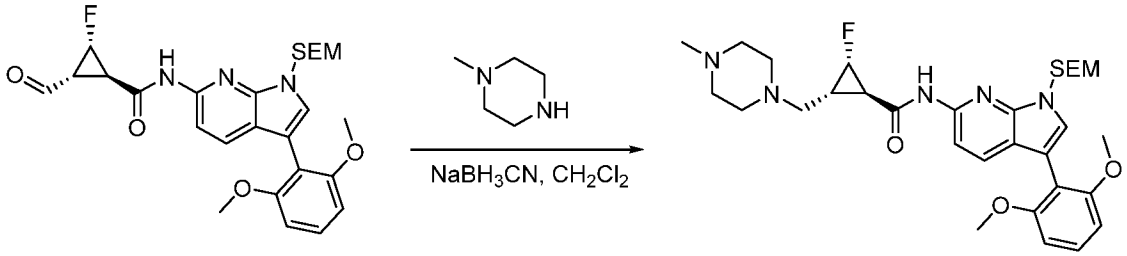
[0892] To a solution of trans-2-((benzyloxy)methyl)-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(S)-fluorocyclopropane-1-carboxamide (1.3 g, 2.15 mmol) in CH_3OH (15.0 mL) was added Pd/C (228.4 mg, dry) at room temperature under N_2. The resulting mixture was stirred at room temperature for 4 h under H_2. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with petroleum CH_3CN/H_2O (28/72, v/v) to afford trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(S)-fluoro-2-(hydroxymethyl)cyclopropane-1-carboxamide (570.0 mg, 25%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =516.2.

Step 6: Synthesis of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(S)-fluoro-2-formylcyclopropane-1-carboxamide



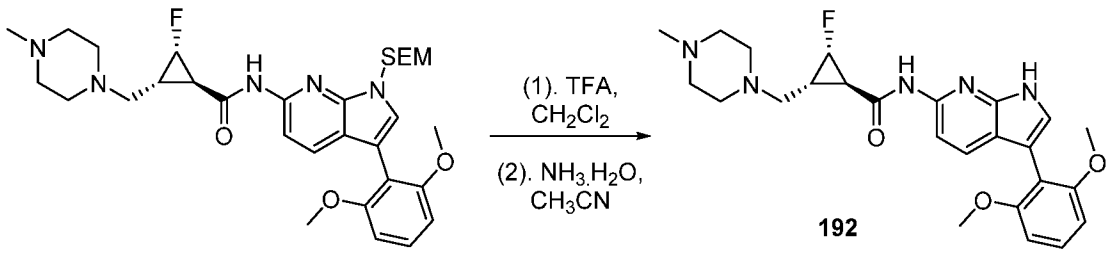
[0893] To a solution of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(S)-fluoro-2-(hydroxymethyl)cyclopropane-1-carboxamide (570.0 mg, 1.11 mmol) in CH_2Cl_2 (10.0 mL) was added Dess-Martin (701.1 mg, 1.62 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with aq. $NaHCO_3$, brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(S)-fluoro-2-formylcyclopropane-1-carboxamide (600.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =514.2.

Step 7: Synthesis of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(S)-fluoro-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide



[0894] To a mixture of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(S)-fluoro-2-formylcyclopropane-1-carboxamide (600.0 mg, crude) and 1-methylpiperazine (351.0 mg, 3.51 mmol) in CH_2Cl_2 (10.0 mL) was added $NaBH_3CN$ (330.3 mg, 3.51 mmol) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC with CH_2Cl_2/CH_3OH (20/1, v/v) to afford trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(S)-fluoro-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (200.0 mg, 34%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =598.3.

Step 8: Synthesis of trans-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(S)-fluoro-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (Compound 192)

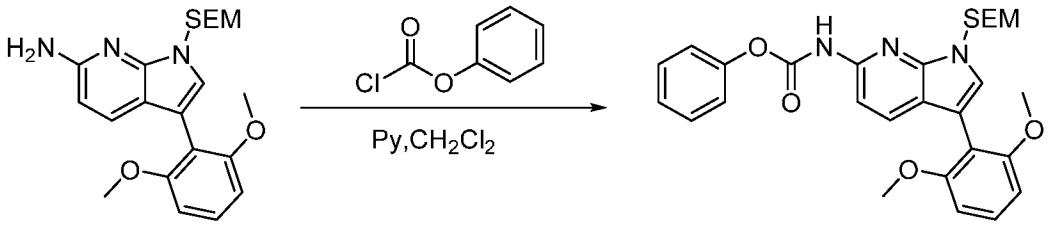


[0895] To a solution of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(S)-fluoro-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (180.0 mg, 0.30 mmol) in CH_2Cl_2

(4.0 mL) was added TFA (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (4.0 mL) was added $NH_3.H_2O$ (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 8 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 30×150 mm, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 50% B in 8 min; Wave Length: 254 nm) to afford trans-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(S)-fluoro-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide **(Compound 192)** (5.2 mg, 4%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =468.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.45 (s, 1H), 10.63 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.30 - 7.26 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 4.99 - 4.82 (m, 1H), 3.69 (s, 6H), 2.73 - 2.66 (m, 1H), 2.62 - 2.50 (m, 1H), 2.47 - 2.26 (m, 8H), 2.09 (s, 3H), 2.06 - 1.99 (m, 1H).

Example S183: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-(2-{6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl}ethyl)urea (Compound 193)

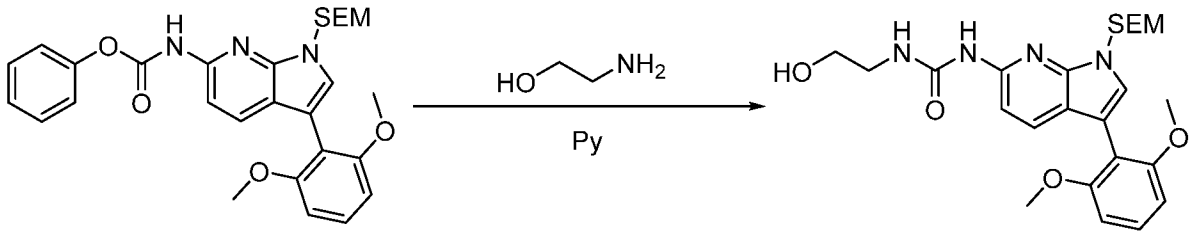
Step 1: Synthesis of Phenyl (3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamate



[0896] To a solution of 3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (300.0 mg, 0.75 mmol) in CH_2Cl_2 (5.0 mL) was added pyridine (224.0 mg, 3.00 mmol) and phenyl chloroformate (140.4 mg, 0.90 mmol) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated in vacuo to afford phenyl (3-(2,6-dimethoxyphenyl)-1-

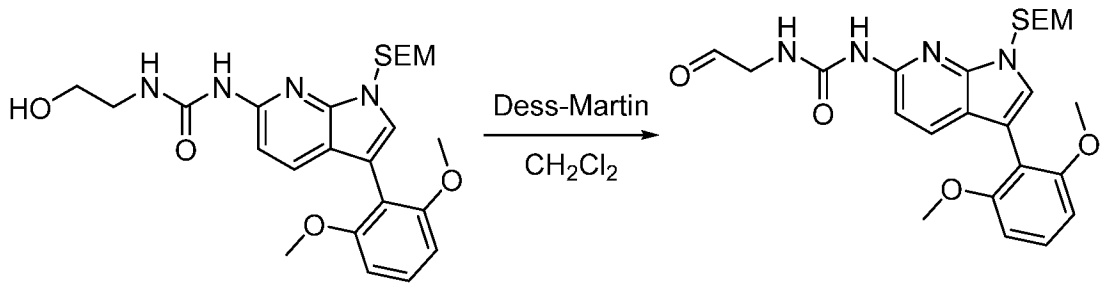
((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamate (400.0 mg, crude) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ = 520.2

Step 2: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-(2-hydroxyethyl)urea



[0897] To a solution of phenyl N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamate (300.0 mg, 0.57 mmol) in pyridine (3.0 mL) was added ethanolamine (42.3 mg, 0.69 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (92/8, v/v) to afford 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-(2-hydroxyethyl)urea (250.0 mg, 78%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =487.2

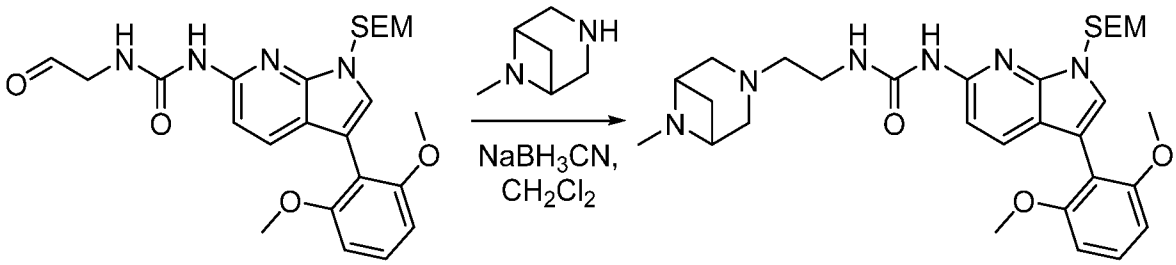
Step 3: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-(2-oxoethyl)urea



[0898] To a solution of 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-(2-hydroxyethyl)urea (100.0 mg, 0.21 mmol) in CH_2Cl_2 (3.0 mL) was added Dess-Martin (348.6 mg, 0.82 mmol) at room temperature under N_2. The resulting mixture was stirred at room temperature for 4 h under

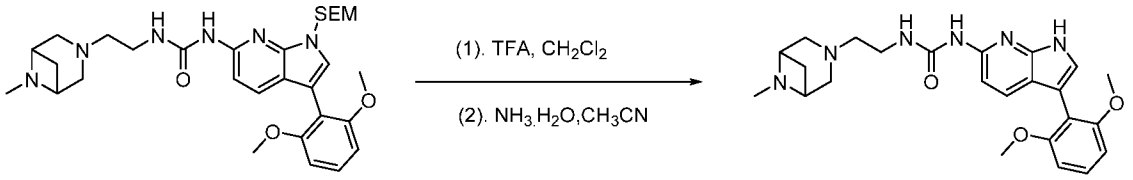
N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-(2-oxoethyl)urea (100.0 mg, crude) as a black solid. LCMS (ESI, m/z): $[M+H]^+$ =485.2

Step 4: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-(2-{6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl}ethyl)urea



[0899] To a solution of 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-(2-oxoethyl)urea (100.0 mg, crude) in CH_2Cl_2 (3.0 mL) was added 6-methyl-3,6-diazabicyclo[3.1.1]heptane (69.4 mg, 0.61 mmol) and $NaBH_3CN$ (13.0 mg, 0.20 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with petroleum CH_3CN/H_2O (60/40, v/v) to afford 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-(2-{6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl}ethyl)urea (30.0 mg, 25%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 581.3.

Step 5: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-(2-{6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl}ethyl)urea (Compound 193)

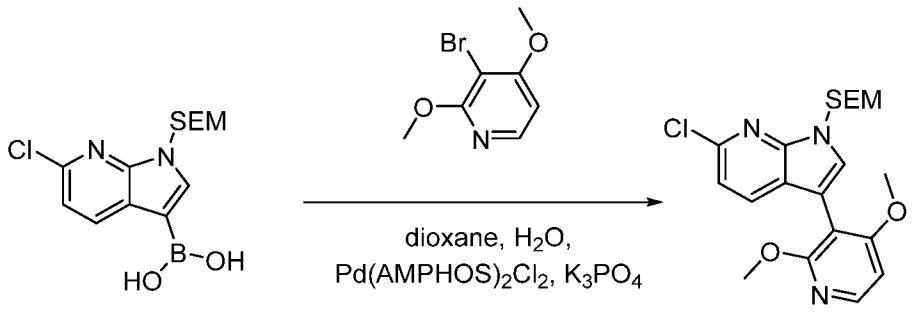


193

[0900] To a solution of 1-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-(2-{6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl}ethyl)urea (30.0 mg, 0.06 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (3.0 mL) was added $NH_3.H_2O$ (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17 % B to 47 % B in 9 min; 254 nm) to afford 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-(2-{6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl}ethyl)urea **(Compound 193)** (1.4 mg, 6%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 451.4. ^1H NMR (400 MHz, DMSO-d_6): δ 11.27 (s, 1H), 9.17 (s, 1H), 8.49 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 2.0 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 2H), 3.68 (s, 6H), 2.93 - 2.83 (m, 4H), 2.76 - 2.73 (m, 2H), 2.26 - 2.12 (m, 1H), 2.01 (s, 3H), 1.87 - 1.82 (m, 1H).

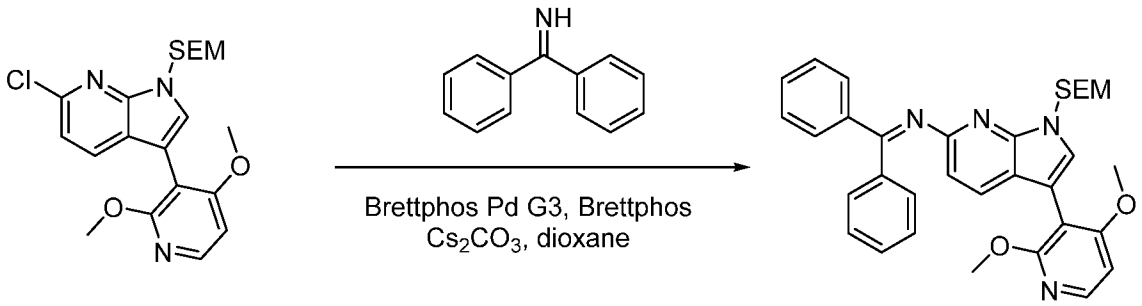
Example S184: Synthesis of 3-[3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-ethylpiperazin-1-yl)ethyl]urea (Compound 194)

Step 1: Synthesis of 6-chloro-3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-b]pyridine



[0901] To a solution of 6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-ylboronic acid (1.20 g, 3.67 mmol) in H_2O (1.5 mL) and dioxane (15.0 mL) was added 3-bromo-2,4-dimethoxypyridine (961.2 mg, 4.48 mmol), $Pd(AMPHOS)_2Cl_2$ (260.1 mg, 0.37 mmol) and K_3PO_4 (2.4 g, 11.24 mmol). The resulting mixture was stirred at 80 °C for 12 h under N_2. After the reaction was completed, the resulting mixture was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford 6-chloro-3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-b]pyridine (830.0 mg, 54%) as a red oil. LCMS (ESI, m/z): $[M+H]^+$ = 420.1.

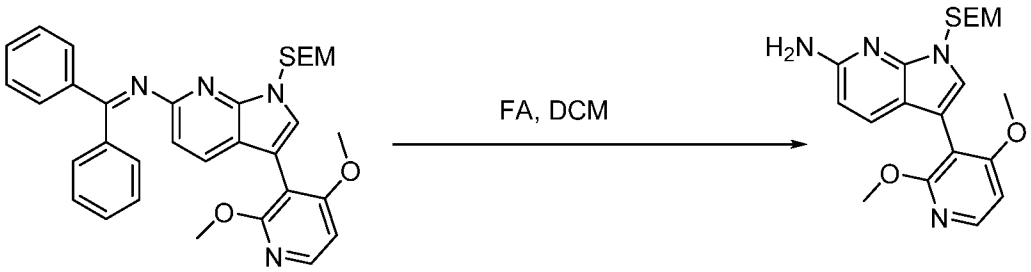
Step 2: Synthesis of N-(3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-b]pyridin-6-yl)-1,1-diphenylmethanimine



[0902] To a solution of 6-chloro-3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-b]pyridine (830.0 mg, 1.98 mmol) in dioxane (10.0 mL) was added diphenylmethanimine (1.0 g, 5.94 mmol), Brettphos Pd G3 (194.5 mg, 0.20 mmol), Brettphos (216.4 mg, 0.40 mmol) and Cs_2CO_3 (1936.4 mg, 5.94 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium

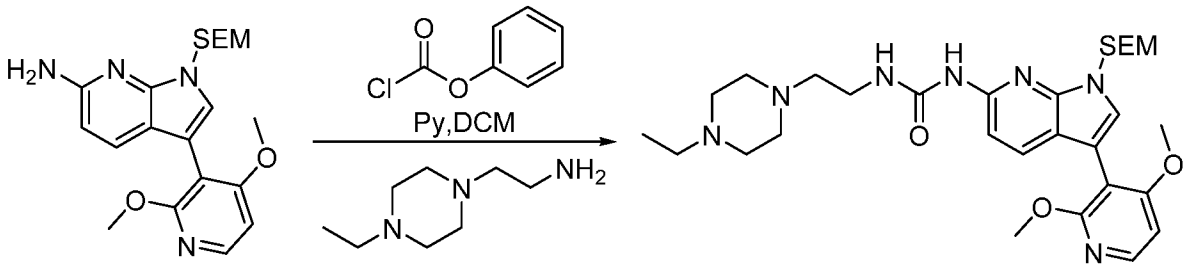
sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/2, v/v) to afford N-(3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-b]pyridin-6-yl)-1,1-diphenylmethanimine (1.0 g, 89%) as a light red oil. LCMS (ESI, m/z): $[M+H]^+$ = 565.3.

Step 3: Synthesis of 3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine



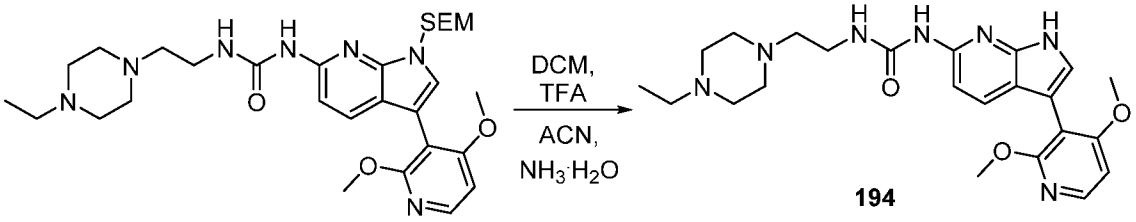
[0903] To a solution of N-(3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-b]pyridin-6-yl)-1,1-diphenylmethanimine (1.0 g, 0.47 mmol) in DCM (10.0 mL) was added FA (5.0 mL) at room temperature. The mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O. The pH value of the mixture was adjusted to 7 with $NaHCO_3$ solution. The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (530.0 mg, 75%) as a red oil. LCMS (ESI, m/z): $[M+H]^+$ = 401.2.

Step 4: Synthesis of 3-[3-(2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-ethylpiperazin-1-yl)ethyl]urea



[0904] To a solution of 3-(2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (200.0 mg, 0.50 mmol) in pyridine/DCM (10.0 mL/5.0 mL) was added phenyl chloroformate (78.18 mg, 0.499 mmol) at 0 °C under N_2. The mixture was stirred at 0 °C for 1 h. The resulting mixture was concentrated under vacuum. To the above mixture was added a solution of 2-(4-ethylpiperazin-1-yl)ethan-1-amine (235.7 mg, 1.49 mmol) in pyridine (10.0 mL). The resulting mixture was stirred at 60 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (9/1, v/v) to afford 3-[3-(2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-ethylpiperazin-1-yl)ethyl]urea (90.0 mg, 31%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+ = 584.3$.

Step 5: Synthesis of 3-[3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-ethylpiperazin-1-yl)ethyl]urea (Compound 194)

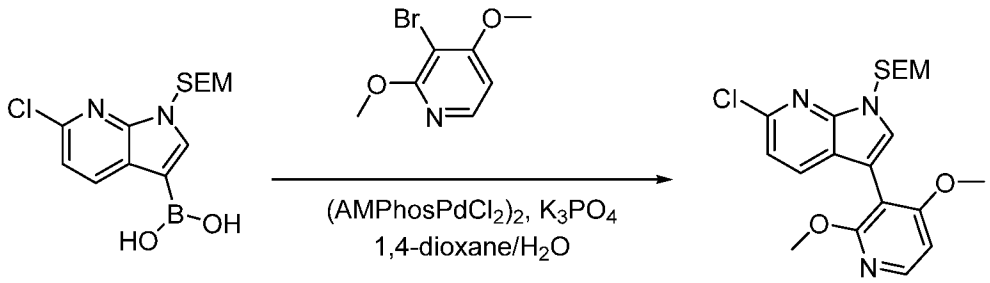


[0905] To a solution of 3-[3-(2,4-dimethoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-ethylpiperazin-1-yl)ethyl]urea (70.0 mg, 0.12 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 40% B in 9 min; 254 nm) to afford 3-[3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-ethylpiperazin-1-yl)ethyl]urea **(Compound 194)** (6.8 mg, 13%) as a white solid. LCMS

(ESI, m/z): $[M+H]^+$ = 454.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.40 (s, 1H), 9.16 (s, 1H), 8.35 (s, 1H), 8.05 (d, J = 5.6 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.25 (d, J = 2.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 6.0 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.52 - 2.44 (m, 5H), 2.36 - 2.26 (m, 5H), 0.99 - 0.96 (m, 3H).

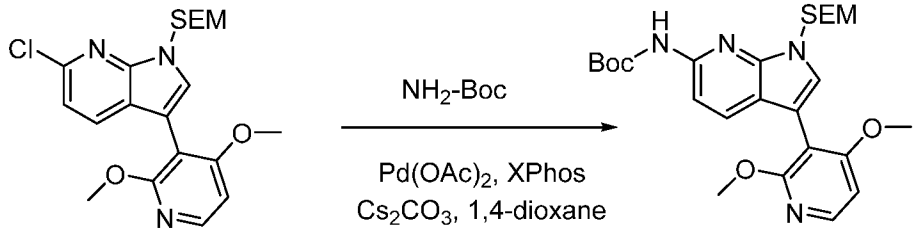
Example S185: Synthesis of 1-(3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)propyl)urea (Compound 195)

Step 1: Synthesis of 6-chloro-3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine



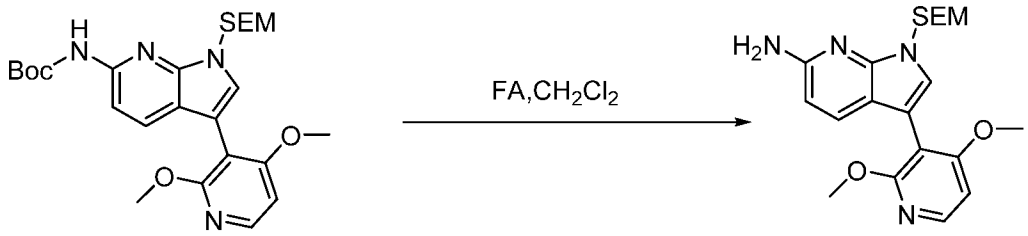
[0906] To a solution of 3-bromo-2,4-dimethoxypyridine (380.0 mg, 1.74 mmol) in 1,4-dioxane/H_2O (10.0 mL/2.0 mL) was added (6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)boronic acid (683.1 mg, 2.09 mmol), K_3PO_4 (1109.8 mg, 5.23 mmol) and $(AMPhosPdCl_2)_2$ (123.4 mg, 0.17 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 3 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (60/40, v/v) to afford 6-chloro-3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (220.0 mg, 30%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 420.1.

Step 2: Synthesis of Tert-butyl (3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamate



[0907] To a solution of 6-chloro-3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (180.0 mg, 0.43 mmol) in 1,4-dioxane (10.0 mL) was added NH_2-Boc (65.3 mg, 0.56 mmol), Cs_2CO_3 (418.9 mg, 1.29 mmol), XPhos (40.9 mg, 0.09 mmol) and $Pd(OAc)_2$ (9.6 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 3 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (50/50, v/v) to afford tert-butyl (3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamate (200.0 mg, 93%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 501.2.

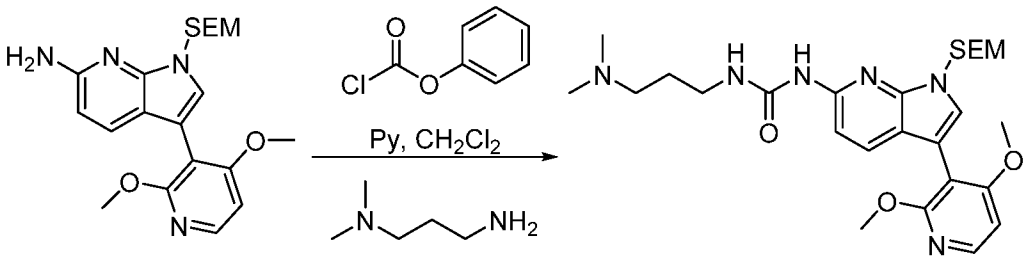
Step 3: Synthesis of 3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine



[0908] To a solution of tert-butyl (3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamate (180.0 mg, 0.45 mmol) in CH_2Cl_2 (10.0 mL) was added FA (15.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 3-(2,4-dimethoxypyridin-3-yl)-1-

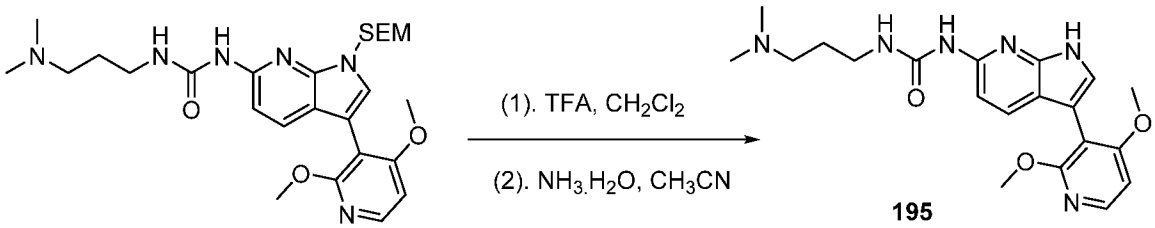
((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (140.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 401.2.

Step 4: Synthesis of 1-(3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)propyl)urea



[0909] To a solution of 3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (100.0 mg, 0.25 mmol) in CH_2Cl_2 (10.0 mL) was added phenyl carbonochloridate (117.3 mg, 0.75 mmol) and pyridine (80.0 mg, 1.00 mmol) at room temperature under N_2. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in pyridine (10.0 mL). Then N^1, N^1-dimethylpropane-1,3-diamine (30.6 mg, 0.30 mmol) was added to the mixture at room temperature. The resulting mixture was stirred at 60 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (86/14, v/v) to afford 1-(3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)propyl)urea (72.0 mg, 55%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 529.3.

Step 5: Synthesis of 1-(3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)propyl)urea (Compound 195)

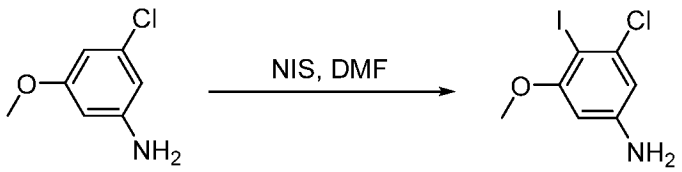


195

[0910] To a solution of 1-(3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)propyl)urea (120.0 mg, 0.23 mmol) in CH_2Cl_2 (4.0 mL) was added TFA (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (4.0 mL) was added $NH_3.H_2O$ (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 47% B in 9 min; 254 nm) to afford 1-(3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)propyl)urea **(Compound 195)** (14.6 mg, 16%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 399.3. ^1H NMR (400 MHz, DMSO-d_6): δ 11.45 (s, 1H), 9.13 (s, 1H), 8.57 (s, 1H), 8.05 (d, J = 6.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 2.4 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 6.0 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.33 - 3.21 (m, 1H), 3.25 - 3.23 (m, 1H), 2.34 - 2.23 (m, 2H), 2.17 (s, 6H), 1.68 - 1.62 (m, 2H).

Example S186: Synthesis of (1S,2S)-N-[3-(7-chloro-5-methoxy-1,3-benzothiazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 196)

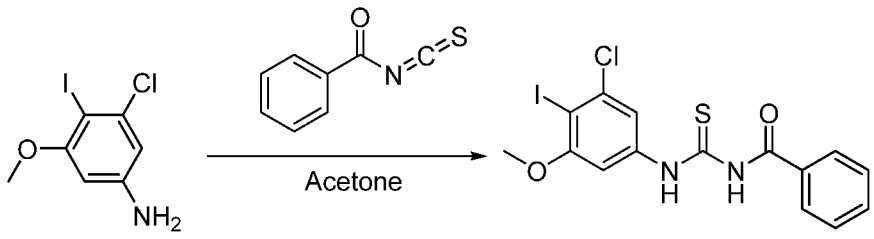
Step 1: Synthesis of 3-chloro-4-iodo-5-methoxyaniline



[0911] To a solution of 3-chloro-5-methoxyaniline (2.0 g, 12.69 mmol) in DMF (10.0 mL) was added NIS (2.6 g, 11.42 mmol) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 0.5 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with

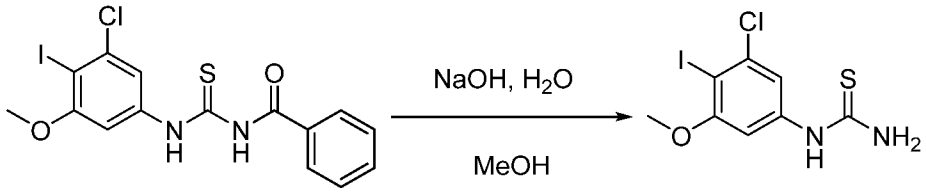
petroleum ether/ethyl acetate (85/15, v/v) to afford 3-chloro-4-iodo-5-methoxyaniline (1.6 g, 44%) as an off-white solid. LCMS (ESI, m/z): $[M+H]^+$ = 283.9.

Step 2: Synthesis of 1-benzoyl-3-(3-chloro-4-iodo-5-methoxyphenyl)thiourea



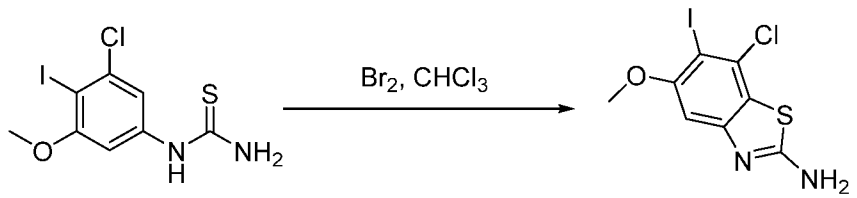
[0912] To a solution of 3-chloro-4-iodo-5-methoxyaniline (1.6 g, 5.64 mmol) in acetone (24.0 mL) was added benzoyl isothiocyanate (921.6 mg, 5.64 mmol) at 0 °C under N_2. The resulting mixture was stirred at 60 °C for 0.5 h. After the reaction was completed, the reaction mixture was filtered. The solid was collected and dried to afford 1-benzoyl-3-(3-chloro-4-iodo-5-methoxyphenyl)thiourea (2.0 g, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 446.9.

Step 3: Synthesis of 3-chloro-4-iodo-5-methoxyphenylthiourea



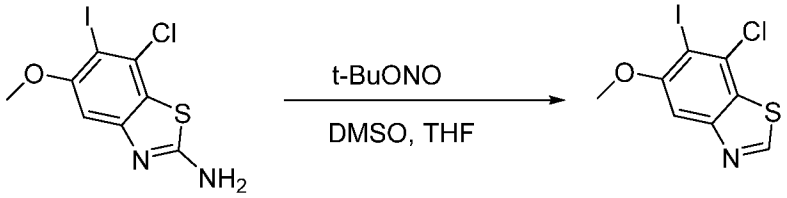
[0913] To a solution of 1-benzoyl-3-(3-chloro-4-iodo-5-methoxyphenyl)thiourea (2.0 g, 4.38 mmol) in MeOH/H_2O (10.0/10.0 mL) was added NaOH (193.3 mg, 4.83 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the mixture was filtered. The solid was collected and dried to afford 3-chloro-4-iodo-5-methoxyphenylthiourea (1.4 g, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 342.9.

Step 4: Synthesis of 7-chloro-6-iodo-5-methoxy-1,3-benzothiazol-2-amine



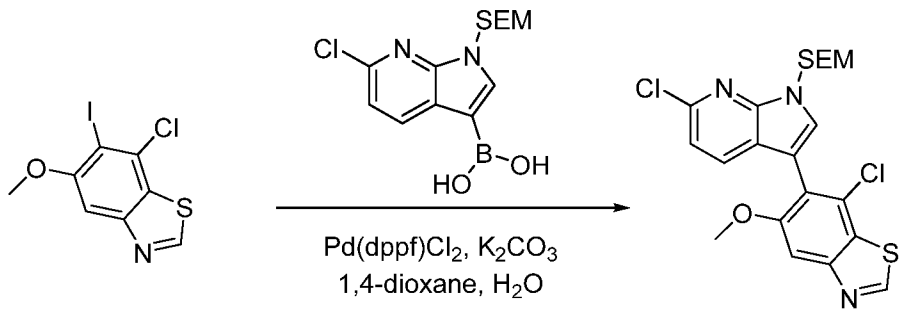
[0914] To a solution of 3-chloro-4-iodo-5-methoxyphenylthiourea (700.0 mg, 2.04 mmol) in $CHCl_3$ (8.0 mL) was added Br_2 (359.2 mg, 2.25 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the reaction was quenched with saturated $NaHSO_3$ solution at 0 °C. The resulting mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 7-chloro-6-iodo-5-methoxy-1,3-benzothiazol-2-amine (560.0 mg, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 340.9.

Step 5: Synthesis of 7-chloro-6-iodo-5-methoxy-1,3-benzothiazole



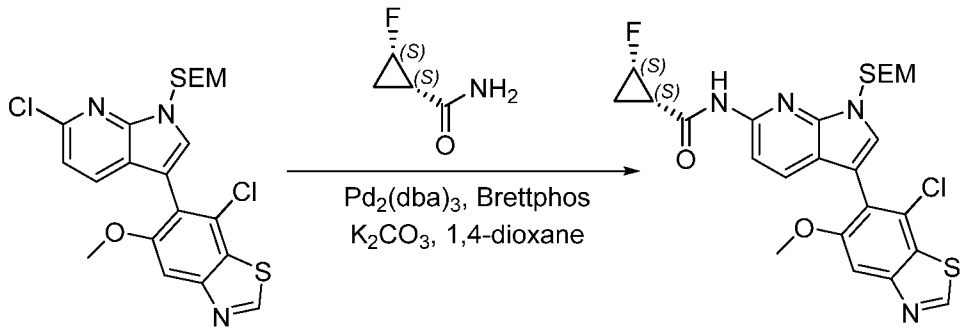
[0915] To a solution of 7-chloro-6-iodo-5-methoxy-1,3-benzothiazol-2-amine (560.0 mg, 1.72 mmol) in THF (10.0 mL) was added t-BuONO (265.3 mg, 2.57 mmol) and DMSO (10.7 mg, 0.14 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (85/15, v/v) to afford 7-chloro-6-iodo-5-methoxy-1,3-benzothiazole (250.0 mg, 44%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 325.9.

Step 6: Synthesis of 7-chloro-6-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-5-methoxy-1,3-benzothiazole



[0916] To a solution of 7-chloro-6-iodo-5-methoxy-1,3-benzothiazole (220.0 mg, 0.68 mmol) in 1,4-dioxane/H_2O (8.0 mL/1.6 mL) was added 6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-ylboronic acid (264.9 mg, 0.81 mmol), K_2CO_3 (280.2 mg, 2.03 mmol) and Pd(dppf)Cl_2 (55.0 mg, 0.07 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (80/20, v/v) to afford 7-chloro-6-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-5-methoxy-1,3-benzothiazole (218.0 mg, 67%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 480.1.

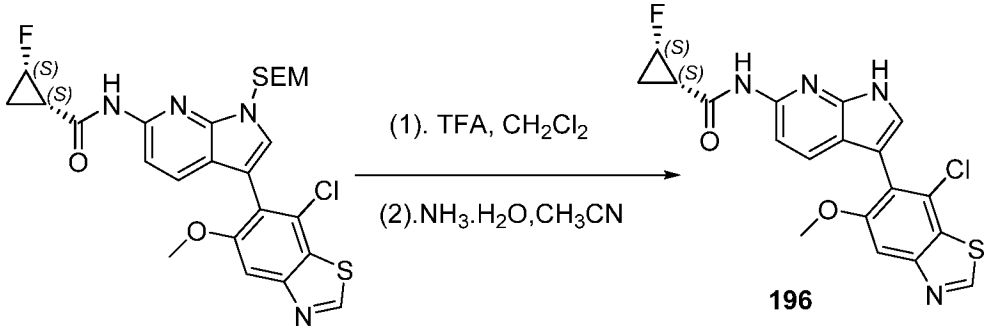
Step 7: Synthesis of (1S,2S)-N-[3-(7-chloro-5-methoxy-1,3-benzothiazol-6-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide



[0917] To a solution of 7-chloro-6-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-5-methoxy-1,3-benzothiazole (188.0 mg, 0.39 mmol) in 1,4-dioxane (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (201.7 mg, 1.96 mmol), K_2CO_3 (162.2 mg, 1.17 mmol), BrettPhos (42.0 mg, 0.08 mmol) and $Pd_2(dba)_3$ (35.8 mg, 0.04 mmol) at room temperature under N_2. The resulting mixture was stirred at room temperature for 4 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum CH_2Cl_2/CH_3OH (95/5, v/v) to afford (1S,2S)-N-[3-(7-chloro-5-methoxy-1,3-benzothiazol-6-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-

b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (140.0 mg, 52%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 547.1.

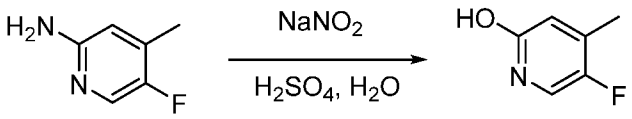
Step 8: Synthesis of (1S,2S)-N-[3-(7-chloro-5-methoxy-1,3-benzothiazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 196)



[0918] To a solution of (1S,2S)-N-[3-(7-chloro-5-methoxy-1,3-benzothiazol-6-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (130.0 mg, 0.24 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3 \cdot H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with CH_3CN/H_2O (70/30, v/v) to afford (1S,2S)-N-[3-(7-chloro-5-methoxy-1,3-benzothiazol-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide **(Compound 196)** (12.3 mg, 11%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 417.1. ^1H NMR (400 MHz, DMSO-d_6): δ 11.77 (s, 1H), 10.68 (s, 1H), 9.45 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.79 (s 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 5.03 - 4.82 (m, 1H), 3.82 (s, 3H), 2.30 - 2.19 (m, 1H), 1.70 - 1.62 (m, 1H), 1.23 - 1.11 (m, 1H).

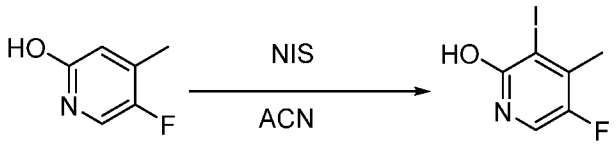
Example S187: Synthesis of (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxy-4-methylpyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 197)

Step 1: Synthesis of 5-fluoro-4-methylpyridin-2-ol



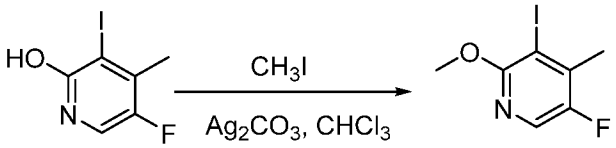
[0919] To a solution of 5-fluoro-4-methylpyridin-2-amine (600.0 mg, 4.76 mmol) in H_2SO_4 (12.0 mL)/H_2O (24.0 mL) was added dropwise a solution of $NaNO_2$ (1641.0 mg, 23.78 mmol) in H_2O (12.0 mL) at 0 °C. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 5-fluoro-4-methylpyridin-2-ol (200.0 mg, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =128.0.

Step 2: Synthesis of 5-fluoro-3-iodo-4-methylpyridin-2-ol



[0920] To a solution of 5-fluoro-4-methylpyridin-2-ol (820.0 mg, 6.45 mmol) in ACN (30.0 mL) was added NIS (1.6 g, 7.10 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/4, v/v) to afford 5-fluoro-3-iodo-4-methylpyridin-2-ol (1.6 g, 98%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =253.9.

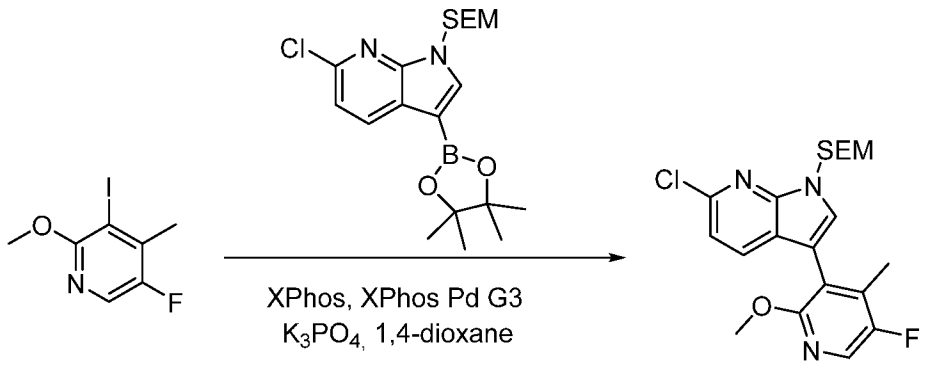
Step 3: Synthesis of 5-fluoro-3-iodo-2-methoxy-4-methylpyridine



[0921] To a solution of 5-fluoro-3-iodo-4-methylpyridin-2-ol (900.0 mg, 3.56 mmol) in $CHCl_3$ (20.0 mL) was added Ag_2CO_3 (3923.4 mg, 14.23 mmol) and CH_3I (2019.6 mg, 14.23 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 4 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with

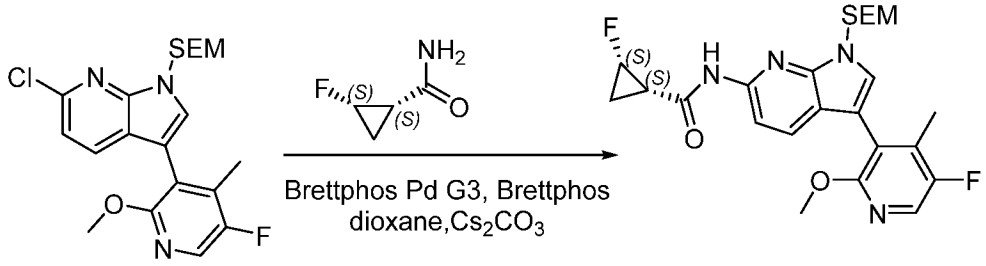
petroleum ether/ethyl acetate (10/1, v/v) to afford 5-fluoro-3-iodo-2-methoxy-4-methylpyridine (130.0 mg, 13%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 268.0

Step 4: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-fluoro-2-methoxy-4-methylpyridine



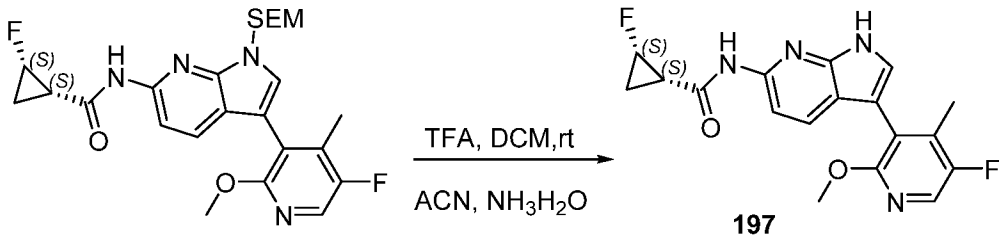
[0922] To a solution of 5-fluoro-3-iodo-2-methoxy-4-methylpyridine (380.0 mg, 1.42 mmol) in 1,4-dioxane/H_2O (10.0/2.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (581.7 mg, 1.42 mmol), XPhos (135.7 mg, 0.29 mmol), K_3PO_4 (906.2 mg, 4.27 mmol) and XPhos Pd G3 (120.5 mg, 0.14 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-fluoro-2-methoxy-4-methylpyridine (320.0 mg, 53%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =422.1.

Step 5: Synthesis of (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxy-4-methylpyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide



[0923] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-5-fluoro-2-methoxy-4-methylpyridine (320.0 mg, 0.76 mmol) in 1,4-dioxane (10.0 mL) were added (1S,2S)-2-fluorocyclopropane-1-carboxamide (390.9 mg, 3.79 mmol), BrettPhos (81.4 mg, 0.15 mmol), Cs_2CO_3 (741.3 mg, 2.28 mmol) and BrettPhos Pd G3 (68.7 mg, 0.07 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 4 h under N_2. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/3, v/v) to afford (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxy-4-methylpyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (180.0 mg, 48%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =489.2.

Step 6: Synthesis of (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxy-4-methylpyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (Compound 197)

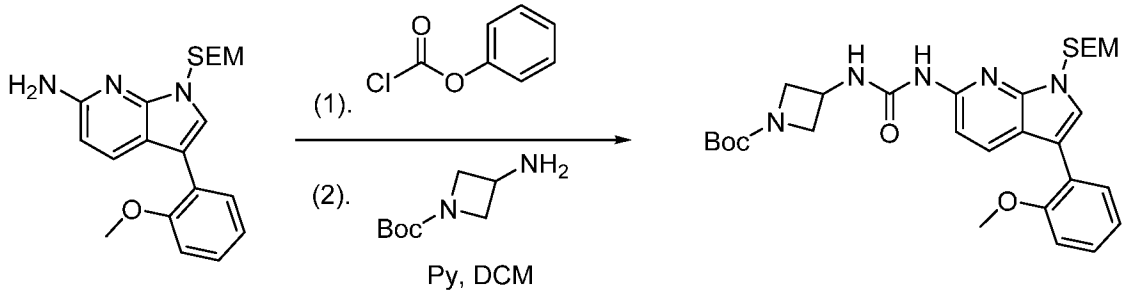


[0924] To a solution of (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxy-4-methylpyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide (180.0 mg, 0.37 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (3.0 mL) was added $NH_3.H_2O$ (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, 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, 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 56% B in 12 min; 254 nm) to afford (1S,2S)-2-fluoro-N-[3-(5-fluoro-2-methoxy-4-methylpyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropane-1-carboxamide

(Compound 197) (27.0 mg, 20%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 359.1. ^1H NMR (300 MHz, DMSO-d_6): δ 11.74 (s, 1H), 10.67 (s, 1H), 8.09 (s, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.46 (s, 1H), 5.05 - 4.81 (m, 1H), 3.77 (s, 3H), 2.25 - 2.16 (m, 4H), 1.70 - 1.61 (m, 1H), 1.19 - 1.12 (m, 1H).

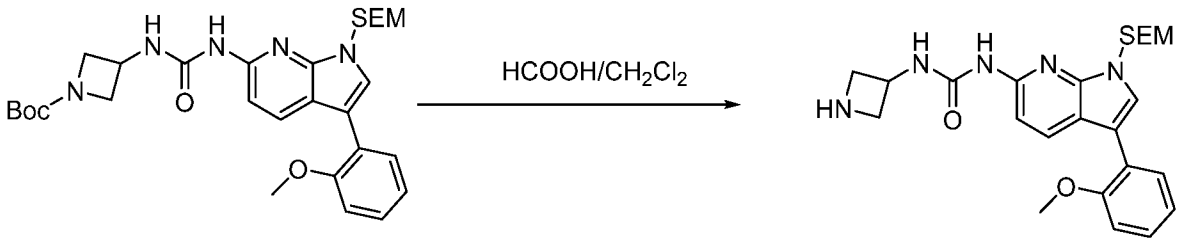
Example S188: Synthesis of 3-[1-[2-(dimethylamino)ethyl]azetidin-3-yl]-1-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (Compound 198)

Step 1: Synthesis of tert-butyl 3-([[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)azetidine-1-carboxylate



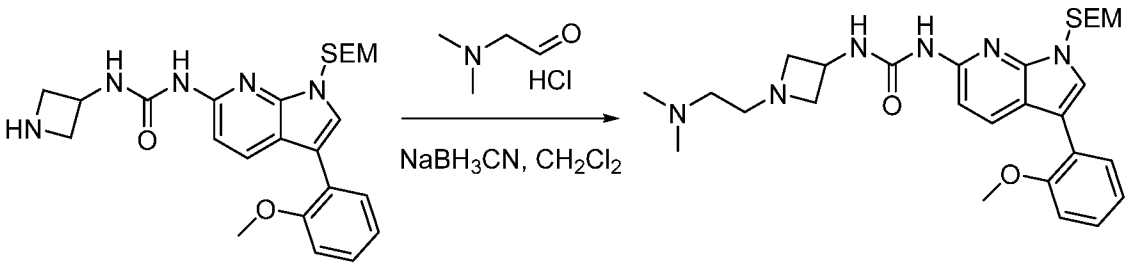
[0925] To a solution of 3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (500.0 mg, 1.35 mmol) in CH_2Cl_2 (5.0 mL) was added pyridine (428.1 mg, 5.41 mmol) and phenyl chloroformate (254.2 mg, 1.62 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was concentrated under vacuum. To the above residue was added pyridine (5.0 mL) and tert-butyl 3-aminoazetidine-1-carboxylate (699.1 mg, 4.06 mmol). The resulting mixture was stirred at 60 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (97/3, v/v) to afford tert-butyl 3-([[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)azetidine-1-carboxylate (600.0 mg, 78%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ = 568.3.

Step 2: Synthesis of 3-(azetidin-3-yl)-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea



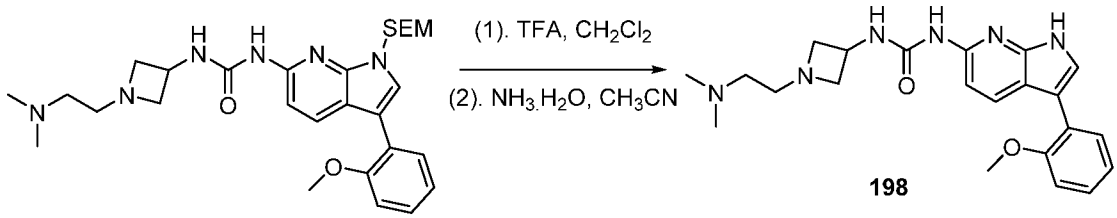
[0926] To a solution of tert-butyl 3-([[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]carbamoyl]amino)azetidine-1-carboxylate (600.0 mg, 1.06 mmo) in CH_2Cl_2 (2.0 mL) was added HCOOH (4.0 mL). The resulting mixture was stirred at room temperature for 6 h. After the reaction was completed, The pH value of the mixture was adjusted to 7 with aq.$NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford 3-(azetidin-3-yl)-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (480.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 468.2.

Step 3: Synthesis of 3-[1-[2-(dimethylamino)ethyl]azetidin-3-yl]-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea



[0927] To a solution of 3-(azetidin-3-yl)-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (480.0 mg, crude) in CH_2Cl_2 (5.0 mL) was added 2-(dimethylamino)acetaldehyde hydrochloride (380.5 mg, 3.08 mmol) and $NaBH_3CN$ (193.5 mg, 3.08 mmol) at room temperature. The mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (97/3, v/v) to afford 3-[1-[2-(dimethylamino)ethyl]azetidin-3-yl]-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (150.0 mg, 27%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 539.3.

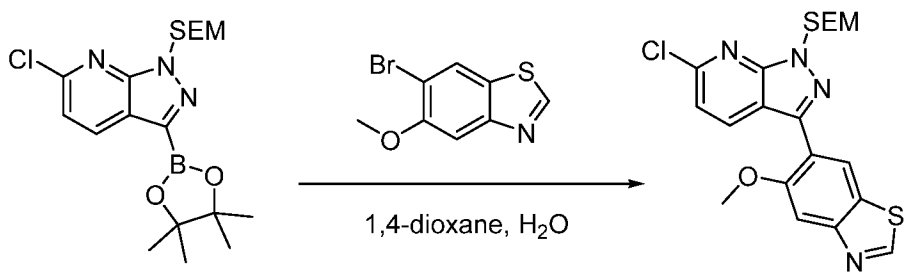
Step 4: Synthesis of 3-[1-[2-(dimethylamino)ethyl]azetidin-3-yl]-1-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea (Compound 198)



[0928] To a solution of 3-[1-[2-(dimethylamino)ethyl]azetidin-3-yl]-1-[3-(2-methoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]urea (150.0 mg, 0.28 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL). The mixture was stirred at room temperature for 3 h. The mixture was concentrated under vacuum. To the above residue was added ACN (3.0 mL) and $NH_3.H_2O$ (3.0 mL). The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD Column, 30×150 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 48% B in 8 min; 254 nm) to afford 3-[1-[2-(dimethylamino)ethyl]azetidin-3-yl]-1-[3-(2-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]urea **(Compound 198)** (11.4 mg, 10%) as a white solid. LCMS (ESI, m/z): $[M+H]^+ = 409.3$. ^1H NMR (300 MHz, DMSO-d_6): δ 11.62 (s, 1H), 9.24 (s, 1H), 8.98 - 8.95 (m, 1H), 7.92 (d, $J = 8.4$ Hz, 1H), 7.53 - 7.50 (m, 2H), 7.30 - 7.24 (m, 1H), 7.11 (d, $J = 7.5$ Hz, 1H), 7.04 - 6.99 (m, 2H), 4.37 - 4.30 (m, 1H), 3.81 (s, 3H), 3.68 - 3.57 (m, 2H), 3.00 - 2.95 (m, 2H), 2.63 - 2.55 (m, 2H), 2.36 - 2.27 (m, 2H), 2.22 (s, 6H).

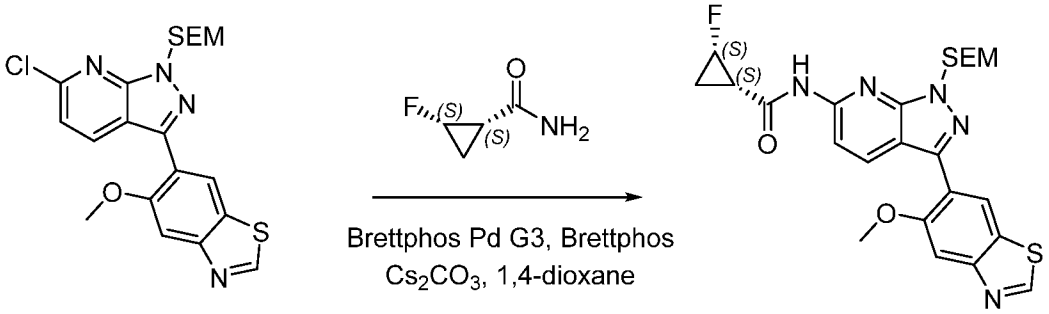
Example S189: Synthesis of (1S,2S)-2-fluoro-N-(3-(5-methoxybenzo[d]thiazol-6-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 199)

Step 1: Synthesis of 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-methoxybenzo[d]thiazole



[0929] To a solution of 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridine (350.0 mg, 1.07 mmol) in 1,4-dioxane (2.0 mL) was added 6-bromo-5-methoxy-1,3-benzothiazole (260.8 mg, 1.07 mmol), K_3PO_4 (680.2 mg, 3.21 mmol), $Pd(AMPHOS)_2Cl_2$ (90.8 mg, 0.13 mmol) and H_2O (0.5 mL) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (60/40, v/v) to afford 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-methoxybenzo[d]thiazole (195.0 mg, 41%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 447.1.

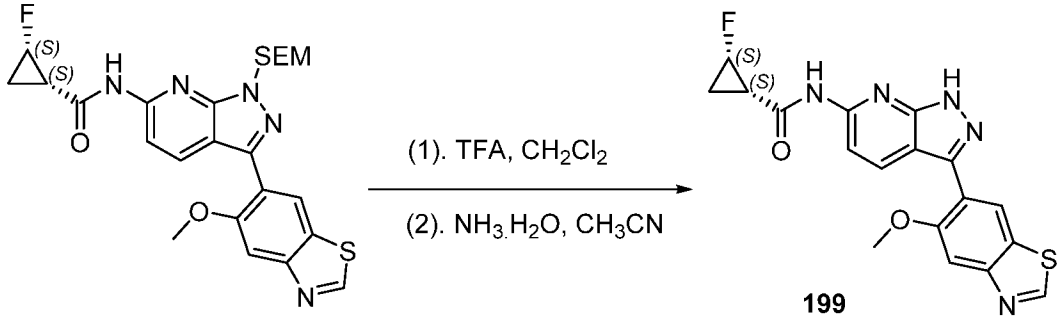
Step 2: Synthesis of (1S,2S)-2-fluoro-N-(3-(5-methoxybenzo[d]thiazol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)cyclopropane-1-carboxamide



[0930] To a solution of 6-(6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-methoxybenzo[d]thiazole (150.0 mg, 0.34 mmol) in 1,4-dioxane (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (173.0 mg, 1.68 mmol), K_2CO_3 (139.1 mg, 1.01 mmol) BrettPhos (36.0 mg, 0.07 mmol) and BrettPhos Pd G3 (30.4 mg, 0.03 mmol) at room temperature under N_2. The resulting mixture was stirred at 100°C for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (70/30, v/v) to afford (1S,2S)-2-fluoro-N-(3-(5-methoxybenzo[d]thiazol-6-

yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)cyclopropane-1-carboxamide (66.0 mg, 38%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =514.2.

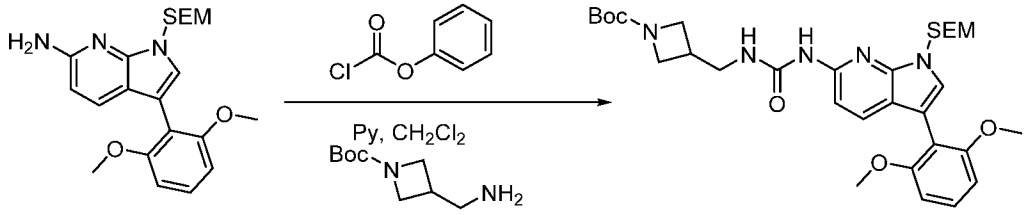
Step 3: Synthesis of (1S,2S)-2-fluoro-N-(3-(5-methoxybenzo[d]thiazol-6-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 199)



[0931] To a solution of (1S,2S)-2-fluoro-N-(3-(5-methoxybenzo[d]thiazol-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)cyclopropane-1-carboxamide (46.0 mg, 0.09 mmol) in DCM (1.0 mL) was added TFA (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in ACN (1.0 mL) was added $NH_3 \cdot H_2O$ (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 ml/min; Gradient: 28% B to 35% B in 8 min; 254 nm) to afford (1S,2S)-2-fluoro-N-(3-(5-methoxybenzo[d]thiazol-6-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl)cyclopropane-1-carboxamide **(Compound 199)** (15.3 mg, 44%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 384.1. ^1H NMR (300 MHz, DMSO-d_6): δ 13.57 (s, 1H), 10.99 (s, 1H), 9.42 (s, 1H), 8.35 (s, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.84 (s, 1H), 5.05 - 4.87 (m, 1H), 3.94 (s, 3H), 2.29 - 2.26 (m, 1H), 1.72 - 1.64 (m, 1H), 1.22 - 1.15 (m, 1H).

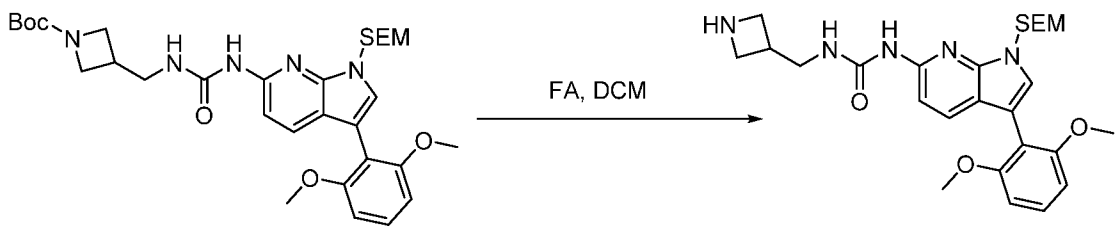
Example S190: Synthesis of 1-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-((1-methylazetidin-3-yl)methyl)urea (Compound 200)

Step 1: Synthesis of Tert-butyl 3-((3-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)ureido)methyl)azetidine-1-carboxylate



[0932] To a solution of 3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (200.0 mg, 0.50 mmol) in CH_2Cl_2 (5.0 mL) was added pyridine (80.0 mg, 2.50 mmol) and phenyl chloroformate (156.7 mg, 1.0 mmol) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. The resulting mixture was concentrated under reduced pressure. To the above mixture in pyridine (5.0 mL) was added tert-butyl 3-(aminomethyl)azetidine-1-carboxylate (372.9 mg, 2.00 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (90/10, v/v) to afford tert-butyl 3-((3-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)ureido)methyl)azetidine-1-carboxylate (150.0 mg, 49%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ = 612.3.

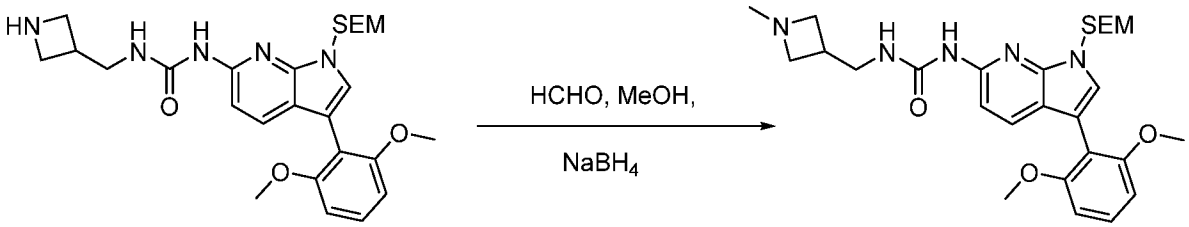
Step 2: Synthesis of 1-(azetidin-3-ylmethyl)-3-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)urea



[0933] To a solution of tert-butyl 3-((3-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)ureido)methyl)azetidine-1-carboxylate (100.0 mg, 0.16 mmol) in DCM (2.0 mL) was added FA (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction

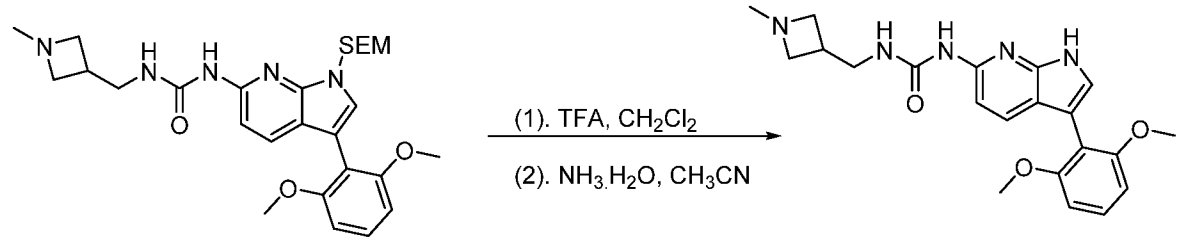
was completed, the pH value of the mixture was adjusted to 7 with aq.$NaHCO_3$ and then extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 1-(azetidin-3-ylmethyl)-3-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)urea (170.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 512.3.

Step 3: Synthesis of 1-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-((1-methylazetidin-3-yl)methyl)urea



[0934] To a solution of 1-(azetidin-3-ylmethyl)-3-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)urea (170.0 mg, 0.33 mmol) in MeOH (3.0 mL) was added HCHO (50.0 mg, 0.67 mmol) and $NaBH_4$ (75.4 mg, 1.99 mmol) at room temperature under N_2. The resulting mixture was stirred at room temperature for 4 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 1-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-((1-methylazetidin-3-yl)methyl)urea (190.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 526.3.

Step 4: Synthesis of 1-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-((1-methylazetidin-3-yl)methyl)urea (Compound 200)

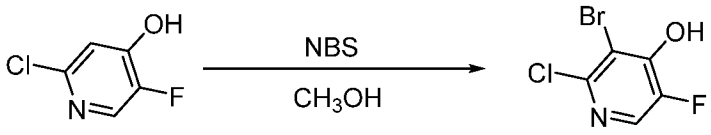


200

[0935] To a solution of 1-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-((1-methylazetidin-3-yl)methyl)urea (200.0 mg, 0.38 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3 \cdot H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31% B to 40% B in 8 min; 254 nm) to afford 1-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-((1-methylazetidin-3-yl)methyl)urea **(Compound 200)** (5.2 mg, 3%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 396.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.37 (s, 1H), 9.14 (s, 1H), 8.82 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.28 - 7.24 (m, 1H), 7.16 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.74 (d, J = 8.8 Hz, 2H), 3.68 (s, 6H), 3.40 - 3.37 (m, 3H), 3.30 - 3.24 (m, 2H), 2.92 - 2.85 (m, 2H), 2.18 (s, 3H).

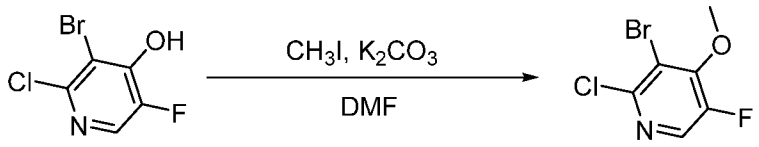
Example S191: Synthesis of (1S,2S)-N-[3-(2-ethoxy-5-fluoro-4-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 201)

Step 1: Synthesis of 3-bromo-2-chloro-5-fluoropyridin-4-ol



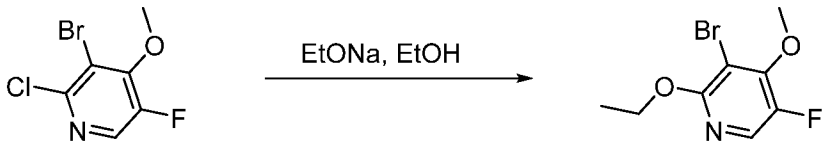
[0936] To a solution of 2-chloro-5-fluoropyridin-4-ol (2.0 g, 13.55 mmol) in CH_3OH (10.0 mL) was added NBS (2.9 g, 16.26 mmol) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (92/8, v/v) to afford 3-bromo-2-chloro-5-fluoropyridin-4-ol (3.0 g, 97%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =225.9.

Step 2: Synthesis of 3-bromo-2-chloro-5-fluoro-4-methoxypyridine



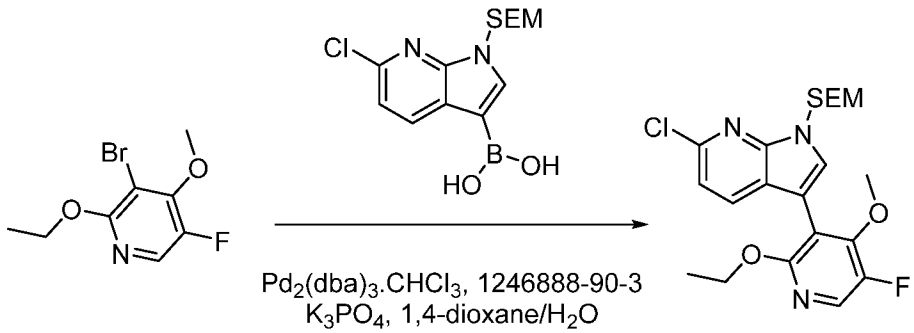
[0937] To a solution of 3-bromo-2-chloro-5-fluoropyridin-4-ol (1.5 g, 6.62 mmol) in DMF (5.0 mL) was added K_2CO_3 (1.8 g, 13.25 mmol) and CH_3I (1.1 g, 7.95 mmol) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (60/40, v/v) to afford 3-bromo-2-chloro-5-fluoro-4-methoxypyridine (600.0 mg, 37%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =239.9.

Step 3: Synthesis of 3-bromo-2-ethoxy-5-fluoro-4-methoxypyridine



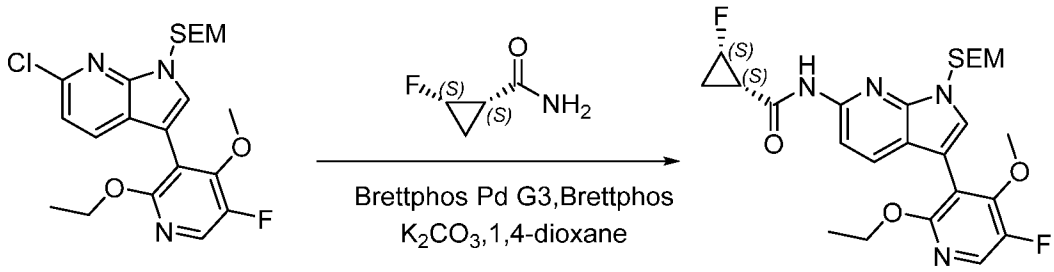
[0938] To a solution of 3-bromo-2-chloro-5-fluoro-4-methoxypyridine (600.0 mg, 2.50 mmol) in EtOH (5.0 mL) was added EtONa (203.6 mg, 3.00 mmol) at room temperature under N_2. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (65/35, v/v) to afford 3-bromo-2-ethoxy-5-fluoro-4-methoxypyridine (500.0 mg, 80%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =250.0.

Step 4: Synthesis of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-ethoxy-5-fluoro-4-methoxypyridine



[0939] To a solution of 3-bromo-2-ethoxy-5-fluoro-4-methoxypyridine (400.0 mg, 1.60 mmol) in 1,4-dioxane/H_2O (5.0/1.0 mL) was added 6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-ylboronic acid (627.0 mg, 1.92 mmol), K_3PO_4 (679.2 mg, 3.20 mmol), 3-tert-butyl-4-(2,6-dimethoxyphenyl)-2,3-dihydro[d]-[1,3]-oxaphosphole (CAS 1246888-90-3) (52.8 mg, 0.16 mmol) and $Pd_2(dba)_3 \cdot CHCl_3$ (80.0 mg, 0.08 mmol) at room temperature under N_2. The resulting mixture was stirred at 90 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (0/100, v/v) to afford 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-ethoxy-5-fluoro-4-methoxypyridine (300.0 mg, 55%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =452.1.

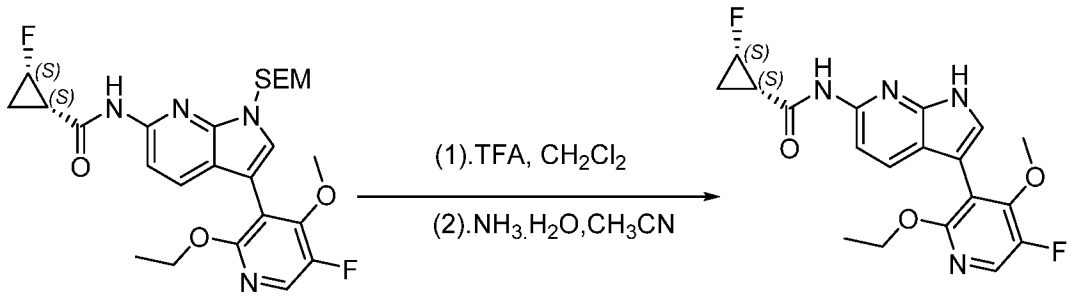
Step 5: Synthesis of (1S,2S)-N-[3-(2-ethoxy-5-fluoro-4-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide



[0940] To a solution of 3-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-2-ethoxy-5-fluoro-4-methoxypyridine (300.0 mg, 0.66 mmol) in 1,4-dioxane (5.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (342.1 mg, 3.32 mmol), Cs_2CO_3 (648.7 mg, 1.99 mmol), BrettPhos (71.1 mg, 0.13 mmol) and BrettPhos Pd G3 (60.6

mg, 0.07 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (0/100, v/v) to afford (1S,2S)-N-[3-(2-ethoxy-5-fluoro-4-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (160.0 mg, 46%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =519.2.

