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

(19) **World Intellectual Property Organization**
International Bureau

(43) **International Publication Date**
07 January 2021 (07.01.2021)

WIPO | PCT

(10) **International Publication Number**
WO 2021/000925 A1

(51) **International Patent Classification:**
C07D 471/00 (2006.01) *A61K 31/517* (2006.01)
C07D 487/00 (2006.01) *A61K 31/519* (2006.01)
C07D 487/04 (2006.01) *A61K 31/437* (2006.01)
C07D 487/02 (2006.01) *A61P 35/00* (2006.01)

(21) **International Application Number:**
PCT/CN2020/100037

(22) **International Filing Date:**
03 July 2020 (03.07.2020)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
PCT/CN2019/094749
04 July 2019 (04.07.2019) CN
PCT/CN2019/123268
05 December 2019 (05.12.2019) CN
PCT/CN2020/089498
09 May 2020 (09.05.2020) CN

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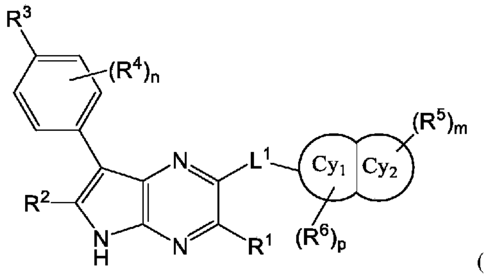
(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, 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).

Published:
— *with international search report (Art. 21(3))*

(54) Title: PYRROLO [2, 3-b] PYRAZINES AS HPK1 INHIBITOR AND THE USE THEREOF

(57) **Abstract:** Disclosed herein is a compound of Formula (I), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, and pharmaceutical compositions comprising thereof. Also disclosed is a method of treating HPK1 related disorders or diseases by using the compound disclosed herein.



(I)

WO 2021/000925 A1

PYRROLO[2, 3-b]PYRAZINES AS HPK1 INHIBITOR AND THE USE THEREOF

FIELD OF THE INVENTION

The disclosure herein provides compounds as well as their compositions and methods of use. The compounds disclosed herein modulate, e.g., inhibit, hematopoietic progenitor kinase 1 (HPK1) activity and are useful in the treatment of various diseases including cancer.

BACKGROUND OF THE INVENTION

HPK1 regulates diverse functions of various immune cells and its kinase activity has been shown to be induced upon activation of T cell receptors (TCR) [*Liou J., et al., Immunity, **2000**. 12 (4): pp. 399-408*], B cell receptors (BCR) [*Liou J., et al., Immunity, **2000**. 12 (4): pp. 399-408*], transforming growth factor receptor (TGF-βR) [*Wang, W., et al., J Biol Chem, **1997**. 272 (36): pp. 22771-5; Zhou, G., et al., J Biol Chem, **1999**. 274 (19): pp. 13133-8*], or Gs-coupled PGE2 receptors (EP2 and EP4) [*Ikegami, R., et al., J Immunol, **2001**. 166 (7): pp. 4689-96*]. Overexpression of HPK1 suppresses TCR-induced activation of AP-1-dependent gene transcription in a kinase-dependent manner, suggesting that HPK1 is required to inhibit the Erk MAPK pathway [*Liou J., et al., Immunity, **2000**. 12 (4): pp. 399-408*] and this blockage is thought to be the inhibitory mechanism that negatively regulates TCR-induced IL-2 gene transcription [*S. Sawasdikosol., et al., Immunol Res, **2012**. 54: pp. 262-265*].

In vitro HPK1-/- T cells have a lower TCR activation threshold, proliferate robustly, produce enhanced amounts of Th1 cytokines, the HPK1-/- mice experience more severe autoimmune symptoms [*S. Sawasdikosol., et al., Immunol Res, **2012**. 54: pp. 262-265*]. In human, HPK1 was downregulated in peripheral blood mononuclear cells of psoriatic arthritis patients or T cells of systemic lupus erythematosus (SLE) patients [*Batliwalla F.M., et al., Mol Med, **2005**. 11 (1-12): pp. 21-9*], which indicated that attenuation of HPK1 activity may contribute to autoimmunity in patients. Furthermore, HPK1 may also control anti-tumor immunity via T cell-dependent mechanisms. In the PGE2-producing Lewis lung carcinoma tumor model, the tumors developed more slowly in HPK1 knockout mice as compared to wild-type mice [**US** patent application No. 2007/0087988]. HPK1 deficient T cells was more effective in controlling tumor growth and metastasis than wild-type T cells [*Alzabin, S., et al., Cancer Immunol Immunother, **2010**. 59 (3): pp. 419-29*]. Similarly, BMDCs from HPK1 knockout mice were more efficient to mount a T cell response to eradicate Lewis lung carcinoma as compared to wild-type BMDCs [*Alzabin, S., et al., J Immunol, **2009**. 182 (10): pp. 6187-94*]. In all, HPK1 may be a good target for enhancing antitumor immunity.

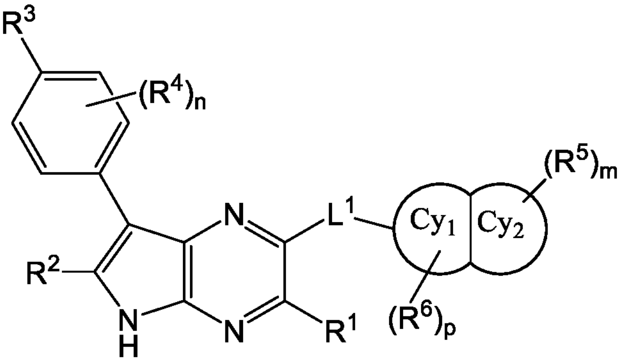
As HPK1 modulators, WO2016205942 discloses benzoimidazoles, WO2018049152A1 discloses pyrazolopyrmidines, WO2018049191A1 discloses pyrazolopyridones, and WO2008124849, WO2018049200A1 and WO2018049214A1 discloses pyrazolopyridines.

However, there is a need to provide new HPK1 kinase inhibitors useful in treating cancer.

SUMMARY OF THE INVENTION

In the first aspect, disclosed herein is pyrrolo[2, 3-b]pyrazine derivatives of Formula (**I**), and the methods of use. The first embodiment comprises the following aspects:

Aspect 1: A compound of Formula (**I**)



(**I**)

or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof,

wherein

R^1 and R^2 are each independently hydrogen, halogen, $-C_{1-8}$alkyl, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo, -CN, $-NO_2$, $-OR^a$, $-SO_2R^a$, $-COR^a$, $-CO_2R^a$, $-CONR^aR^b$, $-C(=NR^a)NR^bR^c$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCONR^bR^c$, $-NR^aCO_2R^b$, $-NR^aSONR^bR^c$, $-NR^aSO_2NR^bR^c$, or $–NR^aSO_2R^b$, each of said $-C_{1-8}$alkyl, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with halogen, hydroxy, $-C_{1-8}$alkyoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

R^a, R^b, and R^c are each independently hydrogen, $-C_{1-8}$alkyl, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

n is 0, 1, 2, 3 or 4;

R^3 and R^4, at each of its occurrence, are independently halogen, $-C_{1-8}$alkyl, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, cycloalkyl, heterocyclyl, $-C_{1-8}$alkyl-heterocyclyl, $-C_{1-8}$alkyl-cycloalkyl, aryl, heteroaryl, oxo, -CN, $-NO_2$, $-OR^{3a}$, $-SO_2R^{3a}$, $-SO_2NR^{3a}R^{3b}$, $-COR^{3a}$, $-CO_2R^{3a}$, $-CONR^{3a}R^{3b}$, $-C(=NR^{3a})NR^{3b}R^{3c}$, $-NR^{3a}R^{3b}$, $-NR^{3a}COR^{3b}$, $-NR^{3a}CONR^{3b}R^{3c}$, $-NR^{3a}CO_2R^{3b}$, $-NR^{3a}SONR^{3b}R^{3c}$, $-NR^{3a}SO_2NR^{3b}R^{3c}$, or $–NR^{3a}SO_2R^{3b}$, each of said $-C_{1-8}$alkyl, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, cycloalkyl, heterocyclyl, $-C_{1-8}$alkyl-heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents R^{3d}; or R^3 and R^4, when on adjacent carbon atoms of the phenyl ring, together with the two intervening carbon atoms to which they are attached, form a 5- to 8-membered ring comprising 0, 1 or 2 heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s), said ring is optionally substituted with at least one substituents R^{3e};

or two R^4, when on adjacent carbon atoms of the phenyl ring, together with the two intervening carbon atoms to which they are attached, form a 5- to 8-membered ring comprising 0, 1 or 2 heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s).

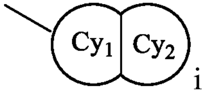
R^{3a}, R^{3b}, and R^{3c} are each independently hydrogen, $-C_{1-8}$alkyl, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of said $-C_{1-8}$alkyl, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents R^{3e}; or

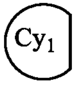
(R^{3a} and R^{3b}), (R^{3b} and R^{3c}), or (R^{3c} and R^{3a}), together with the atom (s) to which they are attached, form a 3- to 12-membered ring, said ring comprising 0, 1 or 2 additional heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s), said ring is optionally substituted with at least one substituents R^{3e};

R^{3d} and R^{3e} are each independently halogen, $-C_{1-8}$alkyl, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo, -CN, $-NO_2$, $-OR^{3f}$, $-SO_2R^{3f}$, $-SO_2NR^{3f}R^{3g}$, $-COR^{3f}$, $-CO_2R^{3f}$, $-CONR^{3f}R^{3g}$, $-C\ (=NR^{3f})NR^{3g}R^{3h}$, $-NR^{3f}R^{3g}$, $-NR^{3f}COR^{3g}$, $-NR^{3f}CONR^{3g}R^{3h}$, $-NR^{3f}CO_2R^{3f}$, $-NR^{3f}SONR^{3f}R^{3g}$, $-NR^{3f}SO_2NR^{3g}R^{3h}$, or $–NR^{3f}SO_2R^{3g}$, each of said $-C_{1-8}$alkyl, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents selected from halogen, $-C_{1-8}$alkyl, $-OR^{3i}$, $-NR^{3i}R^{3j}$, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

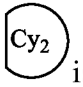
R^{3f}, R^{3g}, R^{3h}, R^{3i}, and R^{3j} are each independently hydrogen, $-C_{1-8}$alkyl, C_{1-8}alkoxy-C_{1-8}alkyl-, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

L^1 is a single bond, alkylene, cycloalkylene, $*^1$-O-alkylene-$**^1$, $*^1$-alkylene-O-$**^1$, $*^1$-NH-alkylene-$**^1$, $*^1$-alkylene-NH-$**^1$, $*^1$-NHC (O)-$**^1$, $*^1$-C (O)NH-$**^1$, alkenylene, or alkynylene; wherein $*^1$ refers to the position attached to Cy1, and $**^1$ refers to the position attached to the pyrrolo[2, 3-b]pyrazine ring;



is a fused heterocyclyl, fused heteroaryl, fused aryl, fused cycloalkyl, fused cycloalkenyl, or fused cycloalkynyl, 

is optionally substituted with R^6;

p is 0, 1, 2, 3, 4; 

is optionally substituted with R^5, m is 0, 1, 2, 3, 4;

R^5 at each of its occurrence, is each independently halogen, $-C_{1-8}$alkyl, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, cycloalkyl, $-C_{1-8}$alkyl-cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo, -CN, $-NO_2$, $-OR^{5a}$, $-SO_2R^{5a}$, $-SO_2NR^{5a}R^{5b}$, $-POR^{5a}R^{5b}$, $-COR^{5a}$, $-CO_2R^{5a}$, $-CONR^{5a}R^{5b}$, $-C\ (=NR^{5a})NR^{5b}R^{5c}$, $-CH_2CONR^{5a}R^{5b}$, $-CH_2CH_2CONR^{5a}R^{5b}$, $-CH_2CH_2CH_2CONR^{5a}R^{5b}$, $-NR^{5a}R^{5b}$, $-CH_2NR^{5a}R^{5b}$, $-CH_2CH_2NR^{5a}R^{5b}$, $-CH_2CH_2CH_2NR^{5a}R^{5b}$, $-NR^{5a}COR^{5b}$, $-NR^{5a}CONR^{5b}R^{5c}$, $-NR^{5a}CO_2R^{5b}$, $-NR^{5a}SONR^{5b}R^{5c}$, $-NR^{5a}SO_2NR^{5b}R^{5c}$, or $-NR^{5a}SO_2R^{5b}$, each of said $-C_{1-8}$alkyl, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, cycloalkyl, $-C_{1-8}$alkyl-cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents R^{5d}; or two R^5 together with the atoms to which they are attached (provided that the valence theory is met), form a 4-, 5-, 6-, 7- or 8-membered ring, said ring comprising 0, 1 or 2 heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s), said ring is optionally substituted with at least one substituents R^{5e};

R^{5a}, R^{5b} and R^{5c} are each independently hydrogen, $-C_{1-8}$alkyl, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, $-C_{1-8}$alkyl-C_{1-8}alkoxy, cycloalkyl, $-C_{1-8}$alkyl-heterocyclyl, $-C_{1-8}$alkyl-aryl, heterocyclyl, aryl, or heteroaryl, each of said $-C_{1-8}$alkyl, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, $-C_{1-8}$alkyl-C_{1-8}alkoxy, cycloalkyl, -

C_{1-8}alkyl-heterocyclyl, -C_{1-8}alkyl-aryl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents R^{5e};

(R^{5a} and R^{5b}), (R^{5b} and R^{5c}), or (R^{5c} and R^{5a}), together with the atom (s) to which they are attached, form a 3- to 12-membered ring, said ring comprising 0, 1 or 2 additional heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s), said ring is optionally substituted with at least one substituents R^{5e};

R^{5d} and R^{5e} are each independently hydrogen, halogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo, -CN, -NO_2, -CF_3, -OR^{5f}, -SO_2R^{5f}, -$SO_2NR^{5f}R^{5g}$, -$POR^{5f}R^{5g}$, -COR^{5f}, -CO_2R^{5f}, -$CONR^{5f}R^{5g}$, -C (=NR^{5h})$NR^{5f}R^{5g}$, -$NR^{5f}R^{5g}$, -$NR^{5f}COR^{5g}$, -$NR^{5h}CONR^{5f}R^{5g}$, -$NR^{5f}CO_2R^{5h}$, -$NR^{5h}SONR^{5f}R^{5g}$, -$NR^{5h}SO_2NR^{5f}R^{5g}$, or –$NR^{5f}SO_2R^{5g}$, each of said -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents selected from halogen, -C_{1-8}alkyl, -OR^{5i}, -$NR^{5i}R^{5j}$, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

R^{5f}, R^{5g}, R^{5h}, R^{5i}, and R^{5j} are each independently hydrogen, oxo, -C_{1-8}alkyl, -C_{1-8}alkoxy, hydroxy, C_{1-8}alkoxy-C_{1-8}alkyl-, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

R^6 at each of its occurrence, is each independently hydrogen, halogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo, -CN, -NO_2, -OR^{6a}, -SO_2R^{6a}, -$SO_2NR^{6a}R^{6b}$, -COR^{6a}, -CO_2R^{6a}, -$CONR^{6a}R^{6b}$, -C (=NR^{6a})$NR^{6b}R^{6c}$, -$CH_2CONR^{6a}R^{6b}$, -$CH_2CH_2CONR^{6a}R^{6b}$, -$CH_2CH_2CH_2CONR^{6a}R^{6b}$, -$NR^{6a}R^{6b}$, -$CH_2NR^{6a}R^{6b}$, -$CH_2CH_2NR^{6a}R^{6b}$, -$CH_2CH_2CH_2NR^{6a}R^{6b}$, -$NR^{6a}COR^{6b}$, -$NR^{6a}CONR^{6b}R^{6c}$, -$NR^{6a}CO_2R^{6b}$, -$NR^{6a}SONR^{6b}R^{6c}$, -$NR^{6a}SO_2NR^{6b}R^{6c}$, or –$NR^{6a}SO_2R^{6b}$, each of said -$C_{1-8}$alkyl, -$C_{2-8}$alkenyl, -$C_{2-8}$alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents R^{6d}; or two R^6, together with the atoms to which they are attached (provided that the valence theory is met), form a 4-, 5-, 6-, 7- or 8-membered ring, said ring comprising 0, 1 or 2 heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s), said ring is optionally substituted with at least one substituents R^{6e};

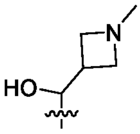
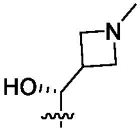
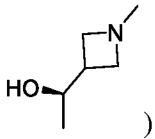
R^{6a}, R^{6b}, and R^{6c} are each independently hydrogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, C_{1-8}alkoxy-C_{1-8}alkyl-, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of said -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents R^{6e};

(R^{6a} and R^{6b}), (R^{6b} and R^{6c}), or (R^{6c} and R^{6a}), together with the atom (s) to which they are attached, form a 3- to 12-membered ring, said ring comprising 0, 1 or 2 additional heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s), said ring is optionally substituted with at least one substituents R^{6e};

R^{6d} and R^{6e} are each independently hydrogen, halogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo, -CN, -NO_2, -OR^{6f}, -SO_2R^{6f}, -$SO_2NR^{6f}R^{6g}$, -COR^{6f}, -CO_2R^{6f}, -$CONR^{6f}R^{6g}$, -C (=NR^{6h})$NR^{6f}R^{6g}$, -$NR^{6f}R^{6g}$, -$NR^{6f}COR^{6g}$, -$NR^{6h}CONR^{6f}R^{6g}$, -$NR^{6f}CO_2R^{6h}$, -$NR^{6h}SONR^{6f}R^{6g}$, -$NR^{6h}SO_2NR^{6f}R^{6g}$, or –$NR^{6f}SO_2R^{6g}$, each of said -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents selected from halogen, $-C_{1-8}$alkyl, $-OR^{6i}$, $-NR^{6i}R^{6j}$, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

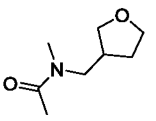
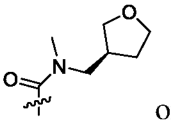
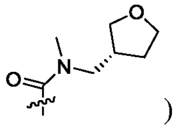
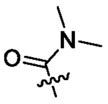
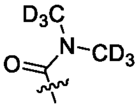
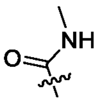
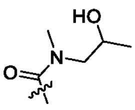
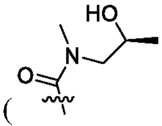
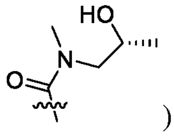
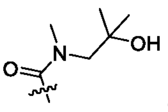
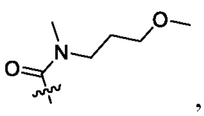
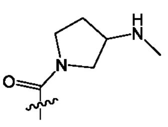
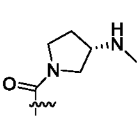
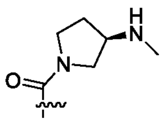
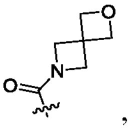
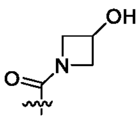
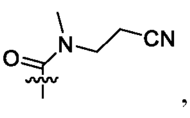
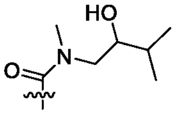
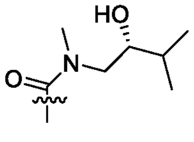
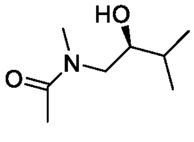
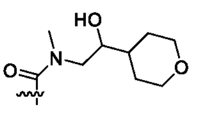
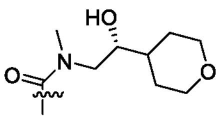
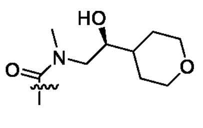
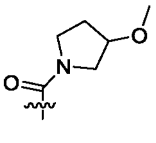
R^{6f}, R^{6g}, R^{6h}, R^{6i}, and R^{6j} are each independently hydrogen, oxo, $-C_{1-8}$alkyl, C_{1-8}alkoxy-C_{1-8}alkyl-, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl.

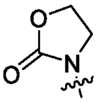
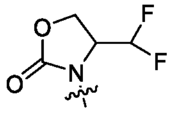
Aspect 2: The compound according to Aspect 1, wherein R^1 and R^2 are each hydrogen or $-C_{1-8}$alkyl (preferably hydrogen or methyl).

Aspect 3: The compound according to Aspect 1 or 2, wherein R^3 is $–C_{1-8}$alkyl, $-C_{1-8}$alkyl-heterocyclyl or $-C_{1-8}$alkyl-cycloalkyl, wherein said $–C_{1-8}$alkyl, $-C_{1-8}$alkyl-heterocyclyl or $-C_{1-8}$alkyl-cycloalkyl is optionally substituted with at least one substituents R^{3d}; R^{3d} is independently selected from $-C_{1-8}$alkyl or $-OR^{3f}$; R^{3f} is each independently hydrogen, $-C_{1-8}$alkyl. Preferably R^3 is  ( or ).

Aspect 4: The compound according to Aspect 1 or 2, wherein R^3 is $-CONR^{3a}R^{3b}$; R^{3a} and R^{3b} are each independently hydrogen or $-C_{1-8}$alkyl (preferably methyl, ethyl, propyl, butyl, pentyl or hexyl); each of said $-C_{1-8}$alkyl is substituted with at least one substituents selected from hydrogen, $-OR^{3f}$, CN, 3- to-7 membered heterocyclyl comprising 1 or 2 heteroatoms selected from nitrogen, oxygen (for example, piperazinyl, piperidinyl, piperidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyranyl, or pyrrolidinyl); R^{3f} is selected from hydrogen or $-C_{1-8}$alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl or hexyl).

Aspect 5: The compound according to any one of Aspect 1-2, wherein R^3 is $-CONR^{3a}R^{3b}$ or $-NR^{3a}R^{3b}$; R^{3a} and R^{3b} together with the nitrogen atom to which they are attached is 4- to 12-membered ring comprising 1 or 2 additional nitrogen or oxygen heteroatoms as ring member. (e.g., monocyclic 3- to 8-membered ring or bicyclic spiro 7- to 12-membered ring), said ring is optionally substituted with at least one substituents R^{3e}; R^{3e} each is selected from oxo, $-C_{1-8}$alkyl, $-OR^{3f}$, $-NR^{3f}R^{3g}$, said $-C_{1-8}$alkyl is optionally substituted by at least one halogen, wherein R^{3f} and R^{3g} are each independently hydrogen, or $-C_{1-8}$alkyl.

Aspect 6: The compound according to any one of Aspect 1-5, wherein R^3 is selected from  ( or ),  ,  ,  ,  ( or ),  ,  ,  ( or ),  ,  ,  ,  ( or ),  ( or ) or  .

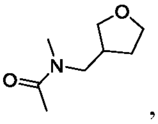
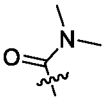
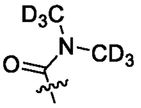
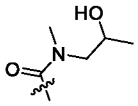
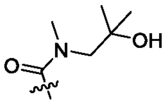
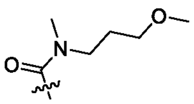
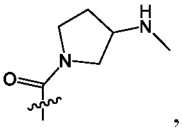
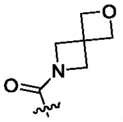
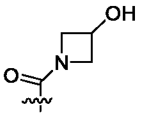
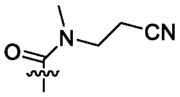
Aspect 7: The compound according to Aspect 5, wherein R^3 is selected from  or .

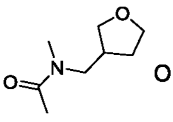
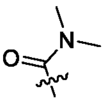
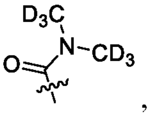
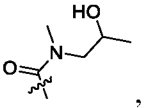
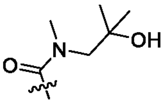
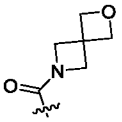
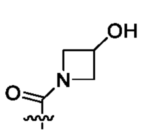
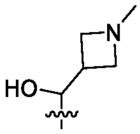
Aspect 8: The compound according to any one of Aspect 1-7, wherein n is 0, 1 or 2; R^4 is selected from halogen, $-C_{1-8}$alkyl (preferably methyl), halogen, CN, $-OR^{3a}$ or $-NR^{3a}CONR^{3b}R^{3c}$; said $-C_{1-8}$alkyl is optionally substituted with at least one substituents R^{3d}; R^{3a}, R^{3b} and R^{3c} are each independently hydrogen, $-C_{1-8}$alkyl (preferably methyl); R^{3d} is each independently halogen or $-C_{1-8}$alkyl.

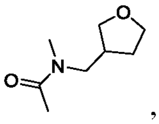
Aspect 9: The compound according to Aspect 8, wherein n is 1, R^4 is selected from $-C_{1-8}$alkyl (preferably methyl), halogen, CN, OR^{3a} or $-NR^{3a}CONR^{3b}R^{3c}$; said $-C_{1-8}$alkyl is optionally substituted with at least one substituents R^{3d}; R^{3a}, R^{3b} and R^{3c} are each independently hydrogen, or $-C_{1-8}$alkyl (preferably methyl); R^{3d} is each independently halogen or $-C_{1-8}$alkyl.

Aspect 10: The compound according to Aspect 8, wherein n is 2, and R^4 is halogen.

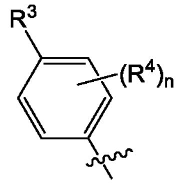
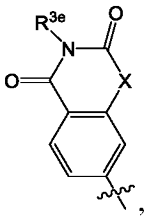
Aspect 11: The compound according to Aspect 8, wherein n is 1 or 2, and R^4 is selected from methyl, F, OH, CN, $-CHF_2$ or $-NHCOCH_3$.

Aspect 12: The compound according to any one of Aspects 1-8, wherein n is 0, and R^3 is selected from , , , , , , , ,  or .

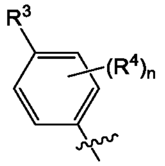
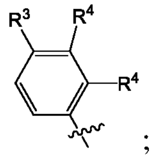
Aspect 13: The compound according to any one of Aspects 1-8, 9, 11, wherein n is 1, and R^3 is selected from  , , , , ,  or ; and R^4 is methyl, F, OH, CN, $-CHF_2$ or $-NHCOCH_3$.

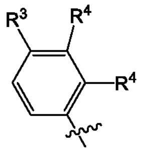
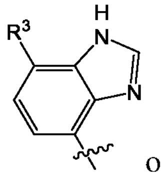
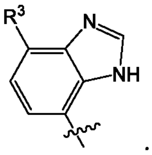
Aspect 14: The compound according to any one of Aspects 1-8, and10-11, wherein n is 2, and R^3 is selected from , and R^4 is F.

Aspect 15: The compound according to any one of Aspects 1-2, wherein R^3 and R^4, when on adjacent carbon atoms of the phenyl ring, together with the two intervening carbon atoms to which they are attached, form a 5- to 8-membered ring comprising 0, 1 or 2 heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s), said ring is optionally substituted with at least one substituents R^{3e}; each R^{3e} is independently selected from $-C_{1-8}$alkyl or oxo.

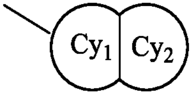
Aspect 16: The compound according to Aspect 15, wherein  is , X=NH or O, and R^{3e} is -C_{1-8}alkyl.

Aspect 17: The compound according to any one of Aspects 1-2, wherein n=2, and two R^4, when on adjacent carbon atoms of the phenyl ring, together with the two intervening carbon atoms to which they are attached, form a 5- to 8-membered ring comprising 0, 1 or 2 heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s).

Aspect 18: The compound according to Aspect 17, wherein  is ; two R^4 when on adjacent carbon atoms of the phenyl ring, together with the two intervening carbon atoms to which they are attached, form a 5-membered ring comprising 2 heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s).

Aspect 19: The compound according to Aspect 18, wherein  is  or .

Aspect 20: The compound according to any one of Aspects 1-19, L^1 is a single bond.

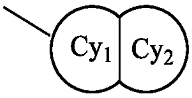
Aspect 21: The compound according to any one of Aspects 1-20, wherein  is benzo fused heterocyclyl, benzo fused heteroaryl, benzo fused cycloalkyl, benzo fused cycloalkenyl, benzo fused cycloalkynyl.

Aspect 22: The compound according to Aspect 21, wherein the benzo fused heterocyclyl is indolinyl, isoindolinyl, benzopyranyl, dihydrothiazolopyrimidinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, dihydrobenzofuranyl, dihydrobenzoxazinyl, dihydrobenzoimidazolyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, benzodioxolyl, benzodioxonyl, chromanyl, chromenyl, octahydrochromenyl, dihydrobenzodioxynyl, dihydrobenzoxezinyl, dihydrobenzodioxepinyl, dihydrothienodioxynyl, dihydrobenzooxazepinyl, tetrahydrobenzooxazepinyl, dihydrobenzoazepinyl, tetrahydrobenzoazepinyl, isochromanyl, or chromanyl.

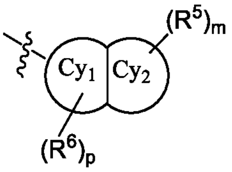
Aspect 23: The compound according to any one of Aspects 21-22, wherein the benzo fused heterocyclyl is indolinyl, isoindolinyl, tetrahydroisoquinolyl, dihydrobenzofuranyl, dihydrobenzoimidazolyl, tetrahydrobenzooxazepinyl, tetrahydrobenzoazepinyl, or isochromanyl.

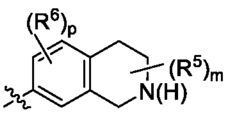
Aspect 24: The compound according to Aspect 23, wherein tetrahydroisoquinolinyl is selected from 1, 2, 3, 4-tetrahydroisoquinolinyl, 1, 2, 3, 4-tetrahydroisoquinolin-6-yl or 1, 2, 3, 4-tetrahydroisoquinolin-7-yl; tetrahydrobenzooxazepinyl is selected from 2, 3, 4, 5-tetrahydrobenzooxazepinyl, 2, 3, 4, 5-tetrahydrobenzo[f][1, 4]oxazepin-8-yl, or 2, 3, 4, 5-tetrahydrobenzo[f][1, 4]oxazepin-7-yl; tetrahydrobenzoazepinyl is selected from 2, 3, 4, 5-tetrahydrobenzoazepinyl, 2, 3, 4, 5-tetrahydro-1H-benzo[c]azepin-7-yl and 2, 3, 4, 5-tetrahydro-1H-benzo[d]azepin-7-yl; isoindolinyl is selected from isoindolin-5-yl; isochromanyl is selected from isochroman-5-yl; dihydroisobenzofuranyl is selected from 1, 3-dihydroisobenzofuran-4-yl.

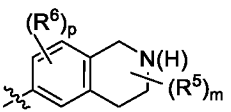
Aspect 25: The compound according to Aspect 21, wherein the benzo fused heteroaryl is benzisoxazolyl, benzodiazolyl, benzofuranyl, benzofurazanyl, benzofuryl, benzoimidazolyl, benzoisothiazolyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzothiophenyl, benzotriazolyl, benzoxadiazolyl, benzoxazolyl, indazolyl, indolyl, isobenzofuryl, isoindolyl, isoquinolinyl (or isoquinolyl), phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinolinyl (or quinolyl), or quinoxalinyl. In some examples, indazolyl is e.g., 1H-indazol-4-yl, 2H-indazol-4-yl, 1H-indazol-5-yl, 2H-indazol-5-yl, 1H-indazol-7-yl; benzodiazolyl is e.g., 1H-benzo[d]imidazol-4-yl, 1H-1, 3-benzodiazol-5-yl or 1H-benzo[d]imidazol-5-yl, 1H-benzo[d]imidazol-4-yl, 1H-benzo[d]imidazol-6-yl; benzooxazolyl is e.g., benzo[d]oxazol-6-yl; benzooxadiazolyl is e.g., benzo[c][1, 2, 5]oxadiazol-4-yl.

Aspect 26: The compound according to Aspect 21, wherein 

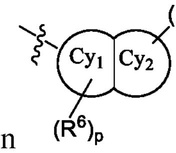
is a bicyclic fused heteroaryl selected from furopyridinyl, furopyrrolyl, imidazopyridinyl, imidazopyridyl, imidazothiazolyl, indolizinyl, naphthyridinyl, pyrazinopyridazinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrazolopyridyl, pyrazolotriazinyl, pyridazolopyridyl, pyrrolopyridinyl, thiazolopyridyl, thienopyrazinyl, thienopyrazolyl, thienopyridyl, thienopyrrolyl, thienothienyl, or triazolopyridyl. In some example, imidazopyridinyl is e.g., imidazo[1, 2-a]pyridin-5-yl or imidazo[1, 5-a]pyridin-5-yl.

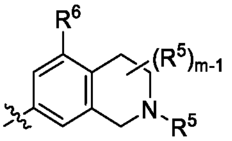
Aspect 27: The compound according to Aspect 21, wherein 

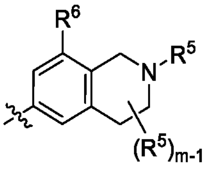
is 

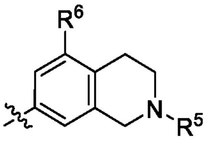
or 

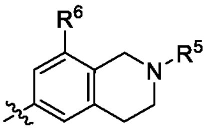
, p=0, 1, 2 or 3; m=0, 1, 2, 3 or 4; R^6 and R^5 are defined for Formula (I).

Aspect 28: The compound according to any one of Aspects 21-27, wherein 

is 

or 

(preferably 

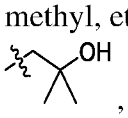
or 

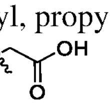
), m=1, 2, 3 or 4; R^6 and R^5 are defined for Formula (I) (preferably R^5 and R^6 are independently $-C_{1-8}$alkyl (e.g., methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-methyl-1-propyl, 1-methylpropyl or t-butyl).

Aspect 29: The compound according to Aspect 27 or 28, wherein R^6 is selected from $-C_{1-8}$alkyl, $-OR^{6a}$ or $-NR^{6a}R^{6b,}$ said $-C_{1-8}$alkyl is optionally substituted with at least one substituents R^{6d}, R^{6a} and R^{6b} are each hydrogen or $-C_{1-8}$alkyl; R^{6d} is each independently hydrogen, halogen or $-C_{1-8}$alkyl.preferably R^6 is selected from $-CH_3$, $-OCH_3$, $-NHCH_3$, $-CHF_2$, or $-C\ (CH_3)_2OH$.

Aspect 30: The compound according to any one of Aspects 27-29, wherein each R^5 is independently selected from $-C_{1-8}$alkyl, $-C_{1-8}$alkyl-cycloalkyl, heterocyclyl or heteroaryl $-CONR^{3a}R^{3b}$, $CH_2CONR^{5a}R^{5b}$, $-CH_2\ CH_2CONR^{5a}R^{5b}$, $-NR^{5a}R^{5b}$, $-CH_2NR^{5a}R^{5b}$, $-CH_2\ CH_2NR^{5a}R^{5b}$, said $-C_{1-8}$alkyl, $-C_{1-8}$alkyl-cycloalkyl or heterocyclyl or heteroaryl is optionally substituted with at least one R^{5d}, and R^{5a}, R^{5b} and R^{5d} are defined for Formula (I).

Aspect 31: The compound according to any one of Aspects 27-30, wherein R^5 is selected from $-C_{1-8}$alkyl (e.g., methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-methyl-1-propyl, 1-methylpropyl or t-butyl), $-C_{1-8}$alkyl-cycloalkyl, heterocyclyl or heteroaryl, said $-C_{1-8}$alkyl, $-C_{1-8}$alkyl-cycloalkyl, heteroaryl or heterocyclyl is optionally substituted with at least one substituents R^{5d}; R^{5d} is selected from $-C_{1-8}$alkyl, $-OR^{5f}$, $-NR^{5f}R^{5g}$, $-CO_2R^{5f}$, heteroaryl, heterocyclyl, $-SO_2R^{5f}$, $-POR^{5f}R^{5g}$, $-CONR^{5f}R^{5g}$, oxo or $-CF_3$; R^{5f} and R^{5g} are each independently hydrogen, $-C_{1-8}$alkyl, $-C_{1-8}$alkoxy or hydroxy.

Aspect 32: The compound according to Aspect 31, wherein, R^5 is methyl, ethyl, propyl, butyl, pentyl or hexyl, $-CH_2OH$, $-C_2H_4OH$, $C_2H_4NHCH_3$, $-C_2H_4OCH_3$, 

, 

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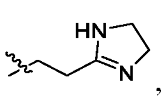
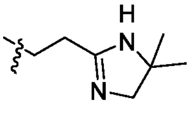
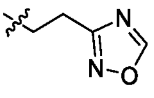
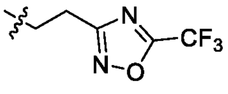
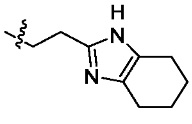
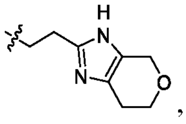


, 



, 

, 

, 

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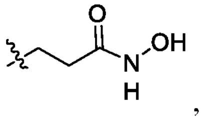
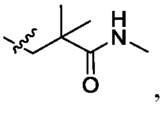
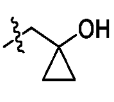
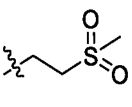
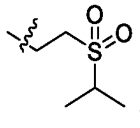
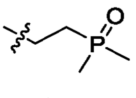


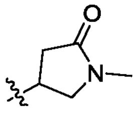
, 

, 

, 

, 

, 

or 

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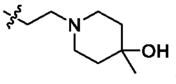
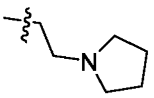
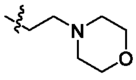
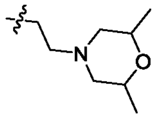
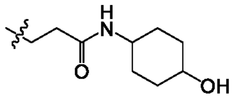
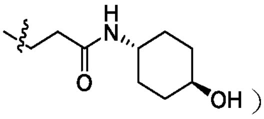
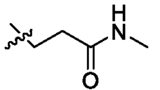
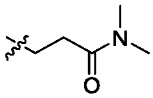
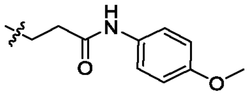
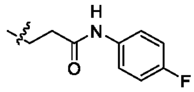
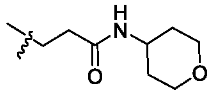
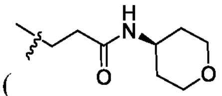
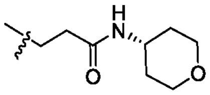
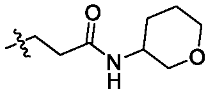
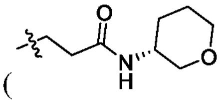
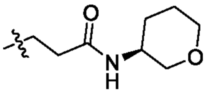
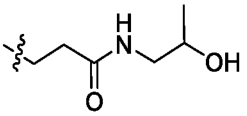
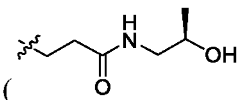
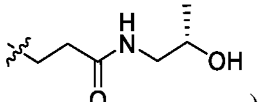
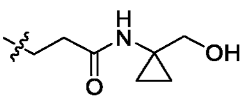
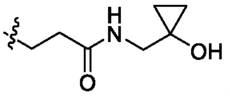
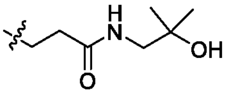
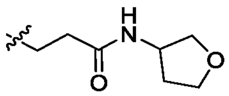
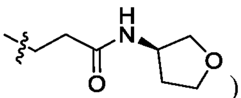
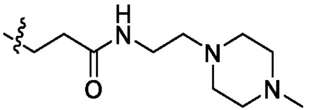
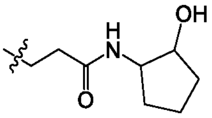
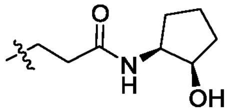
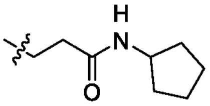
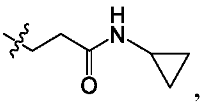
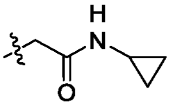
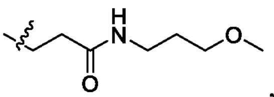
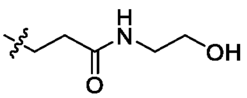
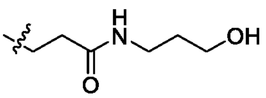
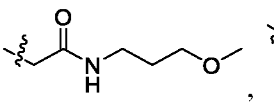
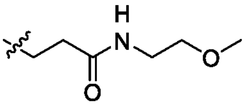
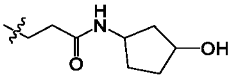
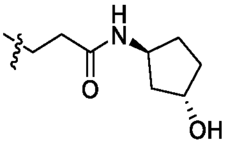
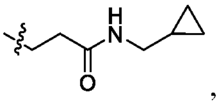
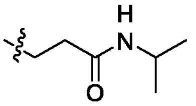
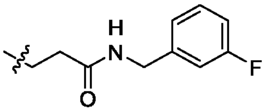
Aspect 33: The compound according to Aspect 30, wherein R^5 is $-NR^{5a}R^{5b}$, $-CH_2NR^{5a}R^{5b}$, $-CH_2\ CH_2NR^{5a}R^{5b}$; R^{5a} and R^{5b} together with the nitrogen atom to which they are attached form a 4- to 7- membered ring, said ring comprising 0, 1 or 2 additional heteroatoms independently selected from nitrogen, oxygen, said ring is optionally substituted with at least one substituents R^{5e}; R^{5e} is each independently selected from C_{1-8}alkyl (preferably methyl, ethyl), OR^{5f}; R^{5f} is each independently selected from hydrogen or $-C_{1-8}$alkyl (e.g., methyl, ethyl).

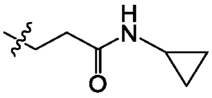
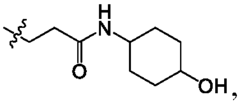
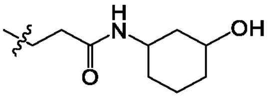
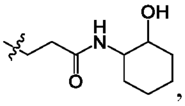
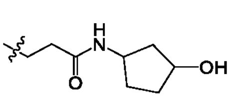
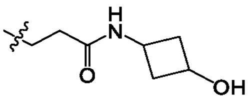
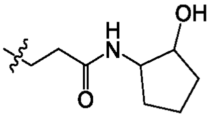
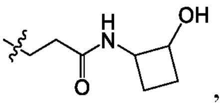
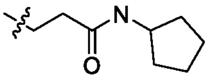
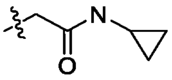
Aspect 34: The compound according to Aspect 33, wherein R^5 is , ,  or .

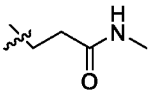
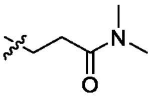
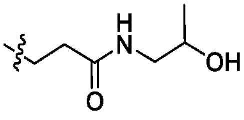
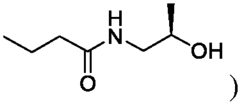
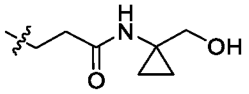
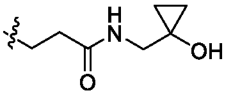
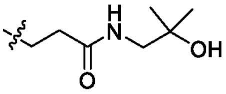
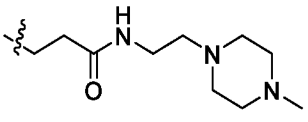
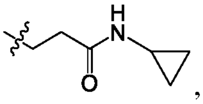
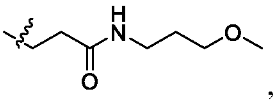
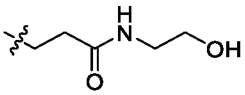
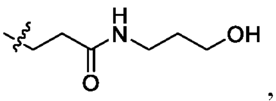
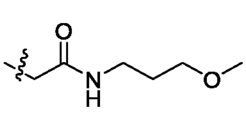
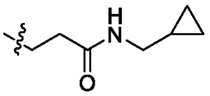
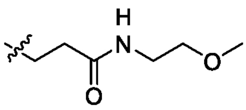
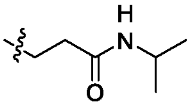
Aspect 35: The compound according to Aspect 30, wherein R^5 is selected from -$CONR^{5a}R^{5b}$, -$CH_2CONR^{5a}R^{5b}$, -$CH_2CH_2CONR^{5a}R^{5b}$, wherein R^{5a} and R^{5b} are each independently hydrogen, -C_{1-8}alkyl, C_{1-8}alkoxy-C_{1-8}alkyl-, cycloalkyl, heterocyclyl, -C_{1-8}alkyl-heterocyclyl, -C_{1-8}alkyl-aryl, -aryl, or heteroaryl, each of said -C_{1-8}alkyl, C_{1-8}alkoxy-C_{1-8}alkyl-, cycloalkyl, heterocyclyl, -C_{1-8}alkyl-heterocyclyl, -C_{1-8}alkyl-aryl, -aryl, or heteroaryl is optionally substituted with at least one substituents R^{5e}; R^{5e} is independently hydrogen, OR^{5f}, -C_{1-8}alkyl, heterocyclyl, -C_{1-8}alkyl-aryl, or C_{1-8}alkoxy-C_{1-8}alkyl-; R^{5f} is each independently selected from hydrogen, -C_{1-8}alkyl (e.g., methyl, ethyl) and cycloalkyl.

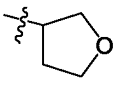
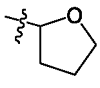
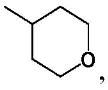
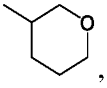
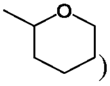
Aspect 36: The compound according to Aspect 35, wherein R^5 is selected from -$CONR^{5a}R^{5b}$, -$CH_2CONR^{5a}R^{5b}$, -$CH_2CH_2CONR^{5a}R^{5b}$, wherein R^{5a} is hydrogen or -C_{1-8}alkyl (e.g., methyl, ethyl); R^{5b} is selected from -C_{1-8}alkyl, cycloalkyl, -C_{1-8}alkyl-heterocyclyl, -C_{1-8}alkyl-aryl, heterocyclyl, aryl, said -C_{1-8}alkyl, cycloalkyl, -C_{1-8}alkyl-heterocyclyl, -C_{1-8}alkyl-aryl, heterocyclyl, aryl is optionally substituted with at least one substituents R^{5e}, R^{5e} is selected from halogen, -CH_2OH or OR^{5f}, R^{5f} is selected from hydrogen, cycloalkyl or -C_{1-8}alkyl.

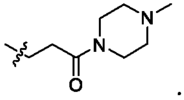
Aspect 37: The compound according to Aspect 36, wherein R^5 is selected from  (preferably ), , , , ,  ( or ),  ( or ),  ( or ), , , ,  (preferably ), ,  (), , , , , , , , ,

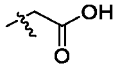
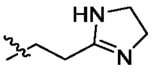
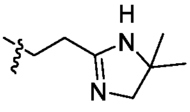
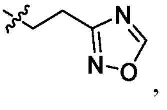
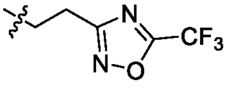
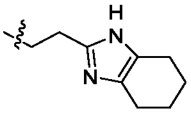
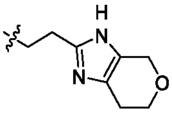
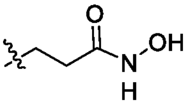
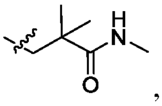
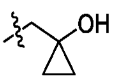
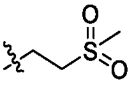
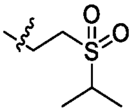
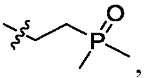
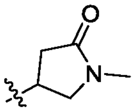
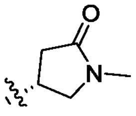
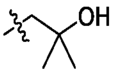
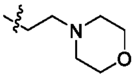
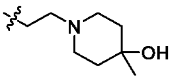
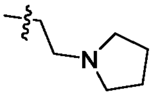
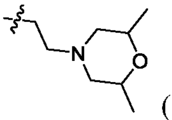
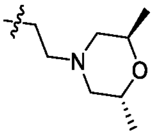
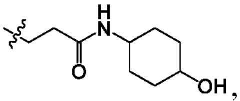
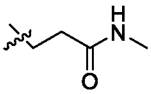
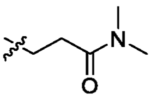
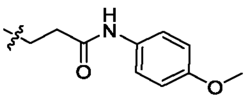
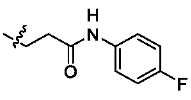
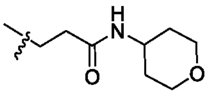
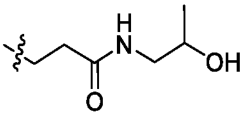
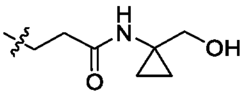
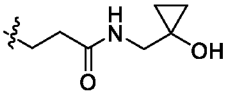
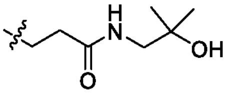
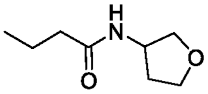
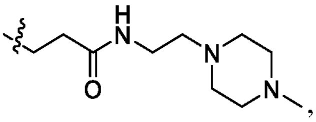
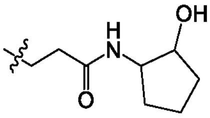
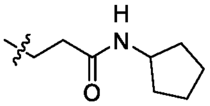
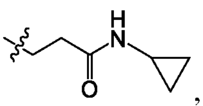
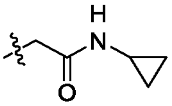
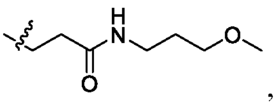
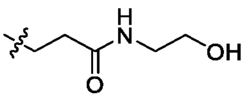
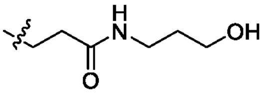
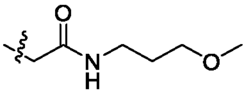
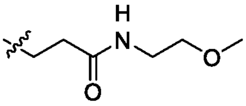
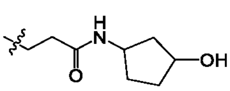
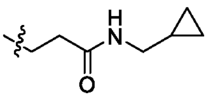
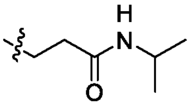
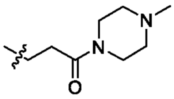
 (preferably ), , , .

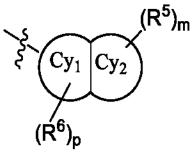
Aspect 38: The compound according to Aspect 35 or 36, wherein R^5 is $-CONR^{3a}R^{3b}$, $CH_2CONR^{5a}R^{5b}$ or $-CH_2\ CH_2CONR^{5a}R^{5b}$, R^{5a} is hydrogen or methyl; and R^{5b} is selected from cycloalkyl, such as cycloalkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, and cyclododecyl groups; said cycloalkyl is optionally substituted with OH, $-CH_3$, $-OCH_3$.Preferably R^5 is , , , , , , , , , .

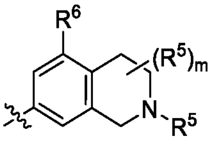
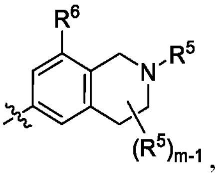
Aspect 39: The compound according to Aspect 35 or 36, wherein R^5 is $-CONR^{5a}R^{5b}$, $CH_2CONR^{5a}R^{5b}$ or $-CH_2CH_2CONR^{5a}R^{5b}$, R^{5a} is hydrogen or methyl; and R^{5b} is selected from $-C_{1-8}$alkyl, cycloalkyl or $-C_{1-8}$alkyl-heterocyclyl, said $-C_{1-8}$alkyl, cycloalkyl or $-C_{1-8}$alkyl-heterocyclyl is optionally substituted with at least one substituents R^{5e}, R^{5e} is selected from cycloalkyl, $-C_{1-8}$alkyl, $-CH_2OH$ or OR^{5f}, OR^{5f} is selected from hydrogen or $-C_{1-8}$alkyl. For example, R^5 is selected from , ,  (preferably ), , , , , , , , , , ,  or .

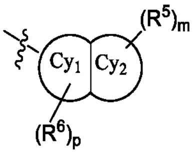
Aspect 40: The compound according to Aspect 35 or 36, wherein R^5 is $-CONR^{5a}R^{5b}$, $CH_2CONR^{5a}R^{5b}$ or $-CH_2\ CH_2CONR^{5a}R^{5b}$, R^{5a} is hydrogen or methyl; and R^{5b} is heterocyclyl (such as , , , , ) or aryl (such as phenyl), said heterocyclyl or aryl is optionally substituted with at least one substituents R^{5e} selected from halogen, $-C_{1-8}$alkyl or $-OR^{5f}$; R^{5f} is each independently hydrogen or $-C_{1-8}$alkyl.

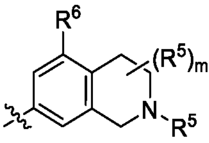
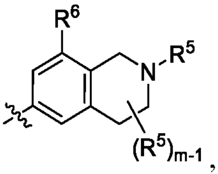
Aspect 41: The compound according to Aspect 30, wherein R^5 is selected from -$CONR^{5a}R^{5b}$, $CH_2CONR^{5a}R^{5b}$, -$CH_2CH_2CONR^{5a}R^{5b}$, wherein R^{5a} and R^{5b} together with the nitrogen atom to which they are attached, form a 4- to 7-membered ring, said ring comprising 0, 1 or 2 additional heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s), said ring is optionally substituted with at least one substituents R^{5e}; R^{5e} is each independently halogen, -C_{1-8}alkyl, -OR^{5f}, R^{5f} is each independently hydrogen or -C_{1-8}alkyl. For example, R^5 is  .

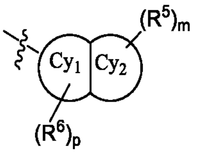
Aspect 42: The compound according to any one of Aspects 1-41, wherein R^5 is selected from methyl, ethyl, propyl, butyl, pentyl or hexyl, -CH_2OH, -C_2H_4OH, $C_2H_4NHCH_3$, -$C_2H_4OCH_3$, , , , , , , , , , , , , ,  (preferably ), , , , ,  (preferably ), , , , , , , , , , , , , , , , , , , , , , , , , .

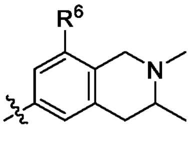
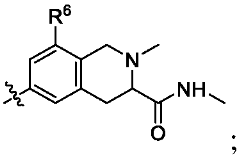
Aspect 43: The compound according to Aspect 28, wherein  is

 or , m=2, 3 or 4, R^5 is each independently halogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, -C_{1-8}alkyl-cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo, -CN, -NO_2, -OR^{5a}, -SO_2R^{5a}, -$SO_2NR^{5a}R^{5b}$, -$POR^{5a}R^{5b}$, -COR^{5a}, -CO_2R^{5a}, -$CONR^{5a}R^{5b}$, -C (=NR^{5a})$NR^{5b}R^{5c}$, -$CH_2CONR^{5a}R^{5b}$, -$CH_2CH_2CONR^{5a}R^{5b}$, -$CH_2CH_2CH_2CONR^{5a}R^{5b}$, -$NR^{5a}R^{5b}$, -$CH_2NR^{5a}R^{5b}$, -$CH_2CH_2NR^{5a}R^{5b}$, -$CH_2CH_2CH_2NR^{5a}R^{5b}$, -$NR^{5a}COR^{5b}$, -$NR^{5a}CONR^{5b}R^{5c}$, -$NR^{5a}CO_2R^{5b}$, -$NR^{5a}SONR^{5b}R^{5c}$, -$NR^{5a}SO_2NR^{5b}R^{5c}$, or -$NR^{5a}SO_2R^{5b}$, each of said -$C_{1-8}$alkyl, -$C_{2-8}$alkenyl, -$C_{2-8}$alkynyl, cycloalkyl, -$C_{1-8}$alkyl-cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents R^{5d}; R^6, R^{5a}, R^{5b}, R^{5c} and R^{5d} are defined for Formula (I).

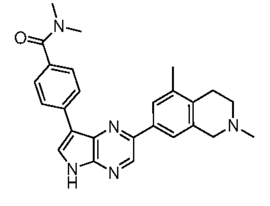
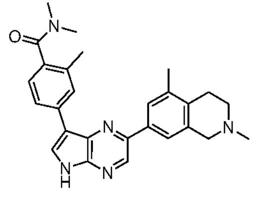
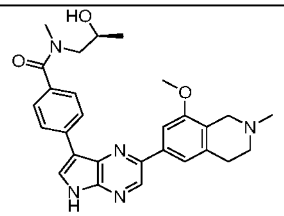
Aspect 44: The compound according to Aspect 43, wherein  is

 or , m=2, R^5 is each independently -C_{1-8}alkyl or -$CONR^{5a}R^{5b}$, R^{5b} and R^{5d} are hydrogen or -C_{1-8}alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl or hexyl); R^6 is selected from -C_{1-8}alkyl, -OR^{6a} or -$NR^{6a}R^{6b,}$ said -C_{1-8}alkyl is optionally substituted with at least one substituents R^{6d}, R^{6a} and R^{6b} are each hydrogen or -C_{1-8}alkyl; R^{6d} is each independently hydrogen, halogen or -C_{1-8}alkyl.preferably R^6 is selected from -CH_3, -OCH_3, -$NHCH_3$, -CHF_2, or -C $(CH_3)_2OH$.

Aspect 45: The compound according to Aspect 44, wherein  is

 or ; R^6 is selected from -CH_3, -OCH_3, -$NHCH_3$, -CHF_2, or -C $(CH_3)_2OH$.

Aspect 46: The compound according to Aspect 1, selected from:

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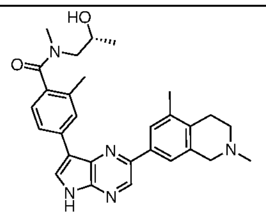	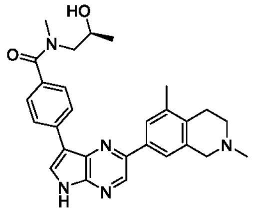	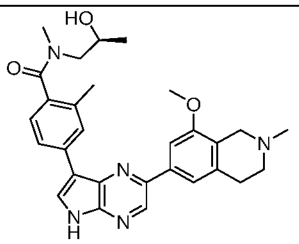
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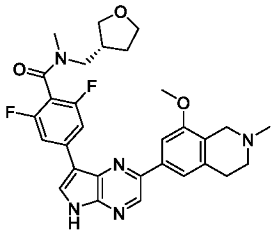	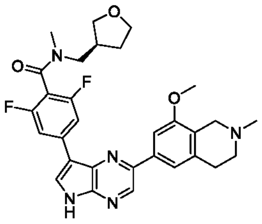	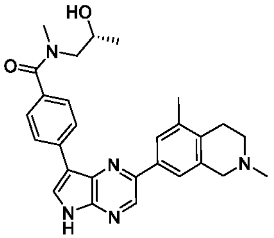
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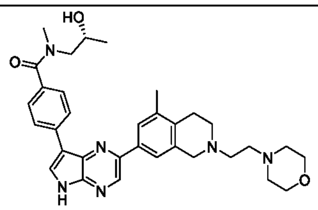	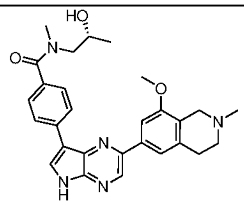	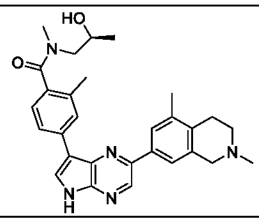
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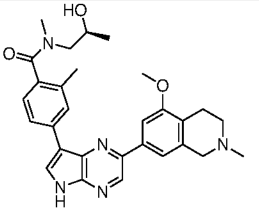	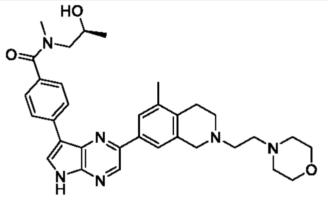	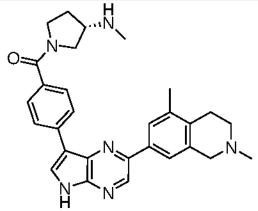
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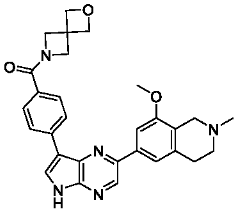	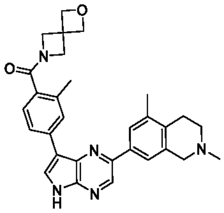	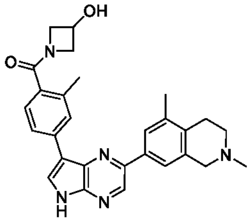
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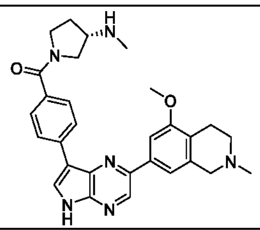	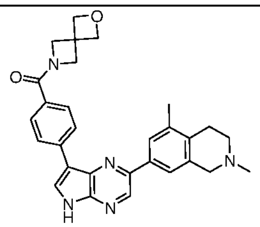	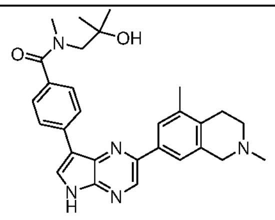
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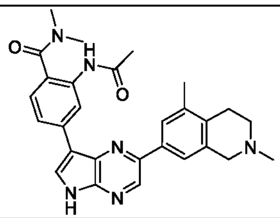	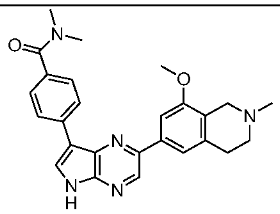	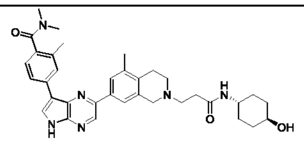

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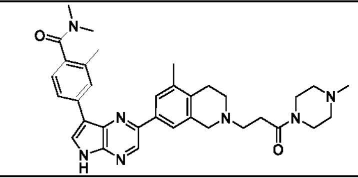	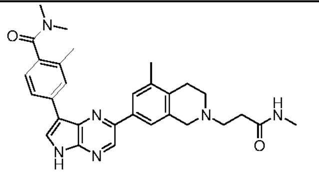	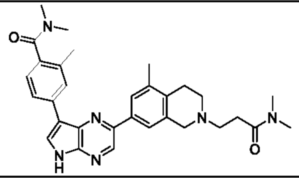
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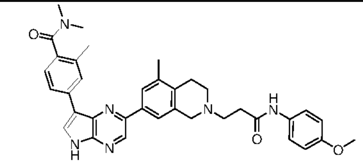	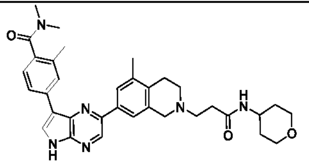	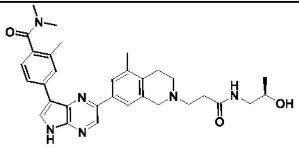
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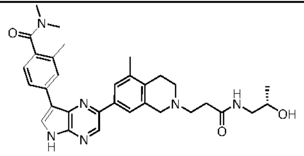	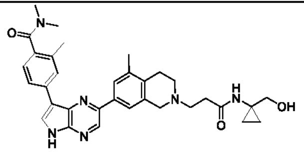	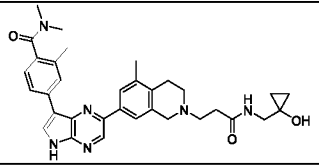
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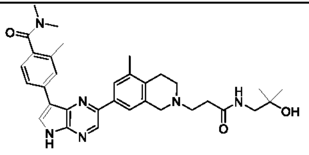	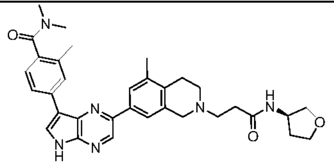	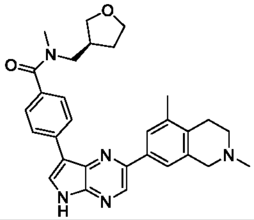
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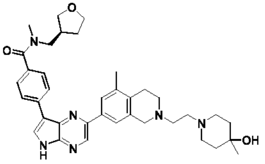	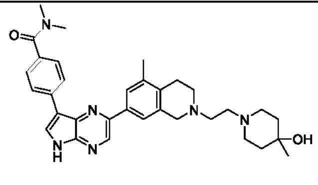	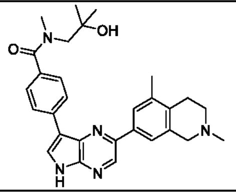
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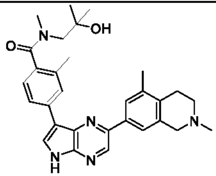	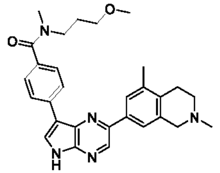	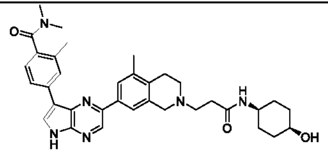
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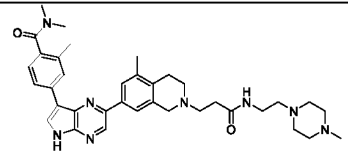	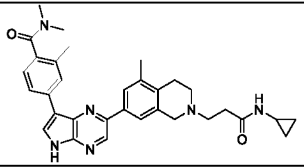	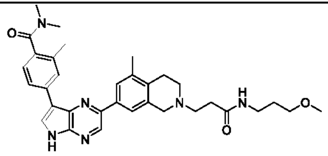
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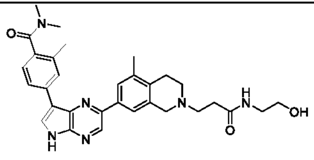	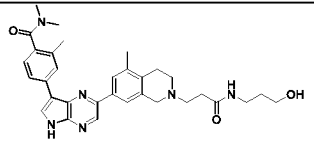	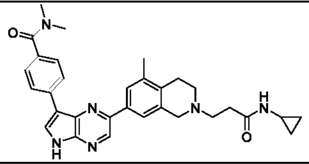
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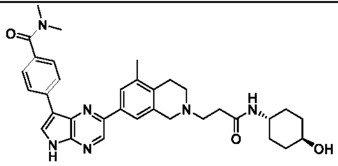	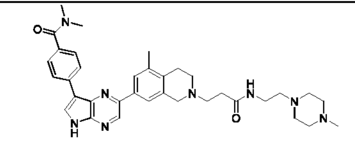	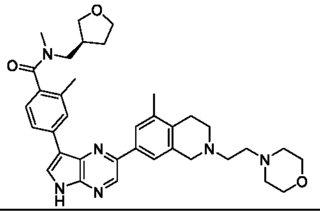
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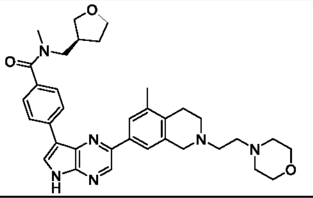	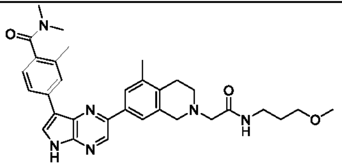	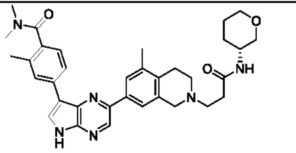
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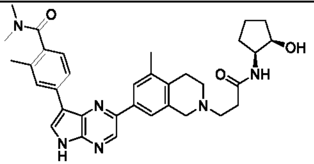	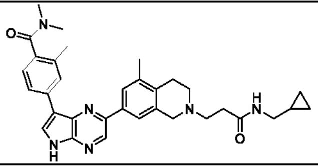	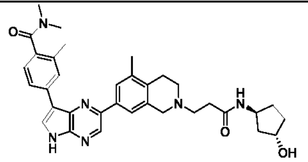
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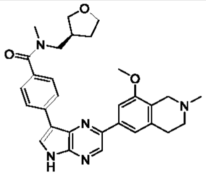	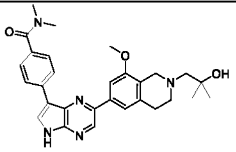	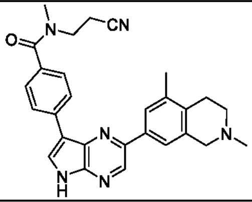
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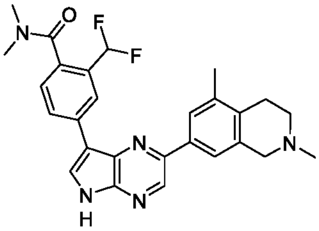	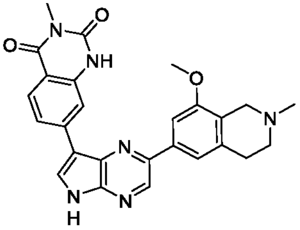	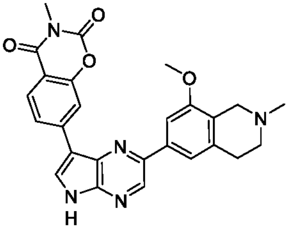
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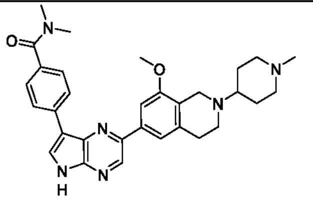	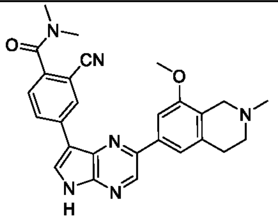	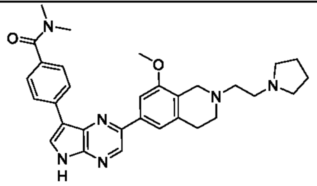
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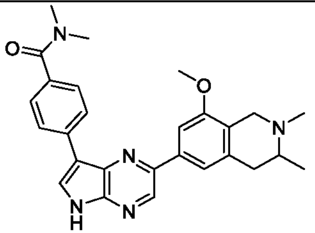	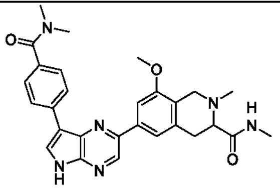	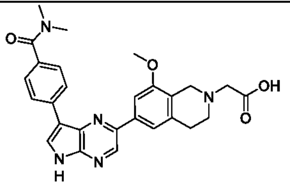
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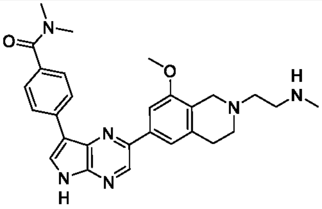	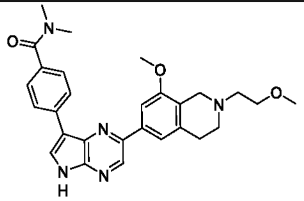	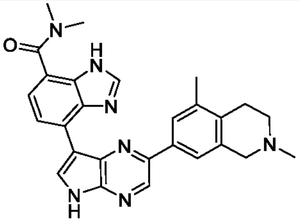
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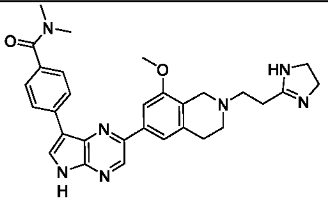	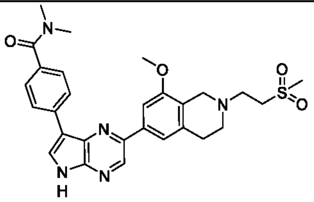	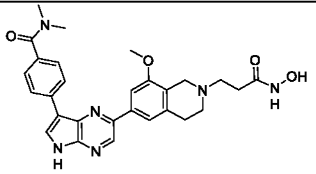
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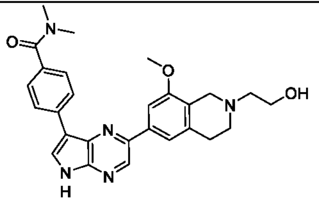	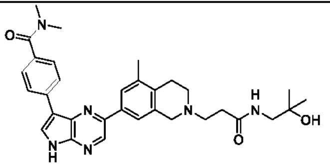	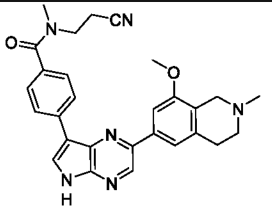
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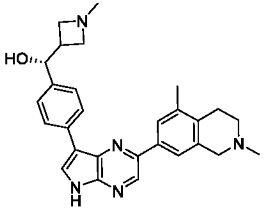	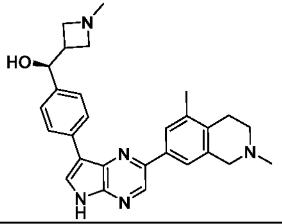	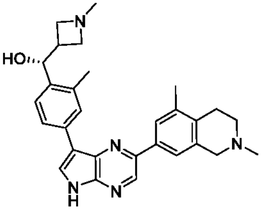
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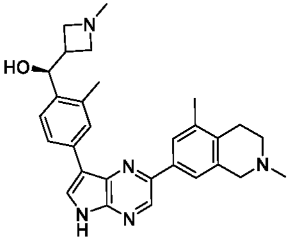	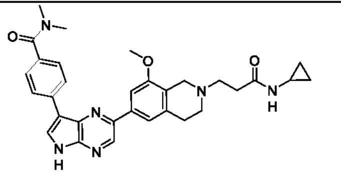	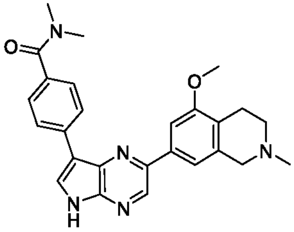
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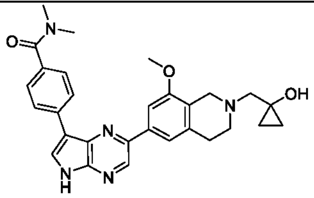	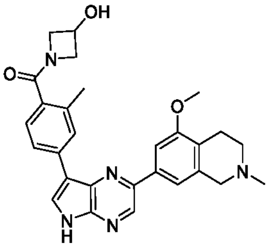	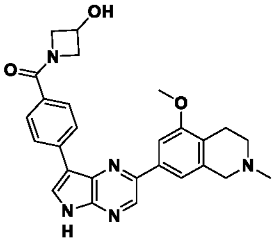
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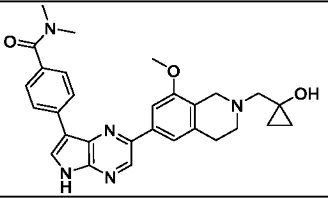	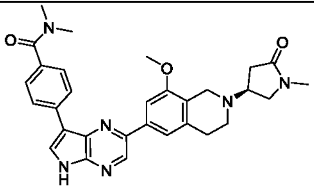	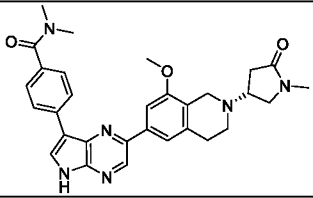
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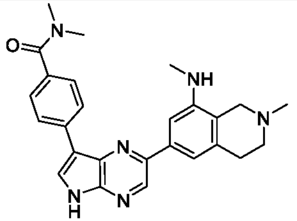	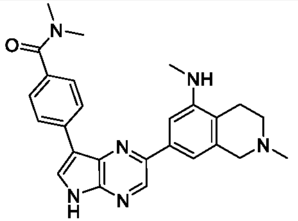	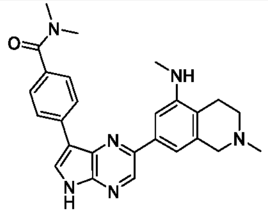
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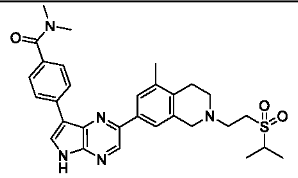	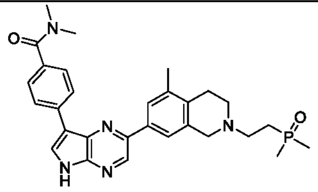	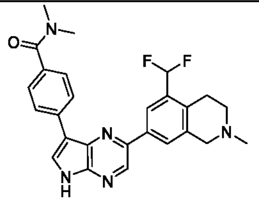
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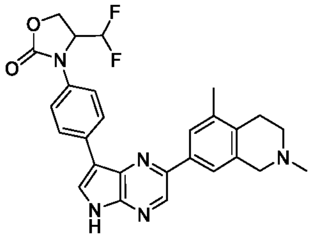	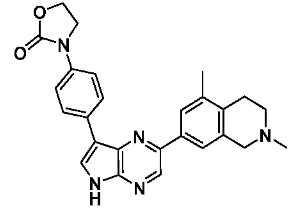	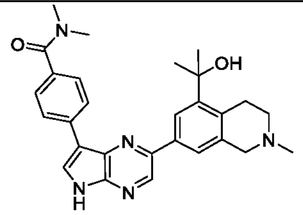
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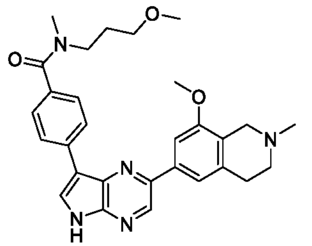	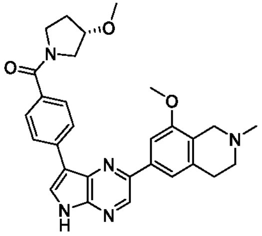	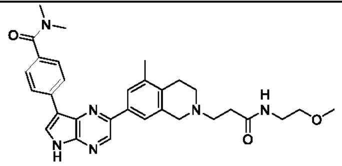
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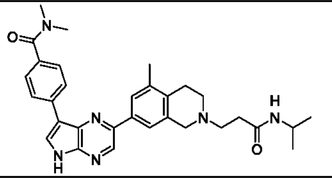	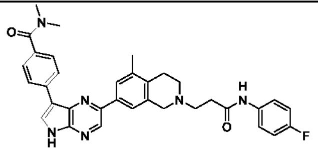	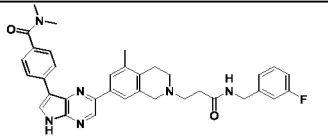
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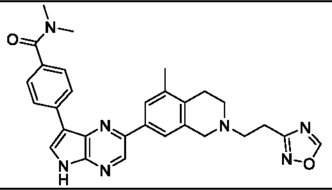	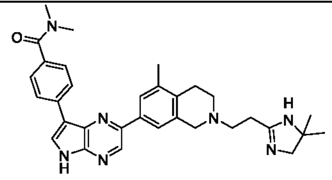	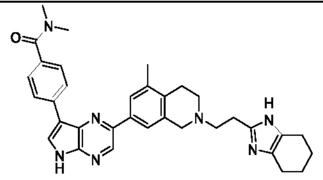
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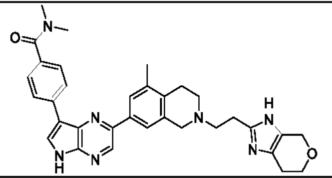	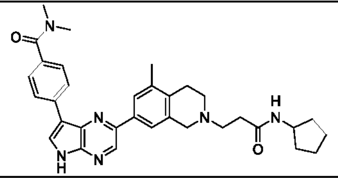	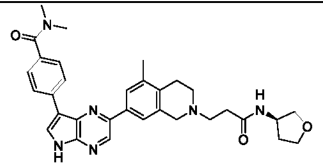
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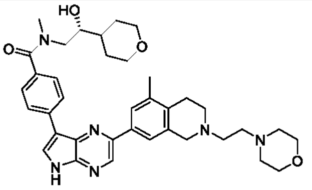	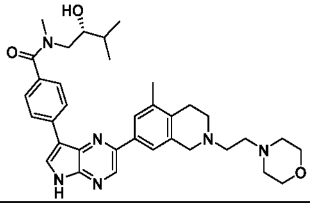	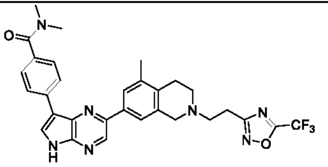
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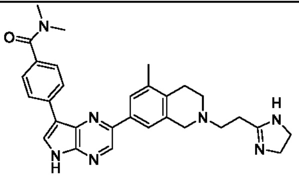	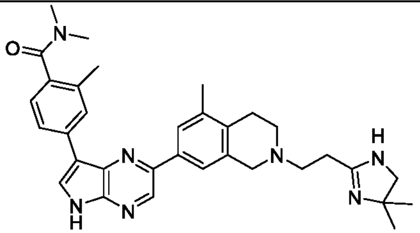	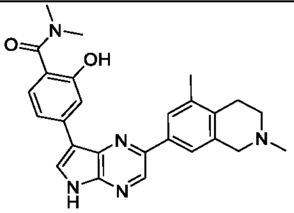
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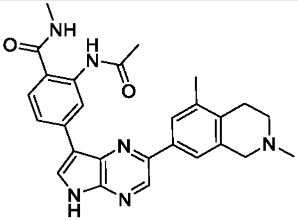	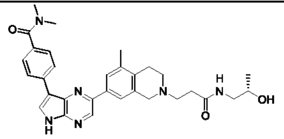	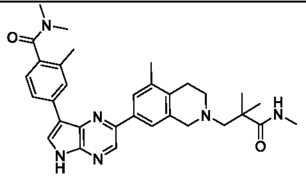
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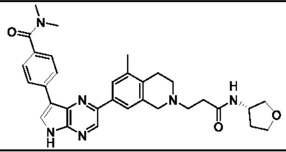	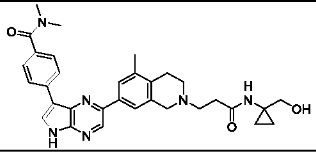	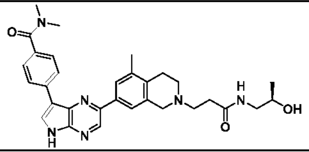
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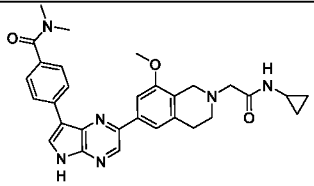	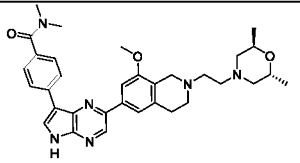	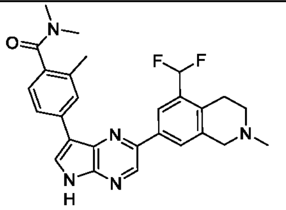
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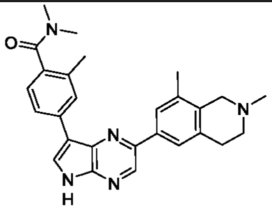	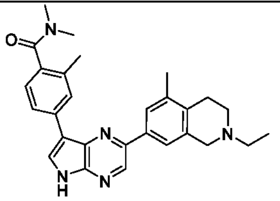	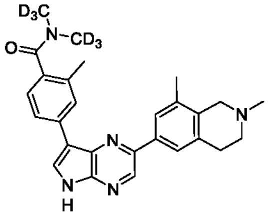
126	127	128

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In the second aspect, disclosed herein is a pharmaceutical composition comprising the compound disclosed herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

In the third aspect, disclosed herein is a method of inhibiting HPK1 activity, which comprise administering to an individual the compound disclosed herein, or a pharmaceutically acceptable salt thereof, including the compound of formula (I) or the specific compounds exemplified herein.

In the fourth aspect, disclosed herein is a method of treating a disease or disorder in a patient comprising administering to the patient a therapeutically effective amount of the compound disclosed herein, or a pharmaceutically acceptable salt thereof as an HPK1 kinase inhibitor, wherein the compound disclosed herein includes the compound of formula (I) or the specific compounds exemplified herein. In some embodiment, the disease or disorder is associated with inhibition of HPK1 interaction. Preferably, the disease or disorder is cancer.

DETAILED DESCRIPTION OF THE INVENTION

The following terms have the indicated meanings throughout the specification:

Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this invention belongs.

The following terms have the indicated meanings throughout the specification:

As used herein, including the appended claims, the singular forms of words such as "a", "an", and "the", include their corresponding plural references unless the context clearly indicates otherwise.

The term "or" is used to mean, and is used interchangeably with, the term “and/or” unless the context clearly dictates otherwise.

The term "alkyl" refers to a hydrocarbon group selected from linear and branched saturated hydrocarbon groups comprising from 1 to 18, such as from 1 to 12, further such as from 1 to 10, more further such as from 1 to 8, or from 1 to 6, or from 1 to 4, carbon atoms. Examples of alkyl groups comprising from 1 to 6 carbon atoms (i.e., C_{1-6} alkyl) include, but not limited to, methyl, ethyl, 1-propyl or n-propyl ("n-Pr"), 2-propyl or isopropyl ("i-Pr"), 1-butyl or n-butyl ("n-Bu"), 2-methyl-1-propyl or isobutyl ("i-Bu"), 1-methylpropyl or s-butyl ("s-Bu"), 1, 1-dimethylethyl or t-butyl ("t-Bu"), 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2, 3-dimethyl-2-butyl and 3, 3-dimethyl-2-butyl groups. An alkyl group defined herein is optionally deuterated or tritiated.

The term “propyl” refers to 1-propyl or n-propyl ("n-Pr"), 2-propyl or isopropyl ("i-Pr").

The term “butyl” refers to 1-butyl or n-butyl ("n-Bu"), 2-methyl-1-propyl or isobutyl ("i-Bu"), 1-methylpropyl or s-butyl ("s-Bu"), 1, 1-dimethylethyl or t-butyl ("t-Bu").

The term “pentyl” refers to 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl.

The term “hexyl” refers to 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2, 3-dimethyl-2-butyl and 3, 3-dimethyl-2-butyl.

The term "halogen” refers to fluoro (F), chloro (Cl), bromo (Br) and iodo (I).

The term "haloalkyl" refers to an alkyl group in which one or more hydrogen is/are replaced by one or more halogen atoms such as fluoro, chloro, bromo, and iodo. Examples of the haloalkyl include haloC_{1-8}alkyl, haloC_{1-6}alkyl or halo C_{1-4}alkyl, but not limited to -CF_3, -CH_2Cl, -CH_2CF_3, -$CHCl_2$, -CF_3, and the like.

The term "alkenyl" refers to a hydrocarbon group selected from linear and branched hydrocarbon groups comprising at least one C=C double bond and from 2 to 18, such as from 2 to 8, further such as from 2 to 6, carbon atoms. Examples of the alkenyl group, e.g., C_{2-6} alkenyl, include, but not limited to ethenyl or vinyl, prop-1-enyl, prop-2-enyl, 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1, 3-dienyl, 2-methylbuta-1, 3-dienyl, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, and hexa-1, 3-dienyl groups.

The term "alkynyl" refers to a hydrocarbon group selected from linear and branched hydrocarbon group, comprising at least one C≡C triple bond and from 2 to 18, such as 2 to 8, further such as from 2 to 6, carbon atoms. Examples of the alkynyl group, e.g., C_{2-6} alkynyl, include, but not limited to ethynyl, 1-propynyl, 2-propynyl (propargyl), 1-butynyl, 2-butynyl, and 3-butynyl groups.

The term "cycloalkyl" refers to a hydrocarbon group selected from saturated cyclic hydrocarbon groups, comprising monocyclic and polycyclic (e.g., bicyclic and tricyclic) groups including fused, bridged or spiro cycloalkyl.

For example, the cycloalkyl group may comprise from 3 to 12, such as from 3 to 10, further such as 3 to 8, further such as 3 to 6, 3 to 5, or 3 to 4 carbon atoms. Even further for example, the cycloalkyl group may be selected from monocyclic group comprising from 3 to 12, such as from 3 to 10, further such as 3 to 8, 3 to 6 carbon atoms. Examples of the monocyclic cycloalkyl group include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, and cyclododecyl groups. In particular, Examples of the saturated monocyclic cycloalkyl group, e.g., C_{3-8}cycloalkyl, include, but not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In a preferred embedment, the cycloalkyl is a monocyclic ring comprising 3 to 6 carbon atoms (abbreviated as C_{3-6} cycloalkyl), including but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Examples of the bicyclic cycloalkyl groups include those having from 7 to 12 ring atoms arranged as a fused bicyclic ring selected from [4, 4], [4, 5], [5, 5], [5, 6] and [6, 6] ring systems, or as a bridged bicyclic ring selected from bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, and bicyclo[3.2.2]nonane. Further Examples of the bicyclic cycloalkyl groups include those arranged as a bicyclic ring selected from [5, 6] and [6, 6] ring systems.

The term "spiro cycloalkyl" refers to a cyclic structure which contains carbon atoms and is formed by at least two rings sharing one atom. The term "7 to 12 membered spiro cycloalkyl" refers to a cyclic structure which contains 7 to 12 carbon atoms and is formed by at least two rings sharing one atom.

The term "fused cycloalkyl" refers to a bicyclic cycloalkyl group as defined herein which is saturated and is formed by two or more rings sharing two adjacent atoms.

The term "bridged cycloalkyl" refers to a cyclic structure which contains carbon atoms and is formed by two rings sharing two atoms which are not adjacent to each other. The term "7 to

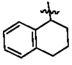
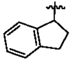
10 membered bridged cycloalkyl" refers to a cyclic structure which contains 7 to 12 carbon atoms and is formed by two rings sharing two atoms which are not adjacent to each other.

The term "cycloalkenyl" refers to non-aromatic cyclic alkyl groups of from 3 to 10 carbon atoms having single or multiple rings and having at least one double bond and preferably from 1 to 2 double bonds. In one embodiment, the cycloalkenyl is cyclopentenyl or cyclohexenyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, preferably cyclohexenyl.

The term "fused cycloalkenyl" refers to a bicyclic cycloalkyl group as defined herein which contain at least one double bond and is formed by two or more rings sharing two adjacent atoms.

The term "cycloalkynyl" refers to non-aromatic cycloalkyl groups of from 5 to 10 carbon atoms having single or multiple rings and having at least one triple bond.

The term "fused cycloalkynyl" refers to a bicyclic cycloalkyl group as defined herein which contains at least one triple bond and is formed by two or more rings sharing two adjacent atoms.

The term a "benzo fused cycloalkyl" is a bicyclic fused cycloalkyl in which a 4- to 8-membered monocyclic cycloalkyl ring fused to a benzene ring. For example, a benzo fused cycloalkyl is  and  wherein the wavy lines indicate the points of attachment.

The term a "benzo fused cycloalkenyl" is a bicyclic fused cycloalkenyl in which a 4- to 8-membered monocyclic cycloalkenyl ring fused to a benzene ring.

The term a "benzo fused cycloalkynyl " is a bicyclic fused cycloalkynyl in which a 4- to 8-membered monocyclic cycloalkynyl ring fused to a benzene ring.

Examples of fused cycloalkyl, fused cycloalkenyl, or fused cycloalkynyl include but are not limited to bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[3.1.0]hexyl, bicyclo[4.1.0]heptyl, bicyclo[3.3.0]octyl, bicyclo[4.2.0]octyl, decalin, as well as benzo 3 to 8 membered cycloalkyl, benzo C_{4-6} cycloalkenyl, 2, 3-dihydro-1H-indenyl, 1H-indenyl, 1, 2, 3, 4-tetralyl, 1, 4-dihydronaphthyl, etc. Preferred embodiments are 8 to 9 membered fused ring, which refer to cyclic structures containing 8 to 9 ring atoms within the above examples.

The term "aryl" used alone or in combination with other terms refers to a group selected from:

a) 5- and 6-membered carbocyclic aromatic rings, e.g., phenyl;
b) bicyclic ring systems such as 7 to 12 membered bicyclic ring systems, wherein at least one ring is carbocyclic and aromatic, e.g., naphthyl and indanyl; and,
c) tricyclic ring systems such as 10 to 15 membered tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, e.g., fluorenyl.

The terms "aromatic hydrocarbon ring" and "aryl" are used interchangeable throughout the disclosure herein. In some embodiments, a monocyclic or bicyclic aromatic hydrocarbon ring has 5 to 10 ring-forming carbon atoms (i.e., C_{5-10} aryl). Examples of a monocyclic or bicyclic aromatic hydrocarbon ring includes, but not limited to, phenyl, naphth-1-yl, naphth-2-yl, anthracenyl, phenanthrenyl, and the like. In some embodiments, the aromatic hydrocarbon ring is a naphthalene ring (naphth-1-yl or naphth-2-yl) or phenyl ring. In some embodiments, the aromatic hydrocarbon ring is a phenyl ring.

Specifically, the term "bicyclic fused aryl" refers to a bicyclic aryl ring as defined herein. The typical bicyclic fused aryl is naphthalene.

The term "heteroaryl" refers to a group selected from:

a) 5-, 6- or 7-membered aromatic, monocyclic rings comprising at least one heteroatom, for example, from 1 to 4, or, in some embodiments, from 1 to 3, in some embodiments, from 1 to 2, heteroatoms, selected from nitrogen (N), sulfur (S) and oxygen (O), with the remaining ring atoms being carbon;
b) 7- to 12-membered bicyclic rings comprising at least one heteroatom, for example, from 1 to 4, or, in some embodiments, from 1 to 3, or, in other embodiments, 1 or 2, heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in the aromatic ring; and
c) 11- to 14-membered tricyclic rings comprising at least one heteroatom, for example, from 1 to 4, or in some embodiments, from 1 to 3, or, in other embodiments, 1 or 2, heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in an aromatic ring.

When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In some embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In some embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1. When the heteroaryl group contains more than one heteroatom ring member, the heteroatoms may be the same or different. The nitrogen atoms in the ring (s) of the heteroaryl group can be oxidized to form N-oxides.

Specifically, the term "bicyclic fused heteroaryl" refers to a 7- to 12-membered, preferably 7- to 10-membered, more preferably 9- or 10-membered fused bicyclic heteroaryl ring as defined herein. Typically, a bicyclic fused heteroaryl is 5-membered/5-membered, 5-membered/6-membered, 6-membered/6-membered, or 6-membered/7-membered bicyclic. The group can be attached to the remainder of the molecule through either ring.

Representative examples of bicyclic fused heteroaryl include, but not limited to, the following groups benzisoxazolyl, benzodiazolyl, benzofuranyl, benzofurazanyl, benzofuryl, benzoimidazolyl, benzoisothiazolyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzothiophenyl, benzotriazolyl, benzoxadiazolyl, benzoxazolyl, furopyridinyl, furopyrrolyl, imidazopyridinyl, imidazopyridyl, imidazothiazolyl, indazolyl, indolizinyl, indolyl, isobenzofuryl, isoindolyl, isoquinolinyl (or isoquinolyl), naphthyridinyl, phthalazinyl, pteridinyl, purinyl, pyrazinopyridazinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrazolopyridyl, pyrazolotriazinyl, pyridazolopyridyl, pyrrolopyridinyl, quinazolinyl, quinolinyl (or quinolyl), quinoxalinyl, thiazolopyridyl, thienopyrazinyl, thienopyrazolyl, thienopyridyl, thienopyrrolyl, thienothienyl, or triazolopyridyl.

The term a "benzo fused heteroaryl" is a bicyclic fused heteroaryl in which a 5- to 7-membered (preferably, 5- or 6-membered) monocyclic heteroaryl ring as defined herein fused to a benzene ring.

The terms "aromatic heterocyclic ring" and "heteroaryl" are used interchangeable throughout the disclosure herein. In some embodiments, a monocyclic or bicyclic aromatic heterocyclic ring has 5-, 6-, 7-, 8-, 9- or 10-ring forming members with 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen (N), sulfur (S) and oxygen (O) and the remaining ring members being carbon. In some embodiments, the monocyclic or bicyclic aromatic heterocyclic ring is a monocyclic or bicyclic ring comprising 1 or 2 heteroatom ring members independently selected from nitrogen (N), sulfur (S) and oxygen (O). In some embodiments, the monocyclic or bicyclic aromatic heterocyclic ring is a 5- to 6-membered heteroaryl ring, which is monocyclic and which has 1 or 2 heteroatom ring members independently selected from nitrogen (N), sulfur (S) and oxygen (O). In some embodiments, the monocyclic or bicyclic aromatic heterocyclic ring is an 8- to 10-membered heteroaryl ring, which is bicyclic and which has 1 or 2 heteroatom ring members independently selected from nitrogen, sulfur and oxygen.

Examples of the heteroaryl group or the monocyclic or bicyclic aromatic heterocyclic ring include, but are not limited to, (as numbered from the linkage position assigned priority 1) pyridyl (such as 2-pyridyl, 3-pyridyl, or 4-pyridyl), cinnolinyl, pyrazinyl, 2, 4-pyrimidinyl, 3, 5-pyrimidinyl, 2, 4-imidazolyl, imidazopyridinyl, isoxazolyl, oxazolyl, thiazolyl, isothiazolyl, thiadiazolyl (such as 1, 2, 3-thiadiazolyl, 1, 2, 4-thiadiazolyl, or 1, 3, 4-thiadiazolyl), tetrazolyl, thienyl (such as thien-2-yl, thien-3-yl), triazinyl, benzothienyl, furyl or furanyl, benzofuryl, benzoimidazolyl, indolyl, isoindolyl, oxadiazolyl (such as 1, 2, 3-oxadiazolyl, 1, 2, 4-oxadiazolyl, or 1, 3, 4-oxadiazolyl), phthalazinyl, pyrazinyl, pyridazinyl, pyrrolyl, triazolyl (such as 1, 2, 3-triazolyl, 1, 2, 4-triazolyl, or 1, 3, 4-triazolyl), quinolinyl, isoquinolinyl, pyrazolyl, pyrrolopyridinyl (such as 1H-pyrrolo[2, 3-b]pyridin-5-yl), pyrazolopyridinyl (such as 1H-pyrazolo[3, 4-b]pyridin-5-yl), benzoxazolyl (such as benzo[d]oxazol-6-yl), pteridinyl, purinyl, 1-oxa-2, 3-diazolyl, 1-oxa-2, 4-diazolyl, 1-oxa-2, 5-diazolyl, 1-oxa-3, 4-diazolyl, 1-thia-2, 3-diazolyl, 1-thia-2, 4-diazolyl, 1-thia-2, 5-diazolyl, 1-thia-3, 4-diazolyl, furazanyl (such as furazan-2-yl, furazan-3-yl), benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl, benzothiazolyl (such as benzo[d]thiazol-6-yl), and indazolyl (such as 1H-indazol-5-yl).

"Heterocyclyl", "heterocycle" or "heterocyclic" are interchangeable and refer to a non-aromatic heterocyclyl group comprising one or more heteroatoms selected from nitrogen, oxygen or optionally oxidized sulfur as ring members, with the remaining ring members being carbon, including monocyclic, fused, bridged, and spiro ring, i.e., containing monocyclic heterocyclyl, bridged heterocyclyl, spiro heterocyclyl, and fused heterocyclic groups.

The term “optionally oxidized sulfur” used herein refer to S, SO or SO_2.

The term "monocyclic heterocyclyl" refers to monocyclic groups in which at least one ring member (e.g., 1-3 heteroatoms, 1 or 2 heteroatoms) is a heteroatom selected from nitrogen, oxygen or optionally oxidized sulfur. A heterocycle may be saturated or partially saturated.

Exemplary monocyclic 4 to 9-membered heterocyclyl groups include, but not limited to, (as numbered from the linkage position assigned priority 1) pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, imidazolidin-2-yl, imidazolidin-4-yl, pyrazolidin-2-yl, pyrazolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, 2, 5-piperazinyl, pyranyl, morpholinyl, morpholino, morpholin-2-yl, morpholin-3-yl, oxiranyl, aziridin-1-yl, aziridin-2-yl, azocan-1-yl, azocan-2-yl, azocan-3-yl, azocan-4-yl, azocan-5-yl, thiiranyl, azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, oxetanyl, thietanyl, 1, 2-dithietanyl, 1, 3-dithietanyl, dihydropyridinyl, tetrahydropyridinyl, thiomorpholinyl, thioxanyl, piperazinyl, homopiperazinyl, homopiperidinyl, azepan-1-yl, azepan-2-yl, azepan-3-yl, azepan-4-yl, oxepanyl, thiepanyl, 1, 4-oxathianyl, 1, 4-dioxepanyl, 1, 4-oxathiepanyl, 1, 4-oxaazepanyl, 1, 4-dithiepanyl, 1, 4-thiazepanyl and 1, 4-diazepanyl, 1, 4-dithianyl, 1, 4-azathianyl, oxazepinyl, diazepinyl, thiazepinyl, dihydrothienyl, dihydropyranyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, 1, 4-dioxanyl, 1, 3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrazolidinyl, imidazolinyl, pyrimidinonyl, or 1, 1-dioxo-thiomorpholinyl.