Step 6: Synthesis of (1S,2S)-N-[3-(2-ethoxy-5-fluoro-4-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 201)



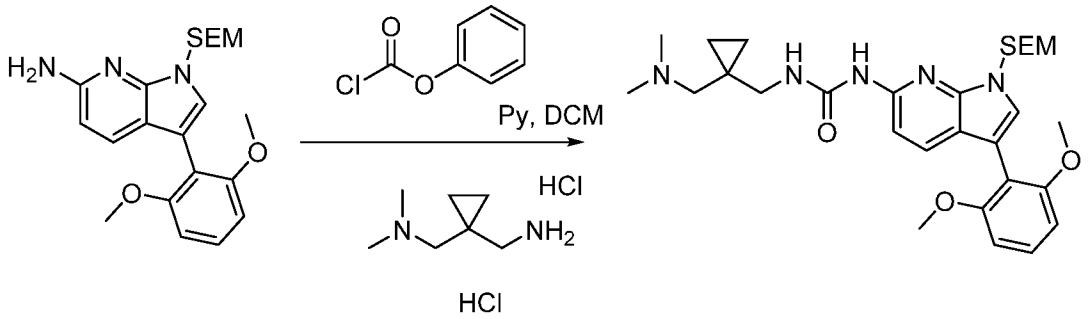
201

[0941] To a solution of (1S,2S)-N-[3-(2-ethoxy-5-fluoro-4-methoxypyridin-3-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (160.0 mg, 0.31 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (3.0 mL) was added $NH_3 \cdot H_2O$ (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 27% B in 9 min, 254 nm) to afford (1S,2S)-N-[3-(2-ethoxy-5-fluoro-4-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide **(Compound 201)** (37.5 mg, 31%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =389.1. ^1H NMR (400 MHz, DMSO-d_6): δ 11.58 (s, 1H), 10.63 (s, 1H), 8.06 (d, J = 7.2 Hz, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.75 (d,

J = 8.4 Hz, 1H), 7.59 (d, *J* = 2.4 Hz, 1H), 5.00 - 4.83 (m, 1H), 3.63 - 3.57 (m, 5H), 2.27 - 2.18 (m, 1H), 1.67 - 1.61 (m, 1H), 1.17 - 1.12 (m, 1H), 0.96 - 0.90 (m, 3H).

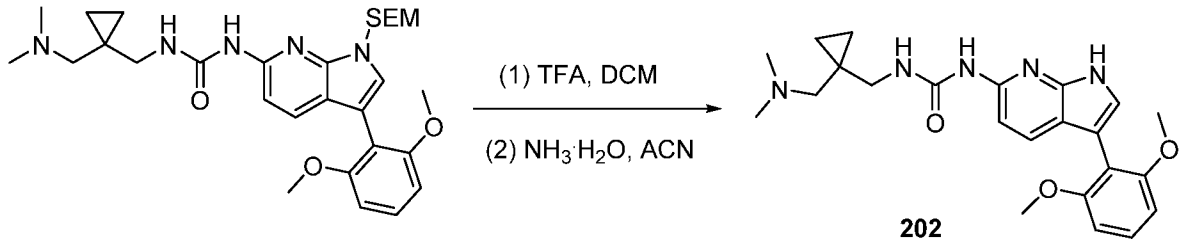
Example S192: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-([1-[(dimethylamino)methyl]cyclopropyl]methyl)urea (Compound 202)

Step 1: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-3-([1-[(dimethylamino)methyl]cyclopropyl]methyl)urea



[0942] To a solution of 3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-amine (180.0 mg, 0.45 mmol) in DCM (10.0 mL) were added pyridine (142.5 mg, 1.80 mmol) and phenyl chloroformate (141.1 mg, 0.90 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the above mixture were added 1-[1-[(dimethylamino)methyl]cyclopropyl]methanamine dihydrochloride (453.1 mg, 2.25 mmol) and pyridine (10.0 mL) at room temperature. The resulting mixture was stirred at 60 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/methanol (6/1, v/v) to afford 1-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-3-([1-[(dimethylamino)methyl]cyclopropyl]methyl)urea (174.0 mg, 69%) as a light brown solid. LCMS (ESI, m/z): $[M+H]^+$ =554.3.

Step 2: Synthesis of 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-([1-[(dimethylamino)methyl]cyclopropyl]methyl)urea (Compound 202)

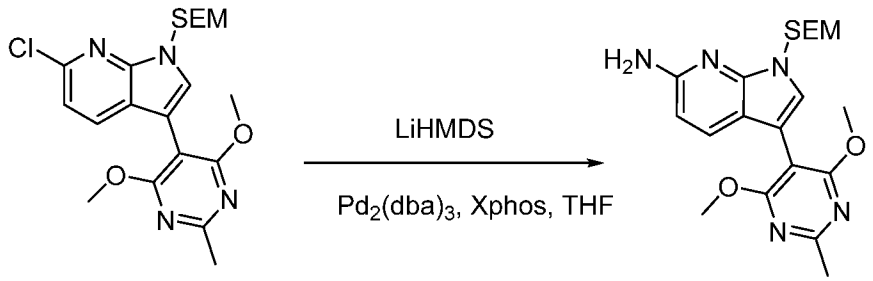


202

[0943] To a solution of 1-[3-(2,6-dimethoxyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-6-yl]-3-([1-[(dimethylamino)methyl]cyclopropyl]methyl)urea (174.0 mg, 0.31 mmol) in CH_2Cl_2 (8.0 mL) was added TFA (8.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (8.0 mL) was added $NH_3 \cdot H_2O$ (8.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 47% B in 10 min; 254/220 nm) to afford 1-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-([1-[(dimethylamino)methyl]cyclopropyl]methyl)urea **(Compound 202)** (30.6 mg, 22%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 424.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.26 (d, J = 1.6 Hz, 1H), 9.11 (s, 1H), 8.46 (s, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.28 - 7.24 (m, 1H), 7.15 (d, J = 2.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 8.4 Hz, 2H), 3.68 (s, 6H), 3.33 - 3.24 (m, 2H), 2.20 - 2.18 (m, 8H), 0.54 - 0.51 (m, 2H), 0.29 - 0.26 (m, 2H).

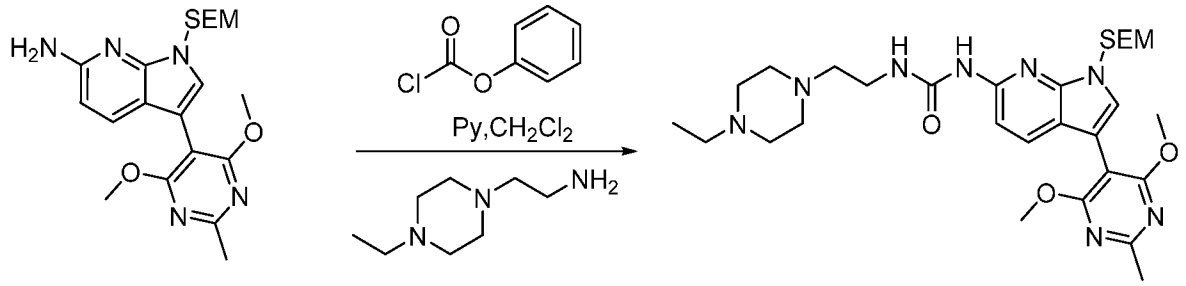
Example S193: Synthesis of 1-(3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(4-ethylpiperazin-1-yl)ethyl)urea (Compound 203)

Step 1: Synthesis of 3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine



[0944] To a solution of 6-chloro-3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (200.0 mg, 0.46 mmol) in THF (10.0 mL) was added LiHMDS (0.9 mL, 1 mol/L), Xphos (43.8 mg, 0.09 mmol) and $Pd_2(dba)_3$ (42.1 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred at 60 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford 3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (160.0 mg, 83%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ = 416.2.

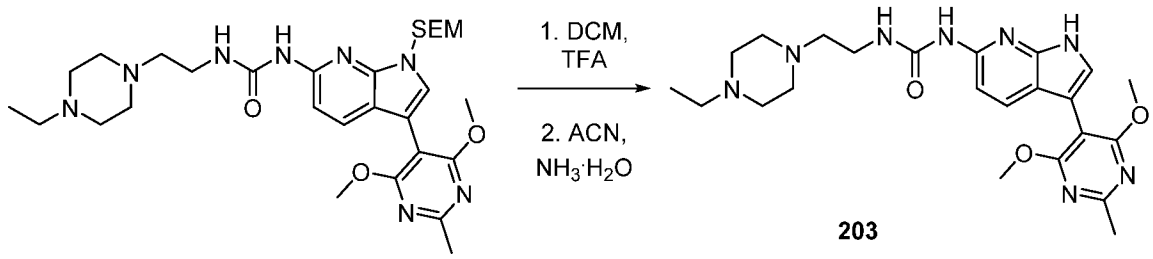
Step 2: Synthesis of 1-(3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(4-ethylpiperazin-1-yl)ethyl)urea



[0945] To a solution of 3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (130.0 mg, 0.31 mmol) in CH_2Cl_2 (5.0 mL) was added phenyl carbonochloridate (146.9 mg, 0.94 mmol) and pyridine (100.2 mg, 1.25 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in pyridine (5.0 mL) was added 2-(4-ethylpiperazin-1-yl)ethan-1-amine (59.0 mg, 0.38 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 16 h. After

the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 1-(3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(4-ethylpiperazin-1-yl)ethyl)urea (80.0 mg, 42%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =599.3.

Step 3: Synthesis of 1-(3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(4-ethylpiperazin-1-yl)ethyl)urea (Compound 203)

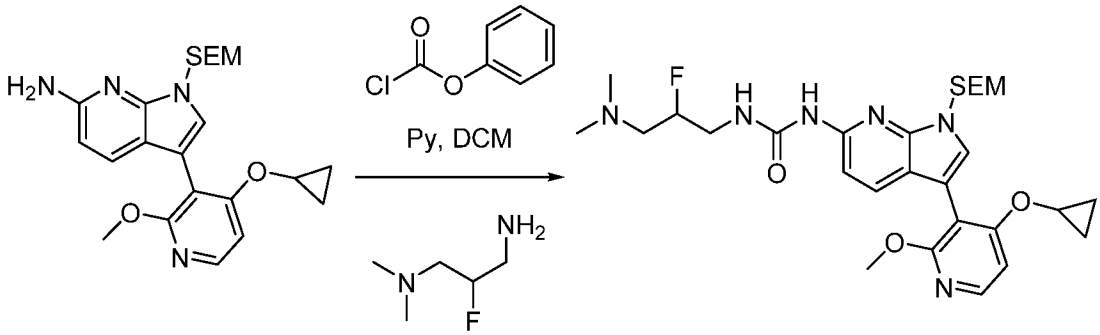


203

[0946] To a solution of 1-(3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(4-ethylpiperazin-1-yl)ethyl)urea (70.0 mg, 0.12 mmol) in DCM (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in ACN (2.0 mL) was added $NH_3 \cdot H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: Xselect CSH OBD Column 30×150 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31% to 41% in 8 min; 254 nm) to afford 1-(3-(4,6-dimethoxy-2-methylpyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(4-ethylpiperazin-1-yl)ethyl)urea **(Compound 203)** (12.1 mg, 22%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =469.4. ^1H NMR (300 MHz, $CDCl_3$): δ 10.14 (s, 1H), 9.73 (s, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 6.43 (d, J = 8.4 Hz, 1H), 3.99 (s, 6H), 3.66 - 3.60 (m, 2H), 2.90 - 2.83 (m, 6H), 2.66 - 2.52 (m, 9H), 1.21 - 1.16 (m, 3H).

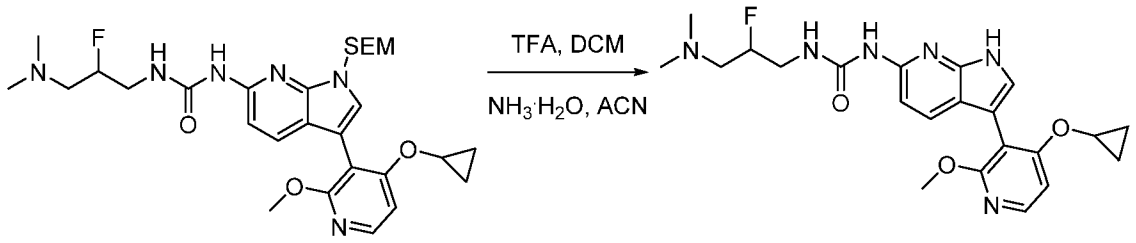
Example S194: Synthesis of 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[(2R)-3-(dimethylamino)-2-fluoropropyl]urea and 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[(2S)-3-(dimethylamino)-2-fluoropropyl]urea (Compound 204 and Compound 205)

Step 1: Synthesis of 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea



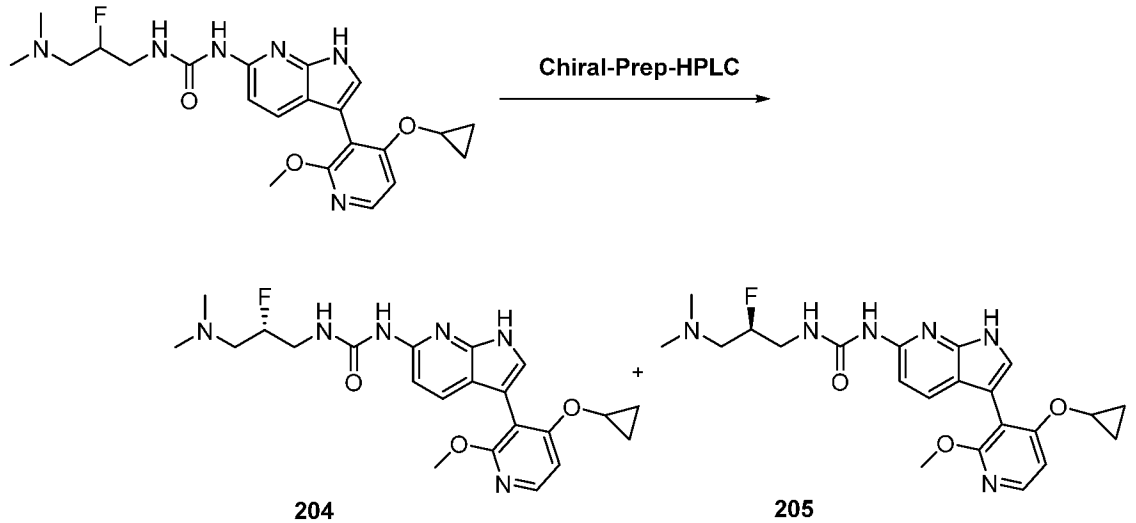
[0947] To a solution of 3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (375.0 mg, 0.88 mmol) in DCM (15.0 mL) was added pyridine (278.1 mg, 3.52 mmol) and phenyl chloroformate (275.3 mg, 1.76 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added (3-amino-2-fluoropropyl)dimethylamine (950.7 mg, 7.91 mmol) and pyridine (15.0 mL) at room temperature. The resulting mixture was stirred at 70 °C for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (11/1, v/v) to afford 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea (420.0 mg, 83%) as a light yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =573.3.

Step 2: Synthesis of 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea



[0948] To a solution of 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea (270.0 mg, 0.47 mmol) in CH_2Cl_2 (10.0 mL) was added TFA (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (10.0 mL) was added $NH_3 \cdot H_2O$ (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with acetonitrile/water (1/1, v/v) to afford 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea (95.0 mg, 45%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =443.2.

Step 3: Synthesis of 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[(2R)-3-(dimethylamino)-2-fluoropropyl]urea and 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[(2S)-3-(dimethylamino)-2-fluoropropyl]urea (Compound 204 and Compound 205)



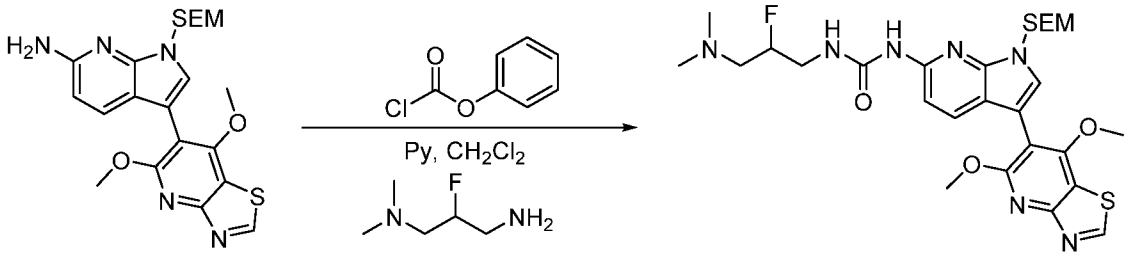
[0949] The racemic 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea (95.0 mg, 0.22 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2x25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 21 min; Wave Length: 220/254 nm) to afford 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea Enantiomer 1 (31.4 mg, 66%) as a white solid and 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea Enantiomer 2 (35.4 mg, 74%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 204 and 205** in Table 1.

[0950] 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea Enantiomer 1: Retention Time 1 = 6.66 min; LCMS (ESI, m/z): $[M+H]^+$ =443.1. ^1H NMR (400 MHz, DMSO-d_6): δ 11.49 (s, 1H), 9.23 (s, 1H), 8.62 (s, 1H), 8.07 (d, J = 5.6 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 7.13 (d, J = 6.0 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 4.81 - 4.68 (m, 1H), 3.94 - 3.91 (m, 1H), 3.81 (s, 3H), 3.65 - 3.52 (m, 1H), 3.45 - 3.35 (m, 1H), 2.56 - 2.51 (m, 2H), 2.22 (s, 6H), 0.81 - 0.76 (m, 2H), 0.63 - 0.58 (m, 2H).

[0951] 1-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea Enantiomer 2: Retention Time 2 = 14.70 min; LCMS (ESI, m/z): $[M+H]^+$ = 443.1. ^1H NMR (400 MHz, DMSO-d_6): δ 11.49 (s, 1H), 9.23 (s, 1H), 8.63 (s, 1H), 8.06 (d, J = 5.6 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 7.13 (d, J = 6.0 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 4.82 - 4.69 (m, 1H), 3.93 - 3.90 (m, 1H), 3.81 (s, 3H), 3.63 - 3.52 (m, 1H), 3.45 - 3.34 (m, 1H), 2.57 - 2.51 (m, 2H), 2.23 (s, 6H), 0.81 - 0.76 (m, 2H), 0.65 - 0.63 (m, 2H).

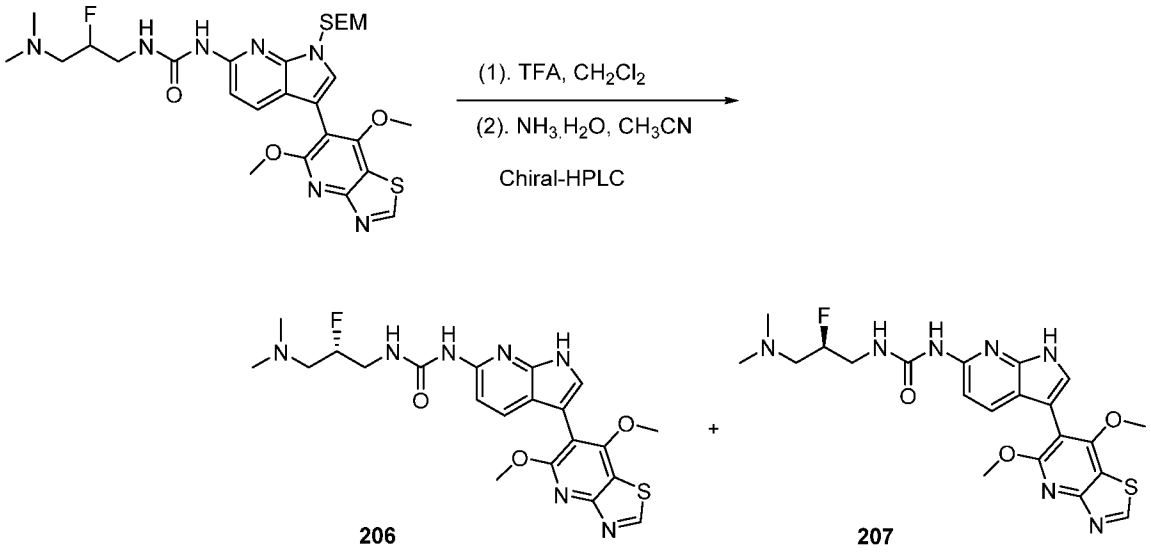
Example S195: Synthesis of 1-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-[(2R)-3-(dimethylamino)-2-fluoropropyl]urea and 1-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-[(2S)-3-(dimethylamino)-2-fluoropropyl]urea (Compound 206 and Compound 207)

Step 1: Synthesis of 1-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl)-3-[3-(dimethylamino)-2-fluoropropyl]urea



[0952] To a solution of 3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (300.0 mg, 0.66 mmol) in CH_2Cl_2 (4.0 mL) was added pyridine (207.4 mg, 2.62 mmol) and phenyl chloroformate (123.2 mg, 0.79 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated under reduced pressure. To the residue in pyridine (6.0 mL) was added (3-amino-2-fluoropropyl)dimethylamine (787.8 mg, 6.56 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 1 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum CH_2Cl_2/CH_3OH (90/10, v/v) to afford 1-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl)-3-[3-(dimethylamino)-2-fluoropropyl]urea (250.0 mg, 63%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =604.2.

Step 2: Synthesis of 1-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-[(2R)-3-(dimethylamino)-2-fluoropropyl]urea and 1-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-[(2S)-3-(dimethylamino)-2-fluoropropyl]urea (Compound 206 and Compound 207)



[0953] To a solution of 1-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl)-3-[3-(dimethylamino)-2-fluoropropyl]urea (250.0 mg, 0.41 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with ACN/H_2O (52/48, v/v) and then separated 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 NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 10.5 min; Wave Length: 220/254 nm) to afford 1-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-[3-(dimethylamino)-2-fluoropropyl]urea Enantiomer 1 (30.9 mg, 31%) as a white solid and 1-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-[3-(dimethylamino)-2-fluoropropyl]urea Enantiomer 2 (40.4 mg, 41%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 206 and 207** in Table 1.

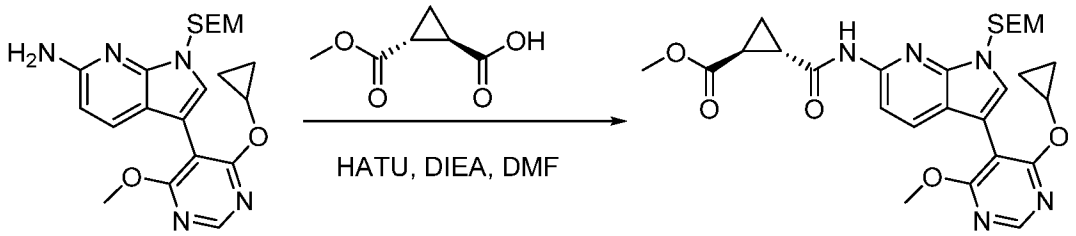
[0954] **1-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-[3-(dimethylamino)-2-fluoropropyl]urea Enantiomer 1:** Retention Time

1=5.876 min; LCMS (ESI, m/z): $[M+H]^+$ =474.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.62 (s, 1H), 9.56 (s, 1H), 9.27 (s, 1H), 8.62 (s, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 2.0 Hz, 1H), 7.05 (d, J = 8.8 Hz, 1H), 4.82 - 4.69 (m, 1H), 3.91 - 3.86 (m, 6H), 3.65 - 3.53 (m, 1H), 3.46 - 3.33 (m, 1H), 2.56 - 2.51 (m, 2H), 2.21 (s, 6H).

[0955] 1-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-[3-(dimethylamino)-2-fluoropropyl]urea Enantiomer 2: Retention Time 2=9.106 min; LCMS (ESI, m/z): $[M+H]^+$ =474.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.62 (s, 1H), 9.56 (s, 1H), 9.27 (s, 1H), 8.62 (s, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.37 (s, 1H), 7.05 (d, J = 8.8 Hz, 1H), 4.82 - 4.69 (m, 1H), 3.91 and 3.89 (s, total 6H), 3.62 - 3.54 (m, 1H), 3.44 - 3.33 (m, 1H), 2.67 - 2.46 (m, 2H), 2.21 (s, 6H).

Example S196: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide and (1R,2R)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (Compound 208 and Compound 209)

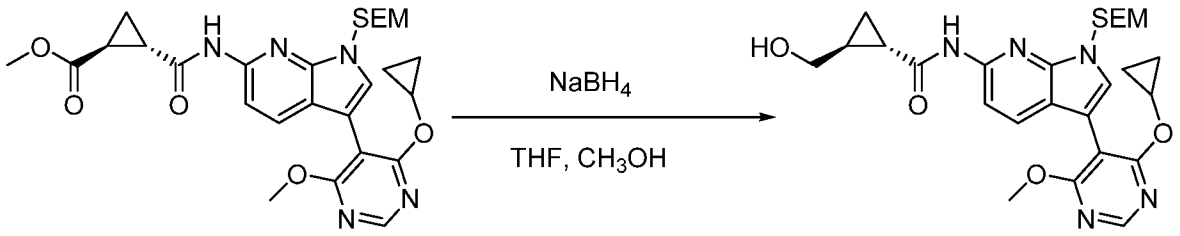
Step 1: Synthesis of Methyl (trans)-2-((3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamoyl)cyclopropane-1-carboxylate



[0956] To a solution of 3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (1.0 g, 2.34 mmol) in DMF (20.0 mL) was added trans-2-(methoxycarbonyl)cyclopropane-1-carboxylic acid (404.5 mg, 2.81 mmol), DIEA (1.5 g, 11.70 mmol) and HATU (1.3 g, 3.51 mmol) at 0 C under N_2. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (86/14, v/v) to afford methyl (trans)-2-

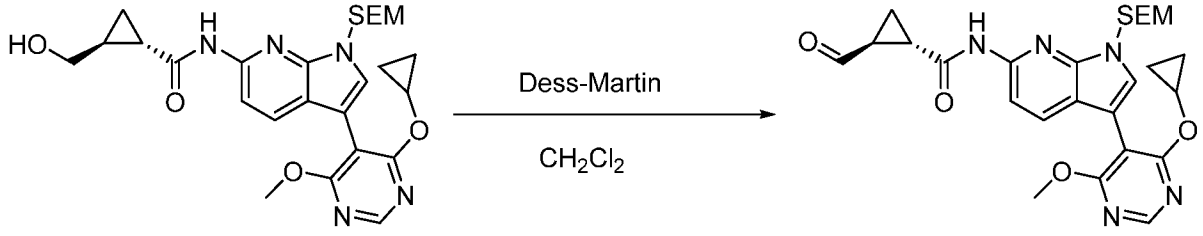
{[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate (510.0 mg, 39%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =554.2.

Step 2: Synthesis of Trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide



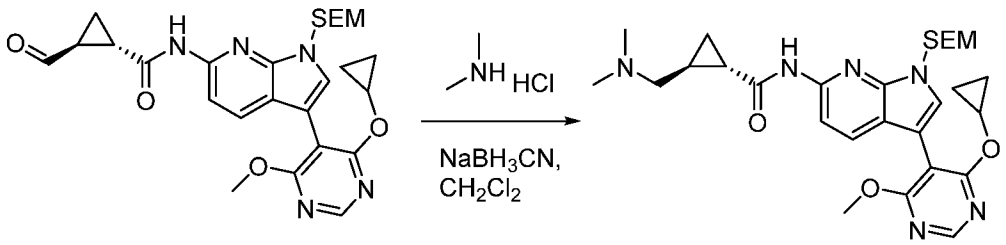
[0957] To a solution of methyl (trans)-2-{[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate (460.0 mg, 0.83 mmol) in THF/CH_3OH (12.0/3.0 mL) was added $NaBH_4$ (3.1 g, 83.10 mmol) at room temperature. The resulting mixture was stirred at 30 °C for 16 h. After the reaction was completed, the reaction mixture was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (57/43, v/v) to afford trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide (265.0 mg, 61%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =526.2.

Step 3: Synthesis of Trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide



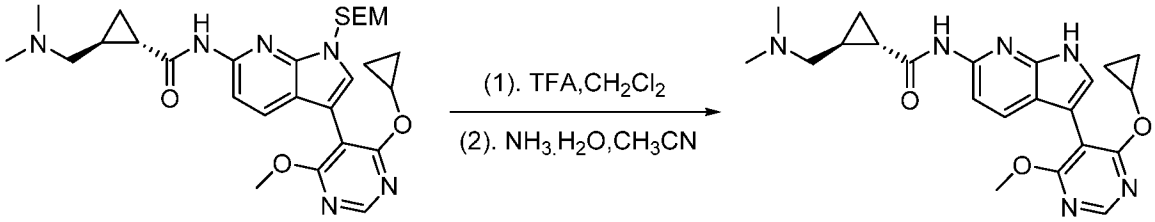
[0958] To a solution of trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide (250.0 mg, 0.48 mmol) in CH_2Cl_2 (10.0 mL) was added Dess-Martin (302.6 mg, 0.71 mmol) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (250.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =524.2.

Step 4: Synthesis of Trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide



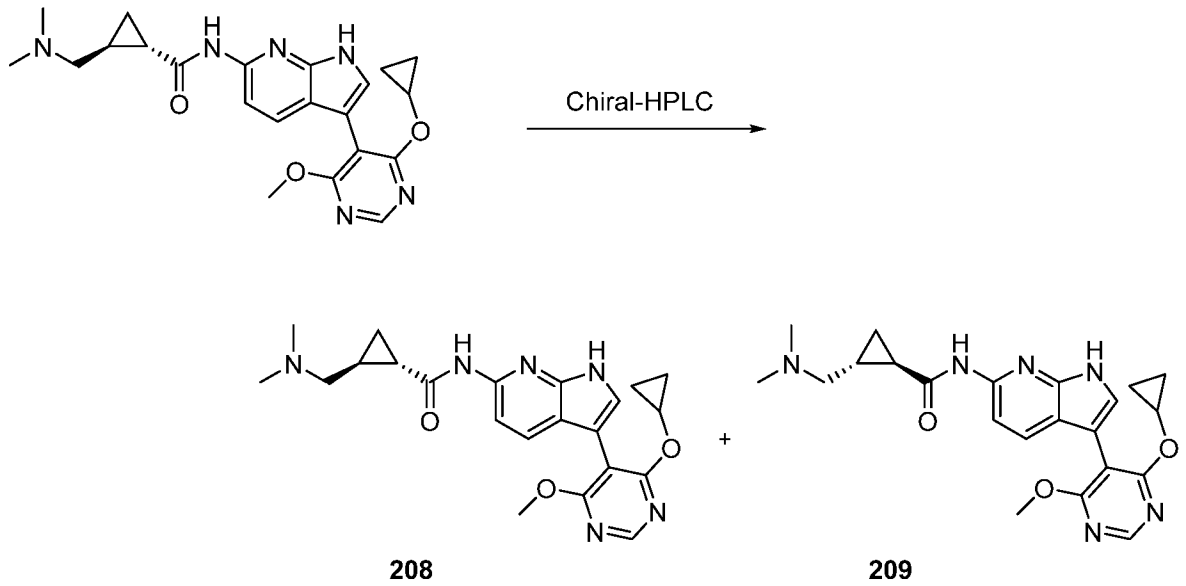
[0959] To a solution of trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (250.0 mg, crude) in CH_2Cl_2 (10.0 mL) were added dimethylamine hydrochloride (116.8 mg, 1.43 mmol) and $NaBH_3CN$ (90.0 mg, 1.43 mmol) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum CH_2Cl_2/CH_3OH (10/01, v/v) to afford trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (150.0 mg, 57%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =553.3.

Step 5: Synthesis of Trans-N-(3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide



[0960] To a solution of trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (130.0 mg, 0.24 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3 \cdot H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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: 20% B to 30% B in 8 min, 30% B; Wave Length: 254 nm) to afford trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (50.0 mg, 50%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =423.2.

Step 6: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide and (1R,2R)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (Compound 208 and Compound 209)



208 209

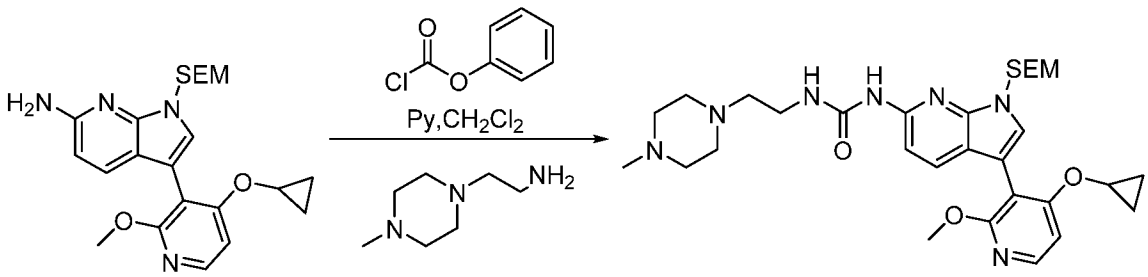
[0961] The product trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (50.0 mg, 0.12 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SC, 2×25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: MeOH: EtOH=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 12.5 min; Wave Length: 220/254 nm) to afford N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide Enantiomer 1 (6.6 mg, 26%) and N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide Enantiomer 2 (5.4 mg, 22%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 208 and 209** in Table 1.

[0962] **N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide Enantiomer 1:** Retention Time 1=9.02 min; LCMS (ESI, m/z): $[M+H]^+$ = 423.4. ^1H NMR (400 MHz, DMSO-d_6): δ 11.62 (s, 1H), 10.54 (s, 1H), 8.49 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 4.38 - 4.35 (m, 1H), 3.92 (s, 3H), 2.31 - 2.27 (m, 1H), 2.19 - 2.14 (m, 7H), 1.90 - 1.87 (m, 1H), 1.35 - 1.33 (m, 1H), 1.07 - 1.03 (m, 1H), 0.76 - 0.70 (m, 3H), 0.69 - 0.62 (m, 2H).

[0963] **N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide Enantiomer 2:** Retention Time 2=11.39 min; LCMS (ESI, m/z): $[M+H]^+$ = 423.4. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.62 (s, 1H), 10.54 (s, 1H), 8.49 (s, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 4.38 - 4.35 (m, 1H), 3.92 (s, 3H), 2.31 - 2.26 (m, 1H), 2.19 - 2.13 (m, 7H), 1.91 - 1.88 (m, 1H), 1.35 - 1.33 (m, 1H), 1.07 - 1.03 (m, 1H), 0.78 - 0.62 (m, 5H).$$

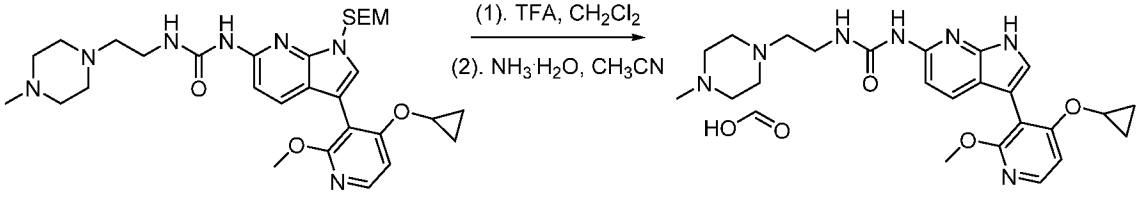
Example S197: Synthesis of 1-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(4-methylpiperazin-1-yl)ethyl)urea formate (Compound 210)

Step 1: Synthesis of 3-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea



[0964] To a solution of 3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (170.0 mg, 0.40 mmol) in pyridine/DCM (3.0 mL/25.0 mL) was added phenyl chloroformate (124.8 mg, 0.80 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The resulting mixture was concentrated under vacuum. To the above residue was added a solution of 2-(4-methylpiperazin-1-yl)ethanamine (285.4 mg, 2.00 mmol) in pyridine (10.0 mL). The resulting mixture was stirred at 60 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (10/1, v/v) to afford 3-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (110.0 mg, 46%) as a red oil. LCMS (ESI, m/z): $[M+H]^+$ =596.3.

Step 2: Synthesis of 1-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(4-methylpiperazin-1-yl)ethyl)urea formate (Compound 210)

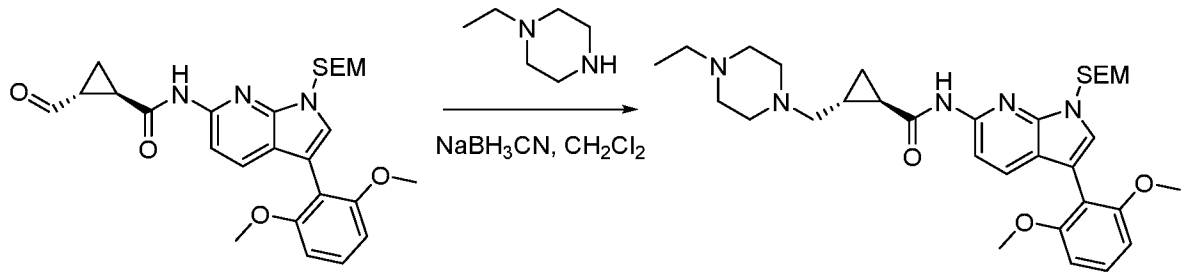


210

[0965] To a solution of 3-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-1-[2-(4-methylpiperazin-1-yl)ethyl]urea (100.0 mg, 0.168 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (5.0 mL) was added $NH_3.H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30×150 mm, 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 25% B in 8 min; 254 nm) to afford 1-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(2-(4-methylpiperazin-1-yl)ethyl)urea formate **(Compound 210)** (55.7 mg, 71%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =466.4. ^1H NMR (400 MHz, Methanol-d_4): δ 8.27 (s, 1H), 8.04 (d, J = 5.6 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.28 (s, 1H), 7.17 (d, J = 6.0 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 3.93 - 3.89 (m, 4H), 3.59 - 3.56 (m, 2H), 3.21 - 3.17 (m, 4H), 2.92 (s, 3H), 2.83 - 2.80 (m, 6H), 0.85 - 0.81 (m, 2H), 0.70 - 0.65 (m, 2H).

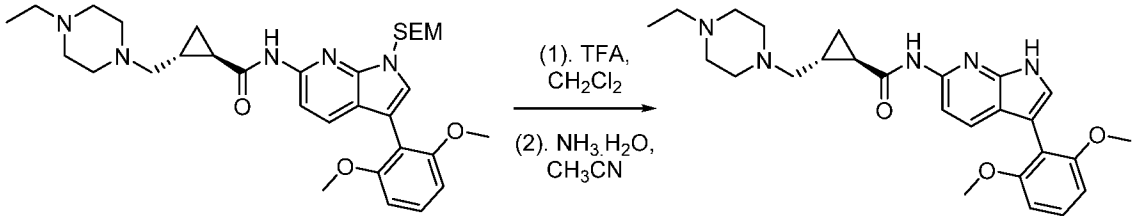
Example S198: Synthesis of (1S,2S)-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide and (1R,2R)-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (Compound 211 and Compound 212)

Step 1: Synthesis of trans-N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide



[0966] To a solution of trans-N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (400.0 mg, crude) in CH_2Cl_2 (20.0 mL) was added 1-ethylpiperazine (276.5 mg, 2.42 mmol) and $NaBH_3CN$ (152.1 mg, 2.42 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was quenched with MeOH. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (8/1, v/v) to afford trans-N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (180.0 mg, 38%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =594.3.

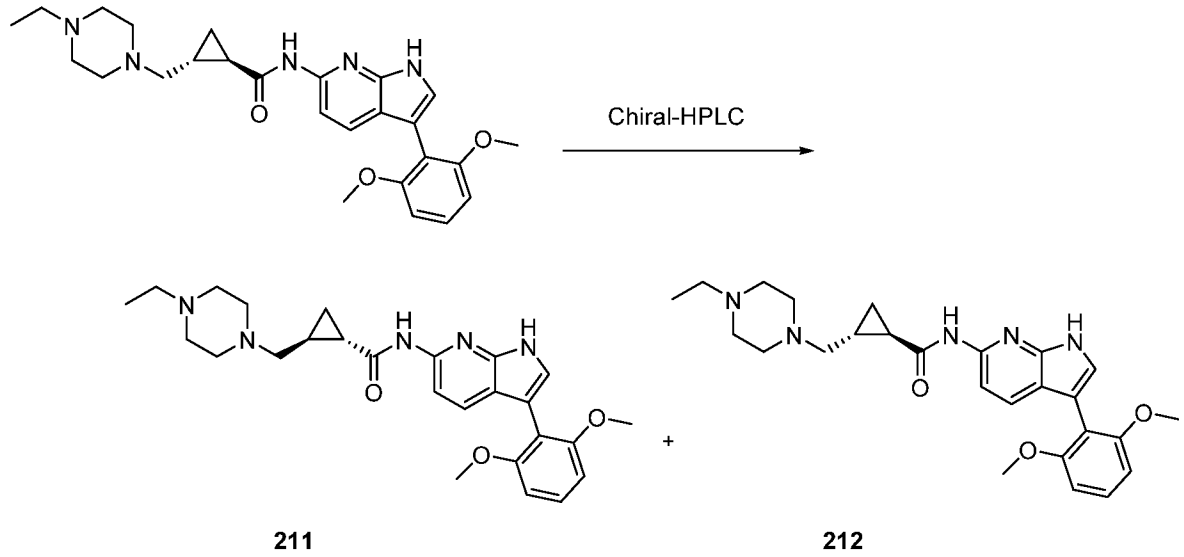
Step 2: Synthesis of trans-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide



[0967] To a solution of trans-N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (150.0 mg, 0.26 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (5.0 mL) was added $NH_3 \cdot H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with CH_3OH/H_2O (7/1, v/v) to afford trans-N-[3-(2,6-

dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (65.7 mg, 55%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =464.3.

Step 3: Synthesis of (1S,2S)-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide and (1R,2R)-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (Compound 211 and Compound 212)



[0968] The product trans-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (65.7 mg, 0.14 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2x25 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 14 min; Wave Length: 220/254 nm) to afford N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 1 (10.7 mg, 16%) as a white solid and N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 2 (8.5 mg, 13%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 211 and 212** in Table 1.

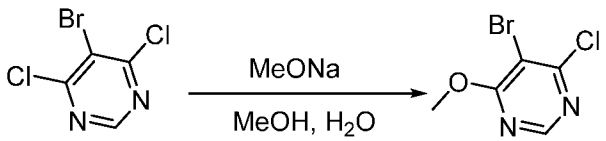
[0969] **N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 1:** Retention Time

1=7.55 min; LCMS (ESI, m/z): $[M+H]^+$ = 464.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.40 (d, J = 1.6 Hz, 1H), 10.52 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.29 - 7.25 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 3.69 (s, 6H), 2.46 - 2.21 (m, 10H), 1.91 - 1.88 (m, 1H), 1.36 - 1.31 (m, 1H), 1.05 - 0.97 (m, 4H), 0.78 - 0.65 (m, 1H).

[0970] N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 2: Retention Time 2=11.05 min; LCMS (ESI, m/z): $[M+H]^+$ = 464.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.40 (d, J = 1.6 Hz, 1H), 10.52 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.30 - 7.25 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 3.69 (s, 6H), 2.46 - 2.21 (m, 10H), 1.90 - 1.88 (m, 1H), 1.36 - 1.31 (m, 1H), 1.05 - 0.97 (m, 4H), 0.78 - 0.65 (m, 1H).

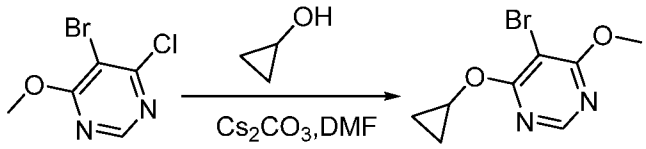
Example S199: Synthesis of (1R,2R)-N-(3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide and (1S,2S)-N-(3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (Compound 213 and Compound 214)

Step 1: Synthesis of 5-bromo-4-chloro-6-methoxypyrimidine



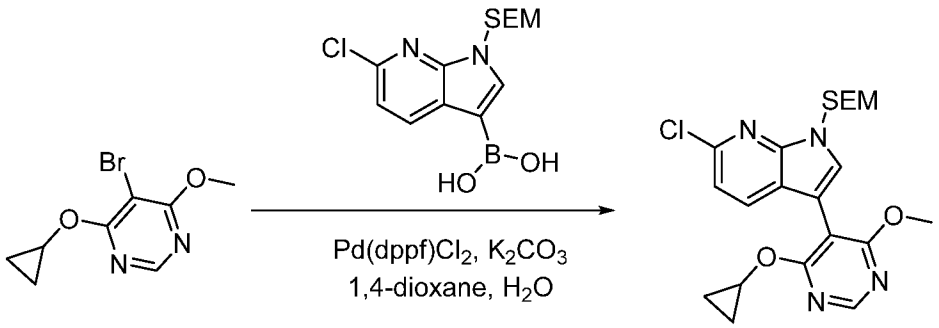
[0971] To a solution of 5-bromo-4,6-dichloropyrimidine (30.0 g, 131.64 mmol) in MeOH/H_2O (200.0/200.0 mL) was added MeONa (6.4 g, 118.47 mmol) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 5-bromo-4-chloro-6-methoxypyrimidine (31.0 g, crude) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =222.9.

Step 2: Synthesis of 5-bromo-4-cyclopropoxy-6-methoxypyrimidine:



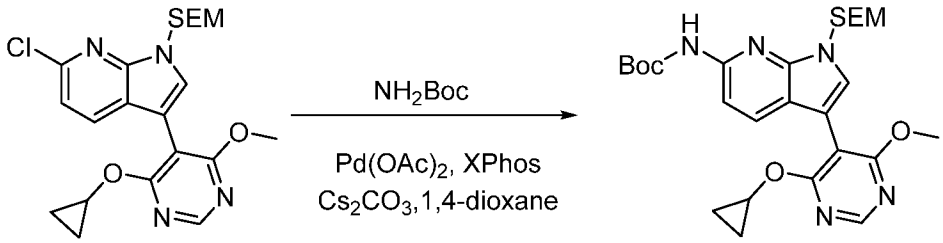
[0972] To a solution of 5-bromo-4-chloro-6-methoxypyrimidine (31.0 g, crude) in DMF (120.0 mL) was added Cs_2CO_3 (57.2 g, 175.59 mmol) and cyclopropanol (8.5 g, 146.31 mmol) at room temperature under N_2. The reaction mixture was stirred at 80 °C for 6 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (91/9, v/v) to afford 5-bromo-4-cyclopropoxy-6-methoxypyrimidine (9.0 g, 12%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =245.0.

Step 3: Synthesis of 5-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-cyclopropoxy-6-methoxypyrimidine



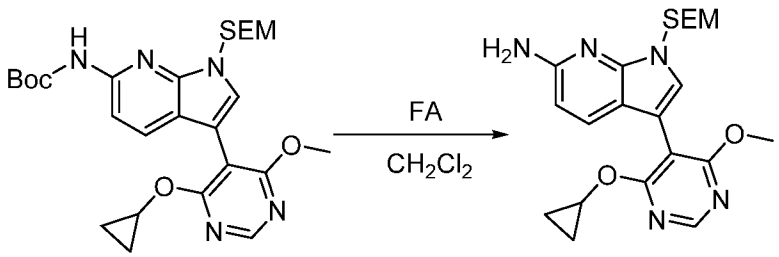
[0973] To a solution of 5-bromo-4-cyclopropoxy-6-methoxypyrimidine (8.0 g, 24.48 mmol) in 1.4-dioxane/H_2O (100.0/20.0 mL) was added 6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-ylboronic acid (12.8 g, 39.17 mmol), K_2CO_3 (13.6 g, 97.92 mmol) and $Pd(dppf)Cl_2$ (5.3 g, 6.51 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (86/14, v/v) to afford 5-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-cyclopropoxy-6-methoxypyrimidine (5.8 g, 39%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =447.2.

Step 4: Synthesis of Tert-butyl N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamate



[0974] To a solution of 5-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-cyclopropoxy-6-methoxypyrimidine (5.0 g, 11.18 mmol) in 1,4-dioxane (120.0 mL) was added NH_2Boc (6.5 g, 55.82 mmol), Cs_2CO_3 (27.8 g, 33.54 mmol), XPhos (1.7 g, 2.23 mmol) and $Pd(OAc)_2$ (251.2 mg, 1.11 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (92/8, v/v) to afford tert-butyl N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamate (5.0 g, 70%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =528.3.

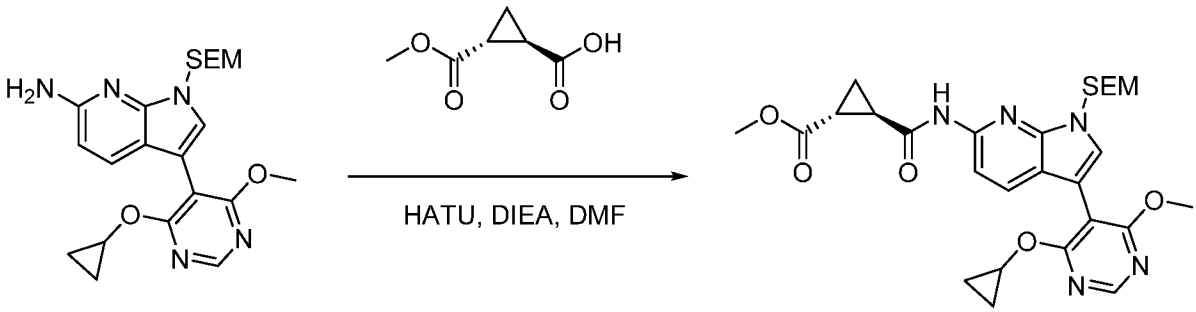
Step 5: Synthesis of 3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine



[0975] A solution of tert-butyl N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamate (5.0 g, 7.56 mmol) in FA/CH_2Cl_2 (20.0/20.0 mL) was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was adjusted pH to 7 with aq. $NaHCO_3$ and then extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 3-

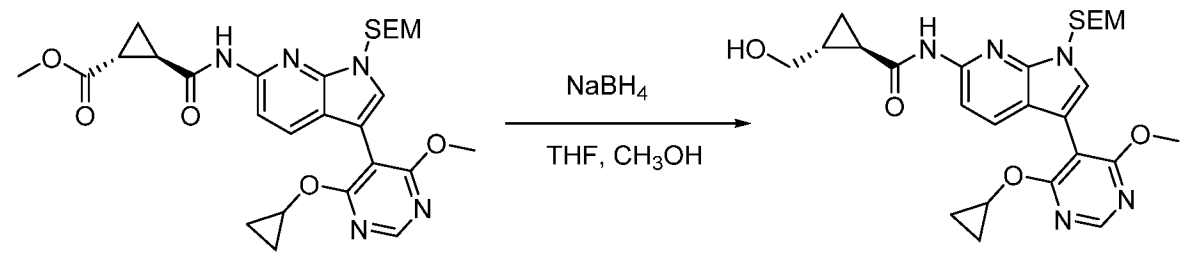
(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (3.0 g, crude) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =428.2.

Step 6: Synthesis of Methyl (trans)-2-{[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate



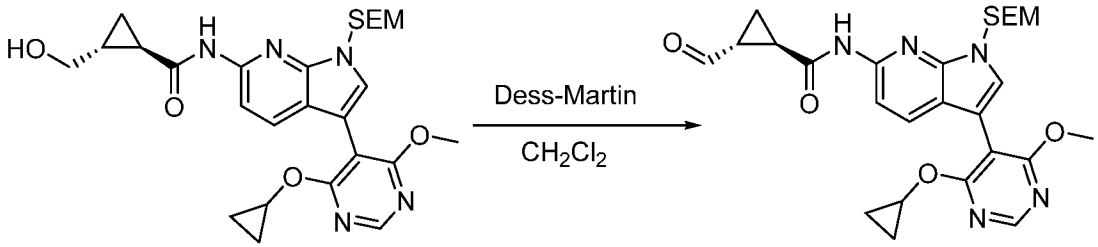
[0976] To a solution of 3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (2.0 g, crude) in DMF (40.0 mL) was added trans-2-(methoxycarbonyl)cyclopropane-1-carboxylic acid (2.1 g, 4.54 mmol), DIEA (2.4 g, 18.94 mmol) and HATU (2.2 g, 5.68 mmol) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (88/12, v/v) to afford methyl (trans)-2-{[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate (1.0 g, 47%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =554.2.

Step 7: Synthesis of Trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide



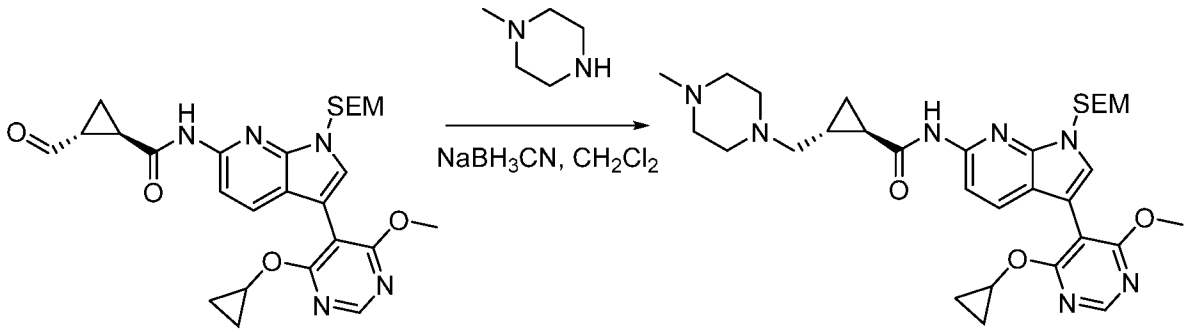
[0977] To a solution of methyl (trans)-2-{[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate (1.0 g, 1.80 mmol) in THF/MeOH (5.0/5.0 mL) was added $NaBH_4$ (2.1 g, 54.18 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed. the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated in vacuo. The residue was purified by reverse phase flash column chromatography with petroleum CH_3CN/H_2O (60/40, v/v) to afford trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide (560.0 mg, 70%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =526.2.

Step 8: Synthesis of Trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide



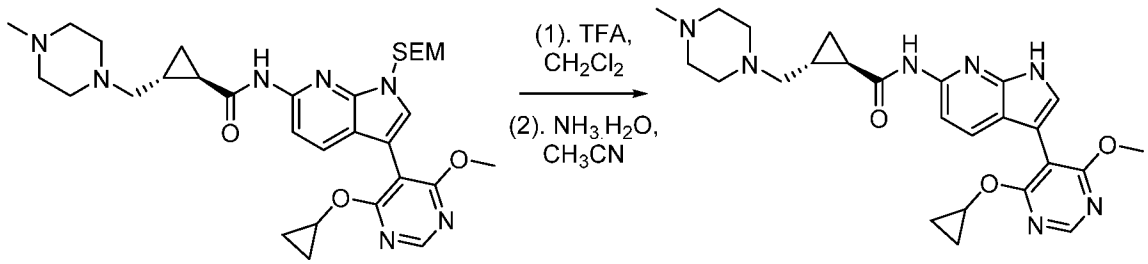
[0978] To a solution of trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide (560.0 mg, 1.23 mmol) in CH_2Cl_2 (8.0 mL) was added Dess-Martin (1.2 g, 3.00 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum to afford trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (400.0 mg, crude) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =524.2.

Step 9: Synthesis of Trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide



[0979] To a solution of trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (400.0 mg, crude) in CH_2Cl_2 (5.0 mL) was added 1-methylpiperazine (400.0 mg, 3.99 mmol) and $NaBH_3CN$ (150.0 mg, 2.40 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (60/40, v/v) to afford trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (200.0 mg, 62%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =608.3.

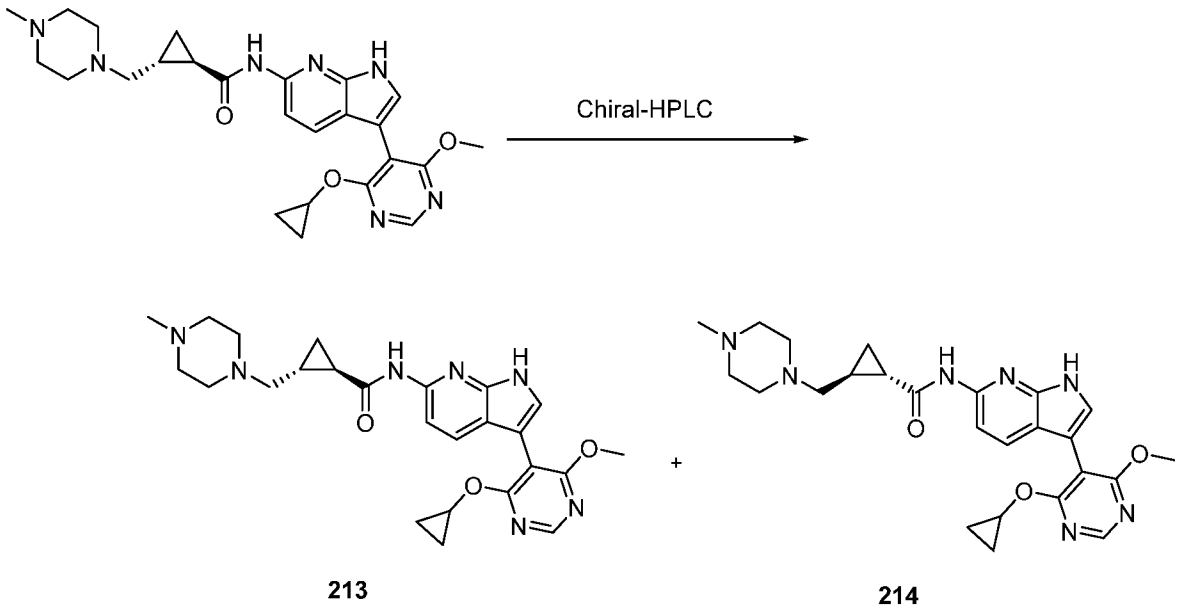
Step 10: Synthesis of Trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide



[0980] To a solution of trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (200.0 mg, 0.33 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the

residue in CH_3CN (2.0 mL) was added $NH_3 \cdot H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with CH_3CN/H_2O (7/4, v/v) to afford trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (110.0 mg, 46%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =478.2.

Step 11: Synthesis of (1R,2R)-N-(3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide and (1S,2S)-N-(3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (Compound 213 and Compound 214)



213 214

[0981] The product trans-N-(3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (110.0 mg, 0.20 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SC, 2×25 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: 30% B to 30% B in 15 min; Wave Length: 220/254 nm) to afford N-(3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-

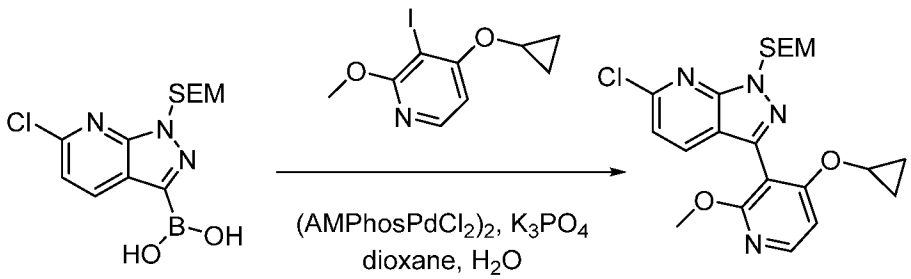
yl)methyl)cyclopropane-1-carboxamide Enantiomer 1 (8.4 mg, 10%) as a white solid and N-(3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide Enantiomer 2 (9.0 mg, 14%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 213 and 214** in Table 1.

[0982] N-(3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide Enantiomer 1: Retention Time 1=11.427 min; LCMS (ESI, m/z): $[M+H]^+$ =478.4. ^1H NMR (400 MHz, CD_3OD): δ 8.41 (s, 1H), 7.78 - 7.70 (m, 2H), 7.43 (s, 1H), 4.42 - 4.39 (m, 1H), 4.00 (s, 3H), 2.81 - 2.53 (m, 7H), 2.43 - 2.23 (m, 5H), 1.83 - 1.78 (m, 1H), 1.64 - 1.54 (m, 1H), 1.43 - 1.21 (m, 2H), 0.98 - 0.52 (m, 5H).

[0983] N-(3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide Enantiomer 2: Retention Time 2=13.695 min; LCMS (ESI, m/z): $[M+H]^+$ =478.4. ^1H NMR (400 MHz, CD_3OD): δ 8.41 (s, 1H), 7.76 - 7.68 (m, 2H), 7.41 (s, 1H), 4.40 - 4.37 (m, 1H), 3.98 (s, 3H), 2.80 - 2.51 (m, 7H), 2.39 - 2.29 (m, 5H), 1.81 - 1.76 (m, 1H), 1.62 - 1.52 (m, 1H), 1.33 - 1.24 (m, 2H), 0.90 - 0.66 (m, 5H).

Example S200: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 215)

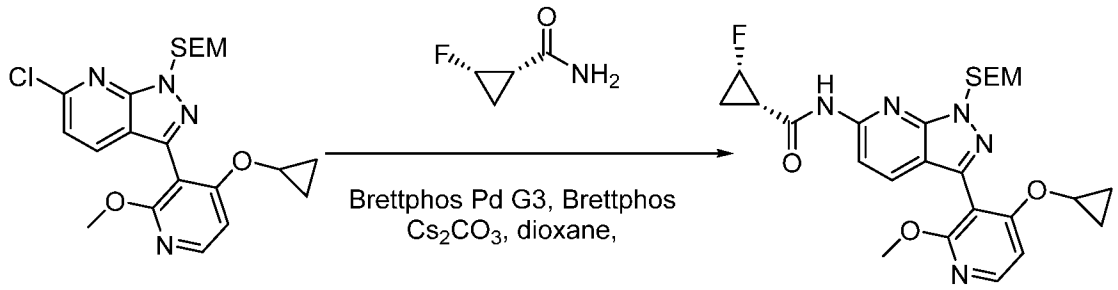
Step 1: Synthesis of 3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridin-3-yl)-4-cyclopropoxy-2-methoxypyridine



[0984] To a solution of 4-cyclopropoxy-3-iodo-2-methoxypyridine (300.0 mg, 1.03 mmol) in dioxane/H_2O (10.0/2.0 mL) was added 6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridin-3-ylboronic acid (337.7 mg, 1.03

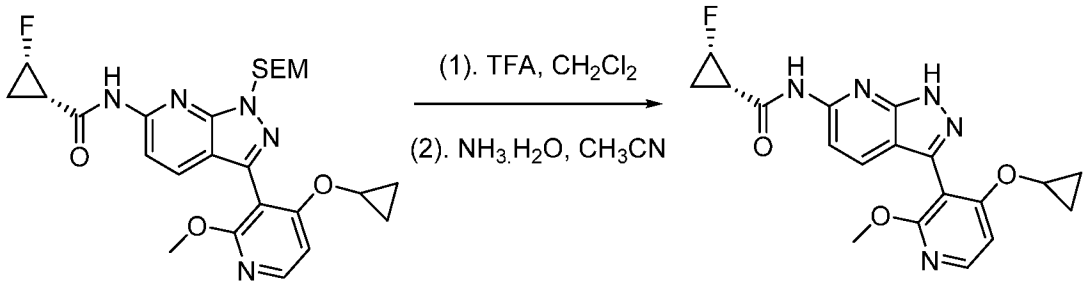
mmol), K_3PO_4 (656.3 mg, 3.09 mmol), $(AMPhosPdCl_2)_2$ (145.9 mg, 0.20 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with ACN/H_2O (2/1, v/v) to afford 3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridin-3-yl)-4-cyclopropoxy-2-methoxypyridine (80.0 mg, 16%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =447.2.

Step 2: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide



[0985] To a solution of 3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridin-3-yl)-4-cyclopropoxy-2-methoxypyridine (110.0 mg, 0.25 mmol) in 1,4-dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (126.8 mg, 1.23 mmol), BrettPhos (26.4 mg, 0.05 mmol), Cs_2CO_3 (240.5 mg, 0.74 mmol) and BrettPhos Pd G3 (22.3 mg, 0.03 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was completed, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford (1S,2S)-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (80.0 mg, 63%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =514.2.

Step 3: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 215)

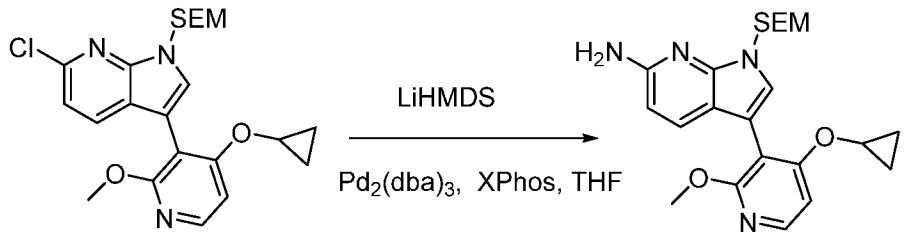


215

[0986] To a solution of (1S,2S)-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (70.0 mg, 0.14 mmol) in DCM (4.0 mL) was added TFA (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. Then $NH_3.H_2O$ (4.0 mL) and ACN (4.0 mL) were added to the residue at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions Column (Xselect CSH OBD Column 30x150 mm, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:30% B to 40% B in 8 min; 254 nm) to afford (1S,2S)-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrazolo[3,4-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide **(Compound 215)** (12.5 mg, 24%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =384.3. ^1H NMR (400 MHz, DMSO-d_6): δ 13.41 (s, 1H), 10.95 (s, 1H), 8.22 (d, J = 5.6 Hz, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 5.6 Hz, 1H), 5.06 - 4.85 (m, 1H), 4.02 - 3.93 (m, 1H), 3.79 (s, 3H), 2.28 - 2.25 (m, 1H), 1.71 - 1.64 (m, 1H), 1.22 - 1.20 (m, 1H), 0.83 - 0.74 (m, 2H), 0.59 - 0.51 (m, 2H).

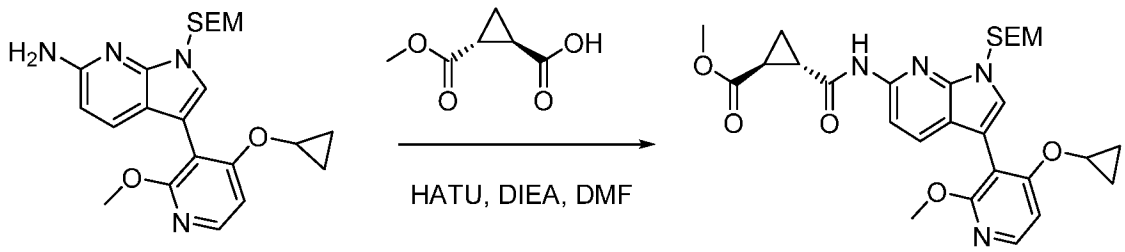
Example S201: Synthesis of (1S,2S)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropanecarboxamide and (1R,2R)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropanecarboxamide (Compound 216 and Compound 217)

Step 1: Synthesis of 3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine



[0987] To a solution of 3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-cyclopropoxy-2-methoxypyridine (950.0 mg, 2.13 mmol) in THF (30.0 mL) was added LiHMDS (6.4 mL, 2 mol/L), XPhos (203.1 mg, 0.43 mmol) and $Pd_2(dba)_3$ (122.5 mg, 0.13 mmol) at room temperature under N_2. The resulting mixture was stirred at 60 °C for 1 h. After the reaction was completed, the reaction mixture was quenched by the addition of sat. NH_4Cl (aq.). The reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford 3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (690.0 mg, 76%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =427.2.

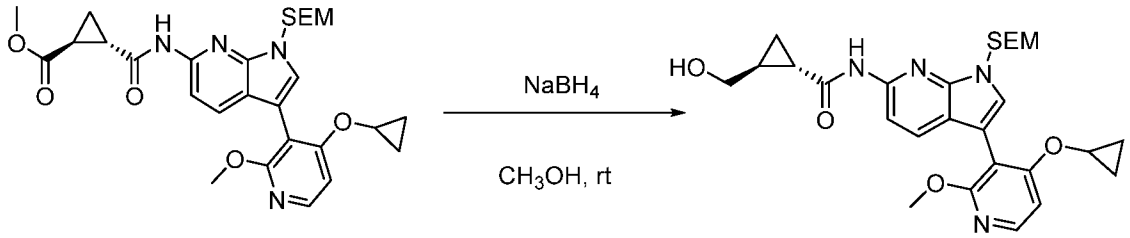
Step 2: Synthesis of Methyl (trans)-2-{[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate



[0988] To a solution of 3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (640.0 mg, 1.50 mmol) in DMF (20.0 mL) was added DIEA (969.5 mg, 7.50 mmol), HATU (855.7 mg, 2.25 mmol) and trans-2-(methoxycarbonyl)cyclopropane-1-carboxylic acid (259.5 mg, 1.80 mmol) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the mixture was purified by reverse phase flash chromatography with ACN/H_2O (2/1, v/v) to afford methyl (trans)- 2-{[3-(4-cyclopropoxy-2-methoxypyridin-3-

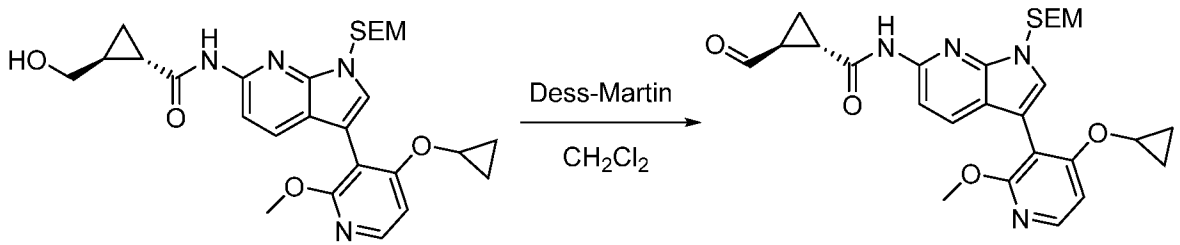
yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate (720.0 mg, 87%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =553.2.

Step 3: Synthesis of trans-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide



[0989] To a solution of methyl (trans) -2-{[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate (700.0 mg, 1.27 mmol) in THF (6.0 mL)/CH_3OH(4.0 mL) was added $NaBH_4$ (958.3 mg, 25.34 mmol) at room temperature. The resulting mixture was stirred at 40 °C for 3 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with ACN/H_2O (2/1, v/v) to afford trans-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide (600.0 mg, 90%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =525.2.

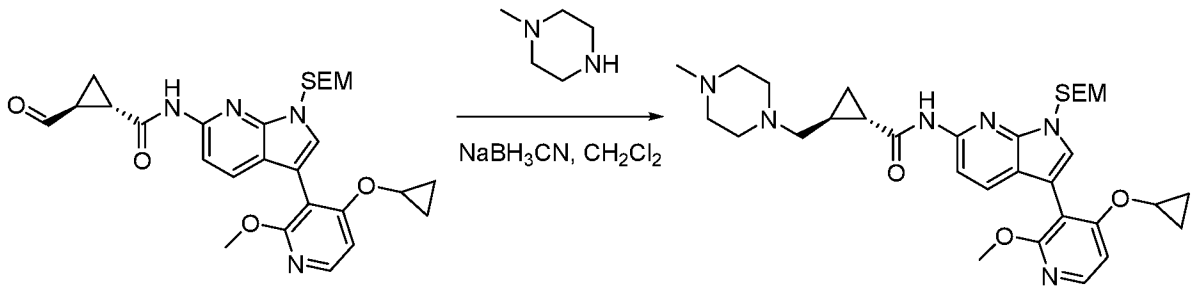
Step 4: Synthesis of trans-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide



[0990] To a solution of trans-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-

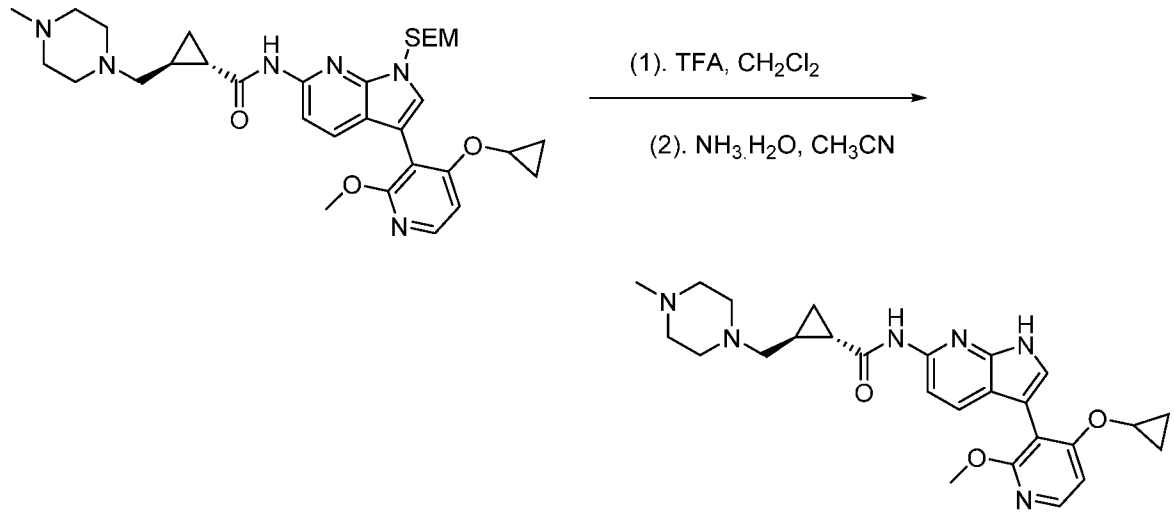
1-carboxamide (200.0 mg, 0.38 mmol) in DCM (10.0 mL) was added Dess-Martin (242.5 mg, 0.57 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was quenched by the addition of sat. $NaHCO_3$ (aq.). The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford trans-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (190.0 mg, crude) as a green oil. LCMS (ESI, m/z): $[M+H]^+$ =523.2.