The term "spiro heterocyclyl" refers to a 5 to 20-membered polycyclic heterocyclyl with rings connected through one common carbon atom (called a spiro atom), comprising one or more heteroatoms selected from nitrogen, oxygen or optionally oxidized sulfur as ring members, with the remaining ring members being carbon. One or more rings of a spiro heterocyclyl group may contain one or more double bonds, but none of the rings has a completely conjugated pi-electron system. Preferably a spiro heterocyclyl is 6 to 14-membered, and more preferably 7 to 12-membered. According to the number of common spiro atoms, a spiro heterocyclyl is divided into mono-spiro heterocyclyl, di-spiro heterocyclyl, or poly-spiro heterocyclyl, and preferably refers to mono-spiro heterocyclyl or di-spiro heterocyclyl, and more preferably 4-membered/3-membered, 4-membered/4-membered, 3-membered/5-membered, 4-membered/5-membered, 4-membered/6-membered, 5-membered/5-membered, or 5-membered/6-membered mono-spiro heterocyclyl. Representative examples of spiro heterocyclyls include, but not limited to the following groups: 2, 3-dihydrospiro[indene-1, 2'-pyrrolidine] (e.g., 2, 3-dihydrospiro[indene-1, 2'-pyrrolidine]-1'-yl), 1, 3-dihydrospiro[indene-2, 2'-pyrrolidine] (e.g., 1, 3-dihydrospiro[indene-2, 2'-pyrrolidine]-1'-yl), azaspiro[2.4]heptane (e.g., 5-azaspiro[2.4]heptane-5-yl), 2-oxa-6-azaspiro[3.3]heptane (e.g., 2-oxa-6-azaspiro[3.3]heptan-6-yl), azaspiro[3.4]octane (e.g., 6-azaspiro[3.4]octane-6-yl), 2-oxa-6-azaspiro[3.4]octane (e.g., 2-oxa-6-azaspiro[3.4]octane-6-yl), azaspiro[3.4]octane (e.g., 6-azaspiro[3.4]octan-6-yl), azaspiro[3.4]octane (e.g., 6-azaspiro[3.4]octan-6-yl), 1, 7-dioxaspiro[4.5]decane, 2-oxa-7-aza-spiro[4.4]nonane (e.g., 2-oxa-7-aza-spiro[4.4]non-7-yl), 7-oxa-spiro[3.5]nonyl and 5-oxa-spiro[2.4]heptyl.

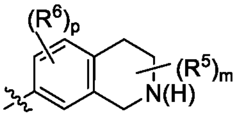
The term "fused heterocyclyl" refers to a 5 to 20-membered polycyclic heterocyclyl group, wherein each ring in the system shares an adjacent pair of atoms (carbon and carbon atoms or carbon and nitrogen atoms) with another ring, comprising one or more heteroatoms selected from nitrogen, oxygen or optionally oxidized sulfur as ring members, with the remaining ring members being carbon. One or more rings of a fused heterocyclic group may contain one or more double bonds, but the fused heterocyclic group does not have a completely conjugated pi-electron system. Preferably, a fused heterocyclyl is 6 to 14-membered, and more preferably 7 to 12-membered, or 7- to 10-membered. According to the number of membered rings, a fused heterocyclyl is divided into bicyclic, tricyclic, tetracyclic, or polycyclic fused heterocyclyl. The group can be attached to the remainder of the molecule through either ring.

Specifically, the term "bicyclic fused heterocyclyl" refers to a 7 to 12-membered, preferably 7- to 10-membered, more preferably 9- or 10-membered fused heterocyclyl as defined herein comprising two fused rings and comprising 1 to 4 heteroatoms selected from nitrogen, oxygen or optionally oxidized sulfur as ring members. Typically, a bicyclic fused heterocyclyl is 5-membered/5-membered, 5-membered/6-membered, 6-membered/6-membered, or 6-membered/7-membered bicyclic fused heterocyclyl. Representative examples of (bicyclic) fused heterocycles include, but not limited to, the following groups octahydrocyclopenta[c]pyrrole, octahydropyrrolo[3, 4-c]pyrrolyl, octahydroisoindolyl, isoindolinyl, octahydro-benzo[b][1, 4]dioxin, indolinyl, isoindolinyl, benzopyranyl, dihydrothiazolopyrimidinyl, tetrahydroquinolyl, tetrahydroisoquinolyl (or tetrahydroisoquinolinyl), dihydrobenzofuranyl, dihydrobenzoxazinyl, dihydrobenzoimidazolyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, benzodioxolyl, benzodioxonyl, chromanyl, chromenyl, octahydrochromenyl, dihydrobenzodioxynyl, dihydrobenzoxezinyl, dihydrobenzodioxepinyl, dihydrothienodioxynyl, dihydrobenzooxazepinyl, tetrahydrobenzooxazepinyl, dihydrobenzoazepinyl, tetrahydrobenzoazepinyl, isochromanyl, chromanyl, or tetrahydropyrazolopyrimidinyl (e.g., 4, 5, 6, 7-tetrahydropyrazolo[1, 5-a]pyrimidin-3-yl).

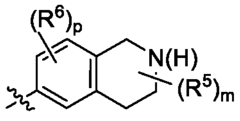
The term a "benzo fused heterocyclyl" is a bicyclic fused heterocyclyl in which a monocyclic 4 to 9-membered heterocyclyl as defined herein (preferably 5- or 6-membered) fused to a benzene ring.

The term "bridged heterocyclyl" refers to a 5 to 14-membered polycyclic heterocyclic alkyl group, wherein every two rings in the system share two disconnected atoms, comprising one or more heteroatoms selected from nitrogen, oxygen or optionally oxidized sulfur as ring members, with the remaining ring members being carbon. One or more rings of a bridged heterocyclyl group may contain one or more double bonds, but none of the rings has a completely conjugated pi-electron system. Preferably, a bridged heterocyclyl is 6 to 14-membered, and more preferably 7 to 10-membered. According to the number of membered rings, a bridged heterocyclyl is divided into bicyclic, tricyclic, tetracyclic or polycyclic bridged heterocyclyl, and preferably refers to bicyclic, tricyclic or tetracyclic bridged heterocyclyl, and more preferably bicyclic or tricyclic bridged heterocyclyl. Representative examples of bridged heterocyclyls include, but not limited to, the following groups: 2-azabicyclo[2.2.1]heptyl, azabicyclo[3.1.0]hexyl, 2-azabicyclo[2.2.2]octyl and 2-azabicyclo[3.3.2]decyl.

If amine is substituted by R^5, it means that the nitrogen atom in structures of



or



is not bonded to a hydrogen.

The term "at least one substituents" disclosed herein includes, for example, from 1 to 4, such as from 1 to 3, further as 1 or 2, substituents, provided the theory of valence is met. For example, "at least one substituents R^{6d}" disclosed herein includes from 1 to 4, such as from 1 to 3, further as 1 or 2, substituents selected from the list of R^{6d} as disclosed herein.

Compounds disclosed herein may contain an asymmetric center and may thus exist as enantiomers. “Enantiomers” refer to two stereoisomers of a compound which are non-superimposable mirror images of one another. Where the compounds disclosed herein possess two or more asymmetric centers, they may additionally exist as diastereomers. Enantiomers and diastereomers fall within the broader class of stereoisomers. All such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereomers are intended to be included. All stereoisomers of the compounds disclosed herein and /or pharmaceutically acceptable salts thereof are intended to be included. Unless specifically mentioned otherwise, reference to one isomer applies to any of the possible isomers. Whenever the isomeric composition is unspecified, all possible isomers are included.

The term "substantially pure" as used herein means that the target stereoisomer contains no more than 35%, such as no more than 30%, further such as no more than 25%, even further such as no more than 20%, by weight of any other stereoisomer (s). In some embodiments, the term "substantially pure" means that the target stereoisomer contains no more than 10%, for example, no more than 5%, such as no more than 1%, by weight of any other stereoisomer (s).

When compounds disclosed herein contain olefinic double bonds, unless specified otherwise, such double bonds are meant to include both E and Z geometric isomers.

When compounds disclosed herein contain a di-substituted cyclic ring system, substituents found on such ring system may adopt *cis* and *trans* formations. *Cis* formation means that both substituents are found on the upper side of the 2 substituent placements on the carbon, while *trans* would mean that they were on opposing sides. For example, the di-substituted cyclic ring system may be cyclohexyl or cyclobutyl ring.

It may be advantageous to separate reaction products from one another and /or from starting materials. The desired products of each step or series of steps is separated and /or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed ("SMB") and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography. One skilled in the art will apply techniques most likely to achieve the desired separation.

“Diastereomers” refers to stereoisomers of a compound with two or more chiral centers but which are not mirror images of one another. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and /or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher’s acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of a chiral HPLC column.

A single stereoisomer, e.g., a substantially pure enantiomer, may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (*Eliel, E. and Wilen, S. Stereochemistry of Organic Compounds. New York: John Wiley & Sons, Inc., 1994; Lochmuller, C. H., et al. "Chromatographic resolution of enantiomers: Selective review." J. Chromatogr., 113 (3) (1975): pp. 283-302*). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions. See: *Wainer, Irving W., Ed. Drug Stereochemistry: Analytical Methods and Pharmacology. New York: Marcel Dekker, Inc., 1993.*

"Pharmaceutically acceptable salts" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A pharmaceutically acceptable salt may be prepared in situ during the final isolation and purification of the compounds disclosed herein, or separately by reacting the free base function with a suitable organic acid or by reacting the acidic group with a suitable base.

In addition, if a compound disclosed herein is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, such as a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used without undue experimentation to prepare non-toxic pharmaceutically acceptable addition salts.

As defined herein, "a pharmaceutically acceptable salt thereof" include salts of at least one compound of Formula (I), and salts of the stereoisomers of the compound of Formula (I), such as salts of enantiomers, and /or salts of diastereomers.

The terms “administration”, “administering”, “treating” and “treatment” herein, when applied to an animal, human, experimental subject, cell, tissue, organ, or biological fluid, mean contact of an exogenous pharmaceutical, therapeutic, diagnostic agent, or composition to the animal, human, subject, cell, tissue, organ, or biological fluid. Treatment of a cell encompasses contact of a reagent to the cell, as well as contact of a reagent to a fluid, where the fluid is in contact with the cell. The term “administration” and “treatment” also means in vitro and ex vivo treatments, e.g., of a cell, by a reagent, diagnostic, binding compound, or by another cell. The term “subject” herein includes any organism, preferably an animal, more preferably a mammal (e.g., rat, mouse, dog, cat, and rabbit) and most preferably a human.

The term "effective amount" or “therapeutically effective amount” refers to an amount of the active ingredient, such as compound that, when administered to a subject for treating a disease, or at least one of the clinical symptoms of a disease or disorder, is sufficient to affect such treatment for the disease, disorder, or symptom. The “therapeutically effective amount” can vary with the compound, the disease, disorder, and/or symptoms of the disease or disorder, severity of the disease, disorder, and/or symptoms of the disease or disorder, the age of the subject to be treated, and/or the weight of the subject to be treated. An appropriate amount in any given instance can be apparent to those skilled in the art or can be determined by routine experiments. In some embodiments, “therapeutically effective amount” is an amount of at least one compound and /or at least one stereoisomer thereof, and /or at least one pharmaceutically acceptable salt thereof disclosed herein effective to “treat” as defined herein, a disease or disorder in a subject. In the case of combination therapy, the “therapeutically effective amount” refers to the total amount of the combination objects for the effective treatment of a disease, a disorder or a condition.

The pharmaceutical composition comprising the compound disclosed herein can be administrated via oral, inhalation, rectal, parenteral or topical administration to a subject in need thereof. For oral administration, the pharmaceutical composition may be a regular solid formulation such as tablets, powder, granule, capsules and the like, a liquid formulation such as water or oil suspension or other liquid formulation such as syrup, solution, suspension or the like; for parenteral administration, the pharmaceutical composition may be solution, water solution, oil suspension concentrate, lyophilized powder or the like. Preferably, the formulation of the pharmaceutical composition is selected from tablet, coated tablet, capsule, suppository, nasal spray or injection, more preferably tablet or capsule. The pharmaceutical composition can be a single unit administration with an accurate dosage. In addition, the pharmaceutical composition may further comprise additional active ingredients.

All formulations of the pharmaceutical composition disclosed herein can be produced by the conventional methods in the pharmaceutical field. For example, the active ingredient can be mixed with one or more excipients, then to make the desired formulation. The “pharmaceutically acceptable excipient” refers to conventional pharmaceutical carriers suitable for the desired pharmaceutical formulation, for example: a diluent, a vehicle such as water, various organic solvents, etc., a filler such as starch, sucrose, etc. a binder such as cellulose derivatives, alginates, gelatin and polyvinylpyrrolidone (PVP); a wetting agent such as glycerol; a disintegrating agent such as agar, calcium carbonate and sodium bicarbonate; an absorption enhancer such as quaternary ammonium compound; a surfactant such as hexadecanol; an absorption carrier such as Kaolin and soap clay; a lubricant such as talc, calcium stearate, magnesium stearate, polyethylene glycol, etc. In addition, the pharmaceutical composition further comprises other pharmaceutically acceptable excipients such as a decentralized agent, a stabilizer, a thickener, a complexing agent, a buffering agent, a permeation enhancer, a polymer, aromatics, a sweetener, and a dye.

The term “disease” refers to any disease, discomfort, illness, symptoms or indications, and can be interchangeable with the term “disorder” or “condition”.

Throughout this specification and the claims which follow, unless the context requires otherwise, the term "comprise", and variations such as "comprises" and "comprising" are intended to specify the presence of the features thereafter, but do not exclude the presence or addition of one or more other features. When used herein the term "comprising" can be substituted with the term "containing", "including" or sometimes "having".

Throughout this specification and the claims which follow, the term “C_{n-m}” indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C_{1-8}, C_{1-6}, and the like.

Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this invention belongs.

General Synthesis

Compounds disclosed herein, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes.

The reaction for preparing compounds disclosed herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials, the intermediates, or products at the temperatures at which the reactions are carried out, e.g., temperatures which can range from room temperature to the solvent’s boiling temperature. A given reaction can be carried out in one solvent or mixture of solvents.

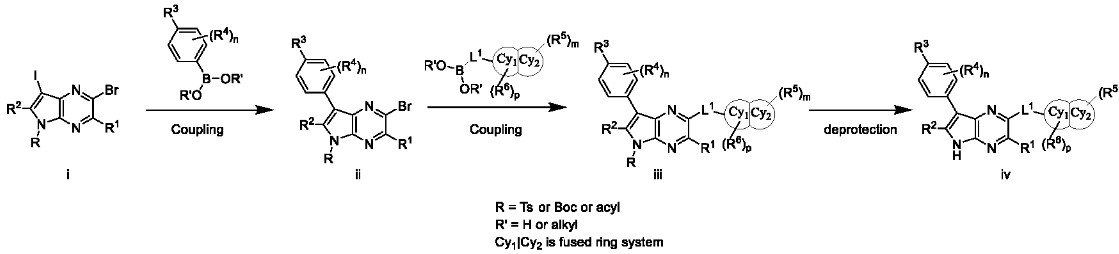
The selection of appropriate protecting group, can be readily determined by one skilled in the art.

Reactions can be monitored according to any suitable method known in the art, such as NMR, UV, HPLC, LC-MS and TLC. Compounds can be purified by a variety of methods, including HPLC and normal phase silica chromatography.

Chiral analytic HPLC was used for the retention time analysis of different chiral examples, the conditions were divided into the methods as below according to the column, mobile phase, solvent ration used.

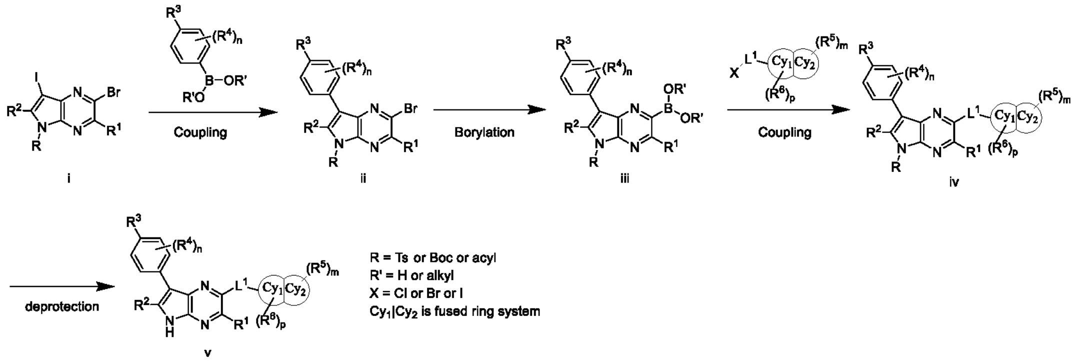
The compounds disclosed herein can be prepared by following Scheme I and Scheme II.

Scheme I



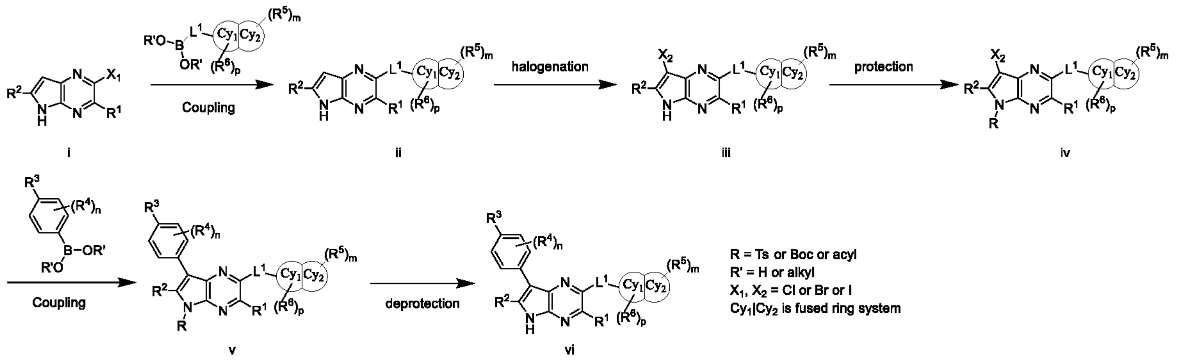
For example, compounds of **Formula (I)** can be formed as shown in **Scheme I**. Compound (i) can be reacted with boronic acid or boronic ester using transition metal catalyzed reaction to give compound (ii); compound (ii) can be reacted with boronic acid or boronic ester using transition metal catalyzed reaction to give compound (iii); compound (iii) can be deprotected *in situ* or stepwise to give compound (iv) [i.e., **Formula (I)**].

Scheme II



For example, compounds of **Formula (I)** can be formed as shown in **Scheme II**. Compound (i) can be reacted with boronic acid or boronic ester using transition metal catalyzed reaction to give compound (ii); compound (ii) can be borylated to give compound (iii); compound (iii) can be reacted with boronic acid or boronic ester using transition metal catalyzed reaction to give compound (iv); compound (iv) can be deprotected *in situ* or stepwise to give compound (v) [i.e., **Formula (I)**].

Scheme III



For example, compounds of **Formula (I)** can be formed as shown in **Scheme III**. Compound (i) can be reacted with boronic acid or boronic ester using transition metal catalyzed reaction to give compound (ii); compound (ii) can be selectively halogenated to give compound (iii); compound (iii) can be protected to give compound (iv); compound (iv) can be reacted with boronic acid or boronic ester to give compound (v); compound (v) can be deprotected *in situ* or stepwise to give compound (vi) [i.e., **Formula (I)**].

Examples

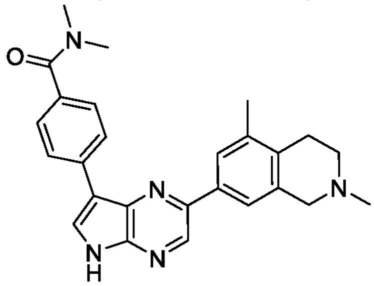
The examples below are intended to be purely exemplary and should not be considered to be limiting in any way. Unless otherwise specified, the experimental methods in the Examples described below are conventional methods. Unless otherwise specified, the reagents and materials are all commercially available. All solvents and chemicals employed are of analytical grade or chemical purity. Solvents are all redistilled before use. Anhydrous solvents are all prepared according to standard methods or reference methods.

Abbreviations

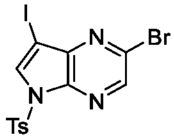
Ts	*p*-toluenesulfonyl (tosyl)
THF	tetrahydrofuran
DCM	dichloromethane
Et	ethyl
Ac	acetyl
LCMS	liquid chromatograph mass spectrometer
Me	methyl
dppf	1, 1'-bis (diphenylphosphino)ferrocene
BPD	bis (pinacolato)diboron
pin	pinnacolyl
Boc	*tert*-butyloxycarbonyl
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
HPLC	high performance liquid chromatography
PE	petroleum ether
TLC	thin layer chromatography
DMF	*N, N*-dimethylformamide
HATU	2- (7-azabenzotriazol-1-yl)-*N, N, N', N'*-tetramethyluronium hexafluorophosphate
DIPEA	*N, N*-diisopropylethylamine
DMSO	dimethyl sulfoxide
TBS	*tert*-butyldimethylsilyl
MTBE	methyl *tert*-butyl ether
T3P	propylphosphonic anhydride
IPA	isopropyl alcohol
UV	ultraviolet

NIS	N-iodosuccinimide
DMAP	4-dimethylaminopyridine

Example 1: 4-[2- (2, 5-dimethyl-3, 4-dihydro-1H-isoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl]-N, N-dimethylbenzamide

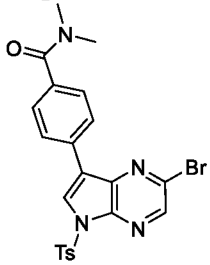


Step 1: 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine



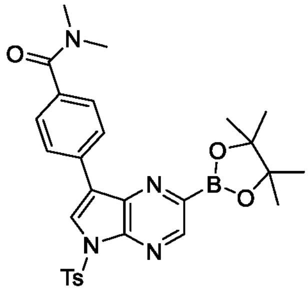
To a solution of 2-bromo-7-iodo-5H-pyrrolo[2, 3-b]pyrazine (162 g, 500 mmol) in anhydrous DMF (1500 mL) was added sodium hydride (30.0 g, 750 mmol) at 0 °C in portions. The resulting mixture was stirred for 15 min at 0 °C, and then TsCl (124 g, 650 mmol) was added in portions. The mixture was warmed to room temperature while being stirred. After 3 h, the reaction mixture was poured into ice water (2 L) and the precipitate was collected by filtration. The solid was rinsed with water (200 mL x 5) then dried under vacuum to give the title compound (239 g, 99%). LCMS $(M+H)^+ = 479.9$.

Step 2: 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide



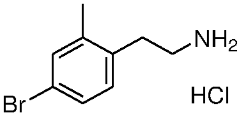
To a solution of 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine (240 mg, 0.50 mmol) and [4- (dimethylcarbamoyl)phenyl]boronic acid (106 mg, 0.52 mmol) in 1, 4-dioxane (6 mL) and water (1 mL) was added K_2CO_3 (207 mg, 1.42 mmol) and Pd $(dppf)Cl_2 \cdot CH_2Cl_2$ (41 mg, 0.048 mmol). After stirring for 3 h at 70 °C under a nitrogen atmosphere, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with $CHCl_3$/MeOH (9:1) to give the title compound (200 mg, 75%). LCMS $(M+H)^+ = 499.2$.

Step 3: N, N-dimethyl-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



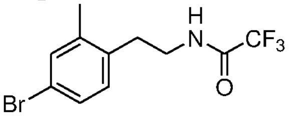
To a stirred solution of 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide (950 mg, 1.90 mmol) and BPD (531 mg, 2.09 mmol) in dioxane (15 mL) was added KOAc (373 mg, 3.80 mmol) and Pd (dppf)$Cl_2{\cdot}CH_2Cl_2$ (155 mg, 0.190 mmol). The reaction mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The mixture was cooled down to room temperature then diluted with water (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with water (30 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give the title compound (1.0 g, 93%). LCMS $(M\text{-}pin)^+ = 465.1$.

Step 4: 2- (4-bromo-2-methylphenyl)ethanamine hydrochloride



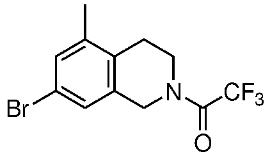
At 0 °C, to a solution of 2- (4-bromo-2-methylphenyl)acetonitrile (30.0 g, 0.143 mol) in MeOH (200 mL) was added $NiCl_2{\cdot}6H_2O$ (3.39 g, 0.0143 mol), Boc_2O (62.3 g, 0.286 mol). Then $NaBH_4$ (64.8 g, 1.71 mol) was added in portions within 15 min. The resulting mixture was stirred for 5 h at room temperature. The reaction mixture was quenched with ice water. The resulting solution was extracted with ethyl acetate (1000 mL x 3). The organic phases were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. To the residue was added HCl in MeOH (7 N, 50 mL, 0.350 mol) at room temperature, and the solution was stirred for 16 h at room temperature. The solvent was concentrated under reduced pressure to give the title compound (35.0 g, crude). LCMS $(M+H)^+ = 214.0$.

Step 5: N-[2- (4-bromo-2-methylphenyl)ethyl]-2, 2, 2-trifluoroacetamide



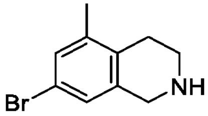
At 0 °C, to a solution of 2- (4-bromo-2-methylphenyl)ethanamine hydrochloride (350 mg, crude) in DCM (15 mL) was added TEA (345 mg, 3.42 mmol) and TFAA (356 mg, 1.70 mmol) with stirring under nitrogen atmosphere. After 15 h, the reaction was then quenched by the addition of water (20 mL). The resulting solution was extracted with DCM (35 mL x 3). The organic phases were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound (271 mg, 61% for 2 steps). LCMS $(M+H)^+ = 310.0$.

Step 6: 1- (7-bromo-5-methyl-3, 4-dihydro-1H-isoquinolin-2-yl)-2, 2, 2-trifluoroethanone



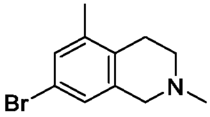
To a solution of N-[2- (4-bromo-2-methylphenyl)ethyl]-2, 2, 2-trifluoroacetamide (271 mg, 0.874 mmol) in AcOH (3 mL) was added H_2SO_4 (2 mL) and paraformaldehyde (176 mg, 1.95 mmol) with stirring at room temperature. After 16 h, the reaction was then diluted by the addition of water (30 mL). The resulting solution was extracted with ethyl acetate (50 mL x 3). The organic phases were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by C18 column chromatography, eluted with MeCN in water (40 % to 70 %) to give the title compound (100 mg, 36%). LCMS $(M+H)^+$ = 322.2.

Step 7: 7-bromo-5-methyl-1, 2, 3, 4-tetrahydroisoquinoline



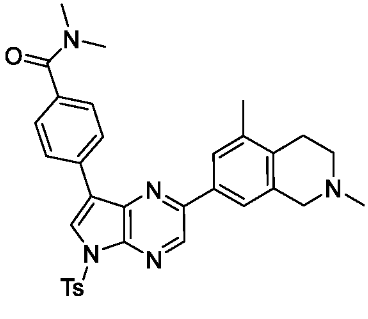
To a solution of 1- (7-bromo-5-methyl-3, 4-dihydro-1H-isoquinolin-2-yl)-2, 2, 2-trifluoroethanone (100 mg, 0.270 mmol) in EtOH (5 mL) and water (1 mL) was added K_2CO_3 (147 mg, 1.06 mmol) with stirring at room temperature. The resulting mixture was warmed to 80 °C. After 2 h, the reaction was cooled down and diluted with water (10 mL). The resulting mixture was extracted with DCM (30 mL x 3). The organic phases were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound (49 mg, 81 %). LCMS $(M+H)^+$ = 226.1.

Step 8: 7-bromo-2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinoline



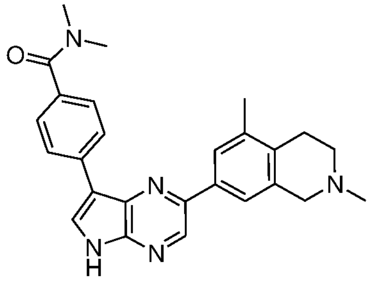
To a stirred solution of 7-bromo-5-methyl-1, 2, 3, 4-tetrahydroisoquinoline (100 mg, 0.398 mmol) and formalin (40%, 45 mg, 0.597 mmol) in MeOH (5 mL) was added $NaBH_3CN$ (39 mg, 0.60 mmol) in portions at room temperature under nitrogen atmosphere. After 3 h, the resulting mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10:1) to give the title compound (102 mg, 99%). LCMS $(M+H)^+$ = 240.0.

Step 9: 4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide



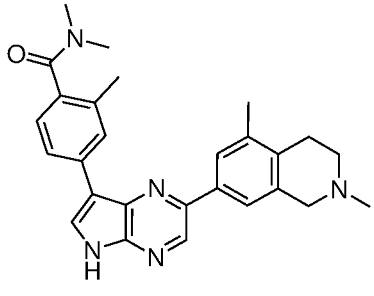
To a stirred solution of N, N-dimethyl-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide (77 mg, 0.166 mmol) and 7-bromo-2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinoline (20 mg, 0.083 mmol) in 1, 4-dioxane (3 mL) and water (0.60 mL) was added K_2CO_3 (35 mg, 0.250 mmol) and Pd (dppf)$Cl_2{\cdot}CH_2Cl_2$ (7 mg, 0.008 mmol) under nitrogen atmosphere. The mixture was heated to 100 °C with stirring. After 2 h, the reaction mixture was cooled down and concentrated under reduced pressure. The residue was diluted with DCM (10 mL) and filtered. The filter cake was washed with DCM (6 mL x 3). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10:1) to give the title compound (27 mg, 16%). LCMS $(M+H)^+ = 580.6$.

Step 10: 4-[2- (2, 5-dimethyl-3, 4-dihydro-1H-isoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl]-N, N-dimethylbenzamide

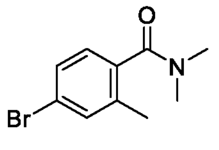


To a stirred mixture of 4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide (34 mg, 0.058 mmol) in MeOH (3 mL) was added K_2CO_3 (57 mg, 0.393 mmol) at 70 °C under ambient atmosphere. The mixture was cooled down to room temperature and water (30 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by prep-HPLC to give Example 1 (9.8 mg, 12%). ^1H NMR (400 MHz, DMSO-*d6*) δ 12.39 (s, 1 H), 8.87 (s, 1 H), 8.51 (s, 1 H), 8.42-8.35 (m, 2 H), 7.85 (d, *J* = 1.9 Hz, 1 H), 7.73 (d, *J* = 1.9 Hz, 1 H), 7.55-7.49 (m, 2 H), 3.60 (s, 2 H), 3.01 (s, 6 H), 2.79-2.71 (m, 2 H), 2.71-2.64 (m, 2 H), 2.38 (s, 3 H), 2.31 (s, 3 H). LC-MS $(M+H)^+ = 426.4$.

Example 2: 4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

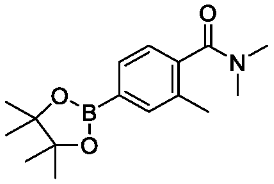


Step 1: 4-bromo-N, N, 2-trimethylbenzamide



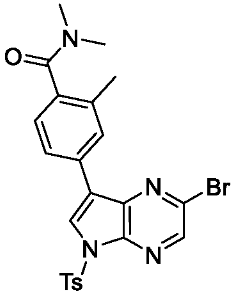
A mixture of 4-bromo-2-methylbenzoic acid (25.0 g, 116 mmol) in $SOCl_2$ (200 mL) was stirred at 60 °C for 3 h. The solvent was removed *in vacuo*. The residue was re-dissolved in anhydrous DCM (200 mL). Dimethylamine hydrochloride (14.0 g, 174.4 mmol) and TEA (80 mL, 581 mmol) was added at 0 °C. The mixture was stirred at room temperature for 2 h. Water (200 mL) was added and the mixture was extracted with DCM (200 mL x 3). The combined organic layer was washed with brine (150 mL), dried over Na_2SO_4, concentrated under reduced pressure to give the title compound (28.0 g, 99 %). LC-MS $(M+H)^+$ =242.0, 244.0.

Step 2: N, N, 2-trimethyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide



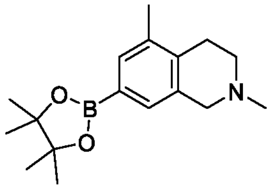
4-bromo-N, N, 2-trimethylbenzamide (28.0 g, 115 mmol), BPD (44.0 g, 174 mmol), Pd (dppf)Cl_2 (5.1 g, 6.94 mmol) and AcOK (22.7 g, 231 mmol) was added to dioxane (400 mL) under nitrogen. The reaction mixture was heated to reflux overnight then cooled to room temperature. EtOAc (400 mL) was added and the mixture was washed with brine (300 mL x 2). The aqueous layer was extracted with EtOAc (400 mL). The combined organic layer was dried over Na_2SO_4 then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (1:5 to 2:1) to give the title compound (26.0 g, 73%). LC-MS $(M+H)^+$ =290.1.

Step 3: 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide



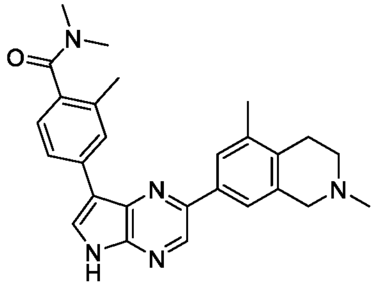
To a solution of 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine (16.5 g, 34.6 mmol) and N, N, 2-trimethyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide (10.0 g, 34.5 mmol) in dioxane (150 mL) and water (50 mL) was added K_2CO_3 (9.55 g, 69.2 mmol) and Pd (dppf)Cl_2 (1.54 g, 2.07 mmol) under nitrogen atmosphere. After stirring for 5 h at 50 °C, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (1:2 to 2:1) to give the title compound (11.0 g, 62%). ^1H NMR (400 MHz, DMSO-*d6*) δ 8.88 (s, 1H), 8.68 (s, 1H), 8.09-8.01 (m, 4H), 7.49-7.44 (m, 2H), 7.29 (d, J = 7.8 Hz, 1H), 3.02 (s, 3H), 2.79 (s, 3H), 2.36 (s, 3H), 2.27 (s, 3H). LCMS $(M+H)^+$ = 513.0.

Step 4: 2, 5-dimethyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline



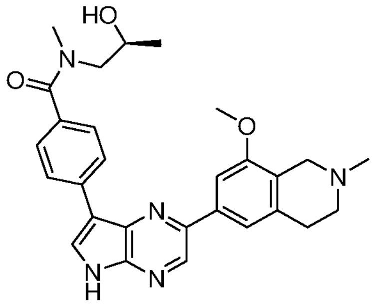
7-bromo-2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinoline (2.5 g, 10.4 mmol), BPD (3.96 g, 15.6 mmol), Pd (dppf)Cl_2 (457 mg, 0.62 mmol) and AcOK (2.0 g, 20.8 mmol) was added to dioxane (50 mL) under nitrogen. The reaction mixture was heated to reflux overnight then cooled to room temperature. EtOAc (50 mL) was added and the mixture was washed with brine (30 mL x 2). The aqueous layer was extracted with EtOAc (50 mL). The combined organic layer was dried over Na_2SO_4 then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (1:15) to give the title compound (2.11 g, 71%). LC-MS $(M+H)^+$ =288.1.

Step 5: 4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

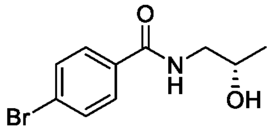


4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide (2.7 g, 5.26 mmol), 2, 5-dimethyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline (2.11 g, 7.37 mmol), Pd (dppf)Cl_2 (231 mg, 0.316 mmol) and K_2CO_3 (2.18 g, 15.8 mmol) was added to dioxane (50 mL) and water (10 mL) under nitrogen. The reaction mixture was heated to reflux overnight then cooled to room temperature. The reaction mixture was partitioned between EtOAc (40 mL) and water (40 mL) then the aqueous layer was extracted with EtOAc (40 mL x 2). The combined organic layer was dried over Na_2SO_4 then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (1:50 to 1:10) to give Example 2 (0.90 g, 39%). ^1H NMR (400 MHz, DMSO-*d6*) δ 12.33 (s, 1 H), 8.87 (s, 1 H), 8.46 (s, 1 H), 8.27-8.18 (m, 2 H), 7.87 (s, 1 H), 7.74 (s, 1 H), 7.25 (d, J = 7.9 Hz, 1 H), 3.63-3.55 (m, 2 H), 3.03 (s, 3 H), 2.84 (s, 3 H), 2.80-2.63 (m, 4 H), 2.39 (s, 3 H), 2.34-2.28 (m, 6 H). LC-MS $(M+H)^+$ = 440.4.

Example 3: (S)-N- (2-hydroxypropyl)-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methylbenzamide

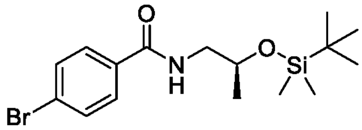


Step 1: 4-bromo-N-[(2S)-2-hydroxypropyl]benzamide



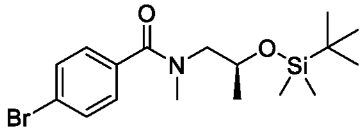
To solution of 4-bromobenzoic acid (11.80 g, 55.8 mmol) in DMF (120 mL) was added DIPEA (10.50 g, 104 mmol), HATU (22.40 g, 58.9 mmol) and (2S)-1-aminopropan-2-ol (4.00 g, 53.3 mmol). The resulting mixture was stirred for 6 h at room temperature. The reaction was quenched by addition of water. The resulting mixture was extracted with EtOAc (600 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (30:70) to give the title compound (12.0 g, 88%). LC-MS $(M+H)^+ = 258.1$

Step 2: 4-bromo-N-[(2S)-2-[(tert-butyldimethylsilyl)oxy]propyl]benzamide



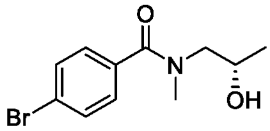
To a stirred mixture of 4-bromo-N-[(2S)-2-hydroxypropyl]benzamide (12.0 g, 46.7 mmol) and TBSCl (15.0 g, 59.0 mmol) in DCM (150 mL) was added Et_3N (15.0 g, 1.49 mmol) dropwise at 0 °C. The resulting mixture was stirred for 15 h at room temperature. The reaction was quenched by addition of water. The resulting mixture was extracted with DCM (500 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to provide the title compound (19.0 g, crude). The crude product was used in step 3 directly without further purification. LC-MS $(M+H)^+ = 372.2$.

Step 3: 4-bromo-N-[(2S)-2-[(tert-butyldimethylsilyl)oxy]propyl]-N-methylbenzamide



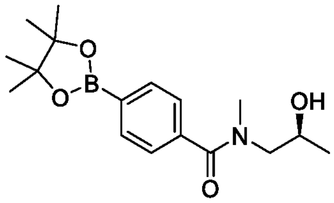
To a stirred solution of 4-bromo-N-[(2S)-2-[(tert-butyldimethylsilyl)oxy]propyl]benzamide (19.0 g, crude from step 2) in DMF (120 mL) was added NaH (5.10 g, 60% in mineral oil, 127 mmol) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min then CH_3I (9.50 g, 63.6 mmol) was added dropwise at 0 °C. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. The reaction was quenched with ice water at 0 °C. The resulting mixture was extracted with EtOAc (700 mL x 3). The combined organic layer was washed with brine (150 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give the title compound (18.0 g, crude). The crude product was used in step 4 directly without further purification. LC-MS $(M+H)^+ = 386.3$.

Step 4: 4-bromo-N-[(2S)-2-hydroxypropyl]-N-methylbenzamide



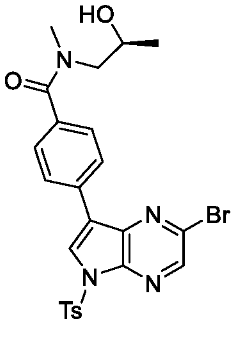
To a solution of 4-bromo-N-[(2S)-2-[(tert-butyldimethylsilyl)oxy]propyl]-N-methylbenzamide (18.0 g, crude from step 3) in THF (200 mL) was added TBAF (1.0 M in THF, 70 mL, 70 mmol). The resulting mixture was stirred for 15 h at room temperature. The reaction mixture was concentrated under vacuum and the residue was purified by silica gel column chromatography, eluted with EtOAc to give the title compound (8.3 g, 65% over 3 steps). LC-MS (M+H) $^{+}$ = 272.0.

Step 5: N-[(2S)-2-hydroxypropyl]-N-methyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide



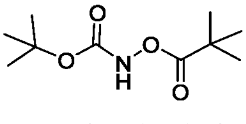
To a solution of 4-bromo-N-[(2S)-2-hydroxypropyl]-N-methylbenzamide (8.3 g, 30.5 mmol) and BPD (12.0 g, 44.9 mmol) in dioxane (200 mL) was added Pd (dppf)Cl_2·DCM (2.60 g, 3.02 mmol) and KOAc (9.30 g, 90.0 mmol). The reaction mixture was stirred for 3 h at 100 °C under nitrogen atmosphere. The mixture was cooled down to room temperature then filtered. The filter cake was rinsed with dioxane (10 mL x 3). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc to give the title compound (7.8 g, 80%). LC-MS (M+H) $^{+}$ = 320.2.

Step 6: (S)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N-methylbenzamide



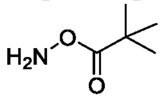
The title compound (866 mg, 88%) was prepared in a manner similar to that in Example 1 step 2 from N-[(2S)-2-hydroxypropyl]-N-methyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide and 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine. LC-MS $(M+H)^+$ = 543.0.

Step 7: tert-butyl (pivaloyloxy)carbamate



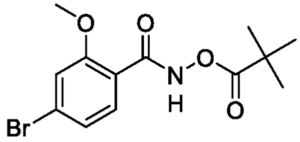
To a stirred solution of pivaloyl anhydride (17.0 g, 86.7 mmol) in $CHCl_3$ (300 mL) was added tert-butyl N-hydroxycarbamate (10.0 g, 71.3 mmol) dropwise at 0 °C. The reaction mixture was heated to 70 °C for 16 h. The mixture was cooled down to room temperature and concentrated under vacuum. The residue was partitioned between EtOAc (500 mL) and water (500 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to provide the title compound (7.2 g, 46%).

Step 8: O-pivaloylhydroxylamine



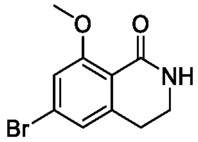
To a solution of tert-butyl (pivaloyloxy)carbamate (26.4 g, 97 mmol) in anhydrous diethyl ether (240 mL) was added TFA (9.6 g, 99 mmol) slowly at room temperature. The resulting mixture was stirred for 1 h then hexane (250 mL) was added. The resulting mixture was rapidly stirred for 10 min. The precipitate was collected by filtration, rinsed with hexane (20 mL x 3), and dried in vacuum oven overnight to give the title compound (24.8 g, 91 %) as a white solid. LCMS $(M+H)^+ = 118.2$.

Step 9: 4-bromo-2-methoxy-N- (pivaloyloxy)benzamide



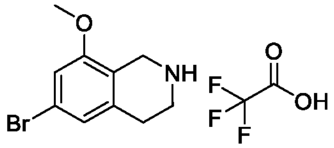
To a solution of 4-bromo-2-methoxybenzoic acid (10.0 g, 43.3 mmol) in THF (150 mL) was added T3P (27.6 g, 86.6 mmol) under nitrogen atmosphere at 0 °C. The resulting mixture was stirred for 0.5 h at room temperature. Then DIPEA (17.1 g, 132 mmol) and O-pivaloylhydroxylamine (12.0 g, 103 mmol) was added in portions at room temperature. The reaction mixture was stirred for additional 16 h. The reaction was quenched by the addition of water (300 mL), then extracted with ethyl acetate (500 mL x 3). The organic phases were combined, washed with brine and dried over Na_2SO_4. The solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluted with EtOAc/hexane (0:1 to 1:10) to give the title compound (9.83 g, 69 %). LCMS $(M+H)^+ = 330.2$.

Step 10: 6-bromo-8-methoxy-3, 4-dihydroisoquinolin-1 (2H)-one



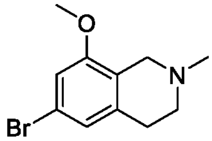
To a stirred solution of 4-bromo-2-methoxy-N- (pivaloyloxy)benzamide (10.0 g, 29.8 mmol) and KOAc (6.67 g, 64.6 mmol) in MeCN (200 mL) was added dichloro (pentamethylcyclopentadienyl)rhodium (III) dimer (968 mg, 1.489 mmol) at room temperature under nitrogen atmosphere. To the mixture was bubbled with ethylene for 1 h at -30 °C. The resulting mixture was stirred for additional 16 h at room temperature under 3 bar of ethylene atmosphere. The resulting mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10:1) to give the title compound (2.3 g, 28%). LCMS $(M+H)^+ = 256.1$.

Step 11: 6-bromo-8-methoxy-1, 2, 3, 4-tetrahydroisoquinoline; trifluoroacetic acid



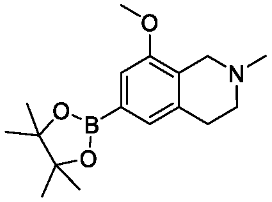
To a stirred solution of 6-bromo-8-methoxy-3, 4-dihydroisoquinolin-1 (2H)-one (400 mg, 1.56 mmol) in THF (20.0 mL) was added BH_3-Me_2S (8.00 mL, 84.3 mmol) at 70 °C under nitrogen atmosphere. The resulting mixture was stirred for 12 h at 70 °C then cooled down to room temperature. The reaction was quenched with iced water. To the above mixture was added NaOH (5 M, 30 mL). The resulting mixture was stirred for additional 30 min at 70 °C then cooled down to room temperature. The resulting mixture was extracted with EtOAc (20 mL x 3). The combined organic layer was washed with brine (60 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by C18 chromatography, eluted with acetonitrile/water (contained 0.05% TFA) (0:1 to 3:7) to give the title compound (240 mg, 43%). LCMS $(M+H)^+ = 242.0$.

Step 12: 6-bromo-8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline



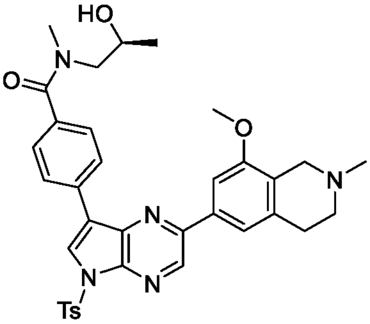
To a stirred solution of 6-bromo-8-methoxy-1, 2, 3, 4-tetrahydroisoquinoline; trifluoroacetic acid (220 mg, 0.620 mmol), HOAc (0.01 mL, 0.173 mmol) and formalin (37%, 104 mg, 1.28 mmol) in MeOH (10 mL) was added $NaBH_3CN$ (85 mg, 1.28 mmol) in portions at 0 °C. The resulting mixture was stirred for 2 h at room temperature then concentrated under vacuum. The residue was purified by C18 chromatography, eluted with acetonitrile/water (contained 0.1% NH_4HCO_3) (1:1 to 8:2) to give the title compound (90 mg, 57%). LCMS $(M+H)^+ = 256.0$.

Step 13: 8-methoxy-2-methyl-6- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline



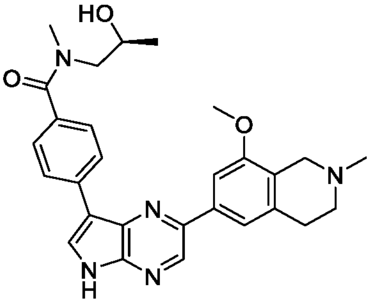
The title compound (210 mg, 81%) was prepared in a manner similar to that in Example 2 step 4 from 6-bromo-8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline and BPD. LC-MS $(M+H)^+ = 304.1$.

Step 14: (S)-N- (2-hydroxypropyl)-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methylbenzamide



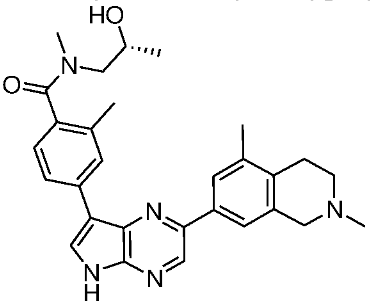
The title compound (62 mg, 64%) was prepared in a manner similar to that in Example 2 step 5 from 8-methoxy-2-methyl-6- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline and (S)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N-methylbenzamide. LC-MS $(M+H)^+$ = 640.5.

Step 15: (S)-N- (2-hydroxypropyl)-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methylbenzamide

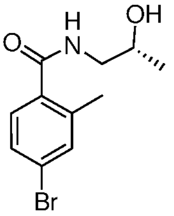


Example 3 (18 mg, 41%) was prepared in a manner similar to that in in Example 1 step 10 from (S)-N- (2-hydroxypropyl)-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methylbenzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.41 (s, 1 H), 8.95 (s, 1 H), 8.52 (s, 1 H), 8.42-8.37 (m, 2 H), 7.60 (d, *J* = 10.7 Hz, 2 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 4.87-4.82 (m, 1 H), 4.07-3.83 (m, 4 H), 3.48 (s, 2 H), 3.31-3.12 (m, 2 H), 3.03 (s, 3 H), 2.98-2.90 (m, 2 H), 2.67-2.62 (m, 2 H), 2.42 (s, 3 H), 1.18-0.75 (m, 3 H). LC-MS $(M+H)^+$ = 486.5.

Example 4: (R)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide

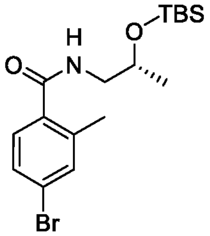


Step 1: (R)-4-bromo-N- (2-hydroxypropyl)-2-methylbenzamide



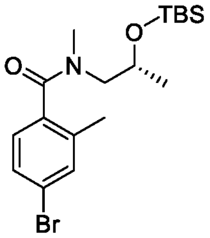
The title compound (24.5 g, 97%) was prepared in a manner similar to that in Example 3 step 1 from 4-bromo-2-methylbenzoic acid and (R)-1-aminopropan-2-ol. LC-MS $(M+H)^+$ = 272.0.

Step 2: (R)-4-bromo-N- (2- (tert-butyldimethylsilyloxy)propyl)-2-methylbenzamide



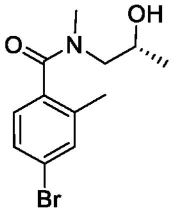
The title compound (48.00 g, crude) was prepared in a manner similar to that in Example 3 step 2 from (R)-4-bromo-N- (2-hydroxypropyl)-2-methylbenzamide. LC-MS $(M+H)^+$ = 386.1.

Step 3: (R)-4-bromo-N- (2- (tert-butyldimethylsilyloxy)propyl)-N, 2-dimethylbenzamide



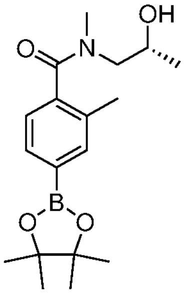
The title compound (32.9 g, 91% over 2 steps) was prepared in a manner similar to that in Example 3 step 3 from (R)-4-bromo-N- (2- (tert-butyldimethylsilyloxy)propyl)-2-methylbenzamide. LC-MS $(M+H)^+$ = 399.9.

Step 4: (R)-4-bromo-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide



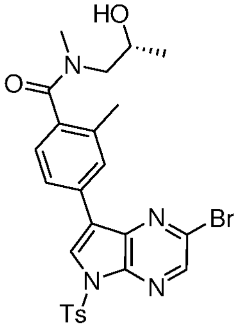
The title compound (21.0 g, 80%) was prepared in a manner similar to that in Example 3 step 4 from (R)-4-bromo-N- (2- (tert-butyldimethylsilyloxy)propyl)-N, 2-dimethylbenzamide. LC-MS $(M+H)^+$ = 286.1.

Step 5: (R)-N- (2-hydroxypropyl)-N, 2-dimethyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide



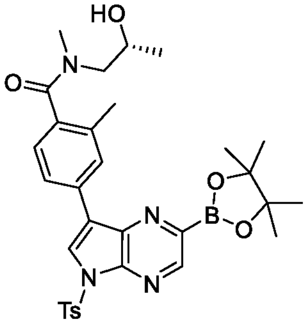
The title compound (11.5 g, 24%) was prepared in a manner similar to that in Example 3 step 5 from (R)-4-bromo-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide and BPD. LC-MS $(M+H)^+$ = 334.2.

Step 6: (R)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide



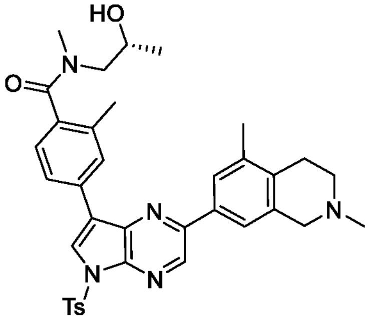
The title compound (170 mg, 51%) was prepared in a manner similar to that in Example 1 step 2 from (R)-N- (2-hydroxypropyl)-N, 2-dimethyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide and 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine. LC-MS $(M+H)^+ = 557.2$.

Step 7: (R)-N- (2-hydroxypropyl)-N, 2-dimethyl-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



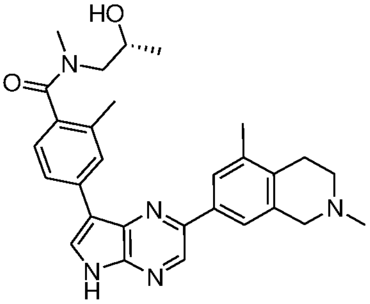
The title compound (100 mg, 71%) was prepared in a manner similar to that in Example 1 step 3 from (R)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide and BPD. LC-MS $(M\text{-}pin)^+ = 523.3$.

Step 8: (R)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide



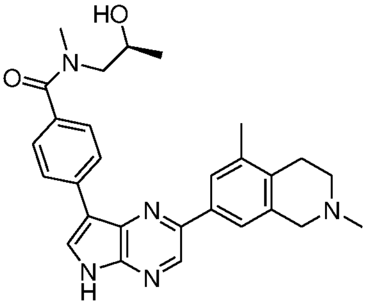
The title compound (40 mg, 32%) was prepared in a manner similar to that in Example 1 step 9 from (R)-N- (2-hydroxypropyl)-N, 2-dimethyl-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide and 7-bromo-2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinoline. LC-MS $(M+H)^+ = 638.5$.

Step 9: (R)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide

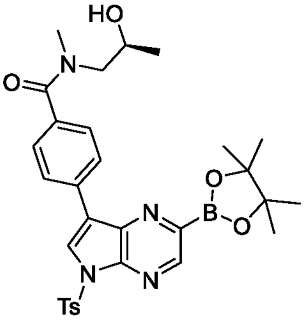


Example 4 (5 mg, 12%) was prepared in a manner similar to that in Example 1 step 10 from (R)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.34 (s, 1 H), 8.87 (s, 1 H), 8.46 (s, 1 H), 8.26-8.19 (m, 2 H), 8.22-8.15 (m, 1 H), 7.88 (s, 1 H), 7.74 (s, 1 H), 7.26 (d, *J* = 7.8 Hz, 1 H), 4.83-4.77 (m, 1 H), 4.06-3.75 (m, 1 H), 3.63 (s, 2 H), 3.57-3.49 (m, 1 H), 3.07-3.01 (m, 2 H), 2.91-2.86 (m, 2 H), 2.79-2.69 (m, 4 H), 2.41 (s, 3 H), 2.35-2.27 (m, 6 H), 1.18-0.86 (m, 3 H). LC-MS $(M+H)^+$ = 484.5.

Example 5: (S)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N-methylbenzamide

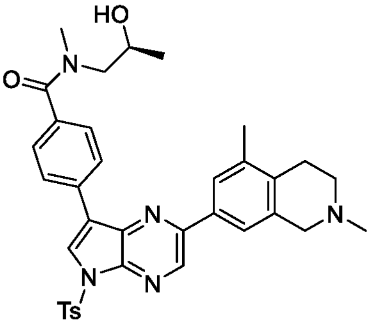


Step 1: (S)-N- (2-hydroxypropyl)-N-methyl-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



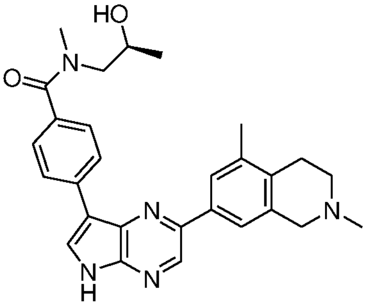
The title compound (71 mg, 83%) was prepared in a manner similar to that in Example 1 step 3 from (S)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N-methylbenzamide and BPD. LC-MS $(M\text{-}pin)^+$ = 509.4.

Step 2: (S)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N-methylbenzamide



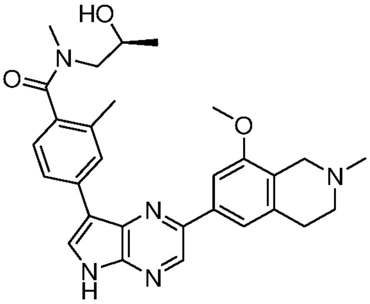
The title compound (150 mg, 50 %) was prepared in a manner similar to that in Example 1 step 9 from (S)-N- (2-hydroxypropyl)-N-methyl-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide and 7-bromo-2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinoline. LC-MS $(M+H)^+ = 624.5$.

Step 3: (S)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N-methylbenzamide

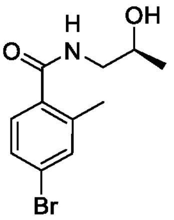


Example 5 (4.5 mg, 4.5%) was prepared in a manner similar to that in Example 1 step 10 from (S)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N-methylbenzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.37 (s, 1 H), 8.87 (s, 1 H), 8.50 (s, 1 H), 8.41-8.34 (m, 2 H), 7.85 (s, 1 H), 7.73 (d, *J* = 1.9 Hz, 1 H), 7.52 (d, *J* = 7.9 Hz, 2 H), 4.83 (s, 1 H), 4.04-3.87 (m, 1 H), 3.60 (s, 2 H), 3.52-3.47 (m, 1 H), 3.22-3.18 (m, 1 H), 3.04 (s, 3 H), 2.79-2.72 (m, 2 H), 2.71-2.64 (m, 2 H), 2.38 (s, 3 H), 2.32 (s, 3 H), 1.18-0.88 (m, 3 H).LC-MS $(M+H)^+ = 470.5$.

Example 6: (S)-N- (2-hydroxypropyl)-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, 2-dimethylbenzamide

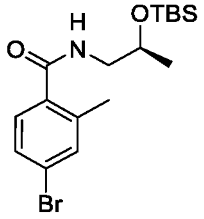


Step 1: (S)-4-bromo-N- (2-hydroxypropyl)-2-methylbenzamide



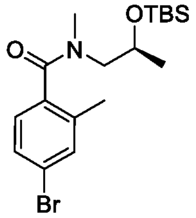
The title compound (14.0 g, 97%) was prepared in a manner similar to that in Example 3 step 1 from (S)-1-aminopropan-2-ol and 3-bromo-5-methylbenzoic acid. LC-MS $(M+H)^+$ = 272.3.

Step 2: (S)-4-bromo-N- (2- (tert-butyldimethylsilyloxy)propyl)-2-methylbenzamide



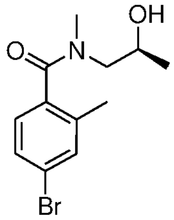
The title compound (21.8 g, 89%) was prepared in a manner similar to that in Example 3 step 2 from (S)-4-bromo-N- (2-hydroxypropyl)-2-methylbenzamide and TBSCl. LC-MS $(M+H)^+$ = 386.2.

Step 3: (S)-4-bromo-N- (2- (tert-butyldimethylsilyloxy)propyl)-N, 2-dimethylbenzamide



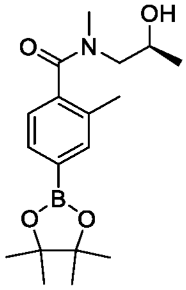
The title compound (13.1 g, 61%) was prepared in a manner similar to that in Example 3 step 3 from (S)-4-bromo-N- (2- (tert-butyldimethylsilyloxy)propyl)-2-methylbenzamide and MeI. LC-MS $(M+H)^+$ = 400.2.

Step 4: (S)-4-bromo-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide



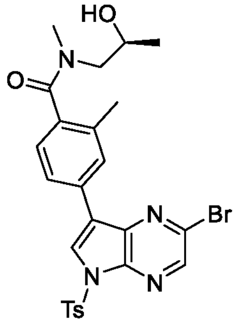
The title compound (6.36 g, 81%) was prepared in a manner similar to that in Example 3 step 4 from (S)-4-bromo-N- (2- (tert-butyldimethylsilyloxy)propyl)-N, 2-dimethylbenzamide. LC-MS $(M+H)^+$ = 286.2.

Step 5: (S)-N- (2-hydroxypropyl)-N, 2-dimethyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide



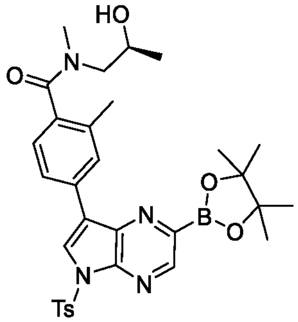
The title compound (7.78 g, 64%) was prepared in a manner similar to that in Example 3 step 5 from (S)-4-bromo-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide and BPD. LC-MS $(M+H)^+$ = 334.4.

Step 6: (S)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide



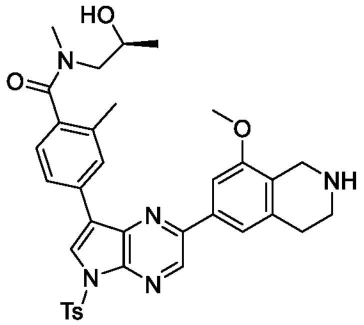
The title compound (495 mg, 34%) was prepared in a manner similar to that in Example 1 step 2 from (S)-N- (2-hydroxypropyl)-N, 2-dimethyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide and 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine. LC-MS $(M+H)^+ = 557.1$.

Step 7: (S)-N- (2-hydroxypropyl)-N, 2-dimethyl-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



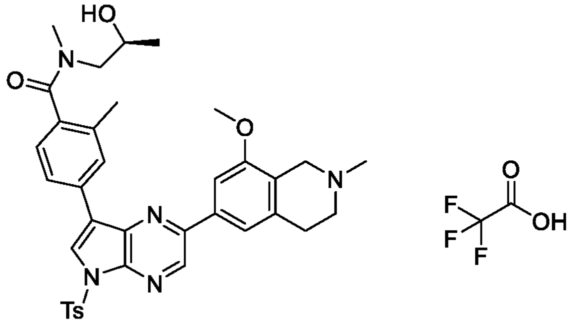
The title compound (330 mg, 60%) was prepared in a manner similar to that in Example 1 step 3 from (S)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide and BPD. LC-MS $(M\text{-}pin)^+ = 523.2$.

Step 8: (S)-N- (2-hydroxypropyl)-4- (2- (8-methoxy-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, 2-dimethylbenzamide



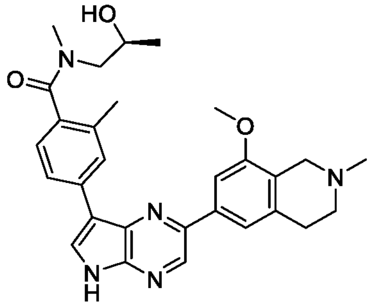
The title compound (203 mg, 59%) was prepared in a manner similar to that in Example 1 step 9 from (S)-7- (4- ((2-hydroxypropyl) (methyl)carbamoyl)-3-methylphenyl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-2-ylboronic acid and 6-bromo-8-methoxy-1, 2, 3, 4-tetrahydroisoquinoline; trifluoroacetic acid. LC-MS $(M+H)^+ = 640.7$.

Step 9: (S)-N- (2-hydroxypropyl)-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, 2-dimethylbenzamide; trifluoroacetic acid



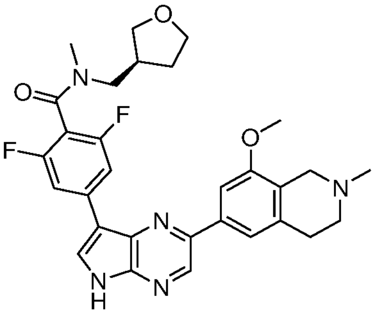
To a stirred solution of (S)-N- (2-hydroxypropyl)-4- (2- (8-methoxy-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, 2-dimethylbenzamide (250 mg, 0.391 mmol) and formalin (30%, 63 mg, 0.63 mmol) in MeOH (10 mL) was added HOAc (1 drop) and $NaBH_3CN$ (39 mg, 0.63 mmol) at room temperature under N_2. After 2 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by C18 chromatography, eluted with acetonitrile/water (contained 0.05% TFA) (0:1 to 3:7) to give the title compound (194 mg, 65%). LC-MS $(M+H)^+$ = 654.5.

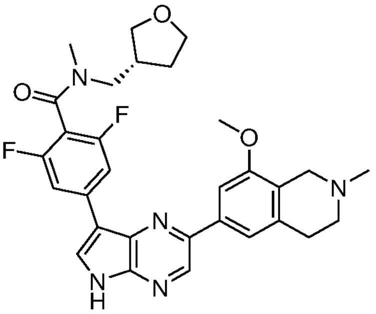
Step 10: (S)-N- (2-hydroxypropyl)-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, 2-dimethylbenzamide



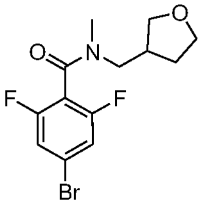
Example 6 (37 mg, 32%) was prepared in a manner similar to that in Example 1 step 10 from (S)-N- (2-hydroxypropyl)-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, 2-dimethylbenzamide; trifluoroacetic acid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.36 (s, 1 H), 8.96 (s, 1 H), 8.48 (s, 1 H), 8.37 (d, *J* = 6.2 Hz, 1 H), 8.19-8.09 (m, 1 H), 7.68 (s, 1 H), 7.61 (s, 1 H), 7.24 (d, *J* = 8.0 Hz, 1 H), 4.83-4.77 (m, 1 H), 4.06-3.76 (m, 4 H), 3.57-3.46 (m, 3 H), 3.16-3.01 (m, 2 H), 2.98-2.85 (m, 4 H), 2.68-2.60 (m, 2 H), 2.41 (s, 3 H), 2.34-2.26 (m, 3 H), 1.18-0.84 (m, 3 H). LC-MS $(M+H)^+$ = 500.3.

Example 7A/7B: (S)-2, 6-difluoro-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide & (R)-2, 6-difluoro-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide



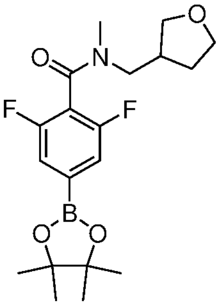


Step 1: 4-bromo-2, 6-difluoro-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide



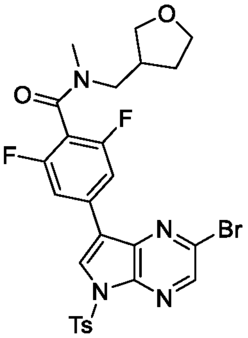
The title compound (1.47 g, 56%) was prepared in a manner similar to that in Example 3 step 1 from 4-bromo-2, 6-difluorobenzoic acid and N-methyl (tetrahydrofuran-3-yl)methanamine. LC-MS $(M+H)^+ = 334.0$.

Step 2: 2, 6-difluoro-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide



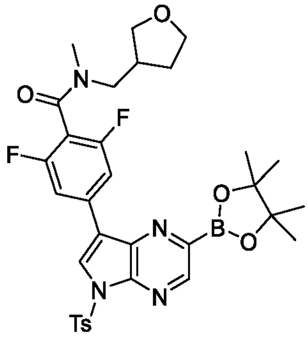
The title compound (0.90 g, 54%) was prepared in a manner similar to that in Example 3 step 5 from 4-bromo-2, 6-difluoro-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide and BPD. LC-MS $(M+H)^+ = 382.2$.

Step 3: 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2, 6-difluoro-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide



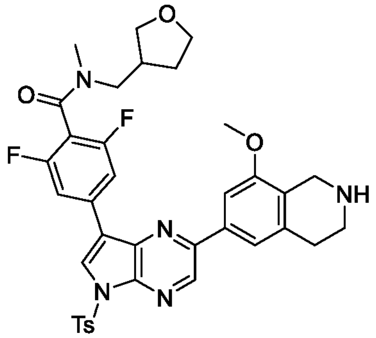
The title compound (47 mg, 76%) was prepared in a manner similar to that in Example 1 step 2 from 2, 6-difluoro-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide and 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine. LC-MS $(M+H)^+ = 605.2$.

Step 4: 2, 6-difluoro-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



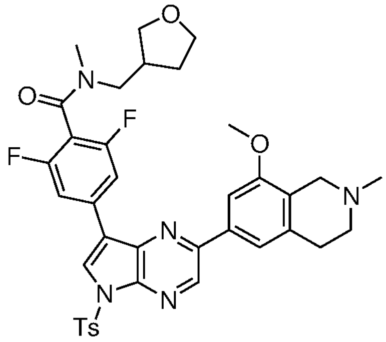
The title compound (131 mg, 32%) was prepared in a manner similar to that in Example 1 step 3 from 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2, 6-difluoro-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide and BPD. LC-MS $(M\text{-}pin)^+ = 571.4$.

Step 5: 2, 6-difluoro-4- (2- (8-methoxy-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide



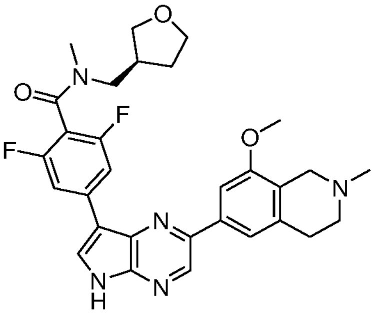
The title compound (66 mg, 87%) was prepared in a manner similar to that in Example 1 step 9 from 2, 6-difluoro-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide and 6-bromo-8-methoxy-1, 2, 3, 4-tetrahydroisoquinoline; trifluoroacetic acid. LC-MS $(M+H)^+ =$ 688.5.

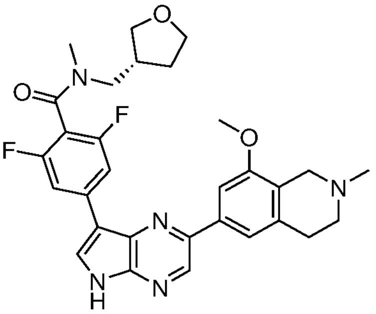
Step 6: 2, 6-difluoro-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide



The title compound (67 mg, 87%) was prepared in a manner similar to that in Example 6 step 9 from 2, 6-difluoro-4- (2- (8-methoxy-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide and formalin. LC-MS $(M+H)^+ = 702.4$.

Step 7: (S)-2, 6-difluoro-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide & (R)-2, 6-difluoro-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide



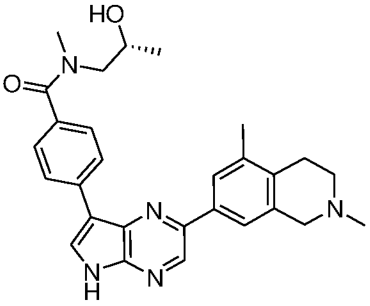


Example 7A/7B was prepared in a manner similar to that in Example 1 step 10 from 2, 6-difluoro-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide. The 2 isomeric products were identified by separation on Chiral-HPLC under the following conditions: Column, Repaired IC, 0.46 x 10 cm, 5.0 m. Mobile phase: (Hex : DCM = 3 : 1) (0.2 % isopropylamine) in IPA, 70 % isocratic in 15 min; detector, UV 254 nm.

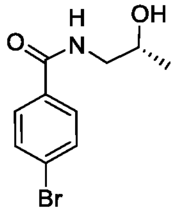
Example 7A: (4 mg, 4%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.64 (s, 1 H), 8.99 (s, 1 H), 8.71 (s, 1 H), 8.28-8.25 (m, 2 H), 7.63 (s, 1 H), 7.58 (s, 1 H), 3.93 (s, 3 H), 3.85-3.47 (m, 5 H), 3.46 (s, 2 H), 3.29-3.22 (m, 1 H), 3.06-2.87 (m, 5 H), 2.72-2.54 (m, 3 H), 2.40 (s, 3 H), 2.04-1.85 (m, 1 H), 1.69-1.33 (m, 1 H). LC-MS (M+H)$^+$ = 548.4. tR=2.83 m at aforementioned Chiral-HPLC condition.

Example 7B: (4 mg, 4%), ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.64 (s, 1 H), 8.99 (s, 1 H), 8.71 (s, 1 H), 8.28-8.25 (m, 2 H), 7.63 (s, 1 H), 7.58 (s, 1 H), 3.93 (s, 3 H), 3.85-3.47 (m, 5 H), 3.46 (s, 2 H), 3.29-3.22 (m, 1 H), 3.06-2.87 (m, 5 H), 2.72-2.54 (m, 3 H), 2.40 (s, 3 H), 2.04-1.85 (m, 1 H), 1.69-1.33 (m, 1 H). LC-MS (M+H)$^+$ = 548.4. tR=3.86 m at aforementioned Chiral-HPLC condition.

Example 8: (R)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N-methylbenzamide

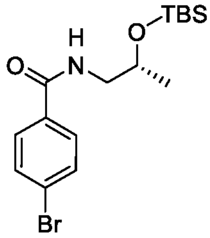


Step 1: <u>4-bromo-N-[(2R)-2-hydroxypropyl]benzamide</u>



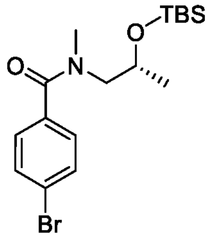
The title compound (4.63 g, 67%) was prepared in a manner similar to that in Example 3 step 1 from 4-bromobenzoic acid and (2R)-1-aminopropan-2-ol. LC-MS $(M+H)^+ = 258.1$.

Step 2: 4-bromo-N-[(2R)-2-[(tert-butyldimethylsilyl)oxy]propyl]benzamide



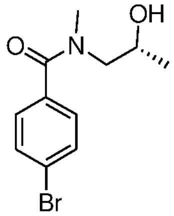
The title compound (12.14 g, 60%) was prepared in a manner similar to that in Example 3 step 2 from 4-bromo-N-[(2R)-2-hydroxypropyl]benzamide and TBSCl. LC-MS $(M+H)^+ =$ 372.3.

Step 3: 4-bromo-N-[(2R)-2-[(tert-butyldimethylsilyl)oxy]propyl]-N-methylbenzamide



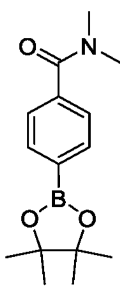
The title compound (9.79 g, 53%) was prepared in a manner similar to that in Example 3 step 3 from 4-bromo-N-[(2R)-2-[(tert-butyldimethylsilyl)oxy]propyl]benzamide and MeI. LC-MS $(M+H)^+ = 386.1$.

Step 4: 4-bromo-N-[(2R)-2-hydroxypropyl]-N-methylbenzamide



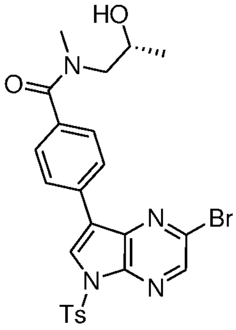
The title compound (5.48 g, 70%) was prepared in a manner similar to that in Example 3 step 4 from 4-bromo-N-[(2R)-2-[(tert-butyldimethylsilyl)oxy]propyl]-N-methylbenzamide. LC-MS $(M+H)^+ = 272.0$.

Step 5: (R)-N- (2-hydroxypropyl)-N-methyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide



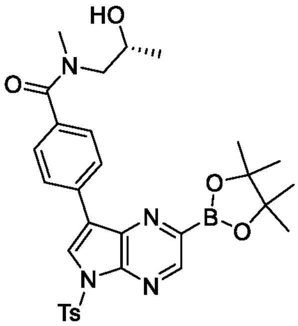
The title compound (3.75 g, 47%) was prepared in a manner similar to that in Example 3 step 5 from 4-bromo-N-[(2R)-2-hydroxypropyl]-N-methylbenzamide and BPD. LC-MS $(M+H)^+$ = 320.1.

Step 6: (R)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N-methylbenzamide



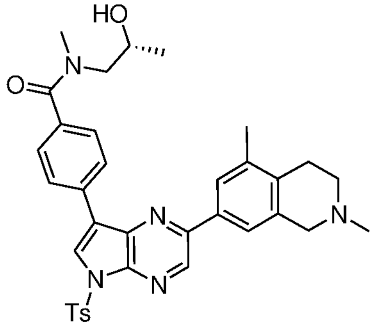
The title compound (488 mg, 52%) was prepared in a manner similar to that in Example 1 step 2 from (R)-N- (2-hydroxypropyl)-N-methyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide and 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine. LC-MS $(M+H)^+$ = 543.2.

Step 7: (R)-N- (2-hydroxypropyl)-N-methyl-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



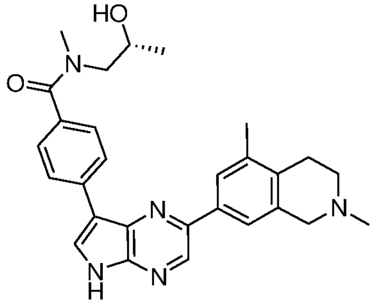
The title compound (200 mg, crude) was prepared in a manner similar to that in Example 1 step 3 from (R)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N-methylbenzamide and BPD. LC-MS $(M\text{-pin})^+$ = 509.2.

Step 8: (R)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N-methylbenzamide



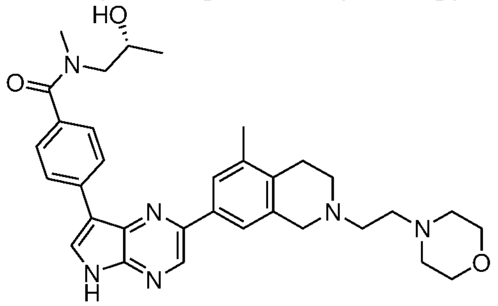
The title compound (50 mg, 22 % over 2 steps) was prepared in a manner similar to that in Example 1 step 9 from (R)-N- (2-hydroxypropyl)-N-methyl-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide and 7-bromo-2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinoline. LC-MS $(M+H)^+$ = 624.5.

Step 9: (R)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N-methylbenzamide

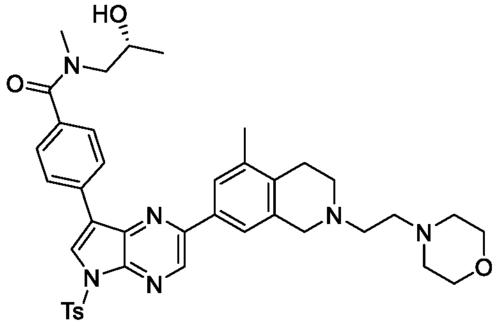


Example 8 (15 mg, 20 %) was prepared in a manner similar to that in Example 1 step 10 from (R)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N-methylbenzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.38 (s, 1 H), 8.87 (s, 1 H), 8.50 (s, 1 H), 8.41-8.35 (m, 2 H), 7.85 (s, 1 H), 7.73 (s, 1 H), 7.55-7.49 (m, 2 H), 4.84 (s, 1 H), 4.06-3.80 (m, 1 H), 3.60 (s, 2 H), 3.54-3.47 (m, 1 H), 3.27-3.12 (m, 1 H), 3.04 (s, 3 H), 2.79-2.71 (m, 2 H), 2.71-2.63 (m, 2 H), 2.38 (s, 3 H), 2.31 (s, 3 H), 1.20-0.86 (m, 3 H). LC-MS $(M+H)^+$ = 470.5.

Example 9: (R)-N- (2-hydroxypropyl)-N-methyl-4- (2- (5-methyl-2- (2-morpholinoethyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide

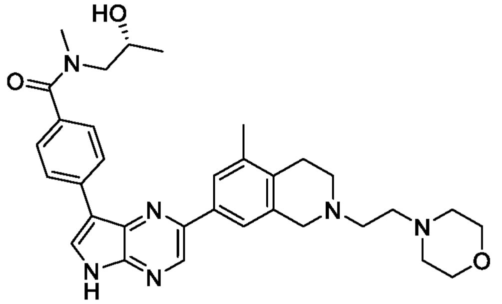


Step 1: (R)-N- (2-hydroxypropyl)-N-methyl-4- (2- (5-methyl-2- (2-morpholinoethyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



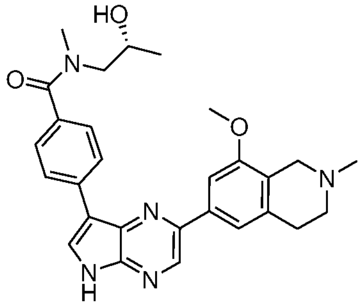
The title compound (81 mg, 33%) was prepared in a manner similar to that in Example 2 step 5 from (R)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N-methylbenzamide and 4- (2- (5-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-3, 4-dihydroisoquinolin-2 (1H)-yl)ethyl)morpholine. LC-MS $(M+H)^+ = 723.1$.

Step 2: (R)-N- (2-hydroxypropyl)-N-methyl-4- (2- (5-methyl-2- (2-morpholinoethyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide

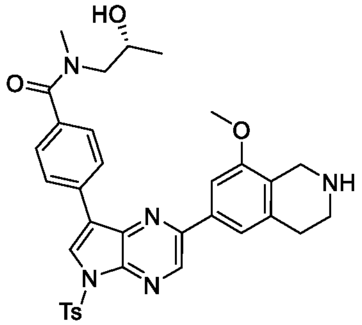


Example 9 (8 mg, 12%) was prepared in a manner similar to that in Example 1 step 10 from (R)-N- (2-hydroxypropyl)-N-methyl-4- (2- (5-methyl-2- (2-morpholinoethyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.39 (s, 1 H), 8.88 (s, 1 H), 8.51 (s, 1 H), 8.37 (s, 2 H), 7.86 (s, 1 H), 7.74 (s, 1 H), 7.52 (d, *J* = 7.9 Hz, 3 H), 4.85 (s, 1 H), 4.05-3.83 (m, 1 H), 3.76-3.71 (m, 2 H), 3.62-3.55 (m, 5 H), 3.50-3.46 (m, 2 H), 3.03 (s, 3 H), 2.84-2.54 (m, 5 H), 2.48-2.43 (m, 6 H), 2.31 (s, 3 H), 1.28-1.19 (m, 1 H), 1.18-0.89 (m, 3 H). LC-MS $(M+H)^+ = 569.1$.

Example 10: (R)-N- (2-hydroxypropyl)-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methylbenzamide

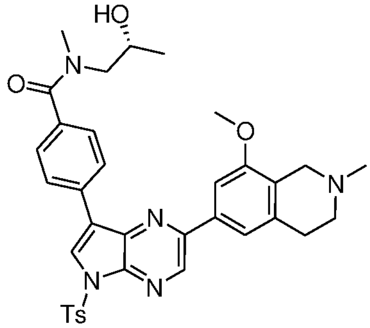


Step 1: (R)-N- (2-hydroxypropyl)-4- (2- (8-methoxy-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methylbenzamide



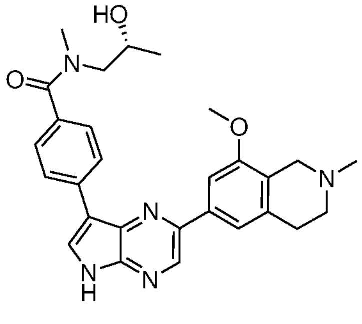
The title compound (33 mg, 22%) was prepared in a manner similar to that in Example 1 step 9 from (R)-N- (2-hydroxypropyl)-N-methyl-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide and 6-bromo-8-methoxy-1, 2, 3, 4-tetrahydroisoquinoline; trifluoroacetic acid. LC-MS $(M+H)^+ = 626.3$.

Step 2: (R)-N- (2-hydroxypropyl)-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methylbenzamide



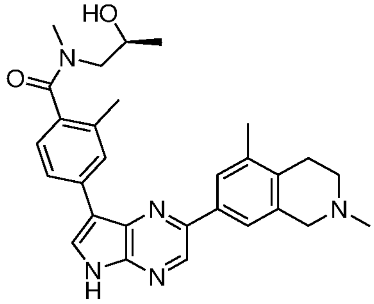
The title compound (25 mg, 83%) was prepared in a manner similar to that in Example 6 step 9 from (R)-N- (2-hydroxypropyl)-4- (2- (8-methoxy-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methylbenzamide and formalin. LC-MS $(M+H)^+ =$ 640.4.

Step 3: (R)-N- (2-hydroxypropyl)-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methylbenzamide

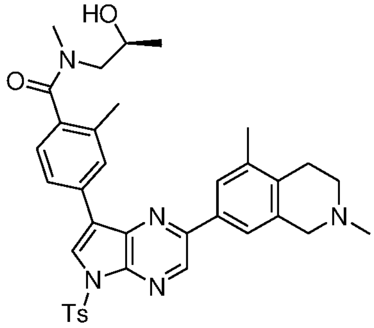


Example 10 (6 mg, 36 %) was prepared in a manner similar to that in Example 1 step 10 from (R)-N- (2-hydroxypropyl)-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methylbenzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.41 (s, 1 H), 8.94 (s, 1 H), 8.52 (s, 1 H), 8.42-8.36 (m, 2 H), 7.63-7.56 (m, 2 H), 7.55-7.48 (m, 2 H), 4.85 (s, 1 H), 3.94 (s, 3 H), 3.45 (s, 2 H), 3.35-3.12 (m, 3 H), 3.03 (s, 3 H), 2.97-2.90 (m, 2 H), 2.65-2.58 (m, 2 H), 2.40 (s, 3 H), 1.19-0.85 (m, 3 H). LC-MS $(M+H)^+ = 486.4$.

Example 11: (S)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide

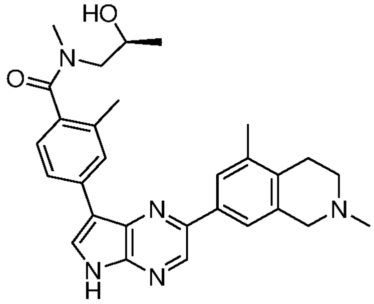


Step 1: (S)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide



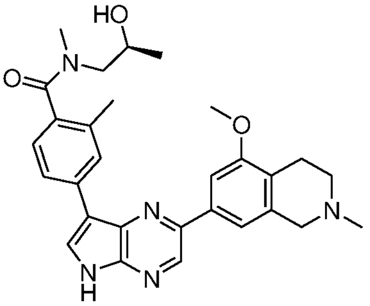
The title compound (87 mg, 32%) was prepared in a manner similar to that in Example 2 step 5 from (S)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide and 2, 5-dimethyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline. LC-MS $(M+H)^+ = 638.5$.

Step 2: (S)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide

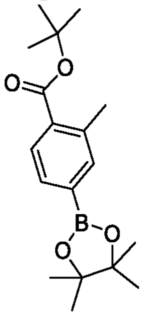


Example 11 (16 mg, 29%) was prepared in a manner similar to that in Example 1 step 10 from (S)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N, 2-dimethylbenzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.35 (s, 1 H), 8.88 (s, 1 H), 8.47 (s, 1 H), 8.28-8.17 (m, 2 H), 7.90 (s, 1 H), 7.77 (s, 1 H), 7.29-7.23 (m, 1 H), 4.83-4.77 (m, 1 H), 4.03-3.97 (m, 1 H), 3.78 (s, 2 H), 3.58-3.49 (m, 1H), 3.43-3.33 (m, 2 H), 3.20-3.02 (m, 2 H), 2.91-2.79 (m, 6 H), 2.35-2.28 (m, 6 H), 1.18-0.83 (m, 3 H). LC-MS $(M+H)^+ = 484.5$.

Example 12: (S)-N- (2-hydroxypropyl)-4- (2- (5-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, 2-dimethylbenzamide

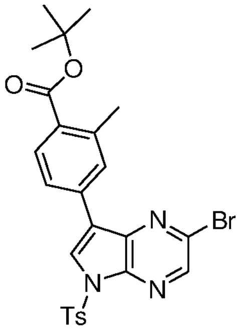


Step 1: tert-butyl 2-methyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzoate



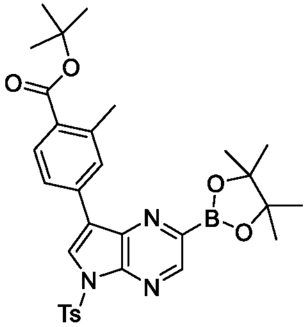
The title compound (1.1 g, 81%) was prepared in a manner similar to that in Example 3 step 5 from tert-butyl 4-bromo-2-methylbenzoate and BPD. LC-MS (M-*t*-Bu)$^+$ = 263.2.

Step 2: tert-butyl 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylbenzoate



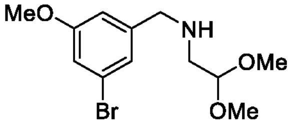
The title compound (1123 mg, 72%) was prepared in a manner similar to that in Example 1 step 2 from 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine and tert-butyl 2-methyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzoate. LC-MS (M+H)$^+$ = 542.1.

Step 3: tert-butyl 2-methyl-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzoate



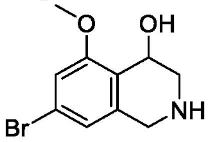
The title compound (136 mg, 76%) was prepared in a manner similar to that in Example 1 step 3 from tert-butyl 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylbenzoate and BPD. LC-MS (M-pin)$^+$ = 508.3.

Step 4: N- (3-bromo-5-methoxybenzyl)-2, 2-dimethoxyethanamine



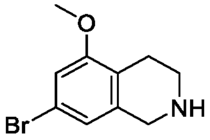
To a solution of 2, 2-dimethoxyethanamine (1.09 g, 10.4 mmol) in toluene (15 mL) was added 3-bromo-5-methoxybenzaldehyde (2.04 g, 9.50 mmol) at room temperature. The resulting mixture was stirred for 15 h at 120 °C under nitrogen atmosphere then cooled down to room temperature. The reaction mixture was concentrated under reduced pressure then re-dissolved in MeOH (15 mL). The mixture was cooled in ice bath and to which was added $NaBH_4$ (4.18 mg, 110 mmol) in portions within 10 min. The resulting mixture was warmed to room temperature. After 5 h, the reaction was quenched with ice water (20 mL). The resulting mixture was extracted with ethyl acetate (50 mL x 3). The organic phases were combined, washed with brine and dried over Na_2SO_4. The solvent was concentrated under reduced pressure to give the title compound (2.80 g, crude). LCMS $(M+H)^+ = 304.4$.

Step 5: 7-bromo-5-methoxy-1, 2, 3, 4-tetrahydroisoquinolin-4-ol



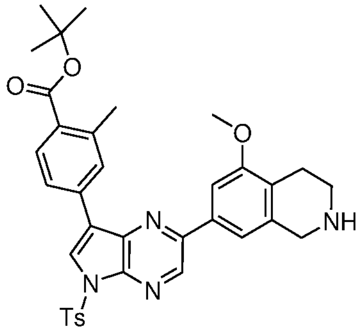
A mixture of N- (3-bromo-5-methoxybenzyl)-2, 2-dimethoxyethanamine (2.80 g, from step 4) in HCl (6 M, 6.0 mL) was stirred for 16 h at 40 °C. The mixture cooled down to room temperature and concentrated under reduced pressure. The residue was purified by prep-HPLC to provide the title compound (108 mg, 5% over 2 steps). LCMS $(M+H)^+ = 258.1$.

Step 6: 7-bromo-5-methoxy-1, 2, 3, 4-tetrahydroisoquinoline



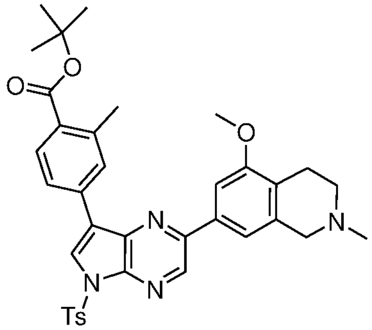
To a stirred mixture of 7-bromo-5-methoxy-1, 2, 3, 4-tetrahydroisoquinolin-4-ol (100 mg, 0.38 mmol) and triethylsilane (1.00 mL, 8.6 mmol) in DCM (5 mL) was added TFA (0.50 mL, 4.4 mmol) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 48 h at 40 °C. The reaction mixture was cooled down to room temperature and concentrated under reduced pressure. The crude was partitioned between EtOAc (30 mL) and saturated $NaHCO_3$ (30 mL). The combined organic layer was separated, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by C18 chromatography, eluted with MeCN in 0.05% aqueous NH_4HCO_3 solution (45 % to 70 %) to give the title compound (75 mg, 81%). ^1H NMR (400 MHz, DMSO-*d6*) δ 6.92 (d, $J = 1.9$ Hz, 1 H), 6.84 (d, $J = 1.9$ Hz, 1 H), 3.82-3.74 (m, 5 H), 2.90 (t, $J = 6.0$ Hz, 2 H), 2.77 (s, 1 H), 2.43 (t, $J = 6.0$ Hz, 2 H). LCMS $(M+H)^+ = 242.1$.

Step 7: tert-butyl 4- (2- (5-methoxy-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylbenzoate



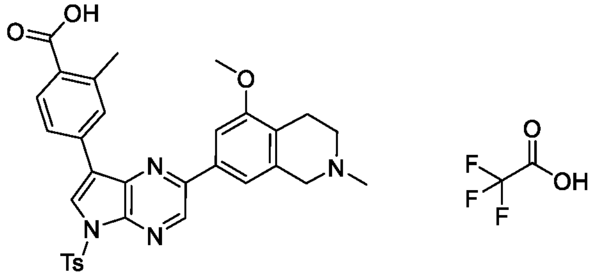
The title compound (50 mg, 49%) was prepared in a manner similar to that in Example 1 step 9 from tert-butyl 2-methyl-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzoate and 7-bromo-5-methoxy-1, 2, 3, 4-tetrahydroisoquinoline. LC-MS (M+H)$^+$ = 625.4.

Step 8: tert-butyl 4- (2- (5-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylbenzoate



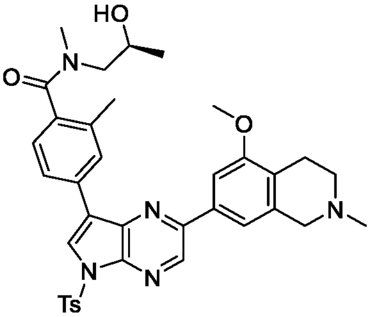
The title compound (43 mg, 47%) was prepared in a manner similar to that in Example 6 step 9 from tert-butyl 4- (2- (5-methoxy-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylbenzoate and formalin. LC-MS (M+H)$^+$ = 639.4.

Step 9: 4- (2- (5-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylbenzoic acid; trifluoroacetic acid



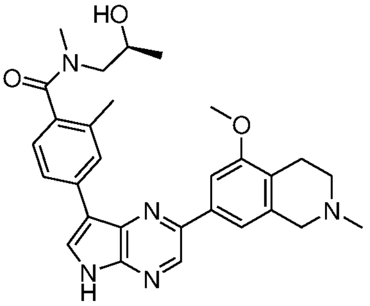
To a solution of tert-butyl 4- (2- (5-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylbenzoate (51 mg, 0.076 mmol, 1.00 equiv, 95%) in DCM (2 mL) was added TFA (2 mL) at 0 °C. The reaction mixture was stirred for 1.5 h at room temperature then concentrated under reduced pressure to provide the title compound (37 mg, 70%). LC-MS (M+H)$^+$ = 583.3.

Step 10: (S)-N- (2-hydroxypropyl)-4- (2- (5-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, 2-dimethylbenzamide



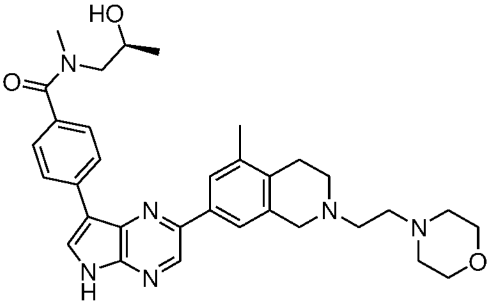
The title compound (33 mg, 89%) was prepared in a manner similar to that in Example 3 step 1 from 4- (2- (5-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylbenzoic acid; trifluoroacetic acid and (S)-1-(methylamino)propan-2-ol. LC-MS $(M+H)^+$ = 654.4.

Step 11: (S)-N- (2-hydroxypropyl)-4- (2- (5-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, 2-dimethylbenzamide

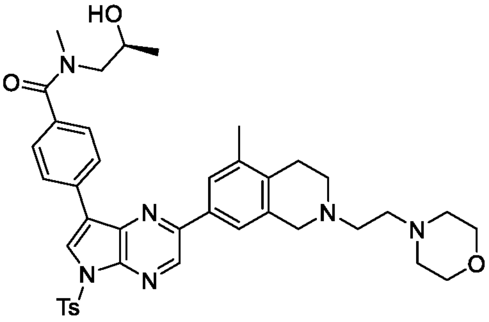


Example 12 (13 mg, 43%) was prepared in a manner similar to that in Example 1 step 10 from (S)-N- (2-hydroxypropyl)-4- (2- (5-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, 2-dimethylbenzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.36 (s, 1 H), 8.95 (d, *J* = 1.6 Hz, 1 H), 8.48 (d, *J* = 2.6 Hz, 1 H), 8.36 (d, *J* = 6.6 Hz, 1 H), 8.20-8.10 (m, 1 H), 7.68 (s, 1 H), 7.54 (s, 1 H), 7.24 (d, *J* = 8.0 Hz, 1 H), 4.84-4.79 (m, 1 H), 4.06-3.72 (m, 4 H), 3.64-3.48 (m, 3 H), 3.17-3.00 (m, 2 H), 2.88 (s, 2 H), 2.76-2.68 (m, 2 H), 2.67-2.60 (m, 2 H), 2.38 (s, 3 H), 2.34-2.26 (m, 3 H), 1.18-0.83 (m, 3 H). LC-MS $(M+H)^+$ = 500.5.

Example 13: (S)-N- (2-hydroxypropyl)-N-methyl-4- (2- (5-methyl-2- (2-morpholinoethyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide

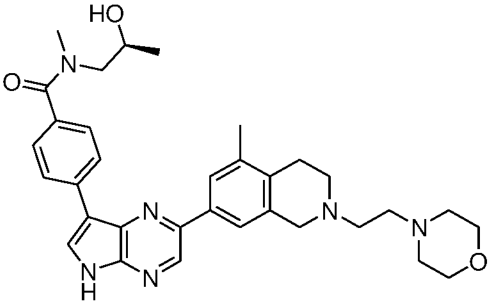


Step 1: (S)-N- (2-hydroxypropyl)-N-methyl-4- (2- (5-methyl-2- (2-morpholinoethyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



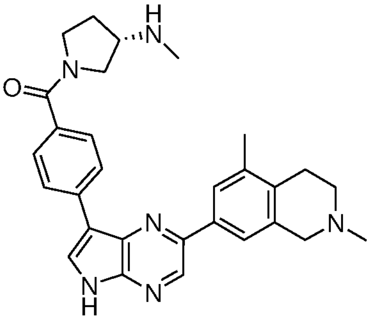
The title compound (64 mg, 43%) was prepared in a manner similar to that in Example 2 step 5 from 4- (2- (5-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-3, 4-dihydroisoquinolin-2 (1H)-yl)ethyl)morpholine and (S)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxypropyl)-N-methylbenzamide. LC-MS $(M+H)^+ = 723.4$.

Step 2: (S)-N- (2-hydroxypropyl)-N-methyl-4- (2- (5-methyl-2- (2-morpholinoethyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide

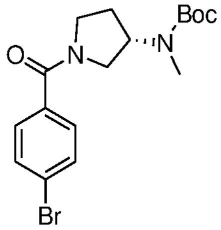


Example 13 (17 mg, 36%) was prepared in a manner similar to that in Example 1 step 10 from (S)-N- (2-hydroxypropyl)-N-methyl-4- (2- (5-methyl-2- (2-morpholinoethyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.39 (s, 1 H), 8.88 (s, 1 H), 8.51 (s, 1 H), 8.38 (s, 2 H), 7.85 (s, 1 H), 7.74 (s, 1 H), 7.55-7.49 (m, 2 H), 4.85 (s, 1 H), 4.07-3.83 (m, 1 H), 3.71 (s, 2 H), 3.63-3.46 (m, 5 H), 3.22-3.18 (m, 1 H), 3.07-3.00 (m, 3 H), 2.81-2.71 (m, 4 H), 2.67-2.60 (m, 2 H), 2.58-2.52 (m, 2 H), 2.48-2.42 (m, 4 H), 2.31 (s, 3 H), 1.16-0.90 (m, 3 H). LC-MS $(M+H)^+ = 569.3$.