Step 5: Synthesis of trans-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide



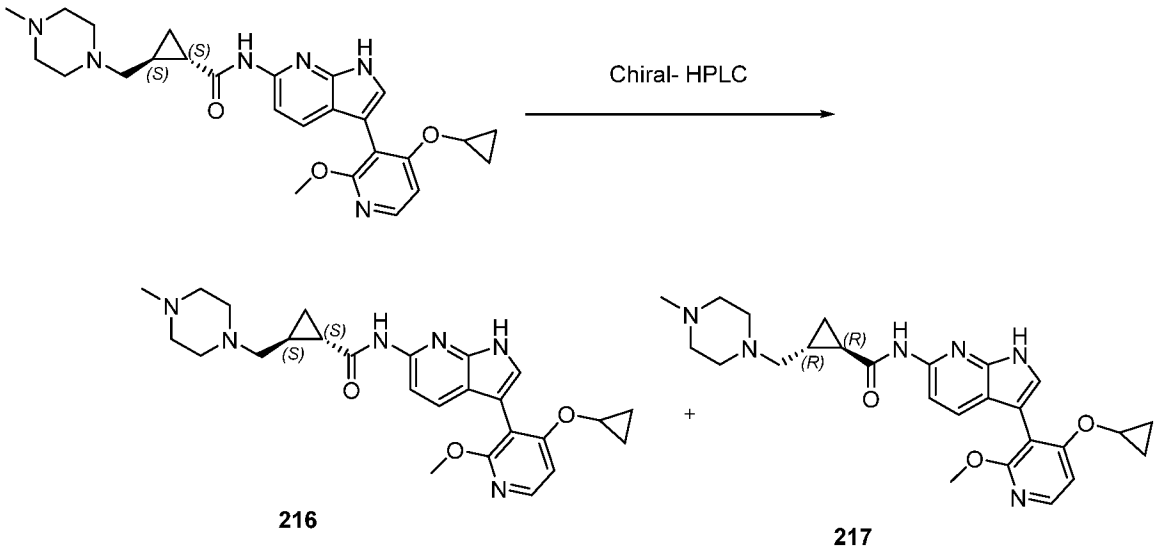
[0991] To a solution of trans-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (190.0 mg, crude) in DCM (6.0 mL) was added 1-methylpiperazine (109.2 mg, 1.09 mmol) and $NaBH_3CN$ (68.5 mg, 1.09 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (10/1, v/v) to afford trans-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (100.0 mg, 45%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =607.3.

Step 6: Synthesis of trans-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide



[0992] To a solution of trans-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (280.0 mg, 0.46 mmol) in CH_2Cl_2 (10.0 mL) was added TFA (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (10.0 mL) was added $NH_3 \cdot H_2O$ (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with ACN/H_2O (2/1, v/v) to afford trans-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (100.0 mg, 45%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =477.3.

Step 7: Synthesis of (1S,2S)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropanecarboxamide and (1R,2R)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropanecarboxamide (Compound 216 and Compound 217)



[0993] The product trans-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (100.0 mg, 0.18 mmol) was separated by Prep-Chiral-HPLC with the following conditions Column: Column (CHIRAL ART Cellulose-SC, 2x25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: MeOH: EtOH=1:1--HPLC; Flow rate: 20 mL/min; Gradient: 40% B to 40% B in 20 min; Wave Length: 220/254 nm) to afford N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 1 (26.5 mg, 29%) as a white solid and N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 2 (20.4 mg, 22%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 216 and 217** in Table 1.

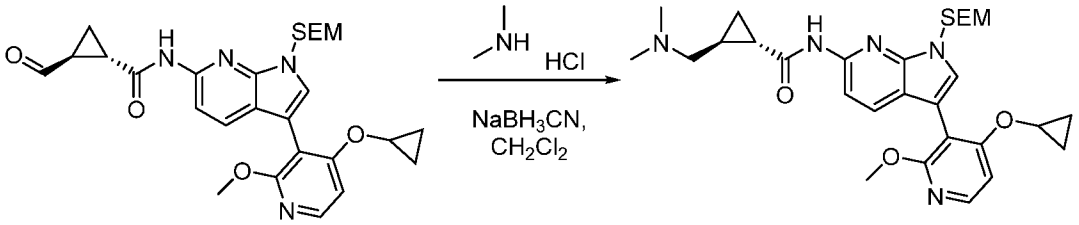
[0994] N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 1: Retention Time 1=18.75 min; LCMS (ESI, m/z): $[M+H]^+$ =477.4. ^1H NMR(400 MHz, DMSO-d_6): δ 11.50 (s, 1H), 10.52 (s, 1H), 8.07 (d, J = 6.0 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 6.0 Hz, 1H), 3.94 - 3.91 (m, 1H), 3.82 (s, 3H), 2.44 - 2.22 (m, 7H), 2.14 (s, 3H), 1.90 - 1.88 (m, 1H), 1.34 - 1.31 (m, 1H), 1.06 - 1.03 (m, 1H), 0.79 - 0.76 (m, 2H), 0.71 - 0.64 (m, 3H).

[0995] N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 2:

Retention Time 2=23.58 min; LCMS (ESI, m/z): $[M+H]^+$ =477.4. ^1H NMR(400 MHz, DMSO-d_6): δ 11.50 (s, 1H), 10.52 (s, 1H), 8.07 (d, J = 6.0 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 6.0 Hz, 1H), 3.94 - 3.91 (m, 1H), 3.82 (s, 3H), 2.45 - 2.22 (m, 9H), 2.14 (s, 3H), 1.90 - 1.88 (m, 1H), 1.34 - 1.31 (m, 1H), 1.06 - 1.03 (m, 1H), 0.79 - 0.76 (m, 2H), 0.71 - 0.64 (m, 3H).

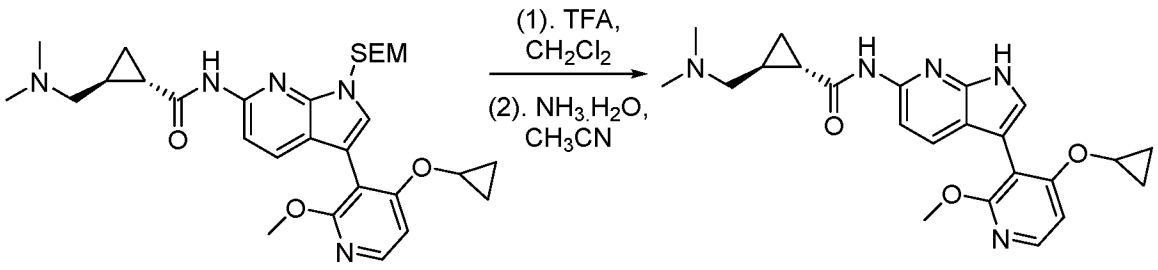
Example S202: Synthesis of (1R,2R)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide and (1S,2S)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (Compound 218 and Compound 219)

Step 1: Synthesis of Trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide



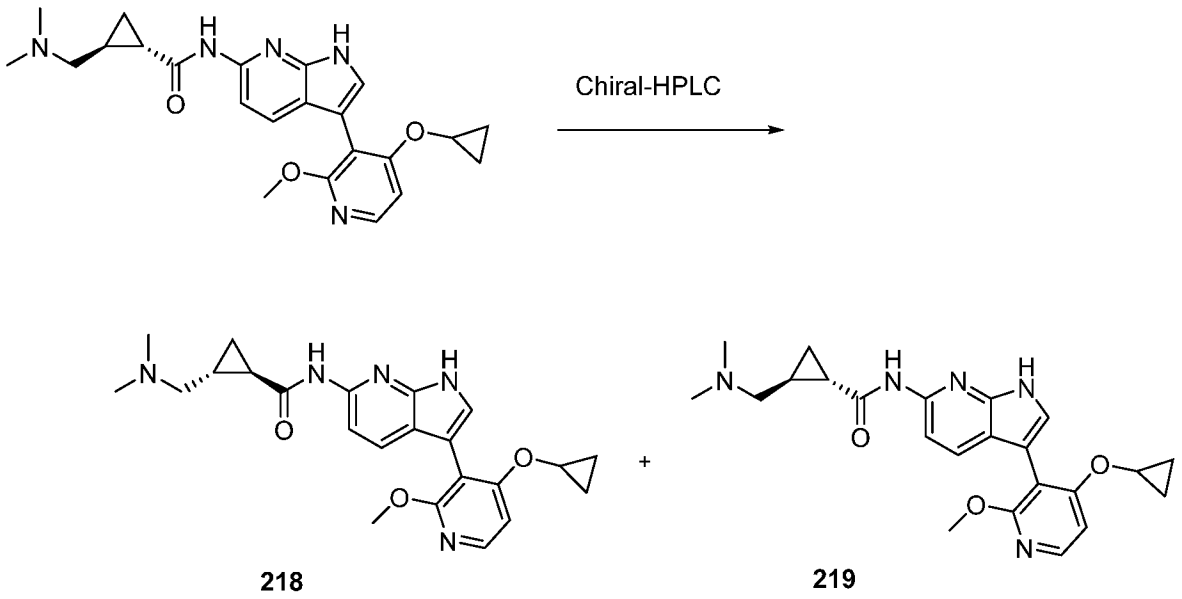
[0996] To a solution of trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-formylcyclopropane-1-carboxamide (400.0 mg, crude) in CH_2Cl_2 (5.0 mL) was added dimethylamine hydrochloride (103.5 mg, 1.27 mmol) and $NaBH_3CN$ (144.3 mg, 3.30 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with acetonitrile/water (16/84, v/v) to afford trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (168.0 mg, 40%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 552.3.

Step 2: Synthesis of trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide



[0997] To a solution of trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (158.0 mg, 0.29 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (5.0 mL) was added $NH_3.H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with acetonitrile/water (65/35, v/v) to afford trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (51.0 mg, 41%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 422.4.

Step 3: Synthesis of (1R,2R)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide and (1S,2S)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (Compound 218 and Compound 219)



[0998] The product trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (100.0 mg, 0.23 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SC, 2×25 cm, 5 um; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) -- HPLC, Mobile Phase B: MeOH:EtOH = 1:1--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 14 min; 254 nm) to afford N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide Enantiomer 1 (11.1 mg, 9%) as a white solid and N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide Enantiomer 2 (19.1 mg, 16%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 218 and 219** in Table 1.

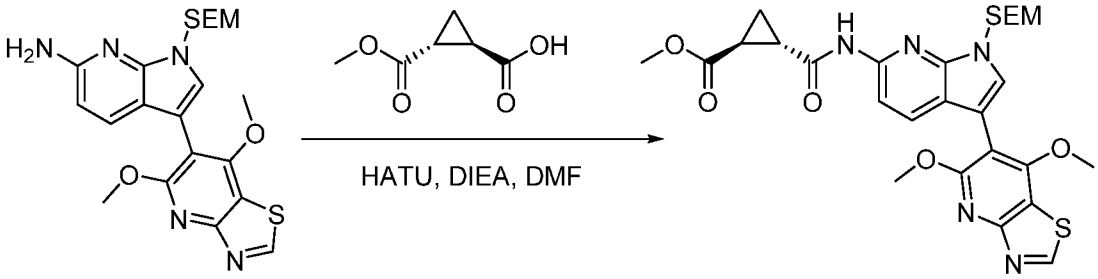
[0999] **N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide Enantiomer 1**: Retention Time 1=9.93 min; LCMS (ESI, m/z): $[M+H]^+$ = 422.4. ^1H NMR (400 MHz, DMSO-d_6): δ 11.50 (s, 1H), 10.52 (s, 1H), 8.07 (d, J = 5.2 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.35 (s, 1H), 7.14 (d, J = 4.4 Hz, 1H), 3.97 - 3.91 (m, 1H), 3.82 (s, 3H), 2.41 - 2.22 (m, 8H), 1.93 - 1.87 (m, 1H), 1.35 - 1.24 (m, 1H), 1.10 - 1.02 (m, 1H), 0.88 - 0.62 (m, 5H).

[1000] **N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide Enantiomer 2**: Retention

Time 2=12.38 min; LCMS (ESI, m/z): $[M+H]^+$ =422.3. 1H NMR (400 MHz, DMSO-d_6): δ 11.50 (s, 1H), 10.52 (s, 1H), 8.07 (d, J = 5.6 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.13 (d, J = 5.6 Hz, 1H), 3.93 - 3.90 (m, 1H), 3.81 (s, 3H), 2.33 - 2.16 (m, 8H), 1.91 - 1.88 (m, 1H), 1.34 - 1.30 (m, 1H), 1.06 - 1.02 (m, 1H), 0.84 - 0.60 (m, 5H).

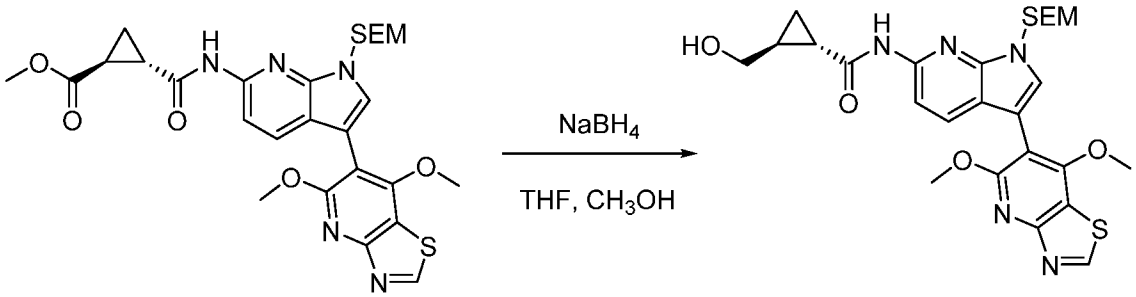
Example S203: Synthesis of (1S,2S)-N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide and (1R,2R)-N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (Compound 220 and Compound 221)

Step 1: Synthesis of Methyl (trans)-2-((3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamoyl)cyclopropane-1-carboxylate



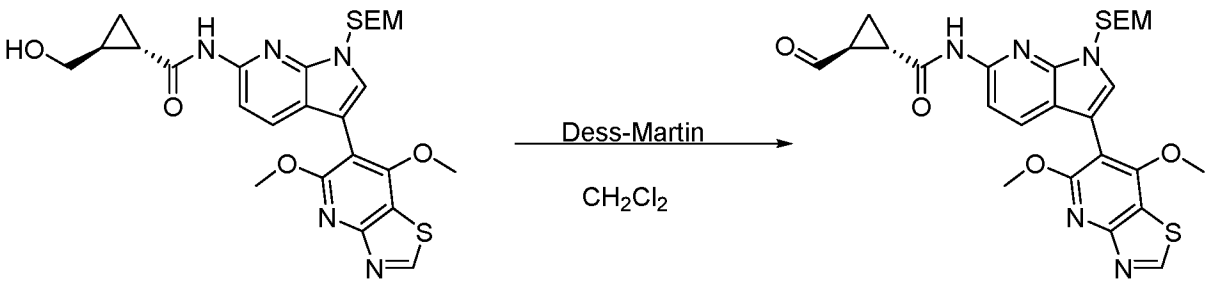
[1001] To a solution of 3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (1.9 g, 4.09 mmol) in DMF (20.0 mL) was DIEA (2.6 g, 20.4 mmol), trans-2-(methoxycarbonyl)cyclopropane-1-carboxylic acid (588.9 mg, 4.09 mmol) and HATU (1.9 g, 4.90 mmol) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 2 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (66/34, v/v) to afford methyl (trans)-2-((3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamoyl)cyclopropane-1-carboxylate (1.6 g, 67%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =584.2.

Step 2: Synthesis of Trans-N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(hydroxymethyl)cyclopropane-1-carboxamide



[1002] To a solution of methyl (trans)-2-((3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamoyl)cyclopropane-1-carboxylate (1.5 g, 2.57 mmol) in THF/CH_3OH (20.0/5.0 mL) was $NaBH_4$ (2.9 g, 77.2 mmol) at room temperature. The resulting mixture was stirred at 40 °C for 16 h. After the reaction was completed, the resulting mixture was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (60/40, v/v) to afford trans-N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(hydroxymethyl)cyclopropane-1-carboxamide (800.0 mg, 50%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =556.2.

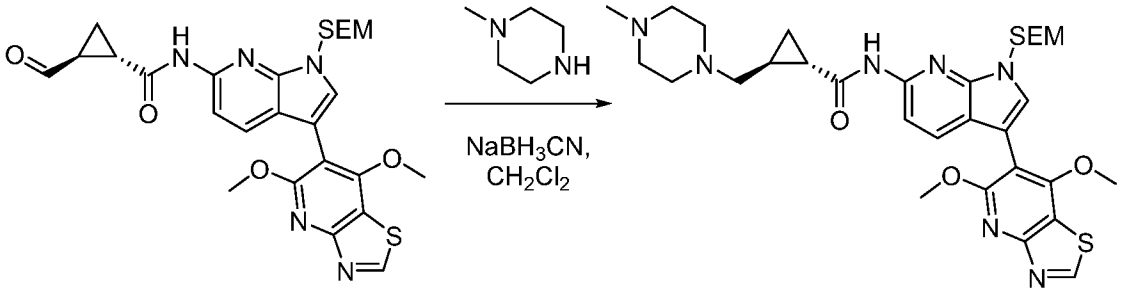
Step 3: Synthesis of Trans-N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-formylcyclopropane-1-carboxamide



[1003] To a solution of trans-N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-

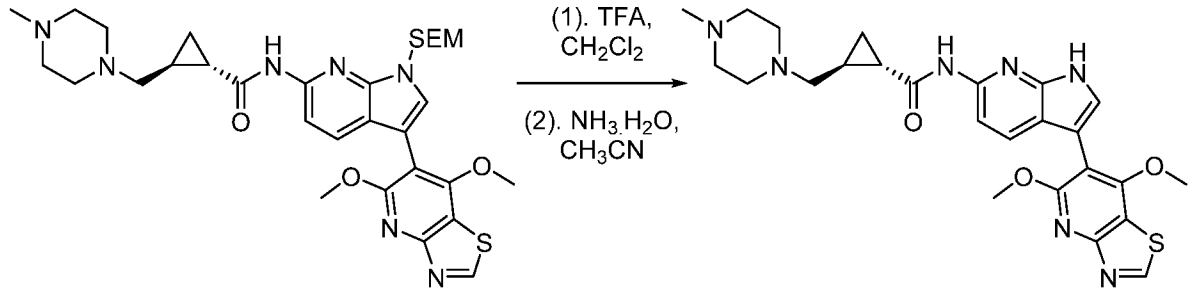
(hydroxymethyl)cyclopropane-1-carboxamide (660.0 mg, 1.19 mmol) in CH_2Cl_2 (15.0 mL) was Dess-Martin (755.6 mg, 1.78 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with aq. $NaHCO_3$, brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford trans-N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-formylcyclopropane-1-carboxamide (850.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =554.2.

Step 4: Synthesis of Trans-N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide



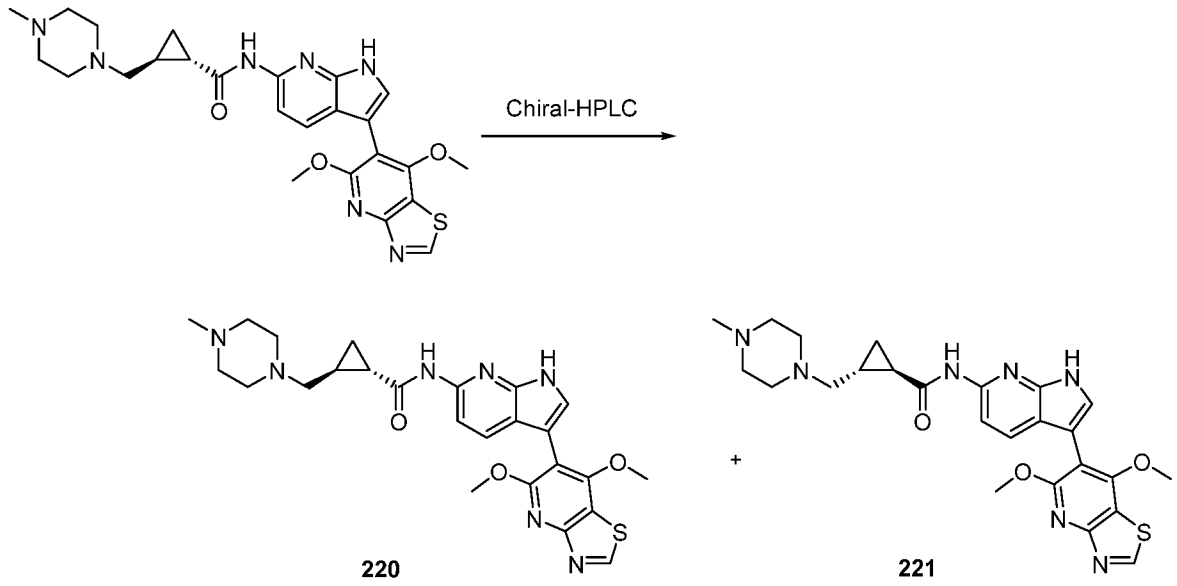
[1004] To a solution of trans-N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-formylcyclopropane-1-carboxamide (850.0 mg, 1.54 mmol) in CH_2Cl_2 (20.0 mL) was added 1-methylpiperazine (307.5 mg, 3.07 mmol) and $NaBH_3CN$ (192.9 mg, 3.07 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (10/1, v/v) to afford trans-N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (170.0 mg, 17%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =638.3.

Step 5: Synthesis of Trans-N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide



[1005] To a solution of trans-N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (170.0 mg, 0.27 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3.H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (10/1, v/v) to afford trans-N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (100.0 mg, 70%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =508.2.

Step 6: Synthesis of (1S,2S)-N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide and (1R,2R)-N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (Compound 220 and Compound 221)



[1006] The product trans-N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (100.0 mg, 0.20 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SC, 2×25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: MeOH: EtOH = 1:1 --HPLC; Flow rate: 20 mL/min; Gradient: 50% B to 50% B in 14.5 min; Wave Length: 220/254 nm) to afford N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide Enantiomer 1 (20.7 mg, 41%) as a white solid and N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide Enantiomer 2 (19.7 mg, 39%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 220 and 221** in Table 1.

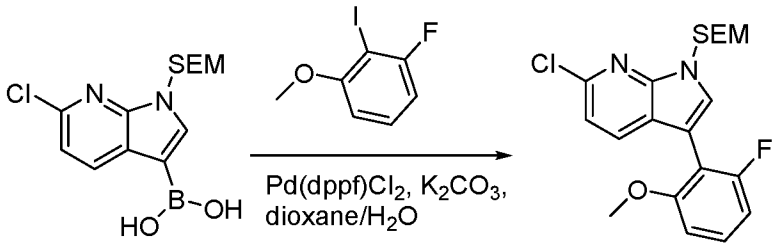
[1007] N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide Enantiomer 1: Retention Time 1: 10.25 min; LCMS (ESI, m/z): $[M+H]^+$ =508.4. ^1H NMR (400 MHz, DMSO-d_6): δ 11.65 (s, 1H), 10.57 (s, 1H), 9.57 (d, J = 5.6 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.47 (s, 1H), 3.91 (s, 6H), 2.44 - 2.11 (m, 9H), 2.10 - 2.01 (m, 4H), 1.91 - 1.89 (m, 1H), 1.37 - 1.33 (m, 1H), 1.11 - 1.00 (m, 1H), 0.77 - 0.64 (m, 1H).

[1008] N-(3-(5,7-dimethoxythiazolo[4,5-b]pyridin-6-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide Enantiomer 2:

Retention Time 2: 12.63 min; LCMS (ESI, m/z): $[M+H]^+$ =508.4. ^1H NMR (400 MHz, DMSO-d_6): δ 11.65 (s, 1H), 10.57 (s, 1H), 9.56 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.47 (s, 1H), 3.91 (s, 6H), 2.44 - 2.20 (m, 10H), 2.14 (s, 3H), 1.91 - 1.89 (m, 1H), 1.35 - 1.32 (m, 1H), 1.11 - 1.00 (m, 1H), 0.77 - 0.64 (m, 1H).

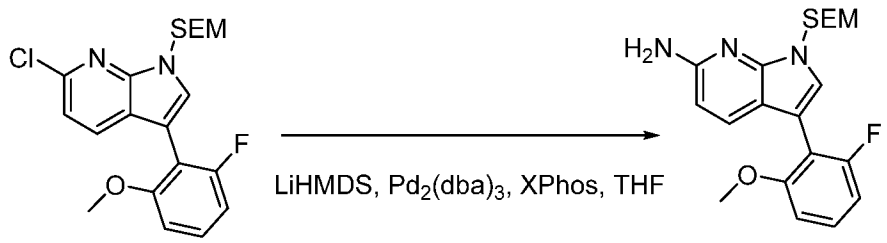
Example S204: Synthesis of (1S,2S)-N-[3-(2-fluoro-6-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide and (1R,2R)-N-[3-(2-fluoro-6-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (Compound 222 and Compound 223)

Step 1: Synthesis of 6-chloro-3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridine



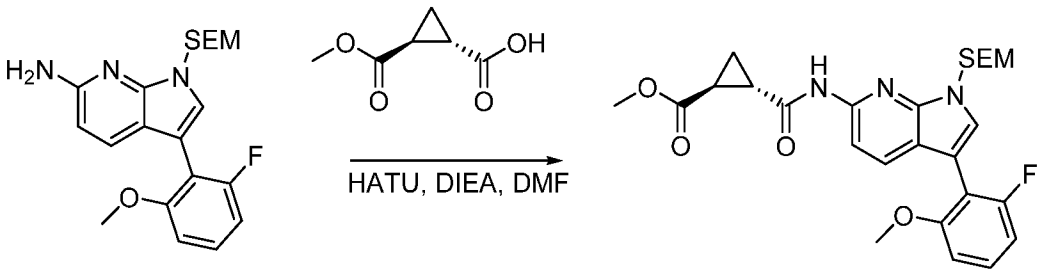
[1009] To a solution of 6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-ylboronic acid (2.0 g, 6.12 mmol) in 1,4 - dioxane/H_2O (40.0 mL/8.0 mL) was added 1-fluoro-2-iodo-3-methoxybenzene (1.5 g, 6.12 mmol), K_2CO_3 (1.7 g, 12.25 mmol) and $Pd(dppf)Cl_2$ (448.0 mg, 0.61 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford 6-chloro-3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridine (2.3 g, 92%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =407.1.

Step 2: Synthesis of 3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine



[1010] To a solution of 6-chloro-3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridine (1.0 g, 2.46 mmol) in THF (10.0 mL) was added XPhos (351.4 mg, 0.74 mmol), $Pd_2(dba)_3$ (225.0 mg, 0.25 mmol) and LiHMDS (7.4 mL, 1 mol/L) at room temperature under N_2. The resulting mixture was stirred at 60 °C for 2 h. After the reaction was completed, the reaction mixture was quenched by the addition of sat. NH_4Cl (aq.) at room temperature. The resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (4/1, v/v) to afford 3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (790.0 mg, 82%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =388.2.

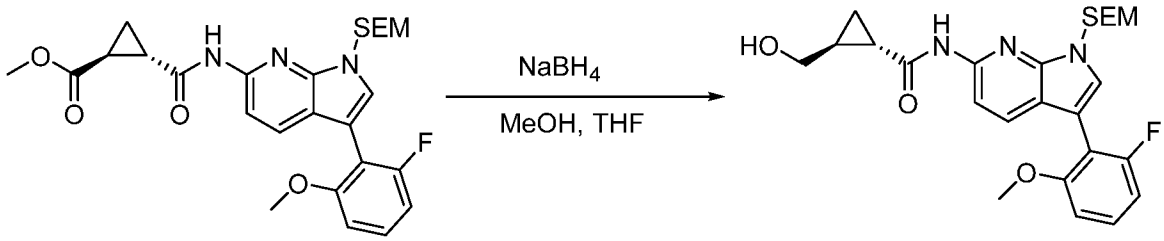
Step 3: Synthesis of methyl trans-2-{[3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate



[1011] To a solution of 3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (770.0 mg, 1.99 mmol) in DMF (20.0 mL) was added DIEA (1.2 g, 9.94 mmol), trans-2-(methoxycarbonyl)cyclopropane-1-carboxylic acid (429.6 mg, 2.98 mmol) and HATU (1.4 g, 3.58 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and

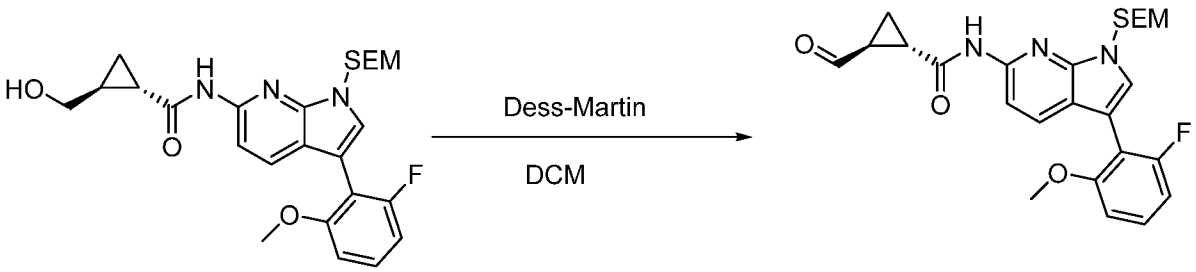
filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with acetonitrile/water (4/1, v/v) to afford methyl trans-2-{[3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate (760.0 mg, 74%) as a light brown oil. LCMS (ESI, m/z): $[M+H]^+$ =514.2.

Step 4: Synthesis of trans-N-[3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide



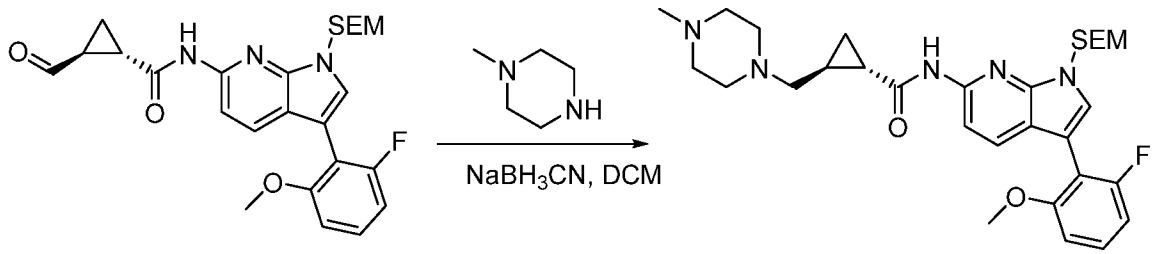
[1012] To a solution of methyl trans-2-{[3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate (750.0 mg, 1.46 mmol) in THF/MeOH (12.0 mL/8.0 mL) was added $NaBH_4$ (1.7 g, 43.8 mmol) at room temperature. The resulting mixture was stirred at 40 °C for 0.5 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with acetonitrile/water (7/3, v/v) to afford trans-N-[3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide (365.0 mg, 51%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =486.2.

Step 5: Synthesis of trans-N-[3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide



[1013] To a solution of trans-N-[3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide (340.0 mg, 0.70 mmol) in CH_2Cl_2 (10.0 mL) was added Dess-Martin (445.4 mg, 1.05 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed. the resulting mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford trans-N-[3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (330.0 mg, crude) as a green oil. LCMS (ESI, m/z): $[M+H]^+$ =484.2.

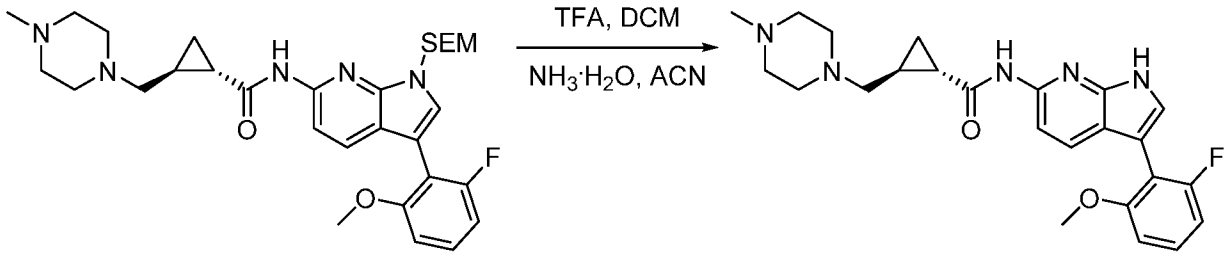
Step 6: Synthesis of trans-N-[3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide



[1014] To a solution of trans-N-[3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (650.0 mg, crude) in DCM (10.0 mL) was added 1-methylpiperazine (403.9 mg, 4.03 mmol) and $NaBH_3CN$ (253.4 mg, 4.03 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (9/1, v/v) to afford trans-N-[3-(2-fluoro-6-

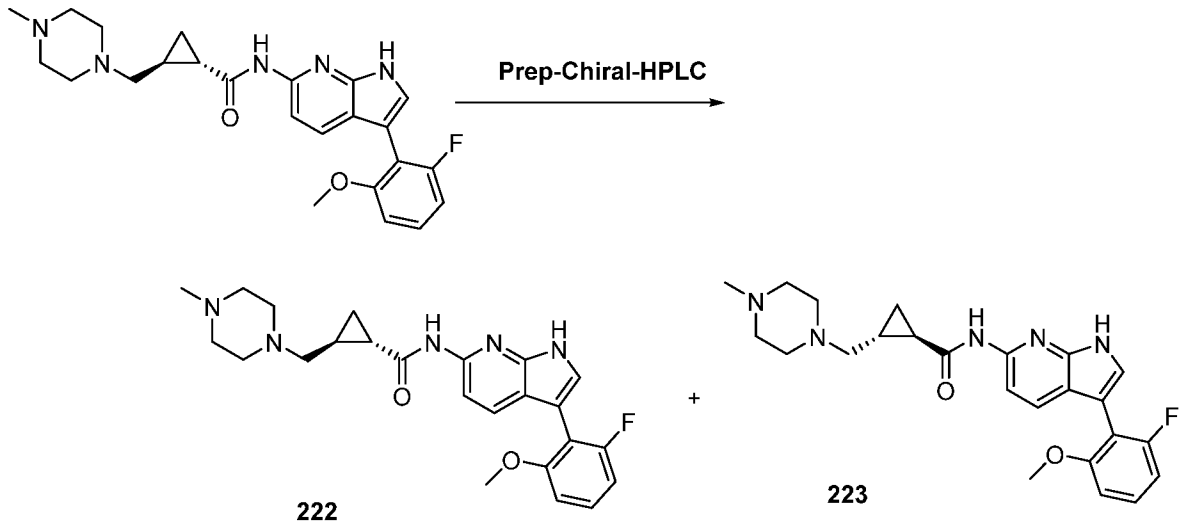
methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (150.0 mg, 19%) as a light brown oil. LCMS (ESI, m/z): $[M+H]^+$ =568.3.

Step 7: Synthesis of trans-N-[3-(2-fluoro-6-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide



[1015] To a solution of trans-N-[3-(2-fluoro-6-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (140.0 mg, 0.25 mmol) in CH_2Cl_2 (6.0 mL) was added TFA (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (6.0 mL) was added $NH_3 \cdot H_2O$ (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with acetonitrile/water (1/4, v/v) to afford trans-N-[3-(2-fluoro-6-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (80.0 mg, 74%) as a light yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =438.2.

Step 8: Synthesis of (1S,2S)-N-[3-(2-fluoro-6-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide and (1R,2R)-N-[3-(2-fluoro-6-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (Compound 222 and Compound 223)



[1016] The product trans-N-[3-(2-fluoro-6-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (80.0 mg, 0.18 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IE, 2x25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: MeOH: EtOH=1: 1--HPLC; Flow rate: 16 mL/min; Gradient: 60% B to 60% B in 29 min; Wave Length: 220/254 nm) to afford N-[3-(2-fluoro-6-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 1 (13.2 mg, 15%) as a white solid and N-[3-(2-fluoro-6-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 2 (12.3 mg, 15%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 222 and 223** in Table 1.

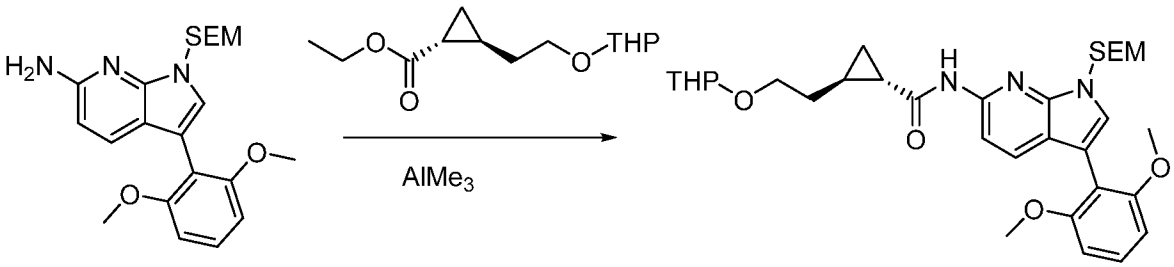
[1017] **N-[3-(2-fluoro-6-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 1:** Retention Time 1=15.57 min; LCMS (ESI, m/z): $[M+H]^+$ =438.4. ^1H NMR (400 MHz, DMSO-d_6): δ 11.63 (s, 1H), 10.55 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.44 (s, 1H), 7.36 - 7.30 (m, 1H), 6.98 - 6.89 (m, 2H), 3.78 (s, 3H), 2.45 - 2.22 (m, 8H), 2.14 (s, 3H), 1.95 - 1.89 (m, 1H), 1.36 - 1.32 (m, 1H), 1.06 - 1.04 (m, 1H), 0.74 - 0.66 (m, 1H).

[1018] **N-[3-(2-fluoro-6-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-methylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 2:** Retention Time 2=22.25 min; LCMS (ESI, m/z): $[M+H]^+$ = 438.4. ^1H NMR(400 MHz, DMSO-d_6): δ

11.63 (s, 1H), 10.55 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.44 (s, 1H), 7.36 - 7.30 (m, 1H), 6.98 - 6.89 (m, 2H), 3.78 (s, 3H), 2.38 - 2.22 (m, 8H), 2.14 (s, 3H), 1.94 - 1.89 (m, 1H), 1.38 - 1.32 (m, 1H), 1.06 - 1.01 (m, 1H), 0.72 - 0.66 (m, 1H).

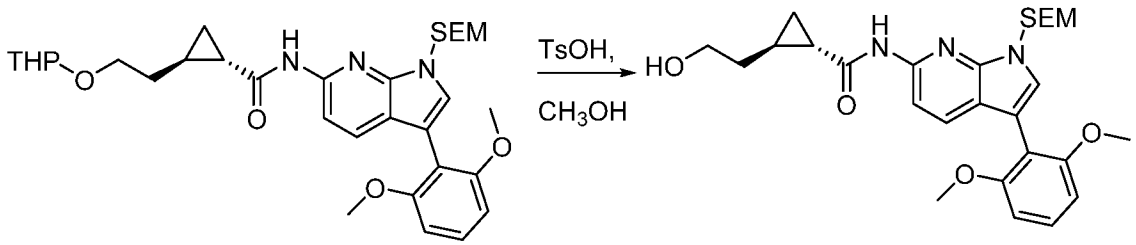
Example S205: Synthesis of (1S,2R)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide and (1R,2S)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide (Compound 224 and Compound 225)

Step 1: Synthesis of Trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)cyclopropane-1-carboxamide



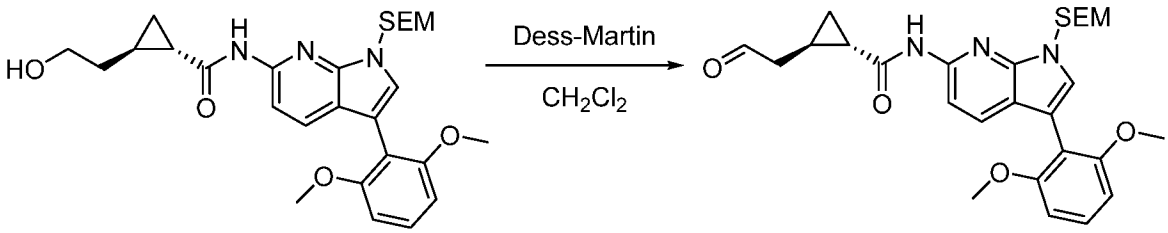
[1019] To a solution of 3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (900.0 mg, 2.52 mmol) in THF (10.0 mL) was added trans-ethyl-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)cyclopropane-1-carboxylate (818.7 mg, 3.38 mmol) and $AlMe_3$ (1.5 mL, 2 mol/L) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 3 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (90/10, v/v) to afford trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)cyclopropane-1-carboxamide (1.3 g, 87%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =596.3.

Step 2: Synthesis of Trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-hydroxyethyl)cyclopropane-1-carboxamide



[1020] To a solution of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)cyclopropane-1-carboxamide (1.1 g, 1.84 mmol) in CH_3OH (10.0 mL) was added TsOH (158.9 mg, 0.92 mmol) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. the residue was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (88/12, v/v) to afford trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-hydroxyethyl)cyclopropane-1-carboxamide (930.0 mg, 88%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =512.3.

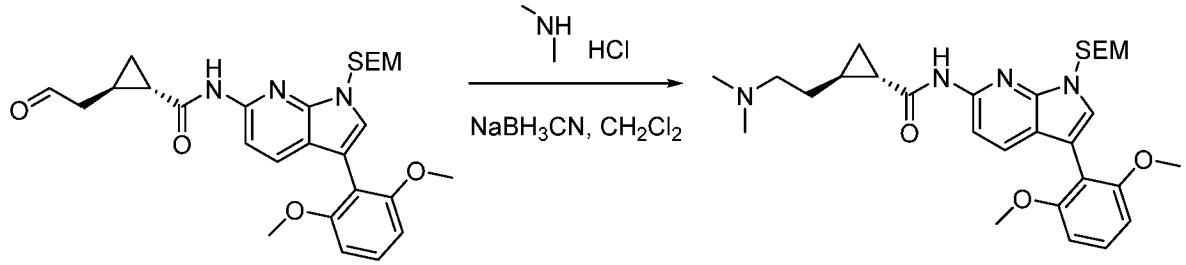
Step 3: Synthesis of Trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-oxoethyl)cyclopropane-1-carboxamide



[1021] To a solution of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-hydroxyethyl)cyclopropane-1-carboxamide (790.0 mg, 1.54 mmol) in CH_2Cl_2 (10.0 mL) was added Dess-Martin (982.2 mg, 2.32 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated

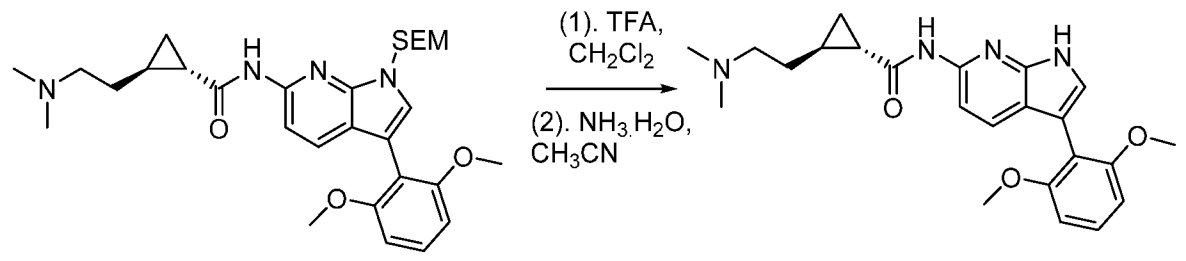
under reduced pressure to afford trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-oxoethyl)cyclopropane-1-carboxamide (790.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =510.2.

Step 4: Synthesis of Trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide



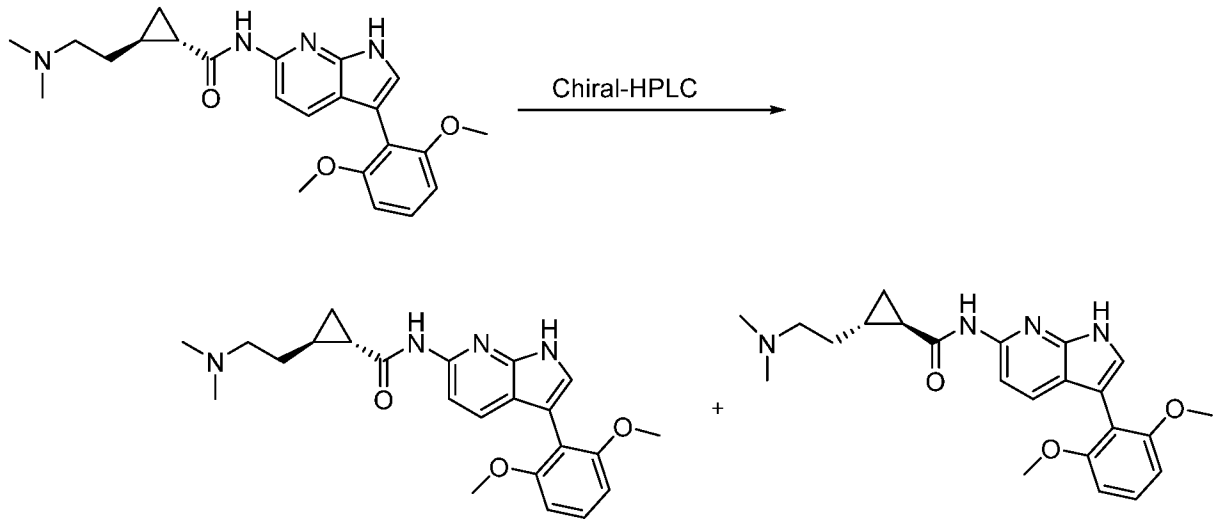
[1022] To a solution of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-oxoethyl)cyclopropane-1-carboxamide (790.0 mg, crude) in CH_2Cl_2 (10.0 mL) was added dimethylamine hydrochloride (376.2 mg, 4.61 mmol) and $NaBH_3CN$ (290.0 mg, 4.61 mmol) at room temperature under N_2. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (90/10, v/v) to afford trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide (750.0 mg, 81%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =539.3.

Step 5: Synthesis of Trans-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide



[1023] To a solution of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide (750.0 mg, 1.26 mmol) in CH_2Cl_2 (4.0 mL) was added TFA (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (4.0 mL) was added $NH_3.H_2O$ (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 8 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (10/1, v/v) to afford trans-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide (200.0 mg, 27%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =409.2.

Step 6: Synthesis of (1S,2R)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide and (1R,2S)-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide (Compound 224 and Compound 225)



224 225

[1024] The product trans-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide (200.0 mg, 0.48 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IH, 2x25 cm, 5

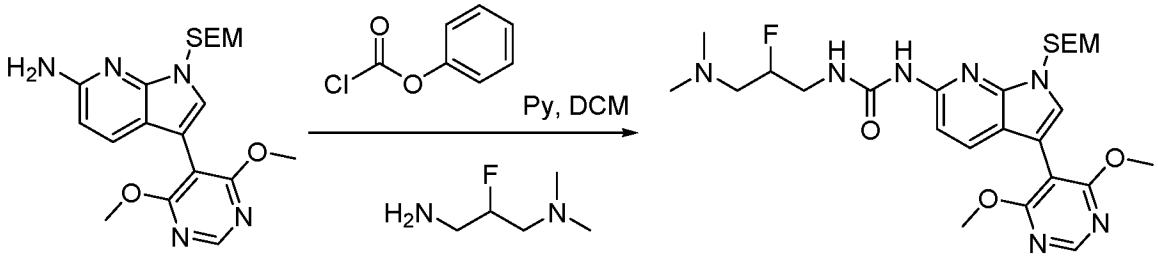
μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: MeOH: EtOH=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 19 min; Wave Length: 220/254 nm) to afford N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide Enantiomer 1 (23.0 mg, 23%) as a white solid and N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide Enantiomer 2 (20.6 mg, 20%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 224 and 225** in Table 1.

[1025] N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide Enantiomer 1: Retention Time 1(min): 10.06; LCMS (ESI, m/z): $[M+H]^+$ =409.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.38 (s, 1H), 10.43 (s, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.29 - 7.25 (m, 2H), 6.80 - 6.74 (m, 2H), 3.69 (s, 6H), 2.36 - 2.29 (m, 2H), 2.20 - 2.13 (m, 6H), 1.85 - 1.82 (m, 1H), 1.50 - 1.36 (m, 2H), 1.24 - 1.21 (m, 1H), 1.02 - 0.98 (m, 1H), 0.70 - 0.66 (m, 1H).

[1026] N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide Enantiomer 2: Retention Time 2(min): 14.10; LCMS (ESI, m/z): $[M+H]^+$ =409.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.38 (s, 1H), 10.43 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.29 - 7.25 (m, 2H), 6.75 (d, J = 8.4 Hz, 2H), 3.69 (s, 6H), 2.33 - 2.28 (m, 2H), 2.13 (s, 6H), 1.85 - 1.82 (m, 1H), 1.49 - 1.35 (m, 2H), 1.24 - 1.21 (m, 1H), 1.02 - 0.98 (m, 1H), 0.70 - 0.66 (m, 1H).

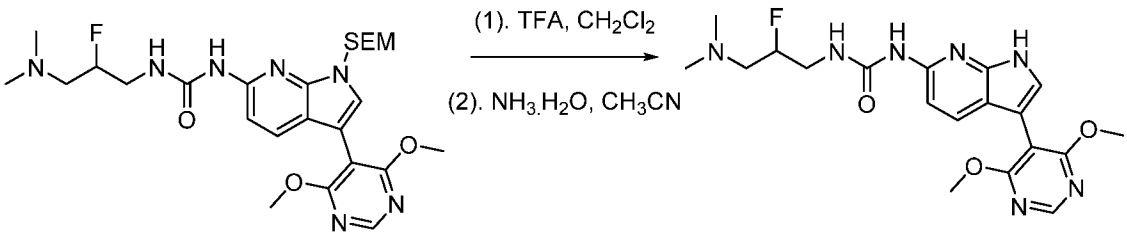
Example S206: Synthesis of (R)-1-(3-(4,6-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)-2-fluoropropyl)urea and (S)-1-(3-(4,6-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)-2-fluoropropyl)urea (Compound 226 and Compound 227)

Step 1: Synthesis of 1-[3-(4,6-dimethoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea



[1027] To a solution of 3-(4,6-dimethoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (474.0 mg, 1.18 mmol) in DCM (10.0 mL) was added Pyridine (373.5 mg, 4.72 mmol) and phenyl chloroformate (369.7 mg, 2.36 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added Pyridine (10.0 mL) and (3-amino-2-fluoropropyl)dimethylamine (1418.6 mg, 11.80 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 3 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (20/1, v/v) to afford 1-[3-(4,6-dimethoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea (440.0 mg, 68%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =548.3.

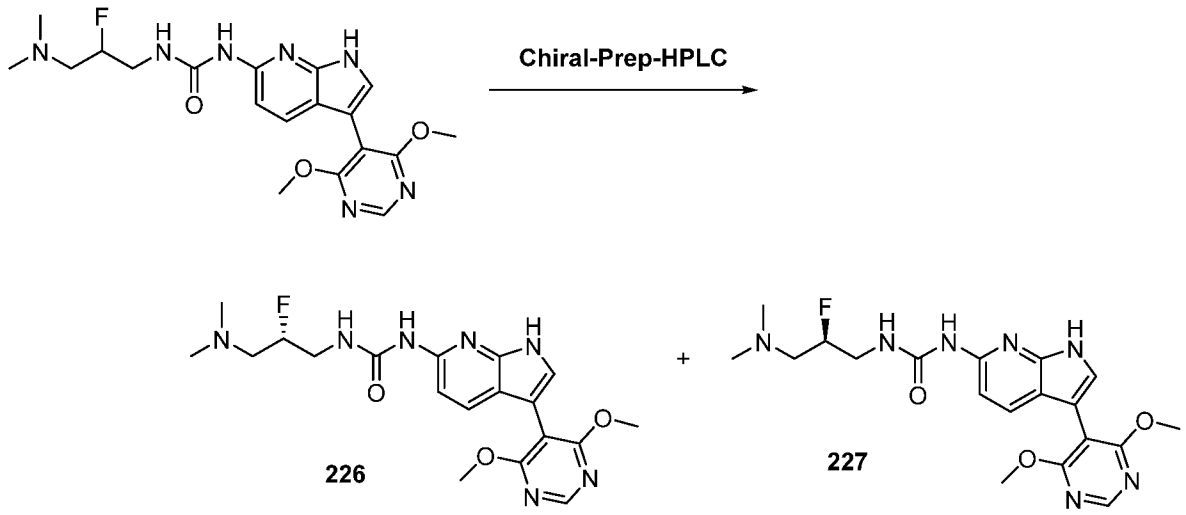
Step 2: Synthesis of 1-(3-(4,6-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)-2-fluoropropyl)urea



[1028] To a solution of 1-[3-(4,6-dimethoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-3-[3-(dimethylamino)-2-fluoropropyl]urea (410.0 mg, 0.75 mmol) in CH_2Cl_2 (8.0 mL) was added TFA (8.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added CH_3CN (8.0 mL) and $NH_3.H_2O$ (8.0 mL) at room temperature. The resulting mixture was

stirred at room temperature for another 3 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography eluted with methanol/H_2O (3/2, v/v) to afford 1-(3-(4,6-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)-2-fluoropropyl)urea (95.0 mg, 30%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =418.2.

Step 3: Synthesis of (R)-1-(3-(4,6-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)-2-fluoropropyl)urea and (S)-1-(3-(4,6-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)-2-fluoropropyl)urea (Compound 226 and Compound 227)



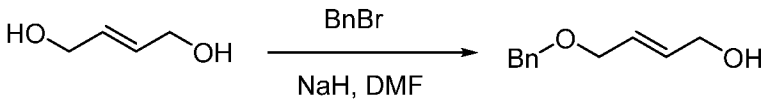
[1029] The racemic 1-(3-(4,6-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)-2-fluoropropyl)urea (95.0 mg, 0.23 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2x25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) --HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 22 min; Wave Length: 220/254 nm) to afford 1-(3-(4,6-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)-2-fluoropropyl)urea Enantiomer 1 (18.9 mg, 20%) as a white solid and 1-(3-(4,6-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)-2-fluoropropyl)urea Enantiomer 2 (11.5 mg, 18%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 226 and 227** in Table 1.

[1030] **1-(3-(4,6-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)-2-fluoropropyl)urea Enantiomer 1:** Retention Time 1=10.16 min; LCMS (ESI, m/z): $[M+H]^+$ =418.3. ^1H NMR (400 MHz, DMSO-d_6): δ 11.61 (s, 1H), 9.27 (s, 1H), 8.61 (s, 1H), 8.46 (s, 1H), 7.65 (s, 1H), 7.37 (s, 1H), 7.05 (s, 1H), 4.81 - 4.69 (m, 1H), 3.91 (s, 6H), 3.74 - 3.55 (m, 1H), 2.21 (s, 6H).

[1031] **1-(3-(4,6-dimethoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3-(3-(dimethylamino)-2-fluoropropyl)urea Enantiomer 2:** Retention Time 2=17.388 min; LCMS (ESI, m/z): $[M+H]^+$ = 418.3. ^1H NMR(400 MHz, DMSO-d_6): δ 11.62 (s, 1H), 9.27 (s, 1H), 8.61 (s, 1H), 8.46 (s, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.37 (s, 1H), 7.05 (d, J = 7.6 Hz, 1H), 4.81 - 4.69 (m, 1H), 3.91 (s, 6H), 3.60 - 3.54 (m, 1H), 2.21 (s, 6H).

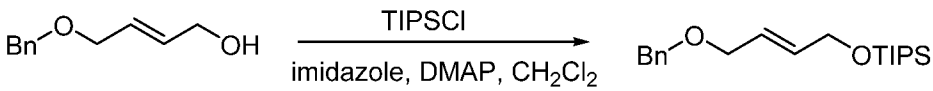
Example S207: Synthesis of trans-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(R)-fluoro-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (Compound 228)

Step 1: Synthesis of (*E*)-4-(benzyloxy)but-2-en-1-ol



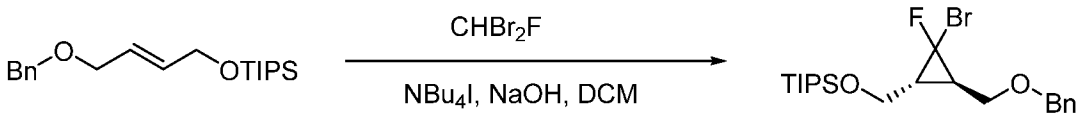
[1032] To a solution of NaH (16.3 g, 60% purity) in DMF (250.0 mL) was added dropwise a solution of (*E*)-but-2-ene-1,4-diol (50.0 g, 567.50 mmol) in DMF (250.0 mL) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h under N_2. Then a solution of BnBr (97.1 g, 567.50 mmol) in DMF (100.0 mL) was added dropwise to the mixture at 0 °C under N_2. The resulting mixture was stirred at 0 °C for additional 1 h under N_2. After the reaction was completed, the resulting mixture was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (75/25, v/v) to afford (*E*)-4-(benzyloxy)but-2-en-1-ol (70.0 g, 69%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =179.1.

Step 2: Synthesis of (*E*)-((4-(benzyloxy)but-2-en-1-yl)oxy)triisopropylsilane



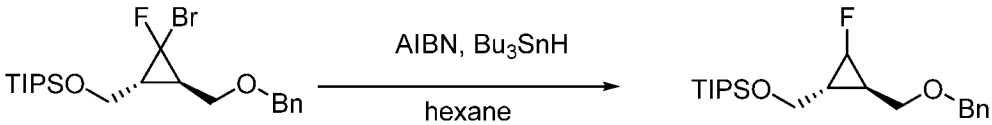
[1033] To a solution of (*E*)-4-(benzyloxy)but-2-en-1-ol (50.0 g, 280.54 mmol) in CH_2Cl_2 (500.0 mL) was added imidazole (42.0 g, 617.17 mmol), DMAP (6.9 g, 56.11 mmol) and TIPSCl (108.2 g, 561.07 mmol) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (96/4, v/v) to afford (*E*)-((4-(benzyloxy)but-2-en-1-yl)oxy)triisopropylsilane (90.0 g, 95%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =335.2.

Step 3: Synthesis of (((1S/R,3S/R)-3-((benzyloxy)methyl)-2-bromo-2-fluorocyclopropyl)methoxy)triisopropylsilane



[1034] To a solution of (*E*)-((4-(benzyloxy)but-2-en-1-yl)oxy)triisopropylsilane (59.0 g, 132.88 mmol) in DCM (300.0 mL) and NaOH (300.0 mL, 50%) was added NBu_4I (4.90 g, 13.29 mmol) and $CHBr_2F$ (50.3 g, 199.32 mmol) at room temperature. The resulting mixture was stirred at room temperature for 12 h. After the reaction was completed, the resulting mixture was quenched with H_2O at 0 °C and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (80/20, v/v) to afford (((1S/R,3S/R)-3-((benzyloxy)methyl)-2-bromo-2-fluorocyclopropyl)methoxy)triisopropylsilane (50.0 g, crude) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =445.1.

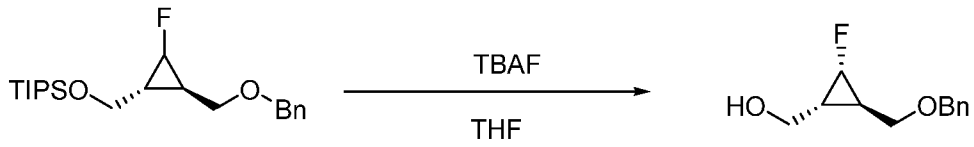
Step 4: Synthesis of (trans-(2-((benzyloxy)methyl)-3-fluorocyclopropyl)methoxy)triisopropylsilane



[1035] To a solution of (((1S/R,3S/R)-3-((benzyloxy)methyl)-2-bromo-2-fluorocyclopropyl)methoxy)triisopropylsilane (50.0 g, 112.24 mmol) in hexane (500.0 mL) was added Bu_3SnH (35.9 g, 123.4 mmol) and AIBN (1.8 g, 11.22 mmol) at room

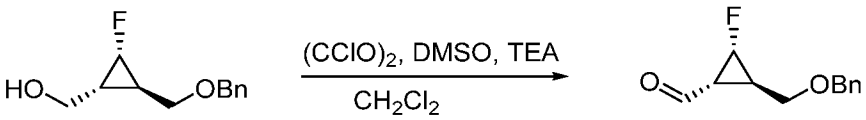
temperature. The resulting mixture was stirred at 90 °C for 4 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (88/12, v/v) to afford (trans-(2-((benzyloxy)methyl)-3-fluorocyclopropyl)methoxy)triisopropylsilane (50.0 g, crude) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =367.2.

Step 5: Synthesis of trans-(2-((benzyloxy)methyl)-3(S)-fluorocyclopropyl)methanol



[1036] To a solution of (trans-(2-((benzyloxy)methyl)-3-fluorocyclopropyl)methoxy)triisopropylsilane (50.0 g, 136.39 mmol) in THF (500.0 mL) was added TBAF (42.8 g, 163.67 mmol) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (40/60, v/v) to afford trans-(2-((benzyloxy)methyl)-3(S)-fluorocyclopropyl)methanol (1.5 g, 10%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =211.1.

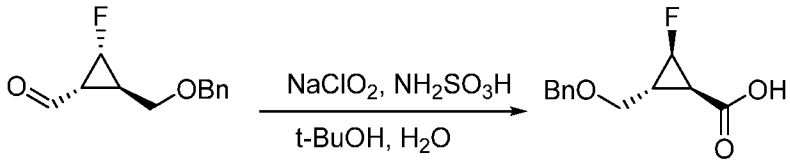
Step 6: Synthesis of trans-(2-((benzyloxy)methyl)-3(R)-fluorocyclopropyl)-1-carbaldehyde



[1037] To a solution of $(COCl)_2$ (1.8 g, 14.27 mmol) in CH_2Cl_2 (10.0 mL) was added dropwise a solution of DMSO (4.5 g, 57.08 mmol) in CH_2Cl_2 (10.0 mL) at -78 °C under N_2. The resulting mixture was stirred at -78 °C for 0.5 h under N_2. Then a solution of trans-(2-((benzyloxy)methyl)-3(S)-fluorocyclopropyl)methanol (1.5 g, 7.13 mmol) in CH_2Cl_2 (10.0 mL) was added dropwise to the mixture at -78 °C under N_2. The resulting mixture was stirred at -78 °C for additional 1 h. After the reaction was completed, TEA (5.8 g, 57.08 mmol) was added dropwise to the mixture at -78 °C under N_2. The resulting mixture was stirred at -78 °C

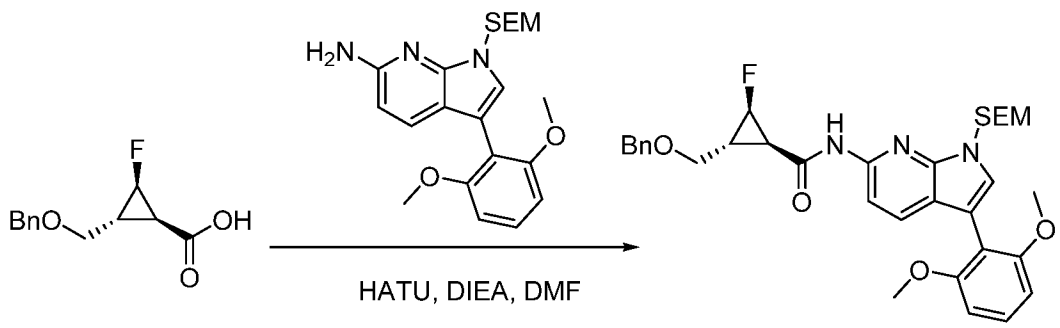
for another 0.5 h under N_2.The resulting mixture was quenched with aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (90/10, v/v) to afford trans-(2-((benzyloxy)methyl)-3(R)-fluorocyclopropyl)-1-carbaldehyde (410.0 mg, 25%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =209.1.

Step 7: Synthesis of trans-(2-((benzyloxy)methyl)-3(R)-fluorocyclopropyl)-1-carboxylic acid



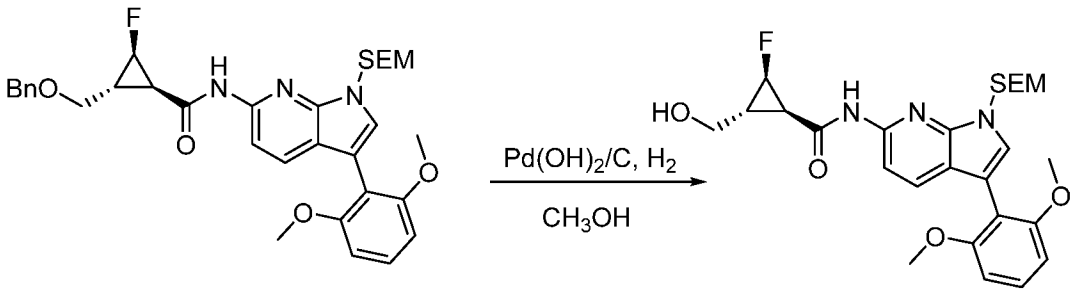
[1038] To a mixture of trans-(2-((benzyloxy)methyl)-3(R)-fluorocyclopropyl)-1-carbaldehyde (360.0 mg, 1.73 mmol) and NH_2SO_3H (1.7 g, 17.29 mmol) in t-BuOH/H_2O (1.0/8.0 mL) was added $NaClO_2$ (1.6 g, 17.29 mmol) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 1.5 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (50/50, v/v) to afford trans-(2-((benzyloxy)methyl)-3(R)-fluorocyclopropyl)-1-carboxylic acid (80.0 mg, 20%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =225.1.

Step 8: Synthesis of trans-2-((benzyloxy)methyl)-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(R)-fluorocyclopropane-1-carboxamide



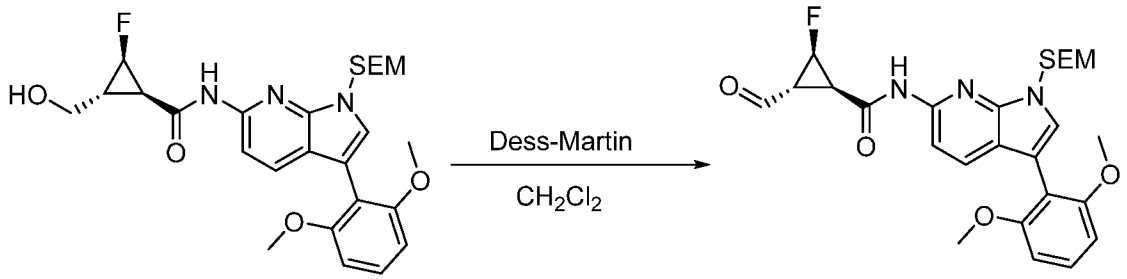
[1039] To a solution of 3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (231.7 mg, 0.58 mmol) in DMF (6.0 mL) were added trans-(2-((benzyloxy)methyl)-3(R)-fluorocyclopropyl)-1-carboxylic acid (130.0 mg, 0.58 mmol), DIEA (224.8 mg, 1.74 mmol) and HATU (264.5 mg, 0.70 mmol) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (90/10, v/v) to afford trans-2-((benzyloxy)methyl)-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(R)-fluorocyclopropane-1-carboxamide (270.0 mg,77%) as a white solid . LCMS (ESI, m/z): $[M+H]^+$ =606.3.

Step 9: Synthesis of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(R)-fluoro-2-(hydroxymethyl)cyclopropane-1-carboxamide



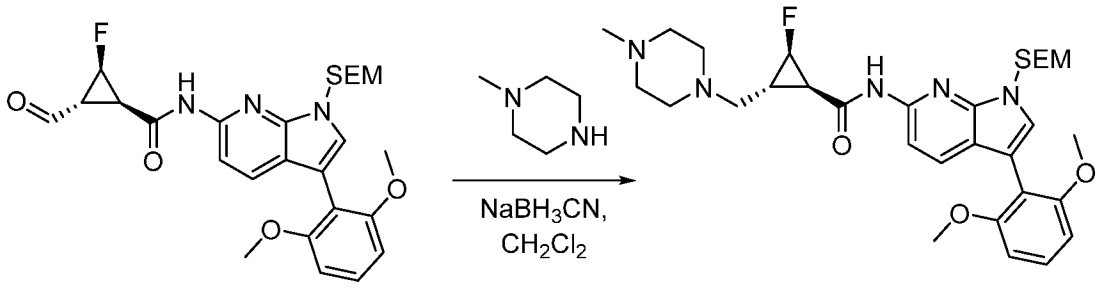
[1040] To a solution of trans-2-((benzyloxy)methyl)-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(R)-fluorocyclopropane-1-carboxamide (230.0 mg, 0.38 mmol) in CH_3OH (5.0 mL) was $Pd(OH)_2/C$ (106.1 mg, dry) at room temperature under N_2. The resulting mixture was stirred at room temperature for 4 h under H_2. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash column chromatography with CH_3CN/H_2O (28/72, v/v) to afford trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(R)-fluoro-2-(hydroxymethyl)cyclopropane-1-carboxamide (200.0 mg, 97%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =516.2.

Step 10: Synthesis of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(R)-fluoro-2-formylcyclopropane-1-carboxamide



[1041] To a solution of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(R)-fluoro-2-(hydroxymethyl)cyclopropane-1-carboxamide (200.0 mg, 0.39 mmol) in CH_2Cl_2 (10.0 mL) was added Dess-Martin (246.8 mg, 0.58 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with aq. $NaHCO_3$, brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(R)-fluoro-2-formylcyclopropane-1-carboxamide (200.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =514.2.

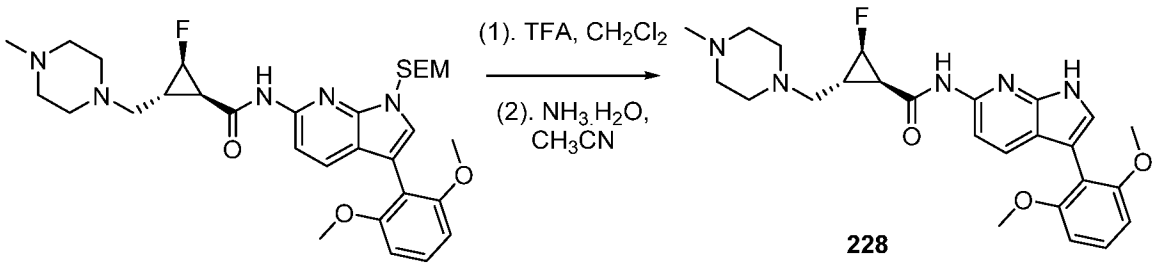
Step 11: Synthesis of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(R)-fluoro-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide



[1042] To a solution of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(R)-fluoro-2-formylcyclopropane-1-carboxamide (200.0 mg, crude) in CH_2Cl_2 (10.0 mL) was added 1-

methylpiperazine (117.0 mg, 1.17 mmol) and $NaBH_3CN$ (110.1 mg, 1.17 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (20/1, v/v) to afford trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(R)-fluoro-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (75.0 mg, 34%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =598.3.