Example 14: (S)- (4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (3- (methylamino)pyrrolidin-1-yl)methanone

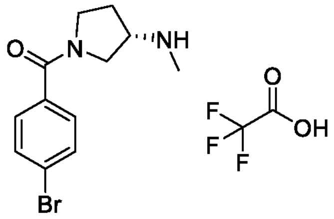


Step 1: (S)-tert-butyl 1- (4-bromobenzoyl)pyrrolidin-3-yl (methyl)carbamate



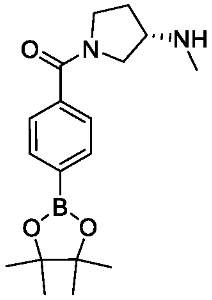
The title compound (1.40 g, 73%) was prepared in a manner similar to that in Example 3 step 1 from (S)-tert-butyl methyl (pyrrolidin-3-yl)carbamate and 4-bromobenzoic acid. LC-MS $(M+H)^+ = 383.2$.

Step 2: (S)- (4-bromophenyl) (3- (methylamino)pyrrolidin-1-yl)methanone; trifluoroacetic acid



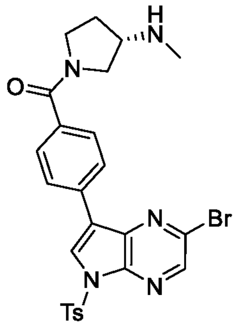
The title compound (1.01 g, 97%) was prepared in a manner similar to that in Example 12 step 9 from (S)-tert-butyl 1- (4-bromobenzoyl)pyrrolidin-3-yl (methyl)carbamate. LC-MS $(M+H)^+ = 283.1$.

Step 3: (S)- (3- (methylamino)pyrrolidin-1-yl) (4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)phenyl)methanone



The title compound (881 mg, 75%) was prepared in a manner similar to that in Example 3 step 5 from (S)- (4-bromophenyl) (3- (methylamino)pyrrolidin-1-yl)methanone; trifluoroacetic acid and BPD. LC-MS $(M+H)^+ = 331.3$.

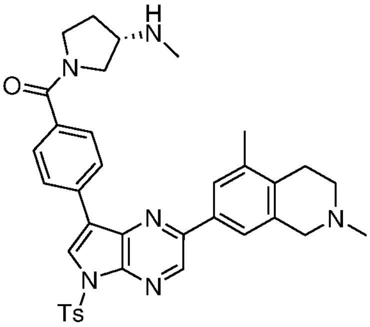
Step 4: (S)- (4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (3- (methylamino)pyrrolidin-1-yl)methanone



The title compound (858 mg, 61%) was prepared in a manner similar to that in Example 1 step 2 from (S)- (3- (methylamino)pyrrolidin-1-yl) (4- (4, 4, 5, 5-tetramethyl-1, 3, 2-

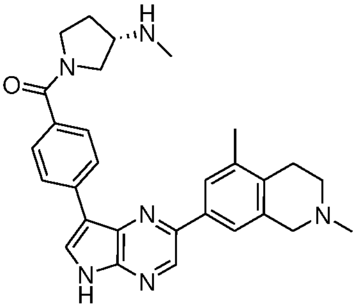
dioxaborolan-2-yl)phenyl)methanone and 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine. LC-MS $(M+H)^+ = 554.3$.

Step 5: (S)- (4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (3- (methylamino)pyrrolidin-1-yl)methanone



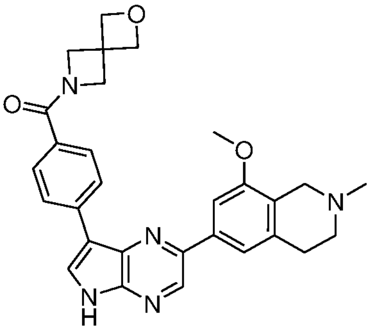
The title compound (167 mg, 73%) was prepared in a manner similar to that in Example 2 step 5 from (S)- (4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (3-(methylamino)pyrrolidin-1-yl)methanone and 2, 5-dimethyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline. LC-MS $(M+H)^+ = 635.5$.

Step 6: (S)- (4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (3- (methylamino)pyrrolidin-1-yl)methanone

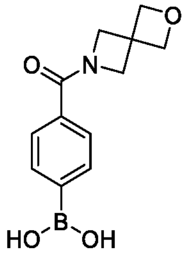


Example 14 (18 mg, 13%) was prepared in a manner similar to that in Example 1 step 10 from (S)- (4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (3- (methylamino)pyrrolidin-1-yl)methanone. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.41 (s, 1 H), 8.88 (s, 1 H), 8.52 (s, 1 H), 8.42-8.36 (m, 2 H), 7.85 (s, 1 H), 7.73 (s, 1 H), 7.66-7.60 (m, 2 H), 3.70-3.55 (m, 4 H), 3.53-3.47 (m, 1 H), 3.27-3.20 (m, 1 H), 3.18-3.12 (m, 1 H), 2.78-2.72 (m, 2 H), 2.71-2.64 (m, 2 H), 2.38 (s, 3 H), 2.36-2.20 (m, 6 H), 2.05-1.93 (m, 1 H), 1.80-1.72 (m, 1 H). LC-MS $(M+H)^+ = 481.4$.

Example 15: (4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone

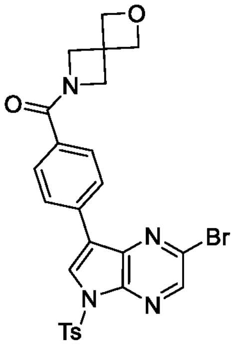


Step 1: (4- (2-oxa-6-azaspiro[3.3]heptane-6-carbonyl)phenyl)boronic acid



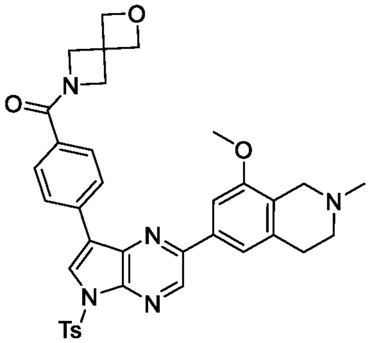
To a solution of 4-boronobenzoic acid (3.32 g, 19.0 mmol) in DMF (20 mL) at 0 °C was added HATU (10.8 g, 28.5 mmol), DIPEA (7.37 g, 57.0 mmol) and 2-oxa-6-azaspiro[3.3]heptane (1.98 g, 19.0 mmol). The resulting mixture was warmed to room temperature. After 16 h, the mixture was concentrated under vacuum then diluted with water (50 mL). The precipitate was collected by filtration and the solid was washed with water (30 mL x 2) to give the title compound (4.7 g, 97%). LC-MS $(M+H)^+ = 248.1$.

Step 2: (4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone



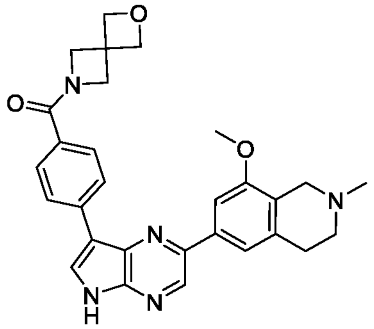
The title compound (350 mg, 76%) was prepared in a manner similar to that in Example 1 step 2 from 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine and (4- (2-oxa-6-azaspiro[3.3]heptane-6-carbonyl)phenyl)boronic acid. LCMS $(M+H)^+ = 553.1$.

Step 3: (4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone



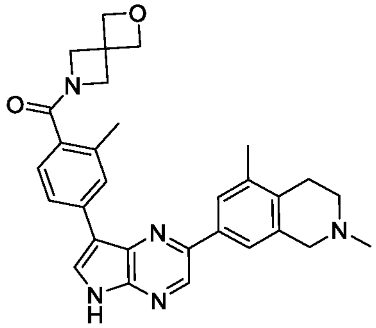
The title compound (74 mg, 34%) was prepared in a manner similar to that in Example 2 step 5 from 8-methoxy-2-methyl-6- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline and (4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone. LC-MS $(M+H)^+ = 650.4$.

Step 4: (4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone

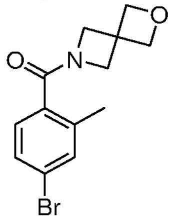


Example 15 (3 mg, 5%) was prepared in a manner similar to that in Example 1 step 10 from (4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.47 (s, 1 H), 8.95 (s, 1 H), 8.56 (s, 1 H), 8.42 (d, *J* = 8.3 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H), 7.62-7.56 (m, 2 H), 4.71 (s, 4 H), 4.56 (s, 2 H), 4.24 (s, 2 H), 3.95 (s, 3 H), 3.50-3.42 (m, 2 H), 2.96-2.90 (m, 2 H), 2.67-2.61 (m, 2 H), 2.41 (s, 3 H). LC-MS $(M+H)^+$ = 496.4.

Example 16: (4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylphenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone

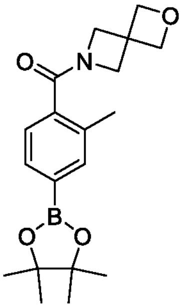


Step 1: 6- (4-bromo-2-methylbenzoyl)-2-oxa-6-azaspiro[3.3]heptane



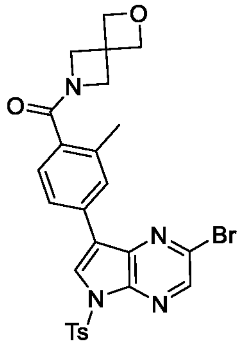
The title compound (250 mg, 78%) was prepared in a manner similar to that in Example 3 step 1 from 4-bromo-2-methylbenzoic acid and 2-oxa-6-azaspiro[3.3]heptane. LCMS $(M+H)^+$ = 296.0.

Step 2: (2-methyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)phenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone



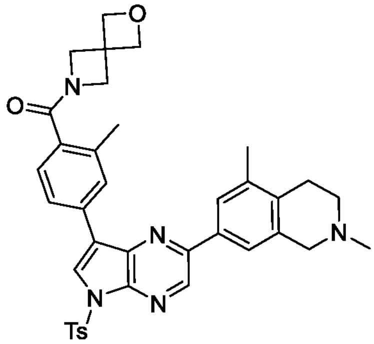
The title compound (200 mg, 67%) was prepared in a manner similar to that in Example 3 step 5 from 6- (4-bromo-2-methylbenzoyl)-2-oxa-6-azaspiro[3.3]heptane and BPD. LCMS $(M+H)^+$ = 344.2.

Step 3: (4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylphenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone



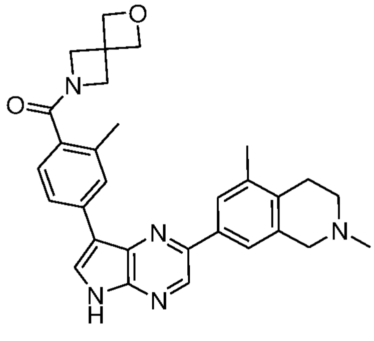
The title compound (185 mg, 67%) was prepared in a manner similar to that in Example 1 step 2 from (2-methyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)phenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone and 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine. LC-MS $(M+H)^+$ = 567.1.

Step 4: (4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylphenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone



The title compound (91 mg, 30%) was prepared in a manner similar to that in Example 2 step 5 from (4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylphenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone and 2, 5-dimethyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline. LC-MS $(M+H)^+$ = 648.3.

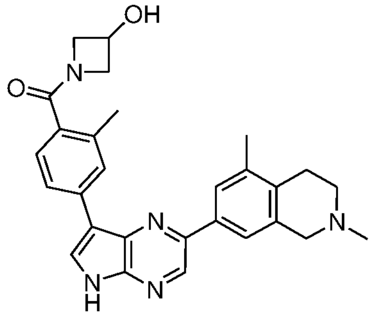
Step 5: (4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylphenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone



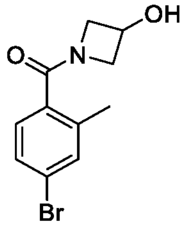
Example 16 (23 mg, 33%) was prepared in a manner similar to that in Example 1 step 10 from (4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-

b]pyrazin-7-yl)-2-methylphenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.36 (s, 1 H), 8.88 (s, 1 H), 8.49 (s, 1 H), 8.27-8.17 (m, 2 H), 7.87 (s, 1 H), 7.73 (s, 1 H), 7.41-7.34 (m, 1 H), 4.74-4.64 (m, 4 H), 4.22 (s, 2 H), 4.16 (s, 2 H), 3.60 (s, 2 H), 2.78-2.72 (m, 2 H), 2.71-2.64 (m, 2 H), 2.42-2.36 (m, 6 H), 2.32 (s, 3 H). LC-MS $(M+H)^+$ = 494.5.

Example 17: (4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylphenyl) (3-hydroxyazetidin-1-yl)methanone

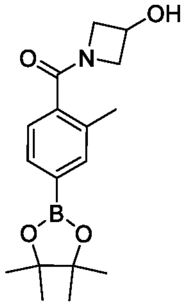


Step 1: (4-bromo-2-methylphenyl) (3-hydroxyazetidin-1-yl)methanone



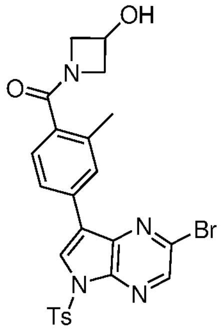
The title compound (750 mg, 61%) was prepared in a manner similar to that in Example 3 step 1 from 4-bromo-2-methylbenzoic acid and azetidin-3-ol hydrochloride. LCMS $(M+H)^+$ = 270.0.

Step 2: (3-hydroxyazetidin-1-yl) (2-methyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)phenyl)methanone



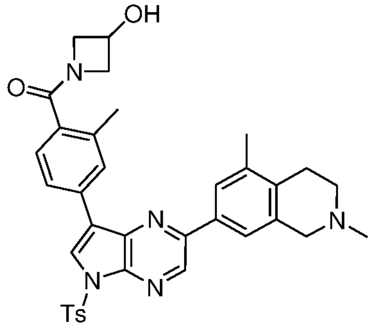
The title compound (150 mg, 37%) was prepared in a manner similar to that in Example 3 step 5 from (4-bromo-2-methylphenyl) (3-hydroxyazetidin-1-yl)methanone and BPD. LCMS $(M+H)^+$ = 318.3.

Step 3: (4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylphenyl) (3-hydroxyazetidin-1-yl)methanone



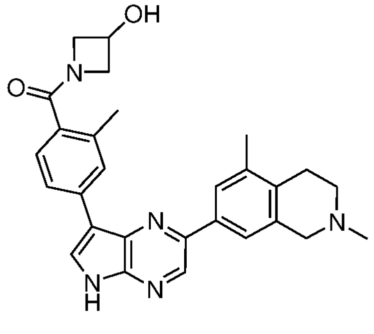
The title compound (854 mg, 75%) was prepared in a manner similar to that in Example 1 step 2 from (3-hydroxyazetidin-1-yl) (2-methyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)phenyl)methanone and 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine. LC-MS $(M+H)^+$ = 541.2.

Step 4: (4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylphenyl) (3-hydroxyazetidin-1-yl)methanone



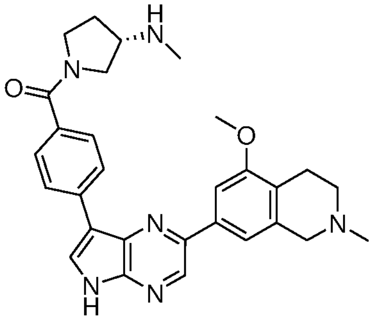
The title compound (60 mg, 36%) was prepared in a manner similar to that in Example 2 step 5 from 2, 5-dimethyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline and (4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylphenyl) (3-hydroxyazetidin-1-yl)methanone. LC-MS $(M+H)^+$ = 622.3.

Step 5: ((4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylphenyl) (3-hydroxyazetidin-1-yl)methanone

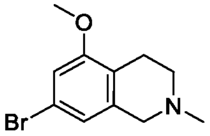


Example 17 (9 mg, 20%) was prepared in a manner similar to that in Example 1 step 10 from (4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-2-methylphenyl) (3-hydroxyazetidin-1-yl)methanone. ^1H NMR (400 MHz, DMSO-*d6*) δ 12.36 (s, 1 H), 8.87 (s, 1 H), 8.48 (s, 1 H), 8.27-8.17 (m, 2 H), 7.87 (s, 1 H), 7.73 (d, *J* = 1.9 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 5.80-5.74 (m, 1 H), 4.54-4.46 (m, 1 H), 4.29-4.20 (m, 1 H), 4.16-4.08 (m, 1 H), 3.82-3.70 (m, 2 H), 3.59 (s, 2 H), 2.79-2.71 (m, 2 H), 2.71-2.64 (m, 2 H), 2.44-2.36 (m, 6 H), 2.31 (s, 3 H). LC-MS $(M+H)^+$ = 468.5.

Example 18: (S)- (4- (2- (5-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (3- (methylamino)pyrrolidin-1-yl)methanone

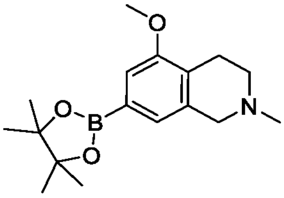


Step 1: 7-bromo-5-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline



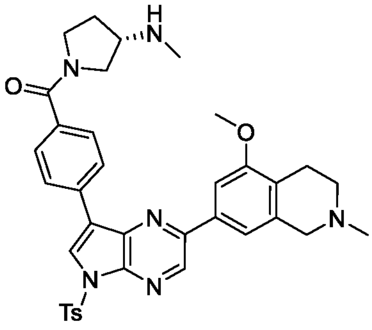
The title compound (600 mg, 99%) was prepared in a manner similar to that in Example 1 step 8 from 7-bromo-5-methoxy-1, 2, 3, 4-tetrahydroisoquinoline. LC-MS $(M+H)^+ = 256.0$.

Step 2: 5-methoxy-2-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline



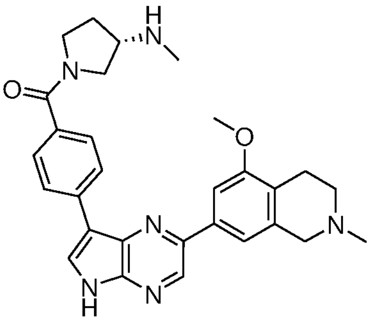
The title compound (705 mg, 99%) was prepared in a manner similar to that in Example 2 step 4 from 7-bromo-5-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline. LC-MS $(M+H)^+ =$ 304.2.

Step 3: (S)- (4- (2- (5-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (3- (methylamino)pyrrolidin-1-yl)methanone



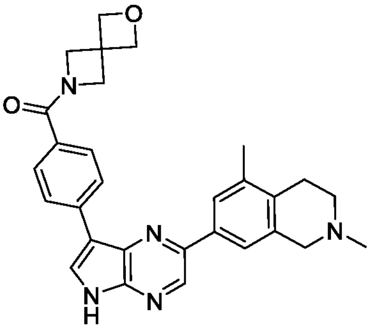
The title compound (62 mg, 24%) was prepared in a manner similar to that in Example 2 step 5 from (S)- (4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (3-(methylamino)pyrrolidin-1-yl)methanone and 5-methoxy-2-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline. LC-MS $(M+H)^+ = 651.6$.

Step 4: (S)- (4- (2- (5-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (3- (methylamino)pyrrolidin-1-yl)methanone

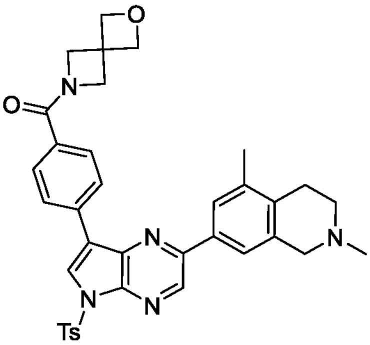


Example 18 (9 mg, 13%) was prepared in a manner similar to that in Example 1 step 10 from (S)- (4- (2- (5-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (3- (methylamino)pyrrolidin-1-yl)methanone. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.42 (s, 1 H), 8.94 (s, 1 H), 8.53 (s, 1 H), 8.44-8.37 (m, 2 H), 7.65-7.55 (m, 4 H), 3.94 (s, 3 H), 3.67-3.55 (m, 2 H), 3.54-3.42 (m, 3 H), 3.30-3.07 (m, 2 H), 2.96-2.89 (m, 2 H), 2.64-2.57 (m, 2 H), 2.39 (s, 3 H), 2.33-2.16 (m, 3 H), 2.05-1.88 (m, 1 H), 1.80-1.66 (m, 1 H). LC-MS $(M+H)^+$ = 497.5.

Example 19: (4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone

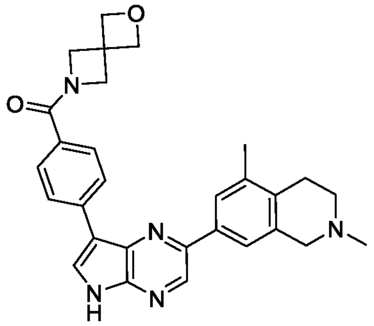


Step 1: (4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone



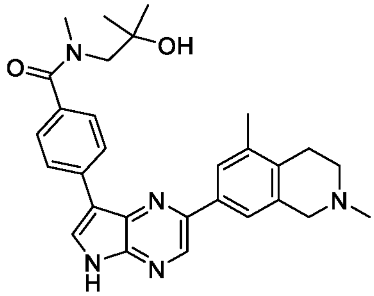
The title compound (78 mg, 56%) was prepared in a manner similar to that in Example 2 step 5 from (4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone and 2, 5-dimethyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline. LC-MS $(M+H)^+$ = 634.5.

Step 2: (4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone

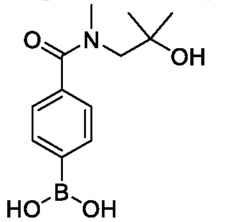


Example 19 (8 mg, 10%) was prepared in a manner similar to that in Example 1 step 10 from (4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)phenyl) (2-oxa-6-azaspiro[3.3]heptan-6-yl)methanone. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.44 (s, 1 H), 8.88 (s, 1 H), 8.55 (s, 1 H), 8.44-8.38 (m, 2 H), 7.85 (s, 1 H), 7.76-7.70 (m, 3 H), 4.71 (s, 4 H), 4.57 (s, 2 H), 4.24 (s, 2 H), 3.62 (s, 2 H), 2.78-2.73 (m, 2 H), 2.73-2.67 (m, 2 H), 2.40 (s, 3 H), 2.32 (s, 3 H). LC-MS $(M+H)^+ = 480.4$.

Example 20: 4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxy-2-methylpropyl)-N-methylbenzamide

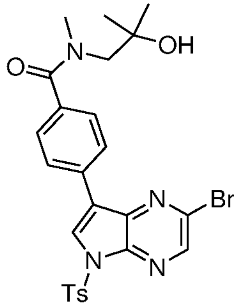


Step 1: 4- ((2-hydroxy-2-methylpropyl) (methyl)carbamoyl)phenylboronic acid



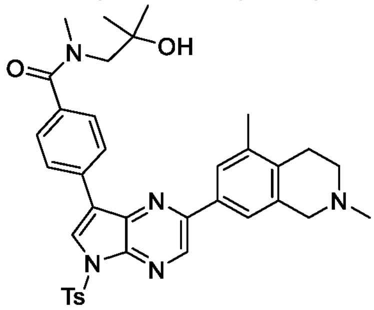
The title compound (415 mg, 45%) was prepared in a manner similar to that in Example 15 step 1 from 2-methyl-1- (methylamino)propan-2-ol and 4-boronobenzoic acid. LC-MS $(M+H)^+ = 252.2$.

Step 2: 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxy-2-methylpropyl)-N-methylbenzamide



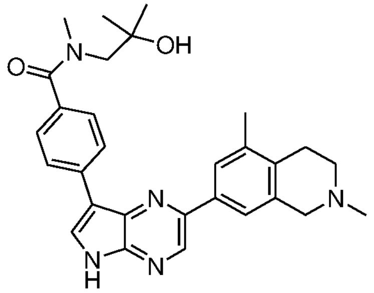
The title compound (241 mg, 32%) was prepared in a manner similar to that in Example 1 step 1 from 4- ((2-hydroxy-2-methylpropyl) (methyl)carbamoyl)phenylboronic acid and 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine. LC-MS $(M+H)^+$ = 557.2.

Step 3: 4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxy-2-methylpropyl)-N-methylbenzamide



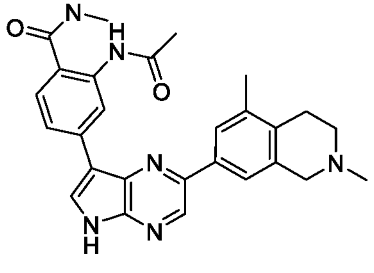
The title compound (190 mg, 81%) was prepared in a manner similar to that in Example 2 step 5 from 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxy-2-methylpropyl)-N-methylbenzamide and 2, 5-dimethyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline. LC-MS $(M+H)^+$ = 638.4.

Step 4: 4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxy-2-methylpropyl)-N-methylbenzamide

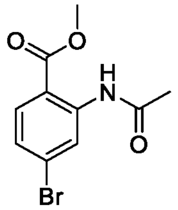


Example 20 (34 mg, 29%) was prepared in a manner similar to that in Example 1 step 10 from 4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxy-2-methylpropyl)-N-methylbenzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.39 (s, 1 H), 8.87 (s, 1 H), 8.51 (s, 1 H), 8.43-8.36 (m, 2 H), 7.85 (s, 1 H), 7.74 (s, 1 H), 7.56-7.42 (m, 2 H), 4.70-4.52 (m, 1 H), 3.60 (s, 2 H), 3.49 (s, 2 H), 3.10 (s, 3 H), 2.77-2.71 (m, 2 H), 2.71-2.63 (m, 2 H), 2.38 (s, 3 H), 2.31 (s, 3 H), 1.25-0.92 (m, 6 H). LC-MS $(M+H)^+$ = 484.4.

Example 21: 2-acetamido-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide

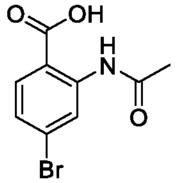


Step 1: methyl 2-acetamido-4-bromobenzoate



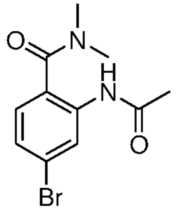
The title compound (980 mg, 87%) was prepared in a manner similar to that in Example 3 step 1 from methyl 2-amino-4-bromobenzoate and AcOH. LC-MS $(M+H)^+ = 272.0$.

Step 2: 2-acetamido-4-bromobenzoic acid



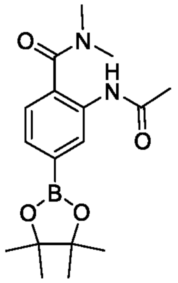
To a solution of methyl 2-acetamido-4-bromobenzoate (980 mg, 3.6 mmol) in THF (10 mL) and water (10 mL) was added LiOH monohydrate (302 mg, 7.2 mmol) at room temperature. After 16 h, THF was evaporated under reduced pressure and the reaction mixture was acidified by HCl (1 M) until pH=1. The solid was collected by filtration and washed with water (20 mL) to give the title compound (850 mg, 92%). LC-MS $(M+H)^+ = 258.0$.

Step 3: 2-acetamido-4-bromo-N, N-dimethylbenzamide



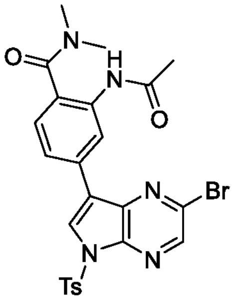
The title compound (325 mg, 76 %) was prepared in a manner similar to that in Example 3 step 1 from 2-acetamido-4-bromobenzoic acid and dimethylamine hydrochloride. LC-MS $(M+H)^+ = 285.1$.

Step 4: 2-acetamido-N, N-dimethyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide



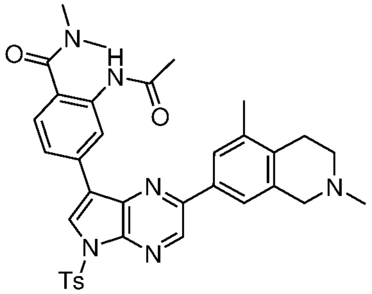
The title compound (209 mg, 60%) was prepared in a manner similar to that in Example 3 step 5 from 2-acetamido-4-bromo-N, N-dimethylbenzamide and BPD. LC-MS $(M+H)^+ = 333.3$.

Step 5: 2-acetamido-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide



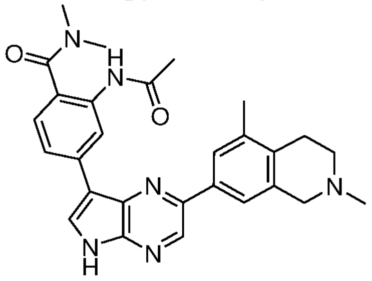
The title compound (199 mg, 81%) was prepared in a manner similar to that in Example 1 step 2 from 2-acetamido-N, N-dimethyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide and 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine. LC-MS $(M+H)^+$ = 556.1.

Step 6: 2-acetamido-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide



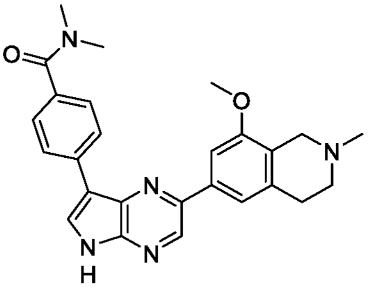
The title compound (125 mg, 57%) was prepared in a manner similar to that in Example 2 step 5 from 2-acetamido-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide and 2, 5-dimethyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline. LC-MS $(M+H)^+$ = 637.4.

Step 7: 2-acetamido-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide

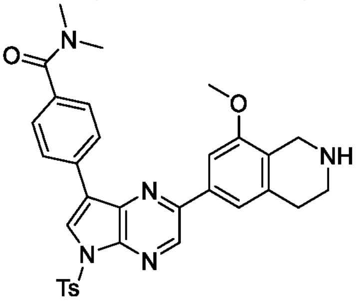


Example 21 (25 mg, 27%) was prepared as similar method to Example 1 step 10 from 2-acetamido-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.36 (s, 1 H), 9.60 (s, 1 H), 9.08 (s, 1 H), 8.92 (s, 1 H), 8.48 (s, 1 H), 8.00 (s, 1 H), 7.97-7.90 (m, 2 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 3.64 (s, 2 H), 3.06-2.86 (m, 6 H), 2.78-2.65 (m, 4 H), 2.39 (s, 3 H), 2.33 (s, 3 H), 2.11 (s, 3 H). LC-MS $(M+H)^+$ = 483.4.

Example 22: 4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide

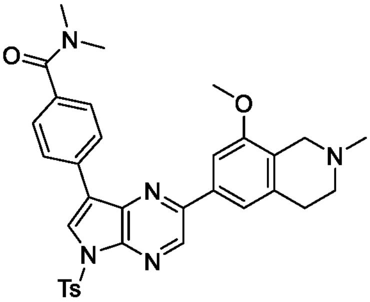


Step 1: 4- (2- (8-methoxy-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide



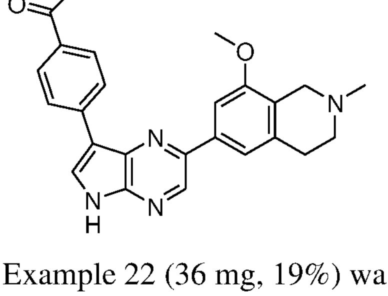
The title compound (390 mg, 65%) was prepared in a manner similar to that in Example 1 step 9 from N, N-dimethyl-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide and 6-bromo-8-methoxy-1, 2, 3, 4-tetrahydroisoquinoline; trifluoroacetic acid. LC-MS $(M+H)^+ = 582.5$.

Step 2: 4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide



The title compound (290 mg, 89%) was prepared in a manner similar to that in Example 6 step 9 from 4- (2- (8-methoxy-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide and formalin. LC-MS $(M+H)^+ = 596.3$.

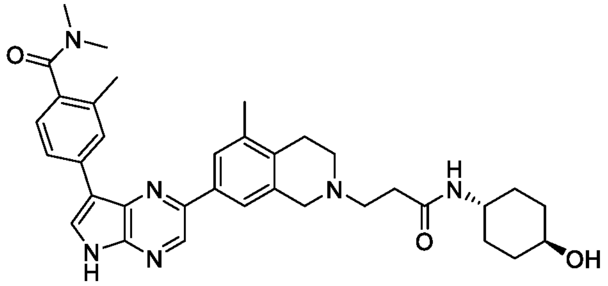
Step 3: 4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide



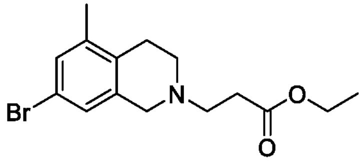
Example 22 (36 mg, 19%) was prepared in a manner similar to that in Example 1 step 10 from 4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-

b]pyrazin-7-yl)-N, N-dimethylbenzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.41 (s, 1 H), 8.94 (s, 1 H), 8.52 (s, 1 H), 8.44-8.37 (m, 2 H), 7.63-7.55 (m, 2 H), 7.55-7.48 (m, 2 H), 3.94 (s, 3 H), 3.46 (s, 2 H), 3.00 (s, 6 H), 2.93 (t, *J* = 5.8 Hz, 2 H), 2.62 (t, *J* = 5.7 Hz, 2 H), 2.40 (s, 3 H). LC-MS $(M+H)^+$ = 442.3.

Example 23: 4- (2- (2- (3- ((trans-4-hydroxycyclohexyl)amino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

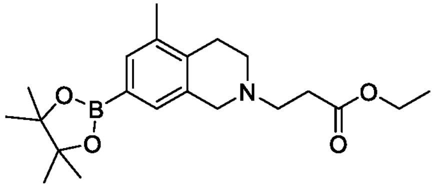


Step 1: ethyl 3- (7-bromo-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoate



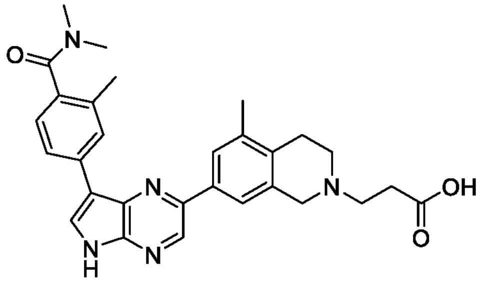
To a 100 mL sealed tube was added 7-bromo-5-methyl-1, 2, 3, 4-tetrahydroisoquinoline (4.5 g, 20 mmol), ethyl acrylate (6.0 g, 60 mmol) and EtOH (30 mL). The mixture was stirred at 50 °C overnight. The mixture was concentrated under vacuum to give the title compound (6.5 g, 99%). LC-MS $(M+H)^+$ = 325.9, 327.9.

Step 2: ethyl 3- (5-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoate



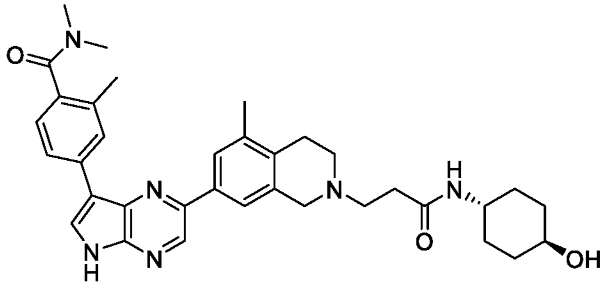
To a solution of ethyl 3- (7-bromo-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoate (6.5 g, 20 mmol) and BPD (6.0 g, 24 mmol) in 1, 4-dioxane (100 mL) was added KOAc (7.0 g, 71 mmol) and Pd $(dppf)Cl_2$ (730 mg, 1.0 mmol) under N_2. The mixture was stirred at 90 °C overnight. The mixture was cooled and diluted with water (100 mL) then extracted with EtOAc (100 mL x 3). The combined organic phase was washed with brine, dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (1:3) to give the title compound (6.5 g, 87%). LC-MS $(M+H)^+$ =374.1.

Step 3: 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid



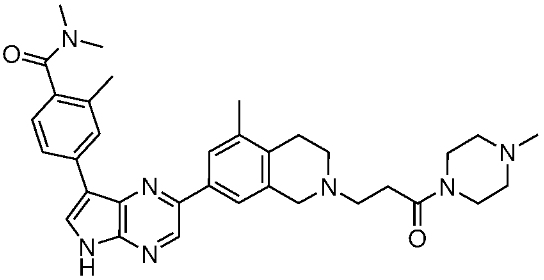
To a solution of ethyl 3- (5-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoate (3.2 g, 8.6 mmol) 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide (4.3 g, 8.3 mmol) in 1, 4-dioxane (100 mL) and water (50 mL) was added K_2CO_3 (3.5 g, 25.4 mmol) and Pd (dppf)Cl_2 (310 mg, 0.40 mmol). The mixture was stirred at 100 °C overnight. The mixture was cooled and diluted with water (50 mL). Solid was filtered off and the mixture was neutralized with HCl (2 M) to pH 6. The precipitate was collected by filtration to give the title compound (4.2 g, 99%). LC-MS $(M+H)^+$ = 498.0.

Step 4: 4- (2- (2- (3- ((trans-4-hydroxycyclohexyl)amino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

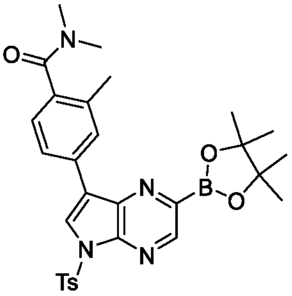


To a solution of 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid (100 mg, 0.20 mmol) and trans-4-aminocyclohexan-1-ol (35 mg, 0.30 mmol) in DMF (2 mL) was added Et_3N (100 mg, 1.0 mmol) and HATU (110 mg, 0.30 mmol). The mixture was stirred at room temperature for 2 h. The mixture was diluted with water (10 mL), extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by prep-TLC, developed with DCM/MeOH/25% aqueous NH_3 (100/10/0.5) to give Example 23 (40 mg, 33%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.34 (d, *J* = 2.6 Hz, 1H), 8.86 (s, 1H), 8.46 (d, *J* = 2.8 Hz, 1H), 8.25 – 8.20 (m, 2H), 7.86 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.73 (s, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 4.50 (d, *J* = 4.4 Hz, 1H), 3.68 (brs, 2H), 3.46 (brs, 1H), 3.03 (s, 3H), 2.83 (s, 3H), 2.73 (brs, 6H), 2.38 – 2.28 (m, 9H), 1.81 – 1.69 (m, 4H), 1.20 – 1.10 (m, 4H). LC-MS $(M+H)^+$ = 595.5.

Example 24: N, N, 2-trimethyl-4- (2- (5-methyl-2- (3- (4-methylpiperazin-1-yl)-3-oxopropyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide

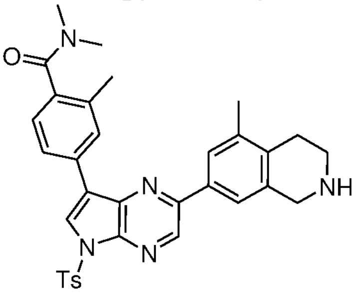


Step 1: N, N, 2-trimethyl-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



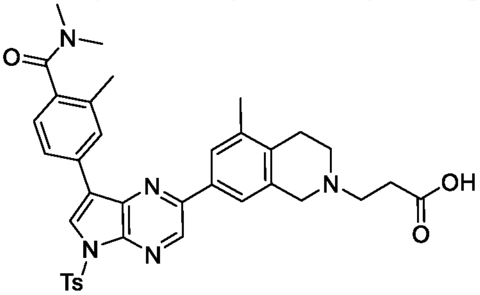
The title compound (2.3 mg, 97%) was prepared in a manner similar to that in Example 1 step 3 from 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide and BPD. LCMS $(M\text{-pin})^+ = 479.1$.

Step 2: N, N, 2-trimethyl-4- (2- (5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



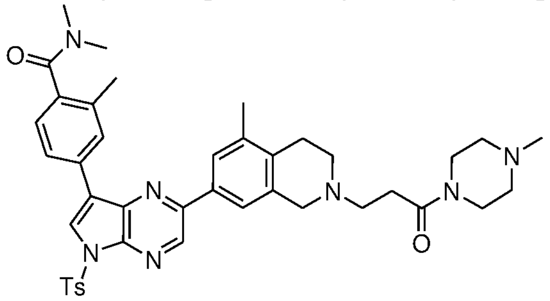
The title compound (1.21 g, 58%) was prepared in a manner similar to that in Example 1 step 9 from N, N, 2-trimethyl-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide and 7-bromo-5-methyl-1, 2, 3, 4-tetrahydroisoquinoline. LC-MS $(M+H)^+ = 580.3$.

Step 3: 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid



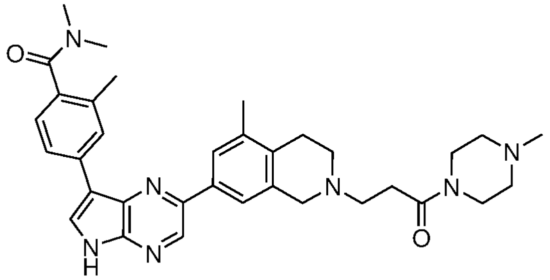
To a mixture of N, N, 2-trimethyl-4-[2- (5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-(4-methylbenzenesulfonyl)pyrrolo[2, 3-b]pyrazin-7-yl]benzamide (1.30 g, 2.08 mmol), KI (364 mg, 2.08 mmol) and Et_3N (666 mg, 6.25 mmol) in DMF (15 mL) was added 3-bromopropionic acid (537 mg, 3.33 mmol) in portions at room temperature. The resulting mixture was stirred for 3 h then diluted with water (20 mL). The precipitate was collected by filtration and washed with water (10 mL x 3) to give the title compound (1.35 g, 90%). LC-MS $(M+H)^+ = 652.2$.

Step 4: N, N, 2-trimethyl-4- (2- (5-methyl-2- (3- (4-methylpiperazin-1-yl)-3-oxopropyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



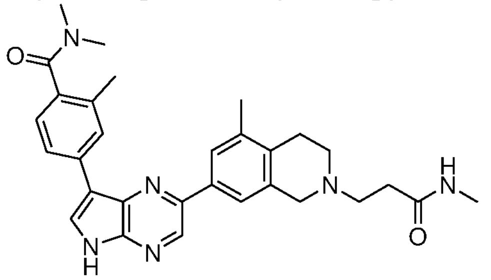
The title compound (79 mg, 51%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and 1-methylpiperazine. LC-MS $(M+H)^+ = 734.3$.

Step 5: N, N, 2-trimethyl-4- (2- (5-methyl-2- (3- (4-methylpiperazin-1-yl)-3-oxopropyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide

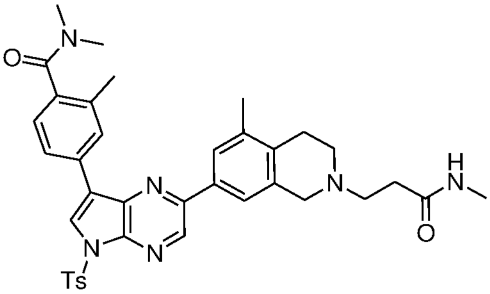


Example 24 (21 mg, 37%) was prepared in a manner similar to that in Example 1 step 10 from N, N, 2-trimethyl-4- (2- (5-methyl-2- (3- (4-methylpiperazin-1-yl)-3-oxopropyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.33 (s, 1 H), 8.86 (s, 1 H), 8.46 (s, 1 H), 8.26-8.18 (m, 2 H), 7.86 (s, 1 H), 7.74 (s, 1 H), 7.25 (d, *J* = 7.8 Hz, 1 H), 3.69 (s, 2 H), 3.52-3.42 (m, 4 H), 3.03 (s, 3 H), 2.83 (s, 3 H), 2.81-2.70 (m, 6 H), 2.65-2.57 (m, 2 H), 2.33-2.26 (m, 8 H), 2.26-2.20 (m, 2 H), 2.17 (s, 3 H). LC-MS $(M+H)^+ = 580.3$.

Example 25: N, N, 2-trimethyl-4- (2- (5-methyl-2- (3- (methylamino)-3-oxopropyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide

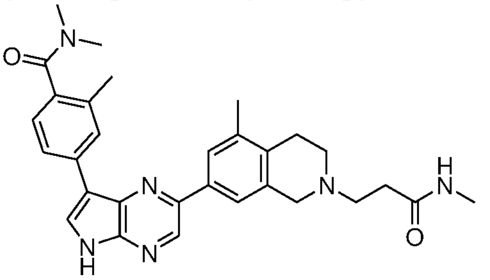


Step 1: N, N, 2-trimethyl-4- (2- (5-methyl-2- (3- (methylamino)-3-oxopropyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)



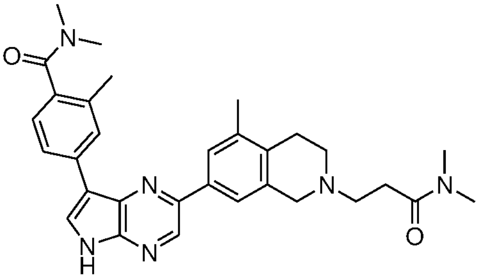
The title compound (92 mg, 45%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and $MeNH_2$. LC-MS $(M+H)^+ = 665.0$.

Step 2: N, N, 2-trimethyl-4- (2- (5-methyl-2- (3- (methylamino)-3-oxopropyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide

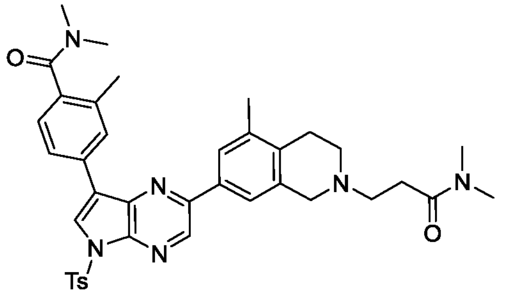


Example 25 (8 mg, 16%) was prepared in a manner similar to that in Example 1 step 10 from N, N, 2-trimethyl-4- (2- (5-methyl-2- (3- (methylamino)-3-oxopropyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide. ^1H NMR (400 MHz, DMSO-*d6*) δ 12.34 (s, 1 H), 8.87 (s, 1 H), 8.46 (s, 1 H), 8.27-8.18 (m, 2 H), 7.89-7.83 (m, 2 H), 7.74 (s, 1 H), 7.25 (d, *J* = 7.7 Hz, 1 H), 3.68 (s, 2 H), 3.03 (s, 3 H), 2.84 (s, 3 H), 2.77-2.69 (m, 6 H), 2.58 (d, *J* = 4.6 Hz, 3 H), 2.37 (t, *J* = 7.2 Hz, 2 H), 2.33-2.28 (m, 6 H). LC-MS $(M+H)^+ = 511.0$.

Example 26: 4- (2- (2- (3- (dimethylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

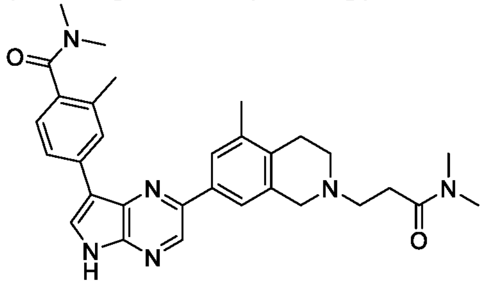


Step 1: 4- (2- (2- (3- (dimethylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide



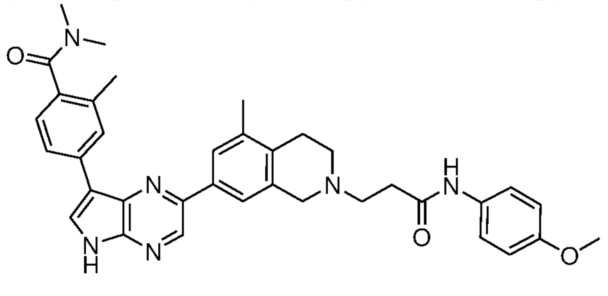
The title compound (75 mg, 41%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and Me_2NH hydrochloride. LC-MS $(M+H)^+ = 679.0$.

Step 2: 4- (2- (2- (3- (dimethylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

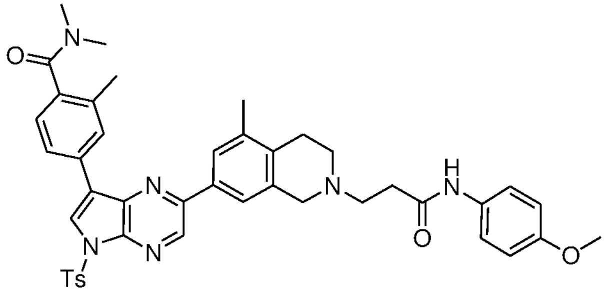


Example 26 (10 mg, 12%) was prepared in a manner similar to that in Example 1 step 10 from 4- (2- (2- (3- (dimethylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide. ^1H NMR (400 MHz, DMSO-*d6*) δ 12.33 (s, 1 H), 8.87 (s, 1 H), 8.46 (s, 1 H), 8.26-8.18 (m, 2 H), 7.86 (s, 1 H), 7.74 (s, 1 H), 7.25 (d, *J* = 7.9 Hz, 1 H), 3.70 (s, 2 H), 3.06-2.99 (m, 6 H), 2.86-2.81 (m, 6 H), 2.80-2.70 (m, 6 H), 2.64-2.56 (m, 2 H), 2.37-2.28 (m, 6 H). LC-MS $(M+H)^+ = 525.0$.