Step 12: Synthesis of trans-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(R)-fluoro-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (Compound 228)

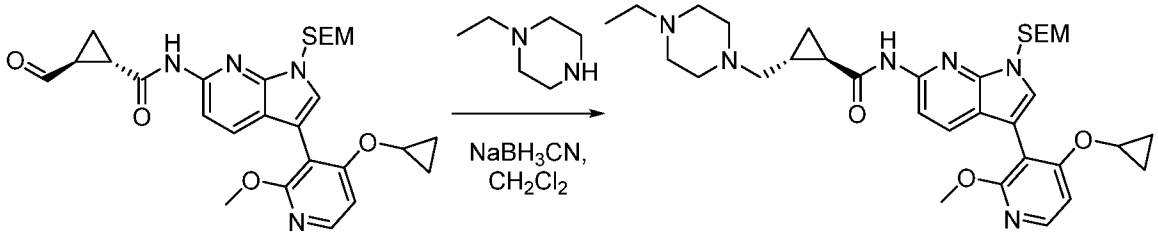


[1043] To a solution of trans-N-(3-(2,6-dimethoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(R)-fluoro-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (70.0 mg, 0.27 mmol) in CH_2Cl_2 (4.0 mL) was added TFA (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (4.0 mL) was added $NH_3.H_2O$ (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for additional 8 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 37% B in 8 min; Wave Length: 254 nm) to afford trans-N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-3(R)-fluoro-2-((4-methylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide **(Compound 228)** (3.6 mg, 7%)

as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =468.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.37 (s, 1H), 10.88 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.30 - 7.26 (m, 2H), 6.76 (d, J = 8.4 Hz, 2H), 5.07 - 4.87 (m, 1H), 3.70 (s, 6H), 2.90 - 2.79 (m, 2H), 2.72 - 2.55 (m, 1H), 2.45 - 2.23 (m, 5H), 2.21 - 2.10 (m, 4H), 1.56 - 1.39 (m, 1H).

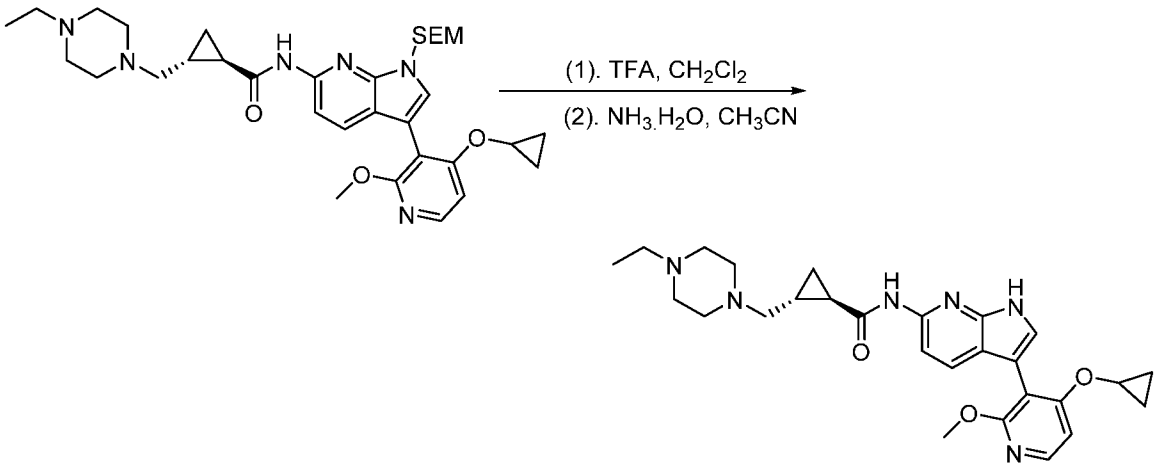
Example S208: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide and (1R,2R)-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (Compound 229 and Compound 230)

Step 1: Synthesis of Trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-ethylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide



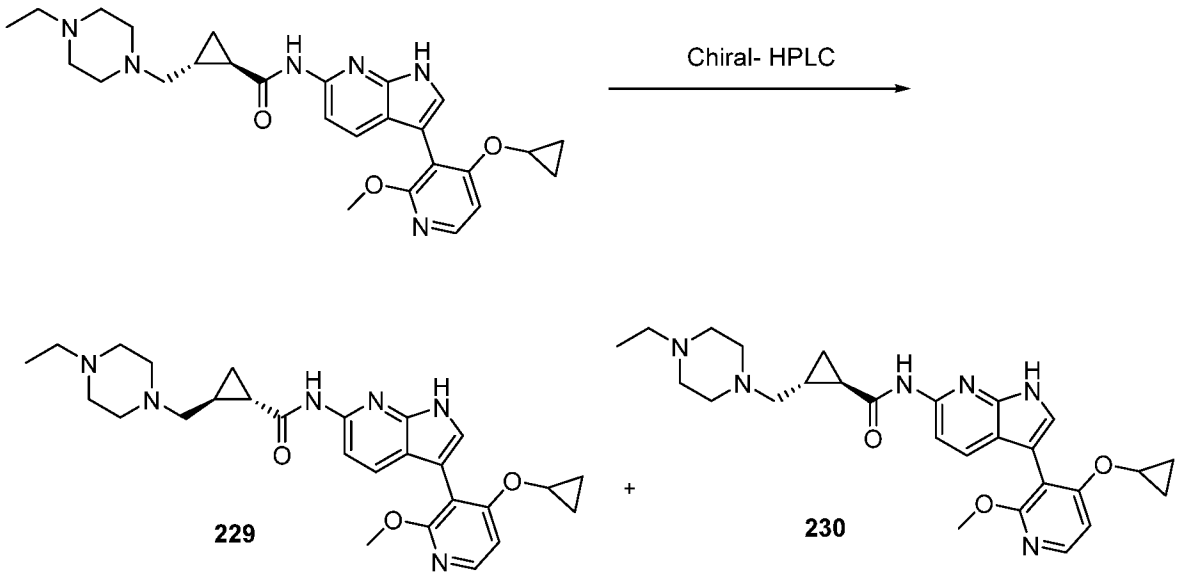
[1044] To a solution of trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-formylcyclopropane-1-carboxamide (250.0 mg, 0.47 mmol) in DCM (4.0 mL) was added $NaBH_3CN$ (90.1 mg, 1.43 mmol) and 1-ethylpiperazine (163.8 mg, 1.43 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (10/1, v/v) to afford trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((4-ethylpiperazin-1-yl)methyl)cyclopropane-1-carboxamide (75.0 mg, 25%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =621.4

Step 2: Synthesis of Trans-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide



[1045] To a solution of trans-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (150.0 mg, 0.09 mmol) in DCM (2.0 mL) was added TFA (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added $NH_3.H_2O$ (1.0 mL) and ACN (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for additional 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with ACN/H_2O (2/1, v/v) to afford trans-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (60.0 mg, 51%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =491.3

Step 3: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide and (1R,2R)-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (Compound 229 and Compound 230)



[1046] The trans-N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (60.0 mg) was separated by Prep-chiral HPLC with the following conditions (Column: CHIRAL ART Cellulose-SC, 2x25 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: 30% B to 30% B in 11 min; Wave Length: 220/254 nm) to afford N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 1 (11.8 mg, 39%) and N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 2 (17.4 mg, 56%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 229 and 230** in Table 1.

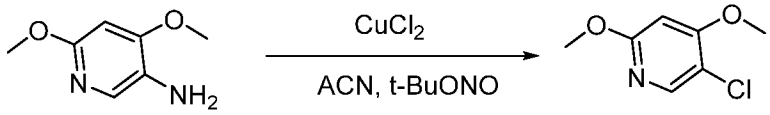
[1047] N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 1: Retention Time 1=7.61 min; LCMS (ESI, m/z): $[M+H]^+$ =491.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.50 (s, 1H), 10.53 (s, 1H), 8.07 (d, J = 6.0 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 2.0 Hz, 1H), 7.14 (d, J = 2.0 Hz, 1H), 3.99 - 3.91 (m, 1H), 3.81 (s, 3H), 2.51 - 2.08 (m, 10H), 1.96 - 1.90 (m, 1H), 1.34 - 1.24 (m, 1H), 1.15 - 0.96 (m, 4H), 0.81 - 0.76 (m, 2H), 0.72 - 0.59 (m, 3H) .

[1048] N-[3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 2:

Retention Time 2=9.31 min; LCMS (ESI, m/z): $[M+H]^+$ =491.3. ^1H NMR (400 MHz, DMSO-d_6): δ 11.50 (s, 1H), 10.53 (s, 1H), 8.07 (d, J = 5.6 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.14 (d, J = 5.6 Hz, 1H), 3.94 - 3.91 (m, 1H), 3.82 (s, 3H), 2.68 - 2.21 (m, 10H), 1.91 - 1.88 (m, 1H), 1.34 - 1.30 (m, 1H), 1.06 - 0.96 (m, 4H), 0.81 - 0.76 (m, 2H), 0.72 - 0.64 (m, 3H).

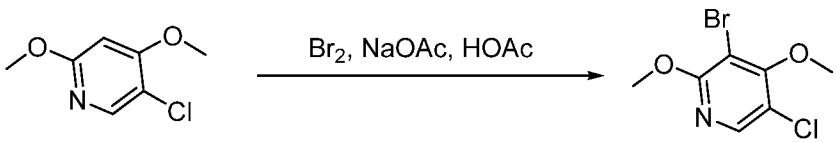
Example S209: Synthesis of (1S,2S)-N-[3-(5-chloro-2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 231)

Step 1: Synthesis of 5-chloro-2,4-dimethoxypyridine



[1049] To a solution of 4,6-dimethoxypyridin-3-amine (2.0 g, 12.97 mmol) in MeCN (20.0 mL) was added t-BuONO (2.0 g, 19.46 mmol), $CuCl_2$ (0.8 g, 6.48 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (9/1, v/v) to afford 5-chloro-2,4-dimethoxypyridine (900.0 mg, 39%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =174.0

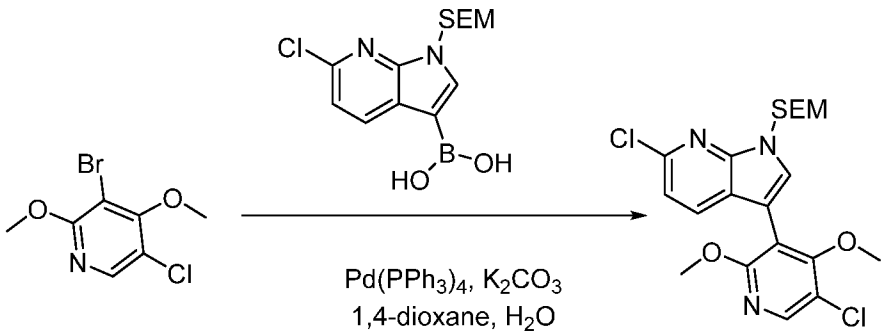
Step 2: Synthesis of 3-bromo-5-chloro-2,4-dimethoxypyridine



[1050] To a solution of 5-chloro-2,4-dimethoxypyridine (500.0 mg, 2.88 mmol) in AcOH (8.0 mL) was added NaOAc (236.2 mg, 2.88 mmol) and Br_2 (690.4 mg, 4.32 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the pH value of the mixture was adjusted to 7 with aq.$NaHCO_3$. The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate

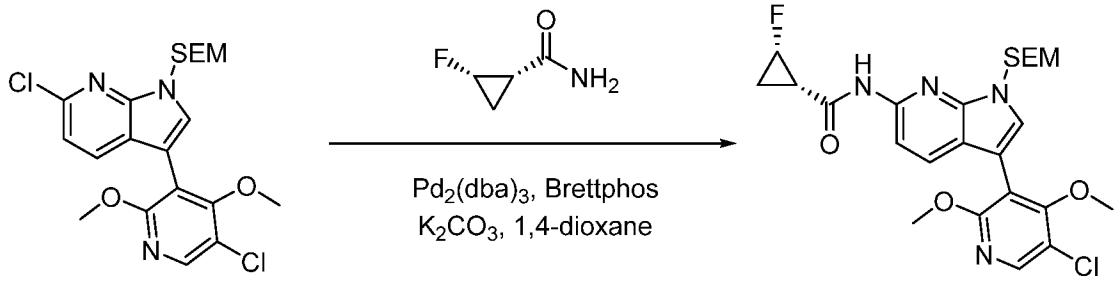
(10/1, v/v) to afford 3-bromo-5-chloro-2,4-dimethoxypyridine (450.0 mg, 61%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =251.9

Step 3: Synthesis of 5-chloro-3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-2,4-dimethoxypyridine



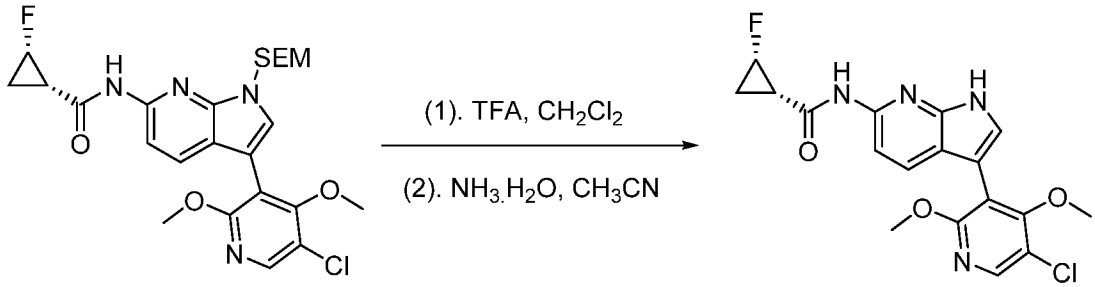
[1051] To a solution of 3-bromo-5-chloro-2,4-dimethoxypyridine (400.0 mg, 1.67 mmol) in 1,4-dioxane/H_2O (10.0/2.0 mL) was added $Pd(PPh_3)_4$ (387.6 mg, 0.33 mmol), 6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-ylboronic acid (657.5 mg, 2.01 mmol) and K_2CO_3 (695.4 mg, 5.03 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with ACN/H_2O (6/1, v/v) to afford 5-chloro-3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-2,4-dimethoxypyridine (250.0 mg, 32%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =454.1.

Step 4: Synthesis of (1S,2S)-N-[3-(5-chloro-2,4-dimethoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide



[1052] To a solution of 5-chloro-3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-2,4-dimethoxypyridine (300.0 mg, 0.66 mmol) in dioxane (10.0 mL) was added (1S,2S)-2-fluorocyclopropane-1-carboxamide (0.3 g, 3.30 mmol), $Pd_2(dba)_3$ (0.1 g, 0.13 mmol), K_2CO_3 (0.3 g, 2.64 mmol) and BrettPhos (0.1 g, 0.26 mmol) at room temperature under N_2. The resulting mixture was stirred at 100 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford (1S,2S)-N-[3-(5-chloro-2,4-dimethoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (150.0 mg, 43%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =521.2

Step 5: Synthesis of (1S,2S)-N-[3-(5-chloro-2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (Compound 231)



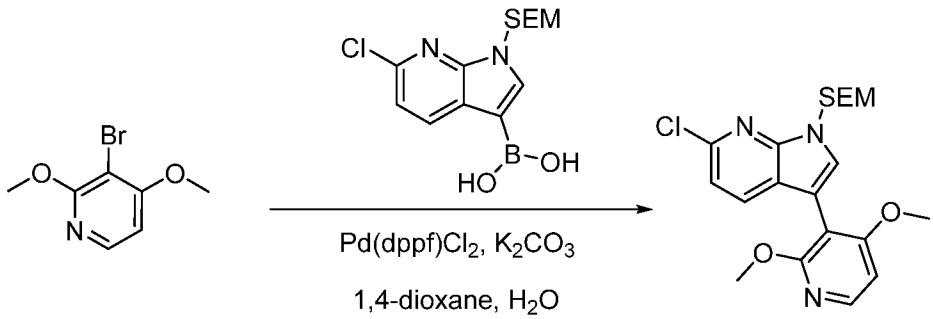
231

[1053] To a solution of (1S,2S)-N-[3-(5-chloro-2,4-dimethoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide (150.0 mg, 0.29 mmol) in DCM (2.0 mL) was added TFA (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the above residue was added $NH_3.H_2O$ (2.0 mL) and ACN (1.0 mL) at room temperature. The resulting mixture was stirred at room temperature for additional 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column, 19x250 mm, 10 μm; Mobile Phase

A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 45% B to 60% B in 8 min, Wave Length: 254 nm) to afford (1S,2S)-N-[3-(5-chloro-2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-fluorocyclopropane-1-carboxamide **(Compound 231)** (10.6 mg, 9%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =391.1. ^1H NMR (400 MHz, DMSO-d_6): δ 11.75 (s, 1H), 10.64 (s, 1H), 8.21 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.54 (s, 1H), 5.01 - 4.84 (m, 1H), 3.84 (s, 3H), 3.46 (s, 3H), 2.29 - 2.18 (m, 1H), 1.69 - 1.63 (m, 1H), 1.19 - 1.08 (m, 1H).

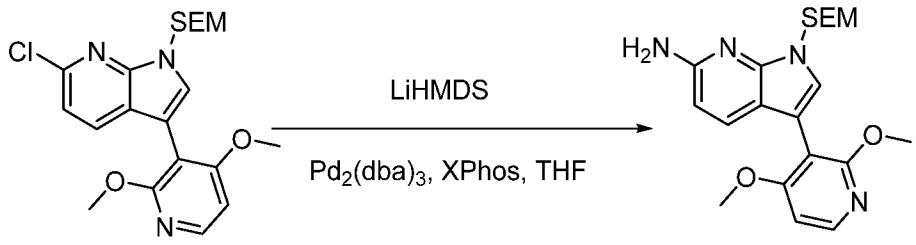
Example S210: Synthesis of (1R,2R)-N-[3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide and (1S,2S)-N-[3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (Compound 232 and Compound 233)

Step 1: Synthesis of 3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-2,4-dimethoxypyridine



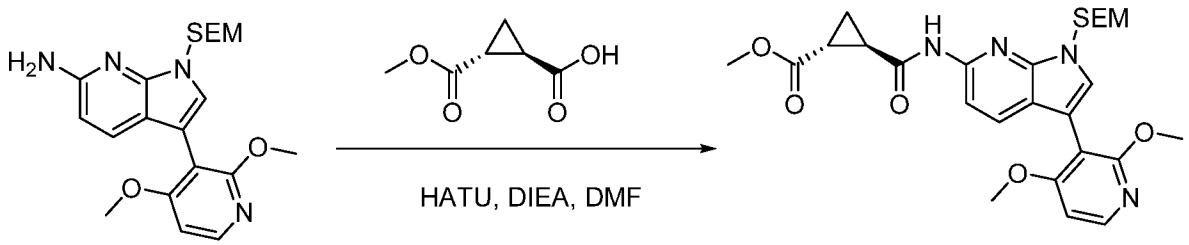
[1054] To a solution of 3-bromo-2,4-dimethoxypyridine (2.0 g, 9.17 mmol) in 1,4-dioxane (20.0 mL)/H_2O (5.0 mL) was added 6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-ylboronic acid (3.6 g, 11.00 mmol), K_2CO_3 (3.8 g, 27.52 mmol) and $Pd(dppf)Cl_2$ (671.1 mg, 0.92 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford 3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-2,4-dimethoxypyridine (1.2 g, 31%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =420.1.

Step 2: Synthesis of 3-(2,4-dimethoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine



[1055] To a solution of 3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-2,4-dimethoxypyridine (1.0 g, 2.38 mmol) in THF (40.0 mL) was added XPhos (454.0 mg, 0.95 mmol), $Pd_2(dba)_3$ (436.1 mg, 0.48 mmol) and LiHMDS (4.7 mL, 1 mol/L) at room temperature under N_2. The resulting mixture was stirred at 60 °C for 1 h. After the reaction was completed, the reaction mixture was quenched with NH_4Cl (aq) at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/1, v/v) to afford 3-(2,4-dimethoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (800.0 mg, 83%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =401.2.

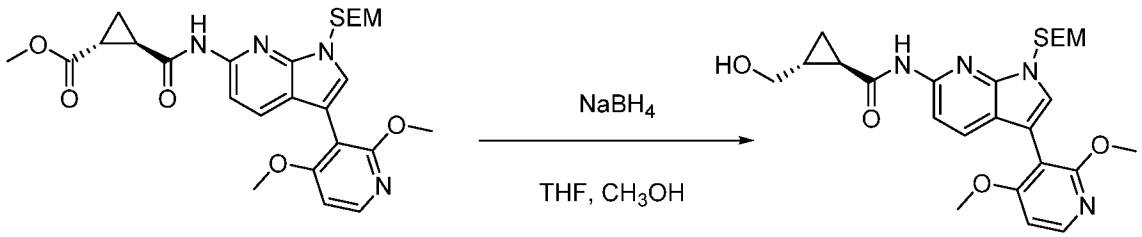
Step 3: Synthesis of Methyl (trans)-2-{[3-(2,4-dimethoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate



[1056] To a solution of 3-(2,4-dimethoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (750.0 mg, 1.87 mmol) in DMF (20.0 mL) was added trans-2-(methoxycarbonyl)cyclopropane-1-carboxylic acid (323.2 mg, 2.24 mmol), DIEA (363.0 mg, 2.81 mmol) and HATU (1.1 g, 2.81 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The

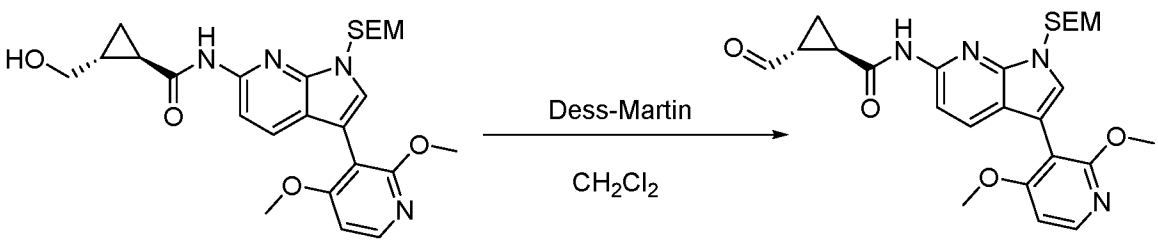
filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford methyl (trans)-2-{[3-(2,4-dimethoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate (860.0 mg, 87%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =527.2.

Step 4: Synthesis of trans-N-[3-(2,4-dimethoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide



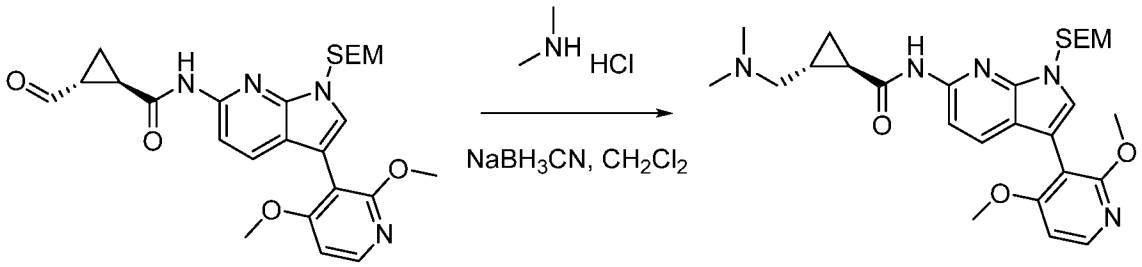
[1057] To a solution of methyl (trans)-2-{[3-(2,4-dimethoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate (850.0 mg, 1.61 mmol) in THF (20.0 mL)/MeOH (30.0 mL) was added $NaBH_4$ (3.1 g, 80.70 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/99, v/v) to afford trans-N-[3-(2,4-dimethoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide (530.0 mg, 65%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =499.2.

Step 5: Synthesis of trans-N-[3-(2,4-dimethoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide



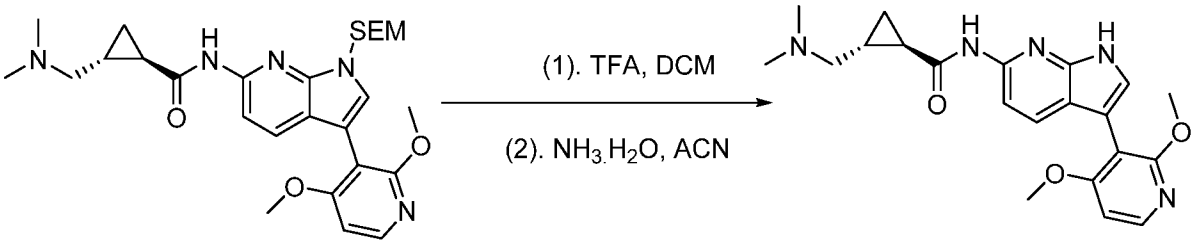
[1058] To a solution of trans-N-[3-(2,4-dimethoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide (500.0 mg, 1.00 mmol) in CH_2Cl_2 (20.0 mL) was added Dess-Martin (637.9 mg, 1.50 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford trans-N-[3-(2,4-dimethoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (495.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =497.2.

Step 6: Synthesis of trans-N-(3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide



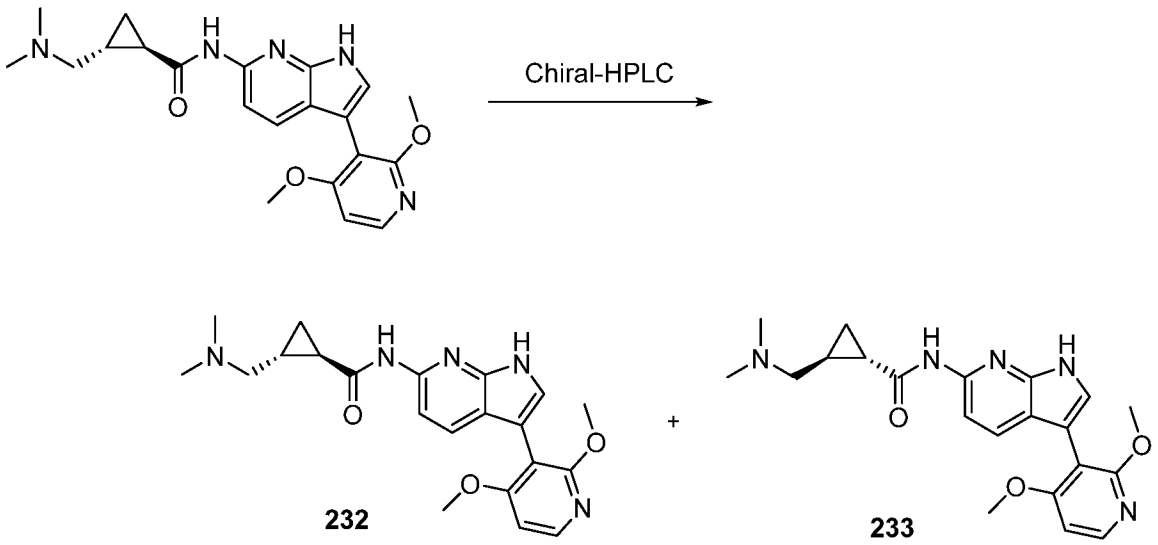
[1059] To a solution of trans-N-[3-(2,4-dimethoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (495.0 mg, 0.99 mmol) in DCM (20.0 mL) was added dimethylamine hydrochloride (245.0 mg, 3.02 mmol) and $NaBH_3CN$ (68.5 mg, 3.02 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the reaction was quenched with water at room temperature. The resulting mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford trans-N-(3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (170.0 mg, 32%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =526.3.

Step 7: Synthesis of trans-N-(3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide



[1060] To a solution of trans-N-(3-(2,4-dimethoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (150.0 mg, 0.29 mmol) in CH_2Cl_2 (8.0 mL) was added TFA (8.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated under reduced pressure. To the residue in ACN (5.0 mL) was added $NH_3.H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (66/34, v/v) to afford trans-N-(3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (80.0 mg, 70%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =396.1.

Step 8: Synthesis of (1R,2R)-N-[3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide and (1S,2S)-N-[3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (Compound 232 and Compound 233)



[1061] The product trans-N-(3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (80.0 mg, 0.20 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SC, 2x25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH) -- HPLC, Mobile Phase B: MeOH: EtOH=1:1--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 14.5 min; Wave Length: 220/254 nm) to afford N-[3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide Enantiomer 1 (8.7 mg, 21%) as a white solid and N-[3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide Enantiomer 2 (7.8 mg, 20%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 232 and 233** in Table 1.

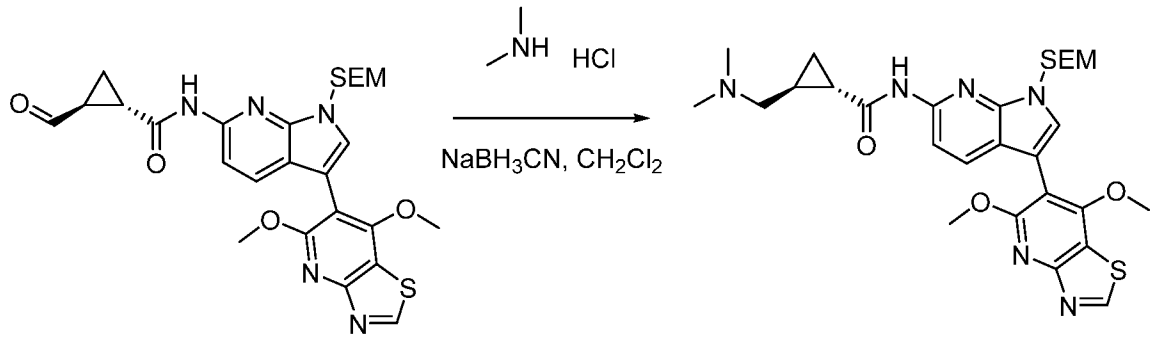
[1062] **N-[3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide Enantiomer 1:** Retention Time 1=10.43 min; LCMS (ESI, m/z): $[M+H]^+$ =396.1. ^1H NMR (400 MHz, DMSO-d_6): δ 11.51 (s, 1H), 10.51 (s, 1H), 8.07 - 8.02 (m, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.60 - 7.55 (m, 1H), 7.37 (d, J = 2.4 Hz, 1H), 6.89 - 6.82 (m, 1H), 3.98 - 3.80 (m, 6H), 2.35 - 2.27 (m, 1H), 2.19 - 2.15 (m, 7H), 1.96 - 1.89 (m, 1H), 1.36 - 1.28 (m, 1H), 1.11 - 1.04 (m, 1H), 0.72 -0.68 (m, 1H).

[1063] **N-[3-(2,4-dimethoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide Enantiomer 2:** Retention Time 2=13.15 min; LCMS (ESI, m/z): $[M+H]^+$ =396.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.50 (s, 1H), 10.51 (s, 1H), 8.07 (d, J = 5.6 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 8.8 Hz,

1H), 7.37 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 6.0 Hz, 1H), 3.99 - 3.72 (m, 6H), 2.35 - 2.27 (m, 1H), 2.19 - 2.14 (m, 7H), 1.90 - 1.85 (m, 1H), 1.34 - 1.24 (m, 1H), 1.06 - 1.03 (m, 1H), 0.72 - 0.70 (m, 1H).

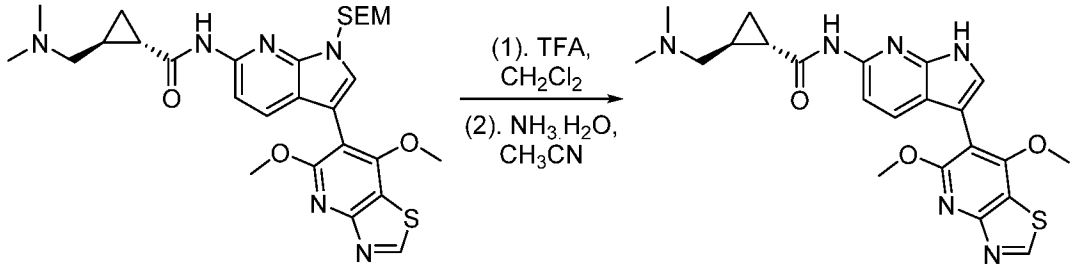
Example S211: Synthesis of (1S,2S)-N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide and (1R,2R)-N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (Compound 234 and Compound 235)

Step 1: Synthesis of Trans-N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl)-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide



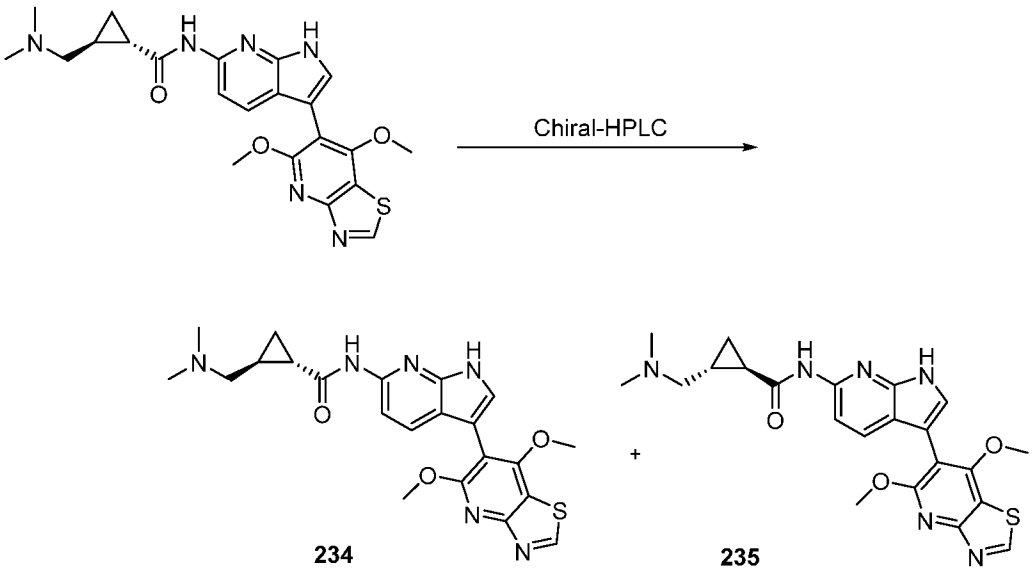
[1064] To a solution of trans-N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl)-2-formylcyclopropane-1-carboxamide (400.0 mg, 0.72 mmol) in CH_2Cl_2 (4.0 mL) was added dimethylamine hydrochloride (176.7 mg, 2.17 mmol) and $NaBH_3CN$ (136.2 mg, 2.17 mmol) at room temperature. The resulting mixture was stirred at room temperature for 0.5 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography with CH_2Cl_2/CH_3OH (12/1, v/v)) to afford trans-N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl)-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (300.0 mg, 75%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =583.2.

Step 2: Synthesis of Trans-N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide



[1065] To a solution of trans-N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl)-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (300.0 mg, 0.52 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (3.0 mL) was added $NH_3.H_2O$ (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for additional 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with H_2O/ACN (46/54, v/v) to afford trans-N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (60.0 mg, 25%) as a green solid. LCMS (ESI, m/z): $[M+H]^+$ =453.2.

Step 3: Synthesis of (1S,2S)-N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide and (1R,2R)-N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (Compound 234 and Compound 235)



[1066] The product of trans-N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (60.0 mg, 0.13 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SC, 2x25 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: 30% B to 30% B in 13 min; Wave Length: 220/254 nm) to afford N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide Enantiomer 1 (17.6 mg, 58%) as a green solid and N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide Enantiomer 2 (18.3 mg, 60%) as a green solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 234 and 235** in Table 1.

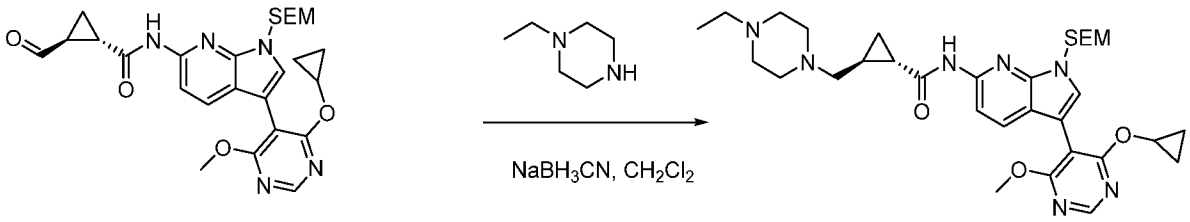
[1067] N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide Enantiomer 1: Retention Time 1: 8.92 min; LCMS (ESI, m/z): $[M+H]^+$ =453.1. ^1H NMR (400 MHz, DMSO-d_6): δ 11.66 (d, J = 1.6 Hz, 1H), 10.58 (s, 1H), 9.57 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 2.4 Hz, 1H), 3.91 - 3.87 (m, 6H), 2.33 - 2.15 (m, 8H), 1.91 - 1.85 (m, 1H), 1.36 - 1.32 (m, 1H), 1.07 - 1.01 (m, 1H), 0.72 - 0.65 (m, 1H).

[1068] N-(3-{5,7-dimethoxy-[1,3]thiazolo[4,5-b]pyridin-6-yl}-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide Enantiomer 2: Retention Time 2: 12.18 min; LCMS (ESI, m/z): $[M+H]^+$ =453.1. ^1H NMR (400 MHz,

DMSO- d_6): δ 11.66 (d, J = 1.6 Hz, 1H), 10.59 (s, 1H), 9.57 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 2.4 Hz, 1H), 3.91 (s, 6H), 2.39 - 2.20 (m, 8H), 1.93 - 1.88 (m, 1H), 1.38 - 1.33 (m, 1H), 1.08 - 1.05 (m, 1H), 0.76 - 0.65 (m, 1H).

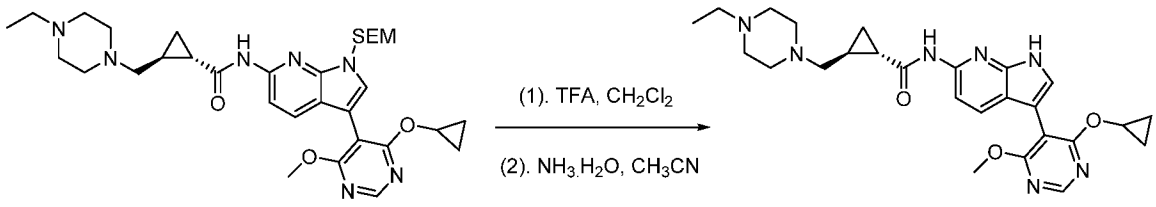
Example S212: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide and (1R,2R)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (Compound 236 and Compound 237)

Step 1: Synthesis of trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide



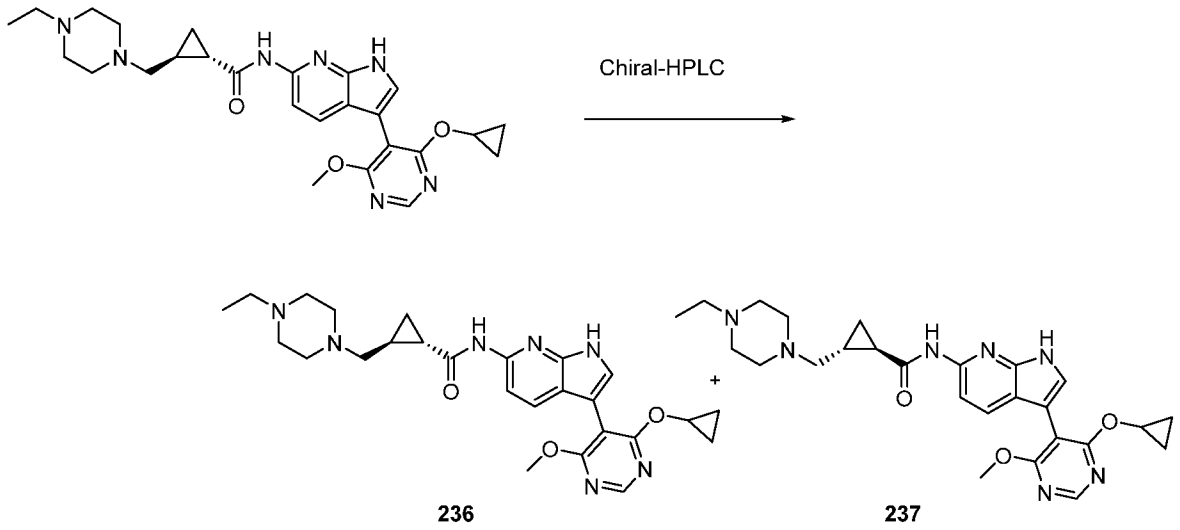
[1069] To a solution of trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (170.0 mg, 0.33 mmol) in DCM (15.0 mL) was added 1-ethylpiperazine (111.2 mg, 0.98 mmol) and $NaBH_3CN$ (61.2 mg, 0.98 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (5/1, v/v) to afford trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (100.0 mg, 49%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =622.3.

Step 2: Synthesis of trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide



[1070] To a solution of trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (300.0 mg, 0.48 mmol) in CH_2Cl_2 (6.0 mL) was added TFA (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (6.0 mL) was added $NH_3 \cdot H_2O$ (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with ACN/H_2O (1/1, v/v) to afford trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (100.0 mg, 42%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =492.3.

Step 3: Synthesis of (1S,2S)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide and (1R,2R)-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (Compound 236 and Compound 237)



[1071] The trans-N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide (100.0 mg, 0.20 mmol) was separated by Prep-Chiral-HPLC with the following conditions Column: Column (CHIRAL ART Cellulose-SC, 2x25 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: 20% B to 20% B in 17 min; Wave Length: 220/254 nm) to afford N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 1 (21.5 mg, 42%) as a white solid and N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 2 (20.6 mg, 41%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 236 and 237** in Table 1.

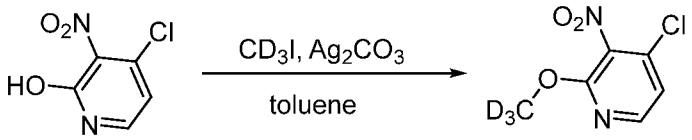
[1072] N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 1: Retention Time 1: 18.75 min; LCMS (ESI, m/z): $[M+H]^+$ =492.3. ^{1}H NMR(400 MHz, DMSO-d_6): δ 11.62 (s, 1H), 10.56 (s, 1H), 8.49 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 4.39 - 4.34 (m, 1H), 3.92 (s, 3H), 2.51 - 2.21 (m, 10H), 1.91 - 1.89 (m, 1H), 1.34 - 1.32 (m, 1H), 1.06 - 0.96 (m, 4H), 0.78 - 0.62 (m, 5H).

[1073] N-[3-(4-cyclopropoxy-6-methoxypyrimidin-5-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(4-ethylpiperazin-1-yl)methyl]cyclopropane-1-carboxamide Enantiomer 2: Retention Time 2: 14.10 min; LCMS (ESI, m/z): $[M+H]^+$ =492.3. ^{1}H NMR(400 MHz,

DMSO-d_6): δ 11.62 (s, 1H), 10.56 (s, 1H), 8.49 (s, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 4.39 - 4.34 (m, 1H), 3.92 (s, 3H), 2.51 - 2.21 (m, 7H), 1.91 - 1.89 (m, 1H), 1.34 - 1.32 (m, 1H), 1.06 - 0.96 (m, 4H), 0.78 - 0.62 (m, 5H).

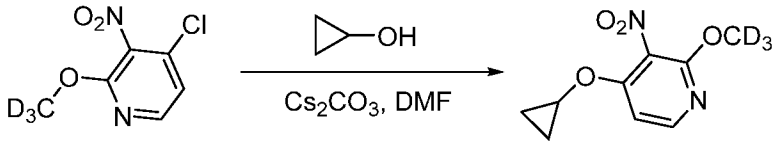
Example S213: Synthesis of (1R,2R)-N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide and (1S,2S)-N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (Compound 238 and Compound 239)

Step 1: Synthesis of 4-chloro-2-(methoxy-d3)-3-nitropyridine



[1074] To a solution of 4-chloro-3-nitropyridin-2-ol (12.0 g, 68.97 mmol) in toluene (150.0 mL) was added CD_3I (20.0 g, 137.94 mmol) and Ag_2CO_3 (28.6 g, 103.46 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (66/34, v/v) to afford 4-chloro-2-(methoxy-d3)-3-nitropyridine (8.0 g, 60%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =192.0.

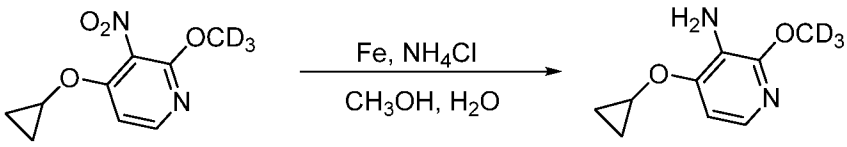
Step 2: Synthesis of 4-cyclopropoxy-2-(methoxy-d3)-3-nitropyridine



[1075] To a solution of 4-chloro-2-(methoxy-d3)-3-nitropyridine (8.0 g, 41.76 mmol) in DMF (100.0 mL) was added cyclopropanol (3.6 g, 62.63 mmol) and Cs_2CO_3 (20.4 g, 62.63 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (74/26, v/v)

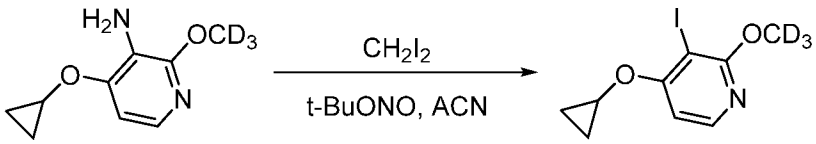
to afford 4-cyclopropoxy-2-(methoxy-d3)-3-nitropyridine (4.7 g, 52%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =214.1.

Step 3: Synthesis of 4-cyclopropoxy-2-(methoxy-d_3)pyridin-3-amine



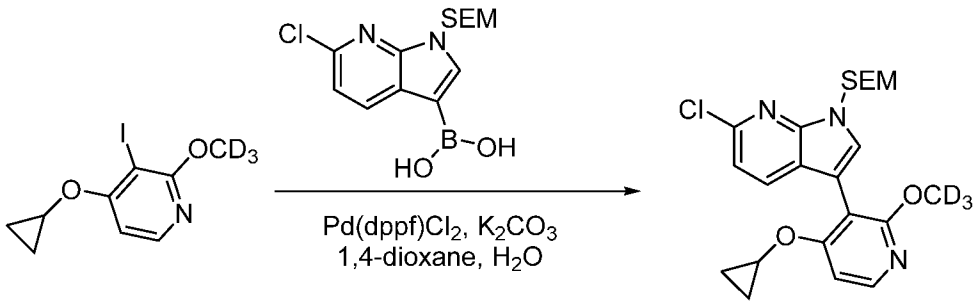
[1076] To a solution of 4-cyclopropoxy-2-(methoxy-d3)-3-nitropyridine (4.7 g, 22.04 mmol) in MeOH (30.0 mL)/H_2O (6.0 mL) was added NH_4Cl (4.7 g, 88.18 mmol) at room temperature. Then Fe (3.7 g, 66.13 mmol) was added to the mixture at 80 °C. The resulting mixture was stirred at 80 °C for 3 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (78/22, v/v) to afford 4-cyclopropoxy-2-(methoxy-d_3)pyridin-3-amine (3.1 g, 76%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =184.1.

Step 4: Synthesis of 4-cyclopropoxy-3-iodo-2-(methoxy-d3)pyridine



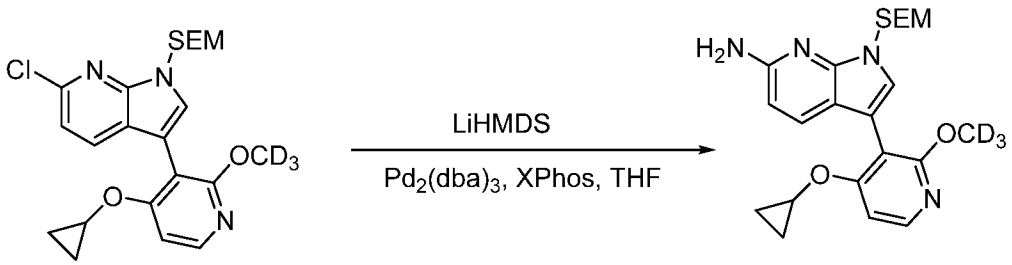
[1077] To a solution of 4-cyclopropoxy-2-(methoxy-d3)pyridin-3-amine (3.1 g, 16.92 mmol) in MeCN (35.0 mL) were added CH_2I_2 (4.5 g, 16.92 mmol) and tert-butyl nitrite (5.2 g, 50.76 mmol) at room temperature. The resulting mixture was stirred at 80 C for 2 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (82/18, v/v) to afford 4-cyclopropoxy-3-iodo-2-(methoxy-d3)pyridine (2.8 g, 56%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =295.0.

Step 5: Synthesis of 6-chloro-3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine



[1078] To a solution of 4-cyclopropoxy-3-iodo-2-(methoxy-d3)pyridine (2.8 g, 9.52 mmol) in 1,4-dioxane (24.0 mL) and H_2O (6.0 mL) were added (6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)boronic acid (3.1 g, 9.52 mmol), K_2CO_3 (3.9 g, 28.56 mmol) and $Pd(dppf)Cl_2$ (1.3 g, 1.90 mmol) at room temperature under N_2. The mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (81/19, v/v) to afford 6-chloro-3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (2.0 g, 46%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =449.2.

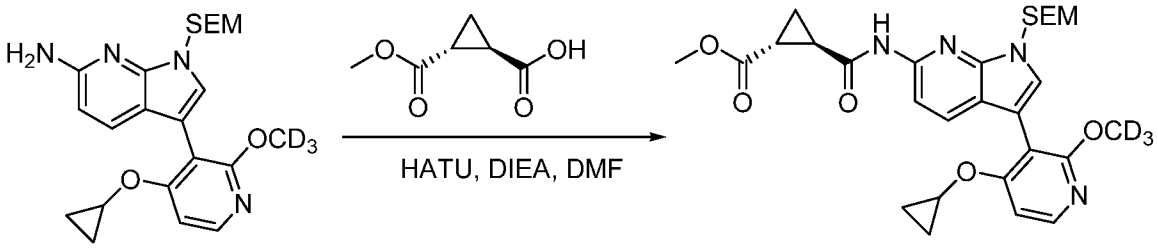
Step 6: Synthesis of 3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine



[1079] To a solution of 6-chloro-3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (2.0 g, 4.45 mmol) in THF (20.0 mL) were added $Pd_2(dba)_3$ (815.7 mg, 0.89 mmol), XPhos (849.3 mg, 1.78 mmol) and LiHMDS (8.9 mL, 1.0 mol/L) at room temperature under N_2. The resulting mixture was stirred at 60 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum

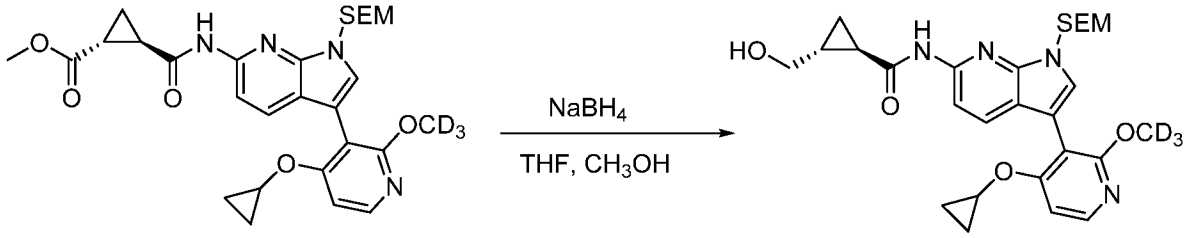
ether/ethyl acetate (87/13, v/v) to afford 3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (1.2 g, 62%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =430.2.

Step 7: Synthesis of Methyl (trans)-2-((3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamoyl)cyclopropane-1-carboxylate



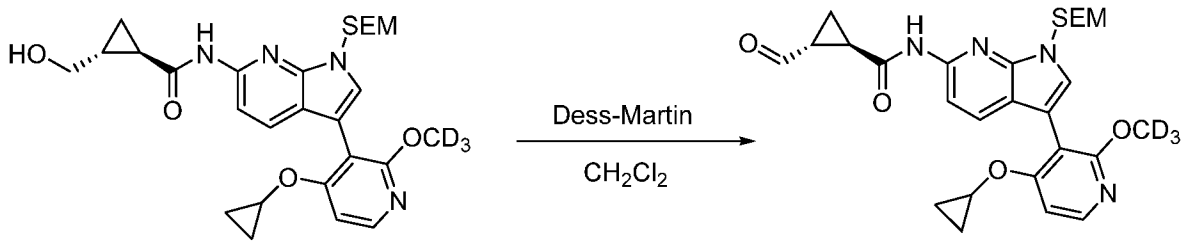
[1080] To a solution of 3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (1.2 g, 2.79 mmol) in DMF (15.0 mL) was added trans-2-(methoxycarbonyl)cyclopropane-1-carboxylic acid (483.1 mg, 3.35 mmol), DIEA (1.8 g, 13.97 mmol) and HATU (1.6 g, 4.19 mmol) at 0 C under N_2. The resulting mixture was stirred at 0 °C for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (80/20, v/v) to afford methyl (trans)-2-((3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamoyl)cyclopropane-1-carboxylate (1.2 g, 77%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =556.3.

Step 8: Synthesis of Trans-N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(hydroxymethyl)cyclopropane-1-carboxamide:



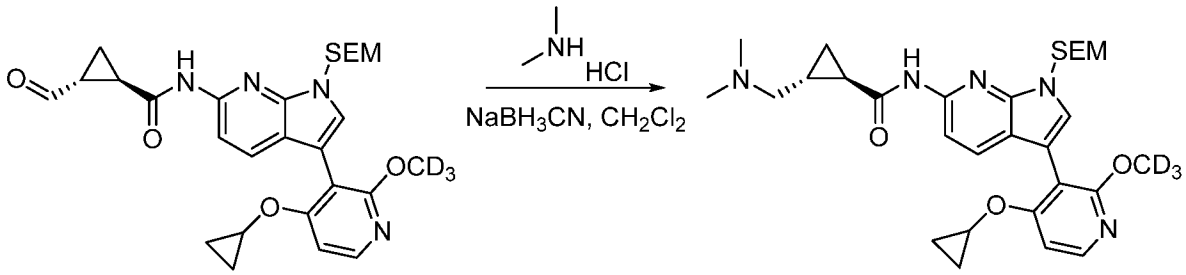
[1081] To a solution of methyl (trans)-2-((3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)carbamoyl)cyclopropane-1-carboxylate (1.2 g, 2.16 mmol) in THF (12.0 mL)/CH_3OH (3.0 mL) was added $NaBH_4$ (1.6 g, 43.18 mmol) at room temperature. The resulting mixture was stirred at room temperature for 6 h. After the reaction was completed, the reaction mixture was quenched with water at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (55/45, v/v) to afford trans-N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(hydroxymethyl)cyclopropane-1-carboxamide (750.0 mg, 65%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =528.3.

Step 9: Synthesis of Trans-N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-formylcyclopropane-1-carboxamide



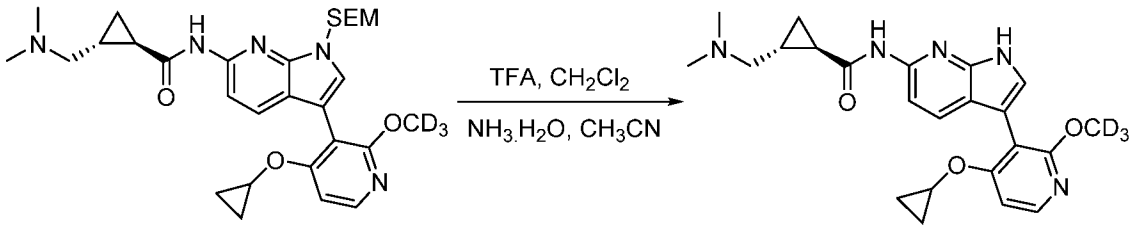
[1082] To a solution of trans-N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(hydroxymethyl)cyclopropane-1-carboxamide (750.0 mg, 1.42 mmol) in CH_2Cl_2 (10.0 mL) was added Dess-Martin (904.2 mg, 2.13 mmol) at 0 C under N_2. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with $NaHCO_3$(aq), brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford trans-N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-formylcyclopropane-1-carboxamide (700.0 mg, crude) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ =526.2.

Step 10: Synthesis of Trans-N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide



[1083] To a solution of trans-N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-formylcyclopropane-1-carboxamide (700.0 mg, crude) in CH_2Cl_2 (10.0 mL) were added dimethylamine hydrochloride (325.7 mg, 4.00 mmol) and $NaBH_3CN$ (251.0 mg, 4.00 mmol) at 0 C under N_2. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum CH_2Cl_2/CH_3OH (10/01, v/v) to afford trans-N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (200.0 mg, 23%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =555.3.

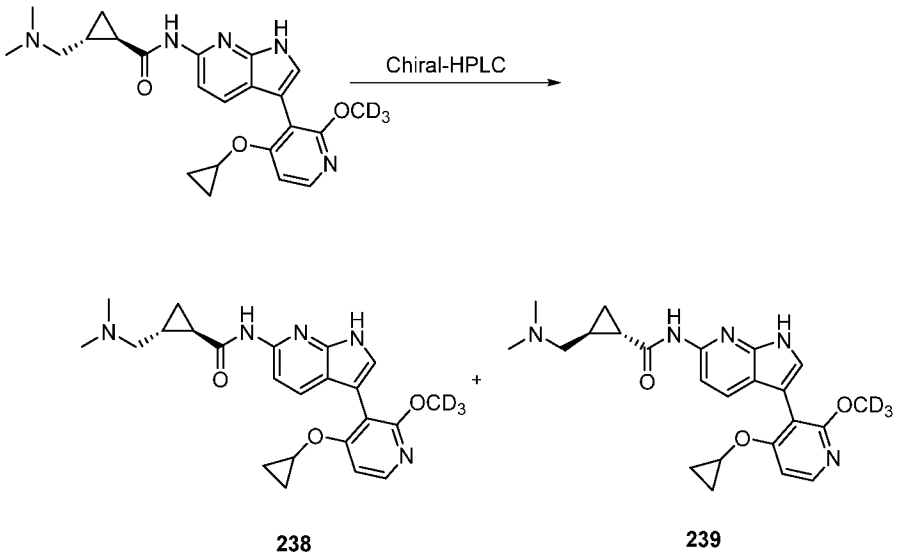
Step 11: Synthesis of Trans-N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide



[1084] To a solution of trans-N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (200.0 mg, 0.36 mmol) in CH_2Cl_2 (1.5 mL) was added TFA (1.5 mL) at room temperature. The resulting mixture was stirred at room

temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (1.5 mL) was added $NH_3 \cdot H_2O$ (1.5 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_3CN/H_2O (55/45, v/v) to afford trans-N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (50.0 mg, 32%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =425.2.

Step 12: Synthesis of (1R,2R)-N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide and **(1S,2S)-N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (Compound 238 and Compound 239)**



238 239

[1085] The product trans-N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide (50.0 mg, 0.12 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SC, 2x25 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: 10% B to 10% B in 12.5 min; Wave Length: 220/254 nm) to afford N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-

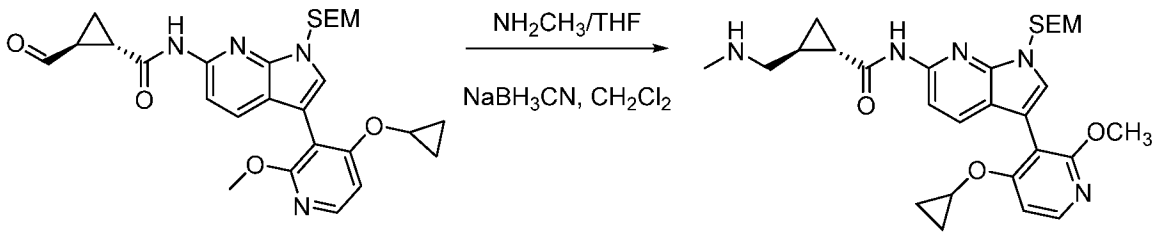
((dimethylamino)methyl)cyclopropane-1-carboxamide Enantiomer 1 (14.4 mg, 57%) as a white solid and N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide Enantiomer 2 (13.3 mg, 52%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 238 and 239** in Table 1.

[1086] N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide Enantiomer 1: Retention Time 1: 8.39 min; LCMS (ESI, m/z): $[M+H]^+$ = 425.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.50 (d, J = 2.0 Hz, 1H), 10.52 (s, 1H), 8.07 (d, J = 5.6 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 6.0 Hz, 1H), 3.94 - 3.91 (m, 1H), 2.35 - 2.30 (m, 1H), 2.24 - 2.19 (m, 7H), 1.91 - 1.88 (m, 1H), 1.37 - 1.33 (m, 1H), 1.07 - 1.03 (m, 1H), 0.81 - 0.76 (m, 2H), 0.74 - 0.69 (m, 1H), 0.66 - 0.62 (m, 2H).

[1087] N-(3-(4-cyclopropoxy-2-(methoxy-d3)pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((dimethylamino)methyl)cyclopropane-1-carboxamide Enantiomer 2: Retention Time 2: 11.34 min; LCMS (ESI, m/z): $[M+H]^+$ = 425.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.50 (d, J = 2.0 Hz, 1H), 10.52 (s, 1H), 8.07 (d, J = 5.6 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 6.0 Hz, 1H), 3.94 - 3.91 (m, 1H), 2.34 - 2.29 (m, 1H), 2.21 - 2.18 (m, 7H), 1.91 - 1.89 (m, 1H), 1.37 - 1.32 (m, 1H), 1.07 - 1.03 (m, 1H), 0.81 - 0.76 (m, 2H), 0.73 - 0.69 (m, 1H), 0.66 - 0.62 (m, 2H).

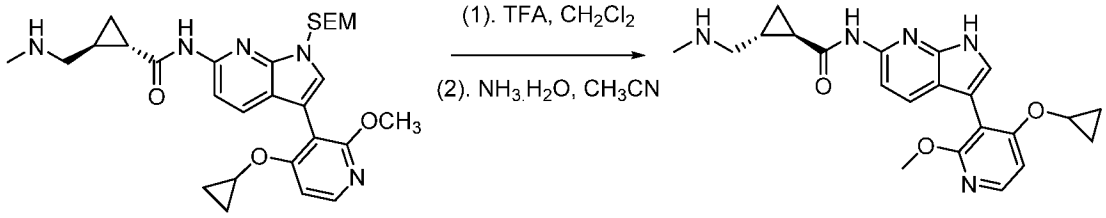
Example S214: Synthesis of (1R,2R)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((methylamino)methyl)cyclopropanecarboxamide and (1S,2S)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((methylamino)methyl)cyclopropanecarboxamide (Compound 240 and Compound 241)

Step 1: Synthesis of trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((methylamino)methyl)cyclopropane-1-carboxamide



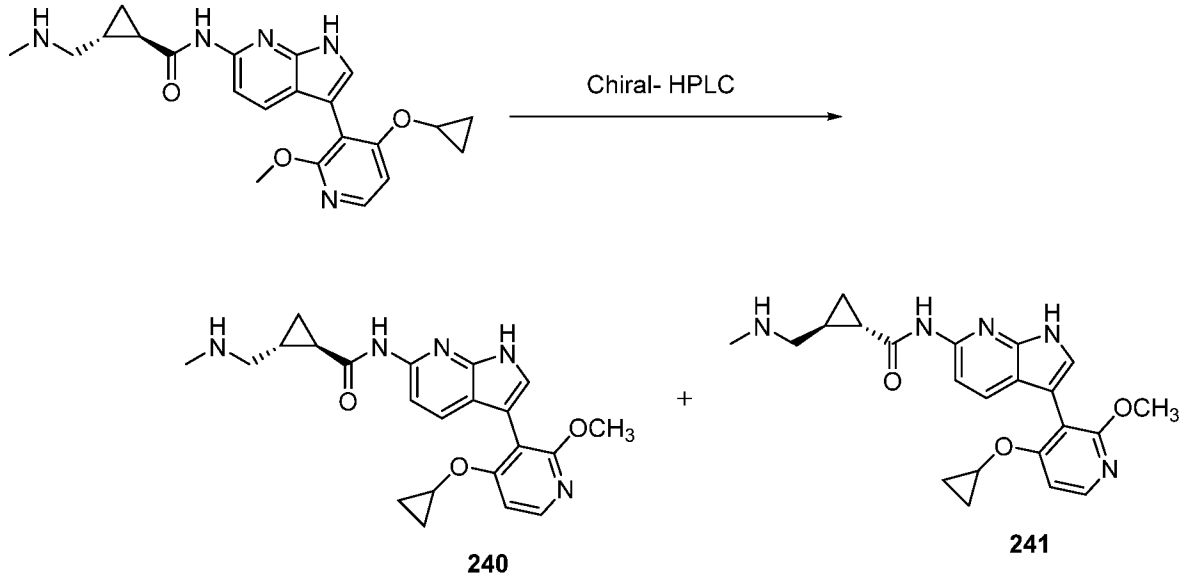
[1088] To a solution of trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-formylcyclopropane-1-carboxamide (450.0 mg, 0.87 mmol) in CH_2Cl_2 (5.0 mL) was added methanamine (0.2 mL, 2 mol/L in THF) and $NaBH_3CN$ (162.3 mg, 2.58 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reversed phase flash column chromatography with water/MeOH (60/40, v/v) to afford trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((methylamino)methyl)cyclopropane-1-carboxamide (100.0 mg, 22%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =538.3.

Step 2: Synthesis of trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((methylamino)methyl)cyclopropane-1-carboxamide



[1089] To a solution of trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((methylamino)methyl)cyclopropane-1-carboxamide (130.0 mg, 0.24mmol) in CH_2Cl_2 (2.0 mL) was added TFA (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3.H_2O$ (4.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reversed phase flash column chromatography with water/MeOH (0/100, v/v) to afford trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((methylamino)methyl)cyclopropane-1-carboxamide (70.0 mg, 71%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =408.2.

Step 3: Synthesis of (1R,2R)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((methylamino)methyl)cyclopropanecarboxamide and (1S,2S)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((methylamino)methyl)cyclopropanecarboxamide (Compound 240 and Compound 241)



240 241

[1090] The compound trans--N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((methylamino)methyl)cyclopropanecarboxamide (70.0 mg, 0.17 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Amylose-SA, 2×25 cm, 5 um; 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 19 min; 254 nm) to afford N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((methylamino)methyl)cyclopropane-1-carboxamide Enantiomer 1 (5.5 mg, 15%) as a white solid and N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((methylamino)methyl)cyclopropane-1-carboxamide Enantiomer 2 (6.1 mg, 18%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 240 and 241** in Table 1.

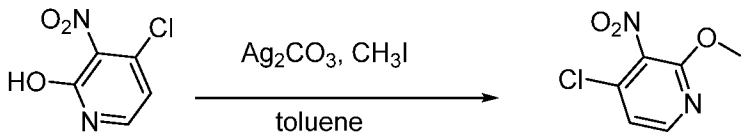
[1091] **N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((methylamino)methyl)cyclopropane-1-carboxamide Enantiomer 1:** Retention Time 1: 22.47 min; LCMS (ESI, m/z): $[M+H]^+$ =408.1. ^1H NMR (400 MHz, DMSO-d_6): δ 11.55 (s, 1H), 10.49 (d, J = 4.8 Hz, 1H), 8.08 (d, J = 5.6 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.56 (d,

J = 8.4 Hz, 1H), 7.35 (s, 1H), 7.14 (d, J = 6.0 Hz, 1H), 4.00 - 3.92 (m, 1H), 3.82 (s, 3H), 2.68 - 2.60 (m, 1H), 2.34 (s, 3H), 1.96 - 1.93 (m, 1H), 1.49 - 1.42 (m, 1H), 1.05 - 1.03 (m, 1H), 0.88 - 0.78 (m, 3H), 0.72 - 0.64 (m, 2H).

[1092] N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-((methylamino)methyl)cyclopropane-1-carboxamide Enantiomer 2: Retention Time 2: 26.92 min; LCMS (ESI, m/z): $[M+H]^+$ =408.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.55 (s, 1H), 10.47 (s, 1H), 8.07 (d, J = 5.6 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.35 (s, 1H), 7.14 (d, J = 5.6 Hz, 1H), 3.95 - 3.91 (m, 1H), 3.81 (s, 3H), 2.68 - 2.60 (m, 1H), 2.32 (s, 3H), 1.97 - 1.91 (m, 1H), 1.49 - 1.42 (m, 1H), 1.05 - 1.02 (m, 1H), 0.81 - 0.74 (m, 3H), 0.70 - 0.64 (m, 2H).

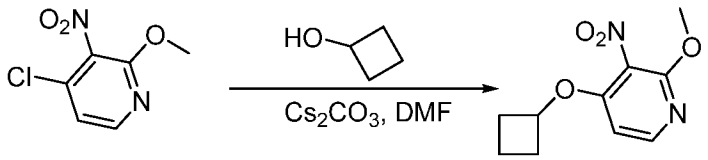
Example S215: Synthesis of (1S,2S)-N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide and (1R,2R)-N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (Compound 242 and Compound 243)

Step 1: Synthesis of 4-chloro-2-methoxy-3-nitropyridine



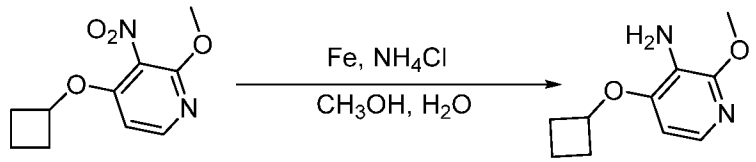
[1093] To a solution of 4-chloro-3-nitropyridin-2-ol (30.0 g, 171.88 mmol) in toluene (900.0 mL) was added Ag_2CO_3 (71.1 g, 257.82 mmol) and CH_3I (48.8 g, 343.76 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 1 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/9, v/v) to afford 4-chloro-2-methoxy-3-nitropyridine (18.7 g, 58%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =189.0.

Step 2: Synthesis of 4-cyclobutoxy-2-methoxy-3-nitropyridine



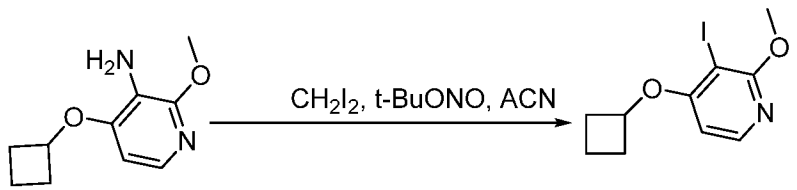
[1094] To a solution of 4-chloro-2-methoxy-3-nitropyridine (18.7 g, 99.17 mmol) in DMF (600.0 mL) was added cyclobutanol (10.7 g, 148.75 mmol) and Cs_2CO_3 (48.5 g, 148.75 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 1 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/9, v/v) to afford 4-cyclobutoxy-2-methoxy-3-nitropyridine (13.8 g, 62%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =225.1

Step 3: Synthesis of 4-cyclobutoxy-2-methoxypyridin-3-amine



[1095] To a solution of 4-cyclobutoxy-2-methoxy-3-nitropyridine (13.8 g, 61.55 mmol) in methanol/H_2O (100.0 mL/100 mL) was added NH_4Cl (13.2 g, 246.19 mmol) and Fe (10.3 g, 184.64 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 1 h. After the reaction was completed, the resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/10, v/v) to afford 4-cyclobutoxy-2-methoxypyridin-3-amine (8.5 g, 71%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =195.1.

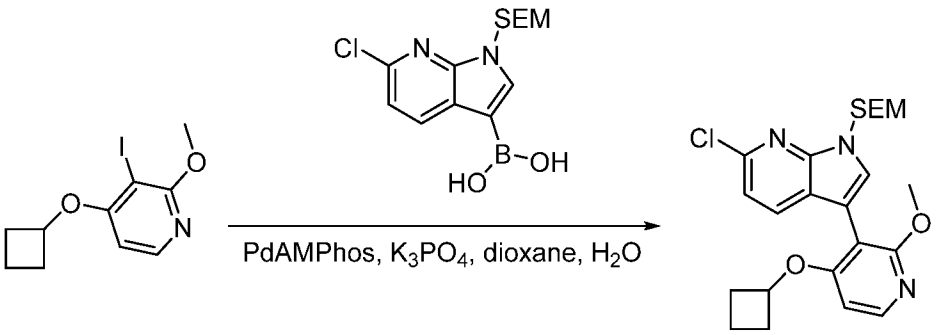
Step 4: Synthesis of 4-cyclobutoxy-3-iodo-2-methoxypyridine



[1096] To a solution of 4-cyclobutoxy-2-methoxypyridin-3-amine (8.5 g, 43.76 mmol) in CAN (300.0 mL) was added CH_2I_2 (11.7 g, 43.76 mmol) and t-$BuNO_2$ (20.3 g, 196.93 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 1 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by

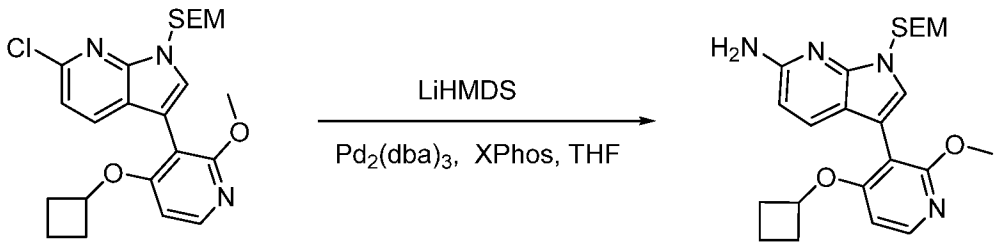
flash column chromatography with petroleum ether/ethyl acetate (1/9, v/v) to afford 4-cyclobutoxy-3-iodo-2-methoxypyridine (4.2 g, 32%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =306.0.

Step 5: Synthesis of 3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-cyclobutoxy-2-methoxypyridine



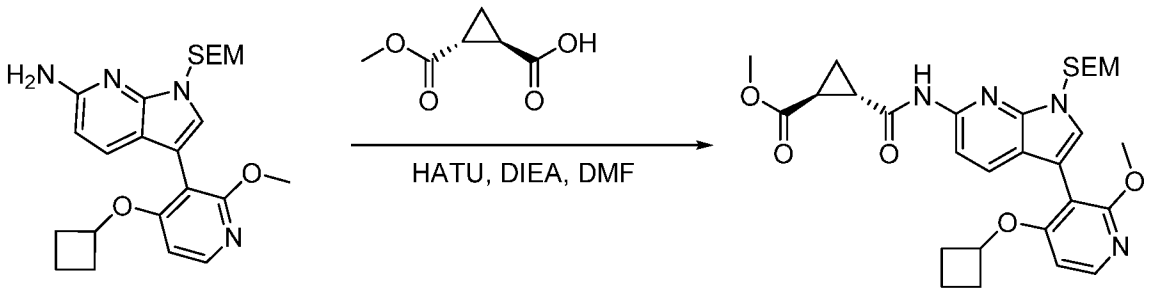
[1097] To a solution of 4-cyclobutoxy-3-iodo-2-methoxypyridine (2.1 g, 10.94 mmol) in 1,4-dioxane/ H_2O (100.0 mL/20.0 mL) was added 6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-ylboronic acid (1.9 g, 5.77 mmol), K_3PO_4 (3.8 g, 17.30 mmol) and PdAMPhos (0.8 g, 1.15 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 1 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/9, v/v) to afford 3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-cyclobutoxy-2-methoxypyridine (2.0 g, 73%) as a brown oil. LCMS (ESI, m/z): $[M+H]^+$ =460.2.

Step 6: Synthesis of 3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine



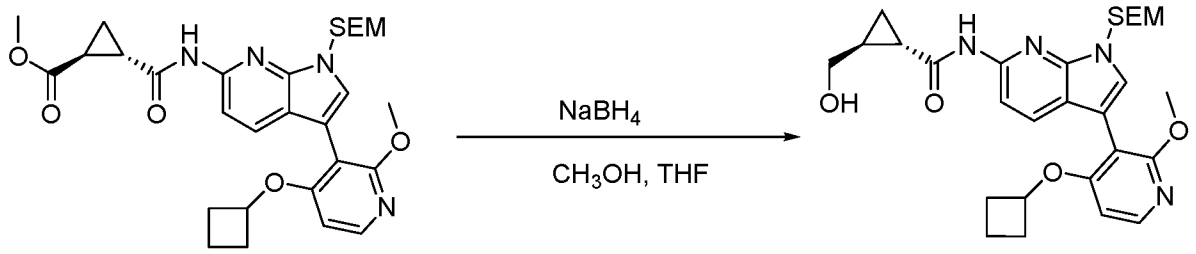
[1098] To a solution of 3-(6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-3-yl)-4-cyclobutoxy-2-methoxypyridine (2.0 g, 4.35 mmol) in THF (60.0 mL) was added $Pd_2(dba)_3$ (0.4 g, 0.44 mmol), XPhos (0.6 g, 1.30 mmol) and LiHMDS (13.0 mL, 1 mol/L) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 1 h. After the reaction was completed, the reaction was quenched by the addition of aq. NH_4Cl at 0 °C and then extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (1/4, v/v) to afford 3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (1.7 g, 89%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =441.2.

Step 7: Synthesis of Methyl trans-2-{[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate



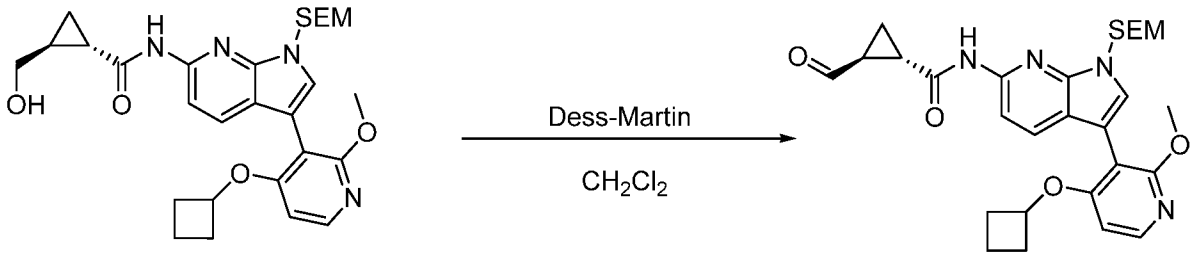
[1099] To a solution of 3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (1.7 g, 3.86 mmol) in DMF (40.0 mL) was added DIEA (2.5 g, 19.29 mmol), trans-2-(methoxycarbonyl)cyclopropane-1-carboxylic acid (0.7 g, 4.63 mmol) and HATU (1.8 g, 4.63 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (7/1, v/v) to afford methyl trans-2-{[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate (853.0 mg, 46%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =567.3.

Step 8: Synthesis of Trans-N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide



[1100] To a solution of methyl trans-2-{[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}cyclopropane-1-carboxylate (800.0 mg, 1.41 mmol) in CH_3OH/THF (6.0 mL/9.0 mL) was added $NaBH_4$ (534.1 mg, 14.12 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (6/1, v/v) to afford trans-N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide (651.4 mg, 86%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =539.3.

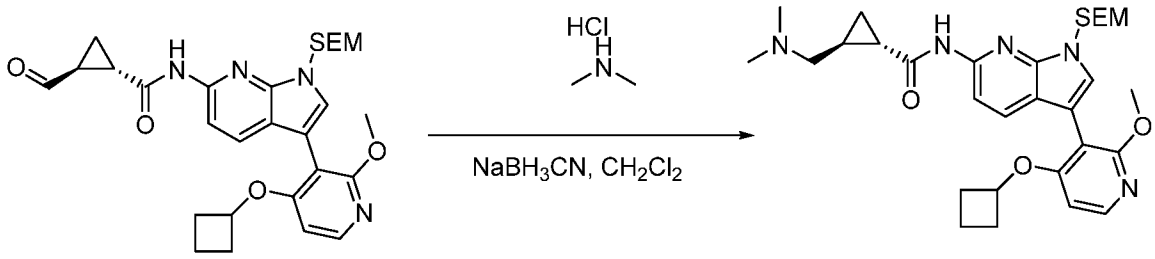
Step 9: Synthesis of Trans-N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide



[1101] To a solution of trans-N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-(hydroxymethyl)cyclopropane-1-carboxamide (600.0 mg, 1.11 mmol) in CH_2Cl_2 (18.0 mL) was added Dess-Martin (708.6 mg, 1.67 mmol) at room temperature. The resulting mixture was stirred at room temperature

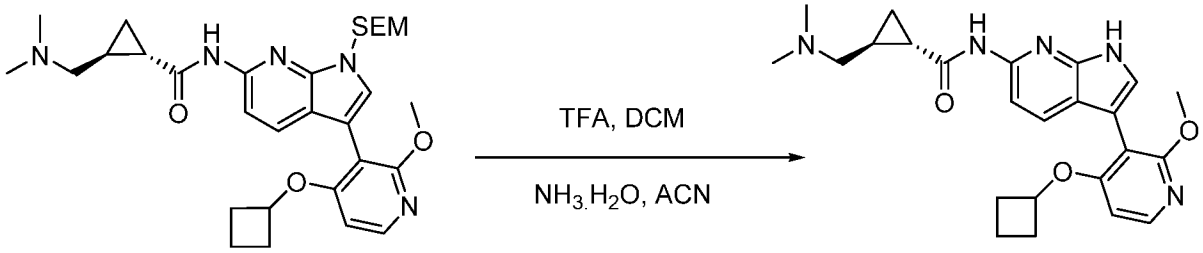
for 3 h. After the reaction was completed, The reaction was diluted with aq.$NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford trans-N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (800.0 mg, crude) as a white oil. LCMS (ESI, m/z): $[M+H]^+$ =537.2.

Step 10: Synthesis of Trans-N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide



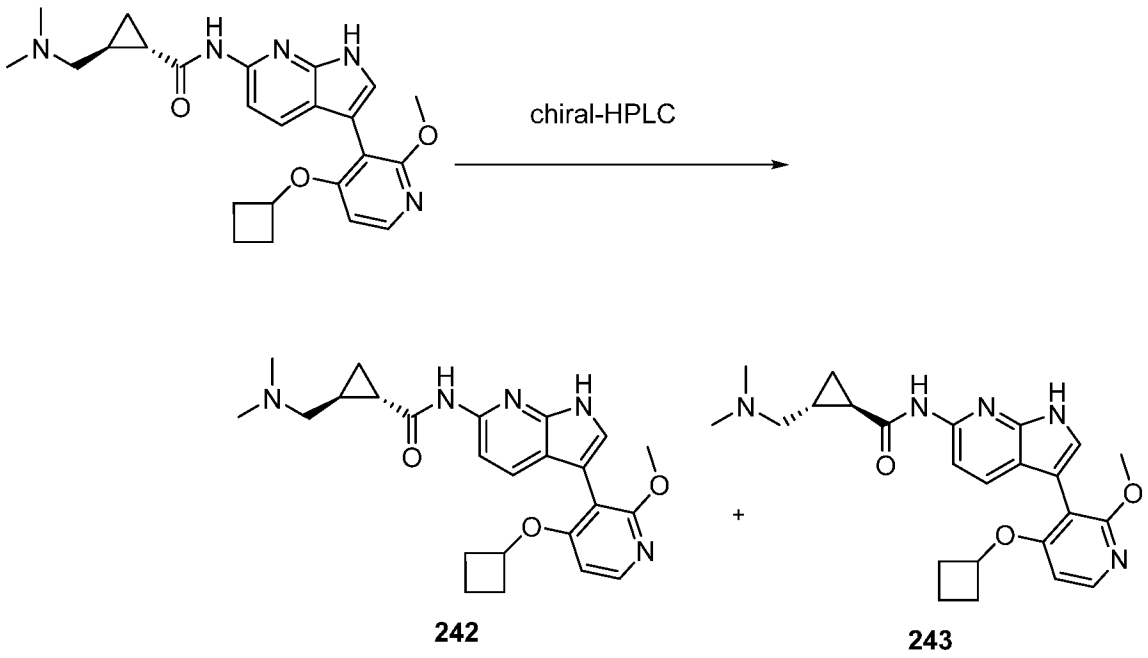
[1102] To a solution of trans-N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-formylcyclopropane-1-carboxamide (480.0 mg, 0.89 mmol) in CH_2Cl_2 (15.0 mL) was added dimethylamine hydrochloride (218.8 mg, 2.68 mmol) and $NaBH_3CN$ (168.6 mg, 2.68 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (6/1, v/v) to afford trans-N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (400.0 mg, 79%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =566.3.

Step 11: Synthesis of Trans-N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide



[1103] To a solution of trans-N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (400.0 mg, 0.71 mmol) in DCM (6.0 mL) was added TFA (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. The mixture was evaporated under reduced pressure. To the above mixture was added ACN/$NH_3.H_2O$ (6.0 mL/6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for additional 1 h. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with CH_3CN/H_2O (3/7, v/v) to afford trans-N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (75.0 mg, 24%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =436.2.

Step 12: Synthesis of (1S,2S)-N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide and **(1R,2R)-N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (Compound 242 and Compound 243)**



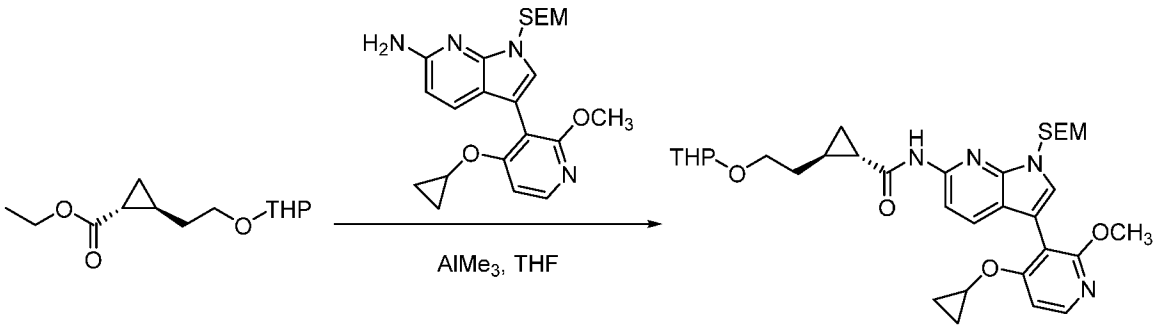
[1104] The product trans-N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide (75.0 mg, 0.17 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SC, 2x25 cm, 5 μm; Mobile Phase A:Hex:DCM=3:1 (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B:EtOH--HPLC; Flow rate:20 mL/min; Gradient: 15% B to 15% B in 8 min; Wave Length: 220/254 nm) to afford N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide Enantiomer 1 (7.2 mg, 19%) as a white solid and N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide Enantiomer 2 (5.8 mg, 15%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 242 and 243** in Table 1.

[1105] **N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide Enantiomer 1:** Retention Time 1(min): 5.14; LCMS (ESI, m/z): $[M+H]^+$ = 436.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.52 (s, 1H), 10.53 (s, 1H), 8.00 (d, J = 5.6 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 6.68 (d, J = 5.6 Hz, 1H), 4.80 - 4.76 (m, 1H), 3.81 (s, 3H), 2.43 - 2.37 (m, 2H), 2.33 - 2.28 (m, 1H), 2.20 - 2.15 (m, 6H), 1.98 - 1.91 (m, 4H), 1.77 - 1.74 (m, 1H), 1.65 - 1.60 (m, 1H), 1.37 - 1.28 (m, 1H), 1.09 - 1.01 (m, 1H), 0.72 - 0.68 (m, 1H).

[1106] N-[3-(4-cyclobutoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-2-[(dimethylamino)methyl]cyclopropane-1-carboxamide Enantiomer 2: Retention Time 2(min): 6.57; LCMS (ESI, m/z): $[M+H]^+$ = 436.2. ^1H NMR(400 MHz, DMSO-d_6): δ 11.53 (s, 1H), 10.55 (s, 1H), 7.99 (d, J = 6.0 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 6.68 (d, J = 5.6 Hz, 1H), 4.79 - 4.76 (m, 1H), 3.81 (s, 3H), 2.43 - 2.37 (m, 2H), 2.32 - 2.27 (m, 1H), 2.20 - 2.15 (m, 6H), 1.98 - 1.89 (m, 4H), 1.76 - 1.74 (m, 1H), 1.65 - 1.60 (m, 1H), 1.36 - 1.24 (m, 1H), 1.07 - 1.02 (m, 1H), 0.73 - 0.68 (m, 1H).

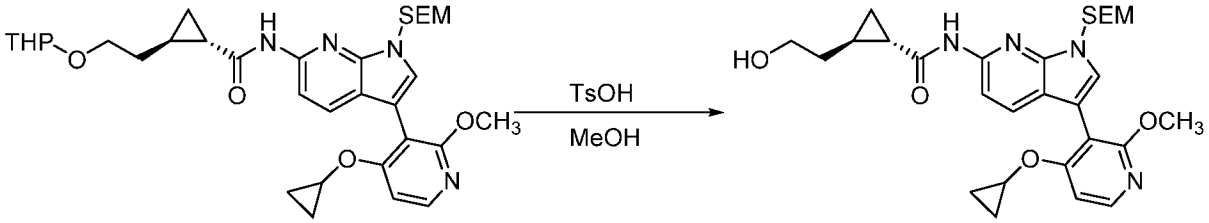
Example S216: Synthesis of (1S,2R)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide and (1R,2S)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide (Compound 244 and Compound 245)

Step 1: Synthesis of Trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)cyclopropane-1-carboxamide



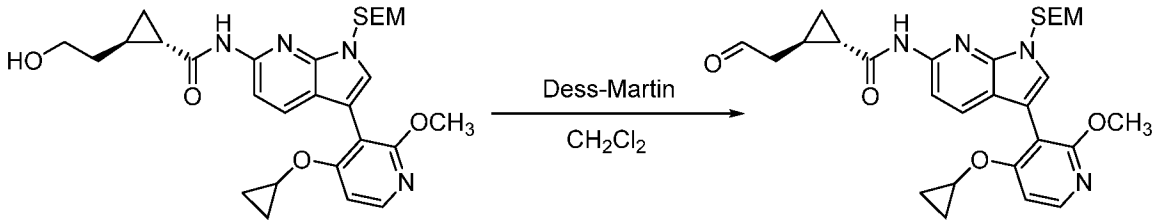
[1107] To a mixture of ethyl trans-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)cyclopropane-1-carboxylate (0.9 g, 3.52 mmol) and 3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (1.0 g, 2.34 mmol) in THF (40.0 mL) was added $AlMe_3$ (3.5 mL, 2 mol/L) at 0 °C under N_2. The resulting mixture was stirred at 80 °C for 2 h. After the reaction was completed, the resulting mixture was quenched with H_2O. The mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (10/1, v/v) to afford trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)cyclopropane-1-carboxamide (1.6 g, 87%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 623.3.

Step 2: Synthesis of Trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-hydroxyethyl)cyclopropane-1-carboxamide



[1108] To a solution of trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)cyclopropane-1-carboxamide (1.6 g, 2.57 mmol) in MeOH (30.0 mL) was added TsOH (0.4 g, 2.57 mmol) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (5/1, v/v) to afford trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-hydroxyethyl)cyclopropane-1-carboxamide (450.0 mg, 32%) as a brown solid. LCMS (ESI, m/z): $[M+H]^+$ = 539.3.

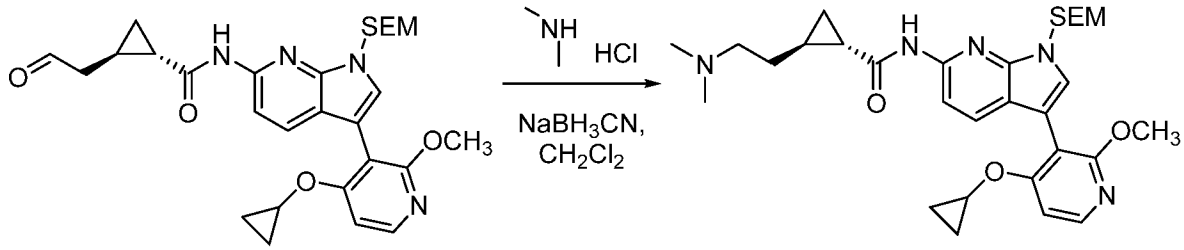
Step 3: Synthesis of Trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-oxoethyl)cyclopropane-1-carboxamide



[1109] To a solution of trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-hydroxyethyl)cyclopropane-1-carboxamide (400.0 mg, 0.74 mmol) in CH_2Cl_2 (30.0 mL) was added Dess-Martin (472.4 mg, 1.12 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried

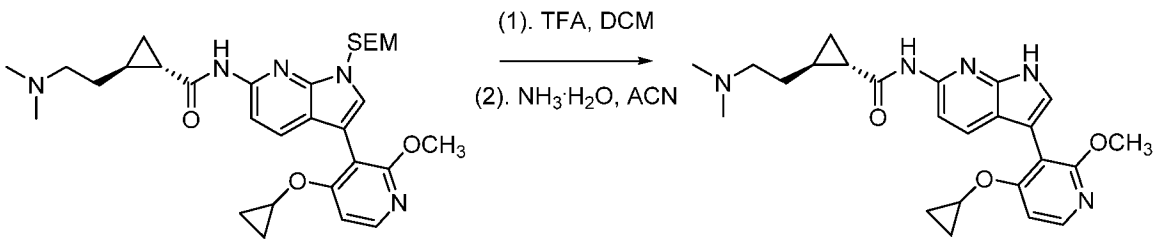
over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-oxoethyl)cyclopropane-1-carboxamide (400.0 mg, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =537.3.

Step 4: Synthesis of Trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide



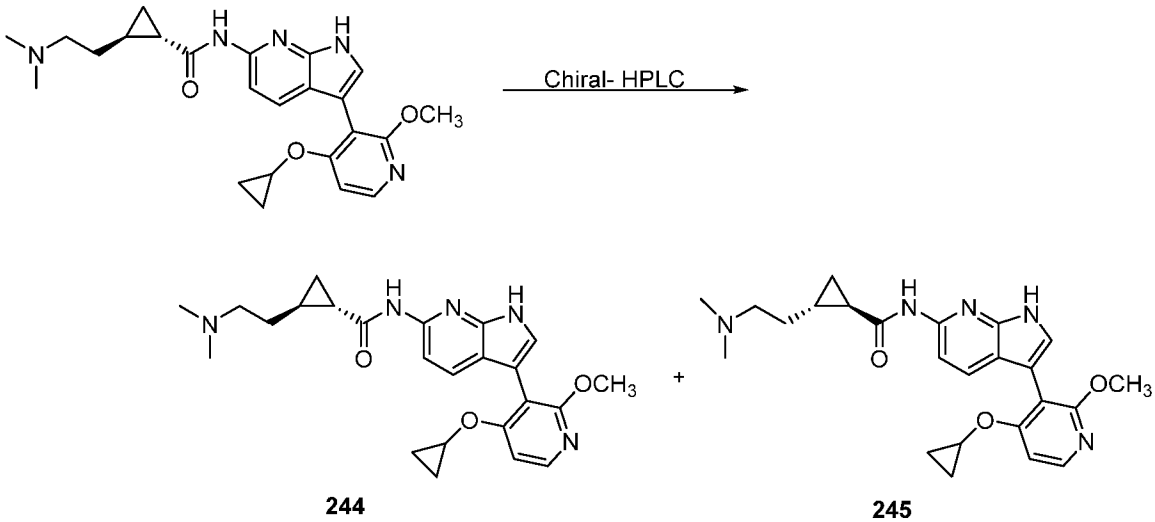
[1110] To a solution of trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-oxoethyl)cyclopropane-1-carboxamide (400.0 mg, crude) in CH_2Cl_2 (20.0 mL) was added dimethylamine hydrochloride (182.3 mg, 2.24 mmol) and $NaBH_3CN$ (140.5 mg, 2.24 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was quenched with CH_3OH. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (5/1, v/v) to afford trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide (90.0 mg, 21%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =566.3.

Step 5: Synthesis of Trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide



[1111] To a solution of trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide (90.0 mg, 0.16 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (2.0 mL) was added $NH_3 \cdot H_2O$ (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (5/1, v/v) to afford trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide (50.0 mg, 72%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =436.2.

Step 6: Synthesis of (1S,2R)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide and (1R,2S)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide (Compound 244 and Compound 245)



244 245

[1112] The product of trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide (50.0 mg, 0.11 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column:

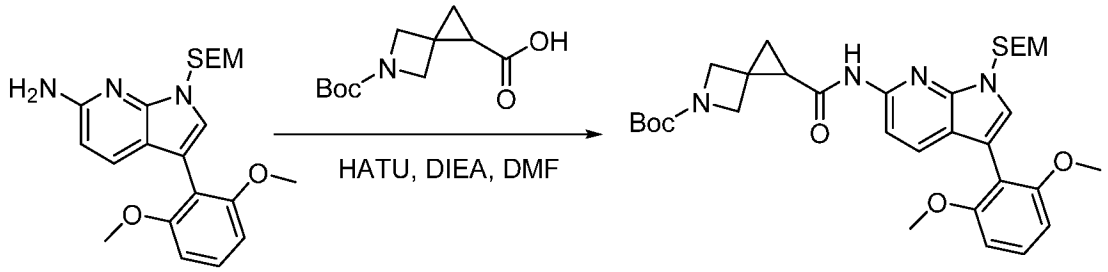
CHIRALPAK IE, 2×25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 12 mL/min; Gradient: 50% to 50% in 27 min; Wave Length: 220/254 nm) to afford N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide Enantiomer 1 (5.3 mg, 10%) as a white solid and N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide Enantiomer 2 (5.1 mg, 10%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 244 and 245** in Table 1.

[1113] N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide Enantiomer 1: Retention Time 1(min): 12.79; LCMS (ESI, m/z): $[M+H]^+$ =436.3. ^1H NMR (400 MHz, DMSO-d_6): δ 11.49 (s, 1H), 10.46 (s, 1H), 8.07 (d, J = 6.0 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.34 (s, 1H), 7.13 (d, J = 5.6 Hz, 1H), 4.01 - 3.93 (m, 1H), 3.81 (s, 3H), 2.33 - 2.30 (m, 2H), 2.13 (s, 6H), 1.88 - 1.82 (m, 1H), 1.47 - 1.37 (m, 2H), 1.24 - 1.16 (m, 1H), 1.09 - 0.91 (m, 1H), 0.89 - 0.75 (m, 2H), 0.73 - 0.58 (m, 3H).

[1114] N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethyl)cyclopropane-1-carboxamide Enantiomer 2: Retention Time 2(min): 18.32; LCMS (ESI, m/z): $[M+H]^+$ =436.3. ^1H NMR (400 MHz, DMSO-d_6): δ 11.49 (s, 1H), 10.46 (s, 1H), 8.07 (d, J = 5.6 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.34 (s, 1H), 7.14 (d, J = 5.6 Hz, 1H), 3.99 - 3.93 (m, 1H), 3.81 (s, 3H), 2.34 - 2.31 (m, 2H), 2.13 (s, 6H), 1.89 - 1.84 (m, 1H), 1.47 - 1.35 (m, 2H), 1.24 - 1.16 (m, 1H), 1.12 - 1.00 (m, 1H), 0.86 - 0.73 (m, 2H), 0.68 - 0.64 (m, 3H).

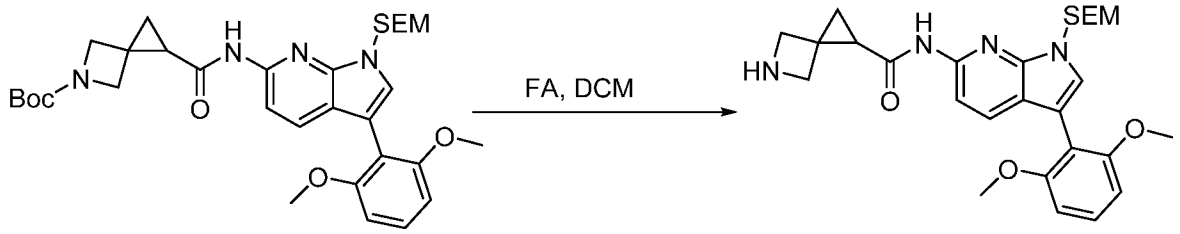
Example S217: Synthesis of (1R)-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide and (1S)-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide (Compound 246 and Compound 247)

Step 1: Synthesis of tert-butyl 1-{[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}-5-azaspiro[2.3]hexane-5-carboxylate



[1115] To a solution of 3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-amine (1.8 g, 4.41 mmol) in DMF (30.0 mL) were added 5-(tert-butoxycarbonyl)-5-azaspiro[2.3]hexane-1-carboxylic acid (1.0 g, 4.41 mmol), DIEA (2.3 g, 17.64 mmol) and HATU (2.4 g, 6.17 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (3/1, v/v) to afford tert-butyl 1-{[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}-5-azaspiro[2.3]hexane-5-carboxylate (2.2 g, 83%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =609.3.

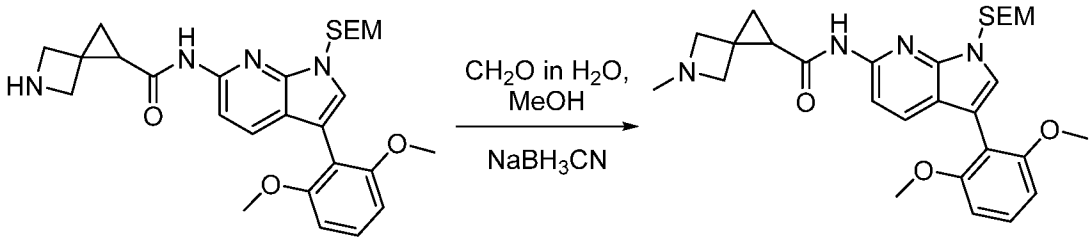
Step 2: Synthesis of N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-5-azaspiro[2.3]hexane-1-carboxamide



[1116] To a solution of tert-butyl 1-{[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]carbamoyl}-5-azaspiro[2.3]hexane-5-carboxylate (1.0 g, 1.64 mmol) in DCM (10.0 mL) was added HCOOH (20.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with water. The pH value of the mixture was adjusted to 8 with aq.$NaHCO_3$. The resulting mixture was extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and

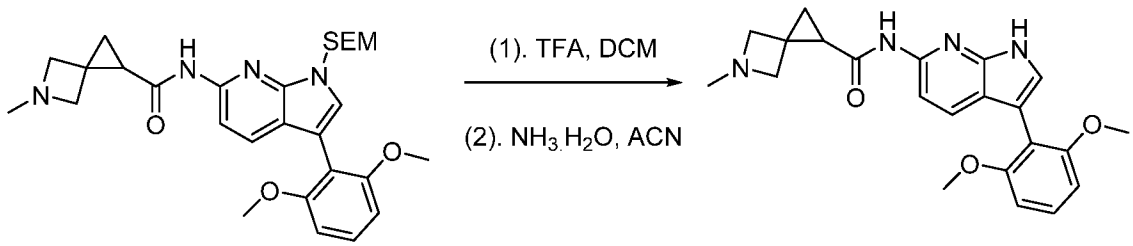
filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (4/1, v/v) to afford N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-5-azaspiro[2.3]hexane-1-carboxamide (0.4 g, 45%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =509.3.

Step 3: Synthesis of N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide



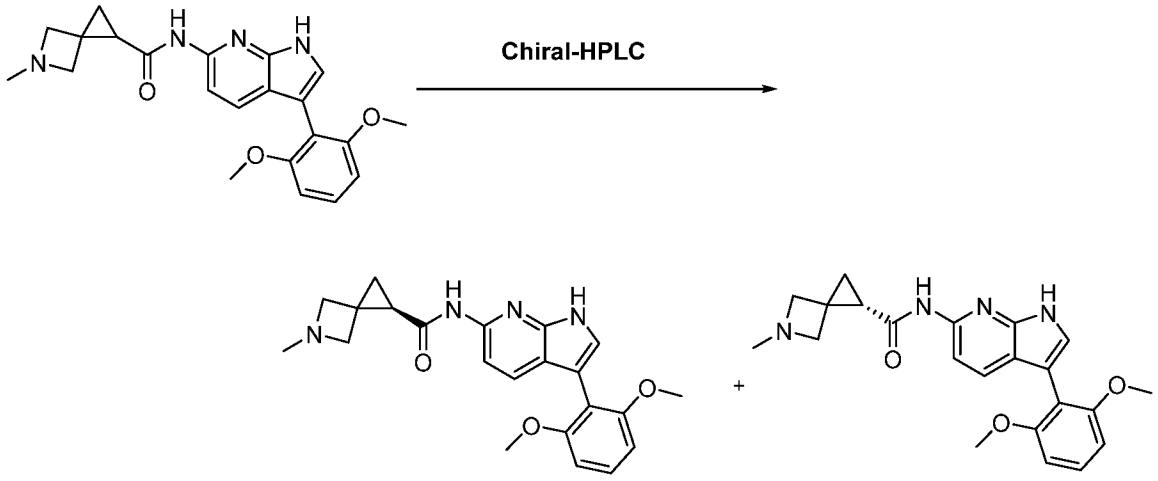
[1117] To a solution of N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-5-azaspiro[2.3]hexane-1-carboxamide (550.0 mg, 1.08 mmol) in CH_3OH (20.0 mL) was added a solution of HCHO in H_2O (1.1 mL, 37%) at room temperature. The resulting mixture was stirred at room temperature for 10 min. Then $NaBH_3CN$ (203.8 mg, 3.24 mmol) was added to the mixture. The resulting mixture was stirred at room temperature for 30 min. After the reaction was completed, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with acetonitrile/water (2/3, v/v) to afford N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide (130.0 mg, 23%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =523.3.

Step 4: Synthesis of N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide



[1118] To a solution of N-[3-(2,6-dimethoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}pyrrolo[2,3-b]pyridin-6-yl]-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide (176.0 mg, 0.34 mmol) in DCM (10.0 mL) was added TFA (10.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1.5 h. The resulting mixture was concentrated under reduced pressure. To the above mixture was added CH_3CN (6.0 mL) and $NH_3.H_2O$ (6.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography with CH_3CN/H_2O (2/3, v/v) to afford N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide (130.0 mg, 98%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =393.2.

Step 5: Synthesis of (1R)-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide and (1S)-N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide (Compound 246 and Compound 247)



246 247

[1119] The racemic N-(3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide (130.0 mg, 0.33 mmol) was separated by Chiral-Prep-HPLC with the following conditions (Column: CHIRALPAK IG, 2x25 cm, 5 μm; Mobile Phase A: Hex: DCM=1: 1 (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 17 mL/min; Gradient: 50 % B to 50 % B in 14.5 min; Wave

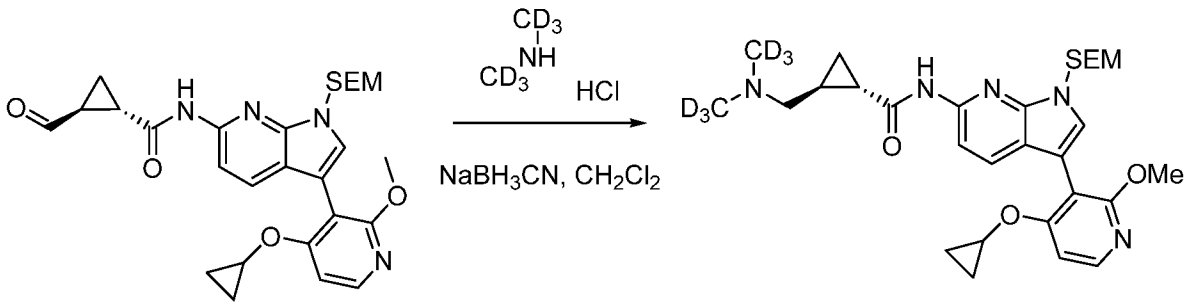
Length: 220/254 nm) to afford N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide Enantiomer 1 (13.5 mg, 13%) as a yellow solid and N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide Enantiomer 2 (14.0 mg, 12%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 246 and 247** in Table 1.

[1120] N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide Enantiomer 1: Retention Time 1: 4.65 min; LCMS (ESI, m/z): $[M+H]^+$=393.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.41 (s, 1H), 10.50 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.30 - 7.27 (m, 2H), 6.76 - 6.72 (m, 2H), 3.67 (s, 6H), 3.36 - 3.24 (m, 4H), 2.30 (s, 3H), 2.13 - 2.10 (m, 1H), 1.10 - 1.04 (m, 2H).

[1121] N-[3-(2,6-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-6-yl]-5-methyl-5-azaspiro[2.3]hexane-1-carboxamide Enantiomer 2: Retention Time 2: 10.92 min; LCMS (ESI, m/z): $[M+H]^+$= 393.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.41 (s, 1H), 10.49 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.30 - 7.22 (m, 2H), 6.76 - 6.70 (m, 2H), 3.72 (s, 6H), 3.34 - 3.21 (m, 4H), 2.29 (s, 3H), 2.15 - 2.02 (m, 1H), 1.12 - 1.03 (m, 2H).

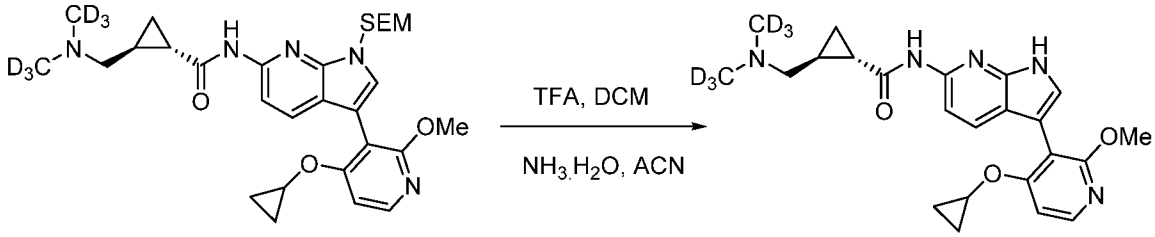
Example S218: Synthesis of (1R,2R)-2-((bis(methyl-d3)amino)methyl)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide and (1S,2S)-2-((bis(methyl-d3)amino)methyl)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 248 and Compound 249)

Step 1: Synthesis of Trans-2-((bis(methyl-d3)amino)methyl)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide



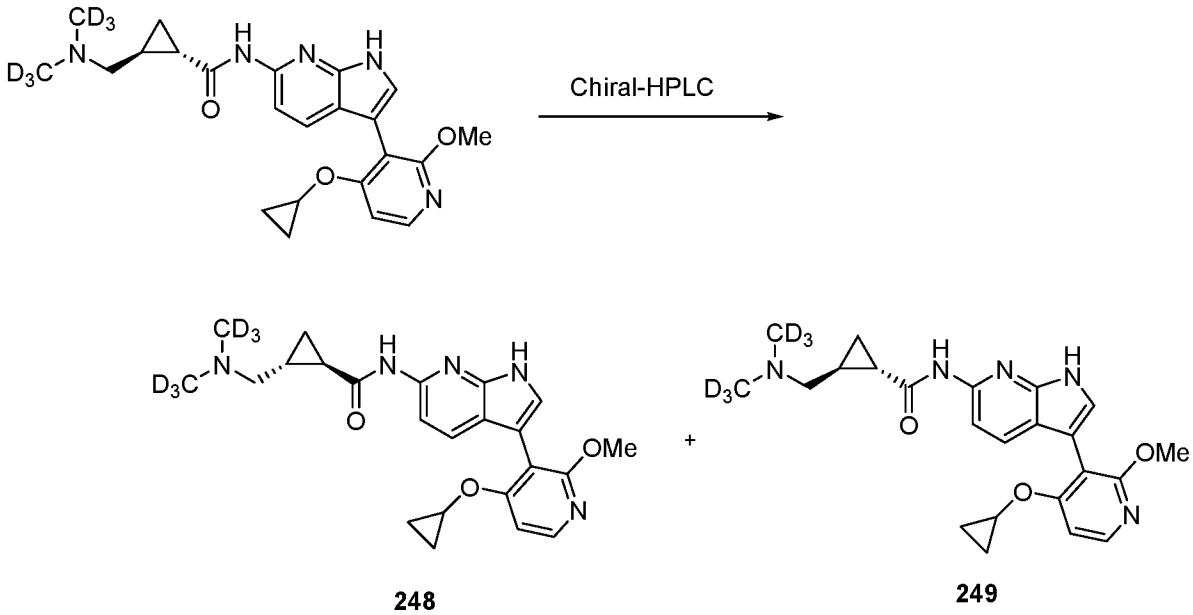
[1122] To a solution of trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-formylcyclopropane-1-carboxamide (670.0 mg, 1.28 mmol) in CH_2Cl_2 (20.0 mL) was added dimethyl-D6-amine hydrochloride (336.8 mg, 3.85 mmol) and $NaBH_3CN$ (241.7 mg, 3.87 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction was quenched with H_2O and extracted with dichloromethane. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with H_2O/CH_3CN (3/7, v/v) to afford trans-2-((bis(methyl-d3)amino)methyl)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (200.0 mg, 27%) as a green solid. LCMS (ESI, m/z): $[M+H]^+$ =558.3.

Step 2: Synthesis of Trans-2-((bis(methyl-d3)amino)methyl)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide



[1123] To a solution of trans-2-((bis(methyl-d3)amino)methyl)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (300.0 mg, 0.54 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (5.0 mL) was added $NH_3.H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for another 2 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with H_2O/CH_3CN (1/1, v/v) to afford trans-2-((bis(methyl-d3)amino)methyl)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (190.0 mg, 82%) as a white solid. LCMS (ESI, m/z): [M+H]+ =428.3.

Step 3: Synthesis of (1R,2R)-2-((bis(methyl-d3)amino)methyl)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide and (1S,2S)-2-((bis(methyl-d3)amino)methyl)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 248 and Compound 249)



248 249

[1124] The product trans-2-((bis(methyl-d3)amino)methyl)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (190.0 mg, 0.34 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SC, 2×25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: MeOH: EtOH= 1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 20% to 20% in 17 min; Wave Length: 220/254 nm) to afford 2-((bis(methyl-d3)amino)methyl)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide Enantiomer 1 (44.7 mg, 60%) as a white solid and 2-((bis(methyl-d3)amino)methyl)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide Enantiomer 2 (30.1 mg, 40%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 248 and 249** in Table 1.

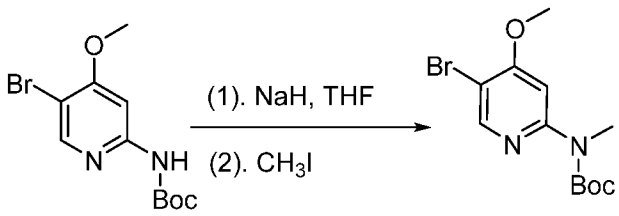
[1125] **2-((bis(methyl-d3)amino)methyl)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide Enantiomer 1**: Retention Time 1 (min): 11.48; LCMS (ESI, m/z): $[M+H]^+$ =428.3. ^1H NMR (400 MHz, DMSO-d_6): δ

11.50 (s, 1H), 10.52 (s, 1H), 8.07 (d, J = 5.6 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 2.0 Hz, 1H), 7.14 (d, J = 5.6 Hz, 1H), 3.94 - 3.91 (m, 1H), 3.82 (s, 3H), 2.32 - 2.28 (m, 1H), 2.21 - 2.16 (m, 1H), 1.91 - 1.89 (m, 1H), 1.38 - 1.30 (m, 1H), 1.07 - 1.03 (m, 1H), 0.87 - 0.76 (m, 2H), 0.73 - 0.64 (m, 3H).

[1126] 2-((bis(methyl-d3)amino)methyl)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide Enantiomer 2: Retention Time 2 (min): 15.63; LCMS (ESI, m/z): $[M+H]^+$ =428.4. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.50 (s, 1H), 10.52 (s, 1H), 8.07 (d, J = 6.0 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 2.0 Hz, 1H), 7.14 (d, J = 5.6 Hz, 1H), 3.99 - 3.91 (m, 1H), 3.81 (s, 3H), 2.29 - 2.25 (m, 1H), 2.18 - 2.13 (m, 1H), 1.90 - 1.88 (m, 1H), 1.37 - 1.32 (m, 1H), 1.08 - 1.02 (m, 1H), 0.81 - 0.76 (m, 2H), 0.71 - 0.63 (m, 3H).

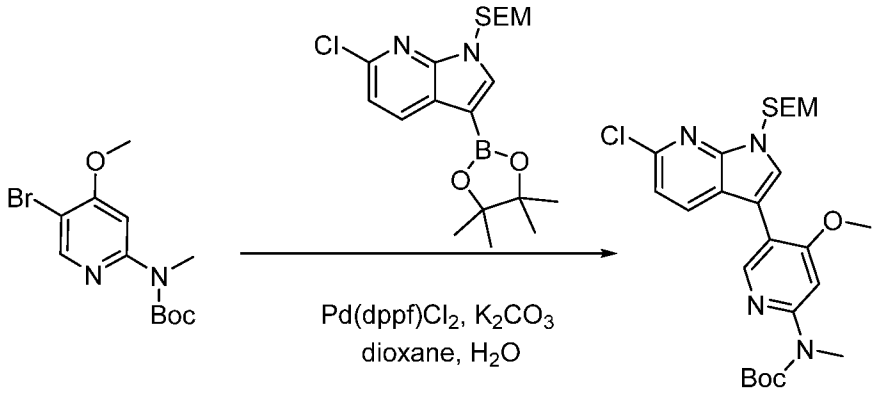
Example S219: Synthesis of N-[3-[4-methoxy-6-(methylamino)pyridin-3-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 250)

Step 1: Synthesis of tert-butyl N-(5-bromo-4-methoxypyridin-2-yl)-N-methylcarbamate



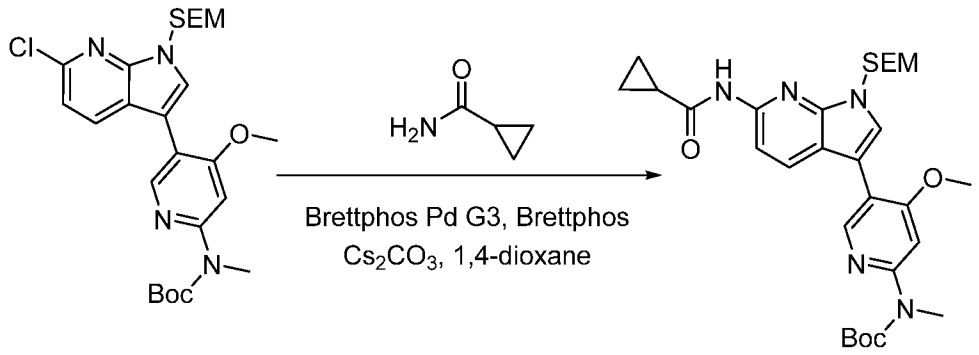
[1127] To a solution of tert-butyl N-(5-bromo-4-methoxypyridin-2-yl)carbamate (635.0 mg, 2.10 mmol) in THF (20.0 mL) was added NaH (251.3 mg, 60%) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h under N_2. Then methyl iodide (1.5 g, 10.47 mmol) was added dropwise to the mixture at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h. After the reaction was completed, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford tert-butyl N-(5-bromo-4-methoxypyridin-2-yl)-N-methylcarbamate (500.0 mg, 75%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =317.0.

Step 2: Synthesis of tert-butyl N-[5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxypyridin-2-yl]-N-methylcarbamate



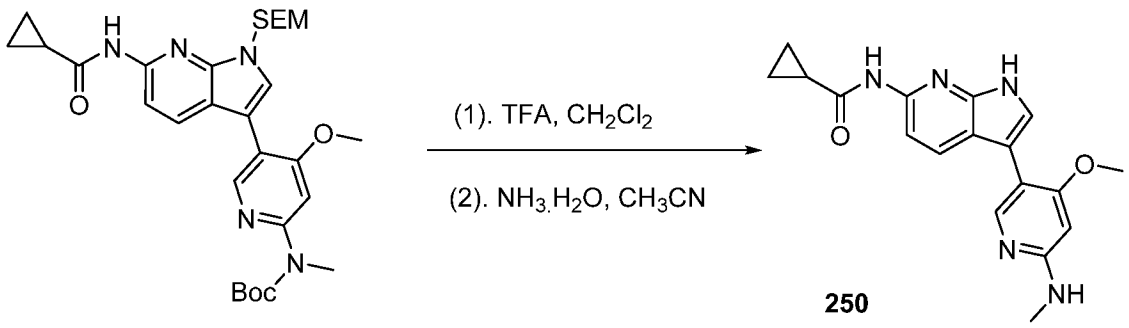
[1128] To a solution of tert-butyl N-(5-bromo-4-methoxypyridin-2-yl)-N-methylcarbamate (460.0 mg, 1.45 mmol) in dioxane/H_2O (10.0 mL/2.0 mL) was added 6-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridine (592.9 mg, 1.45 mmol), K_2CO_3 (601.3 mg, 4.35 mmol) and $Pd(dppf)Cl_2$ (118.4 mg, 0.15 mmol) at room temperature under N_2. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was completed, the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford tert-butyl N-[5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxypyridin-2-yl]-N-methylcarbamate (278.0 mg, 37%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ =519.2.

Step 3: Synthesis of tert-butyl (5-(6-(cyclopropanecarboxamido)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-4-methoxypyridin-2-yl)(methyl)carbamate



[1129] To a solution of tert-butyl N-[5-(6-chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxypyridin-2-yl]-N-methylcarbamate (258.0 mg, 0.50 mmol) in 1,4-dioxane (8.0 mL) was added cyclopropanecarboxamide (211.5 mg, 2.49 mmol), BrettPhos (53.4 mg, 0.10 mmol), Cs_2CO_3 (485.8 mg, 1.49 mmol) and BrettPhos Pd G3 (45.1 mg, 0.05 mmol) at room temperature under N_2. The resulting mixture was stirred with microwave at 120 °C for 1.5 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (2/1, v/v) to afford tert-butyl (5-(6-(cyclopropanecarboxamido)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-4-methoxypyridin-2-yl)(methyl)carbamate (168.0 mg, 72%) as a white oil. LCMS (ESI, m/z): $[M+H]^+$ =568.3.

Step 4: Synthesis of N-[3-[4-methoxy-6-(methylamino)pyridin-3-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (Compound 250)

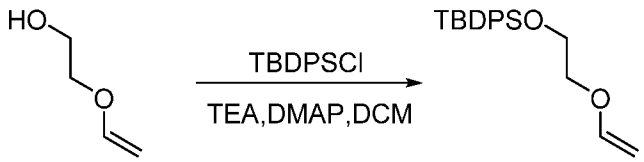


[1130] To a solution of tert-butyl N-[5-(6-cyclopropaneamido-1-[[2-(trimethylsilyl)ethoxy]methyl]pyrrolo[2,3-b]pyridin-3-yl)-4-methoxypyridin-2-yl]-N-methylcarbamate (168.0 mg, 0.30 mmol) in DCM (3.0 mL) was added TFA (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The resulting

mixture was concentrated under reduced pressure. To the residue in CH_3CN (3.0 mL) was added $NH_3.H_2O$ (3.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate 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, 5 um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:23% B to 53% B in 7 min; 254 nm) to afford N-[3-[4-methoxy-6-(methylamino)pyridin-3-yl]-1H-pyrrolo[2,3-b]pyridin-6-yl]cyclopropanecarboxamide (16.1 mg, 16%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ =338.2. ^1H NMR (300 MHz, DMSO-d_6): δ 11.39 (s, 1H), 10.52 (s, 1H), 8.00 (s, 1H), 7.91 - 7.82 (m, 2H), 7.36 (d, J = 2.4 Hz, 1H), 6.38 - 6.34 (m, 1H), 6.10 (s, 1H), 3.78 (s, 3H), 2.81 (d, J = 4.8 Hz, 3H), 2.07 - 1.99 (m, 1H), 0.82 - 0.74 (m, 4H).

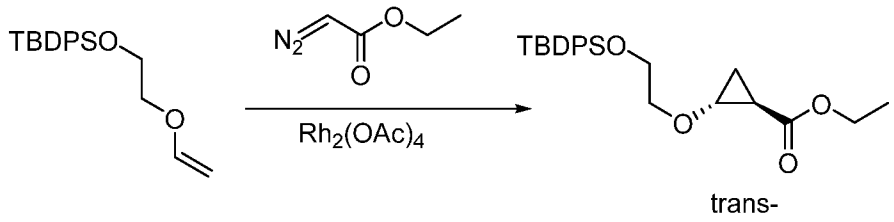
Example S220: Synthesis of (1R,2R)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxamide *and* ***(1S,2S)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxamide (Compound 251 and Compound 252)***

Step 1: Synthesis of tert-butyldiphenyl(2-(vinyloxy)ethoxy)silane



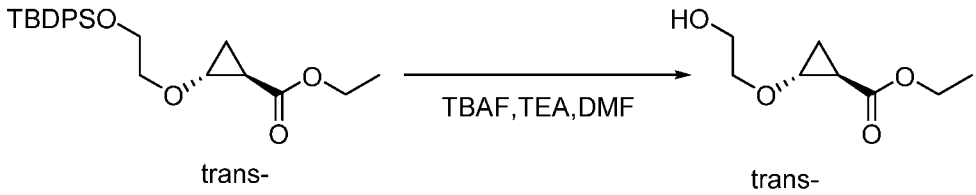
[1131] To a solution of 2-(vinyloxy)ethan-1-ol (20.0 g, 227.0 mmol) in DCM (200.0 mL) was added TEA (68.9 g, 681.00 mmol), DMAP (2.8 g, 22.70 mmol) and tert-butylchlorodiphenylsilane (74.9 g, 272.40 mmol) at room temperature under N_2. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (10/1, v/v) to afford tert-butyldiphenyl(2-(vinyloxy)ethoxy)silane (40.0 g, 53%) as a yellow oil.

Step 2: Synthesis of ethyl (trans)-2-(2-((tert-butyldiphenylsilyl)oxy)ethoxy)cyclopropane-1-carboxylate



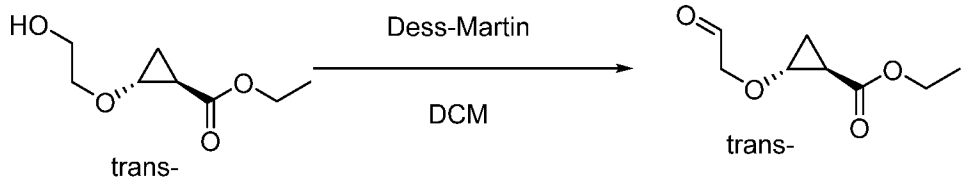
[1132] To a mixture of $Rh_2(OAc)_4$ (0.2 g, 0.46 mmol) in tert-butyldiphenyl(2-(vinyloxy)ethoxy)silane (5.0 g, 15.31 mmol) was added dropwise ethyl 2-diazoacetate (8.7 g, 76.57 mmol) at room temperature under N_2 in 10 h. The resulting mixture was stirred at room temperature for 16 h under N_2. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with petroleum ether/ethyl acetated (10/1, v/v) to afford ethyl (trans)-2-(2-((tert-butyldiphenylsilyl)oxy)ethoxy)cyclopropane-1-carboxylate (2.3 g, 36%) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ = 413.2.

Step 3: Synthesis of ethyl (trans)-2-(2-hydroxyethoxy)cyclopropane-1-carboxylate



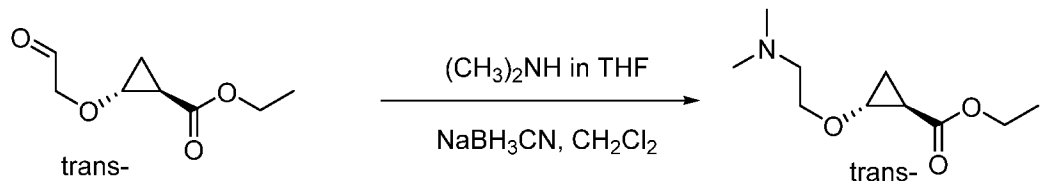
[1133] To a solution of ethyl (trans)-2-(2-((tert-butyldiphenylsilyl)oxy)ethoxy)cyclopropane-1-carboxylate (2.2 g, 5.33 mmol) in DMF (20.0 mL) was added TEA (1.6 g, 16.00 mmol) and TBAF (4.2 g, 16.00 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford ethyl (trans)-2-(2-hydroxyethoxy)cyclopropane-1-carboxylate (1.3 g, crude) as a colorless oil. LCMS (ESI, m/z): $[M+H]^+$ = 175.1.

Step 4: Synthesis of ethyl (trans)-2-(2-oxoethoxy)cyclopropane-1-carboxylate



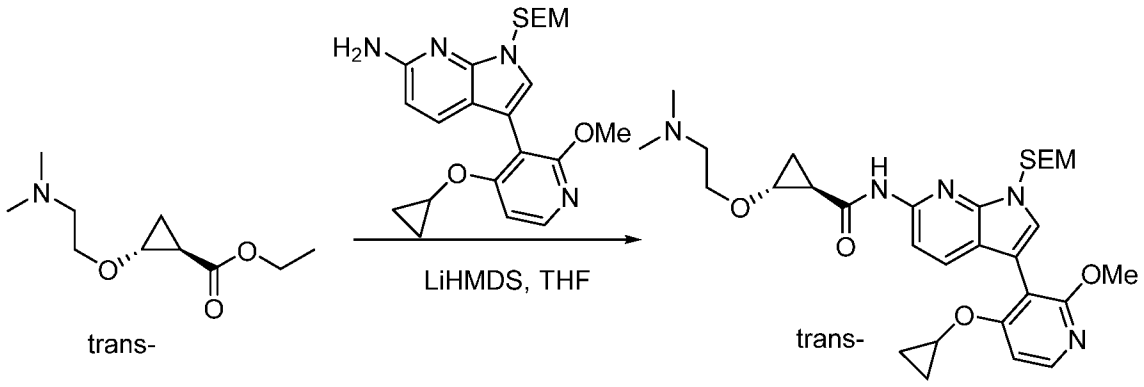
[1134] To a solution of ethyl (trans)-2-(2-hydroxyethoxy)cyclopropane-1-carboxylate (1.2 g, crude) in CH_2Cl_2 (30.0 mL) was added Dess-Martin (4.4 g, 10.33 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford ethyl (trans)-2-(2-oxoethoxy)cyclopropane-1-carboxylate (1.1 g, crude) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ =173.1.

Step 5: Synthesis of ethyl (trans)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxylate



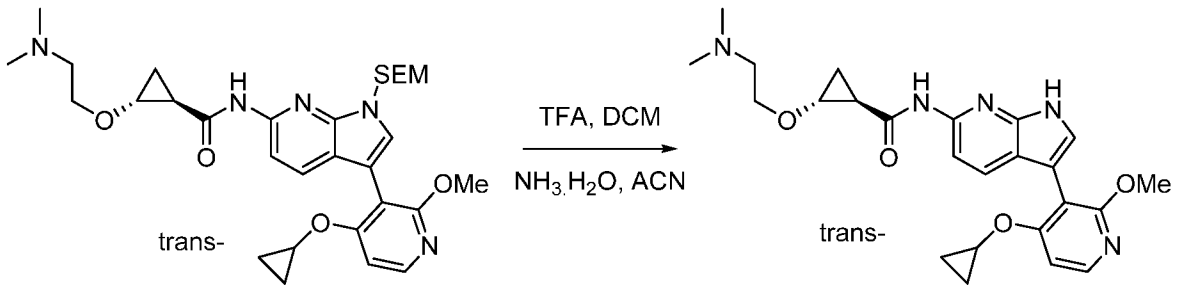
[1135] To a solution of ethyl (trans)-2-(2-oxoethoxy)cyclopropane-1-carboxylate (1.1 g, crude) in CH_2Cl_2 (20.0 mL) was added $(CH_3)_2NH$ in THF (9.6 mL, 2 mol/L) and $NaBH_3CN$ (1.2 g, 19.17 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was quenched with CH_3OH. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (10/1, v/v) to afford ethyl (trans)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxylate (300.0 mg, 23%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =202.1.

Step 6: Synthesis of (Trans)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxamide



[1136] To a solution of ethyl (trans)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxylate (471.8 mg, 2.34 mmol) in THF (20.0 mL) was added 3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (500.0 mg, 1.17 mmol) and LiHMDS (3.5 mL, 1 mol/L) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (10/1, v/v) to afford (trans)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxamide (180.0 mg, 26%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+ = 582.3$.

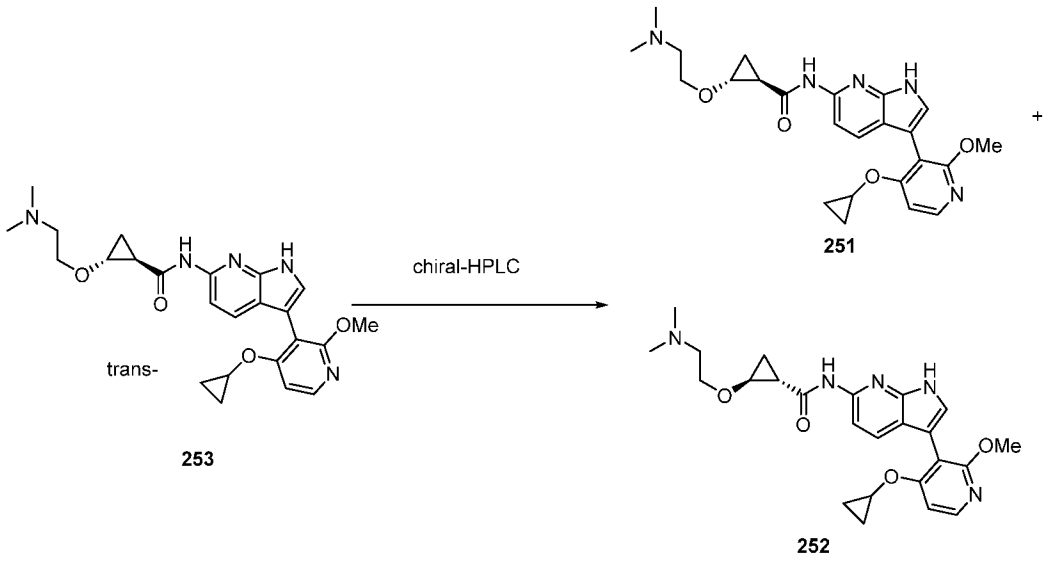
Step 7: Synthesis of Trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxamide



[1137] To a solution of (trans)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxamide (500.0 mg, 0.86 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the

residue in CH_3CN (5.0 mL) was added $NH_3 \cdot H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with H_2O/CH_3OH (2/3, v/v) to afford trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxamide (220.0 mg, 56%) as a white solid. LCMS (ESI, m/z): $[M+H]^+$ = 452.2.

Step 8: Synthesis of (1R,2R)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxamide and **(1S,2S)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxamide (Compounds 251 and 252)**



[1138] The product of trans-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxamide (220.0 mg, 0.49 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2×25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: MeOH: EtOH= 1:1--HPLC; Flow rate: 20 mL/min; Gradient: 80% to 80% in 21 min; Wave Length: 220/254 nm; RT1(min): 10.36; RT2(min): 15.92) to afford N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxamide Enantiomer 1 (RT1: 10.36 min, 58.7

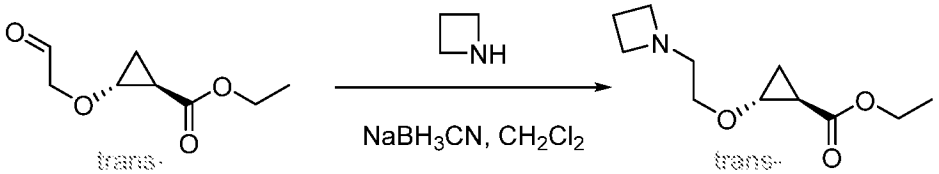
mg, 53%) as a white solid and N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxamide Enantiomer 2 (RT2: 15.92 min, 57.5 mg, 52%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 251 and 252** in Table 1.

[1139] N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxamide Enantiomer 1: RT1(min): 10.36; LCMS (ESI, m/z): $[M+H]^+$ =452.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.53 (s, 1H), 10.61 (s, 1H), 8.08 (d, J = 5.6 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 6.0 Hz, 1H), 3.95 - 3.91 (m, 1H), 3.81 (s, 3H), 3.64 - 3.52 (m, 3H), 2.61 - 2.53 (m, 1H), 2.22 - 2.18 (m, 7H), 1.16 - 1.13 (m, 2H), 0.82 - 0.78 (m, 2H), 0.68 - 0.59 (m, 2H).

[1140] N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-2-(2-(dimethylamino)ethoxy)cyclopropane-1-carboxamide Enantiomer 2: RT2(min): 15.92; LCMS (ESI, m/z): $[M+H]^+$ =452.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.53 (s, 1H), 10.61 (s, 1H), 8.08 (d, J = 5.6 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 6.0 Hz, 1H), 3.95 - 3.91 (m, 1H), 3.81 (s, 3H), 3.63 - 3.52 (m, 3H), 2.49 - 2.47 (m, 2H), 2.21 - 2.15 (m, 7H), 1.16 - 1.13 (m, 2H), 0.82 - 0.73 (m, 2H), 0.68 - 0.59 (m, 2H).

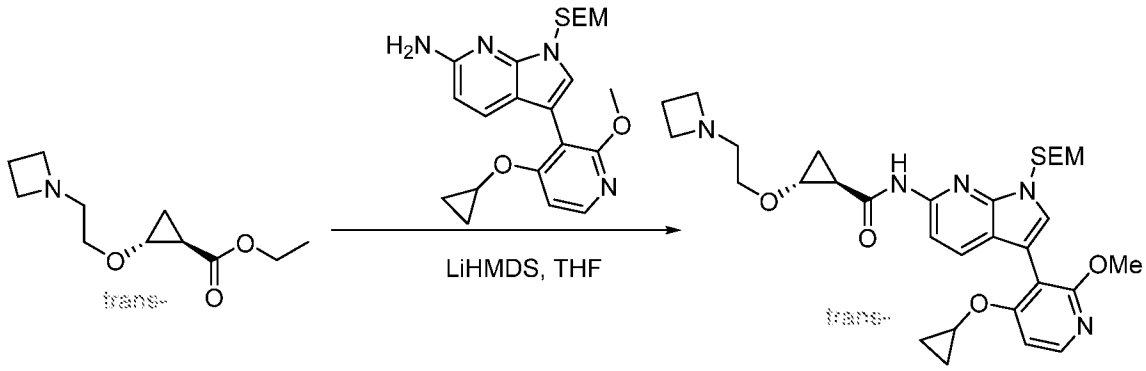
Example S221: Synthesis of (1R,2R)-2-(2-(azetidin-1-yl)ethoxy)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide *and* ***(1S,2S)-2-(2-(azetidin-1-yl)ethoxy)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 254 and Compound 255)***

Step 1: Synthesis of ethyl (trans)-2-(2-(azetidin-1-yl)ethoxy)cyclopropane-1-carboxylate



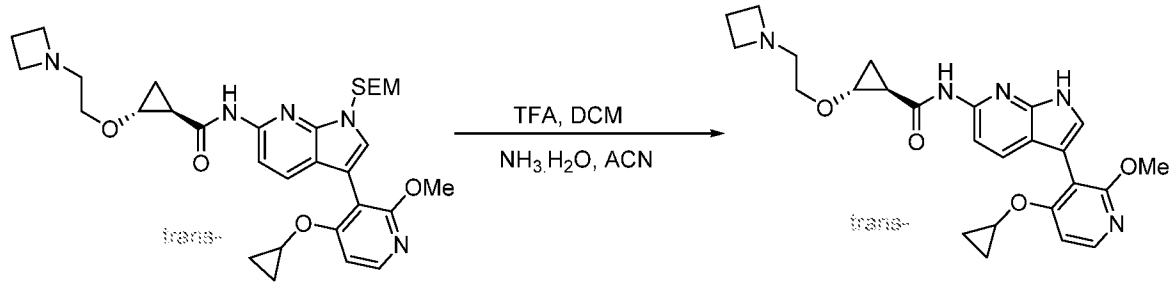
[1141] To a solution of ethyl (trans)-2-(2-oxoethoxy)cyclopropane-1-carboxylate (1.1 g, 6.39 mmol) in CH_2Cl_2 (20.0 mL) was added azetidine (1.1 g, 19.17 mmol) and $NaBH_3CN$ (1.2 g, 19.17 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. After the reaction was completed, the resulting mixture was quenched with CH_3OH. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (10/1, v/v) to afford ethyl (trans)-2-(2-(azetidin-1-yl)ethoxy)cyclopropane-1-carboxylate (500.0 mg, 36%) as a yellow oil. LCMS (ESI, m/z): $[M+H]^+$ =214.1.

Step 2: Synthesis of (Trans)-2-(2-(azetidin-1-yl)ethoxy)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide



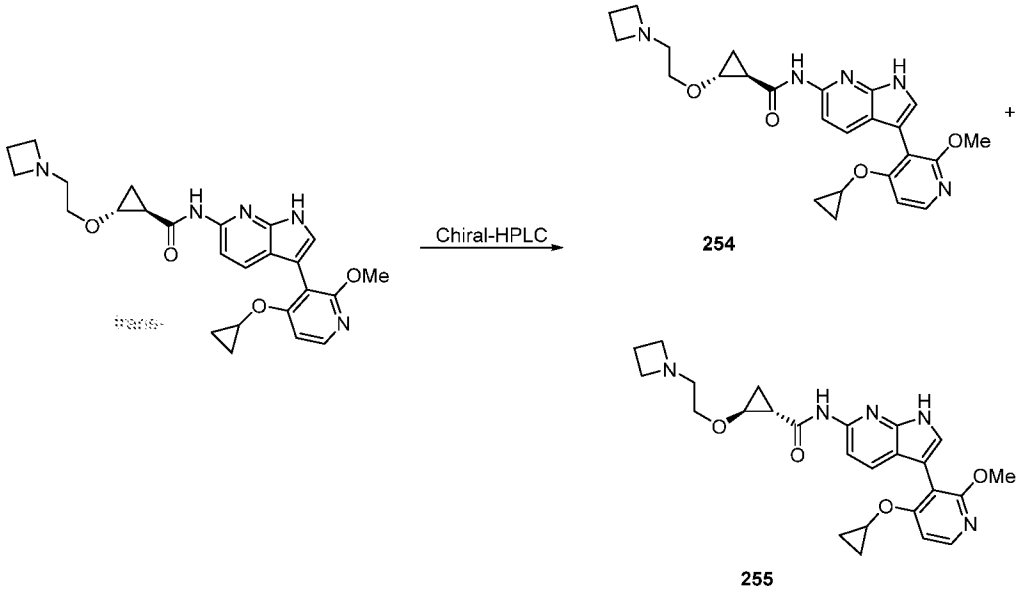
[1142] To a solution of ethyl (trans)-2-(2-(azetidin-1-yl)ethoxy)cyclopropane-1-carboxylate (440.0 mg, 2.06 mmol) in THF (20.0 mL) was added 3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-amine (220.0 mg, 0.52 mmol) and LiHMDS (1.6 mL, 1 mol/L) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 16 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2/CH_3OH (10/1, v/v) to afford (trans)-2-(2-(azetidin-1-yl)ethoxy)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (130.0 mg, 42%) as a yellow solid. LCMS (ESI, m/z): $[M+H]^+$ = 594.3.

Step 3: Synthesis of Trans-2-(2-(azetidin-1-yl)ethoxy)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide



[1143] To a solution of (trans)-2-(2-(azetidin-1-yl)ethoxy)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (180.0 mg, 0.30 mmol) in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. To the residue in CH_3CN (5.0 mL) was added $NH_3 \cdot H_2O$ (5.0 mL) at room temperature. The resulting mixture was stirred at room temperature for 4 h. After the reaction was completed, the resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography with H_2O/CH_3CN (3/2, v/v) to afford trans-2-(2-(azetidin-1-yl)ethoxy)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (49.0 mg, 34%) as a white solid. LCMS (ESI, m/z): $[M+H]^+ = 464.2$.