Example 27: 4- (2- (2- (3- (4-methoxyphenylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

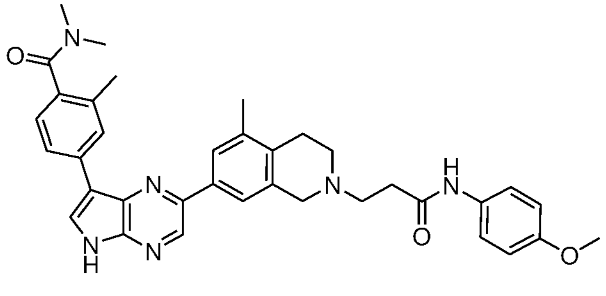


Step 1: 4- (2- (2- (3- (4-methoxyphenylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide



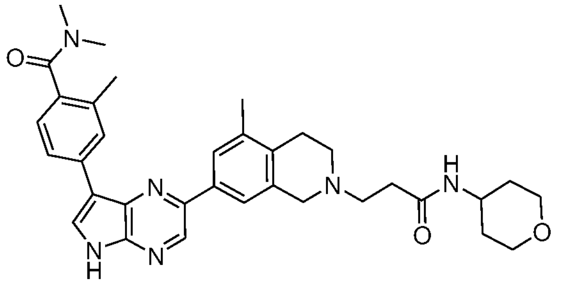
The title compound (103 mg, 54%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and 4-methoxybenzenamine. LC-MS $(M+H)^+ = 757.3$.

Step 2: 4- (2- (2- (3- (4-methoxyphenylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

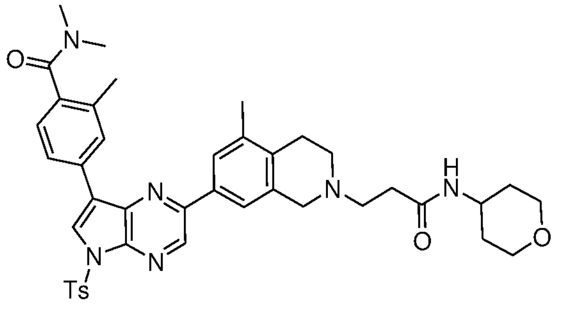


Example 27 (35 mg, 42%) was prepared in a manner similar to that in Example 1 step 10 from 4- (2- (2- (3- (4-methoxyphenylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.34 (s, 1 H), 9.92 (s, 1 H), 8.87 (s, 1 H), 8.46 (d, *J* = 2.9 Hz, 1 H), 8.25-8.19 (m, 2 H), 7.87 (s, 1 H), 7.75 (s, 1 H), 7.53-7.45 (m, 2 H), 7.25 (d, *J* = 8.4 Hz, 1 H), 6.90-6.81 (m, 2 H), 3.74 (s, 2 H), 3.70 (s, 3 H), 3.03 (s, 3 H), 2.88-2.78 (m, 7 H), 2.78-2.70 (m, 2 H), 2.62-2.54 (m, 2 H), 2.34-2.27 (m, 6 H). LC-MS $(M+H)^+ = 603.5$.

Example 28: N, N, 2-trimethyl-4- (2- (5-methyl-2- (3-oxo-3- (tetrahydro-2H-pyran-4-ylamino)propyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



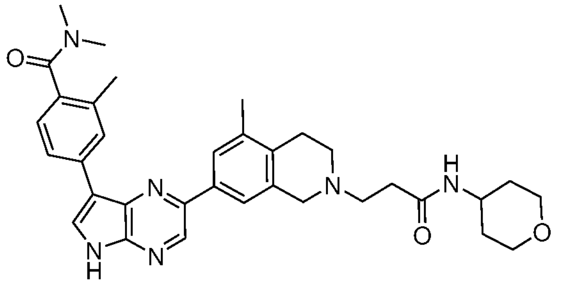
Step 1: N, N, 2-trimethyl-4- (2- (5-methyl-2- (3-oxo-3- (tetrahydro-2H-pyran-4-ylamino)propyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



The title compound (107 mg, 47%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5-tosyl-5H-pyrrolo[2, 3-

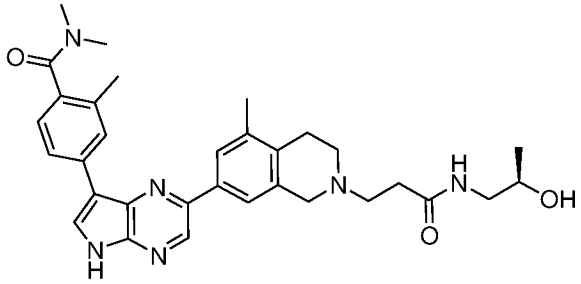
b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and tetrahydro-2H-pyran-4-amine. LC-MS $(M+H)^+ = 735.3$.

Step 2: N, N, 2-trimethyl-4- (2- (5-methyl-2- (3-oxo-3- (tetrahydro-2H-pyran-4-ylamino)propyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide

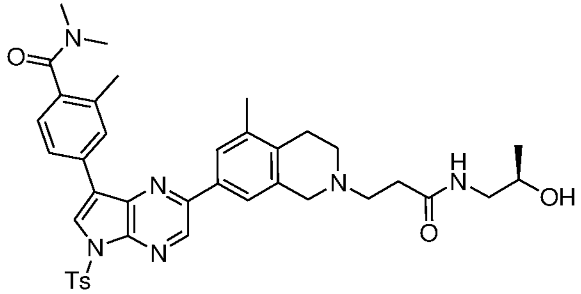


Example 28 (30 mg, 37%) was prepared in a manner similar to that in Example 1 step 10 from N, N, 2-trimethyl-4- (2- (5-methyl-2- (3-oxo-3- (tetrahydro-2H-pyran-4-ylamino)propyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.34 (s, 1 H), 8.87 (s, 1 H), 8.46 (s, 1 H), 8.26-8.19 (m, 2 H), 7.97 (d, *J* = 7.6 Hz, 1 H), 7.86 (s, 1 H), 7.73 (s, 1 H), 7.25 (d, *J* = 8.4 Hz, 1 H), 3.83-3.70 (m, 3 H), 3.69 (s, 2 H), 3.37-3.34 (m, 1 H), 3.32-3.29 (m, 1 H), 3.03 (s, 3 H), 2.84 (s, 3 H), 2.79-2.70 (m, 6 H), 2.41-2.33 (m, 2 H), 2.33-2.27 (m, 6 H), 1.73-1.65 (m, 2 H), 1.43-1.29 (m, 2 H). LC-MS $(M+H)^+ = 581.3$.

Example 29: (R)-4- (2- (2- (3- (2-hydroxypropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

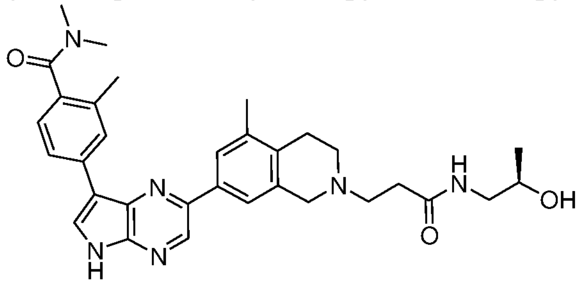


Step 1: (R)-4- (2- (2- (3- (2-hydroxypropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide



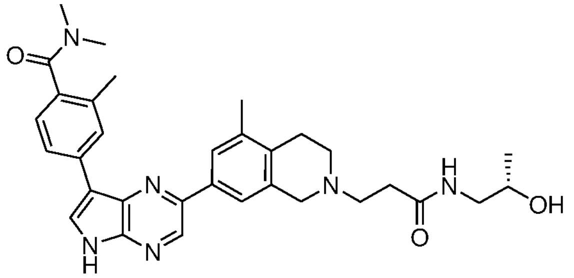
The title compound (69 mg, 48%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and (R)-1-aminopropan-2-ol. LC-MS $(M+H)^+ = 709.4$.

Step 2: (R)-4- (2- (2- (3- (2-hydroxypropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

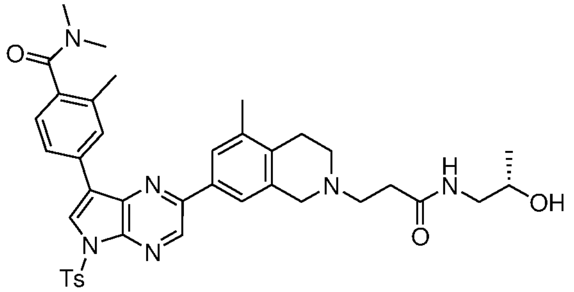


Example 29 (20 mg, 23%) was prepared in a manner similar to that in Example 1 step 10 from (R)-4- (2- (2- (3- (2-hydroxypropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.33 (s, 1 H), 8.86 (s, 1 H), 8.46 (s, 1 H), 8.25-8.19 (m, 2 H), 8.00-7.93 (m, 1 H), 7.86 (s, 1 H), 7.73 (s, 1 H), 7.28-7.19 (m, 1 H), 4.66-4.60 (m, 1 H), 3.68 (s, 2 H), 3.67-3.57 (m, 1 H), 3.05-2.95 (m, 5 H), 2.84 (s, 3 H), 2.80-2.70 (m, 6 H), 2.40 (t, J = 7.2 Hz, 2 H), 2.33-2.27 (m, 6 H), 1.03-0.97 (m, 3 H). LC-MS $(M+H)^+$ = 555.3.

Example 30: (S)-4- (2- (2- (3- (2-hydroxypropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

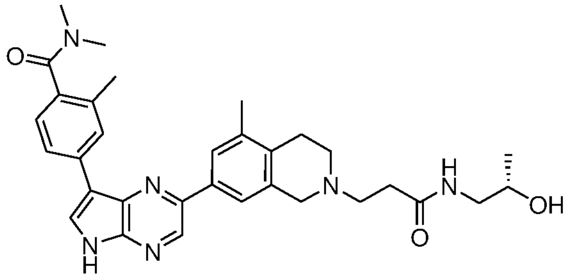


Step 1: (S)-4- (2- (2- (3- (2-hydroxypropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide



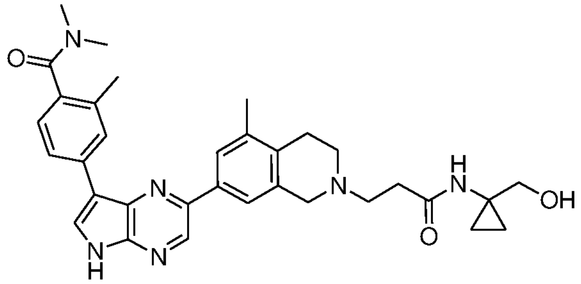
The title compound (74 mg, 54%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and (S)-1-aminopropan-2-ol. LC-MS $(M+H)^+$ = 709.6.

Step 2: (S)-4- (2- (2- (3- (2-hydroxypropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

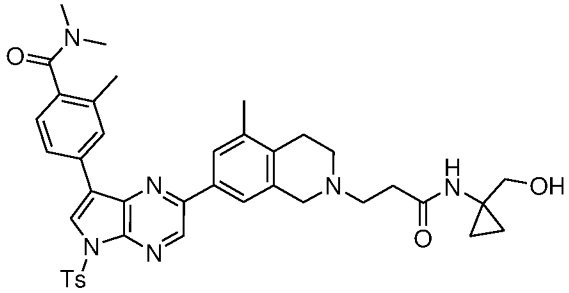


Example 30 (11 mg, 18%) was prepared in a manner similar to that in Example 1 step 10 from (S)-4- (2- (2- (3- (2-hydroxypropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.33 (s, 1 H), 8.86 (s, 1 H), 8.46 (s, 1 H), 8.25-8.19 (m, 2 H), 8.01-7.94 (m, 1 H), 7.86 (s, 1 H), 7.73 (s, 1 H), 7.28-7.22 (m, 1 H), 4.64 (s, 1 H), 3.68 (s, 2 H), 3.67-3.57 (m, 1 H), 3.05-2.95 (m, 5 H), 2.84 (s, 3 H), 2.80-2.69 (m, 6 H), 2.40 (t, *J* = 7.1 Hz, 2 H), 2.33-2.27 (m, 6 H), 1.03-0.97 (m, 3 H). LC-MS $(M+H)^+$ = 555.5.

Example 31: 4- (2- (2- (3- (1- (hydroxymethyl)cyclopropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

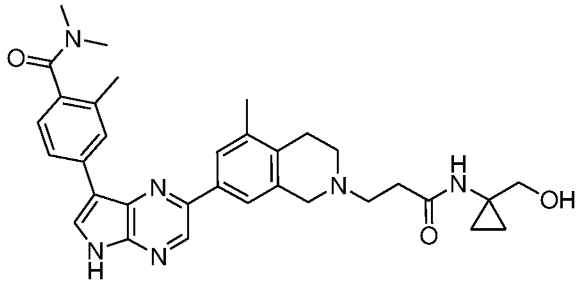


Step 1: 4- (2- (2- (3- (1- (hydroxymethyl)cyclopropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide



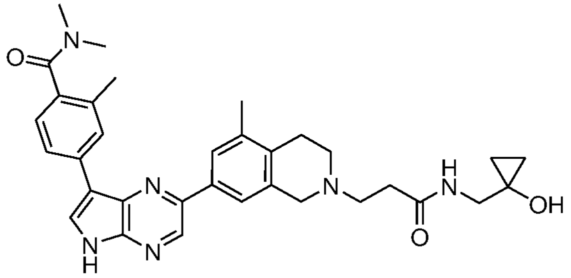
The title compound (81 mg, 73%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and (1-aminocyclopropyl)methanol. LC-MS $(M+H)^+$ = 721.1.

Step 2: 4- (2- (2- (3- (1- (hydroxymethyl)cyclopropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

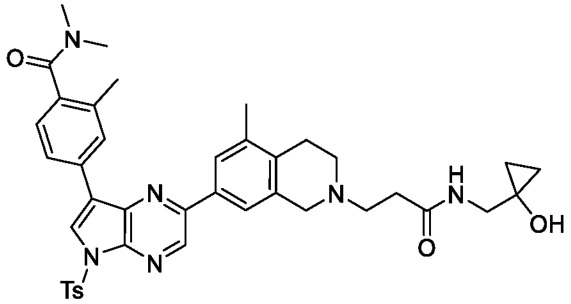


Example 31 (35 mg, 40%) was prepared in a manner similar to that in Example 1 step 10 from 4- (2- (2- (3- (1- (hydroxymethyl)cyclopropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.34 (s, 1 H), 8.87 (s, 1 H), 8.46 (s, 1 H), 8.27-8.19 (m, 3 H), 7.86 (s, 1 H), 7.73 (s, 1 H), 7.25 (d, *J* = 8.3 Hz, 1 H), 4.74-4.67 (m, 1 H), 3.67 (s, 2 H), 3.43-3.38 (m, 2 H), 3.03 (s, 3 H), 2.84 (s, 3 H), 2.75-2.71 (m, 6 H), 2.37-2.28 (m, 8 H), 0.69-0.58 (m, 2 H), 0.61-0.50 (m, 2 H). LC-MS $(M+H)^+ = 567.3$.

Example 32: 4- (2- (2- (3- ((1-hydroxycyclopropyl)methylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

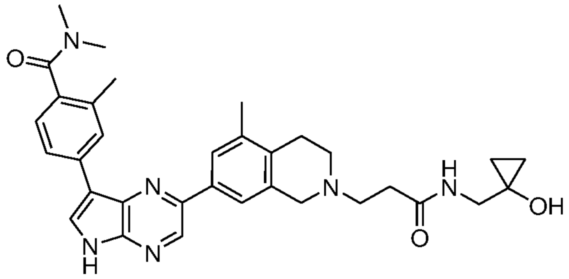


Step 1: 4- (2- (2- (3- ((1-hydroxycyclopropyl)methylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide



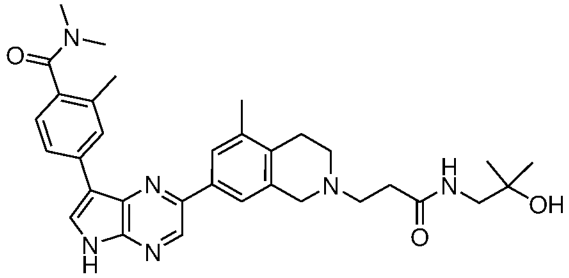
The title compound (106 mg, 52%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and 1-(aminomethyl)cyclopropanol. LC-MS $(M+H)^+ = 721.6$.

Step 2: 4- (2- (2- (3- ((1-hydroxycyclopropyl)methylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

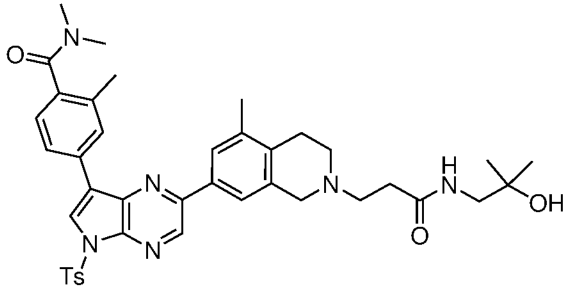


Example 32 (34 mg, 47%) was prepared in a manner similar to that in Example 1 step 10 from 4- (2- (2- (3- ((1-hydroxycyclopropyl)methylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.34 (s, 1 H), 8.87 (s, 1 H), 8.46 (s, 1 H), 8.26-8.20 (m, 2 H), 8.06-8.02 (m, 1 H), 7.87 (s, 1 H), 7.74 (s, 1 H), 7.25 (d, *J* = 8.3 Hz, 1 H), 5.28 (s, 1 H), 3.70 (s, 2 H), 3.22 (d, *J* = 5.7 Hz, 2 H), 3.03 (s, 3 H), 2.84 (s, 3 H), 2.78-2.73 (m, 6 H), 2.45-2.40 (m, 2 H), 2.34-2.28 (m, 6 H), 0.52-0.41 (m, 4 H). LC-MS $(M+H)^+$ = 567.5.

Example 33: 4- (2- (2- (3- (2-hydroxy-2-methylpropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

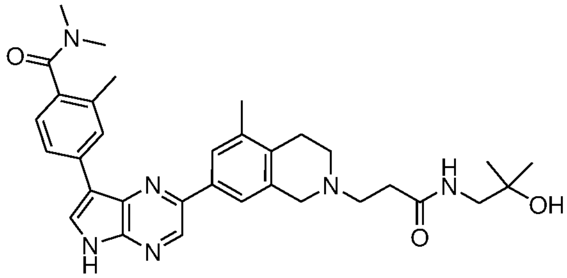


Step 1: 4- (2- (2- (3- (2-hydroxy-2-methylpropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide



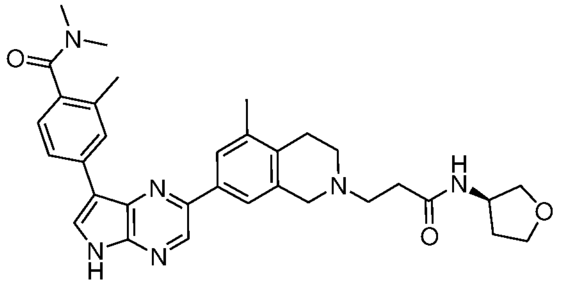
The title compound (93 mg, 63%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and 1-amino-2-methylpropan-2-ol. LC-MS $(M+H)^+$ = 723.4.

Step 2: 4- (2- (2- (3- (2-hydroxy-2-methylpropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

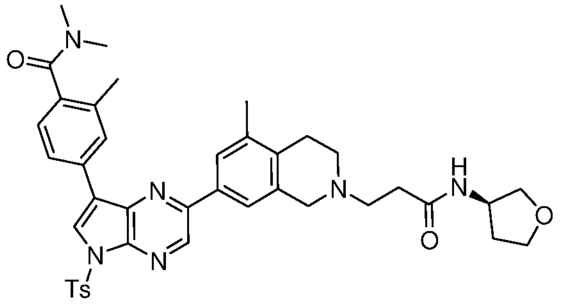


Example 33 (29 mg, 31%) was prepared in a manner similar to that in Example 1 step 10 from 4- (2- (2- (3- (2-hydroxy-2-methylpropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.33 (s, 1 H), 8.86 (s, 1 H), 8.46 (s, 1 H), 8.26-8.19 (m, 2 H), 7.98-7.90 (m, 1 H), 7.86 (s, 1 H), 7.73 (s, 1 H), 7.25 (d, *J* = 8.4 Hz, 1 H), 4.40 (s, 1 H), 3.71 (s, 2 H), 3.06-3.00 (m, 5 H), 2.84 (s, 3 H), 2.80-2.72 (m, 6 H), 2.44 (t, *J* = 6.9 Hz, 2 H), 2.33-2.27 (m, 6 H), 1.02 (s, 6 H).LC-MS $(M+H)^+$ = 569.4.

Example 34: (R)-N, N, 2-trimethyl-4- (2- (5-methyl-2- (3-oxo-3- (tetrahydrofuran-3-ylamino)propyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide

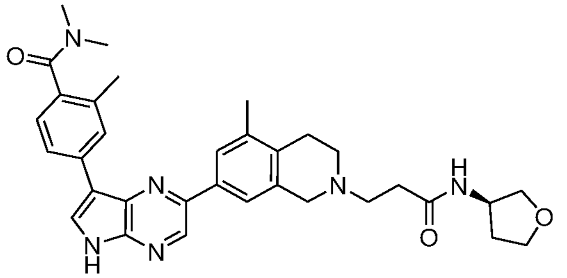


Step 1: (R)-N, N, 2-trimethyl-4- (2- (5-methyl-2- (3-oxo-3- (tetrahydrofuran-3-ylamino)propyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



The title compound (103 mg, 51%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and (R)-tetrahydrofuran-3-amine. LC-MS $(M+H)^+$ = 721.5.

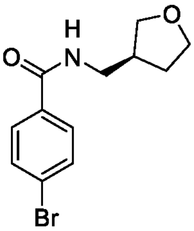
Step 2: (R)-N, N, 2-trimethyl-4- (2- (5-methyl-2- (3-oxo-3- (tetrahydrofuran-3-ylamino)propyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



Example 34 (22 mg, 18%) was prepared in a manner similar to that in Example 1 step 10 from (R)-N, N, 2-trimethyl-4- (2- (5-methyl-2- (3-oxo-3- (tetrahydrofuran-3-ylamino)propyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide. ^1H NMR (400 MHz, DMSO-*d6*) δ 12.34 (s, 1 H), 8.87 (s, 1 H), 8.46 (s, 1 H), 8.26-8.17 (m, 3 H), 7.86 (s, 1 H), 7.73 (s, 1 H), 7.25 (d, *J* = 8.3 Hz, 1 H), 4.29-4.18 (m, 1 H), 3.79-3.61 (m, 5 H), 3.47-3.39 (m, 1 H), 3.03 (s, 3 H), 2.84 (s, 3 H), 2.78-2.70 (m, 6 H), 2.38 (t, *J* = 7.2 Hz, 2 H), 2.33-2.28 (m, 6 H), 2.13-1.99 (m, 1 H), 1.75-1.64 (m, 1 H). LC-MS $(M+H)^+$ = 567.4.

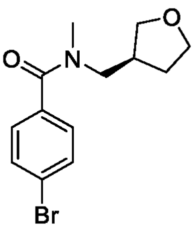
Example 35: (S)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide

Step 1: (S)-4-bromo-N- ((tetrahydrofuran-3-yl)methyl)benzamide



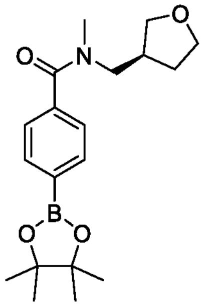
To a solution of 4-bromobenzoic acid (2.0 g, 9.9 mmol) and (S)- (tetrahydrofuran-3-yl)methanamine (1.0 g, 9.9 mmol) in DMF (20 mL) was added HATU (5.64 g, 14.9 mmol) and DIPEA (2.55 g, 19.8 mmol). The resulting solution was stirred at room temperature overnight. Water (20 mL) was added and the solution extracted with EtOAc (20 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography, eluted with CH_2Cl_2 / MeOH (100:1) to give the title compound (4.6 g, contained DMF). The material was used in step 2 without further purifications. LC-MS $(M+H)^+$ = 283.8, 285.8.

Step 2: (S)-4-bromo-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide



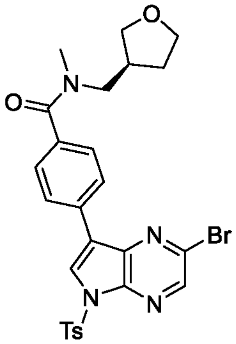
NaH (1.3 g, 32.4 mmol, 60%) was added to a solution of (S)-4-bromo-N-((tetrahydrofuran-3-yl)methyl)benzamide (4.6 g, from step 1) in DMF (30 mL) at 0 °C under N_2. The resulting solution was stirred at 0 °C for 1 h, and MeI (3.45 g, 24.3 mmol) was added dropwise. The solution was warmed to room temperature and stirred for 1 h. Water (30 mL) was added and the solution was extracted with EtOAc (30 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography, eluted with DCM/MeOH (100:1) to give the title compound (2.42 g, 82% for 2 steps). LC-MS $(M+H)^+ = 297.8, 299.8$.

Step 3: (S)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide



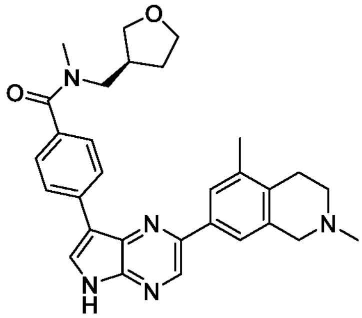
To a solution of (S)-4-bromo-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide (2.42 g, 8.12 mmol) in 1, 4-dioxane (50 mL) was added BPD (3.09 g, 12.2 mmol) and Pd (dppf)Cl_2·DCM (332 mg, 0.406 mmol) and KOAc (1.59 g, 16.2 mmol) under N_2. The resulting solution was stirred at 90 °C overnight. Water (50 mL) was added and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography, eluted with EtOAc/PE (1:3) to give the title compound (2.53 g, 90%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.1 Hz, 2H), 4.02 – 3.19 (m, 6H), 3.16 – 2.89 (m, 3H), 2.79 – 2.45 (m, 1H), 2.15 – 1.66 (m, 2H), 1.35 (s, 12H). LC-MS $(M+H)^+ = 346.0$.

Step 4: (S)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide



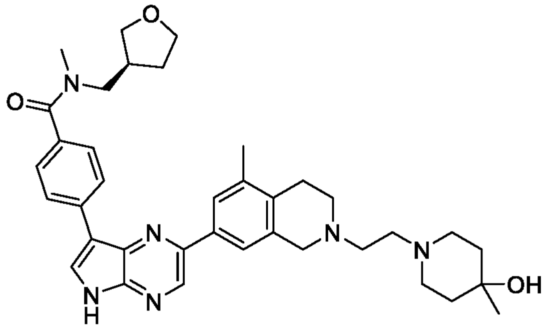
To a solution of (S)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide (400 mg, 1.16 mmol) and 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine (665 mg, 1.39 mmol) in dioxane (40 mL) and H_2O (8 mL) were added Pd (dppf)Cl_2 (85 mg, 0.116 mmol) and K_2CO_3 (320 mg, 2.32 mmol) under N_2. The mixture was refluxed for 5 h under a condenser. The mixture was cooled to room temperature and diluted with EtOAc (50 mL), then washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluted with EtOAc/PE (1:3) to give the title compound (350 mg, 58%). LC-MS $(M+H)^+ = 568.9, 570.9$.

Step 5: (S)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide

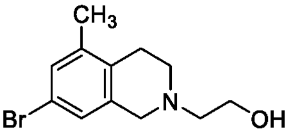


((S)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide (150 mg, 0.263 mmol), 2, 5-dimethyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline (100 mg, 0.35 mmol), Pd (dppf)Cl_2 (19 mg, 0.026 mmol) and K_2CO_3 (73 mg, 0.526 mmol) was added to dioxane (10 mL) and water (4 mL) under nitrogen. The reaction mixture was heated to reflux overnight. The mixture was partitioned between EtOAc (10 mL) and water (10 mL) and the aqueous layer was extracted with EtOAc (10 mL x 2). The combined organic layer was dried over Na_2SO_4 then concentrated under reduced pressure. The residue was purified by prep-TLC, developed with MeOH/DCM (1:10) to give Example 35 (55 mg, 42%). ^1H NMR (400 MHz, DMSO-*d6*) δ 12.39 (s, 1H), 8.87 (s, 1H), 8.52 (d, $J = 2.6$ Hz, 1H), 8.43-8.35 (m, 2H), 7.85 (s, 1H), 7.74 (s, 1H), 7.54-7.42 (m, 2H), 3.85 – 3.44 (m, 8H), 3.00 (s, 3H), 2.79 – 2.63 (m, 5H), 2.39 (s, 3H), 2.31 (s, 3H), 2.08-1.52 (m, 2H). LC-MS $(M+H)^+$ =496.0.

Example 36: (S)-4- (2- (2- (2- (4-hydroxy-4-methylpiperidin-1-yl)ethyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide

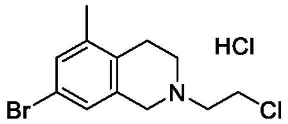


Step 1: 2- (7-bromo-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)ethan-1-ol



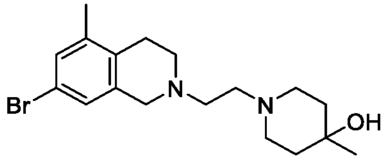
A suspension of 7-bromo-5-methyl-1, 2, 3, 4-tetrahydroisoquinoline (630 mg, 2.79 mmol), 2-bromoethan-1-ol (383 mg, 3.07 mmol) and K_2CO_3 (770 mg, 5.58 mmol) in MeCN (20 mL) was stirred at 75 °C overnight. The reaction mixture was cooled and concentrated. The crude was purified by silica gel chromatography, eluted with DCM/MeOH (20:1) to give the title compound (0.50 g, 66%). LCMS $(M+H)^+$ = 269.9, 271.9.

Step 2: 7-bromo-2- (2-chloroethyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinoline hydrochloride



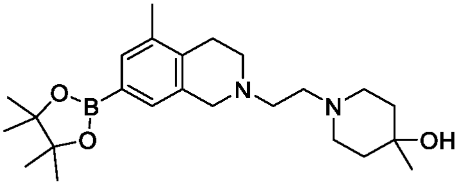
A solution of 2- (7-bromo-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)ethan-1-ol (500 mg, 1.85 mmol) in $SOCl_2$ (5 mL) was stirred at reflux for 2 h. The reaction was cooled to room temperature and the solvent was removed *in vacuo* to give the title compound (0.60 g, 99%). LCMS $(M+H)^+$ = 287.9, 289.9.

Step 3: 1- (2- (7-bromo-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)ethyl)-4-methylpiperidin-4-ol



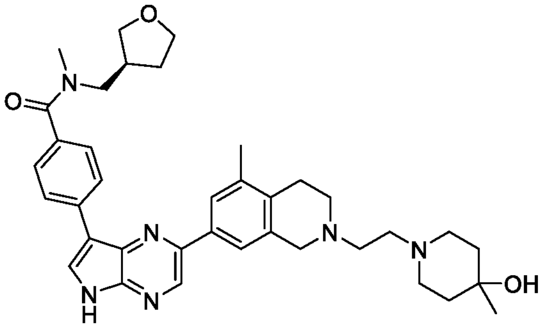
A suspension of 7-bromo-2- (2-chloroethyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinoline hydrochloride (600 mg, 1.85 mmol), 4-methylpiperidin-4-ol (213 mg, 1.85 mmol) and K_2CO_3 (1.02 g, 7.4 mmol) in MeCN (30 mL) was stirred at 75 °C overnight. The reaction was cooled to room temperature and the solvent was removed *in vacuo*. The crude was purified by silica gel chromatography, eluted with DCM/MeOH (20:1) to give the title compound (0.48 g, 70%). LCMS $(M+H)^+$ = 367.0, 369.0.

Step 4: 4-methyl-1- (2- (5-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-3, 4-dihydroisoquinolin-2 (1H)-yl)ethyl)piperidin-4-ol



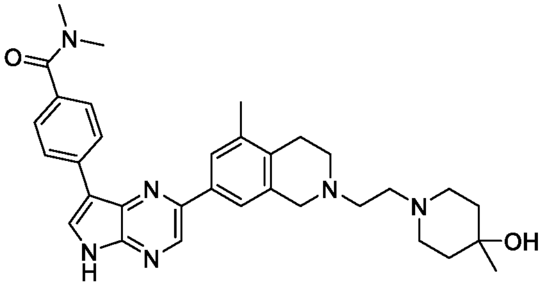
1- (2- (7-bromo-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)ethyl)-4-methylpiperidin-4-ol (480 mg, 1.3 mmol), BPD (497 mg, 1.96 mmol), Pd (dppf)Cl_2 (95 mg, 0.13 mmol) and AcOK (255 mg, 2.6 mmol) was added to dioxane (15 mL) under nitrogen. The reaction mixture was stirred at reflux overnight. EtOAc (20 mL) was added and the solution was washed with brine (20 mL x 2). The combined organic layer was dried over Na_2SO_4 and concentrated. The crude was purified by silica gel chromatography, eluted with DCM/MeOH (50:1 to 30:1) to give the title compound (400 mg, 74%). LC-MS $(M+H)^+$ =415.1.

Step 5: (S)-4- (2- (2- (2- (4-hydroxy-4-methylpiperidin-1-yl)ethyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide



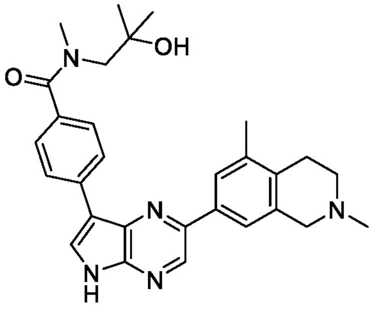
Example 36 (48 mg, 29%) was prepared in a manner similar to that in Example 35 step 5 from ((S)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide and 4-methyl-1- (2- (5-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-3, 4-dihydroisoquinolin-2 (1H)-yl)ethyl)piperidin-4-ol. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.39 (s, 1H), 8.87 (s, 1H), 8.51 (s, 1H), 8.40 (s, 1H), 8.38 (s, 1H), 7.85 (s, 1H), 7.73 (s, 1H), 7.53-7.43 (m, 2H), 4.13 (s, 1H), 3.85-3.67 (m, 4H), 3.59-3.41 (m, 4H), 2.99 (s, 3H), 2.81-2.71 (m, 4H), 2.67-2.56 (m, 4H), 2.49 – 2.40 (m, 4H), 2.31 (s, 3H), 2.07-1.82 (m, 2H), 1.70-1.61 (m, 1H), 1.53-1.44 (m, 4H), 1.10 (s, 3H). LC-MS $(M+H)^+$ =623.0.

Example 37: 4- (2- (2- (2- (4-hydroxy-4-methylpiperidin-1-yl)ethyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide

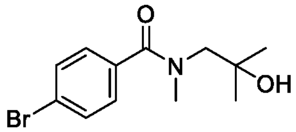


Example 37 (50 mg, 30%) was prepared in a manner similar to that in Example 35 step 5 from 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide and 4-methyl-1- (2- (5-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-3, 4-dihydroisoquinolin-2 (1H)-yl)ethyl)piperidin-4-ol. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.39 (s, 1H), 8.87 (s, 1H), 8.51 (s, 1H), 8.39 (s, 1H), 8.37 (s, 1H), 7.84 (s, 1H), 7.72 (s, 1H), 7.53 (s, 1H), 7.50 (s, 1H), 4.09 (s, 1H), 3.69 (s, 2H), 3.01 (s, 6H), 2.80-2.69 (m, 4H), 2.64 – 2.55 (m, 4H), 2.47 – 2.38 (m, 4H), 2.30 (s, 3H), 1.50-1.43 (m, 4H), 1.09 (s, 3H). LC-MS $(M+H)^+$ =553.0.

Example 38: 4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxy-2-methylpropyl)-N-methylbenzamide

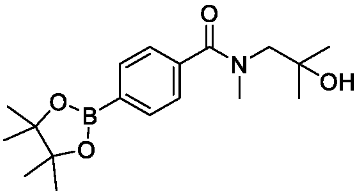


Step 1: 4-bromo-N- (2-hydroxy-2-methylpropyl)-N-methylbenzamide



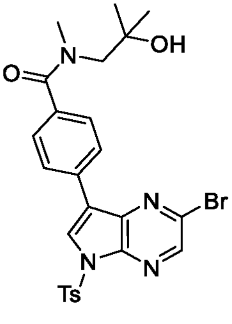
4-bromobenzoic acid (1.93 g, 9.61 mmol), 2-methyl-1- (methylamino)propan-2-ol (1.0 g, 9.61 mmol), HATU (4.75 g, 12.5 mmol) and TEA (2.8 mL, 19.2 mmol) was added in DMF (30 mL). The mixture was stirred at room temperature overnight. Water (60 mL) was added and the mixture was extracted with EtOAc (40 mL x 3). The combined organic layer was washed with brine (50 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluted with EtOAc/PE (1:5 to 2:1) to give the title compound (2.5 g, 91%). LC-MS $(M+H)^+$ =286.0, 288.0.

Step 2: N- (2-hydroxy-2-methylpropyl)-N-methyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide



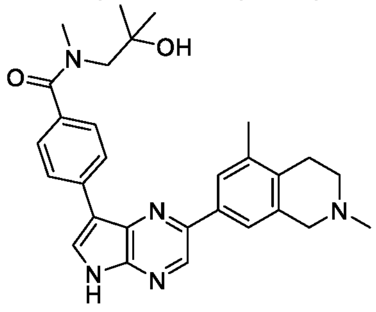
4-bromo-N- (2-hydroxy-2-methylpropyl)-N-methylbenzamide (2.5 g, 8.7 mmol), BPD (2.2 g, 13 mmol), Pd $(dppf)Cl_2$ (382 mg, 0.52 mmol) and AcOK (1.7 g, 17.4 mmol) was added in dioxane (50 mL) under nitrogen. The reaction mixture was heated to reflux overnight then cooled to room temperature. EtOAc (50 mL) was added and the solution was washed with brine (30 mL x 2). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (1:5 to 2:1) to give the title compound (2.8 g, 97%). LC-MS $(M+H)^+$ =334.2.

Step 3: 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxy-2-methylpropyl)-N-methylbenzamide



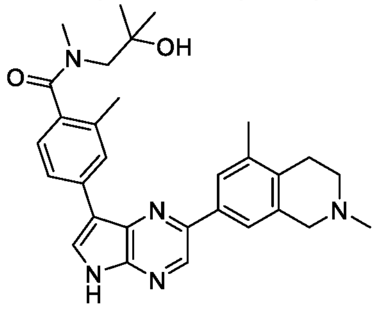
To a solution of 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine (4.3 g, 9.0 mmol) and N- (2-hydroxy-2-methylpropyl)-N-methyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide (2.8 g, 8.6 mmol) in dioxane (50 mL) and water (10 mL) was added K_2CO_3 (1.6 g, 11.7 mmol) and Pd $(dppf)Cl_2$ (395 mg, 0.54 mmol) under nitrogen atmosphere. After stirring for 5 h at 50 °C under nitrogen atmosphere, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude was purified by silica gel column chromatography, eluted with EtOAc/PE (1:2 to 2:1) to give the title compound (2.5 g, 50%). LCMS $(M+H)^+$ = 557.0.

Step 4: 4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxy-2-methylpropyl)-N-methylbenzamide

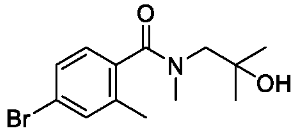


Example 38 (28 mg, 21%) was prepared in a manner similar to that in Example 35 step 5 from 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxy-2-methylpropyl)-N-methylbenzamide and 2, 5-dimethyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.45 (s, 1H), 8.93 (s, 1H), 8.57 (d, *J* = 2.8 Hz, 1H), 8.46 (s, 1H), 8.44 (s, 1H), 7.91 (s, 1H), 7.80 (s, 1H), 7.63-7.45 (m, 2H), 4.74 (4.59, 1H), 3.68 (s, 2H), 3.55 (s, 2H), 3.16 (s, 3H), 2.86-2.79 (m, 2H), 2.78-2.73 (m, 2H), 2.45 (s, 3H), 2.38 (s, 3H), 1.28-0.97 (m, 6H). LC-MS $(M+H)^+$ =484.0.

Example 39: 4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxy-2-methylpropyl)-N, 2-dimethylbenzamide

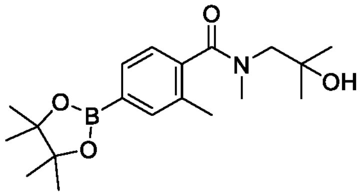


Step 1: 4-bromo-N- (2-hydroxy-2-methylpropyl)-N, 2-dimethylbenzamide



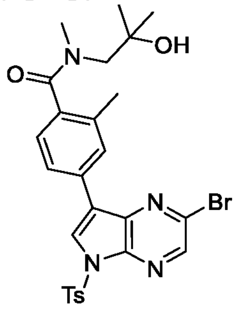
The title compound (2.5 g, 86%) was prepared in a manner similar to that in Example 38 step 1 from 4-bromo-2-methylbenzoic acid and 2-methyl-1- (methylamino)propan-2-ol. LCMS $(M+H)^+$ = 300.0, 302.0.

Step 2: N- (2-hydroxy-2-methylpropyl)-N, 2-dimethyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide



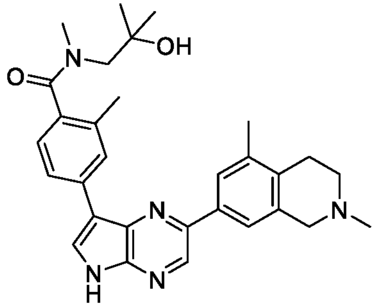
The title compound (2.5 g, 87%) was prepared in a manner similar to that in Example 38 step 2 from 4-bromo-N- (2-hydroxy-2-methylpropyl)-N, 2-dimethylbenzamide and BPD. LC-MS $(M+H)^+$ =348.0.

Step 3: 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxy-2-methylpropyl)-N, 2-dimethylbenzamide



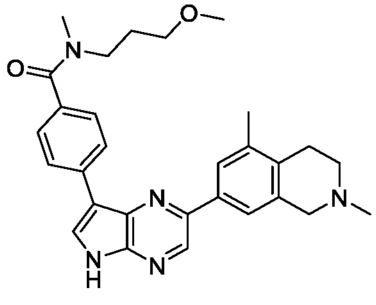
The title compound (2.5 g, 87%) was prepared in a manner similar to that in Example 38 step 3 from 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine and N- (2-hydroxy-2-methylpropyl)-N, 2-dimethyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide. LC-MS $(M+H)^+$ =571.0.

Step 4: 4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxy-2-methylpropyl)-N, 2-dimethylbenzamide

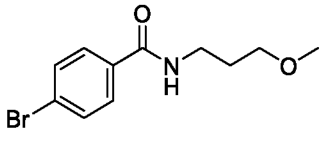


Example 39 (59 mg, 44%) was prepared in a manner similar to that in Example 35 step 5 from 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-hydroxy-2-methylpropyl)-N, 2-dimethylbenzamide and 2, 5-dimethyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.33 (s, 1H), 8.87 (s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 8.27 – 8.18 (m, 2H), 7.86 (s, 1H), 7.74 (s, 1H), 7.25 (d, J = 8.3 Hz, 1H), 4.63-4.54 (m, 1H), 3.59 (s, 2H), 3.49 (s, 2H), 3.14-2.93 (m, 3H), 2.78-2.71 (m, 2H), 2.70-2.64 (m, 2H), 2.38 (s, 3H), 2.35-2.77 (m, 6H), 1.22-0.93 (m, 6H). LC-MS $(M+H)^+$ =498.0.

Example 40: 4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (3-methoxypropyl)-N-methylbenzamide

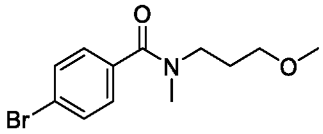


Step 1: 4-bromo-N- (3-methoxypropyl)benzamide



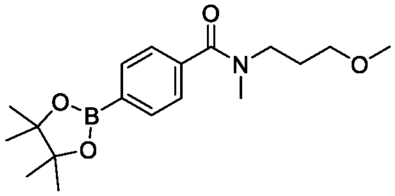
The title compound (1.6 g, 52%) was prepared in a manner similar to that in Example 38 step 1 from 4-bromobenzoic acid and 3-methoxypropan-1-amine. LCMS $(M+H)^+$ = 272.0, 274.0.

Step 2: 4-bromo-N- (3-methoxypropyl)-N-methylbenzamide



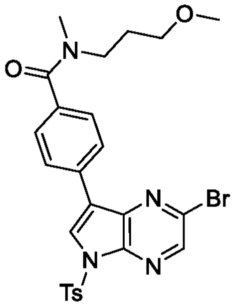
The title compound (1.6 g, 95%) was prepared in a manner similar to that in Example 35 step 2 from 4-bromo-N- (3-methoxypropyl)benzamide and MeI. LC-MS $(M+H)^+$ =286.0, 288.0.

Step 3: N- (3-methoxypropyl)-N-methyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide



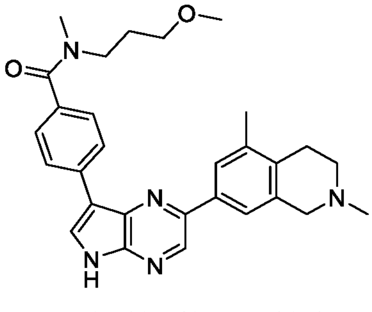
The title compound (2.5 g, 87%) was prepared in a manner similar to that in Example 38 step 2 from 4-bromo-N- (3-methoxypropyl)-N-methylbenzamide and BPD. LC-MS $(M+H)^+$ =334.0.

Step 4: 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (3-methoxypropyl)-N-methylbenzamide



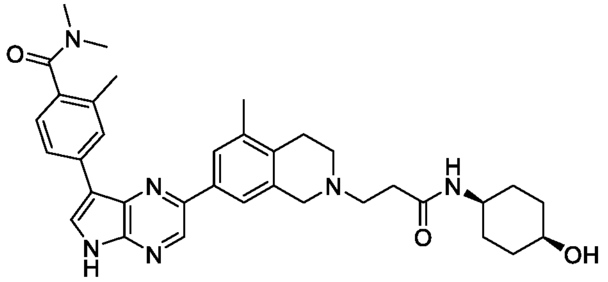
The title compound (0.80 g, 32%) was prepared in a manner similar to that in Example 38 step 3 from 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine and N- (3-methoxypropyl)-N-methyl-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide. LC-MS $(M+H)^+$ =557.0, 559.0.

Step 5: 4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (3-methoxypropyl)-N-methylbenzamide



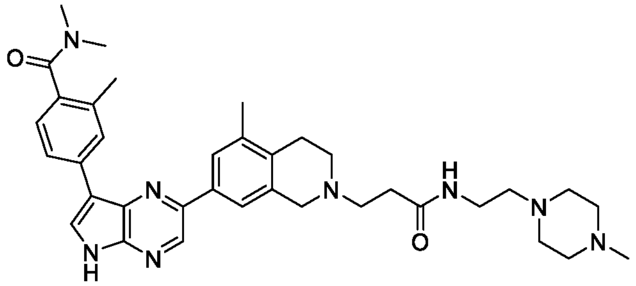
Example 40 (60 mg, 41%) was prepared in a manner similar to that in Example 35 step 5 from 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (3-methoxypropyl)-N-methylbenzamide and 2, 5-dimethyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.39 (s, 1H), 8.87 (s, 1H), 8.51 (s, 1H), 8.30-8.40 (m, 2H), 7.85 (s, 1H), 7.73 (s, 1H), 7.57-7.42 (m, 2H), 3.59 (s, 2H), 3.55-3.37 (m, 3H), 3.29-3.11 (m, 4H), 2.97 (s, 3H), 2.78-2.72 (m, 2H), 2.71-2.64 (m, 2H), 2.37 (s, 3H), 2.31 (s, 3H), 1.89-1.72 (m, 2H). LC-MS (M+H)$^+$ =484.8.

Example 41: 4- (2- (2- (3- ((cis-4-hydroxycyclohexyl)amino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide



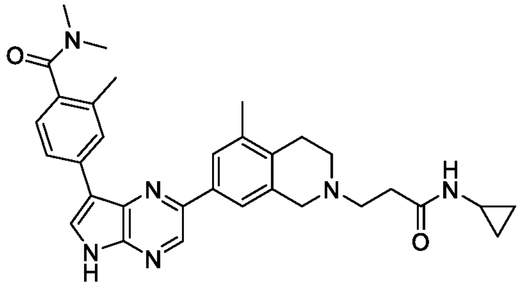
Example 41 (60 mg, 50%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and cis-4-aminocyclohexan-1-ol. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.33 (s, 1H), 8.86 (s, 1H), 8.46 (d, *J* = 2.6 Hz, 1H), 8.25 – 8.20 (m, 2H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.86 (s, 1H), 7.72 (s, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 4.36 (d, *J* = 2.8 Hz, 1H), 3.68 (s, 2H), 3.66 – 3.55 (m, 3H), 3.03 (s, 3H), 2.83 (s, 3H), 2.79 – 2.69 (m, 6H), 2.37 (t, *J* = 7.0 Hz, 2H), 2.32 – 2.28 (m, 8H), 1.60 – 1.49 (m, 4H), 1.49 – 1.38 (m, 4H). LC-MS (M+H)$^+$ = 595.5.

Example 42: N, N, 2-trimethyl-4- (2- (5-methyl-2- (3- ((2- (4-methylpiperazin-1-yl)ethyl)amino)-3-oxopropyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



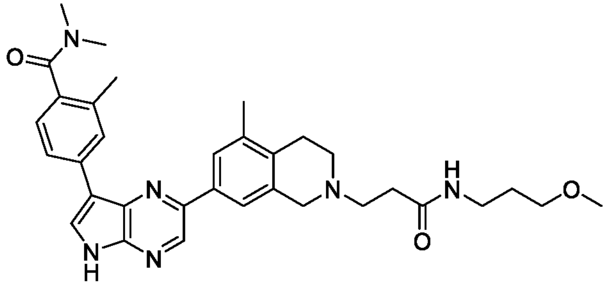
Example 42 (30 mg, 24%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and 2- (4-methylpiperazin-1-yl)ethan-1-amine. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.33 (d, *J* = 2.4 Hz, 1H), 8.86 (s, 1H), 8.46 (d, *J* = 2.4 Hz, 1H), 8.25 – 8.19 (m, 2H), 7.99 (t, *J* = 5.4 Hz, 1H), 7.86 (s, 1H), 7.73 (s, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 3.69 (s, 2H), 3.19 – 3.11 (m, 2H), 3.03 (s, 3H), 2.83 (s, 3H), 2.79 – 2.68 (m, 6H), 2.37 (t, *J* = 6.8 Hz, 2H), 2.34 – 2.26 (m, 12H), 2.19 (brs, 4H), 2.05 (s, 3H). LC-MS (M+H)$^+$ = 623.6.