Step 4: Synthesis of (1R,2R)-2-(2-(azetidin-1-yl)ethoxy)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide and **(1S,2S)-2-(2-(azetidin-1-yl)ethoxy)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (Compound 254 and Compound 255)**



[1144] The product of trans-2-(2-(azetidin-1-yl)ethoxy)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide (48.0 mg, 0.10 mmol) was separated by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2×25 cm, 5 μm; Mobile Phase A: Hex (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 45% B to 45% B in 24.5 min; Wave Length: 220/254 nm; RT1(min): 9.43; RT2(min): 17.99) to afford 2-(2-(azetidin-1-yl)ethoxy)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide Enantiomer 1 (12.8 mg, 53%) as a white solid and 2-(2-(azetidin-1-yl)ethoxy)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide Enantiomer 2 (11.6 mg, 48%) as a white solid. The absolute stereochemistry of Enantiomers 1 and 2 was not assigned. The two enantiomeric structures that could be obtained from chiral separation of the enantiomeric mixture as described above are shown as **Compounds 254 and 255** in Table 1.

[1145] **2-(2-(azetidin-1-yl)ethoxy)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide Enantiomer 1**: RT1(min): 9.43; LCMS (ESI, m/z): $[M+H]^+$ =464.2. ^1H NMR (400 MHz, DMSO-d_6): δ 11.54 (s, 1H), 10.61 (s, 1H), 8.08 (d, J = 6.0 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 5.6 Hz, 1H), 3.94 - 3.92 (m, 1H), 3.82 (s, 3H), 3.58 - 3.45 (m, 4H), 3.19 - 3.13 (m, 4H), 2.24 - 2.18 (m, 1H), 1.99 - 1.92 (m, 2H), 1.14 - 1.11 (m, 2H), 0.81 - 0.77 (m, 2H), 0.67 - 0.63 (m, 2H).

[1146] **2-(2-(azetidin-1-yl)ethoxy)-N-(3-(4-cyclopropoxy-2-methoxypyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-6-yl)cyclopropane-1-carboxamide Enantiomer 2:** RT2(min): 17.99; LCMS (ESI, m/z): $[M+H]^+$ =464.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.54 (s, 1H), 10.61 (s, 1H), 8.08 (d, J = 5.6 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 6.0 Hz, 1H), 3.94 - 3.92 (m, 1H), 3.82 (s, 3H), 3.52 - 3.44 (m, 3H), 3.18 - 3.11 (m, 4H), 2.24 - 2.18 (m, 1H), 1.98 - 1.91 (m, 2H), 1.14 - 1.11 (m, 2H), 0.81 - 0.77 (m, 2H), 0.74 - 0.64 (m, 2H).

Biological Examples

K562 and HL60 Cell Proliferation Assay

[1147] K562 and HL60 cells, cultured in Iscove's Modified Dulbecco's Media (IMDM) supplemented with 10% FBS, were harvested at 50-80% confluency and plated at 2,000 cells per well (K562) or 1,500 cells per well (HL60) in 384-well tissue culture plates. A subset of wells contained media only (low control, LC). Compounds were serially diluted in DMSO. 40 nL of compound or DMSO only (high control, HC) were added to each well using an Echo 550 liquid handler (Labcyte). The plates were placed in a 37°C incubator with 5% CO_2 for 72 hours. Cell viability was measured using a CellTiter-Glo luminescent cell viability assay (Promega), which allows for relative quantification of metabolically active cells by luminescence-based measurements of intracellular ATP concentrations. Briefly, plates were removed from the incubator and equilibrated for 15 minutes at room temperature prior to the addition of 40 µL of CellTiter-Glo reagent. Plates were then incubated for 30 minutes at room temperature. Luminescence was measured using an EnSpire plate reader (Perkin Elmer). As noted above, luminescence values from wells with DMSO only or media without cells were used as high and low controls (HC and LC), respectively. Normalized percent viability was calculated as follows: percent viability = 100 x (Lum_{Sample} – Lum_{LC}) / (Lum_{HC} – Lum_{LC}). IC_{50} values were calculated using the XLFit software and are shown in Table 2.

Table 2.

Cmpd No.	Cell Line (IC_{50}, nM)	
	K562	HL60
1	101	> 10.0E+03
2	176	> 10.0E+03
3	80.3	> 10.0E+03
4	223	> 10.0E+03
5	713	> 10.0E+03

Cmpd No.	Cell Line (IC_{50}, nM)	
	K562	HL60
6	452	> 10.0E+03
13	202	4450
14	416	> 10.0E+03
15	181	1710
17	229	> 10.0E+03

Cmpd No.	Cell Line (IC_{50}, nM)	
	K562	HL60
19	147	287
21	286	1570
22	421	> 10.0E+03
26	220	> 10.0E+03
27	156	> 10.0E+03
28	62.1	385
29	454	470
37	231	> 10.0E+03
41	654	> 10.0E+03
42	254	> 10.0E+03
43	779	> 10.0E+03
44	151	> 10.0E+03
45	52.7	> 10.0E+03
47	292	> 10.0E+03
48	777	9210
49	295	> 10.0E+03
50	120	> 10.0E+03
51	668	> 10.0E+03
52	829	> 10.0E+03
53	267	3110
54	88.4	> 10.0E+03
56	183	120
58	132	> 10.0E+03
60	5170	> 10.0E+03
61	36.9	> 10.0E+03
62	137	> 10.0E+03
63	255	> 10.0E+03
64	610	> 10.0E+03
66	603	> 10.0E+03
67	1140	> 10.0E+03
68	607	3690
69	162	> 10.0E+03
70	312	> 10.0E+03
71	292	334
72	1020	> 10.0E+03
74	351	> 10.0E+03
75	54.6	> 10.0E+03
76	35.8	> 10.0E+03
77	727	> 10.0E+03
78	94.8	> 10.0E+03

Cmpd No.	Cell Line (IC_{50}, nM)	
	K562	HL60
79	719	> 10.0E+03
81	96.2	> 10.0E+03
82	437	> 10.0E+03
83	48.8	> 10.0E+03
84	150	> 10.0E+03
85	46	7250
86	30.5	> 10.0E+03
87	94.1	> 10.0E+03
88	84.1	> 10.0E+03
90	1100	> 10.0E+03
91	1080	> 10.0E+03
92	248	> 10.0E+03
94	55.6	7580
95	221	> 10.0E+03
96	862	> 10.0E+03
98	106	> 10.0E+03
99	129	> 10.0E+03
101	94.2	> 10.0E+03
102	48	> 10.0E+03
103	751	> 10.0E+03
105	489	> 10.0E+03
106	275	> 10.0E+03
108	419	> 10.0E+03
109	278	> 10.0E+03
110	382	> 10.0E+03
111	321	> 10.0E+03
112	1860	> 10.0E+03
113	174	> 10.0E+03
115	382	> 10.0E+03
116	142	> 10.0E+03
117	67.1	> 10.0E+03
118	24.4	> 10.0E+03
119	32.2	> 10.0E+03
121	365	> 10.0E+03
124	359	> 10.0E+03
125	104	> 10.0E+03
126	2010	> 10.0E+03
127	100	> 10.0E+03
130	169	> 10.0E+03
131	83.3	> 10.0E+03

Cmpd No.	Cell Line (IC_{50}, nM)	
	K562	HL60
132	234	> 10.0E+03
133	9.36	4040
135	165	> 10.0E+03
136	333	> 10.0E+03
137	733	> 10.0E+03
138	527	> 10.0E+03
139	1380	> 10.0E+03
142	34.5	> 10.0E+03
144	32	> 10.0E+03
145	120	> 10.0E+03
146	9.9	> 10.0E+03
147	16.1	> 10.0E+03
Example S150, Enantiomer 1	40.5	--
153	8.67	> 10.0E+03
Example S205, Enantiomer 1	21.5	--
Example S205, Enantiomer 2	55.3	--
Example S220, Enantiomer 1	24.9	> 10.0E+03
Example S220, Enantiomer 2	57.3	> 10.0E+03
253	30.8	> 10.0E+03
Example S221, Enantiomer 1	11.1	6590
Example S221, Enantiomer 2	39.7	8660

Luminescence-based ABL Kinase Assay (300μM ATP)

[1148] Kinase activity of ABL1 was measured using the ADP-Glo system (Promega), which measures formation of ADP using a luminescence-based method. Compounds were serially diluted in DMSO. 20 nL of compound or DMSO only (high control, HC) were added to a 384-well plate (OptiPlate-384, PerkinElmer) using an Echo550 liquid handler (Labcyte). 15 μL of kinase solution (10 mM $MgCl_2$, 0.01% Brij-35, 2 mM DTT, 0.05% BSA, 1 mM EGTA, 50 mM HEPES pH 7.5, and 3.325 nM ABL1 [Carna Biosciences]) were added to each well of the 384-well plate containing the compounds. No enzyme control wells were included (low control, LC). The plate was incubated at room temperature for 30 minutes. 5 μL of a second solution containing 10 mM $MgCl_2$, 0.01% Brij-35, 2 mM DTT, 0.05% BSA, 1 mM EGTA, 50 mM HEPES pH 7.5, 6 μM Peptide 2 (Perkin Elmer, Cat No 760346), and 1.2 mM ATP were added to each well to start the kinase reaction. The plate was incubated for 90 minutes at room temperature. 20 μL of ADP-Glo reagent (Promega) were then added to each well and the plate was incubated for 40 minutes at room temperature. 40 μL of kinase detection reagent (Promega) was added to each well and the plate was incubated for an additional 45 minutes at room temperature. During this step, ADP was converted to ATP, a

substrate for luciferase, to produce luminescence signal. Luminescence was measured on an Envision plate reader (Perkin Elmer). Luminescence signal positively correlates with kinase activity. The percent kinase activity was calculated as follows: percent kinase activity = 100 x (Lum_{Sample} – Lum_{LC})/(Lum_{HC} – Lum_{LC}). As noted above, DMSO only and no enzyme wells were used as high and low controls, respectively. IC50 values were calculated using the XLFit software.

[1149] IC_{50} data obtained using the screening procedures described above for certain compounds disclosed herein are listed in Table 3.

Table 3.

Cmpd No.	Kinase, IC_{50} (nM)	
	ABL1	ABL1 (T315I)
1	37.9	11.3
2	22.2	9.96
3	8.17	0.896
4	113	32.3
5	119	32.9
6	123	65.6
13	96.6	9.74
14	91.2	52.8
15	12.1	2.78
16	> 10.0E+03	> 10.0E+03
17	55.1	28.6
18	33	14.5
19	11.2	4.57
20	110	27.7
21	94.8	8.74
22	78.9	7.17
24	149	33
25	776	74.3
26	62.9	68.4
27	29	20.2
28	7.58	2.84
29	41.8	10.5
30	148	90.2
31	169	359
32	135	183
33	319	603

Cmpd No.	Kinase, IC_{50} (nM)	
	ABL1	ABL1 (T315I)
34	159	731
35	599	774
36	202	690
37	46.1	103
38	689	332
39	195	245
40	121	170
41	106	26.8
42	45.4	12.7
43	91.1	15.6
44	23.1	39.8
45	4.64	4.62
46	86.4	20.6
47	7.47	0.705
48	94.9	244
49	4.33	3.04
50	3.9	2.51
51	15.4	4.41
52	8.95	13.7
53	6.92	5.63
54	14.3	16.3
55	114	1030
56	30.3	53.5
57	1090	3870
58	2.92	3.4
59	8.62	11

Cmpd No.	Kinase, IC_{50} (nM)	
	ABL1	ABL1 (T315I)
60	218	417
61	3.28	5.08
62	20.8	43
63	40.7	64.5
64	56.9	140
65	158	8700
66	91.5	38.7
67	157	37.7
68	78.2	19.2
69	27.6	27.4
70	60.3	140
71	48	55.2
72	70.2	162
73	2460	> 10.0E+03
74	55.6	63
75	15.1	17.6
76	5.14	7.38
77	106	137
78	17.8	139
79	143	108
80	1050	659
81	12.2	12.9
82	13.5	20.5
83	1.52	1.74
84	37	14.9
85	5.34	27.8
86	5.97	5.48
87	9.54	6.59
88	18.6	30.9
89	337	219
90	21.7	15
91	166	24.6
92	39.4	27.3
93	5.3	2.94
94	10.8	6.36
95	6.32	2.14
96	8.87	8.93
97	199	61.6
98	16.4	12.9
99	14.9	25.7

Cmpd No.	Kinase, IC_{50} (nM)	
	ABL1	ABL1 (T315I)
100	98.2	105
101	16.4	15.3
102	12.5	17.8
103	99.2	32.5
104	102	29.1
105	109	19.9
106	78.1	26.1
107	151	19.5
108	78.6	17.8
109	39	7.08
110	74.8	18.2
111	14.3	151
112	271	157
113	20.9	15.9
114	51.4	150
115	124	151
116	49.4	59.3
117	11.3	9.08
118	3.73	1.48
119	4.67	2.57
120	65.5	60.8
121	31.8	5.98
122	73.4	19.9
123	56.5	17.6
124	317	30.6
125	22.2	39.5
126	2580	3860
127	22.1	0.745
128	24.9	97.1
129	32.9	35.8
130	67	33.7
131	42.7	28.1
132	143	97.5
133	3.57	6.1
134	64.8	227
135	24.9	15.8
136	27.4	54.5
137	36	40.6
138	51.2	140
139	18.6	16.8

Cmpd No.	Kinase, IC_{50} (nM)	
	ABL1	ABL1 (T315I)
140	30.6	82.5
141	45.5	31.2
142	14.6	14.3
145	51.6	44.3
146	3.74	14
147	5.54	1.71
Example S148, Enantiomer 1	408	1810
Example S150, Enantiomer 1	5.42	1.73

Cmpd No.	Kinase, IC_{50} (nM)	
	ABL1	ABL1 (T315I)
Example S150, Enantiomer 2	30	27.2
153	4.65	1.37
Example S205, Enantiomer 1	10.6	15
Example S205, Enantiomer 2	15	20.9
250	411	408
253	6.71	8.81

pCRKL ELISA assay:

[1150] K562 or Ba/F3 ABL T315I cells ($2.0*10^5$cells/100µl/well) were seeded in 96 well (Corning, cat # 3799). Compounds were dissolved in DMSO, serially diluted in DMSO and then were added, mixed, and incubated for 90 minutes at 37°C, 5% CO_2. Following the 90-minute incubation, plates were centrifuged for 5 min at 3000 RPM and supernatant was removed from each well. Cells were washed 3 times with 150µl PBS prior to addition of 100µl cell RIPA lysis buffer (Boston BioProducts, cat # BP-115D) supplied with 1x complete ULTRA cocktail inhibitor (Roche, 05892791001) and1x PhosSTOP Phosphatase Inhibitor Cocktail Tablets (Roche,04906837001). Cells were incubated with lysis buffer for 1 hour at 4°C prior to storage at -80C.

[1151] A capture antibody able to detect phosphorylated and non-phosphorylated CRKL (R&D Systems, cat # AF5127) was added to Meso Scale Discovery (MSD) standard bind plates (MSD, cat# L15XA-3) at 5ug/mL and incubated at 4°C overnight. The next day, plates were washed with PBS+ 0.05% Tween20 (PBST) and 150µl of 5% BSA blocking solution was added for 1 hour at room temperature with shaking. Plates were washed with PBST. Lysates were thawed and 30µl of lysate was added to the MSD plates and incubated for 2 hours at room temperature with shaking. MSD plates were washed with PBST and 30µl of a detection antibody that binds phosphorylated pCRKL (R&D Systems, cat # MAB6910) was added at 1ug/mL to each well. Plates were incubated for 1 hour at room temperature with shaking. Plates were washed with PBST prior to addition of 30µl of a sulfo tagged goat anti mouse detection antibody (MSD cat# R32AC-1). Plates were incubated for 1 hour at room temperature with shaking. Plates were washed with PBST prior to addition of 150ul of 1x

MSD read buffer T (MSD, cat #R92TC-2). Electrochemiluminescence (ECLU) was read on an MSD plate reader (Meso Scale Discovery). The remaining activity by calculated as follows: % Relative activity = 100 x ($ELCU_{sample}$- $ECLU_{LC}$) / ($ECLU_{HC}$ -$ECLU_{LC}$). The low and high controls (LC/HC) are generated from lysate from wells without cells or with cells treated with 0.1% DMSO, respectively. IC50 values were calculated using XLFit software using a nonlinear regression model with a sigmoidal dose response and are shown in Table 4 and Table 5 below.

Table 4.

Cmpd No.	pCRKL ELISA, Cell Line IC_{50} (nM)
	K562
3	174
15	468
26	680
27	164
42	88.3
44	275
47	685
49	585
50	151
51	1350
52	3120
53	584
54	95.8
56	745
58	281
61	88.4
62	171
63	328

Cmpd No.	pCRKL ELISA, Cell Line IC_{50} (nM)
	K562
66	702
74	572
75	86.3
76	65.4
77	1120
82	1050
95	656
98	174
131	272
133	278
135	1210
145	399
146	32
147	35.7
Example S150, Enantiomer 1	453

Table 5.

Compound No.	pCRKL ELISA, Cell Line IC_{50} (nM)
	Ba/F3 ABL1 (T315I)
27	183
54	198
75	162
76	50.1
86	84.2
95	429
98	241
116	1060

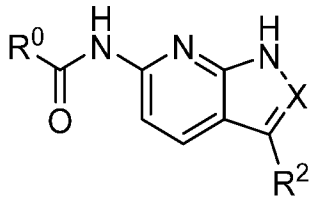
Compound No.	pCRKL ELISA, Cell Line IC_{50} (nM)
	Ba/F3 ABL1 (T315I)
117	124
146	112
147	35.7
Example S150, Enantiomer 1	1460

[1152] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced in light of the above teaching. Therefore, the description and examples should not be construed as limiting the scope of the invention.

CLAIMS

What is claimed is:

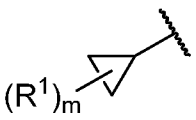
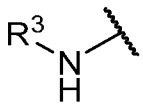
Claim 1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

X is N or CR^8;

R^0 is a group  or  ;

m is an integer from 0 to 3;

each R^1 is independently -D, -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, -O-C_1-C_3 alkylene-NR^4R^5, -O-C_1-C_3 alkylene-$NR^{4'}R^{5'}$,C_1-C_3 alkylene-OH, C_0-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^5$, C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene moieties in R^1 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

or

two R^1 are taken together with the carbon atom or carbon atoms to which they are attached to form a 3- to 7-membered heterocyclic ring, wherein the heterocyclic ring contains nitrogen atom and wherein the nitrogen atom is optionally substituted with C_1-C_3 alkyl;

R^2 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein the C_6-C_{14} aryl and 5-to-10-membered heteroaryl are optionally substituted with 1-5 R^6 groups;

R^3 is -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkylene-NR^4R^5, C_1-C_6 alkylene-$NR^{4'}R^{5'}$, C_1-C_6 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_3 alkylene-(C_3-C_6 cycloalkyl), C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-O-(C_1-C_3 alkylene)-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_3 alkylene-(4- to 8-membered heterocycloalkyl), C_1-C_3 alkylene-(C_3-C_7 heterocycloalkyl), C_1-C_3 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, (4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, or (C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, heterocycloalkyl, and heterocycloalkylene moieties in R^3 are optionally substituted with 1-3 fluorine atoms, 1-3 CN groups and/or 1-6 deuterium atoms and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, C_2-C_3 heteroalkyl, 4- to 8-membered heterocycloalkyl, or C_3-C_7 heterocycloalkyl;

each R^4 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-6 deuterium atoms;

each R^5 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-6 deuterium atoms;

each pair of $R^{4'}$ and $R^{5'}$ taken together with the nitrogen atom to which they are attached independently form a 3-to-7-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each additional nitrogen atom, if present, is independently optionally

substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

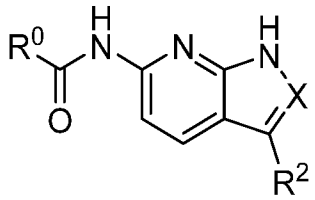
each R^6 is independently halogen, -OR^7, -NR^4R^5, -$NR^{4'}R^{5'}$, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, -CN, $S(O)_nC_1$-C_3 alkyl, or $S(O)_nC_3$-C_6 cycloalkyl,

wherein n is an integer from 0 to 2;

each R^7 is independently -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, or C_1-C_3-alkylene-C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-6 deuterium atoms; and

R^8 is -H, -F, or C_1-C_3 alkyl.

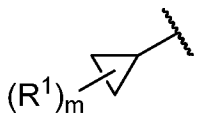
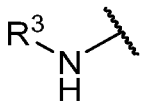
Claim 2. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

X is N or CR^8;

R^0 is a group  or  ;

m is an integer from 0 to 3;

each R^1 is independently -D, -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, C_0-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-

(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene moieties in R^1 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

R^2 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein the C_6-C_{14} aryl and 5-to-10-membered heteroaryl are optionally substituted with 1-5 R^6 groups;

R^3 is -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkylene-NR^4R^5, C_1-C_6 alkylene-$NR^{4'}R^{5'}$, C_1-C_6 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_3 alkylene-(C_3-C_6 cycloalkyl), C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, C_1-C_3 alkylene-O-(C_1-C_3 alkylene)-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_3 alkylene-(C_4-C_6 heterocycloalkyl), C_1-C_3 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, or C_1-C_3 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, heterocycloalkyl, and heterocycloalkylene moieties in R^3 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, C_2-C_3 heteroalkyl, or C_4-C_6 heterocycloalkyl;

each R^4 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl;

each R^5 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl;

each pair of $R^{4'}$ and $R^{5'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

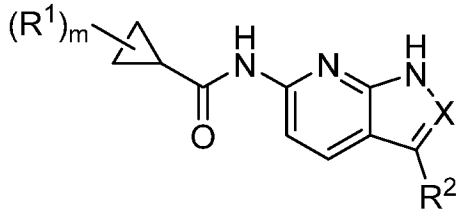
each R^6 is independently halogen, $-OR^7$, $-NR^4R^5$, $-NR^{4'}R^{5'}$, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, -CN, $S(O)_nC_1$-C_3 alkyl, or $S(O)_nC_3$-C_6 cycloalkyl,

wherein n is an integer from 0 to 2;

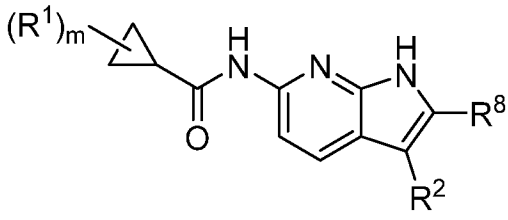
each R^7 is independently -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-6 deuterium atoms; and

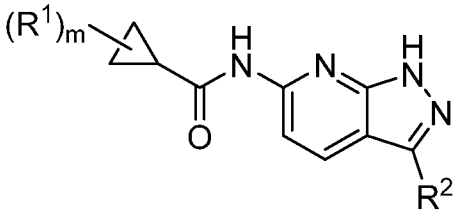
R^8 is -H, -F, or C_1-C_3 alkyl.

Claim 3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein the compound of formula (I) is a compound of formula (I-A)


(I-A).

Claim 4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein the compound of formula (I) is a compound of formula (I-A-i) or formula (I-A-ii):


(I-A-i), or

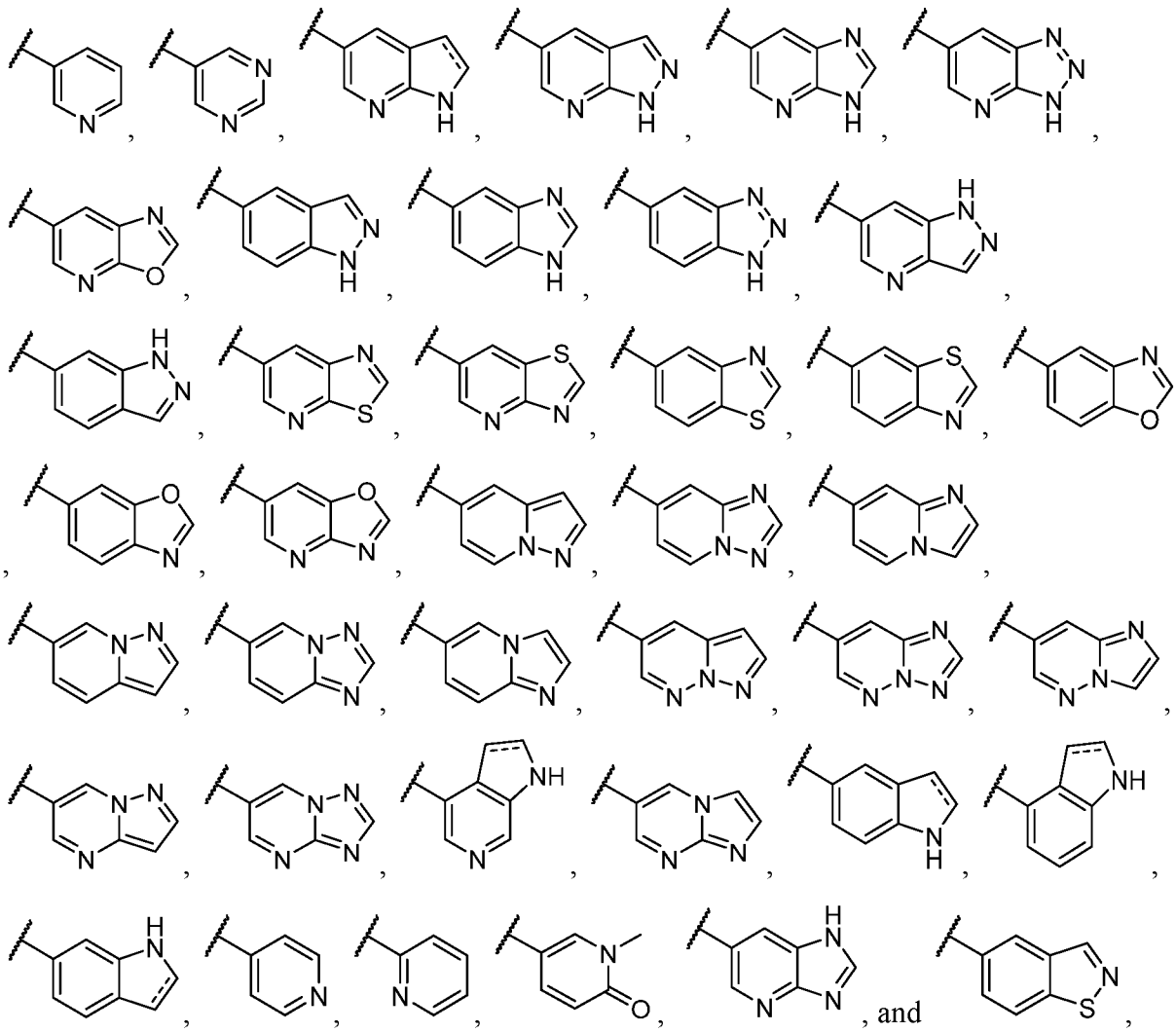

(I-A-ii),

wherein:

m is an integer from 0 to 2;

each R^1 is independently -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, C_0-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5 or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene moieties in R^1 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

R^2 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of:



wherein ≡ indicates a single or double bond, and wherein the C_6-C_{14} aryl and 5-to-10-membered heteroaryl are optionally substituted with 1-5 R^6 groups;

each R^4 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^5 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each pair of $R^{4'}$ and $R^{5'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^6 is independently halogen, $-OR^7$, $-NR^4R^5$, C_1-C_3 alkyl, $-CF_2H$, $-CF_3$, C_3-C_6 cycloalkyl, or -CN;

each R^7 is independently -H, C_1-C_3 alkyl, $-CD_3$, $-CF_2H$, $-CF_3$, or C_3-C_6 cycloalkyl; and

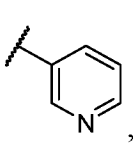
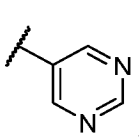
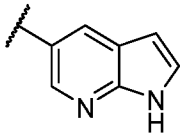
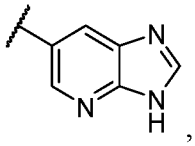
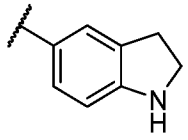
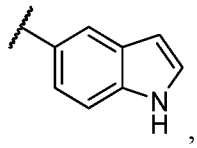
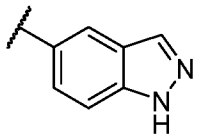
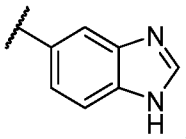
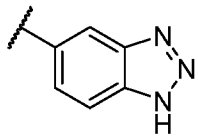
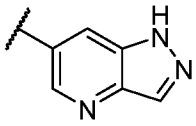
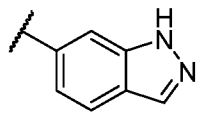
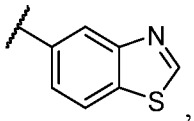
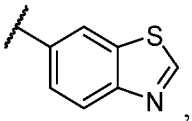
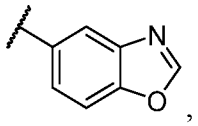
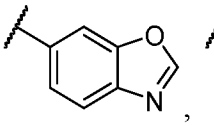
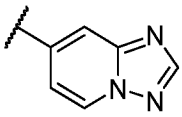
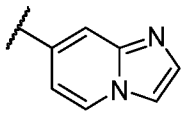
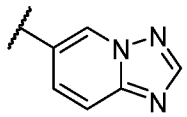
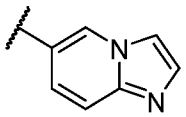
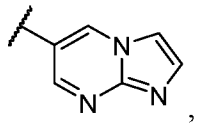
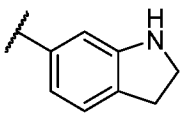
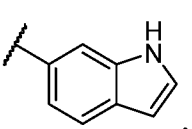
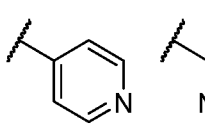
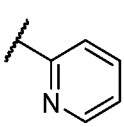
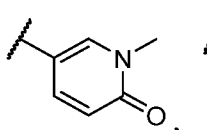
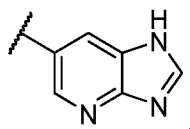
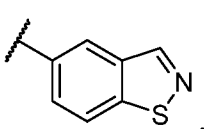
R^8 is -H, -F, or $-CH_3$.

Claim 5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

each R^1 is independently -F, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, or C_0-C_3 alkylene-CN,

wherein each pair of $R^{4'}$ and $R^{5'}$ of R^1 taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl.

Claim 6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

R^2 is phenyl,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , each of which is optionally substituted with 1-5 R^6 groups.

Claim 7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

each R^6 is independently halogen, $-OR^7$, $-NR^4R^5$, C_1-C_3 alkyl, $-CF_3$, or -CN,

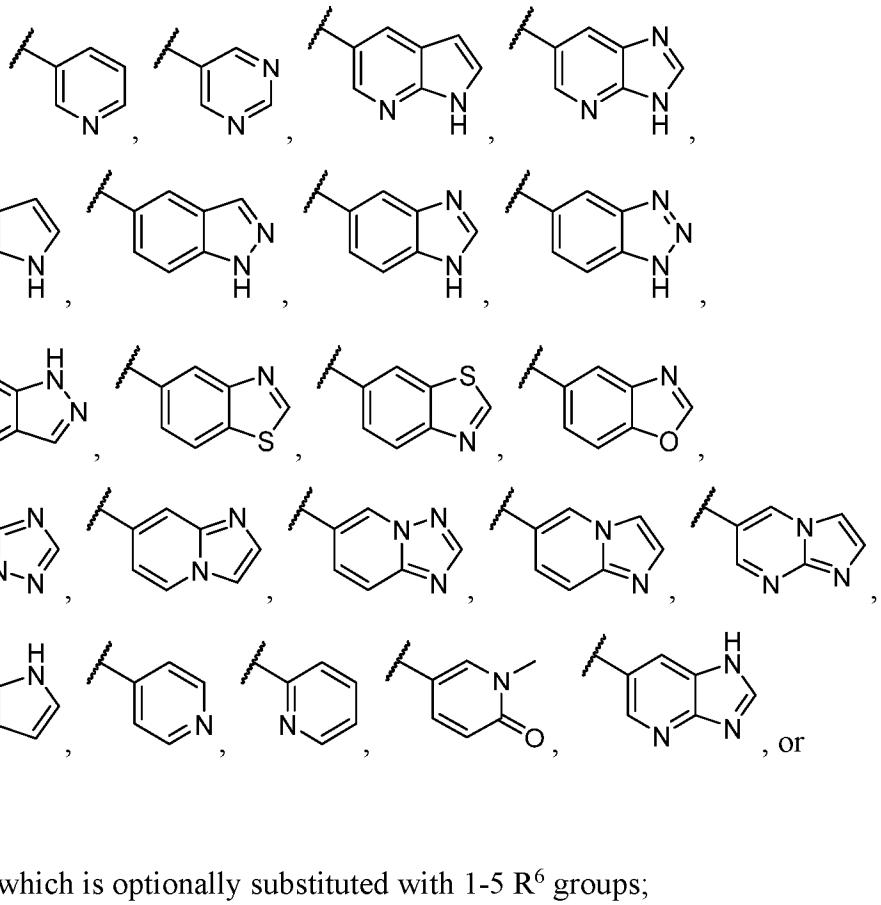
wherein each R^4 of R^6 and each R^5 of R^6 are independently -H or C_1-C_3 alkyl; and

each R^7 is independently -H, C_1-C_2 alkyl, $-CD_3$, C_1-C_2 haloalkyl, or C_3 cycloalkyl.

Claim 8. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

each R^1 is independently -F, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, or C_0-C_3 alkylene-CN,

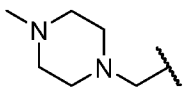
wherein each pair of $R^{4'}$ and $R^{5'}$ of R^1 taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl;

R^2 is phenyl,  , each of which is optionally substituted with 1-5 R^6 groups;

each R^6 is independently halogen, $-OR^7$, $-NR^4R^5$, C_1-C_3 alkyl, $-CF_3$, or -CN, wherein each R^4 of R^6 and each R^5 of R^6 are independently -H or C_1-C_3 alkyl; and

each R^7 is independently -H, C_1-C_2 alkyl, $-CD_3$, C_1-C_2 haloalkyl, or C_3 cycloalkyl.

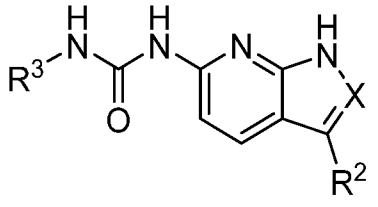
Claim 9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

each R^1 is independently F,  , $-CH_2OH$, $-CH_2CH_2OH$, -CN, or $-CH_2CN$.

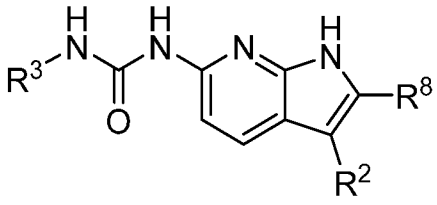
Claim 10. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

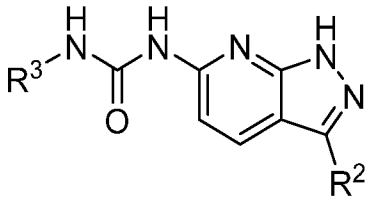
each R^6 is independently -F, -Cl, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-OCD_3$, cyclopropyloxy, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-CH_3$, $-CF_3$, or -CN.

Claim 11. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein the compound of formula (I) is a compound of formula (I-B)


(I-B).

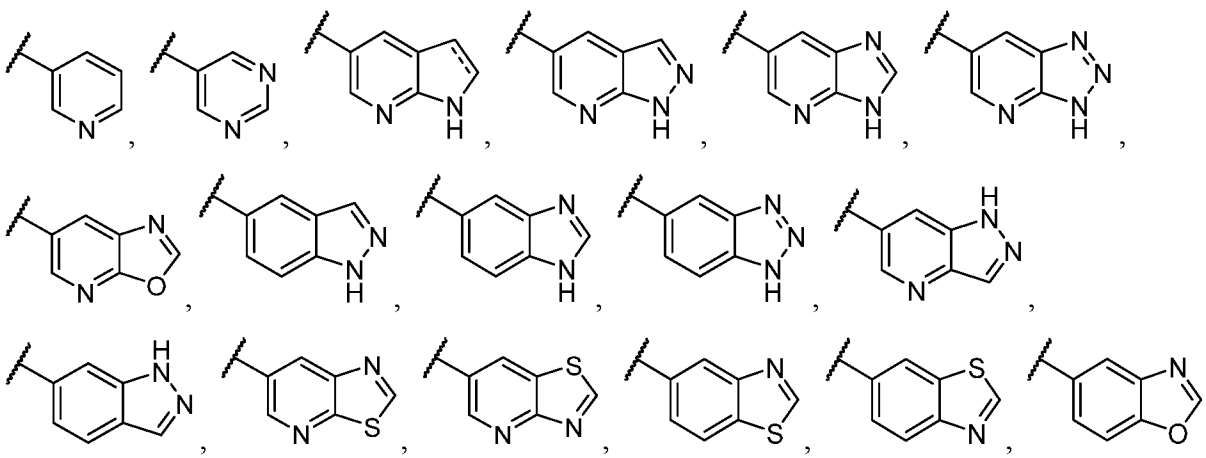
Claim 12. The compound of any one of claims 1 to 2 and 11, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein the compound of formula (I) is a compound of formula (I-B-i) or formula (I-B-ii)

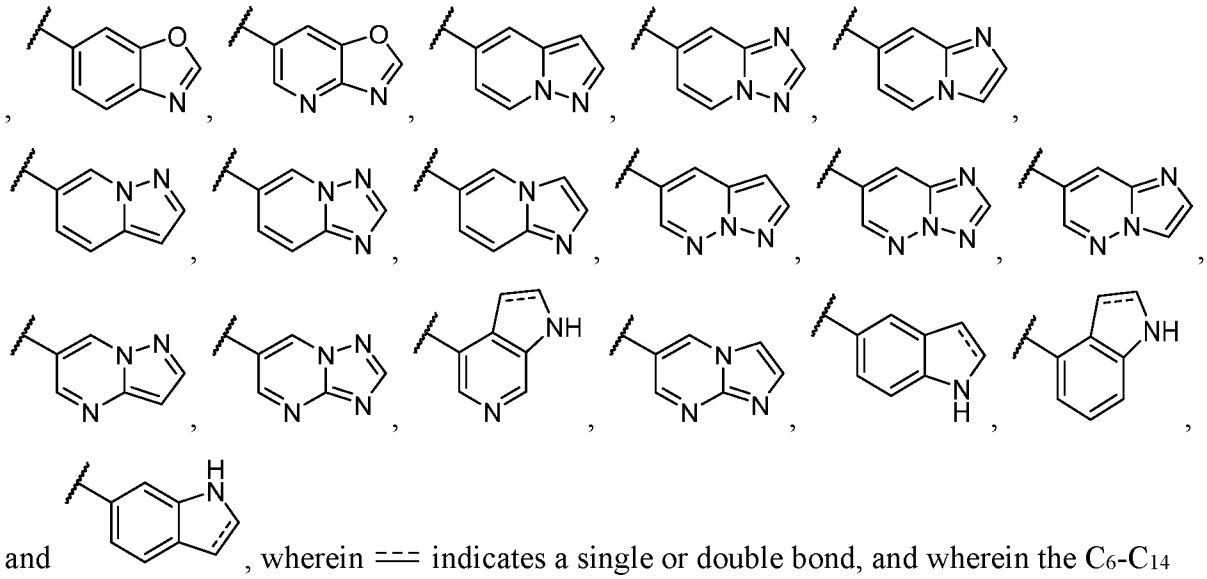

(I-B-i), or


(I-B-ii),

wherein:

R^2 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of:





and , wherein ≡ indicates a single or double bond, and wherein the C_6-C_{14} aryl and 5-to-10-membered heteroaryl are optionally substituted with 1-5 R^6 groups;

R^3 is C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkyl), C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, C_1-C_2 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkyl), C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^4R^5, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{4'}R^{5'}$, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, heterocycloalkyl, and heterocycloalkylene moieties in R^3 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, C_2-C_3 heteroalkyl, or C_4-C_6 heterocycloalkyl;

each R^4 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^5 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each pair of $R^{4'}$ and $R^{5'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally

substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^6 is independently halogen, -OR^7, C_1-C_3 alkyl, -CF_2H, -CF_3, C_3-C_6 cycloalkyl, or -CN;

each R^7 is independently -H, C_1-C_3 alkyl, -CD_3, -CF_2H, -CF_3, or C_3-C_6 cycloalkyl; and

R^8 is -H, -F, or -CH_3.

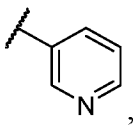
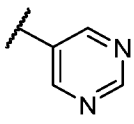
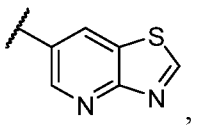
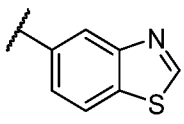
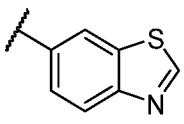
Claim 13. The compound of any one of claims 1, 2, 11 and 12, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

R^3 is C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkyl), C_1-C_2 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkyl), wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl or C_4-C_6 heterocycloalkyl,

wherein the R^4 and R^5 of R^3 are independently -H or C_1-C_3 alkyl, and

the $R^{4'}$ and $R^{5'}$ of R^3 taken together with the nitrogen atom to which they are attached form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl.

Claim 14. The compound of any one of claims 1 to 2 and 11 to 13, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

R^2 is phenyl,  ,  ,  ,  , or  , each of which is optionally substituted with 1-5 R^6 groups.

Claim 15. The compound of any one of claims 1 to 2 and 11 to 14, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

each R^6 is independently halogen or -OR^7; and

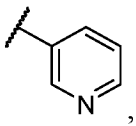
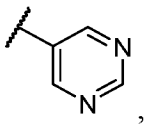
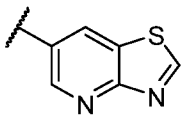
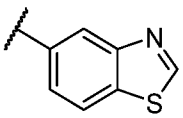
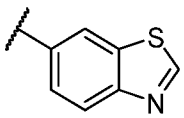
each R^7 is independently C_1-C_2 alkyl or C_3 cycloalkyl.

Claim 16. The compound of any one of claims 1 to 2 and 11 to 12, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

R^3 is C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkylene-NR^4R^5, C_1-C_3 alkylene-$NR^{4'}R^{5'}$, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkyl), C_1-C_2 alkylene-O-(C_1-C_2 alkylene)-NR^4R^5, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkyl), wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl or C_4-C_6 heterocycloalkyl,

wherein the R^4 and R^5 of R^3 are independently -H or C_1-C_3 alkyl, and

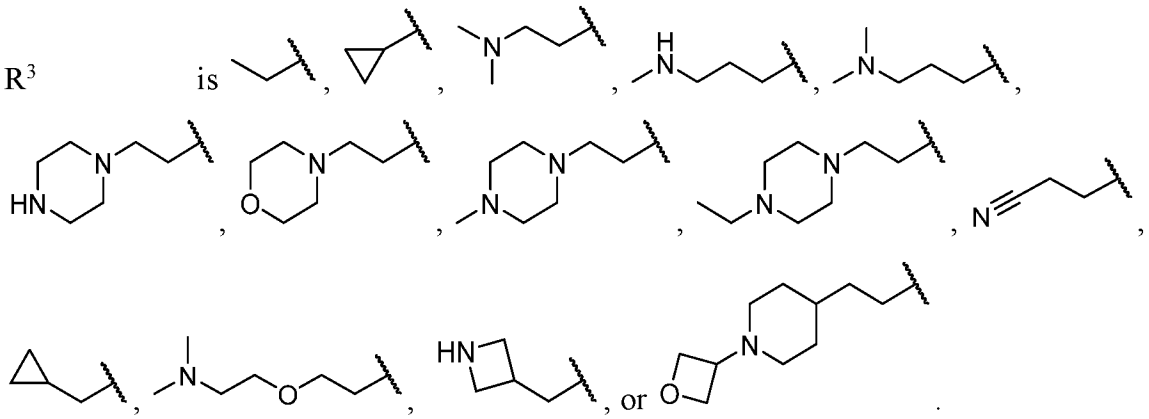
the $R^{4'}$ and $R^{5'}$ of R^3 taken together with the nitrogen atom to which they are attached form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein each additional nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl;

R^2 is phenyl,  ,  ,  ,  , or  ,
each of which is optionally substituted with 1-5 R^6 groups;

each R^6 is independently halogen or -OR^7; and

each R^7 is independently C_1-C_2 alkyl or C_3 cycloalkyl.

Claim 17. The compound of claim any one of claims 1 to 2 and 11 to 16, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein

R^3 is 

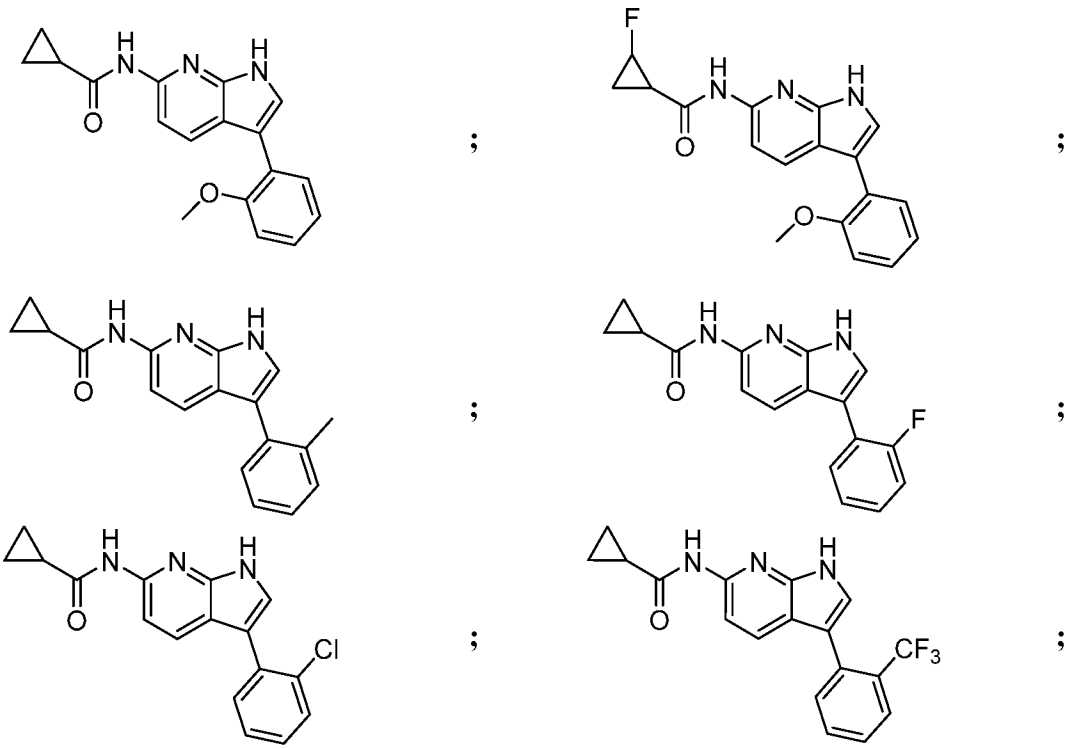
Claim 18. The compound of any one of claims 1 to 2 and 11 to 17, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein

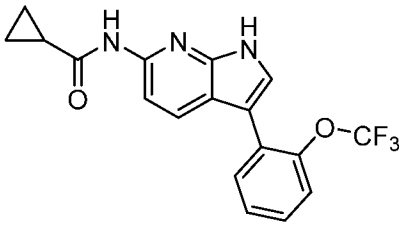
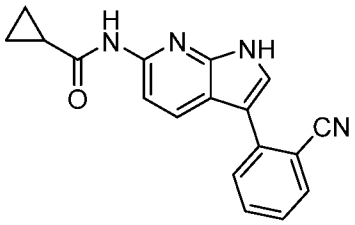
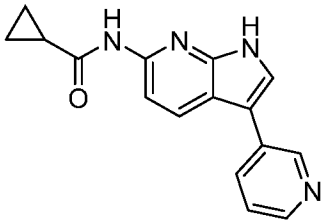
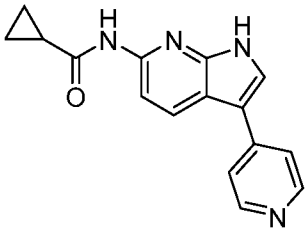
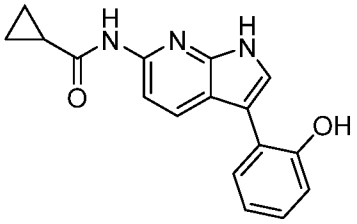
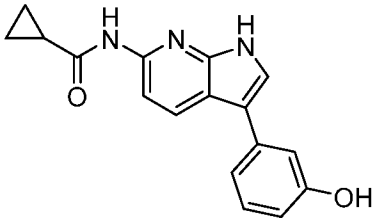
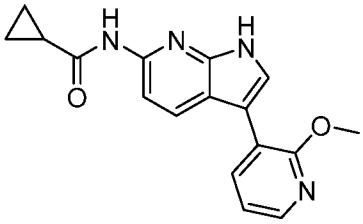
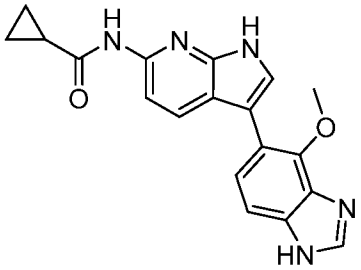
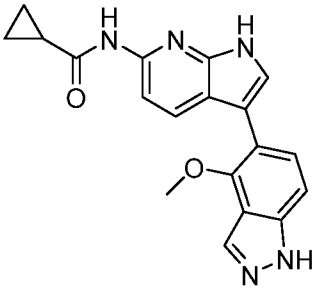
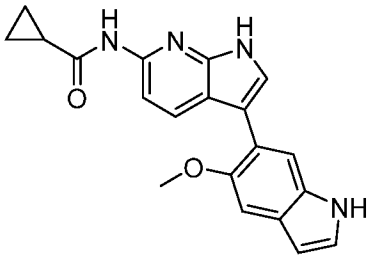
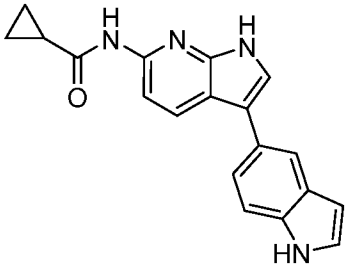
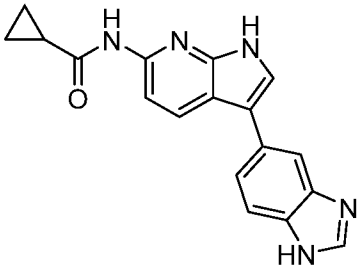
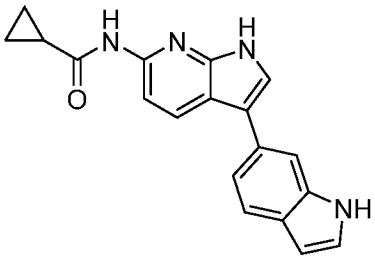
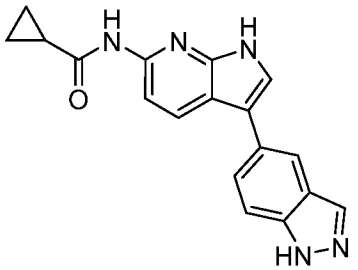
each R^6 is independently -F, $-OCH_3$, or cyclopropyloxy.

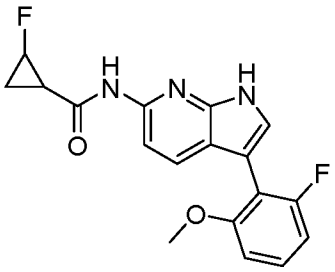
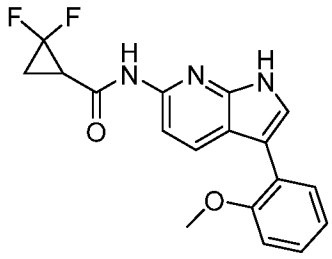
Claim 19. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein

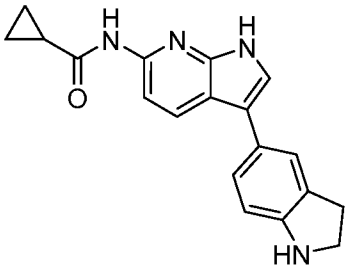
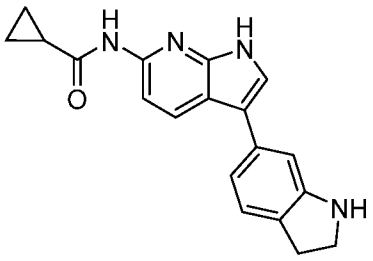
R^8 is H.

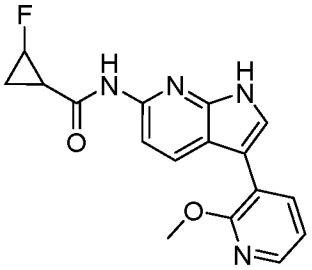
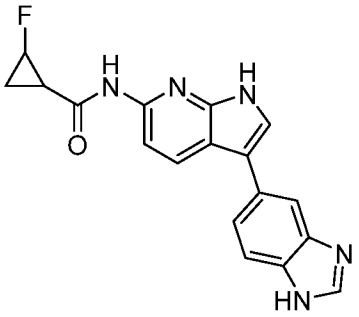
Claim 20. A compound selected from the group consisting of:

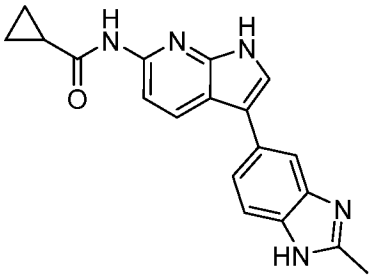
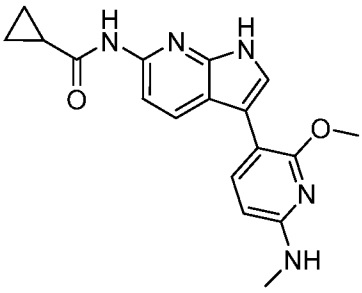


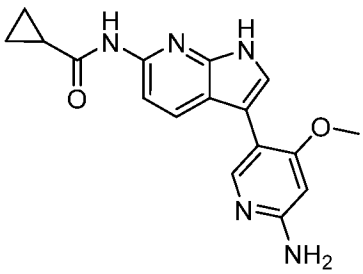
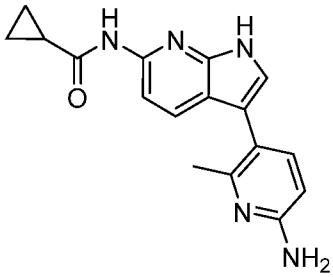

;

;

;

;

;

;

;

;

;

;

;

;

;

;

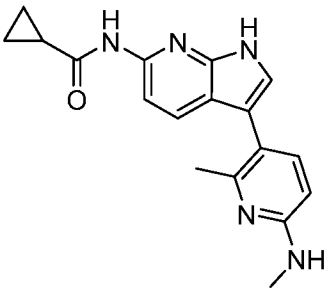
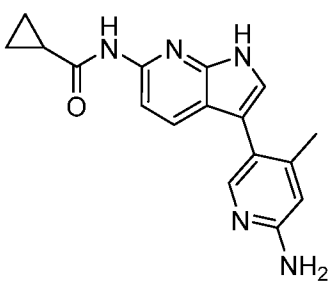

;

;

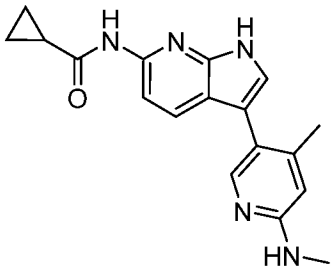
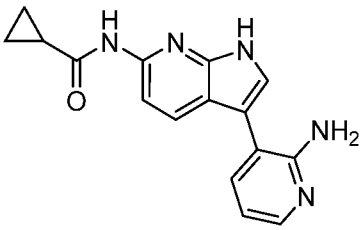
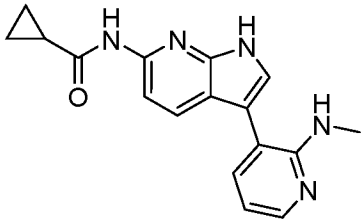
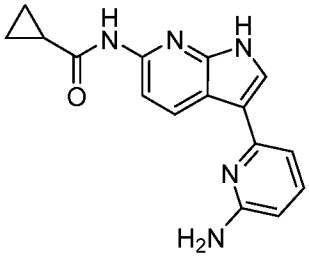
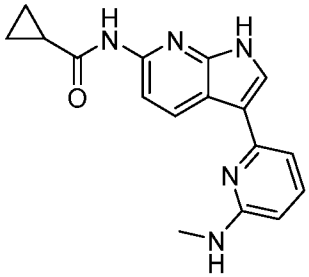
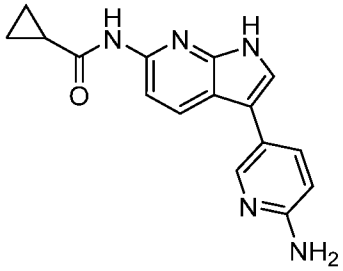
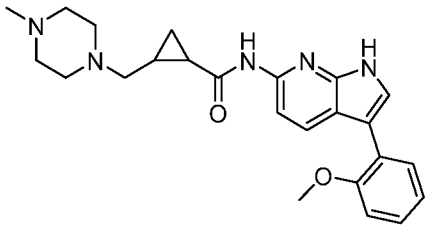
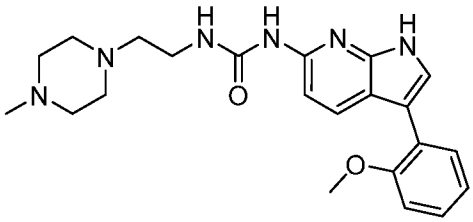
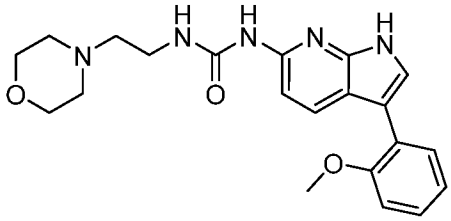
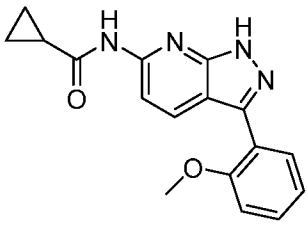
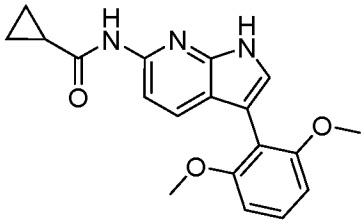
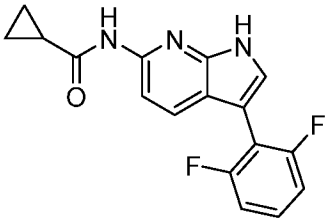
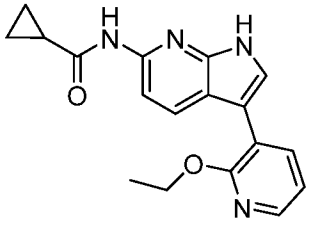
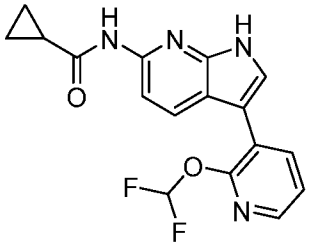

;

;

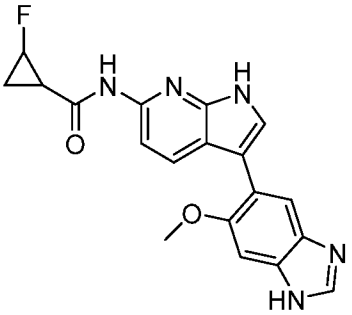
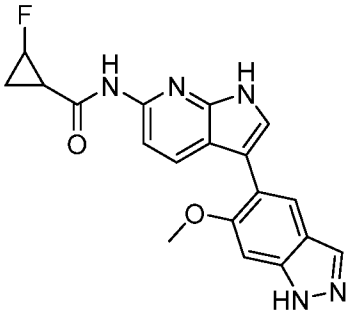

;

;

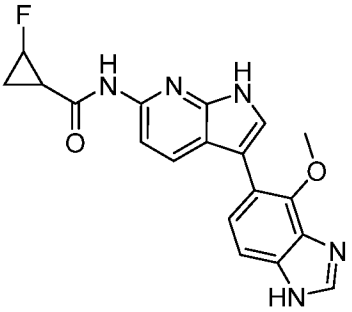
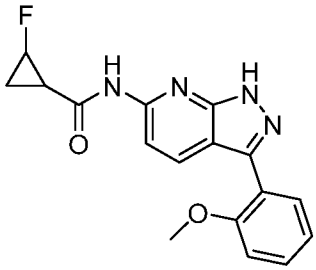

;

;

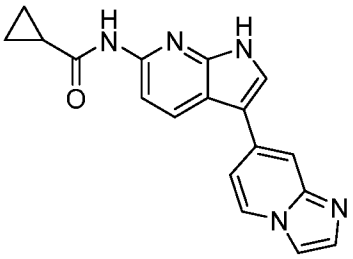
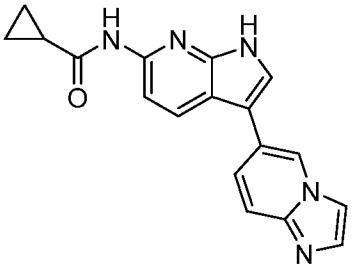

;

;

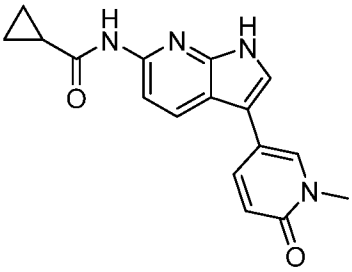
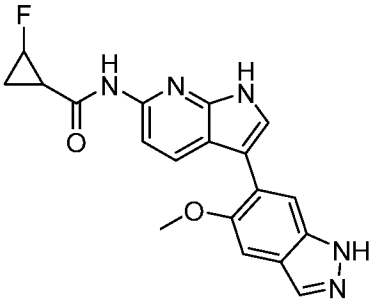

;

;

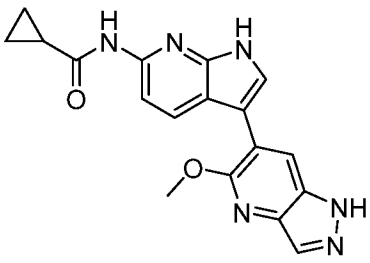
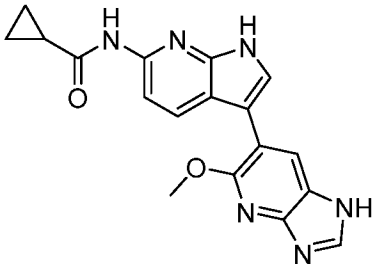

;

;

;

;

;

;

;

;

;

;

;

;

;

;

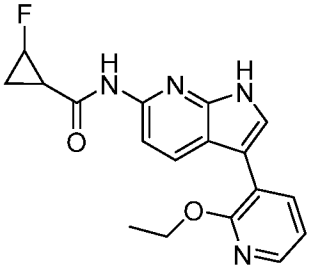
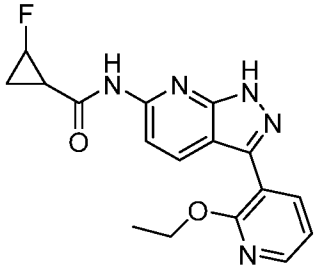

;

;

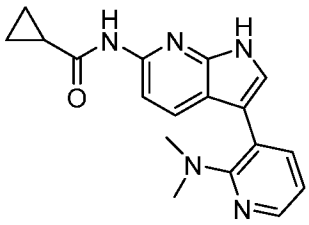
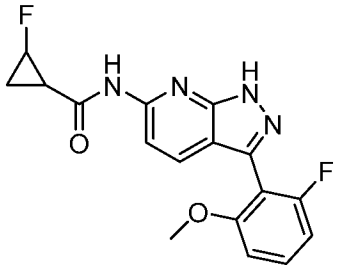

;

;

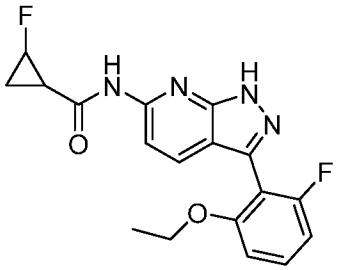
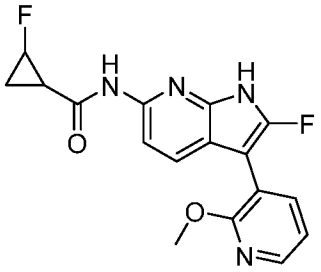

;

;

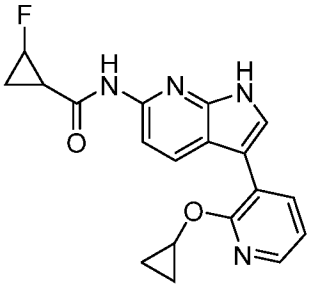
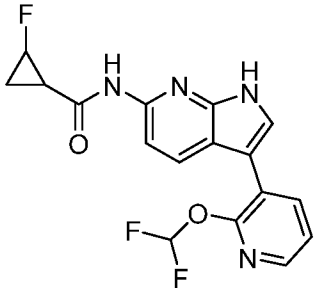

;

;

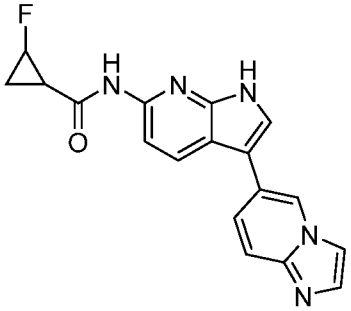
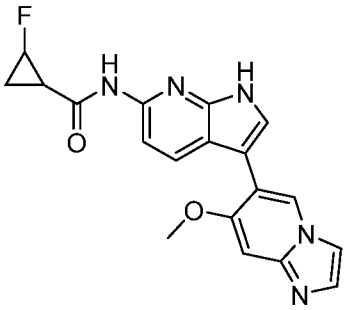

;

;

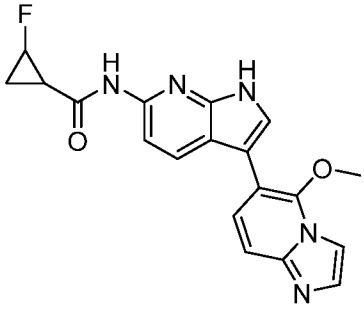
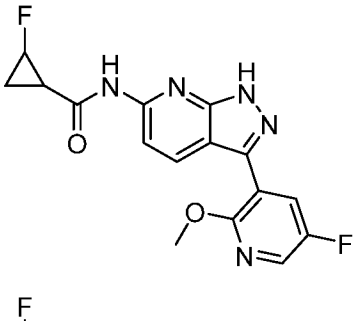

;

;

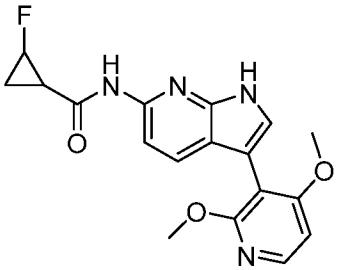
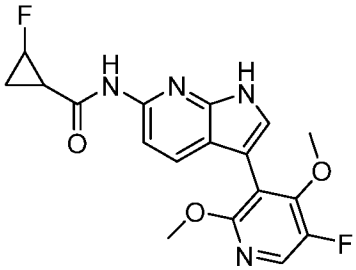

;

;

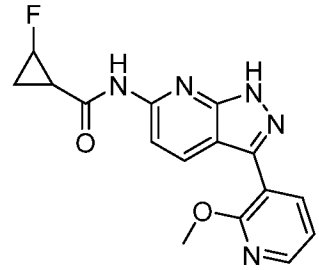
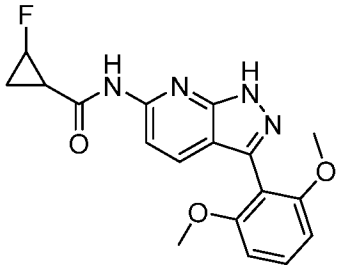
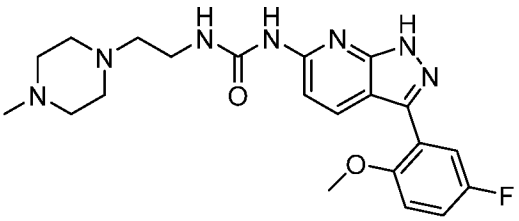
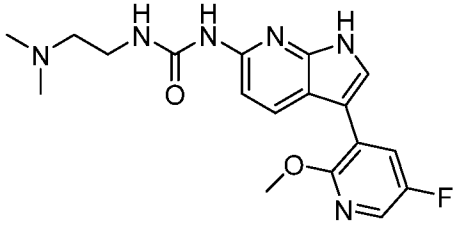
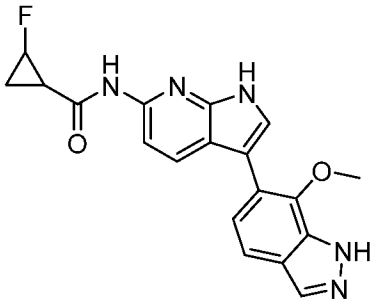
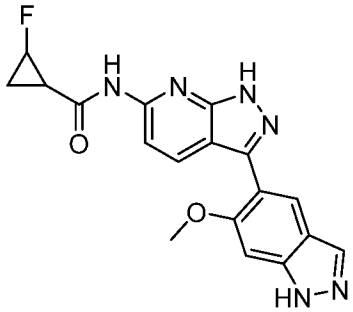
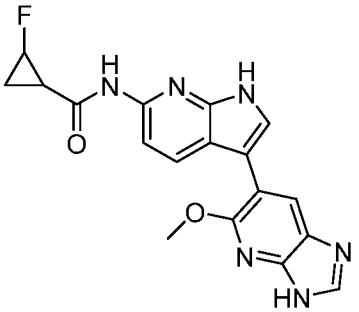
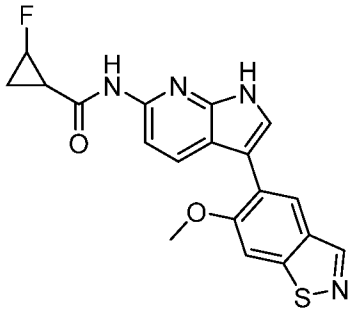
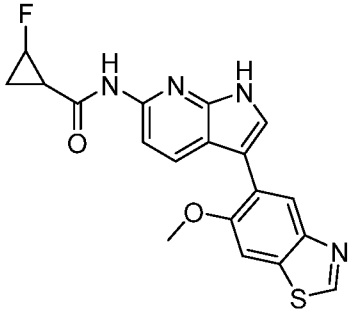
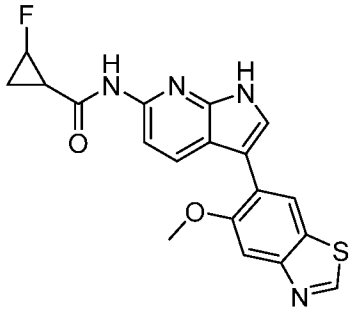
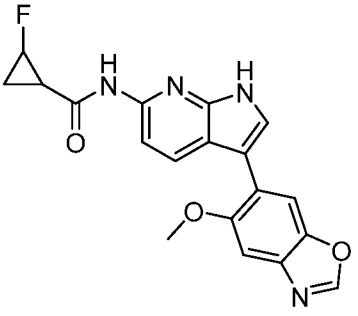
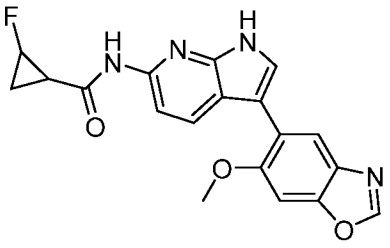

;

;

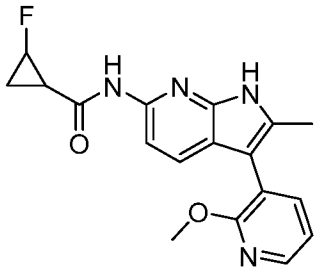
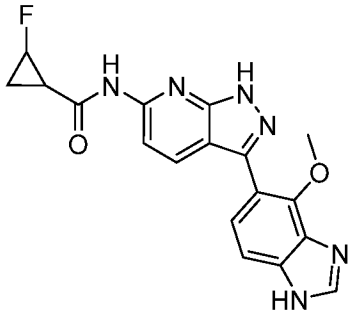