Example 43: 4- (2- (2- (3- (cyclopropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide



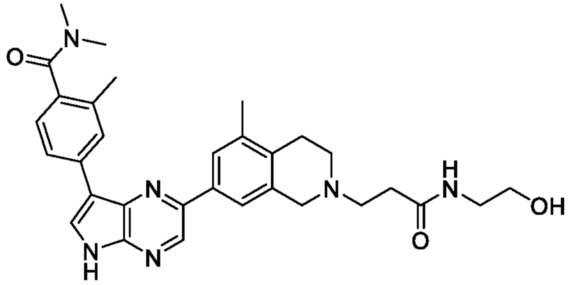
Example 43 (30 mg, 27%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and cyclopropylamine. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.33 (d, *J* = 2.3 Hz, 1H), 8.86 (s, 1H), 8.46 (d, *J* = 2.8 Hz, 1H), 8.24 – 8.20 (m, 2H), 7.99 (d, *J* = 4.1 Hz, 1H), 7.86 (s, 1H), 7.72 (s, 1H), 7.24 (d, *J* = 4.5 Hz, 1H), 3.66 (s, 2H), 3.03 (s, 3H), 2.83 (s, 3H), 2.76 – 2.68 (m, 6H), 2.65 – 2.57 (m, 1H), 2.34 – 2.28 (m, 8H), 0.64 – 0.55 (m, 2H), 0.40 – 0.31 (m, 2H). LC-MS (M+H)$^+$ = 537.5.

Example 44: 4- (2- (2- (3- ((3-methoxypropyl)amino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide



Example 44 (60 mg, 52%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and 3-methoxypropan-1-amine. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.33 (d, *J* = 2.6 Hz, 1H), 8.86 (s, 1H), 8.46 (d, *J* = 2.8 Hz, 1H), 8.24 – 8.20 (m, 2H), 7.95 (t, *J* = 5.6 Hz, 1H), 7.86 (s, 1H), 7.73 (s, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 3.68 (s, 2H), 3.28 (t, *J* = 6.6 Hz, 2H), 3.15 (s, 3H), 3.08 (dd, *J* = 12.7, 6.7 Hz, 2H), 3.03 (s, 3H), 2.83 (s, 3H), 2.78 – 2.69 (m, 6H), 2.36 (t, *J* = 7.1 Hz, 2H), 2.33 – 2.25 (m, 6H), 1.60 (p, *J* = 6.7 Hz, 2H). LC-MS (M+H)$^+$ = 569.5.

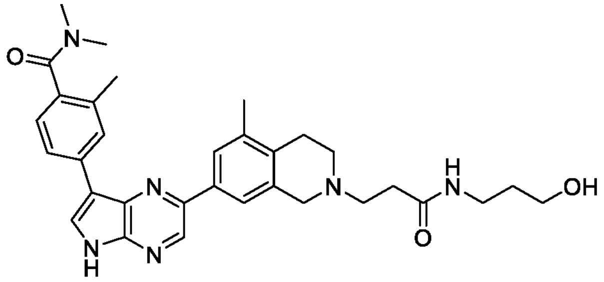
Example 45: 4- (2- (2- (3- ((2-hydroxyethyl)amino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide



Example 45 (30 mg, 27%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and 2-aminoethan-1-ol. ^{1}H NMR (400

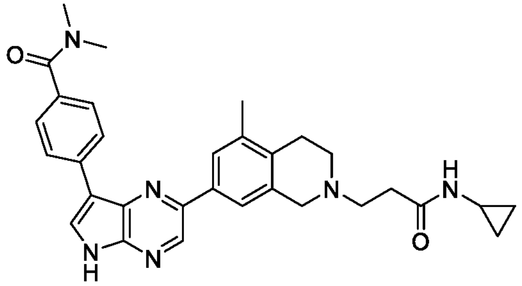
MHz, DMSO-*d6*) δ 12.33 (d, *J* = 2.7 Hz, 1H), 8.87 (s, 1H), 8.46 (d, *J* = 2.8 Hz, 1H), 8.24 - 8.20 (m, 2H), 7.98 (t, *J* = 5.3 Hz, 1H), 7.86 (s, 1H), 7.73 (s, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 4.64 (t, *J* = 5.4 Hz, 1H), 3.68 (s, 2H), 3.38 (q, *J* = 5.9 Hz, 2H), 3.12 (q, *J* = 5.9 Hz, 2H), 3.03 (s, 3H), 2.83 (s, 3H), 2.74 (s, 6H), 2.38 (t, *J* = 7.2 Hz, 2H), 2.30 (d, *J* = 4.9 Hz, 6H). LC-MS $(M+H)^+$ = 541.5.

Example 46: 4- (2- (2- (3- ((3-hydroxypropyl)amino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

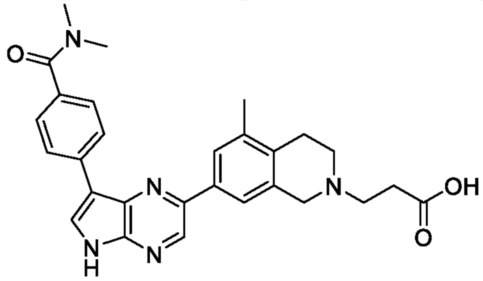


Example 46 (30 mg, 27%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and 3-aminopropan-1-ol. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.33 (d, *J* = 2.5 Hz, 1H), 8.87 (s, 1H), 8.46 (d, *J* = 2.7 Hz, 1H), 8.24 – 8.20 (m, 2H), 7.93 (t, *J* = 5.5 Hz, 1H), 7.86 (s, 1H), 7.73 (s, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 4.41 (t, *J* = 5.2 Hz, 1H), 3.67 (s, 2H), 3.39 (dd, *J* = 11.6, 6.1 Hz, 2H), 3.10 (dd, *J* = 12.7, 6.7 Hz, 2H), 3.03 (s, 3H), 2.83 (s, 3H), 2.72 (d, *J* = 7.3 Hz, 6H), 2.36 (t, *J* = 7.1 Hz, 2H), 2.30 (d, *J* = 4.5 Hz, 6H), 1.53 (p, *J* = 6.6 Hz, 2H). LC-MS $(M+H)^+$ = 555.5.

Example 47: 4- (2- (2- (3- (cyclopropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide

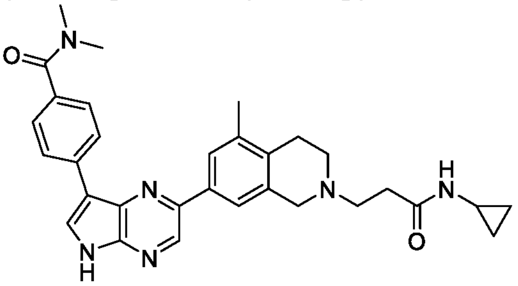


Step 1: 3- (7- (7- (4- (dimethylcarbamoyl)phenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid



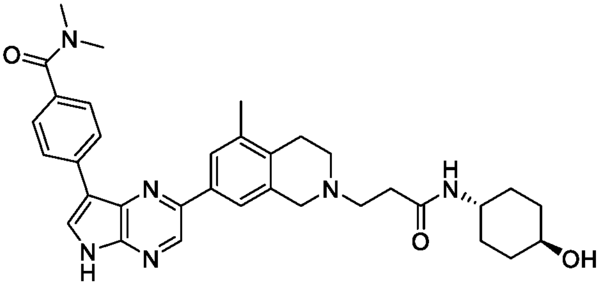
The title compound (400 mg, crude) was prepared in a manner similar to that in Example 23 step 3 from 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide and ethyl 3- (5-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoate. LC-MS $(M+H)^+$ = 484.1.

Step 2: 4- (2- (2- (3- (cyclopropylamino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide



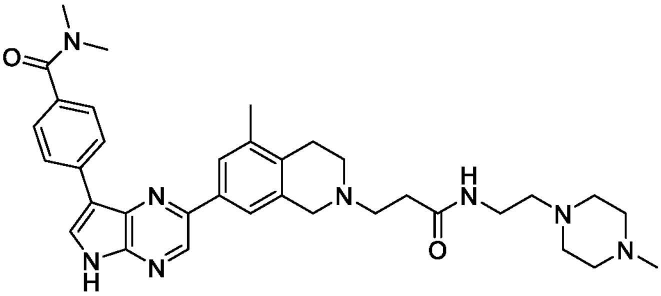
Example 47 (30 mg, 28%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-phenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and cyclopropylamine. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.39 (d, *J* = 2.5 Hz, 1H), 8.87 (s, 1H), 8.51 (d, *J* = 2.8 Hz, 1H), 8.38 (d, *J* = 8.3 Hz, 2H), 7.99 (d, *J* = 3.9 Hz, 1H), 7.84 (s, 1H), 7.72 (s, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 3.67 (s, 2H), 3.01 (s, 6H), 2.77 – 2.69 (m, 6H), 2.65 – 2.57 (m, 1H), 2.36 – 2.28 (m, 5H), 0.63 – 0.54 (m, 2H), 0.39 – 0.32 (m, 2H). LC-MS $(M+H)^+$ = 523.5.

Example 48: 4- (2- (2- (3- (((1r, 4r)-4-hydroxycyclohexyl)amino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide



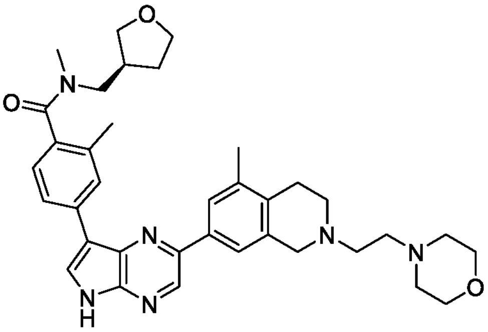
Example 48 (10 mg, 17%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-phenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and trans-4-aminocyclohexan-1-ol. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.47 (s, 1H), 10.59 (s, 1H), 8.92 (s, 1H), 8.54 (s, 1H), 8.38 (d, *J* = 8.3 Hz, 2H), 8.03 (s, 1H), 7.89 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 4.72 – 4.58 (m, 1H), 4.57 – 4.51 (m, 1H), 4.51 – 4.37 (m, 1H), 3.84 – 3.71 (s, 1H), 3.57 – 3.39 (m, 3H), 3.09 – 2.94 (m, 8H), 2.81 – 2.69 (m, 2H), 2.40 – 2.31 (m, 4H), 1.85 – 1.70 (m, 4H), 1.23 – 1.12 (m, 5H). LC-MS $(M+H)^+$ = 580.9.

Example 49: N, N-dimethyl-4- (2- (5-methyl-2- (3- ((2- (4-methylpiperazin-1-yl)ethyl)amino)-3-oxopropyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide

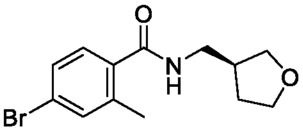


Example 49 (10 mg, 16%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-phenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and 2- (4-methylpiperazin-1-yl)ethan-1-amine. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.39 (s, 1H), 8.86 (s, 1H), 8.51 (d, *J* = 2.3 Hz, 1H), 8.38 (d, *J* = 8.3 Hz, 2H), 8.00 (t, *J* = 5.4 Hz, 1H), 7.84 (s, 1H), 7.73 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 3.69 (s, 2H), 3.15 (dd, *J* = 12.3, 6.4 Hz, 2H), 3.01 (s, 6H), 2.79 – 2.69 (m, 6H), 2.43 – 2.10 (m, 15H), 2.05 (s, 3H). LC-MS $(M+H)^+$ = 609.0.

Example 50: (S)-N, 2-dimethyl-4- (2- (5-methyl-2- (2-morpholinoethyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- ((tetrahydrofuran-3-yl)methyl)benzamide

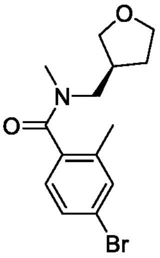


Step 1: (S)-4-bromo-2-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide



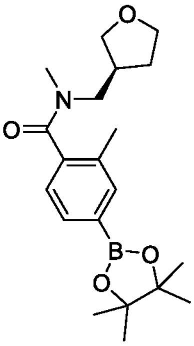
The title compound (1.10 g, 81%) was prepared in a manner similar to that in Example 35 step 1 from 4-bromo-2-methylbenzoic acid and (S)- (tetrahydrofuran-3-yl)methanamine. LC-MS $(M+H)^+$ =298.0, 300.0.

Step 2: (S)-4-bromo-N, 2-dimethyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide



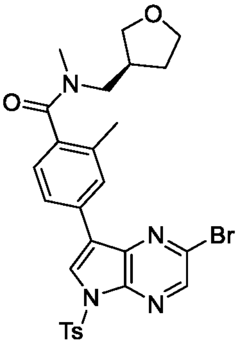
The title compound (1.07 g, 93%) was prepared in a manner similar to that in Example 35 step 2 from (S)-4-bromo-2-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide and iodomethane. LC-MS $(M+H)^+$ = 311.9, 313.9.

Step 3: (S)-N, 2-dimethyl-N- ((tetrahydrofuran-3-yl)methyl)-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide



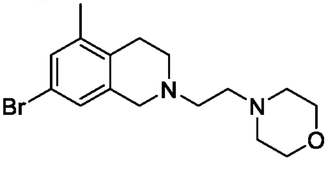
The title compound (1.20 g, 99%) was prepared in a manner similar to that in Example 35 step 3 from (S)-4-bromo-N, 2-dimethyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide and BPD. LC-MS $(M+H)^+ = 359.9$.

Step 4: (S)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, 2-dimethyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide



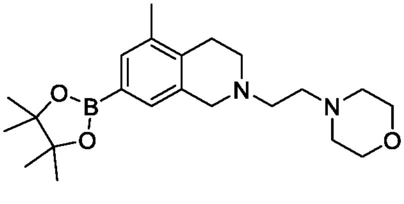
The title product (400 mg, 41%) was prepared in a manner similar to that in Example 35 step 4 from 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine and (S)-N, 2-dimethyl-N- ((tetrahydrofuran-3-yl)methyl)-4- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)benzamide. LC-MS $(M+H)^+ = 582.9, 584.9$.

Step 5: 4- (2- (7-bromo-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)ethyl)morpholine



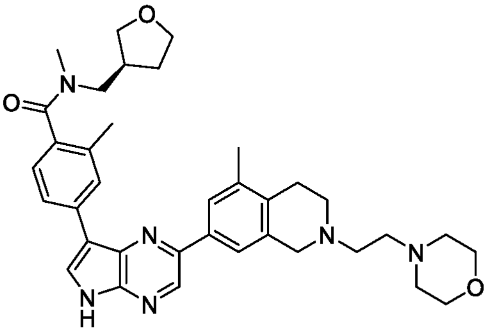
7-bromo-2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinoline (1.0 g, 4.5 mmol), 4- (2-bromoethyl)morpholine hydrogen bromide (1.6 g, 5.9 mmol) and K_2CO_3 (1.87 g, 13.6 mmol) was dissolved in CH_3CN (30 mL). The mixture was heated to reflux overnight then cooled to room temperature. Solvent was removed in *vacuo* and the residue was purified by silica gel column chromatography, eluted with MeOH/DCM (1:50) to give the title compound (1.0 g, 67%). LC-MS $(M+H)^+ = 339.0$.

Step 6: 4- (2- (5-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-3, 4-dihydroisoquinolin-2 (1H)-yl)ethyl)morpholine



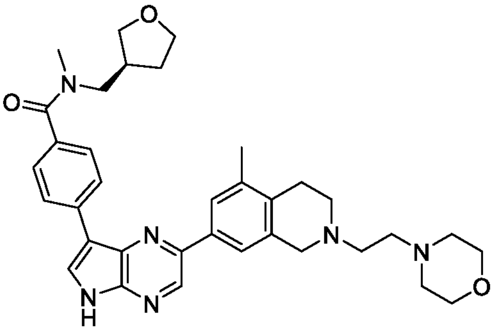
The title product (90 mg, 33%) was prepared in a manner similar to that in Example 36 step 4 from 4- (2- (7-bromo-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)ethyl)morpholine and BPD. LC-MS $(M+H)^+ = 387.0$.

Step 7: (S)-N, 2-dimethyl-4- (2- (5-methyl-2- (2-morpholinoethyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- ((tetrahydrofuran-3-yl)methyl)benzamide



Example 50 (60 mg, 29%) was prepared in a manner similar to that in Example 35 step 5 from (S)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, 2-dimethyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide and 4- (2- (5-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-3, 4-dihydroisoquinolin-2 (1H)-yl)ethyl)morpholine. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.34 (s, 1H), 8.87 (s, 1H), 8.47 (s, 1H), 8.30 – 8.17 (m, 2H), 7.86 (s, 1H), 7.73 (s, 1H), 7.27 – 7.18 (m, 1H), 3.84 – 3.77 (m, 1H), 3.74 – 3.60 (m, 3H), 3.60 – 3.54 (m, 4H), 3.54 – 3.42 (m, 2H), 3.19 (brs, 1H), 3.01 (s, 1H), 2.82 (s, 2H), 2.76 – 2.72 (m, 3H), 2.68 – 2.58 (m, 2H), 2.53 – 2.51 (m, 2H), 2.43 (s, 4H), 2.30 (brs, 6H), 2.04 – 1.96 (m, 1H), 1.70 – 1.61 (m, 1H). LC-MS $(M+H)^+ = 609.0$.

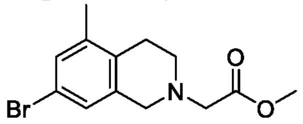
Example 51: (S)-N-methyl-4- (2- (5-methyl-2- (2-morpholinoethyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- ((tetrahydrofuran-3-yl)methyl)benzamide



Example 51 (27 mg, 17%) was prepared in a manner similar to that in Example 35 step 5 from (S)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide and 4- (2- (5-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-3, 4-dihydroisoquinolin-2 (1H)-yl)ethyl)morpholine. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.39 (s, 1H), 8.87 (s, 1H), 8.52 (d, *J* = 2.0 Hz, 1H), 8.40 (s, 1H), 8.38 (s, 1H), 7.85 (s, 1H), 7.74 (s, 1H), 7.50 - 7.48 (m, 2H), 3.77 - 3.72 (m, 4H), 3.58 (s, 5H), 3.43 (brs, 3H), 2.99 (s, 3H), 2.78 (brs, 2H), 2.73 (brs, 2H), 2.64 (brs, 3H), 2.55 (brs, 2H), 2.44 (s, 4H), 2.31 (s, 3H), 1.95 (brs, 1H), 1.64 (brs, 1H). LC-MS $(M+H)^+ = 594.9$.

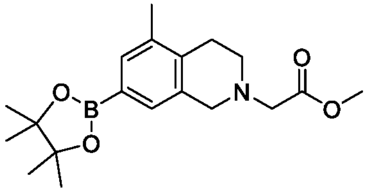
Example 52: 4- (2- (2- (2- ((3-methoxypropyl)amino)-2-oxoethyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

Step 1: methyl 2- (7-bromo-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)acetate



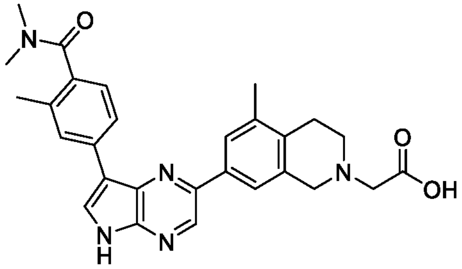
A mixture of 7-bromo-5-methyl-1, 2, 3, 4-tetrahydroisoquinoline (2.3 g, 10 mmol), methyl 2-chloroacetate (1.09 g, 10 mmol) and Cs_2CO_3 (3.28 g, 7.75 mmol) in DMF (40 mL) was stirred at room temperature overnight. Solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column, eluted with EtOAc/PE (1:4) to give the title compound (2.07 g, 70%). LC-MS $(M+H)^+$ =297.9, 299.9.

Step 2: methyl 2- (5-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-3, 4-dihydroisoquinolin-2 (1H)-yl)acetate



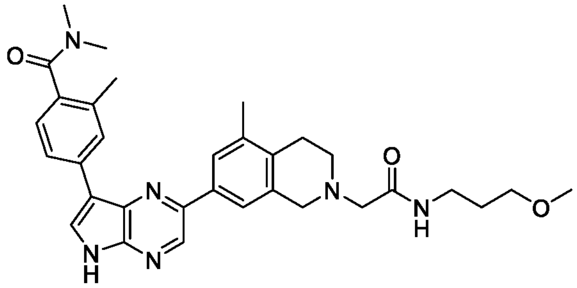
To methyl 2- (7-bromo-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)acetate (2.07 g, 6.95 mmol), BPD (2.65 g, 10.4 mmol), Pd (dppf)Cl_2 (512 mg, 0.70 mmol) and AcOK (1.36 g, 13.9 mmol) was added dioxane (40 mL) under nitrogen. The reaction mixture was stirred at reflux overnight then cooled to room temperature. EtOAc (30 mL) was added and the mixture was washed with brine (30 mL x 2). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (1:2) to give the title compound (2.64 g, 100%). LC-MS $(M+H)^+$ =346.0.

Step 3: 2- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)acetic acid



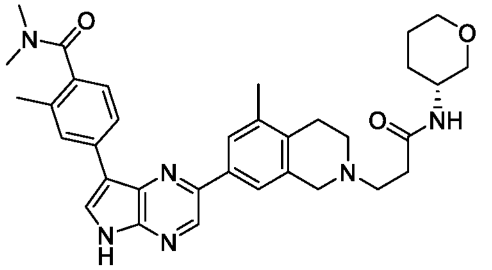
The title compound (1.2 g, 44%) was prepared in a manner similar to that in Example 23 step 3 from 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide and methyl 2- (5-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-3, 4-dihydroisoquinolin-2 (1H)-yl)acetate. LC-MS $(M+H)^+$ = 484.0.

Step 4: 4- (2- (2- (2- ((3-methoxypropyl)amino)-2-oxoethyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide



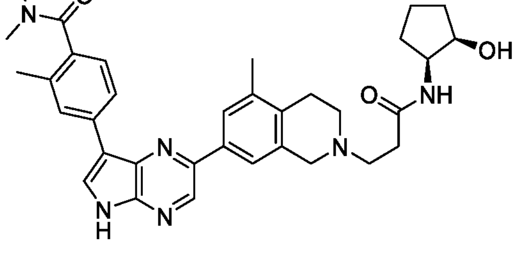
Example 52 (35 mg, 30%) was prepared in a manner similar to that in Example 23 step 4 from 2- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)acetic acid and 3-methoxypropan-1-amine. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.33 (s, 1H), 8.88 (s, 1H), 8.46 (d, *J* = 2.4 Hz, 1H), 8.24 (s, 1H), 8.20 (d, *J* = 8.1 Hz, 1H), 7.89 (s, 1H), 7.88 – 7.85 (m, 1H), 7.75 (s, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 3.74 (s, 2H), 3.37 – 3.30 (m, 2H), 3.20 – 3.15 (m, 5H), 3.12 (s, 2H), 3.03 (s, 3H), 2.83 (s, 3H), 2.79 (s, 4H), 2.32 (s, 3H), 2.29 (s, 3H), 1.70 – 1.63 (m, 2H). LC-MS $(M+H)^+ = 555.0$.

Example 53: (R)-N, N, 2-trimethyl-4- (2- (5-methyl-2- (3-oxo-3- ((tetrahydro-2H-pyran-3-yl)amino)propyl)-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide



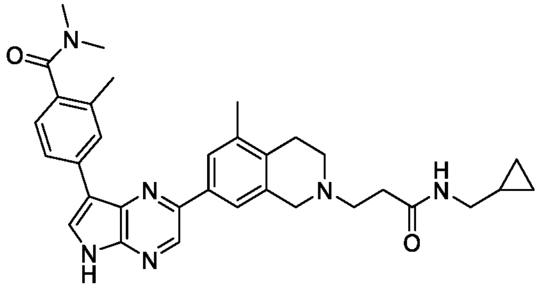
Example 53 (10 mg, 9%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and (R)-tetrahydro-2H-pyran-3-amine hydrochloride. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.40 (s, 1H), 8.91 (s, 1H), 8.49 (s, 1H), 8.26 – 8.17 (m, 3H), 8.02 (s, 1H), 7.86 (s, 1H), 7.25 (d, *J* = 7.9 Hz, 1H), 3.74 – 3.61 (m, 4H), 3.55-3.36 (m, 4H), 3.18-2.08 (m, 2H), 3.06-3.02 (m, 4H), 2.88-2.70 (m, 6H), 2.40-2.25 (m, 7H), 1.86-1.78 (m, 1H), 1.72-1.62 (m, 1H), 1.54-1.42 (m, 2H). LC-MS $(M+H)^+ = 581.0$.

Example 54: 4- (2- (2- (3- (((1S, 2R)-2-hydroxycyclopentyl)amino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide



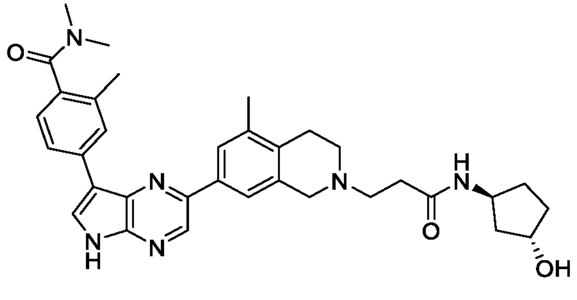
Example 54 (10 mg, 9%) was prepared in a manner similar to that in Example 23 step 4 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and (1R, 2S)-2-aminocyclopentan-1-ol hydrochloride. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.32 – 10.13 (m, 1H), 8.90 (s, 1H), 8.48 (s, 1H), 8.26-8.18 (m, 2H), 7.86 (s, 3H), 7.25 (d, *J* = 7.9 Hz, 1H), 4.70-4.55 (m, 1H), 3.96-3.80 (m, 2H), 3.31 (s, 3H), 3.07-2.70 (m, 11H), 2.40-2.25 (m, 7H), 1.80-1.60 (m, 3H), 1.60-1.40 (m, 3H). LC-MS (M+H)$^+$ = 581.0.

Example 55: 4- (2- (2- (3- ((cyclopropylmethyl)amino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide



To a stirring solution of 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid (150 mg, 0.301 mmol) and cyclopropylmethanamine (22 mg, 0.301 mmol) in DMF (5 mL) was added HATU (172 mg, 0.452 mmol) and Et_3N (456 mg, 0.452 mmol). The resulting solution was stirred at r.t for 2 h. Water (10 mL) was added and the mixture was extracted with EtOAc (10 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column, eluted with MeOH/DCM (1:20) then by prep-TLC, developed with MeOH/DCM (1:15) to give Example 55 (24 mg, 15%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.33 (s, 1H), 8.86 (s, 1H), 8.46 (s, 1H), 8.25 – 8.19 (m, 2H), 8.04 (t, *J* = 5.5 Hz, 1H), 7.86 (s, 1H), 7.73 (s, 1H), 7.27 – 7.22 (m, 1H), 3.72 - 3.64 (m, 2H), 3.03 (s, 3H), 2.94 (t, *J* = 6.1 Hz, 2H), 2.83 (s, 3H), 2.79 – 2.69 (m, 6H), 2.37 (t, *J* = 7.1 Hz, 2H), 2.34 – 2.26 (m, 6H), 0.92 – 0.80 (m, 1H), 0.40 – 0.31 (m, 2H), 0.17 - 0.09 (m, 2H). LC-MS (M+H)$^+$ = 551.5

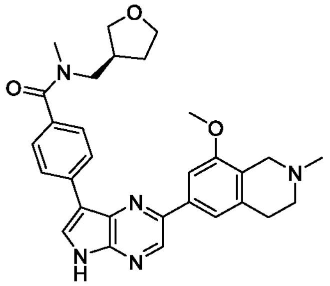
Example 56: 4- (2- (2- (3- (((1S, 3S)-3-hydroxycyclopentyl)amino)-3-oxopropyl)-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide



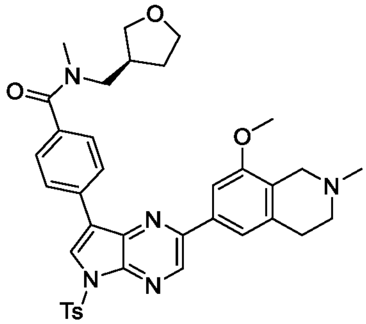
Example 56 (25 mg, 21%) was prepared in a manner similar to that in Example 55 from 3- (7- (7- (4- (dimethylcarbamoyl)-3-methylphenyl)-5H-pyrrolo[2, 3-b]pyrazin-2-yl)-5-methyl-3, 4-dihydroisoquinolin-2 (1H)-yl)propanoic acid and (1S, 3S)-3-aminocyclopentan-1-ol. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.38 (s, 1H), 10.48 – 10.12 (m, 1H), 8.89 (s, 1H), 8.48 (d, *J* = 2.5 Hz, 1H), 8.27 – 8.18 (m, 2H), 8.18 – 7.70 (m, 3H), 7.25 (d, *J* = 7.8 Hz, 1H), 4.82 – 4.27 (m, 2H), 4.26 – 4.10 (m, 2H), 4.09 – 3.36 (m, 3H), 3.03 (s, 3H), 3.00 - 2.85 (m, 2H), 2.83 (s, 3H), 2.81 –

2.55 (m, 3H), 2.34 (s, 3H), 2.30 (s, 3H), 2.04 – 1.91 (m, 1H), 1.89 – 1.72 (m, 2H), 1.56 – 1.47 (m, 1H), 1.46 – 1.37 (m, 1H), 1.37 – 1.26 (s, 1H). LC-MS $(M+H)^+ = 581.6$.

Example 57: (S)-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide

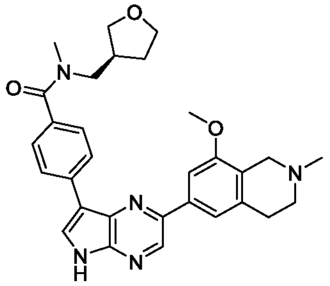


Step 1: (S)-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide



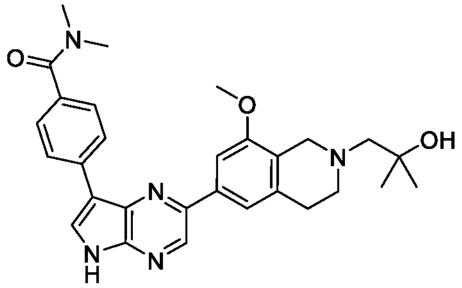
The title compound (70 mg, 58%) was prepared in a manner similar to that in Example 2 step 5 from (S)-4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide and 8-methoxy-2-methyl-6- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline. LC-MS $(M+H)^+ = 666.4$.

Step 2: (S)-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide

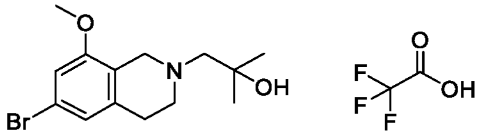


Example 57 (8 mg, 12%) was prepared in a manner similar to that in Example 1 step 10 from (S)-4- (2- (8-methoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methyl-N- ((tetrahydrofuran-3-yl)methyl)benzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.42 (d, *J* = 2.4 Hz, 1H), 8.95 (s, 1H), 8.54 (d, *J* = 2.8 Hz, 1H), 8.41 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.53-7.45 (m, 2H), 3.94 (s, 3H), 3.89-3.40 (m, 7H), 3.30-3.20 (m, 1H), 3.00 (s, 3H), 2.97-2.91 (m, 2H), 2.71-2.60 (m, 3H), 2.41 (s, 3H), 2.10-1.80 (m, 1H), 1.70-1.30 (m, 1H). LC-MS $(M+H)^+ = 512.3$.

Example 58: 4- (2- (2- (2-hydroxy-2-methylpropyl)-8-methoxy-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide

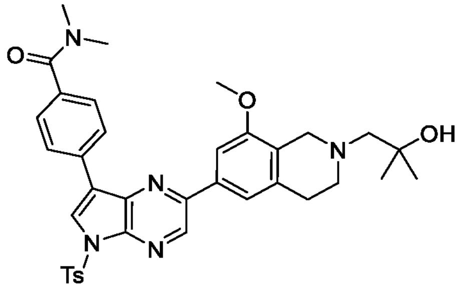


Step 1: 1- (6-bromo-8-methoxy-3, 4-dihydroisoquinolin-2 (1H)-yl)-2-methylpropan-2-ol; trifluoroacetic acid



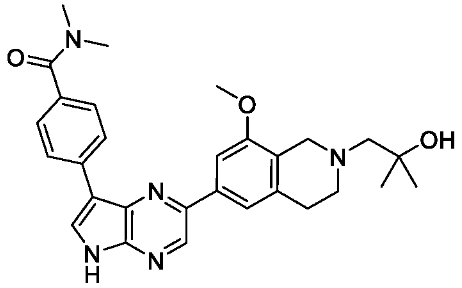
A solution of 6-bromo-8-methoxy-1, 2, 3, 4-tetrahydroisoquinoline (250 mg, 1.03 mmol) and 2, 2-dimethyloxirane (112 mg, 1.55 mmol) in EtOH (5 mL) was irradiated under microwave for 90 min at 110 °C. The mixture was cooled down to room temperature and concentrated under reduced pressure. The residue was purified by C18 chromatography, eluted with acetonitrile/water (contained 0.05% TFA) (0:1 to 1:1) to give the title compound (300 mg, 70%). LC-MS $(M+H)^+ = 314.0$.

Step 2: 4- (2- (2- (2-hydroxy-2-methylpropyl)-8-methoxy-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide



The title compound (300 mg, 65%) was prepared in a manner similar to that in Example 1 step 9 from N, N-dimethyl-4- (2- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)benzamide and 1- (6-bromo-8-methoxy-3, 4-dihydroisoquinolin-2 (1H)-yl)-2-methylpropan-2-ol; trifluoroacetic acid. LC-MS $(M+H)^+ = 654.3$.

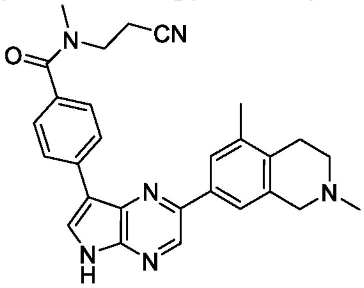
Step 3: 4- (2- (2- (2-hydroxy-2-methylpropyl)-8-methoxy-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide



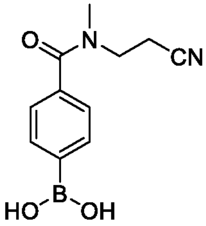
Example 58 (35 mg, 18%) was prepared in a manner similar to that in Example 1 step 10 from 4- (2- (2- (2-hydroxy-2-methylpropyl)-8-methoxy-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide. ^{1}H NMR (400 MHz, DMSO-

d6) δ 12.41 (s, 1H), 8.94 (s, 1H), 8.53 (s, 1H), 8.41 (d, *J* = 8.4 Hz, 2H), 7.64-7.54 (m, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 4.18 (s, 1H), 3.93 (s, 3H), 3.79-3.60 (m, 2H), 3.09-2.98 (m, 6H), 2.97-2.88 (m, 2H), 2.88-2.75 (m, 2H), 2.48-2.37 (m, 2H), 1.14 (s, 6H). LC-MS $(M+H)^+ = 500.3$.

Example 59: N- (2-cyanoethyl)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methylbenzamide

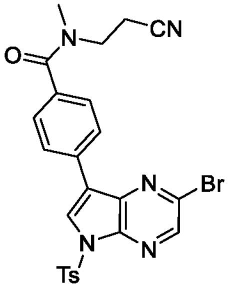


Step 1: (4- ((2-cyanoethyl) (methyl)carbamoyl)phenyl)boronic acid



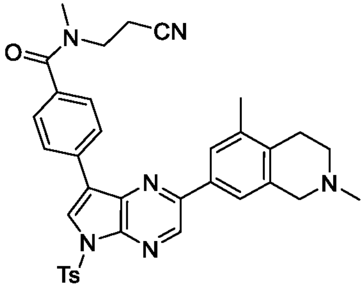
The title compound (2.4 g, 63%) was prepared in a manner similar to that in Example 15 step 1 from 4-boronobenzoic acid and 3- (methylamino)propanenitrile. LC-MS $(M+H)^+ = 233.1$.

Step 2: 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-cyanoethyl)-N-methylbenzamide



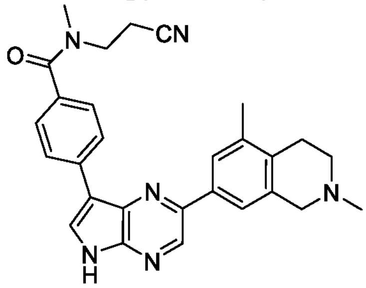
The title compound (330 mg, 44%) was prepared in a manner similar to that in Example 1 step 2 from 2-bromo-7-iodo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazine and (4- ((2-cyanoethyl) (methyl)carbamoyl)phenyl)boronic acid. LCMS $(M+H)^+ = 538.1$.

Step 3: N- (2-cyanoethyl)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methylbenzamide



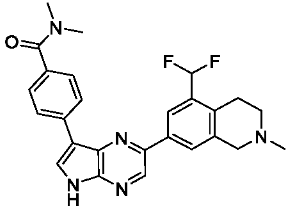
The title compound (185 mg, 55%) was prepared in a manner similar to that in Example 2 step 5 from 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N- (2-cyanoethyl)-N-methylbenzamide and 2, 5-dimethyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline. LC-MS $(M+H)^+ = 619.4$.

Step 4: N- (2-cyanoethyl)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methylbenzamide

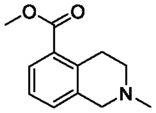


Example 59 (29 mg, 12%) was prepared in a manner similar to that in Example 1 step 10 from N- (2-cyanoethyl)-4- (2- (2, 5-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N-methylbenzamide. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.41 (d, *J* = 2.4 Hz, 1H), 8.88 (s, 1H), 8.53 (d, *J* = 2.4 Hz, 1H), 8.41 (d, *J* = 8.0 Hz, 2H), 7.86 (s, 1H), 7.74 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 3.87-3.56 (m, 4H), 3.04 (s, 3H), 2.98-2.86 (m, 2H), 2.81-2.65 (m, 4H), 2.40 (s, 3H), 2.32 (s, 3H). LC-MS $(M+H)^+ = 465.3$.

Example 95: 4- (2- (5- (difluoromethyl)-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide

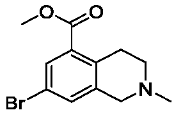


Step 1: methyl 2-methyl-1, 2, 3, 4-tetrahydroisoquinoline-5-carboxylate



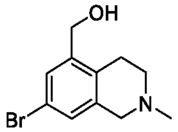
The title compound (830 mg, 71%) was prepared in a manner similar to that in Example 1 step 8 from methyl 1, 2, 3, 4-tetrahydroisoquinoline-5-carboxylate and formalin. LC-MS $(M+H)^+ = 206.1$.

Step 2: methyl 7-bromo-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline-5-carboxylate



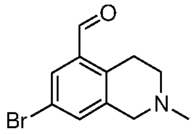
To a stirred mixture of methyl 2-methyl-1, 2, 3, 4-tetrahydroisoquinoline-5-carboxylate (200 mg, 0.97 mmol) in aqueous H_2SO_4 (55%, 1.0 mL) was added $KBrO_3$ (170 mg, 0.97 mmol) in portions at 0 °C. The mixture was stirred for 15 h at room temperature then quenched with water (10 mL) at 0 °C. The mixture was basified to pH 8 with NaOH (4 M) then successively extracted with DCM (30 mL x 2). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (1:10) to give the title compound (82 mg, 30%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.77 (s, 1 H), 7.54 (s, 1 H), 3.82 (s, 3 H), 3.51 (s, 2 H), 3.04-2.96 (m, 2 H), 2.60-2.54 (m, 2 H), 2.31 (s, 3 H). LC-MS $(M+H)^+$ = 284.0.

Step 3: (7-bromo-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-5-yl)methanol



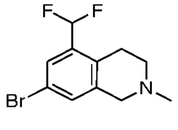
At 0 °C, to a solution of methyl 7-bromo-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline-5-carboxylate (507 mg, 1.78 mmol) in THF (12 mL) was added $LiBH_4$ in THF (2.0 M, 5.0 mL, 10 mmol) dropwise. To the mixture was added MeOH (3 mL). The solution was stirred for 15 h at 70 °C. The mixture was cooled to room temperature then quenched with water (15 mL). The mixture was extracted with ethyl acetate (25 mL x 3). The organic phases were combined, washed with brine and dried over Na_2SO_4. The solvent was concentrated under reduced pressure and the residue was purified by silica gel flash chromatography eluting with MeOH/DCM (0:1 to 1:9) to give the title compound (190 mg, 41%). LC-MS $(M+H)^+$ = 256.1.

Step 4: 7-bromo-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline-5-carbaldehyde



At 0 oC, to a solution of (7-bromo-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-5-yl)methanol (60 mg, 0.233 mmol) in DCM (3 mL) was added Dess-Martin periodinane (119 mg, 0.280 mmol) under nitrogen. The mixture was stirred for 2 h at room temperature then quenched with saturated $NaHCO_3$ (20 mL). The mixture was extracted with DCM (20 mL x 3). The combined organic layer was washed with brine (20 mL) and dried over Na_2SO_4 then filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel flash chromatography, eluted with EtOAc/hexane (0:1 to 1:9) to give the title compound (38 mg, 65%). LC-MS $(M+H)^+$ = 254.1.

Step 5: 7-bromo-5- (difluoromethyl)-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline

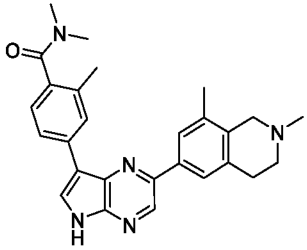


At 0 °C, to a solution of 7-bromo-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline-5-carbaldehyde (38 mg, 0.151 mmol) in DCM (4 mL) was added diethylaminosulfur trifluoride (148 mg, 0.914 mmol) dropwise. The mixture was stirred for 3 h at room temperature under nitrogen then quenched with saturated $NaHCO_3$ (15 mL) The mixture was extracted with ethyl acetate (15 mL x 3). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. The solvent was concentrated under reduced pressure and the residue was purified by silica gel flash chromatography, eluted with MeOH/DCM (0:1 to 1:9) to give the title compound (27 mg, 65%). LC-MS $(M+H)^+$ = 276.1.

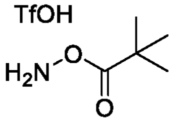
Step 6: 4- (2- (5- (difluoromethyl)-2-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N-dimethylbenzamide

Example 95 (19 mg, 42%) was prepared in a manner similar to that in Example 1 step 9 from 7-bromo-5- (difluoromethyl)-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline and 7- (4-(dimethylcarbamoyl)phenyl)-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-2-ylboronic acid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.47 (s, 1 H), 8.95 (s, 1 H), 8.54 (s, 1 H), 8.38 (d, *J* = 8.0 Hz, 2 H), 8.23 (s, 1 H), 8.07 (s, 1 H), 7.52 (d, *J* = 7.9 Hz, 2 H), 7.24 (t, *J* = 54.8 Hz, 1 H), 3.68 (s, 2 H), 3.01 (app s, 8 H), 2.71-2.64 (m, 2 H), 2.39 (s, 3 H). LC-MS $(M+H)^+$ = 462.3.

Example 126: 4- (2- (2, 8-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

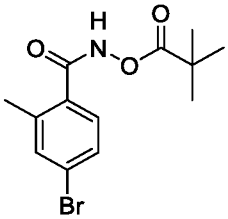


Step 1: O-pivaloylhydroxylamine trifluoromethanesulfonate salt



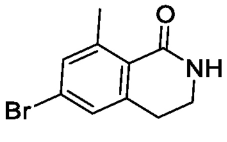
TfOH (18.9 g, 125.7 mmol) was added to a solution of tert-butyl (pivaloyloxy)carbamate (24.8 g, 114.3 mmol) in MTBE (230 mL) at 0 °C and stirred at room temperature for 4 h. The volume of solution was reduced to about 100 mL under reduced pressure and the precipitate was collected by filtration. The solid was dried under vacuum to give the title compound (26.0 g, 85%). LC-MS $(M+H)^+$ =118.0.

Step 2: 4-bromo-2-methyl-N- (pivaloyloxy)benzamide



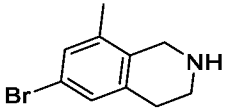
DIPEA (15.7 g, 121.6 mmol) was added to a solution of 4-bromo-2-methylbenzoic acid (8.82 g, 40.52 mmol) in THF (150 mL) at 0 °C, followed by T3P (25.8 g, 81.1 mmol) and O-pivaloylhydroxylamine trifluoromethanesulfonate salt (26.0 g, 97.3 mmol). The reaction was stirred at room temperature overnight. Brine (100 mL) was added and the mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (7.5 g, 59%). LC-MS $(M+H)^+$ =314.0.

Step 3: 6-bromo-8-methyl-3, 4-dihydroisoquinolin-1 (2H)-one



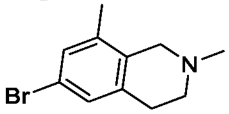
KOAc (5.16 g, 52.5 mmol) and dichloro (pentamethylcyclopentadienyl)rhodium (III) dimer (737.7 mg, 1.19 mmol) were added to a solution of 4-bromo-2-methyl-N-(pivaloyloxy)benzamide (7.5 g, 23.9 mmol) in acetonitrile (150 mL). The solution was stirred under an ethylene atmosphere (3 bar) at room temperature for overnight. The solvent was removed in vacuo and the residue was partitioned between water (20 mL) and ethyl acetate (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography to give the title compound (4.67 g, 82%). LC-MS $(M+H)^+$ =240.0.

Step 4: 6-bromo-8-methyl-1, 2, 3, 4-tetrahydroisoquinoline



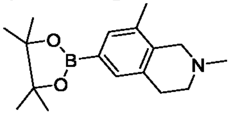
To 6-bromo-8-methyl-3, 4-dihydroisoquinolin-1 (2H)-one (4.67 g, 19.5 mmol) was added BH_3 in THF (1.0 M, 77.8 mL, 77.8 mmol) and the reaction mixture was refluxed overnight. The mixture was cooled to 0 °C and MeOH (5 mL) was added followed by HCl (2 M, 25 mL). The solution was heated to 80 °C for 3 h. The mixture was cooled to room temperature and solvent was removed in vacuo. The residue was dissolved in DCM (50 mL) and the solution was successively washed with saturated $NaHCO_3$ (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography to give the title compound (3.79 g, 86%). LC-MS $(M+H)^+$ =226.0.

Step 5: 6-bromo-2, 8-dimethyl-1, 2, 3, 4-tetrahydroisoquinoline



Formalin (37%, 3.48 g, 42.90 mmol) was added to a solution of 6-bromo-8-methyl-1, 2, 3, 4-tetrahydroisoquinoline (1.94 g, 8.58 mmol) in DCM (30 mL). After 5 min, NaBH $(OAc)_3$ (3.64 g, 17.2 mmol) was added and the mixture was stirred at room temperature overnight. Saturated $NaHCO_3$ (20 mL) was added and the mixture was extracted with DCM (30 mL x 2). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography to give the title compound (1.85 g, 90%). LC-MS $(M+H)^+$ =240.0.

Step 6: 2, 8-dimethyl-6- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline

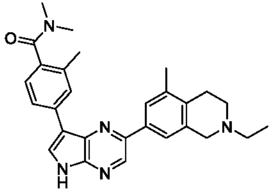


6-bromo-2, 8-dimethyl-1, 2, 3, 4-tetrahydroisoquinoline (1.85 g, 7.71 mmol), BPD (3.92 g, 15.4 mmol), Pd (dppf)Cl2 (282 mg, 0.385 mmol) and KOAc (2.27 g, 23.1 mmol) were added to 1, 4-dioxane (25 mL) and the mixture was heated to 95 °C under N_2 overnight. After cooled to room temperature, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography to give the title compound (1.77 g, 80%). LC-MS $(M+H)^+$ =288.0.

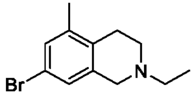
Step 7: 4- (2- (2, 8-dimethyl-1, 2, 3, 4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide (879 mg, 1.71 mmol), 2, 8-dimethyl-6- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline (590 mg, 2.06 mmol), K_2CO_3 (473 mg, 3.43 mmol) and Pd (dppf)Cl_2 (63 mg, 0.086 mmol) was added to 1, 4-dioxane (20 mL) and water (3 mL), and the mixture was heated to 100 °C under N_2 then stirred for overnight. The mixture was cooled to room temperature and concentrated in vacuo. The residue was diluted with water (30 mL) and extracted with DCM (30 mL x 2). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The crude was purified by silica gel flash chromatography to give Example 126 (120 mg, 16%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.34 (s, 1H), 8.88 (s, 1H), 8.46 (s, 1H), 8.27 (s, 1H), 8.20 (d, *J* = 7.9 Hz, 1H), 7.84 (s, 1H), 7.80 (s, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 3.47 (s, 2H), 3.03 (s, 3H), 2.98-2.91 (m, 2H), 2.83 (s, 3H), 2.67-2.60 (m, 2H), 2.42 (s, 3H), 2.33-2.25 (m, 6H). LC-MS $(M+H)^+$ =440.0.

Example 127: 4- (2- (2-ethyl-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

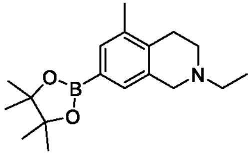


Step 1: 7-bromo-2-ethyl-5-methyl-1, 2, 3, 4-tetrahydroisoquinoline



The title compound (787 mg, 100%) was prepared in the same manner which described in Example 1 step 8 from 7-bromo-5-methyl-1, 2, 3, 4-tetrahydroisoquinoline and acetaldehyde. LCMS $(M+H)^+$ = 254.0, 256.0.