;

;

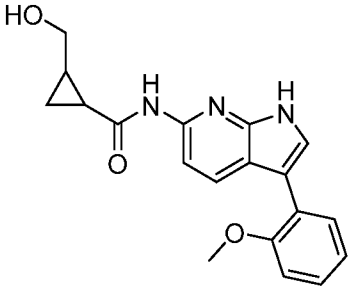
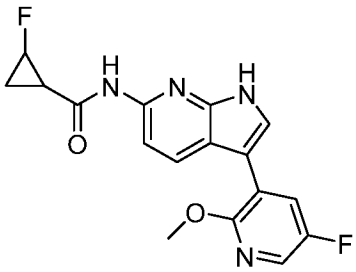

;

;

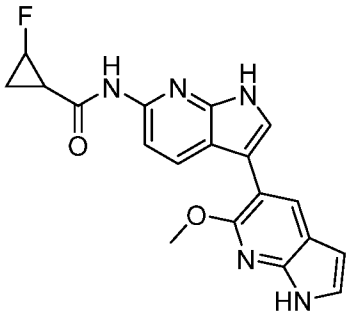
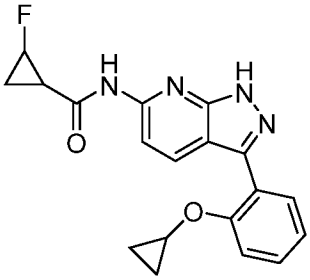

;

;

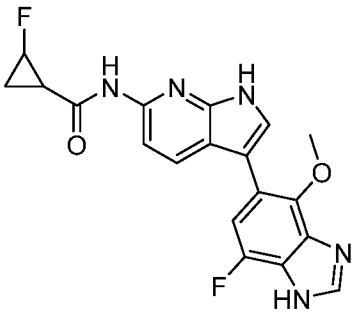
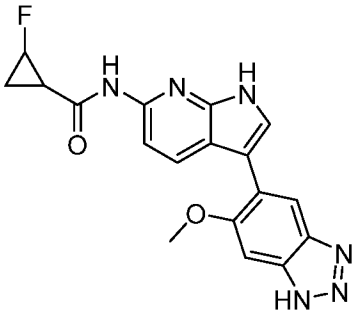

;

;

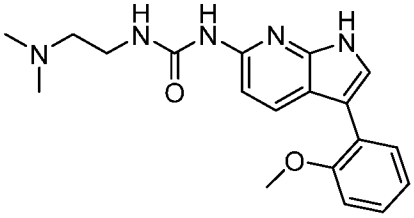
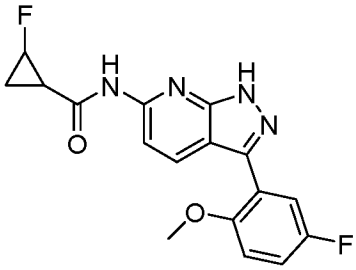

;

;

;

;

;

;

;

;

;

;

;

;

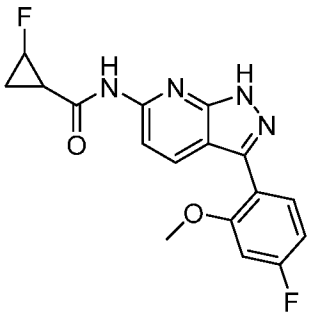
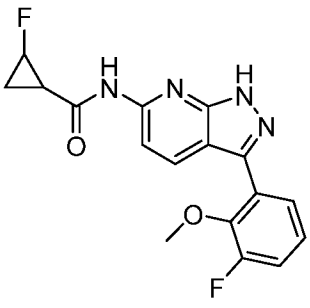

;

;

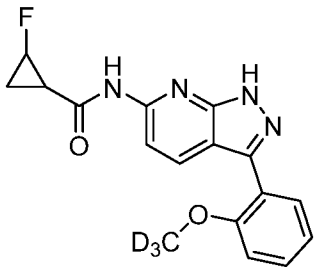
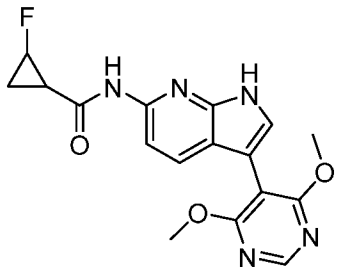
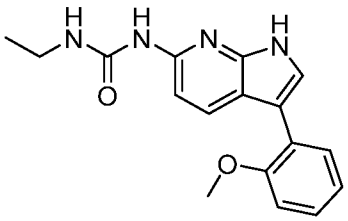
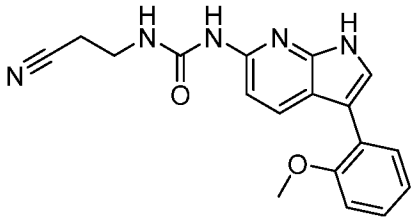
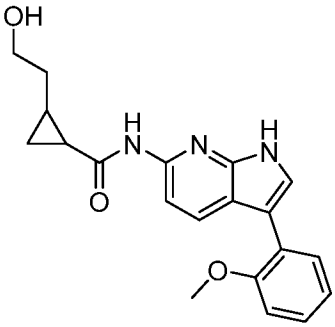
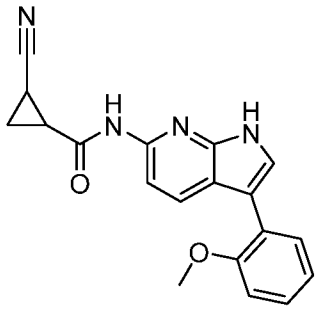
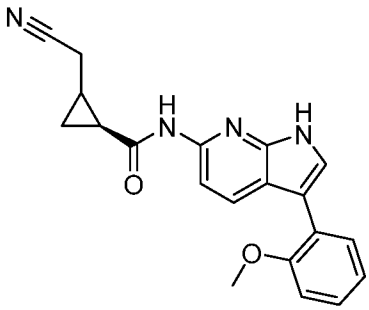
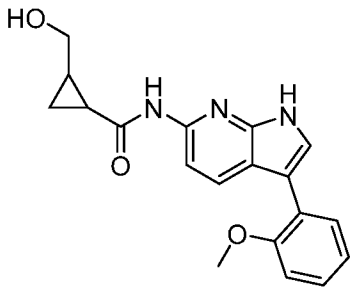
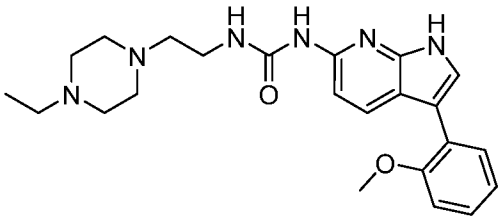
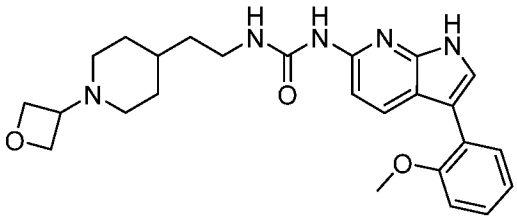
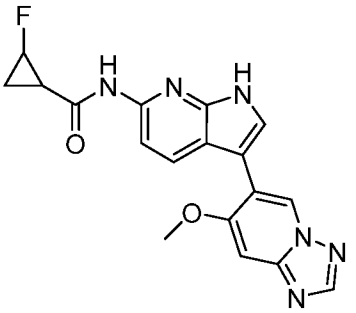
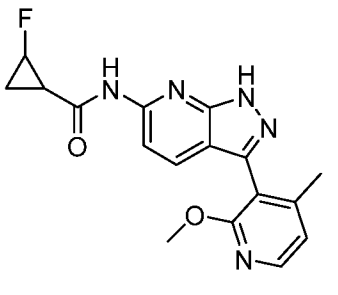

;

;

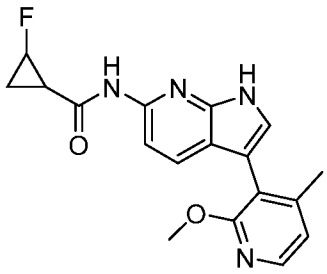
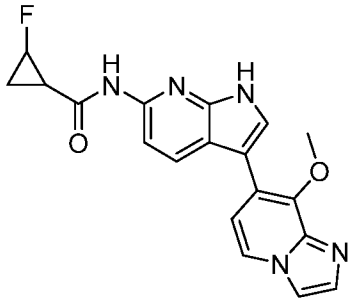
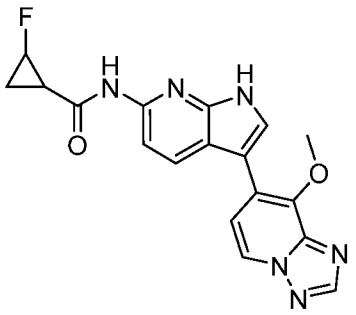
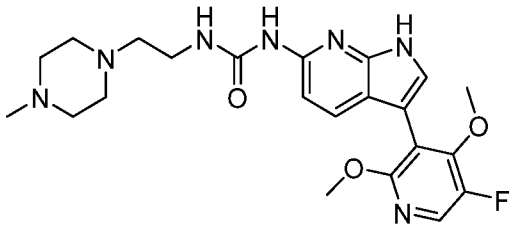
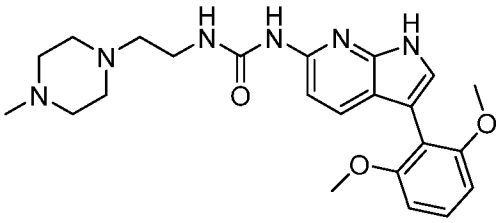
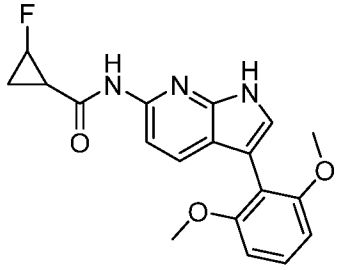
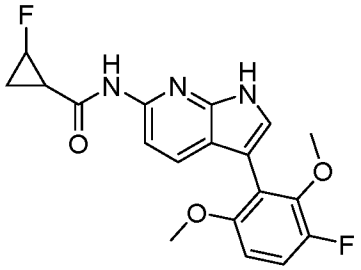
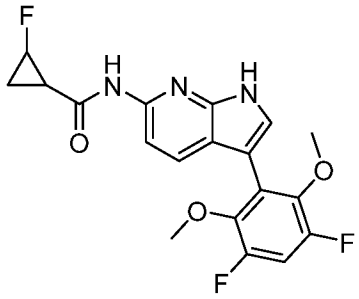
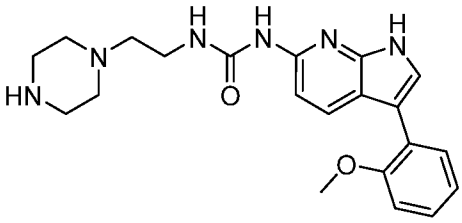
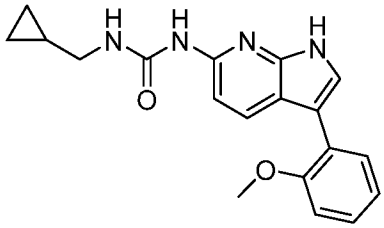
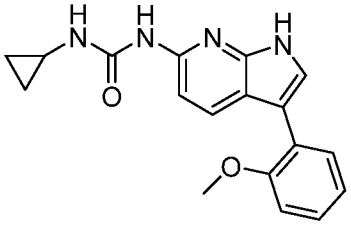
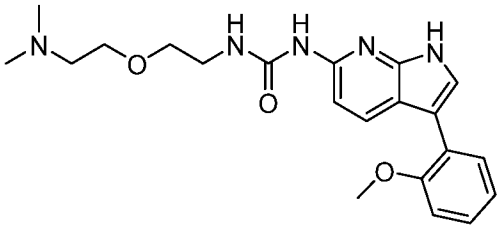

;

;

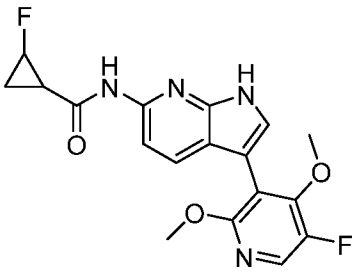
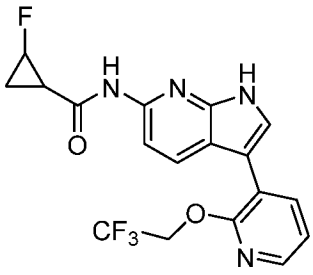
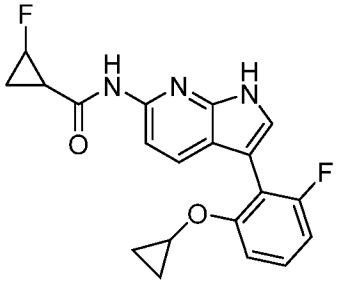
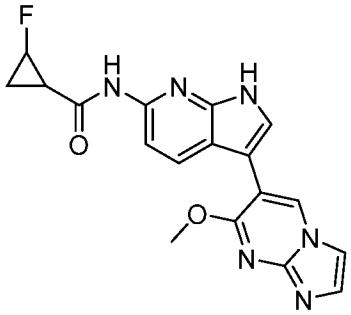
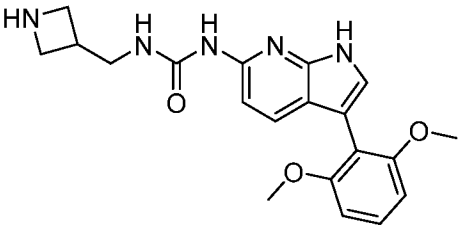
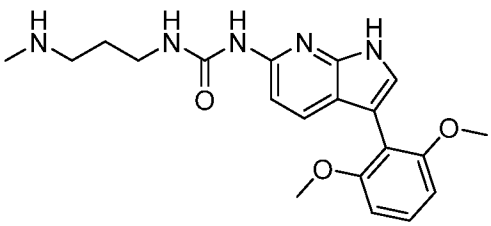
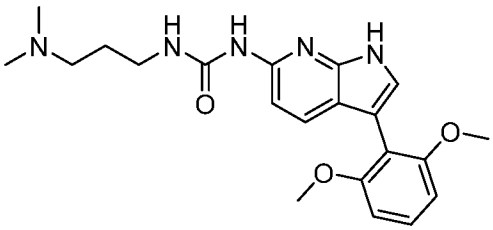
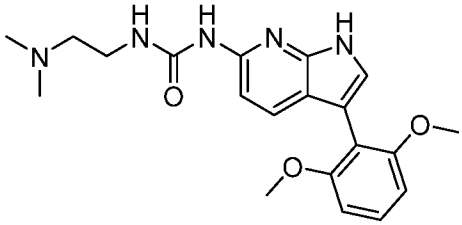
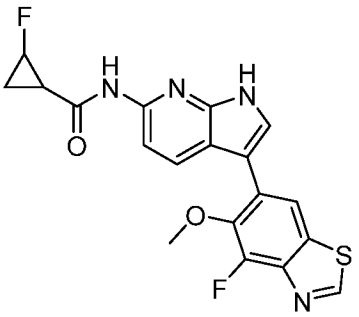
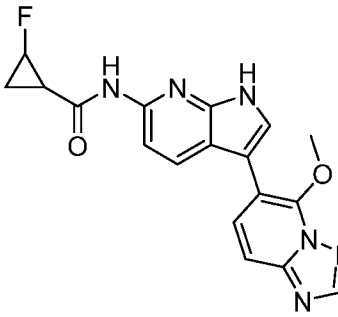
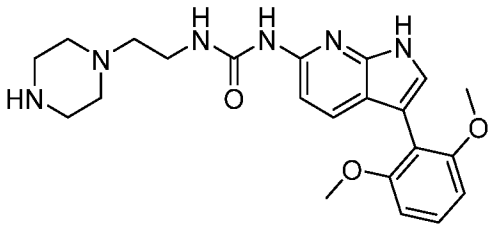
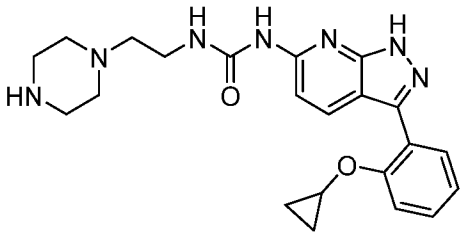
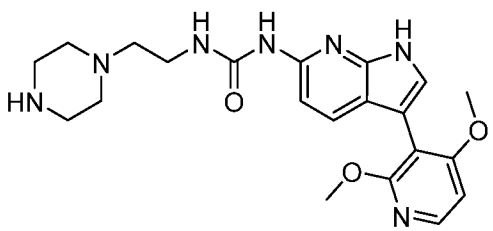
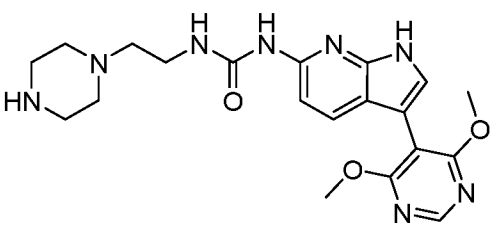

;

;

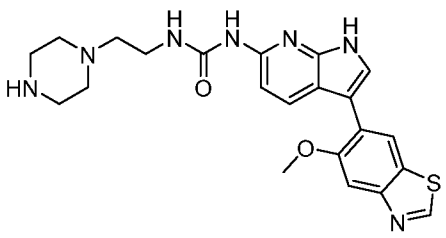
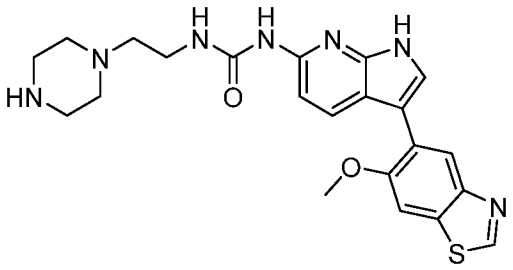

;

;

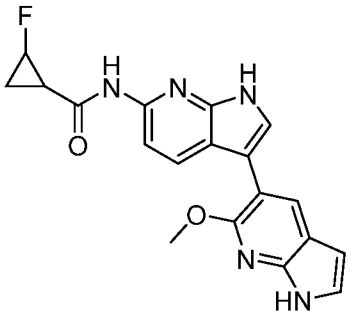
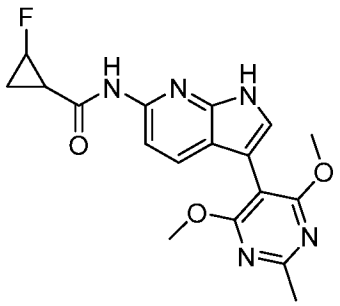

;

;

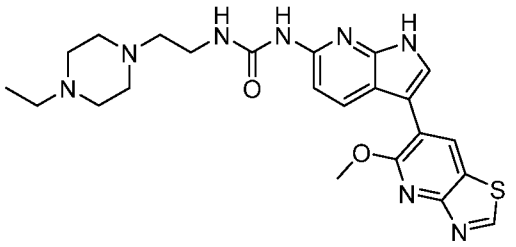
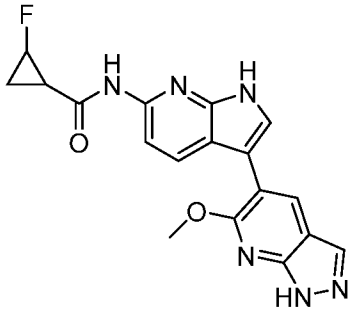

;

;

;

;

;

;

;

;

;

;

;

;

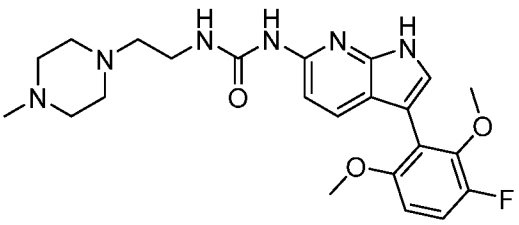
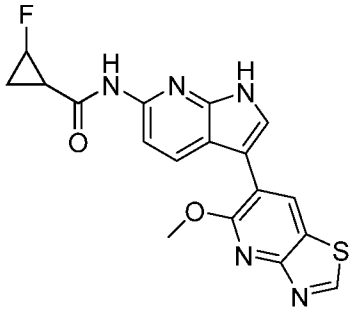

;

;

;

;

;

;

;

;

;

;

;

;

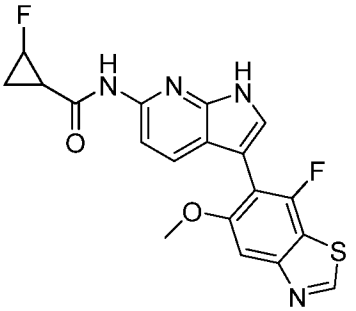
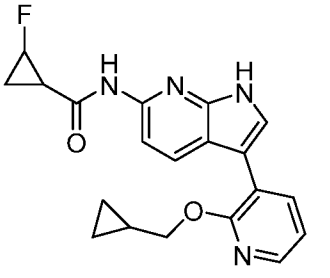

;

;

;

;

;

;

;

;

;

;

;

;

;

;

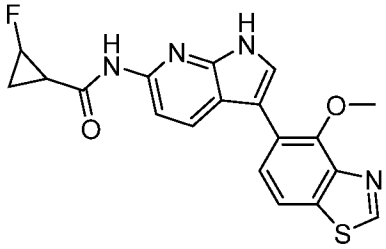
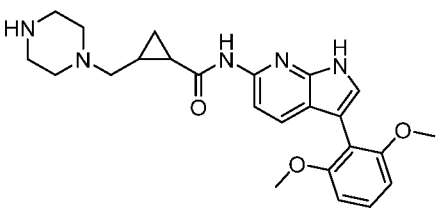

;

;

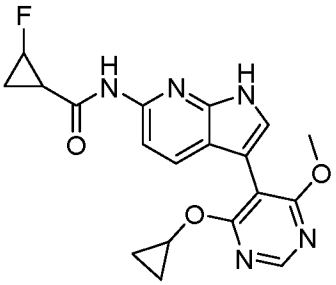
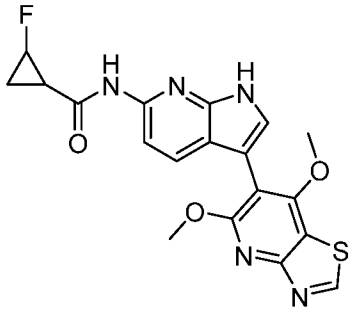

;

;

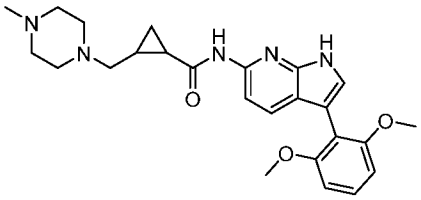
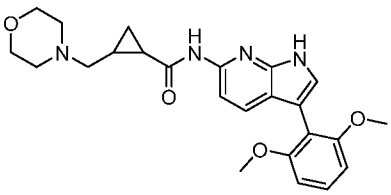

;

;

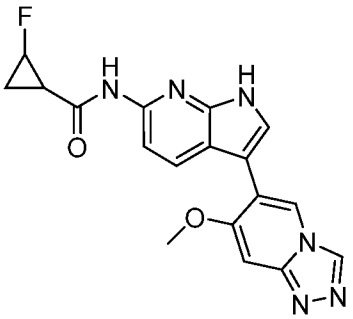
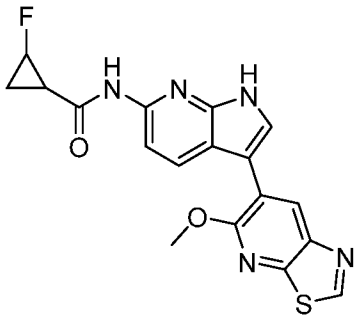

;

;

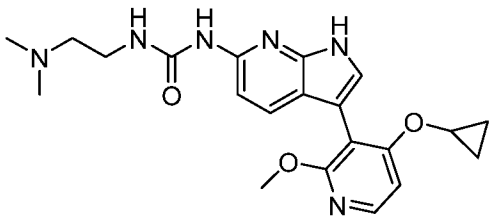
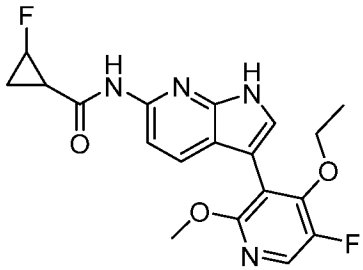

;

;

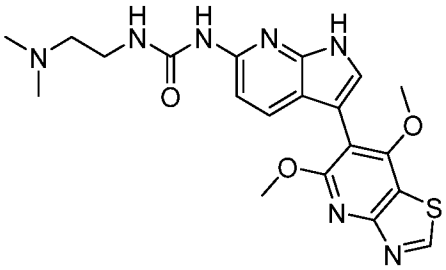
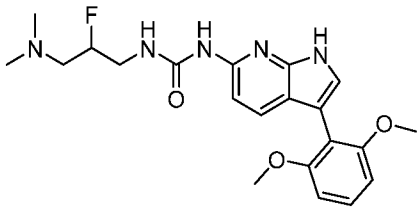

;

;

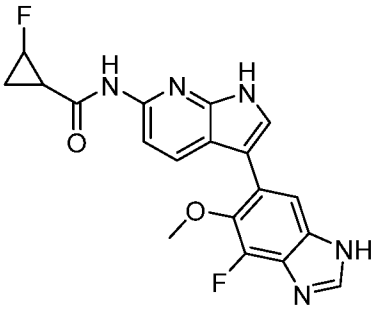
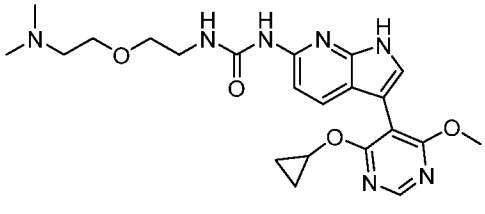

;

;

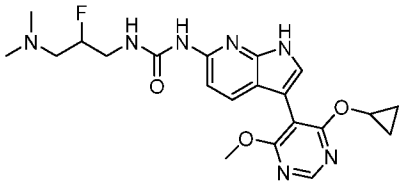
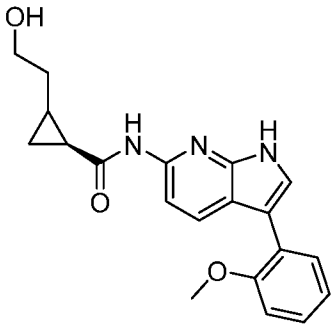

;

;

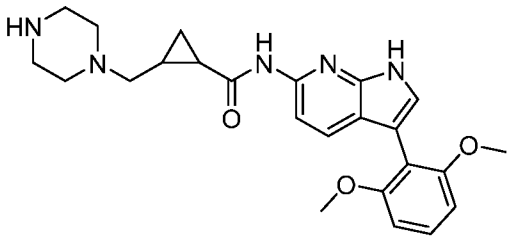
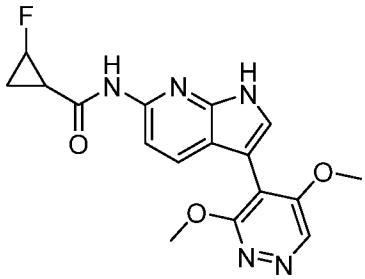

;

;

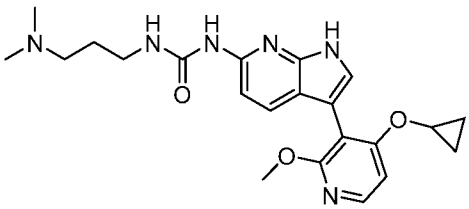
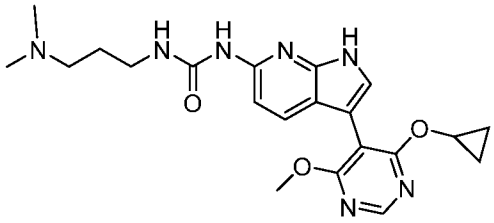

;

;

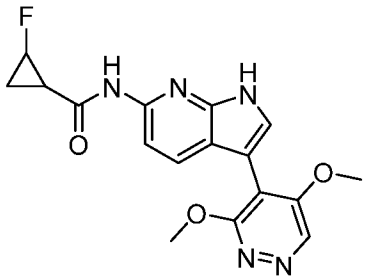
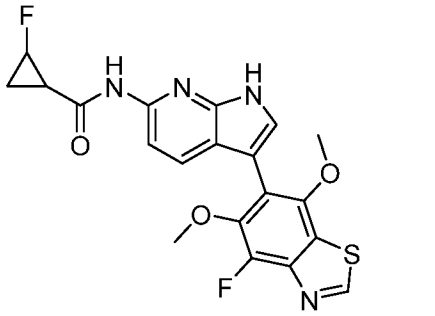

;

;

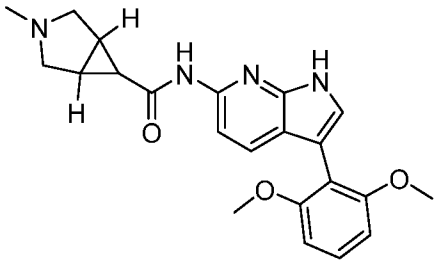
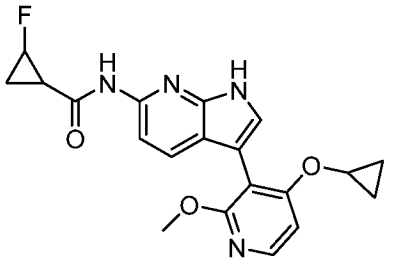

;

;

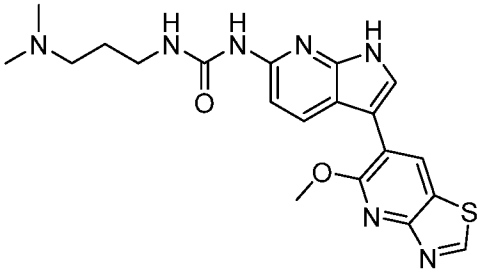
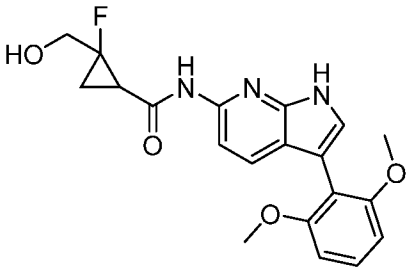

;

;

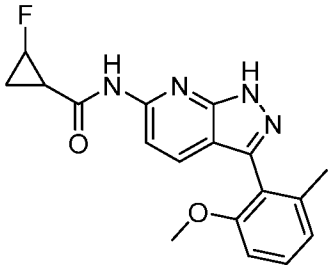
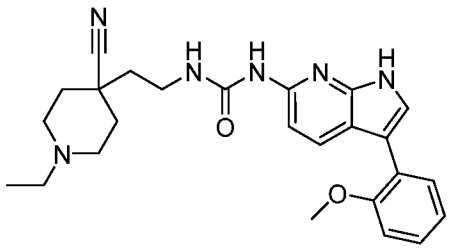
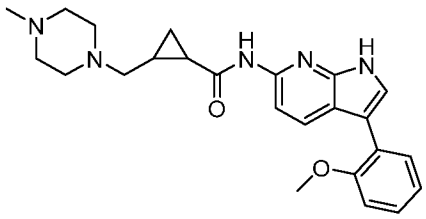
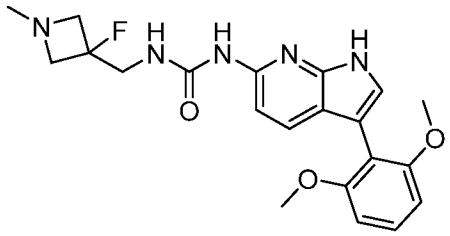
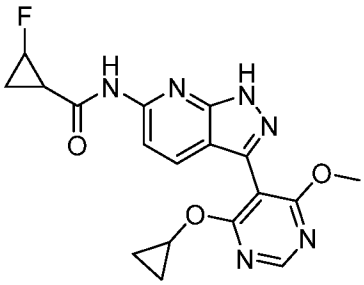
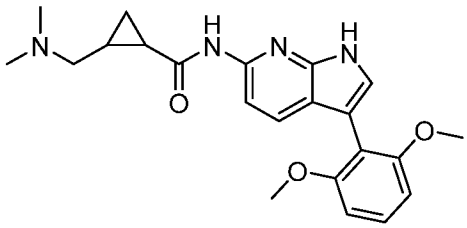
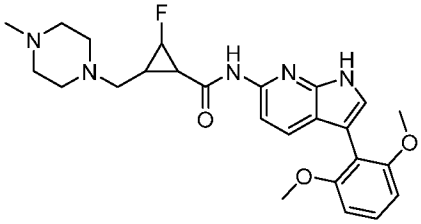
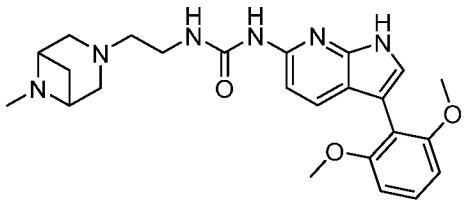
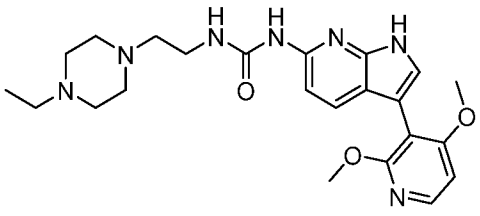
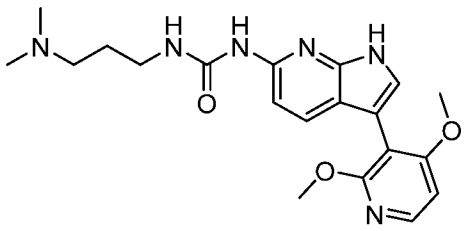
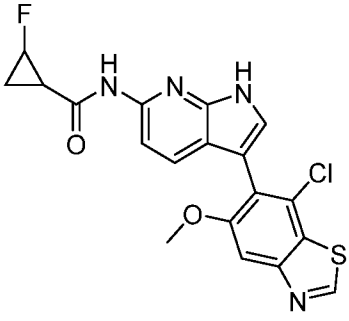
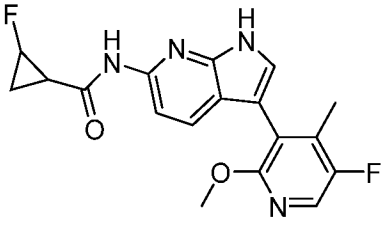

;

;

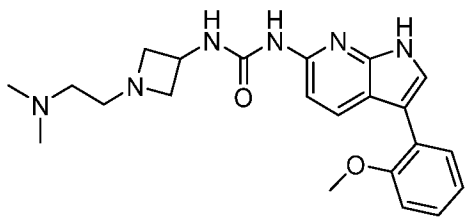
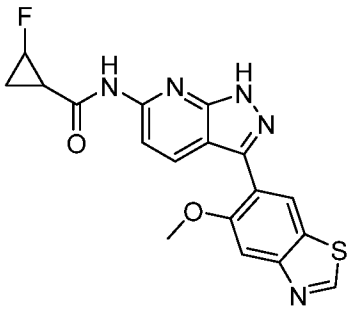

;

;

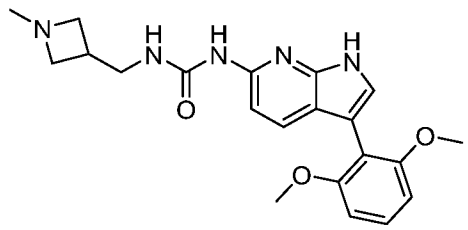
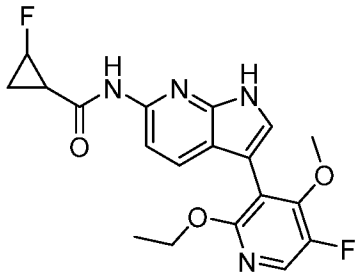

;

;

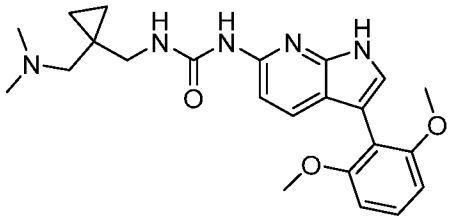
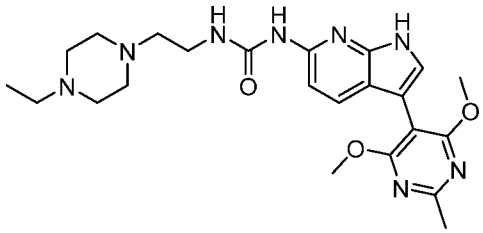

;

;

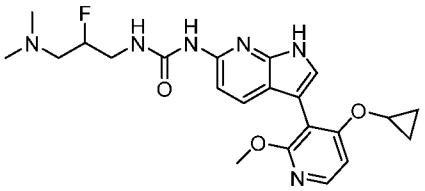
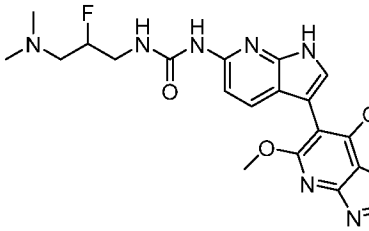

;

;

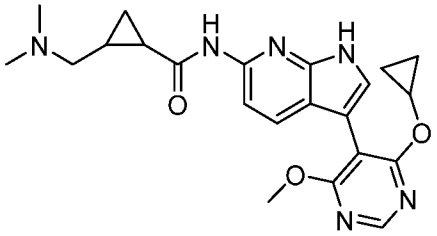
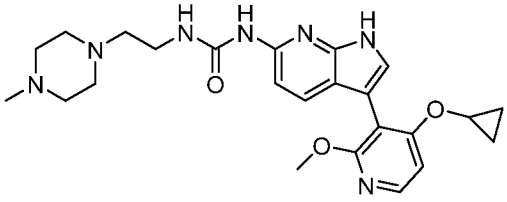

;

;

;

;

;

;

;

;

;

;

;

;

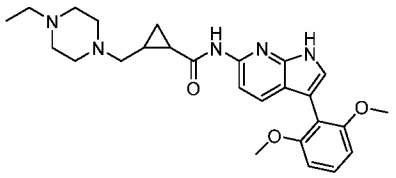

;

;


;

;

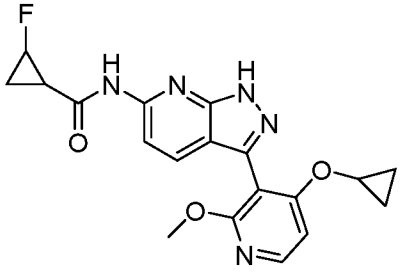
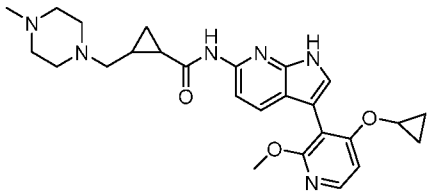

;

;

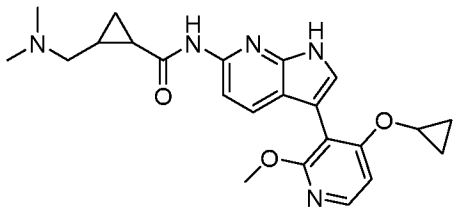
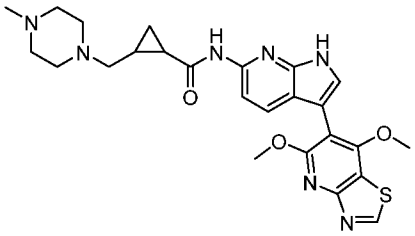
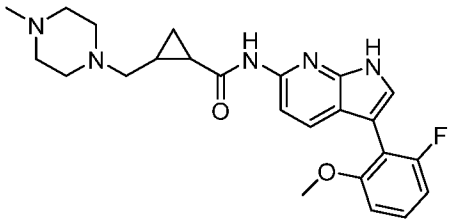
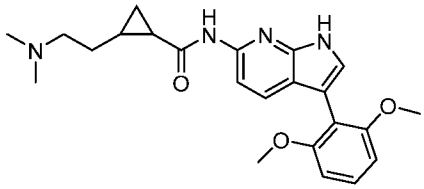
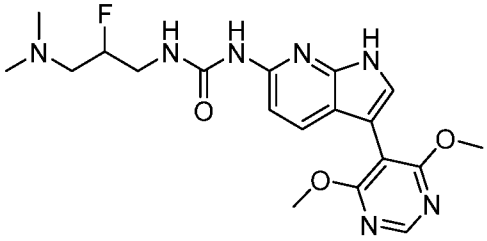
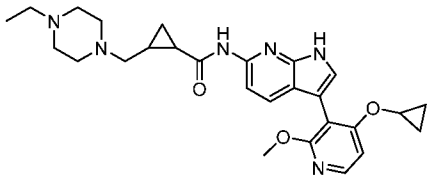
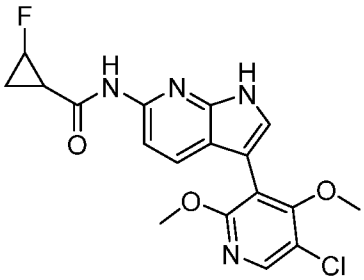
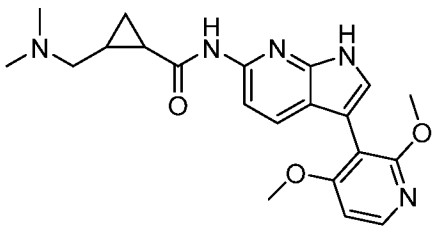
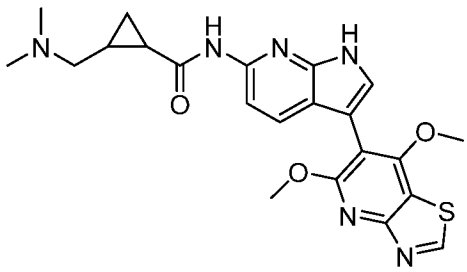
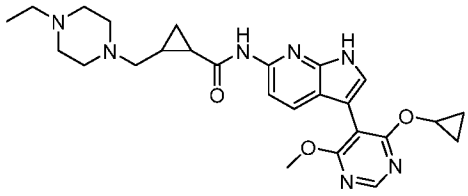
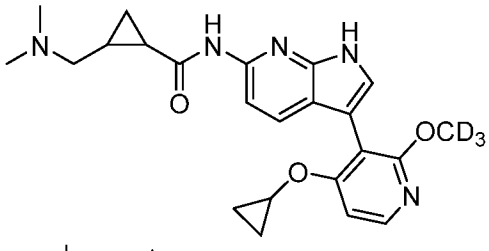
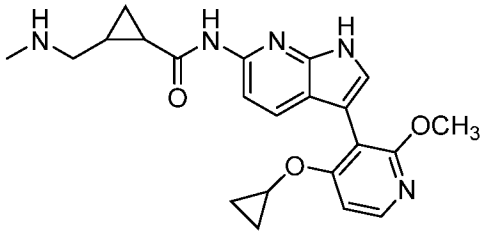
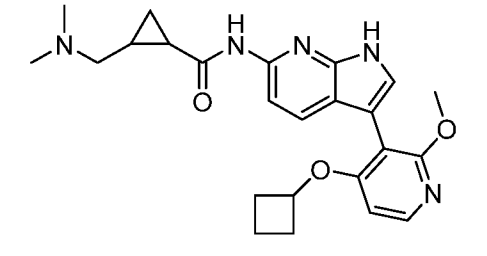
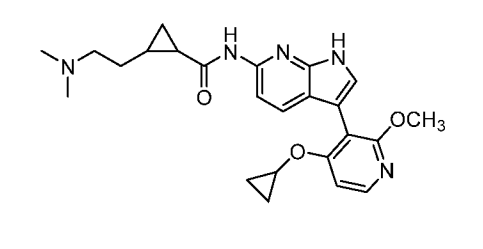

;

;


;

;


;

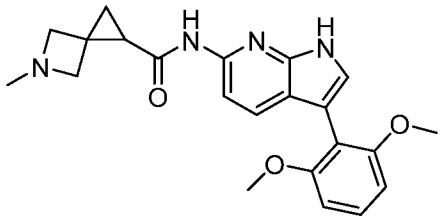
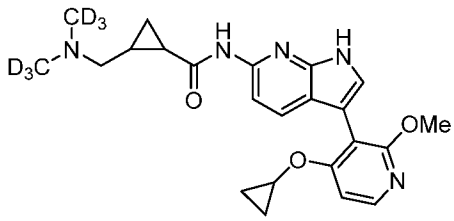
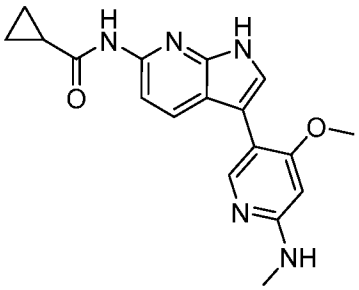
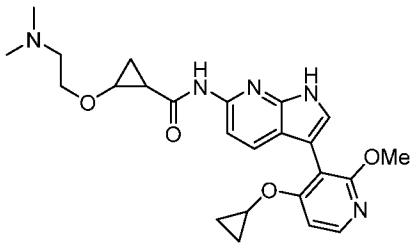
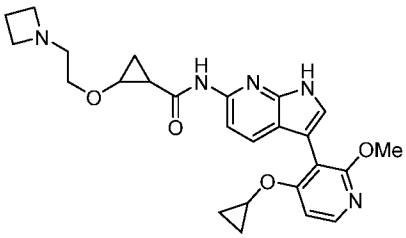
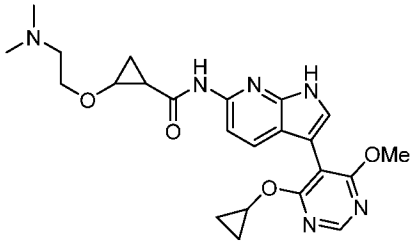
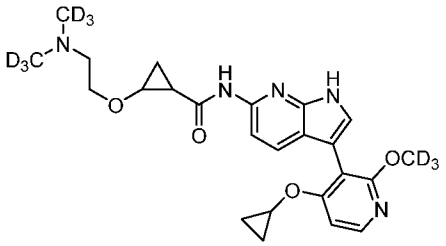
;


;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

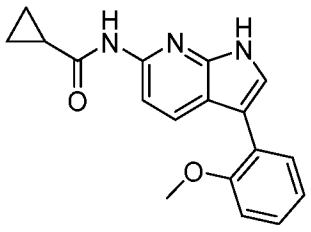
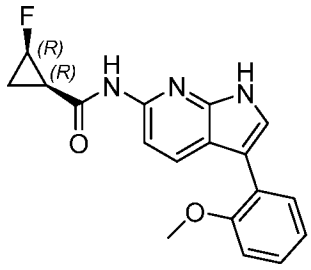
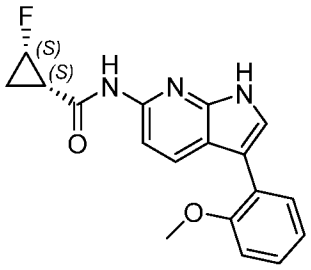
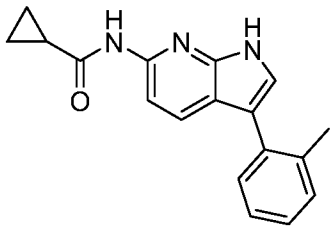
;

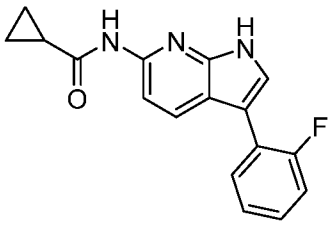
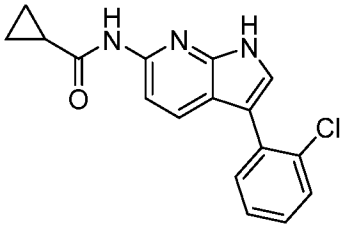
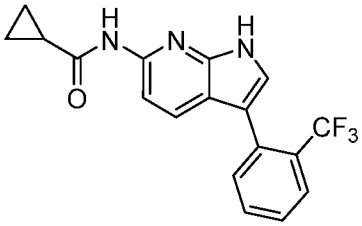
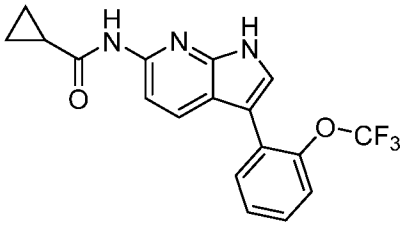
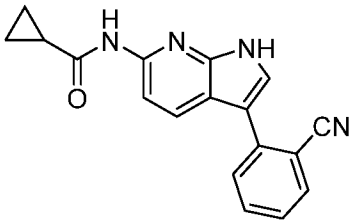
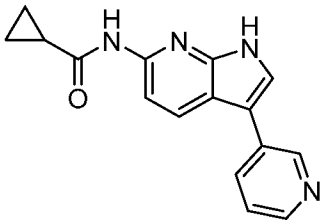
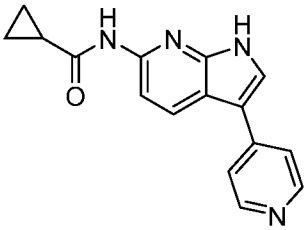
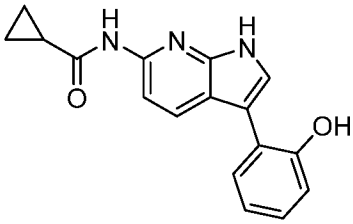
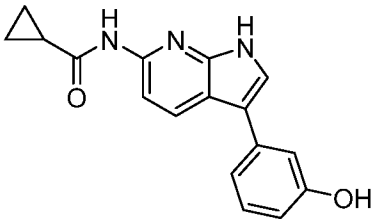
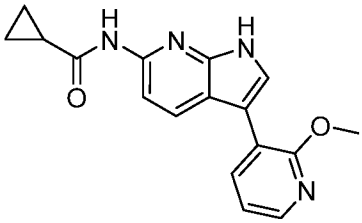
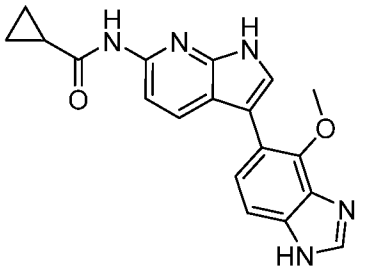
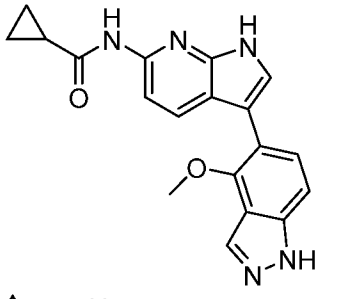
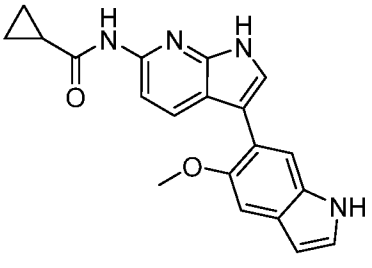
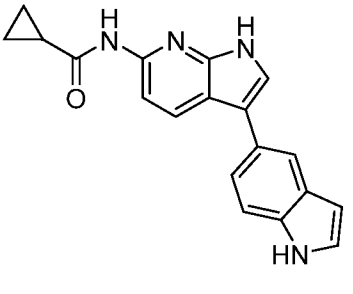
;


;

;

;

;

;

;
and

,

or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing.

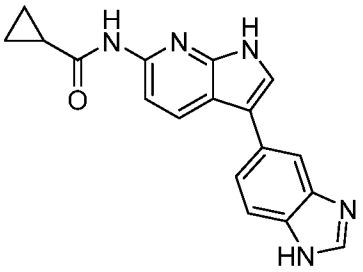
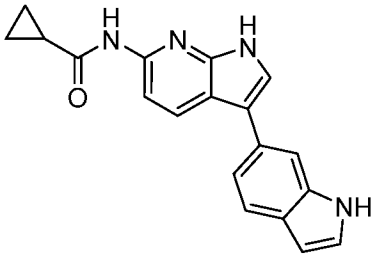
Claim 21. A compound selected from the group consisting of:

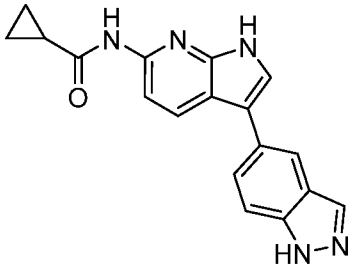
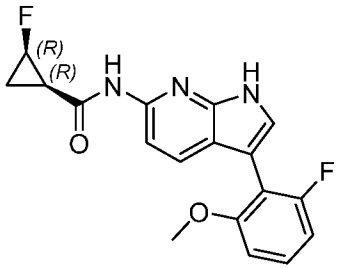

;

;

;

;

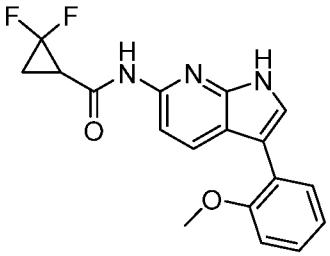
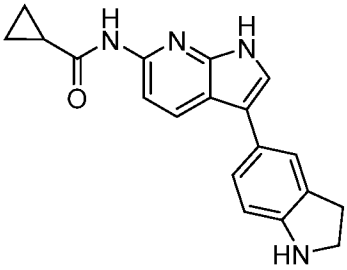

;

;

;

;

;

;

;

;

;

;

;

;

;

;

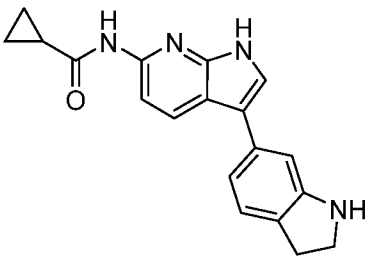
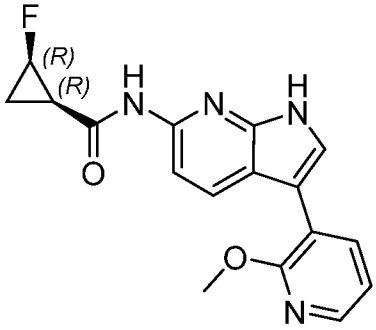
;

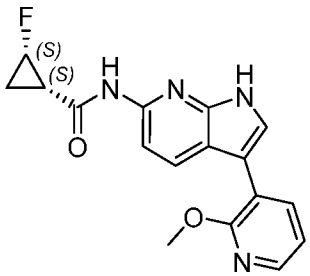
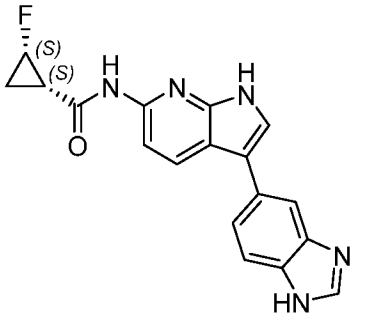
;

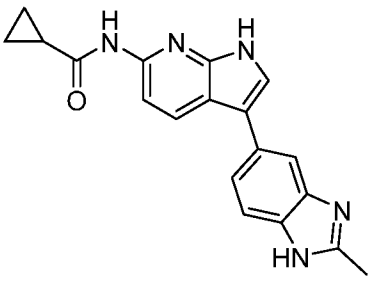
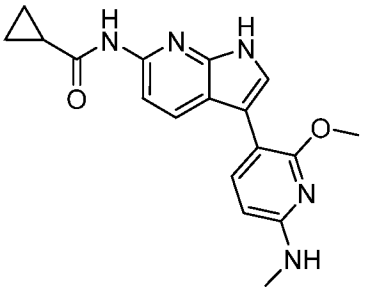

;

;

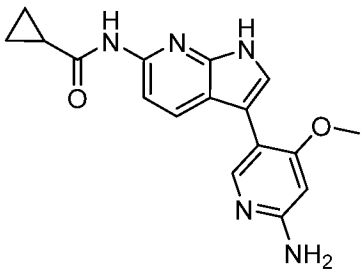
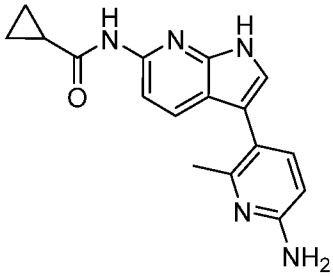
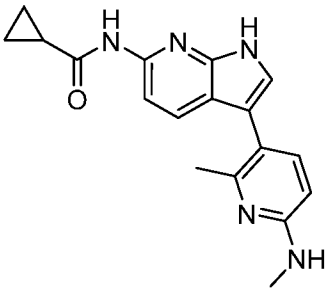
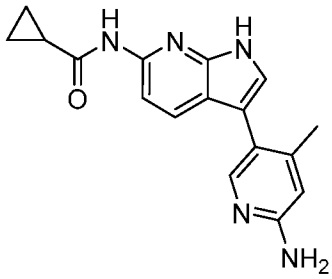
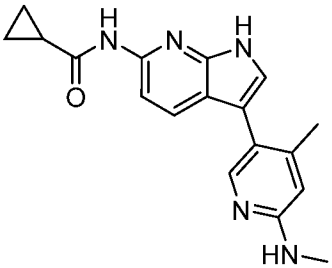
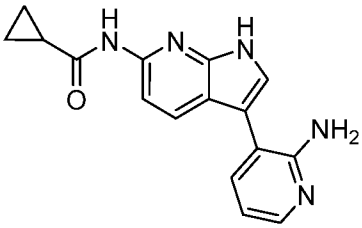
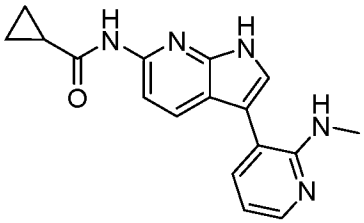
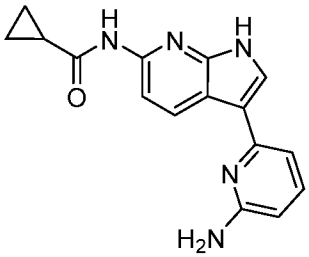
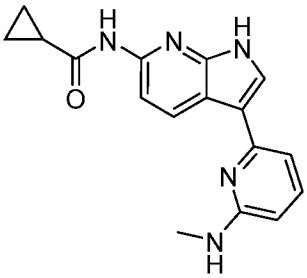
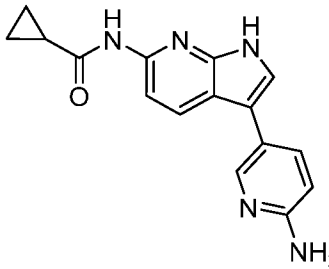
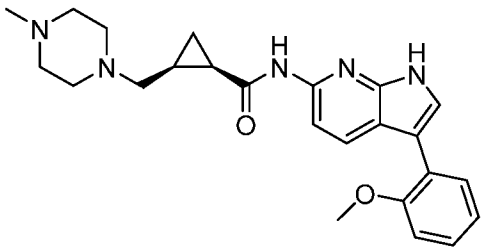
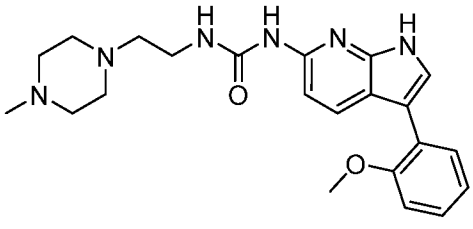
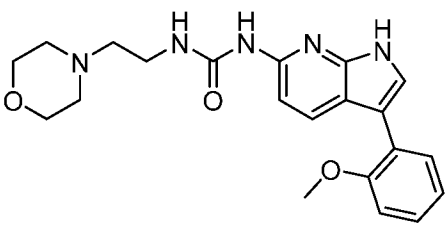
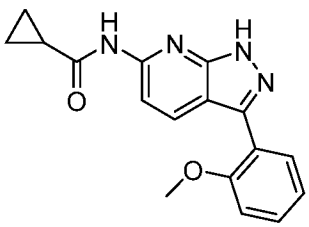

;

;

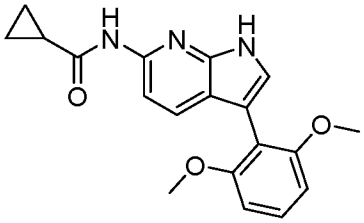
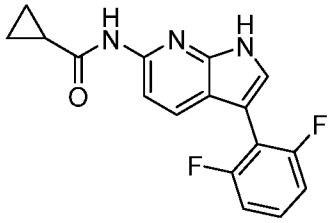
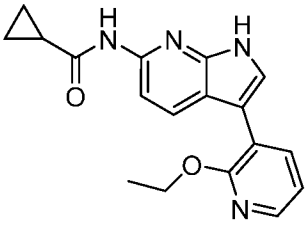
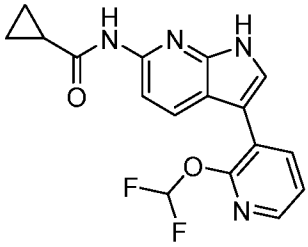
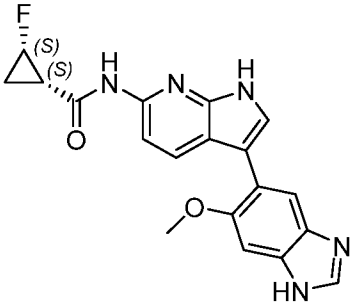
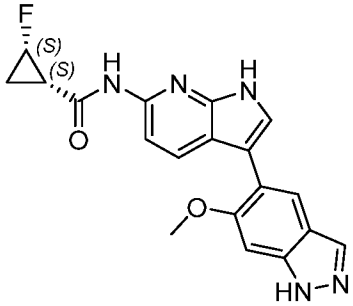
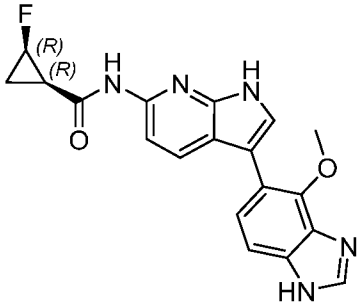
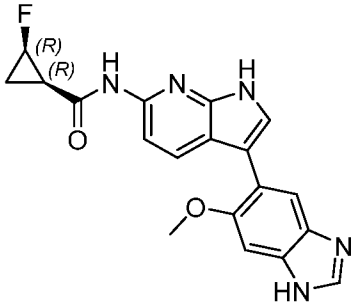
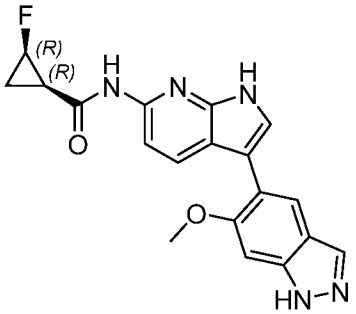
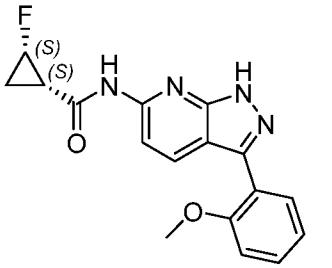
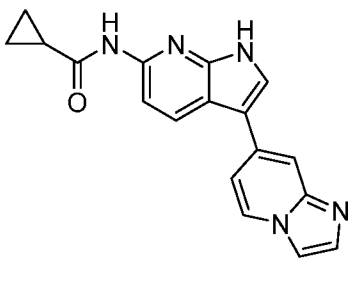
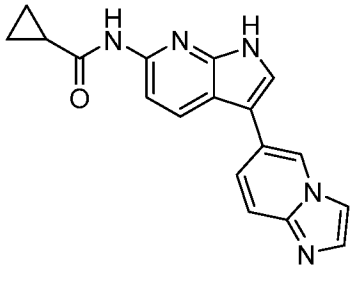

;

;

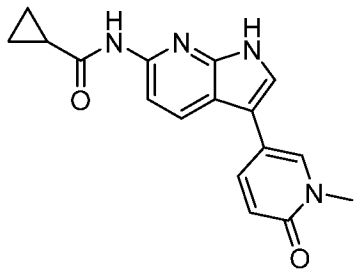
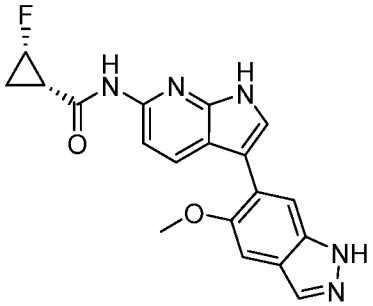

;

;

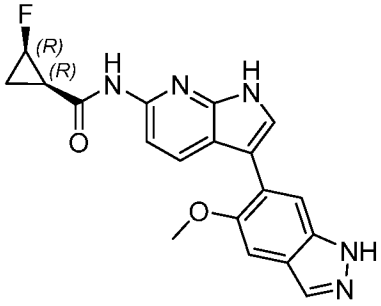
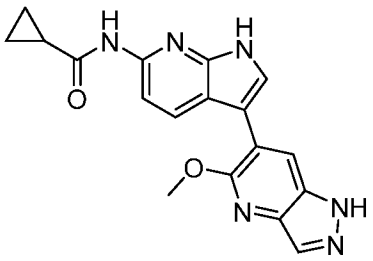

;

;

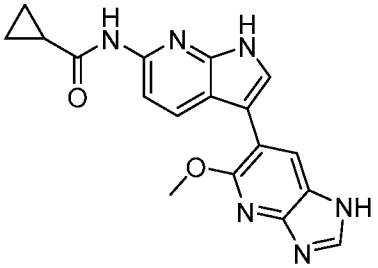
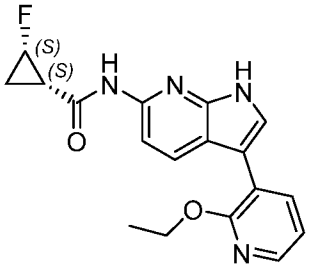

;

;

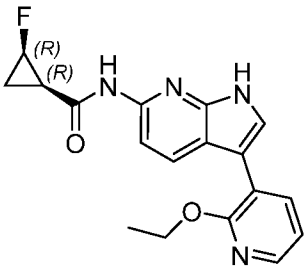
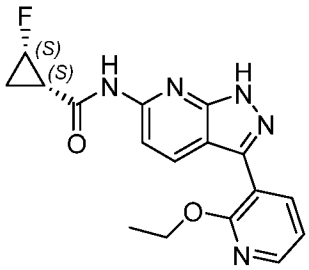

;

;

;

;

;

;

;

;

;

;

;

;

;

;

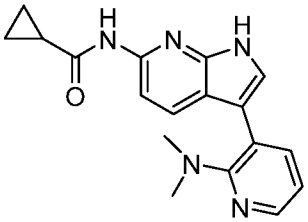
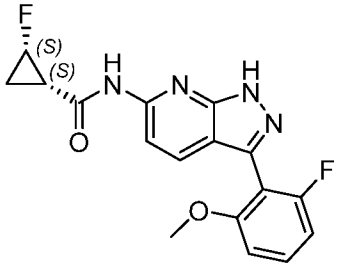

;

;

;

;

;

;

;

;

;

;

;

;

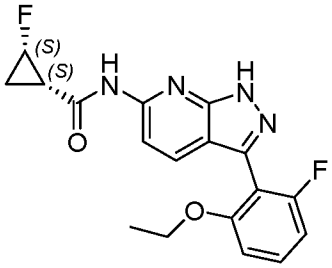
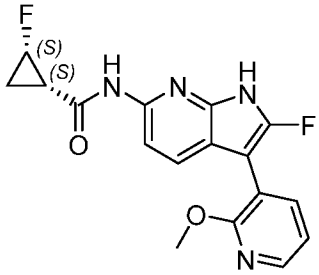

;

;

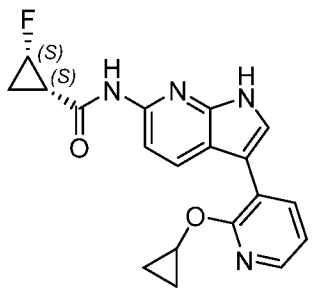
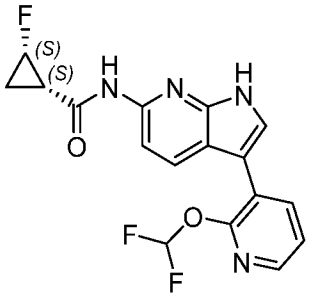

;

;

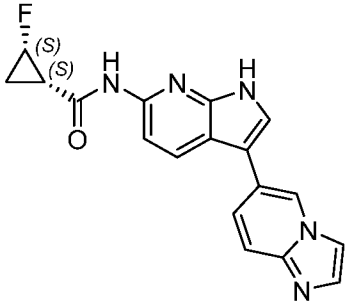
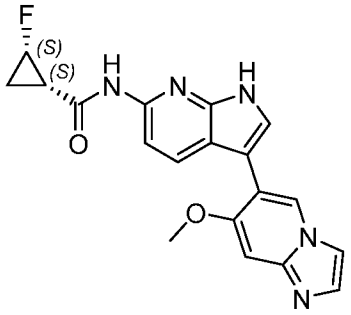

;

;

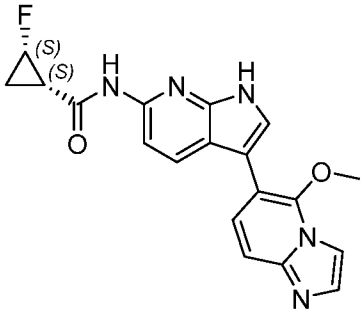
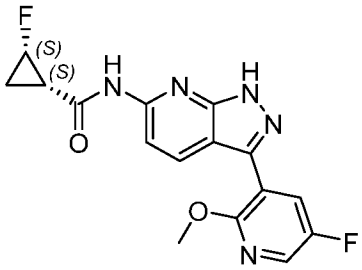

;

;

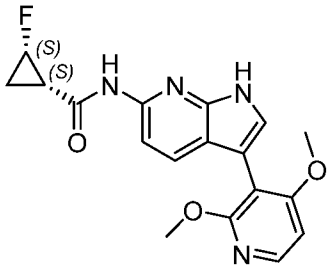
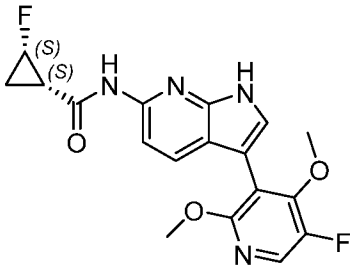

;

;

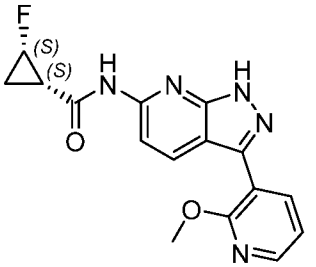
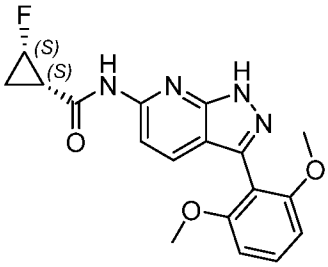

;

;

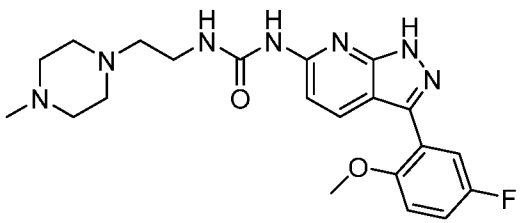
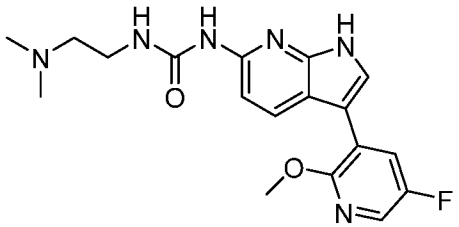

;

;

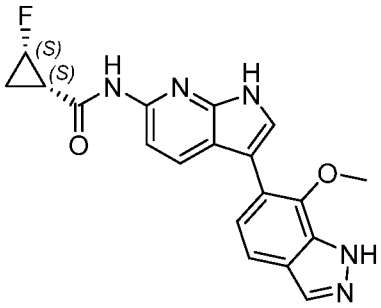
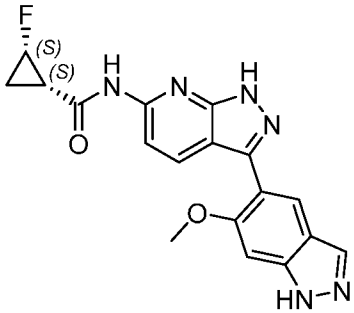

;

;

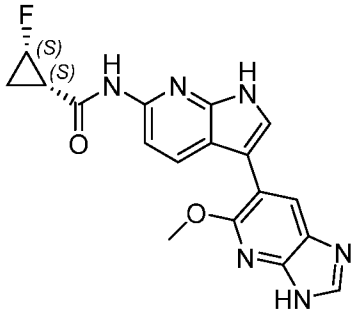
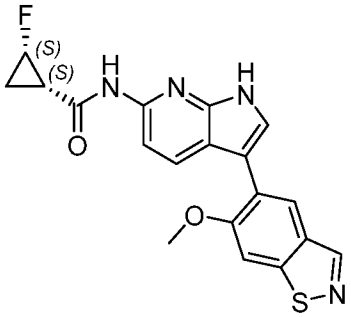

;

;

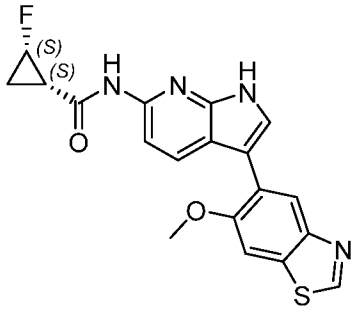
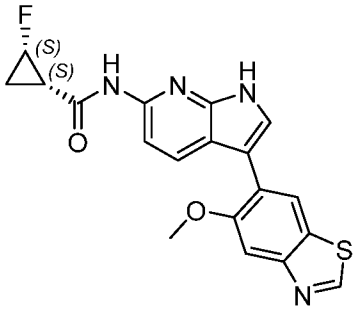

;

;

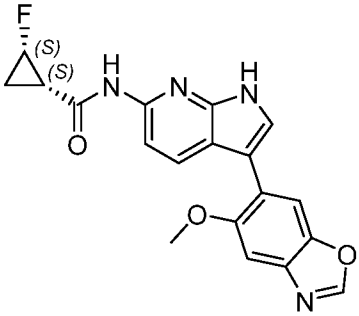
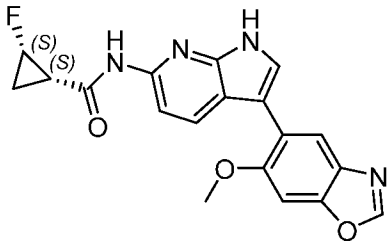

;

;

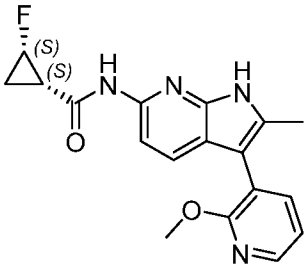
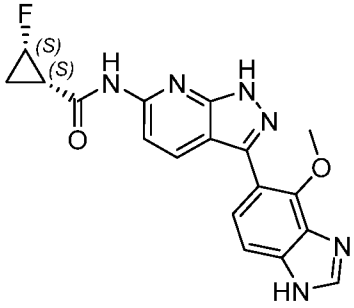

;

;

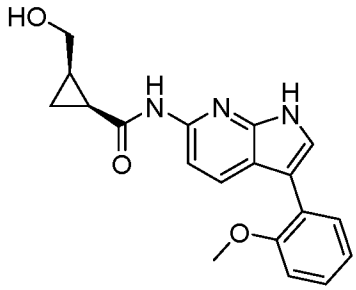
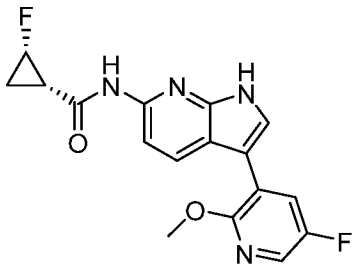
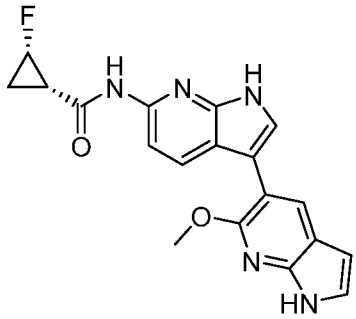
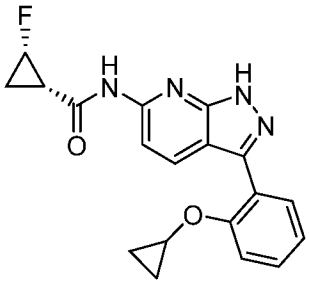
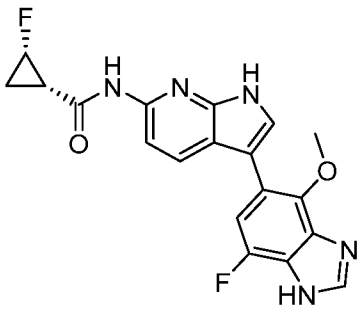
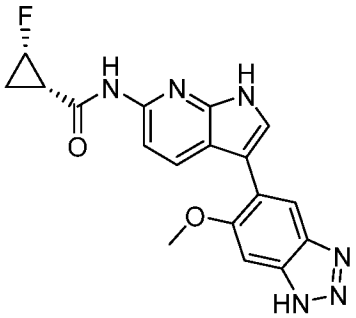
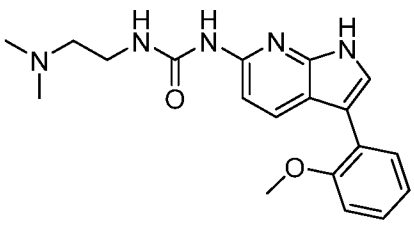
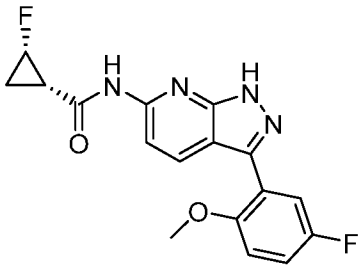
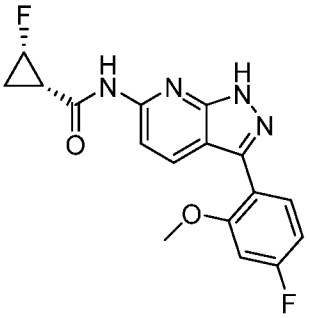
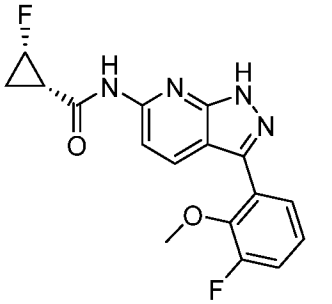
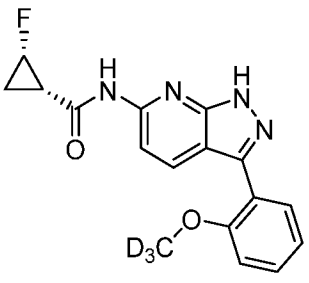
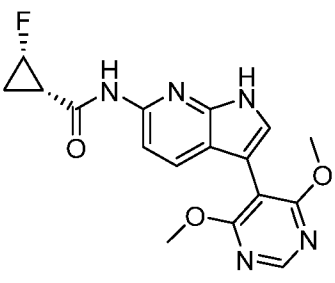

;

;


;

;


;

;

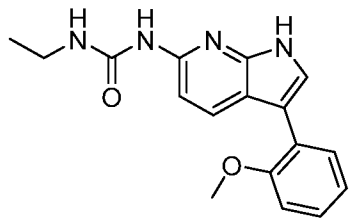
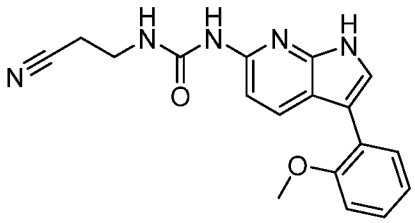
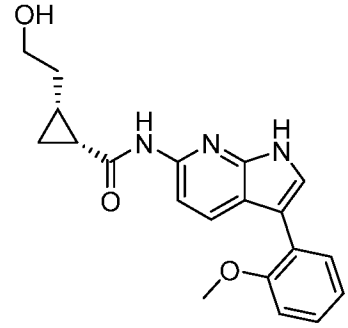
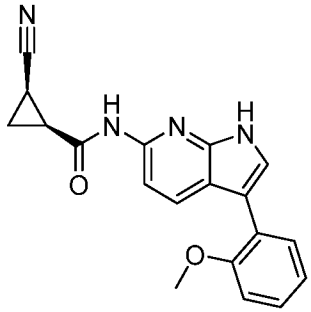
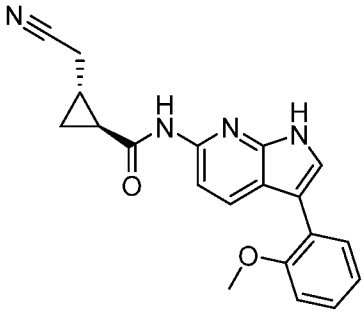
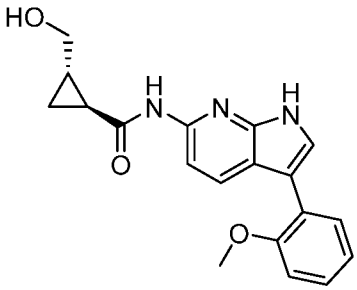
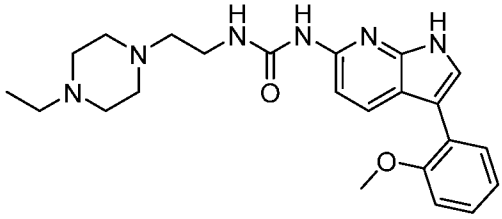
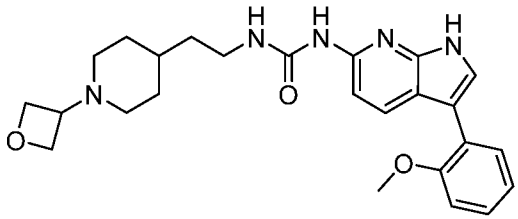
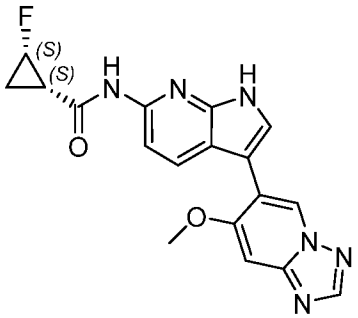
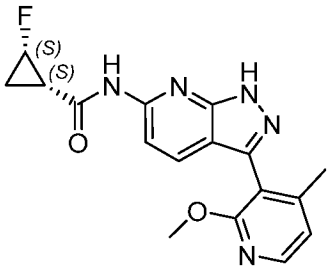
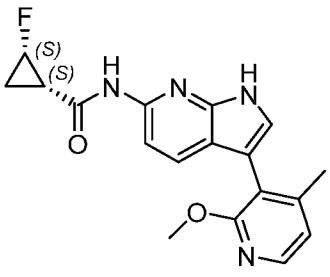
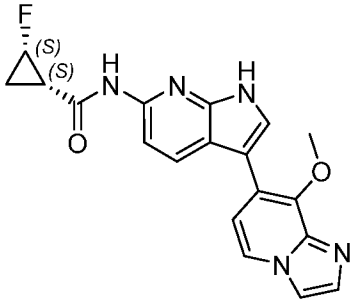

;

;

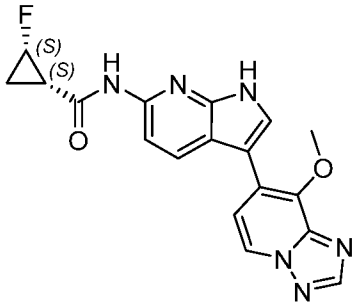
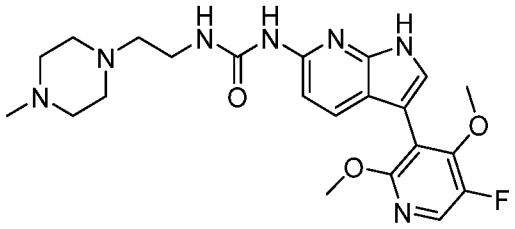
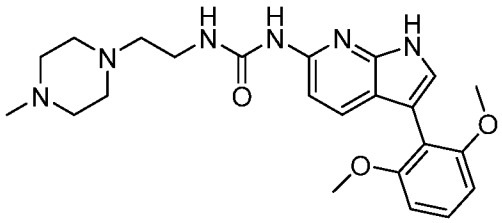
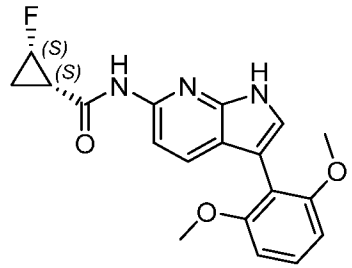
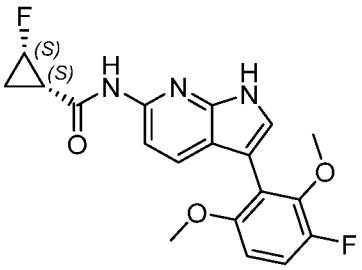
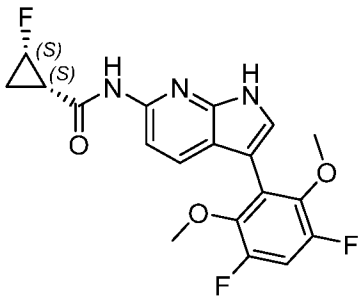
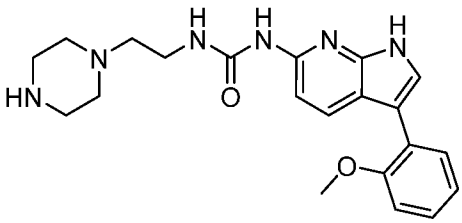
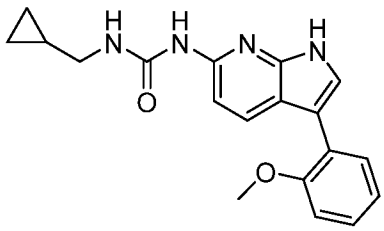
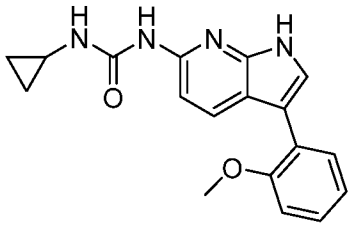
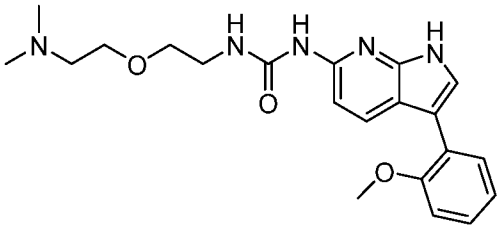
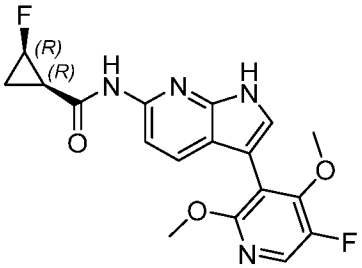
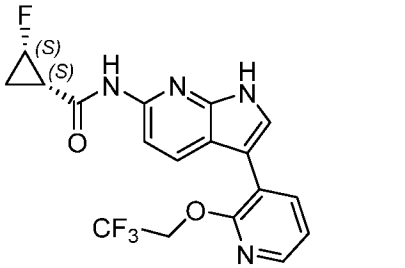

;

;

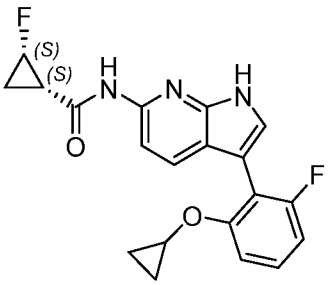
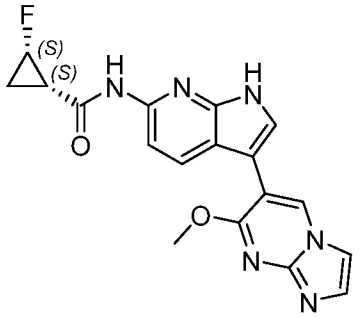
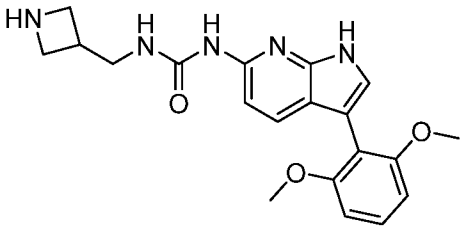
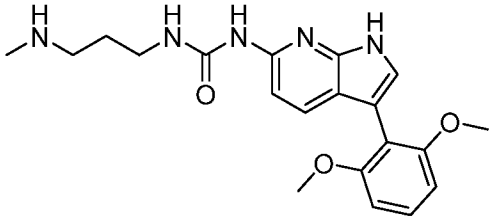
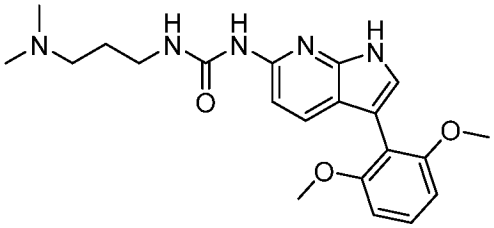
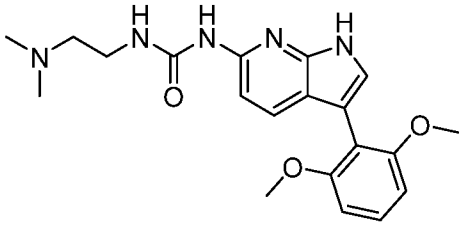
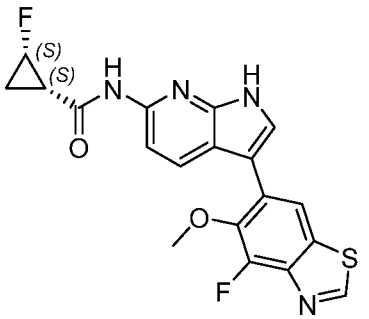
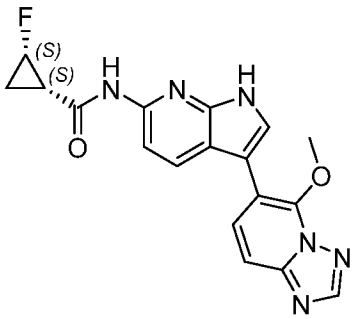
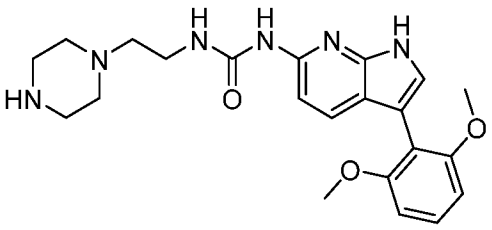
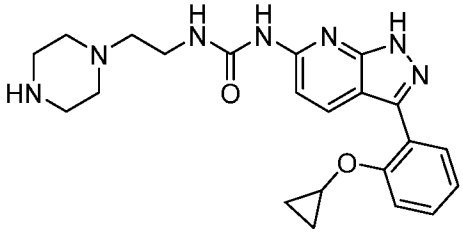
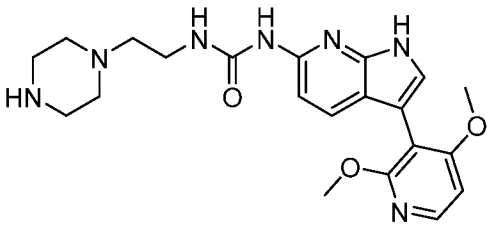
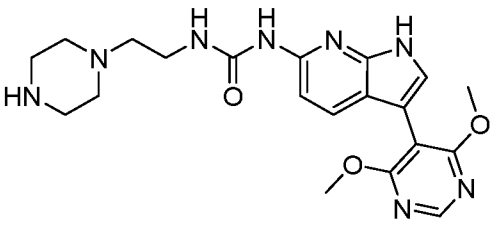
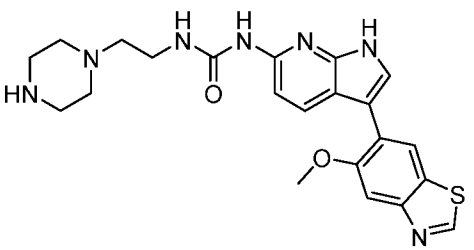
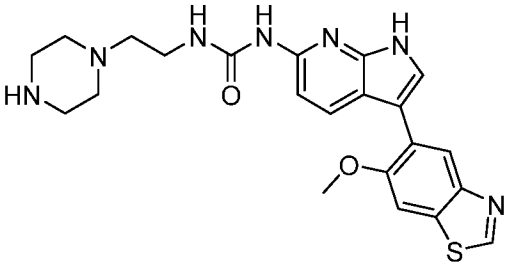

;

;

;

;

;

;

;

;

;

;

;

;

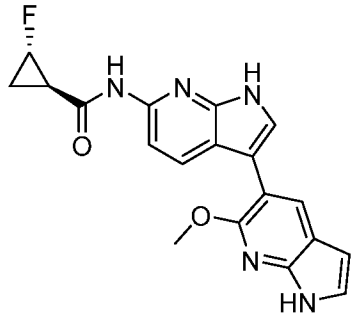
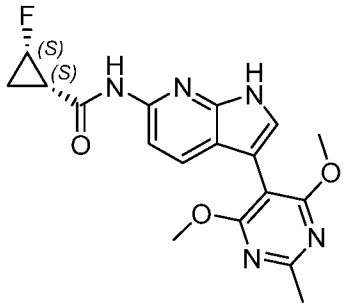
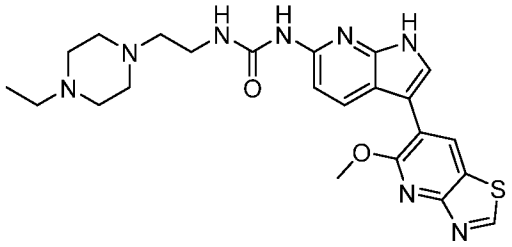
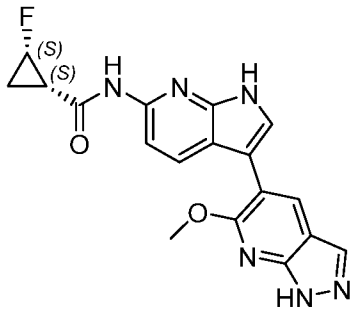
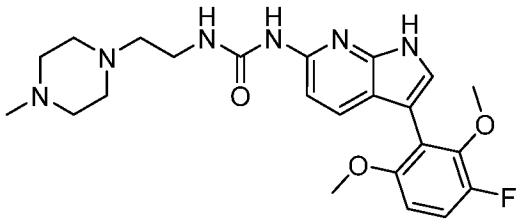
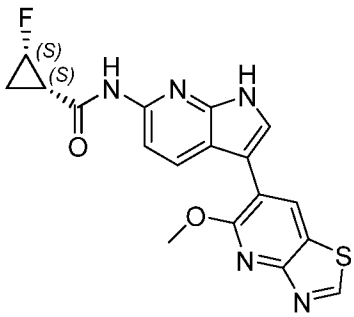
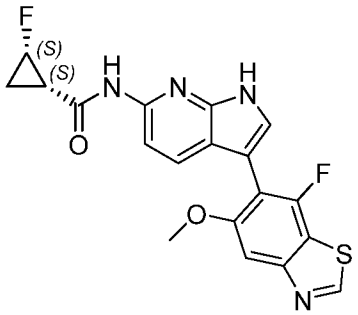
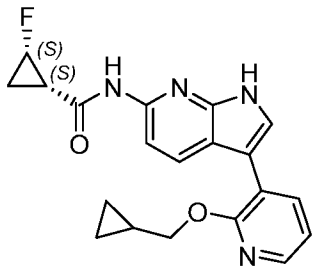
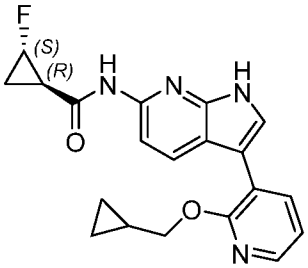
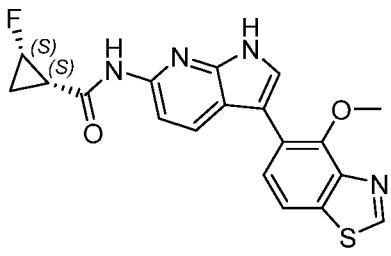
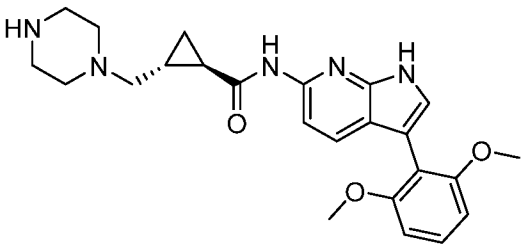
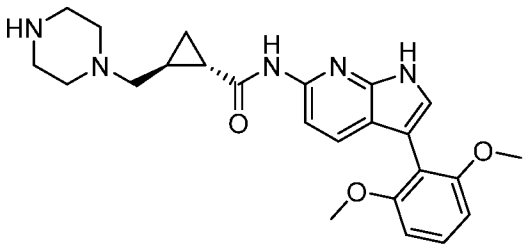
;

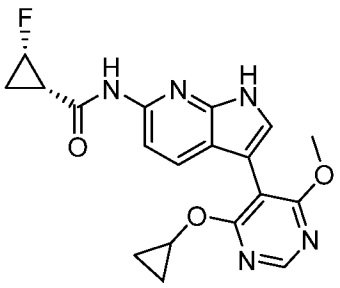
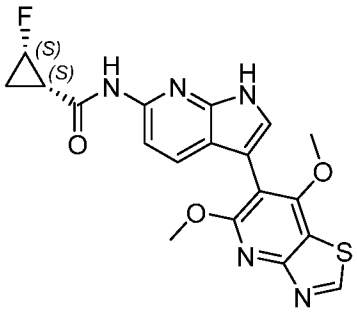
;

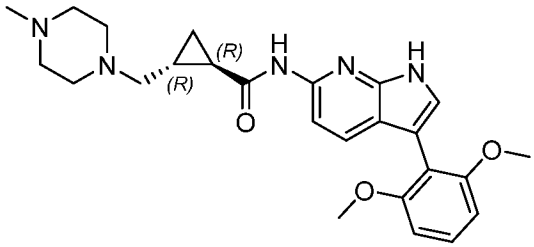
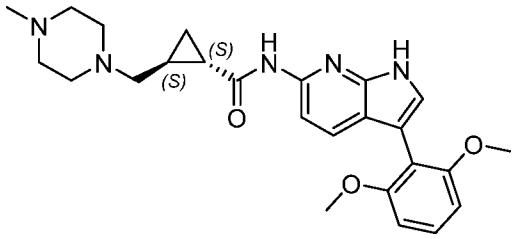

;

;

;

;

;

;

;

;

;

;

;

;

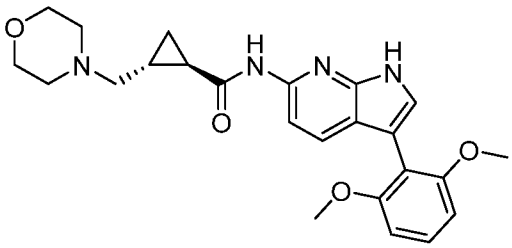
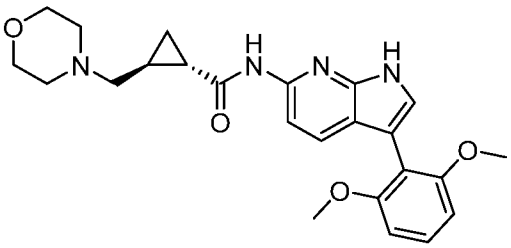

;

;

;

;

;

;

;

;

;

;

;

;

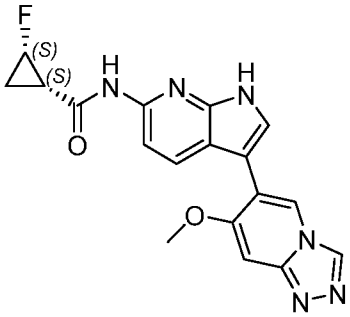
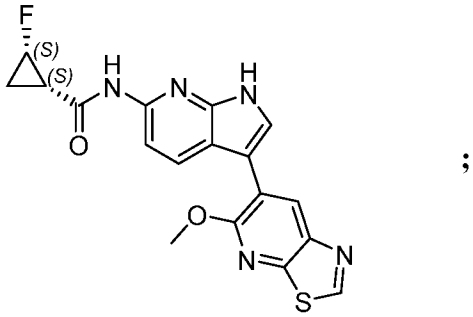

;

;

;

;

;

;

;

;

;

;

;

;

;

;

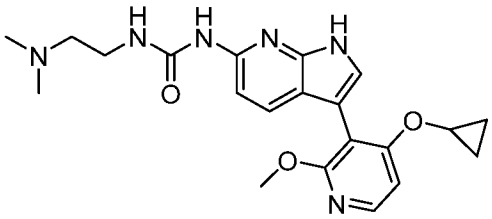
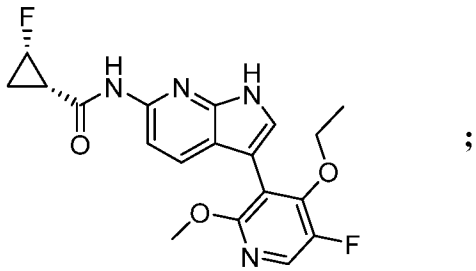

;

;

;

;

;

;

;

;

;

;

;

;

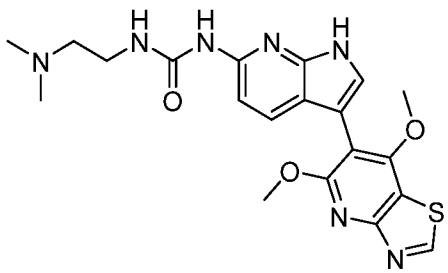
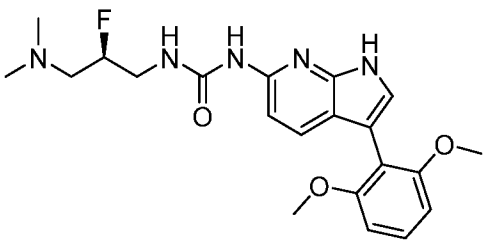

;

;

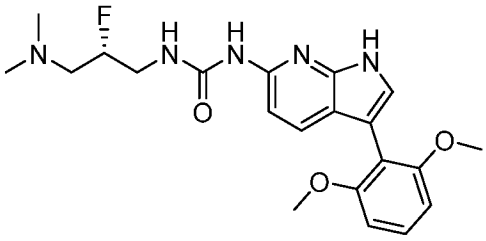
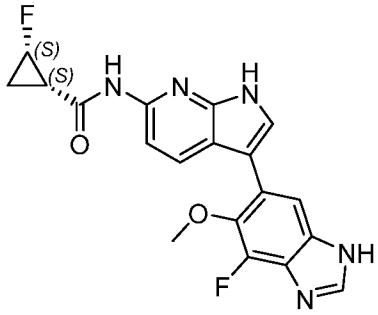
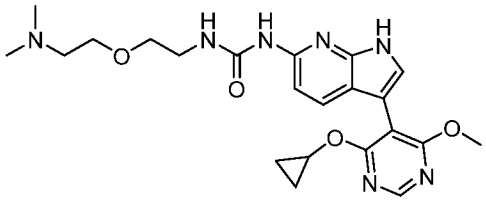
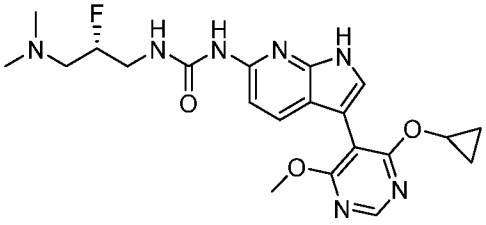
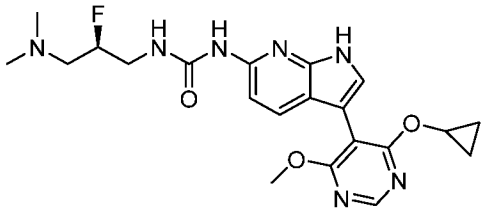
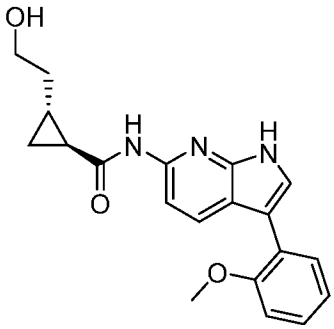
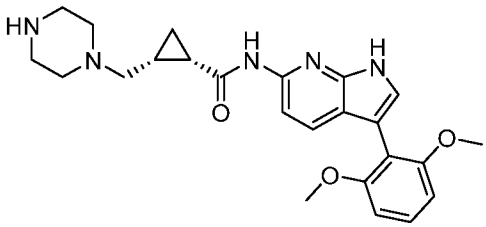
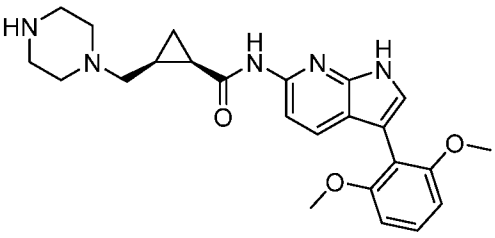
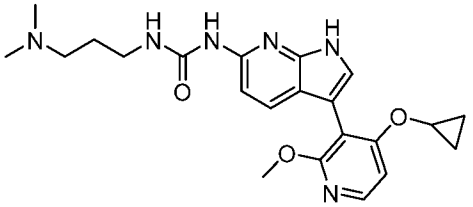
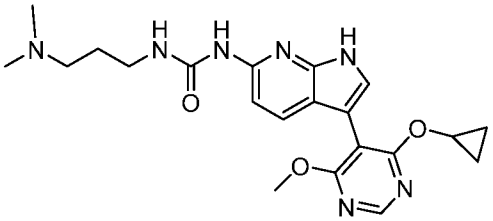
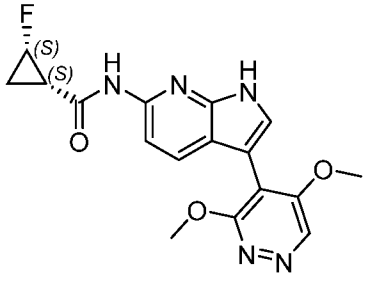
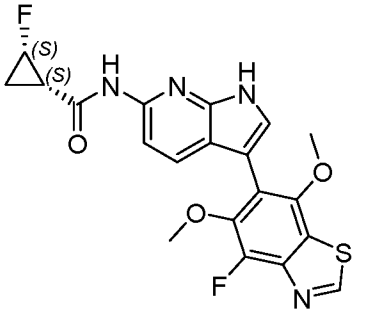

;

;

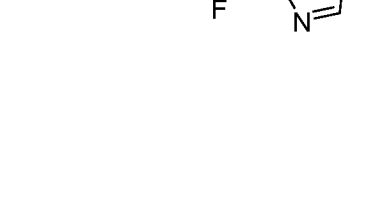

;

;

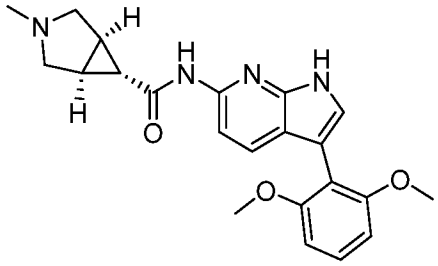
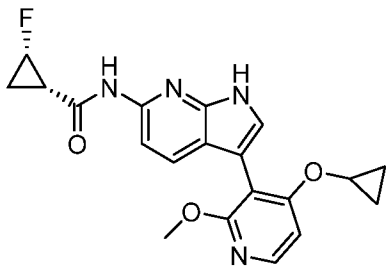
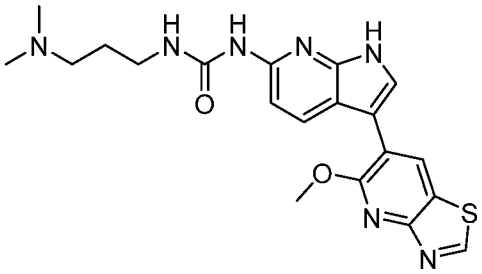
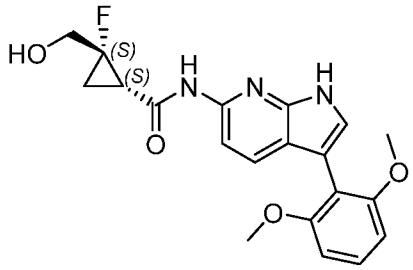
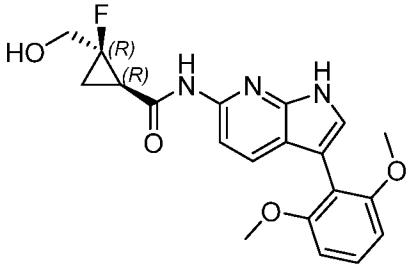
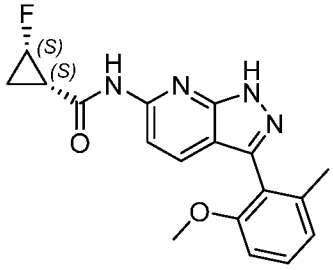
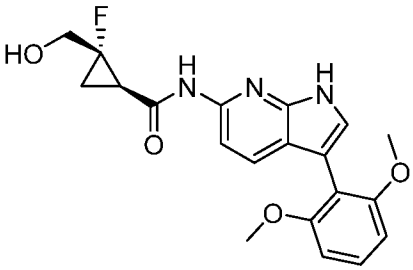
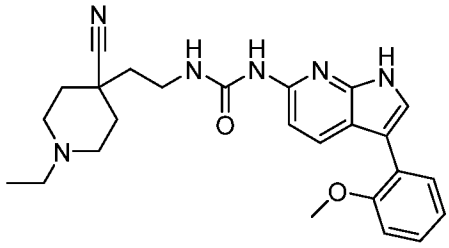
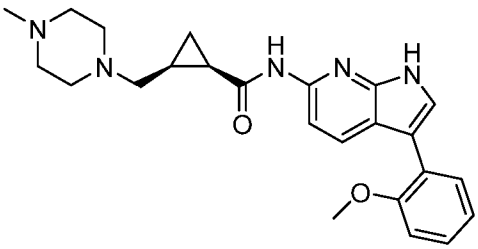
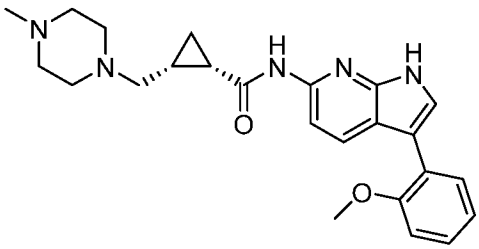
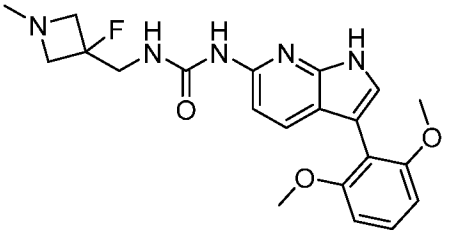
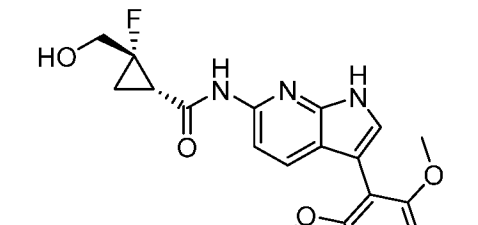

;

;


;

;


;

;

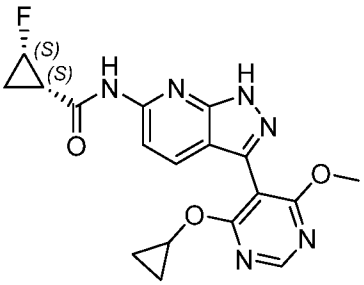
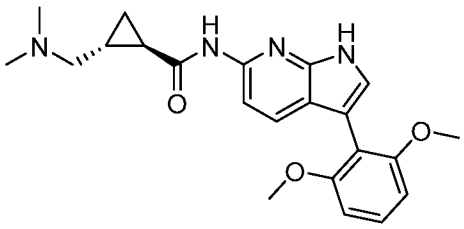
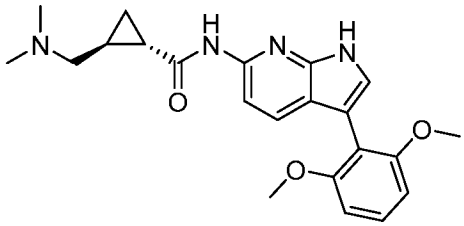
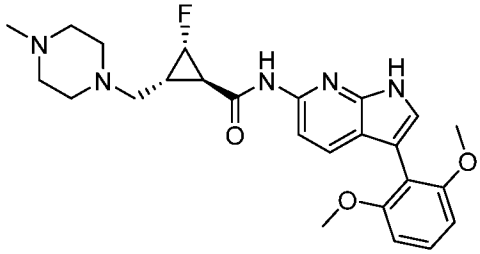
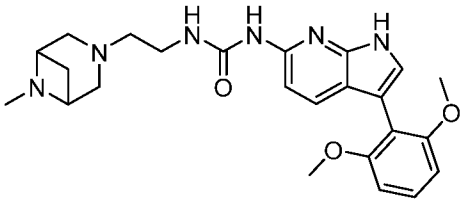
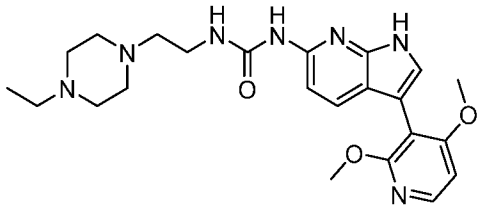
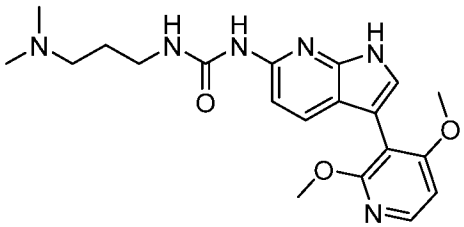
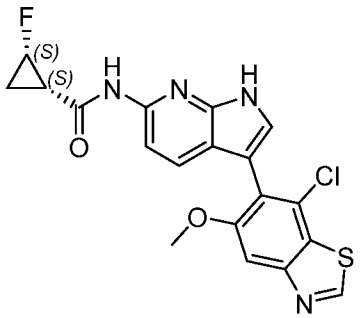
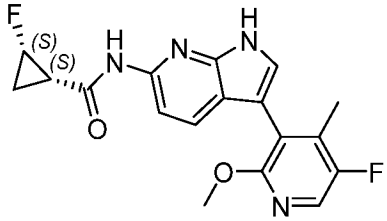
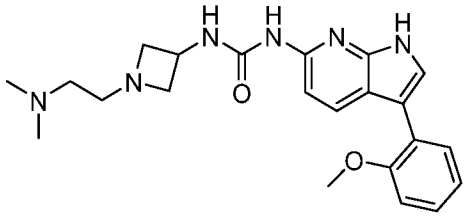
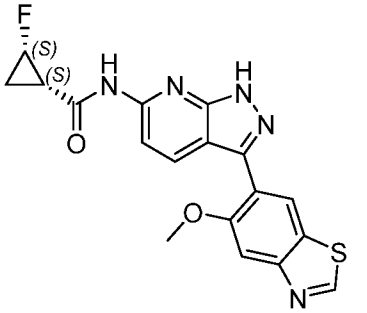
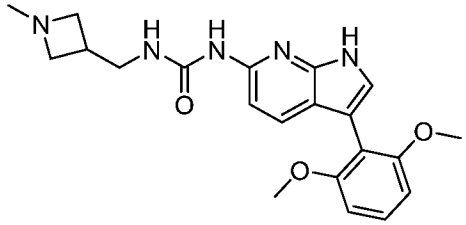

;

;

;

;

;

;

;

;

;

;

;

;

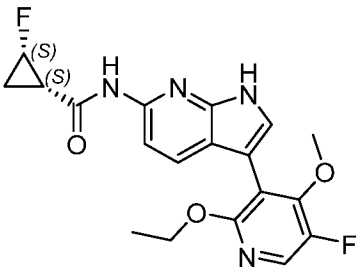
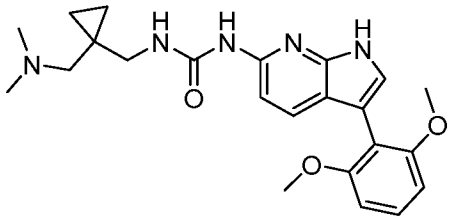
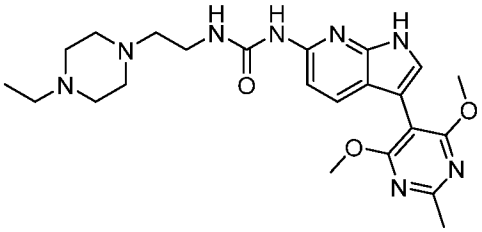
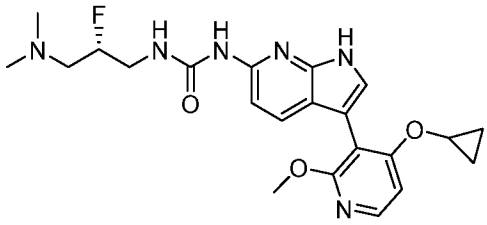
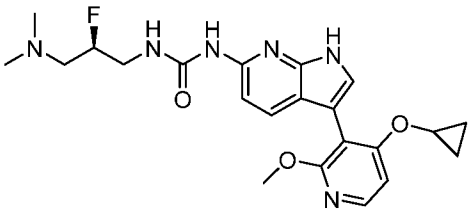
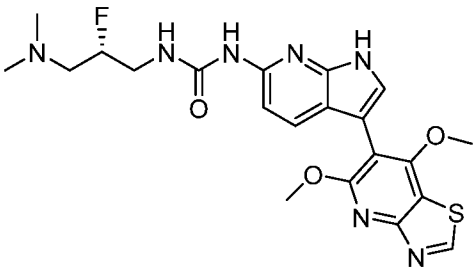
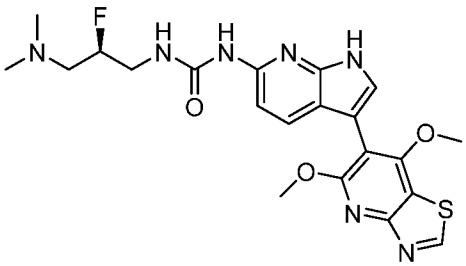
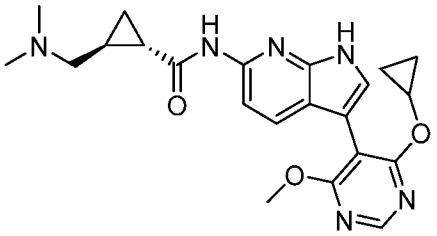
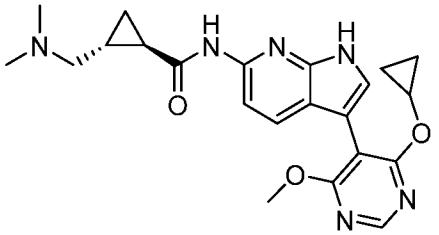
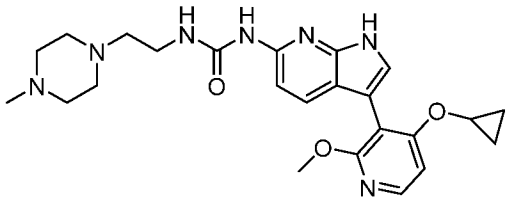
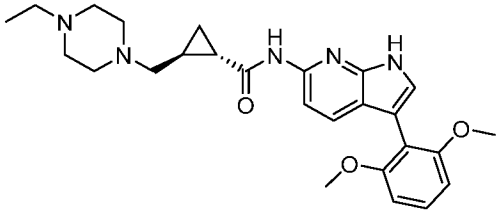
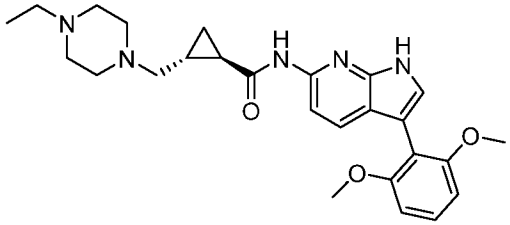
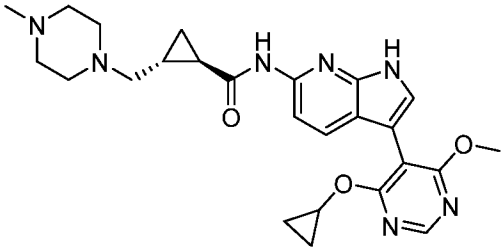
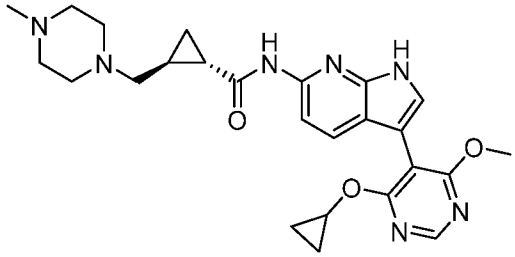
;

;

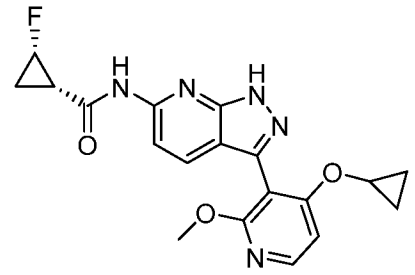
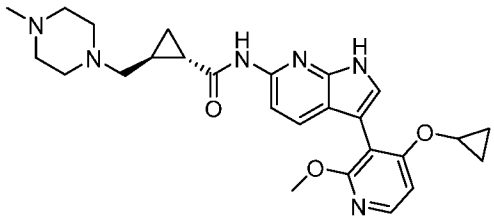
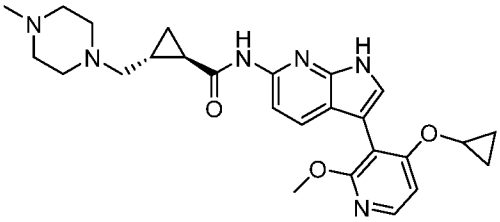
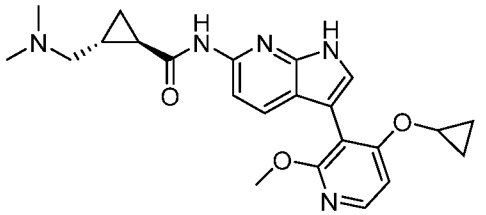
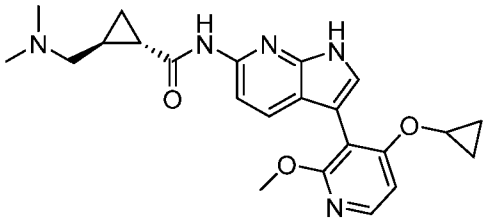
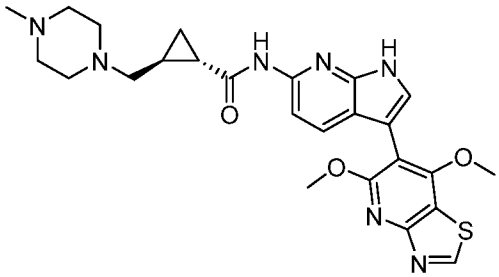
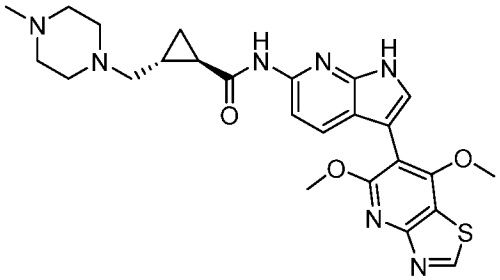
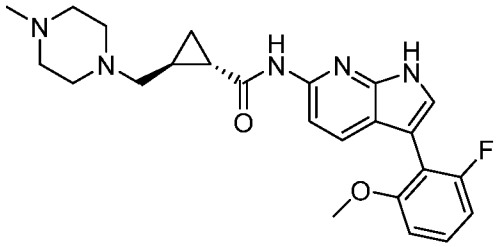
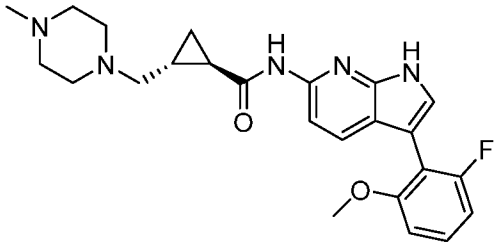
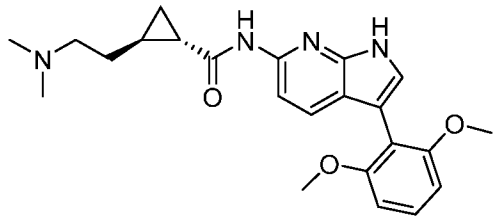
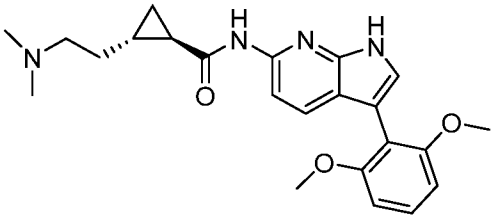
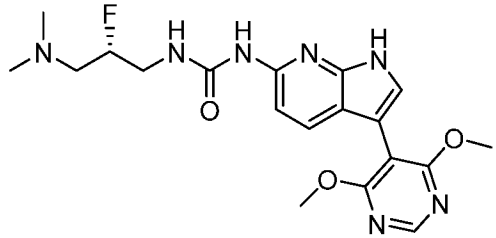
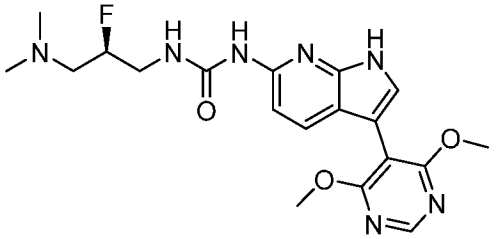
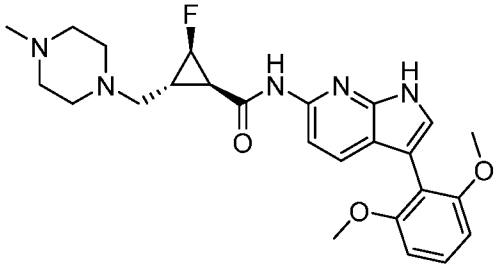

;

;

;

;

;

;

;

;

;

;

;

;

;

;

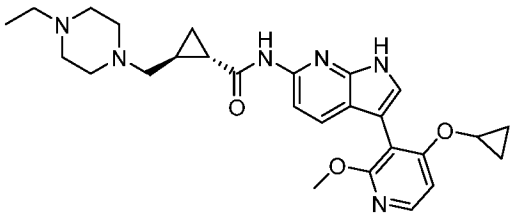
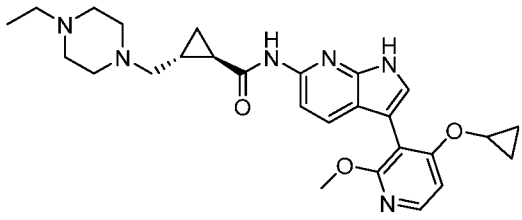
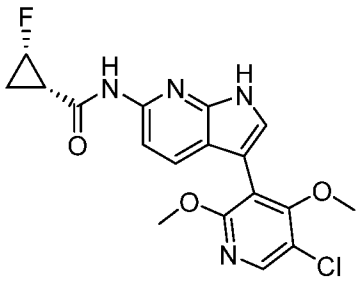
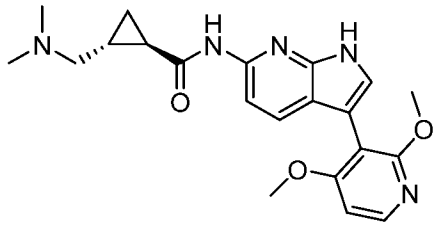
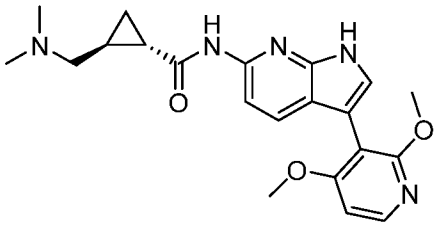
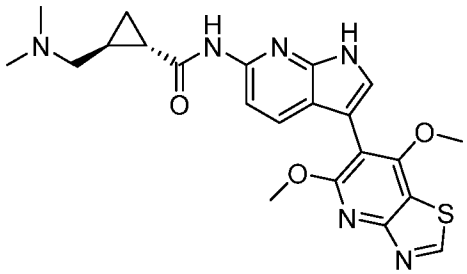
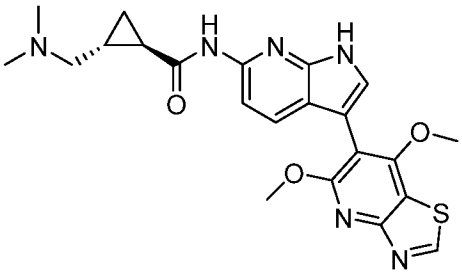
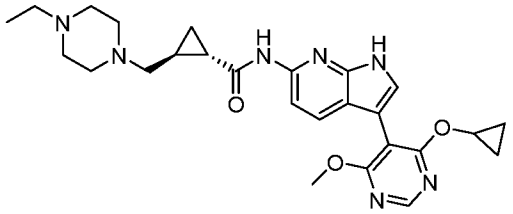
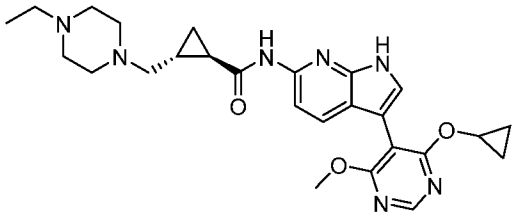
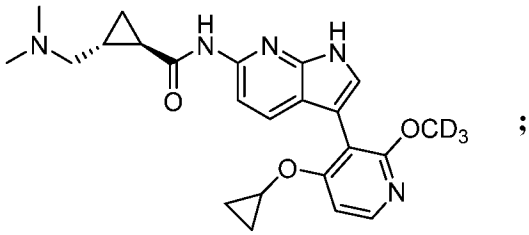
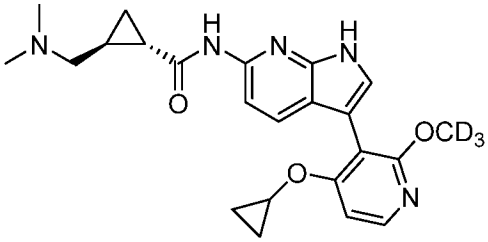
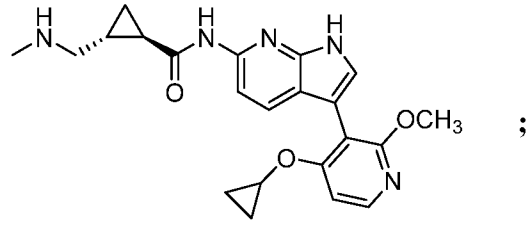
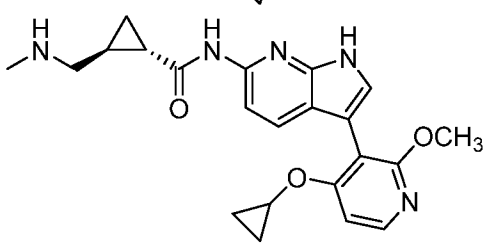
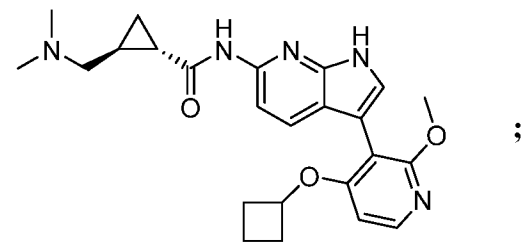

;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

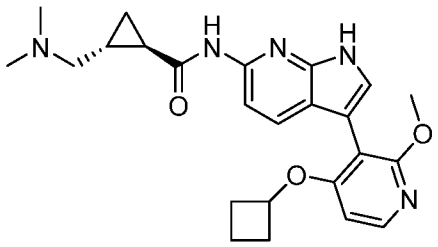
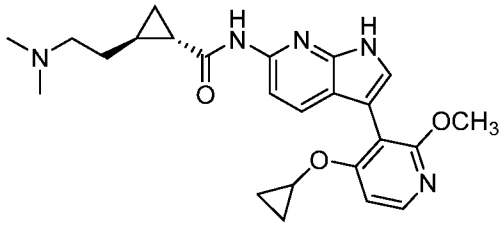
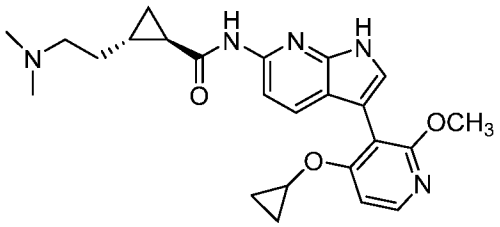
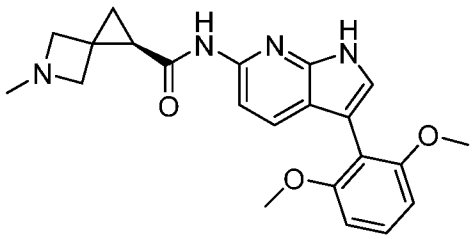
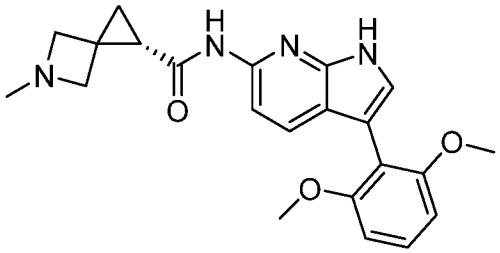
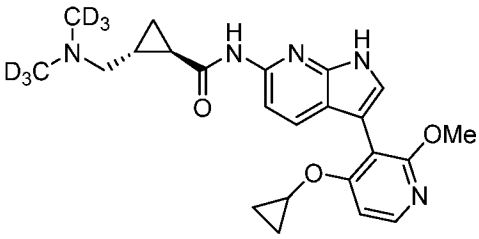
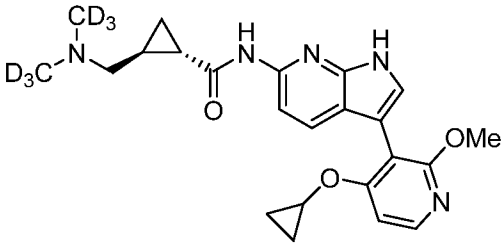
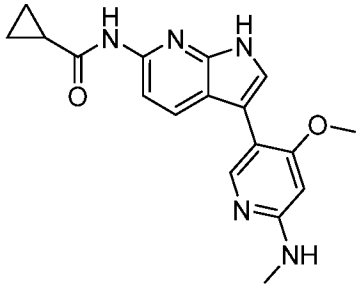
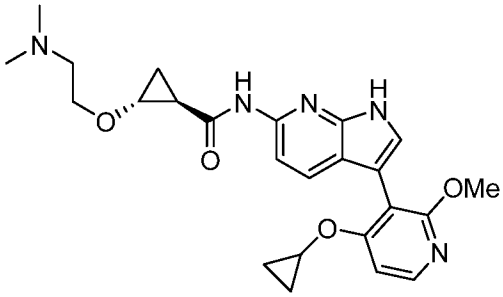
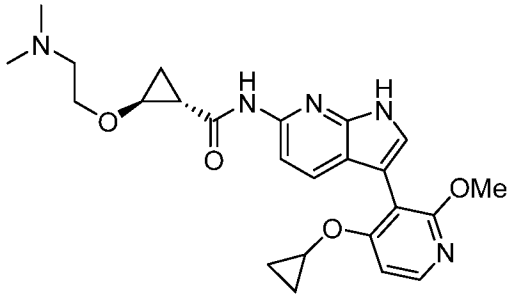
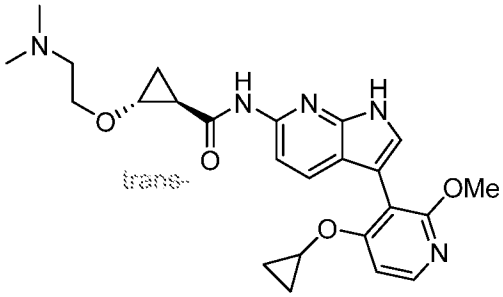
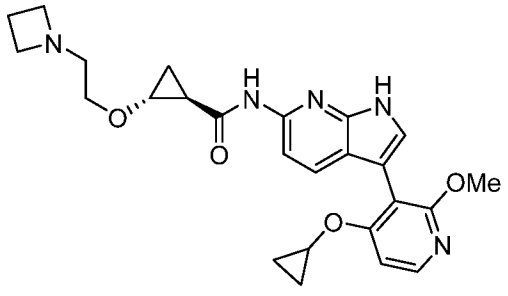
;

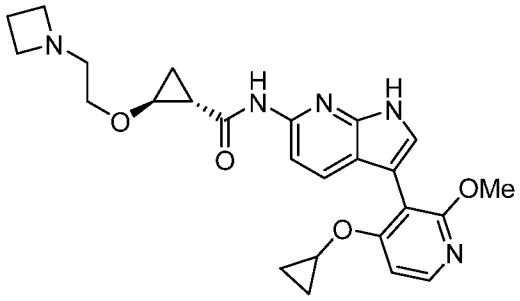
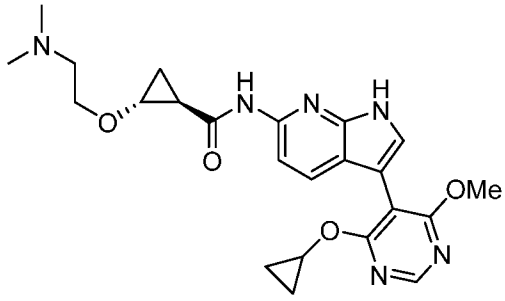
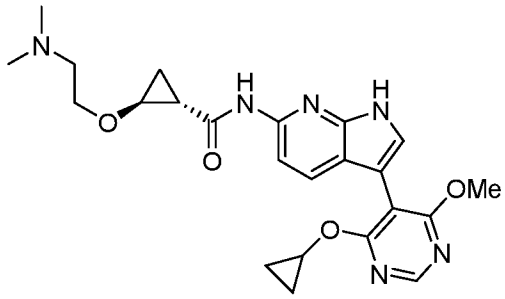
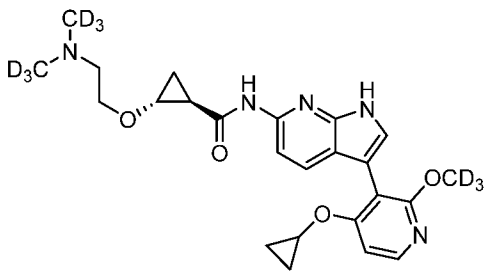
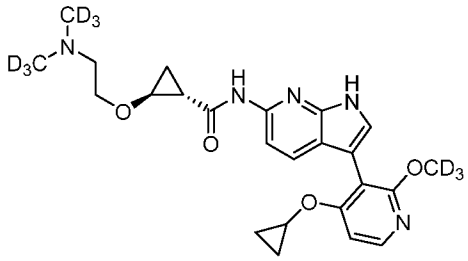
;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;



;

;

;

;
and

,

or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing.

Claim 22. A pharmaceutical composition comprising the compound of any one of claims 1 to 21, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, and one or more pharmaceutically acceptable excipients.

Claim 23. A method of inhibiting Bcr-Abl enzymatic activity in a cell, comprising exposing the cell with an effective amount of the compound of any one of claims 1 to 21, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or the pharmaceutical composition of claim 22.

Claim 24. A method of treating chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or a mixed phenotype acute leukemia, in a human in need thereof, comprising administering to the human the compound of any one of claims 1 to 21, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or the pharmaceutical composition of claim 22.

Claim 25. The method of claim 24, wherein the leukemia is refractory leukemia.

Claim 26. The method of claim 25, wherein the refractory leukemia is associated with a mutation in the Bcr-Abl tyrosine kinase gene resulting in specific amino acid substitutions selected from the group consisting of M244V, L248V, G250E, G250A, Q252H, Q252R, Y253F, Y253H, E255K, E255V, D276G, F311L, T315N, T315A, F317V, F317L, M343T, M351T, E355G, F359A, F359V, V379I, F382L, L387M, H396P, H396R, S417Y, E459K, F486S, and T315I.

Claim 27. The method of claim 26, wherein the refractory leukeumia is associated with a mutation in the Bcr-Abl tyrosine kinase gene resulting in specific amino acid substitution T315I.

Claim 28. The method of claim 25, wherein the human having refractory leukemia has one or more mutations in the Bcr-Abl tyrosine kinase gene resulting in specific amino acid substitutions selected from the group consisting of M244V, L248V, G250E, G250A, Q252H, Q252R, Y253F, Y253H, E255K, E255V, D276G, F311L, T315N, T315A, F317V, F317L, M343T, M351T, E355G, F359A, F359V, V379I, F382L, L387M, H396P, H396R, S417Y, E459K, F486S, and T315I.

Claim 29. The method of claim 28, wherein the human having refractory leukemia has a mutation in the Bcr-Abl tyrosine kinase gene resulting in specific amino acid substitution T315I.

Claim 30. The method of any one of claims 23 to 29, further comprising administering one or more pharmaceutical agents including including anti-microtubular therapies (e.g. paclitaxel, vincristine), topoisomerase inhibitors, alkylating agents, nucleotide synthesis inhibitors, DNA synthesis inhibtiors, protein synthesis inhibitors, developmental signaling pathway inhibitors, pro-apoptotic agents, Abl myristoyl-pocket binding inhibitors, MEK1/2 inhibitors, AKT inhibitors, PI3K inhibitors and/or radiation.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/71692

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07D 239/94; C07D 495/04; A61K 31/517 (2022.01)

CPC - C07D 473/34; C07D 417/04; A61P 35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	"Pubchem CID 152209919" Create Date: 13 August 2020 (13.08.2020) Date Accessed: 26 January 2022 (26.01.2022); pg. 2	1-3
A	US 2007/0015758 A1 (Baruah et al.) 18 January 2007 (18.01.2007); para [0626]	1-3
A	US 2011/0312959 A1 (Yasri et al.) 22 December 2011 (22.12.2011); para [0555]	1-3
A	US 2010/0210476 A1 (Salom et al.) 19 August 2010 (19.08.2010); entire document	1-3
A	US 2015/0353539 A1 (ORIBASE PHARMA) 10 December 2015 (10.12.2015); entire document	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 January 2022 (26.01.2022)	FEB 23 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/71692

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-10, 12-19, 22-30
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(see supplemental page)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

--continued from Box No. III--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-3, 11 and 20-21, directed to a compound of formula I. The compound of claim 1 will be searched to the extent that it encompasses the first species of claim 1, represented by a compound of formula I wherein X is N; R0 is first structure listed; m is 0; R2 is C6 aryl (wherein optional groups are omitted). It is believed that claims 1-3, read on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of formula I wherein X is N; R0 is second structure listed; R2 is C6 aryl; R3 is H (wherein optional groups are omitted) (i.e., claims 1-2 and 11).

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of formula I, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Groups I+ share the technical feature of a compound of formula I.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by a document entitled "Pubchem CID 152209919" (hereinafter Pubchem-919). Pubchem-919 discloses a compound of formula I wherein X is CR8; R0 is 2nd structure listed; R2 is 9 membered hteroaryl; R3 is C2 alkyl; R8 is H (pg. 2, compound listed).

As said compound was known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+. The inventions of Group I+ thus lack unity under PCT Rule 13.

Note: Claims 4-10, 12-19, 22-30 have been found to be unsearchable because they are not drafted in accordance with the second and third sentences of Rule 6.4(a).