Step 2: 2-ethyl-5-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline

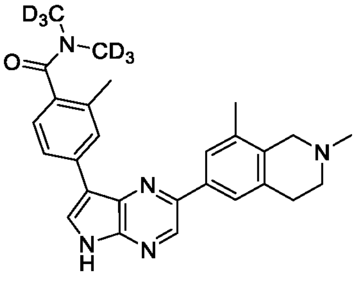


The title compound (530 mg, 57%) was prepared in the same manner which described in Example 2 step 4 from 7-bromo-2-ethyl-5-methyl-1, 2, 3, 4-tetrahydroisoquinoline. LCMS $(M+H)^+$ = 302.1.

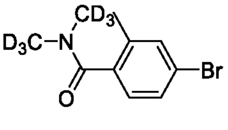
Step 3: 4- (2- (2-ethyl-5-methyl-1, 2, 3, 4-tetrahydroisoquinolin-7-yl)-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide

Example 127 (120 mg, 22%) was prepared in a manner similar to that in Example 2 step 5 from 4- (2-bromo-5-tosyl-5H-pyrrolo[2, 3-b]pyrazin-7-yl)-N, N, 2-trimethylbenzamide and 2-ethyl-5-methyl-7- (4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.32 (s, 1H), 8.86 (s, 1H), 8.45 (s, 1H), 8.27-8.20 (m, 2H), 7.86 (s, 1H), 7.74 (s, 1H), 7.25 (d, J = 7.6 Hz, 1H), 3.65 (s, 2H), 3.03 (s, 3H), 2.83 (s, 3H), 2.78-2.70 (m, 4H), 2.57-2.51 (m, 2H), 2.31 (s, 3H), 2.29 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H). LCMS $(M+H)^+$ = 454.6.

Example 128: 4-(2-(2,8-dimethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2-methyl-N,N-bis(methyl-d3)benzamide

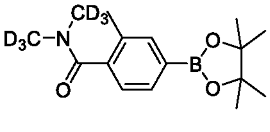


Step 1: 4-bromo-2-methyl-N,N-bis(methyl-d3)benzamide



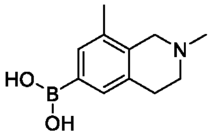
A mixture of 4-bromo-2-methylbenzoic acid (12.4 g, 57.6 mmol) and $SOCl_2$ (30 mL) was stirred at 60 °C for 3 h under a refluxing condenser. The mixture was cooled to room temperature and concentrated under vacuum. The crude residue was dissolved in anhydrous DCM (50 mL) and the solution was added dropwise into a solution of bis(methyl-d3)amine HCl salt (5.0 g, 57 mmol) and Et_3N (20 g, 200 mmol) in anhydrous DCM (200 mL) at 0 °C. The mixture was warmed to room temperature, stirred for 2 h then diluted with water (200 mL). The organic layer was separated, dried over Na_2SO_4 then concentrated under reduced pressure to give the title compound (12.7 g, 88%). LC-MS $(M+H)^+$ = 248.1.

Step 2: 2-methyl-N,N-bis(methyl-d3)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide



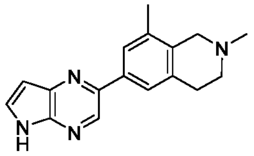
The title compound (7.4 g, 62%) was prepared in a manner similar to that in Example 2 step 2 from 4-bromo-2-methyl-N,N-bis(methyl-d3)benzamide and BPD. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 2H), 7.17 (d, J = 6.9 Hz, 1H), 2.29 (s, 3H), 1.35 (s, 12H). LC-MS $(M+H)^+$ = 296.2.

Step 3: (2,8-dimethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)boronic acid



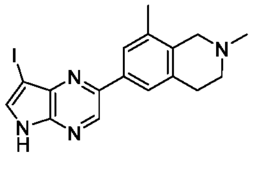
To a solution of 6-bromo-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline (46 g, 191 mmol) in THF (500 mL) was added n-BuLi (2.4 M, 95 mL, 228 mmol) dropwise at -78 °C and the mixture was stirred at -78°C for 30 min. To the mixture was added triisopropyl borate (54 g, 287 mmol) dropwise and the mixture was stirred at -78°C for 2 h. The mixture was quenched with water (500 mL), and most of THF was evaporated under reduced pressure. The mixture was washed with EtOAc (100 mL x 2) and the aqueous layer was neutralized with HCl (2 M) until its pH reached 9. The precipitate was collected by filtration and dried under vacuum to give the title compound (28 g, 71%). LC-MS $(M+H)^+ = 206.1$.

Step 4: 2,8-dimethyl-6-(5H-pyrrolo[2,3-b]pyrazin-2-yl)-1,2,3,4-tetrahydroisoquinoline



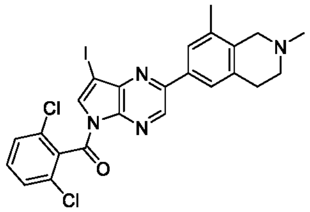
To a solution of 2-bromo-5H-pyrrolo[2,3-b]pyrazine (16.0 g, 81.3 mmol) and (2,8-dimethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)boronic acid (20.0 g, 97.6 mmol) in dioxane (300 mL) and water (75 mL) was added K_2CO_3 (22.5 g, 163 mmol) and Pd(dppf)Cl_2 (1.78 g, 2.44 mmol) under nitrogen atmosphere. After being stirred for 15 h at 90 °C, the reaction mixture was cooled to room temperature and extracted with EtOAc (100 mL x 2). The combined organic layer was concentrated under reduced pressure. The residue was partitioned in between aq. HCl (200 mL, 1 N) and DCM (100 mL), then stirred at 20 minutes. The organic layer was discarded and the pH of aqueous layer was adjusted to 8-9 with aq. NaOH (6 M). The mixture was extracted DCM (200 mL x 3). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was triturated with TBME (100 mL) for 30 minutes, and the solid was collected by filtration to give the title compound (16.4 g, 60%). ^1H NMR (400 MHz, DMSO-*d6*) δ 12.07 (s, 1H), 8.79 (s, 1H), 7.87 (app s, 1H), 7.75 (s, 1H), 7.72 (s, 1H), 6.65 (app s, 1H), 3.45 (s, 2H), 2.96-2.87 (m, 2H), 2.64-2.57 (m, 2H), 2.41 (s, 3H), 2.25 (s, 3H). LCMS $(M+H)^+ = 279.0$.

Step 5: 6-(7-iodo-5H-pyrrolo[2,3-b]pyrazin-2-yl)-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline



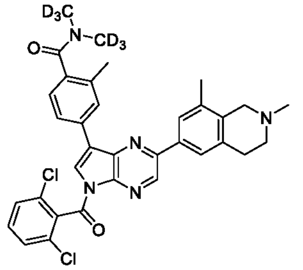
To a solution of 2,8-dimethyl-6-(5H-pyrrolo[2,3-b]pyrazin-2-yl)-1,2,3,4-tetrahydroisoquinoline (16.4 g, 59 mmol) in DMF (200 mL) was added NIS (13.3 g, 59 mmol) in portions at 0 °C. After being stirred for 30 minutes, water (600 mL) and saturated $Na_2S_2O_3$ (50 mL) was added with vigorous stirring. After 10 minutes, lots of solid appeared and the precipitate was collected by filtration to give the title compound (21.0 g, 88%). LCMS $(M+H)^+ = 405.0$.

Step 6: (2,6-dichlorophenyl)(2-(2,8-dimethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-7-iodo-5H-pyrrolo[2,3-b]pyrazin-5-yl)methanone



To a solution of 6-(7-iodo-5H-pyrrolo[2,3-b]pyrazin-2-yl)-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline (21.0 g, 51.85 mmol) in 2-methyl-THF (400 mL) was added triethylamine (11.2 mL, 77.8 mmol) and DMAP (634 mg, 5.2 mmol) at 0 °C, followed by dropwise addition of a solution of 2,6-dichlorobenzoyl chloride (13.0 g, 62.2 mmol) in 2-methyl-THF (50 mL). The mixture was warmed to room temperature and stirred for 2 h, then quenched with water (200 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (200 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was triturated with MTBE (200 mL) for 30 minutes, and the precipitate was collected by filtration to give the title compound (24.0 g, 80%). LCMS $(M+H)^+ = 577.0$.

Step 7: 4-(5-(2,6-dichlorobenzoyl)-2-(2,8-dimethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2-methyl-N,N-bis(methyl-d3)benzamide



To a mixture of (2,6-dichlorophenyl)(2-(2,8-dimethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-7-iodo-5H-pyrrolo[2,3-b]pyrazin-5-yl)methanone (7.3 g, 12.7 mmol) and 2-methyl-N,N-bis(methyl-d3)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (4.1 g, 13.9 mmol) in 1,4-dioxane (100 mL) and water (50 mL) was added K_2CO_3 (4.4 g, 31.8 mmol) and Pd(dppf)Cl_2 (470 mg, 0.60 mmol). The mixture was stirred at 100 °C for 3 h under N_2, then cooled to room temperature. The mixture was successively extracted with EtOAc (100 mL x 3). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated.

The residue was purified by silica gel column chromatography, eluting with MeOH/DCM (1:20) to give the title compound (6.7 g, 86%). LC-MS $(M+H)^+ = 618.2$.

Step 8: 4-(2-(2,8-dimethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2-methyl-N,N-bis(methyl-d3)benzamide

To a suspension of 4-(5-(2,6-dichlorobenzoyl)-2-(2,8-dimethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl)-2-methyl-N,N-bis(methyl-d3)benzamide (6.7 g, 10.9 mmol) in dioxane (100 mL) was added a solution of NaOH (2.0 g, 50 mmol) in water (50 mL). The mixture was stirred at 100 °C for 3 h. The mixture was cooled to room temperature then extracted with EtOAc (100 mL x 3). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by crystallization in EtOH to give Example 128 (3.5 g, 72%). ^1H NMR (400 MHz, DMSO) δ 12.34 (s, 1H), 8.88 (s, 1H), 8.46 (s, 1H), 8.26 (s, 1H), 8.19 (d, $J = 6.6$ Hz, 1H), 7.84 (s, 1H), 7.80 (s, 1H), 7.24 (d, $J = 7.3$ Hz, 1H), 3.46 (brs, 2H), 2.95 (brs, 2H), 2.62 (brs, 2H), 2.41 (s, 3H), 2.29 (brs, 6H). LC-MS $(M+H)^+ = 446.5$.

Biological Activity

HPK1 Kinase Activity Assay at 1 mM ATP

Compounds disclosed herein were tested for inhibition of HPK1 kinase (aa1-346, Life Technologies) activity in assays based on the time-resolved fluorescence-resonance energy transfer (TR-FRET) methodology. The assays were carried out in 384-well low volume black plates in a reaction mixture containing HPK1 kinase (40 nM), 1 mM ATP, 0.5 μM STK1 substrate and 0-10 μM compound in buffer containing 50 mM HEPES, 0.01% BSA, 0.1 mM Orthovanadate, 10 mM $MgCl_2$, 1 mM DTT, pH=7.0, 0.005% Tween-20. The kinase was incubated with the compounds disclosed herein or DMSO for 60 minutes at room temperature and the reaction was initiated by the addition of ATP and STK1 substrate. After reaction at room temperature for 120 minutes, an equal volume of stop/detection solution was added according to the manufacturer's instruction (CisBio). The stop/detection solution contained STK Antibody-Cryptate and XL665-conjugated streptavidin in Detection Buffer. The TR-FRET signals (ratio of fluorescence emission at 665 nm over emission at 620 nm with excitation at 337 nm wavelength) were recorded on a PHERAstar FS plate reader (BMG Labtech). Phosphorylation of STK1 substrate led to the binding of STK Antibody-Cryptate to the biotinylated STK1 substrate, which places fluorescent donor (Eu^{3+} crypate) in close proximity to the accepter (Streptavidin-XL665), thus resulting in a high degree of fluorescence resonance energy transfer. The inhibition of HPK1 in presence of increasing concentrations of compounds was calculated based on the ratio of fluorescence at 665 nm to that at 620 nm. The IC_{50} for each compound was derived from fitting the data to the four-parameter logistic equation by Graphpad Prism software. The compounds disclosed herein showed the enzymatic activity values as in Table 1.

Table 1. Enzymatic activity IC_{50} (nM) for the compounds disclosed herein

Comp No.	Enzymatic activity IC_{50} (nM)	Comp No.	Enzymatic activity IC_{50} (nM)
1	24	2	26
3	12	4	92
5	21	6	32
7A	34	7B	31
8	36	9	62
10	11	11	74
12	52	13	45
14	12	15	17
16	88	17	24
18	7	19	13
20	65	21	75
22	11	23	122
24	75	25	49
26	63	27	26
28	67	29	46
30	63	31	53
32	71	33	49
34	42	35	19
36	39	37	35
38	65	39	186
40	17	41	54
42	85	43	37
44	82	45	52
46	65	47	22
48	65	49	67
50	137	51	36
52	74	53	78
54	68	55	89
56	93	57	14
58	21	59	16
95	71	126	43
127	86	128	21

Cytotoxicity on HEK293 Cells Proliferation (HEK293 Cell Viability Assay)

Methods:

HEK293 cell line were used in this study. Cell lines were maintained in DMEM (Dulbecco's Modified Eagle Medium) supplemented with 10% fetal bovine serum (Thermo Fisher), 50 units/mL penicillin and streptomycin (Thermo Fisher) and kept at 37° C in a humidified atmosphere containing 5% CO_2 in air. Cell lines were reinstated from frozen stocks that were laid down within 50 passages from the original cells purchased. The growth-inhibitory activity of compounds in HEK293 cells was determined using CellTiter-Glo luminescent cell viability assay (Promega). 3000 cells per well were seeded into a 96-well plate to ensure logarithmic growth for 3 days treatment period. Cells were treated with a 10-point dilution series. The final compound concentration was from 0 to 10 μM. Following a 3-day exposure to the test compounds, 30 μL of CellTiter-Glo reagent was added into 100 μL cell culture medium per well. Mixture was mixed on an orbital shaker for 2 minutes to allow cell lysis, followed by 10 minutes of incubation at room temperature to allow development and stabilization of luminescent signal, which corresponded to the quantity of ATP and thus the quantity of metabolically active cells. Luminescent signal was measured using PHERAstar FS reader (BMG Labtech). IC_{50} values for cell viability were determined with Dotmatics.

Comp No.	HEK293 cell viability IC_{50} (nM)	Comp No.	HEK293 cell viability IC_{50} (nM)
1	3646	2	3338
3	1272	6	5559
10	1417	15	1037
16	>10000	20	3872
38	2187	95	5181
126	>10000	127	3128

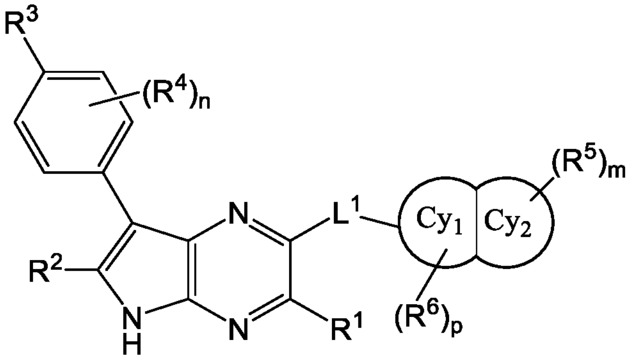
It is to be understood that, if any prior art publication is referred to herein; such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art in any country.

The disclosures of all publications, patents, patent applications and published patent applications referred to herein by an identifying citation are hereby incorporated herein by reference in their entirety.

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. Therefore, the description and examples should not be construed as limiting the scope of the invention.

WHAT IS CLAIMED IS:

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, wherein

R^1 and R^2 are each independently hydrogen, halogen, -$C_{1\text{-}8}$alkyl, -$C_{2\text{-}8}$alkenyl, -$C_{2\text{-}8}$alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo, -CN, -NO_2, -OR^a, -SO_2R^a, -COR^a, -CO_2R^a, -$CONR^aR^b$, -C (=NR^a)NR^bR^c, -NR^aR^b, -NR^aCOR^b, -$NR^aCONR^bR^c$, -$NR^aCO_2R^b$, -$NR^aSONR^bR^c$, -$NR^aSO_2NR^bR^c$, or –$NR^aSO_2R^b$, each of said -$C_{1\text{-}8}$alkyl, -$C_{2\text{-}8}$alkenyl, -$C_{2\text{-}8}$alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with halogen, hydroxy, -$C_{1\text{-}8}$alkyoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

R^a, R^b, and R^c are each independently hydrogen, -$C_{1\text{-}8}$alkyl, -$C_{2\text{-}8}$alkenyl, -$C_{2\text{-}8}$alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

n is 0, 1, 2, 3 or 4;

R^3 and R^4, at each of its occurrence, are independently halogen, -$C_{1\text{-}8}$alkyl, -$C_{2\text{-}8}$alkenyl, -$C_{2\text{-}8}$alkynyl, cycloalkyl, heterocyclyl, -$C_{1\text{-}8}$alkyl-heterocyclyl, -$C_{1\text{-}8}$alkyl-cycloalkyl, aryl, heteroaryl, oxo, -CN, -NO_2, -OR^{3a}, -SO_2R^{3a}, -$SO_2NR^{3a}R^{3b}$, -COR^{3a}, -CO_2R^{3a}, -$CONR^{3a}R^{3b}$, -C (=NR^{3a})$NR^{3b}R^{3c}$, -$NR^{3a}R^{3b}$, -$NR^{3a}COR^{3b}$, -$NR^{3a}CONR^{3b}R^{3c}$, -$NR^{3a}CO_2R^{3b}$, -$NR^{3a}SONR^{3b}R^{3c}$, -$NR^{3a}SO_2NR^{3b}R^{3c}$, or –$NR^{3a}SO_2R^{3b}$, each of said -$C_{1\text{-}8}$alkyl, -$C_{2\text{-}8}$alkenyl, -$C_{2\text{-}8}$alkynyl, cycloalkyl, heterocyclyl, -$C_{1\text{-}8}$alkyl-heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents R^{3d}; or R^3 and R^4, when on adjacent carbon atoms of the phenyl ring, together with the two intervening carbon atoms to which they are attached, form a 5- to 8-membered ring comprising 0, 1 or 2 heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s), said ring is optionally substituted with at least one substituents R^{3e};

or two R^4, when on adjacent carbon atoms of the phenyl ring, together with the two intervening carbon atoms to which they are attached, form a 5- to 8-membered ring comprising 0, 1 or 2 heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s);

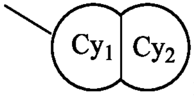
R^{3a}, R^{3b}, and R^{3c} are each independently hydrogen, -$C_{1\text{-}8}$alkyl, -$C_{2\text{-}8}$alkenyl, -$C_{2\text{-}8}$alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of said -$C_{1\text{-}8}$alkyl, -$C_{2\text{-}8}$alkenyl, -$C_{2\text{-}8}$alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents R^{3e}; or

(R^{3a} and R^{3b}), (R^{3b} and R^{3c}), or (R^{3c} and R^{3a}), together with the atom (s) to which they are attached, form a 3- to 12-membered ring, said ring comprising 0, 1 or 2 additional heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s), said ring is optionally substituted with at least one substituents R^{3e};

R^{3d} and R^{3e} are each independently halogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo, -CN, -NO_2, -OR^{3f}, -SO_2R^{3f}, -$SO_2NR^{3f}R^{3g}$, -COR^{3f}, -CO_2R^{3f}, -$CONR^{3f}R^{3g}$, -C (=NR^{3f})$NR^{3g}R^{3h}$, -$NR^{3f}R^{3g}$, -$NR^{3f}COR^{3g}$, -$NR^{3f}CONR^{3g}R^{3h}$, -$NR^{3f}CO_2R^{3f}$, -$NR^{3f}SONR^{3f}R^{3g}$, -$NR^{3f}SO_2NR^{3g}R^{3h}$, or –$NR^{3f}SO_2R^{3g}$, each of said -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents selected from halogen, -C_{1-8}alkyl, -OR^{3i}, -$NR^{3i}R^{3j}$, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

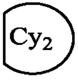
R^{3f}, R^{3g}, R^{3h}, R^{3i}, and R^{3j} are each independently hydrogen, -C_{1-8}alkyl, C_{1-8}alkoxy-C_{1-8}alkyl-, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

L^1 is a single bond, alkylene, cycloalkylene, $*^1$-O-alkylene-$**^1$, $*^1$-alkylene-O-$**^1$, $*^1$-NH-alkylene-$**^1$, $*^1$-alkylene-NH-$**^1$, $*^1$-NHC (O)-$**^1$, $*^1$-C (O)NH-$**^1$, alkenylene, or alkynylene; wherein $*^1$ refers to the position attached to Cy1, and $**^1$ refers to the position attached to the pyrrolo[2, 3-b]pyrazine ring;



is a fused heterocyclyl, fused heteroaryl, fused aryl, fused cycloalkyl, fused cycloalkenyl, or fused cycloalkynyl, 

is optionally substituted with R^6;

p is 0, 1, 2, 3, 4; 

is optionally substituted with R^5, m is 0, 1, 2, 3, 4;

R^5 at each of its occurrence, is each independently halogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, -C_{1-8}alkyl-cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo, -CN, -NO_2, -OR^{5a}, -SO_2R^{5a}, -$SO_2NR^{5a}R^{5b}$, -$POR^{5a}R^{5b}$, -COR^{5a}, -CO_2R^{5a}, -$CONR^{5a}R^{5b}$, -C (=NR^{5a})$NR^{5b}R^{5c}$, -$CH_2CONR^{5a}R^{5b}$, -$CH_2CH_2CONR^{5a}R^{5b}$, -$CH_2CH_2CH_2CONR^{5a}R^{5b}$, -$NR^{5a}R^{5b}$, -$CH_2NR^{5a}R^{5b}$, -$CH_2CH_2NR^{5a}R^{5b}$, -$CH_2CH_2CH_2NR^{5a}R^{5b}$, -$NR^{5a}COR^{5b}$, -$NR^{5a}CONR^{5b}R^{5c}$, -$NR^{5a}CO_2R^{5b}$, -$NR^{5a}SONR^{5b}R^{5c}$, -$NR^{5a}SO_2NR^{5b}R^{5c}$, or -$NR^{5a}SO_2R^{5b}$, each of said -$C_{1-8}$alkyl, -$C_{2-8}$alkenyl, -$C_{2-8}$alkynyl, cycloalkyl, -$C_{1-8}$alkyl-cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents R^{5d}; or two R^5, together with the atoms to which they are attached (provided that the valence theory is met), form a 4-, 5-, 6-, 7- or 8-membered ring, said ring comprising 0, 1 or 2 heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s), said ring is optionally substituted with at least one substituents R^{5e};

R^{5a}, R^{5b} and R^{5c} are each independently hydrogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, -C_{1-8}alkyl-C_{1-8}alkoxy, cycloalkyl, -C_{1-8}alkyl-heterocyclyl, -C_{1-8}alkyl-aryl, heterocyclyl, aryl, or heteroaryl, each of said -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, -C_{1-8}alkyl-C_{1-8}alkoxy, cycloalkyl, -C_{1-8}alkyl-heterocyclyl, -C_{1-8}alkyl-aryl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents R^{5e};

(R^{5a} and R^{5b}), (R^{5b} and R^{5c}), or (R^{5c} and R^{5a}), together with the atom (s) to which they are attached, form a 3- to 12-membered ring, said ring comprising 0, 1 or 2 additional heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s), said ring is optionally substituted with at least one substituents R^{5e};

R^{5d} and R^{5e} are each independently hydrogen, halogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo, -CN, -NO_2, -CF_3, -OR^{5f}, -SO_2R^{5f}, -$SO_2NR^{5f}R^{5g}$, -$POR^{5f}R^{5g}$, -COR^{5f}, -CO_2R^{5f}, -$CONR^{5f}R^{5g}$, -C (=NR^{5h})$NR^{5f}R^{5g}$, -$NR^{5f}R^{5g}$, -$NR^{5f}COR^{5g}$, -$NR^{5h}CONR^{5f}R^{5g}$, -$NR^{5f}CO_2R^{5h}$, -$NR^{5h}SONR^{5f}R^{5g}$, -$NR^{5h}SO_2NR^{5f}R^{5g}$, or –$NR^{5f}SO_2R^{5g}$, each of said -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents selected from halogen, -C_{1-8}alkyl, -OR^{5i}, -$NR^{5i}R^{5j}$, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

R^{5f}, R^{5g}, R^{5h}, R^{5i}, and R^{5j} are each independently hydrogen, oxo, -C_{1-8}alkyl, -C_{1-8}alkoxy, hydroxy, C_{1-8}alkoxy-C_{1-8}alkyl-, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

R^6 at each of its occurrence, is each independently hydrogen, halogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo, -CN, -NO_2, -OR^{6a}, -SO_2R^{6a}, -$SO_2NR^{6a}R^{6b}$, -COR^{6a}, -CO_2R^{6a}, -$CONR^{6a}R^{6b}$, -C (=NR^{6a})$NR^{6b}R^{6c}$, -$CH_2CONR^{6a}R^{6b}$, -CH_2 $CH_2CONR^{6a}R^{6b}$, -$CH_2CH_2CH_2CONR^{6a}R^{6b}$, -$NR^{6a}R^{6b}$, -$CH_2NR^{6a}R^{6b}$, -$CH_2$ $CH_2NR^{6a}R^{6b}$, -$CH_2CH_2CH_2NR^{6a}R^{6b}$, -$NR^{6a}COR^{6b}$, -$NR^{6a}CONR^{6b}R^{6c}$, -$NR^{6a}CO_2R^{6b}$, -$NR^{6a}SONR^{6b}R^{6c}$, -$NR^{6a}SO_2NR^{6b}R^{6c}$, or –$NR^{6a}SO_2R^{6b}$, each of said -$C_{1-8}$alkyl, -$C_{2-8}$alkenyl, -$C_{2-8}$alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents R^{6d}; or two R^6, together with the atom to which they are attached (provided that the valence theory is met), form a 4-, 5-, 6-, 7- or 8-membered ring, said ring comprising 0, 1 or 2 heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s), said ring is optionally substituted with at least one substituents R^{6e};

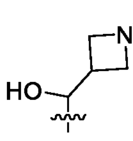
R^{6a}, R^{6b}, and R^{6c} are each independently hydrogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, C_{1-8}alkoxy-C_{1-8}alkyl-, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of said -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents R^{6e};

(R^{6a} and R^{6b}), (R^{6b} and R^{6c}), or (R^{6c} and R^{6a}), together with the atom (s) to which they are attached, form a 3- to 12-membered ring, said ring comprising 0, 1 or 2 additional heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s), said ring is optionally substituted with at least one substituents R^{6e};

R^{6d} and R^{6e} are each independently hydrogen, halogen, -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo, -CN, -NO_2, -OR^{6f}, -SO_2R^{6f}, -$SO_2NR^{6f}R^{6g}$, -COR^{6f}, -CO_2R^{6f}, -$CONR^{6f}R^{6g}$, -C (=NR^{6h})$NR^{6f}R^{6g}$, -$NR^{6f}R^{6g}$, -$NR^{6f}COR^{6g}$, -$NR^{6h}CONR^{6f}R^{6g}$, -$NR^{6f}CO_2R^{6h}$, -$NR^{6h}SONR^{6f}R^{6g}$, -$NR^{6h}SO_2NR^{6f}R^{6g}$, or –$NR^{6f}SO_2R^{6g}$, each of said -C_{1-8}alkyl, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents selected from halogen, -C_{1-8}alkyl, -OR^{6i}, -$NR^{6i}R^{6j}$, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

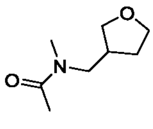
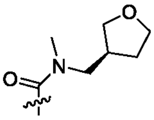
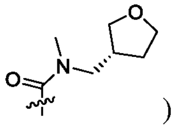
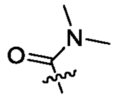
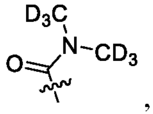
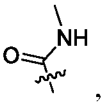
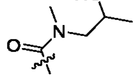
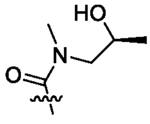
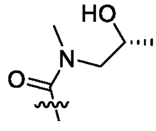
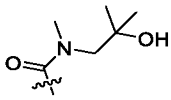
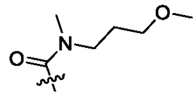
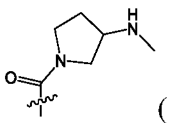
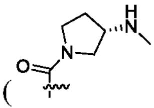
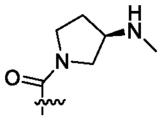
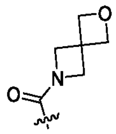
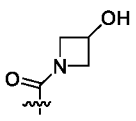
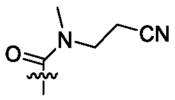
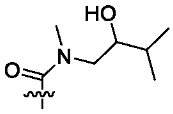
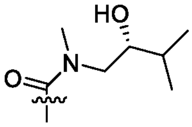
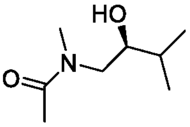
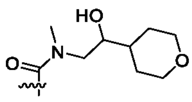
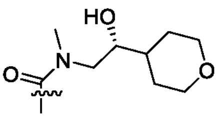
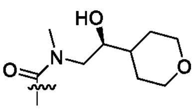
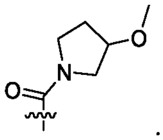
R^{6f}, R^{6g}, R^{6h}, R^{6i}, and R^{6j} are each independently hydrogen, oxo, -C_{1-8}alkyl, C_{1-8}alkoxy-C_{1-8}alkyl-, -C_{2-8}alkenyl, -C_{2-8}alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl.

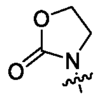
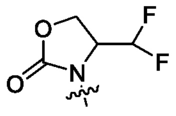
2. The compound of claim 1, wherein R^1 and R^2 are each hydrogen or -C_{1-8}alkyl (preferably hydrogen or methyl).

3. The compound of claim 1 or 2, wherein R^3 is –C_{1-8}alkyl, -C_{1-8}alkyl-heterocyclyl or -C_{1-8}alkyl-cycloalkyl, wherein said –C_{1-8}alkyl, -C_{1-8}alkyl-heterocyclyl or -C_{1-8}alkyl-cycloalkyl is optionally substituted with at least one substituents R^{3d}; R^{3d} is independently selected from -C_{1-8}alkyl or -OR^{3f}; R^{3f} is each independently hydrogen, -C_{1-8}alkyl; preferably R^3 is  .

4. The compound of claim 1 or 2, wherein R^3 is -$CONR^{3a}R^{3b}$; R^{3a} and R^{3b} are each independently hydrogen or -C_{1-8}alkyl (preferably methyl, ethyl, propyl, butyl, pentyl or hexyl); each of said -C_{1-8}alkyl is substituted with at least one substituents selected from hydrogen, -OR^{3f}, CN, 3- to-7 membered heterocyclyl comprising 1 or 2 heteroatoms selected from nitrogen, oxygen (for example, piperazinyl, piperidinyl, piperidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyranyl, or pyrrolidinyl); R^{3f} is selected from hydrogen or -C_{1-8}alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl or hexyl).

5. The compound of claim 1 or 2, wherein R^3 is -$CONR^{3a}R^{3b}$ or -$NR^{3a}R^{3b}$; R^{3a} and R^{3b} together with the nitrogen atom to which they are attached is 4- to 12-membered ring comprising 1 or 2 additional nitrogen or oxygen heteroatoms as ring member (e.g., monocyclic 3- to 8-membered ring or bicyclic spiro 7- to 12-membered ring), said ring is optionally substituted with at least one substituents R^{3e}; R^{3e} each is selected from oxo, -C_{1-8}alkyl, -OR^{3f}, -$NR^{3f}R^{3g}$, said-C_{1-8}alkyl is optionally substituted by at least one halogen, wherein R^{3f} and R^{3g} are each independently hydrogen, or -C_{1-8}alkyl.

6. The compound of any claims 1-5, wherein R^3 is selected from  ( or ),,  ,  ,  ,  ( or ),  ,  ,  ( or ),  ,  ,  ,  ( or ),  ( or ) or  .

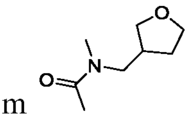
7. The compound of any claims 1-5, wherein R^3 is selected from  or  .

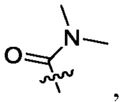
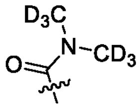
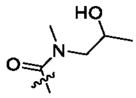
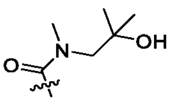
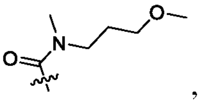
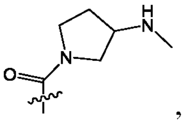
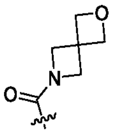
8. The compound of any claims 1-7, wherein n is 0, 1 or 2; R^4 is selected from halogen, $-C_{1-8}$alkyl (preferably methyl), halogen, CN, $-OR^{3a}$ or $-NR^{3a}CONR^{3b}R^{3c}$; said $-C_{1-8}$alkyl is optionally substituted with at least one substituents R^{3d}; R^{3a}, R^{3b} and R^{3c} are each independently hydrogen, $-C_{1-8}$alkyl (preferably methyl); R^{3d} is each independently halogen or $-C_{1-8}$alkyl.

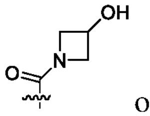
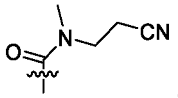
9. The compound of claim 8, wherein n is 1, R^4 is selected from $-C_{1-8}$alkyl (preferably methyl), halogen, CN, OR^{3a} or $-NR^{3a}CONR^{3b}R^{3c}$; said $-C_{1-8}$alkyl is optionally substituted with at least one substituents R^{3d}; R^{3a}, R^{3b} and R^{3c} are each independently hydrogen, or $-C_{1-8}$alkyl (preferably methyl); R^{3d} is each independently halogen or $-C_{1-8}$alkyl.

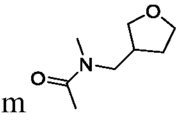
10. The compound of claim 8, wherein n is 2, and R^4 is halogen.

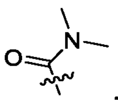
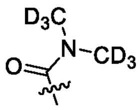
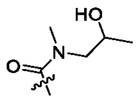
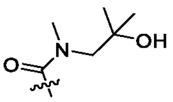
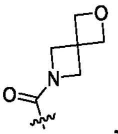
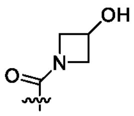
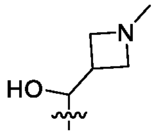
11. The compound of claim 8, wherein n is 1 or 2, and R^4 is selected from methyl, F, OH, CN, $-CHF_2$ or $-NHCOCH_3$.

12. The compound of any claims 1-8, wherein n is 0, and R^3 is selected from  ,

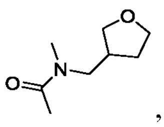
 ,  ,  ,  ,  ,  ,  ,

 or  .

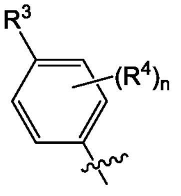
13. The compound of any claims 1-9, 11, wherein n is 1, and R^3 is selected from 

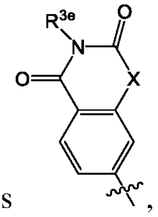
 ,  ,  ,  ,  ,  or  ; and R^4 is methyl, F, OH, CN, $-CHF_2$ or $-NHCOCH_3$.

14. The compound of any claims 1-8, 10-11, wherein n is 2, and R^3 is selected from

 , and R^4 is F.

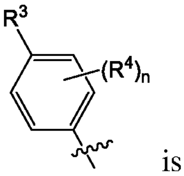
15. The compound of any claims 1-2, wherein R^3 and R^4, when on adjacent carbon atoms of the phenyl ring, together with the two intervening carbon atoms to which they are attached, form a 5- to 8-membered ring comprising 0, 1 or 2 heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s), said ring is optionally substituted with at least one substituents R^{3e}; each R^{3e} is independently selected from $-C_{1-8}$alkyl or oxo.

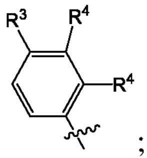
16. The compound of claim 15, wherein 

is 

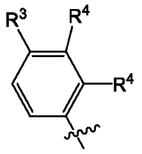
, X=NH or O, and R^{3e} is $-C_{1-8}$alkyl.

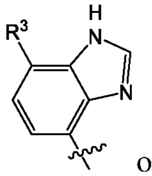
17. The compound of any claims 1-2, wherein n=2, two R^4 when on adjacent carbon atoms of the phenyl ring, together with the two intervening carbon atoms to which they are attached, form a 5- to 8-membered ring comprising 0, 1 or 2 heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s).

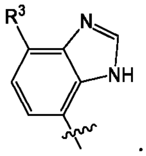
18. The compound of claim 17, wherein 

is 

; and two R^4, when on adjacent carbon atoms of the phenyl ring, together with the two intervening carbon atoms to which they are attached, form a 5-membered ring comprising 2 heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s).

19. The compound of claim 18, wherein 

is 

or 

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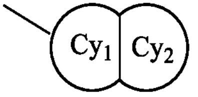
20. The compound of any claims 1-19, L^1 is a single bond.

21. The compound of any claims 1-20, wherein 

is benzo fused heterocyclyl, benzo fused heteroaryl, benzo fused cycloalkyl, benzo fused cycloalkenyl, benzo fused cycloalkynyl.

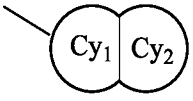
22. The compound of claim 21, wherein the benzo fused heterocyclyl is indolinyl, isoindolinyl, benzopyranyl, dihydrothiazolopyrimidinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, dihydrobenzofuranyl, dihydrobenzoxazinyl, dihydrobenzoimidazolyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, benzodioxolyl, benzodioxonyl, chromanyl, chromenyl, octahydrochromenyl, dihydrobenzodioxynyl, dihydrobenzoxezinyl, dihydrobenzodioxepinyl, dihydrothienodioxynyl, dihydrobenzooxazepinyl, tetrahydrobenzooxazepinyl, dihydrobenzoazepinyl, tetrahydrobenzoazepinyl, isochromanyl, or chromanyl.

23. The compound of claim 21 or22, wherein the benzo fused heterocyclyl is indolinyl, isoindolinyl, tetrahydroisoquinolyl, dihydrobenzofuranyl, dihydrobenzoimidazolyl, tetrahydrobenzooxazepinyl, tetrahydrobenzoazepinyl, or isochromanyl.

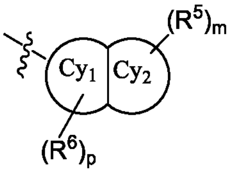
24. The compound of claim 23, wherein tetrahydroisoquinolinyl is selected from 1, 2, 3, 4-tetrahydroisoquinolinyl, 1, 2, 3, 4-tetrahydroisoquinolin-6-yl or 1, 2, 3, 4-tetrahydroisoquinolin-7-yl; tetrahydrobenzooxazepinyl is selected from 2, 3, 4, 5-tetrahydrobenzooxazepinyl, 2, 3, 4, 5-tetrahydrobenzo[f][1, 4]oxazepin-8-yl, or 2, 3, 4, 5-tetrahydrobenzo[f][1, 4]oxazepin-7-yl;

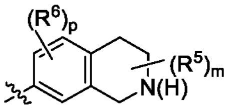
tetrahydrobenzoazepinyl is selected from 2, 3, 4, 5-tetrahydrobenzoazepinyl, 2, 3, 4, 5-tetrahydro-1H-benzo[c]azepin-7-yl and 2, 3, 4, 5-tetrahydro-1H-benzo[d]azepin-7-yl; isoindolinyl is selected from isoindolin-5-yl; isochromanyl is selected from isochroman-5-yl; dihydroisobenzofuranyl is selected from 1, 3-dihydroisobenzofuran-4-yl.

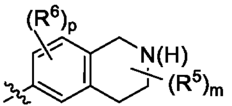
25. The compound of claim 21, wherein the benzo fused heteroaryl is benzisoxazolyl, benzodiazolyl, benzofuranyl, benzofurazanyl, benzofuryl, benzoimidazolyl, benzoisothiazolyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzothiophenyl, benzotriazolyl, benzoxadiazolyl, benzoxazolyl, indazolyl, indolyl, isobenzofuryl, isoindolyl, isoquinolinyl (or isoquinolyl), phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinolinyl (or quinolyl), or quinoxalinyl; in some examples, indazolyl is e.g., 1H-indazol-4-yl, 2H-indazol-4-yl, 1H-indazol-5-yl, 2H-indazol-5-yl, 1H-indazol-7-yl; benzodiazolyl is e.g., 1H-benzo[d]imidazol-4-yl, 1H-1, 3-benzodiazol-5-yl or 1H-benzo[d]imidazol-5-yl, 1H-benzo[d]imidazol-4-yl, 1H-benzo[d]imidazol-6-yl; benzooxazolyl is e.g., benzo[d]oxazol-6-yl; benzooxadiazolyl is e.g., benzo[c][1, 2, 5]oxadiazol-4-yl.

26. The compound of claim 21, wherein 

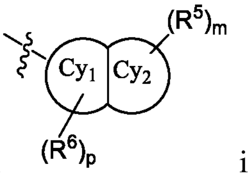
is a bicyclic fused heteroaryl selected from furopyridinyl, furopyrrolyl, imidazopyridinyl, imidazopyridyl, imidazothiazolyl, indolizinyl, naphthyridinyl, pyrazinopyridazinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrazolopyridyl, pyrazolotriazinyl, pyridazolopyridyl, pyrrolopyridinyl, thiazolopyridyl, thienopyrazinyl, thienopyrazolyl, thienopyridyl, thienopyrrolyl, thienothienyl, or triazolopyridyl; in some example, imidazopyridinyl is e.g., imidazo[1, 2-a]pyridin-5-yl or imidazo[1, 5-a]pyridin-5-yl.

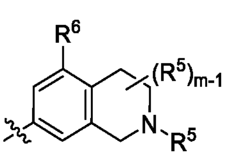
27. The compound of claim 21, wherein 

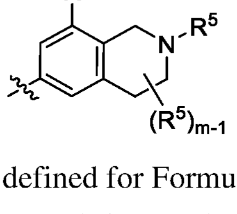
is 

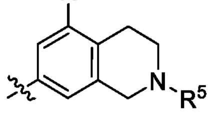
or 

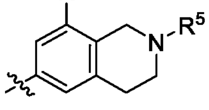
, p=0, 1, 2 or 3; m=0, 1, 2, 3 or 4; R^6 and R^5 are defined for Formula (I).

28. The compound of any claims 21-27, wherein 

is 

or 

(preferably 

or 

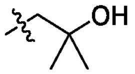
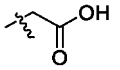
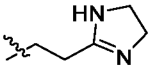
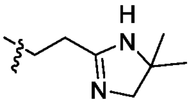
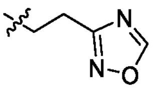
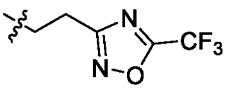
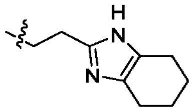
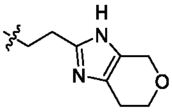
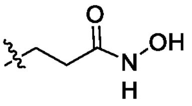
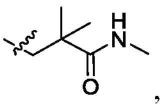
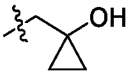
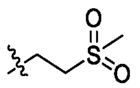
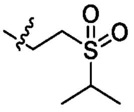
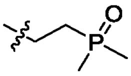
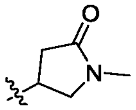
), m=1, 2, 3 or 4; R^6 and R^5 are defined for Formula (I) (preferably R^5 and R^6 are independently -C_{1-8}alkyl (e.g., methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-methyl-1-propyl, 1-methylpropyl or t-butyl).

29. The compound of any claims 27-28, wherein R^6 is selected from -C_{1-8}alkyl, -OR^{6a} or -$NR^{6a}R^{6b}$, said -C_{1-8}alkyl is optionally substituted with at least one substituents R^{6d}, R^{6a} and R^{6b}

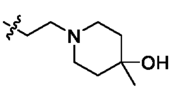
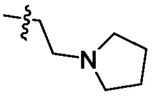
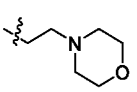
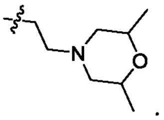
are each hydrogen or $-C_{1-8}$alkyl; R^{6d} is each independently hydrogen, halogen or $-C_{1-8}$alkyl; preferably R^6 is selected from $-CH_3$, $-OCH_3$, $-NHCH_3$, $-CHF_2$, or $-C(CH_3)_2OH$.

30. The compound of any claims 27-29, wherein each R^5 is independently selected from $-C_{1-8}$alkyl, $-C_{1-8}$alkyl-cycloalkyl, heterocyclyl or heteroaryl $-CONR^{3a}R^{3b}$, $CH_2CONR^{5a}R^{5b}$, $-CH_2CH_2CONR^{5a}R^{5b}$, $-NR^{5a}R^{5b}$, $-CH_2NR^{5a}R^{5b}$, $-CH_2CH_2NR^{5a}R^{5b}$, said $-C_{1-8}$alkyl, $-C_{1-8}$alkyl-cycloalkyl or heterocyclyl or heteroaryl is optionally substituted with at least one R^{5d}, and R^{5a}, R^{5b} and R^{5d} are defined for Formula (I).

31. The compound of any claims 27-30, wherein R^5 is selected from $-C_{1-8}$alkyl (e.g., methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-methyl-1-propyl, 1-methylpropyl or t-butyl), $-C_{1-8}$alkyl-cycloalkyl, heterocyclyl or heteroaryl, said $-C_{1-8}$alkyl, $-C_{1-8}$alkyl-cycloalkyl, heteroaryl or heterocyclyl is optionally substituted with at least one substituents R^{5d}; R^{5d} is selected from $-C_{1-8}$alkyl, $-OR^{5f}$, $-NR^{5f}R^{5g}$, $-CO_2R^{5f}$, heteroaryl, heterocyclyl, $-SO_2R^{5f}$, $-POR^{5f}R^{5g}$, $-CONR^{5f}R^{5g}$, oxo or $-CF_3$; R^{5f} and R^{5g} are each independently hydrogen, $-C_{1-8}$alkyl, $-C_{1-8}$alkoxy or hydroxy.

32. The compound of claim 31, wherein, R^5 is methyl, ethyl, propyl, butyl, pentyl or hexyl, $-CH_2OH$, $-C_2H_4OH$, $C_2H_4NHCH_3$, $-C_2H_4OCH_3$, , , , , , , , , , , , , ,  or .

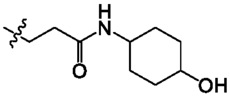
33. The compound of claim 30, wherein R^5 is $-NR^{5a}R^{5b}$, $-CH_2NR^{5a}R^{5b}$, $-CH_2CH_2NR^{5a}R^{5b}$; R^{5a} and R^{5b} together with the nitrogen atom to which they are attached form a 4- to 7- membered ring, said ring comprising 0, 1 or 2 additional heteroatoms independently selected from nitrogen, oxygen, said ring is optionally substituted with at least one substituents R^{5e}; R^{5e} is each independently selected from C_{1-8}alkyl (preferably methyl, ethyl), OR^{5f}; R^{5f} is each independently selected from hydrogen or $-C_{1-8}$alkyl (e.g., methyl, ethyl).

34. The compound of claim 33, wherein R^5 is , ,  or .

35. The compound of claim 30, wherein R^5 is selected from $-CONR^{5a}R^{5b}$, $-CH_2CONR^{5a}R^{5b}$, $-CH_2CH_2CONR^{5a}R^{5b}$, wherein R^{5a} and R^{5b} are each independently hydrogen, $-C_{1-8}$alkyl, C_{1-8}alkoxy-C_{1-8}alkyl-, cycloalkyl, heterocyclyl, $-C_{1-8}$alkyl-heterocyclyl, $-C_{1-8}$alkyl-aryl, -aryl, or heteroaryl, each of said $-C_{1-8}$alkyl, C_{1-8}alkoxy-C_{1-8}alkyl-, cycloalkyl, heterocyclyl, $-C_{1-8}$alkyl-heterocyclyl, $-C_{1-8}$alkyl-aryl, -aryl, or heteroaryl is optionally substituted with at least one substituents R^{5e}; R^{5e} is independently hydrogen, OR^{5f}, $-C_{1-8}$alkyl, heterocyclyl, $-C_{1-8}$alkyl-aryl, or C_{1-8}alkoxy-C_{1-8}alkyl-; R^{5f} is each independently selected from hydrogen, $-C_{1-8}$alkyl (e.g., methyl, ethyl) and cycloalkyl.

36. The compound of claim 35, wherein R^5 is selected from $-CONR^{5a}R^{5b}$, $-CH_2CONR^{5a}R^{5b}$, $-CH_2CH_2CONR^{5a}R^{5b}$, wherein R^{5a} is hydrogen or $-C_{1-8}$alkyl (e.g., methyl, ethyl); R^{5b} is selected from $-C_{1-8}$alkyl, cycloalkyl, $-C_{1-8}$alkyl-heterocyclyl, $-C_{1-8}$alkyl-aryl, heterocyclyl, aryl, said $-C_{1-8}$alkyl, cycloalkyl, $-C_{1-8}$alkyl-heterocyclyl, $-C_{1-8}$alkyl-aryl, heterocyclyl, aryl is optionally substituted with at least one substituents R^{5e}, R^{5e} is selected from halogen, $-CH_2OH$ or OR^{5f}, R^{5f} is selected from hydrogen, cycloalkyl or $-C_{1-8}$alkyl.

37. The compound of claim 36, wherein R^5 is selected from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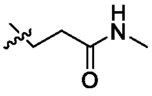
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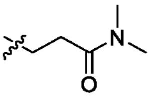
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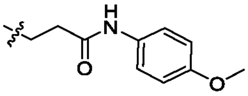
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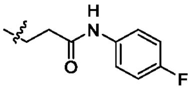
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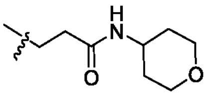
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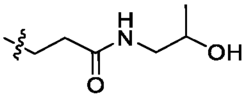
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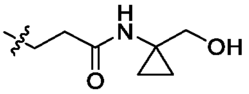
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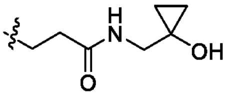
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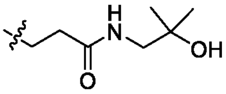
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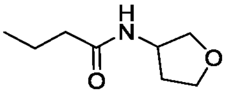
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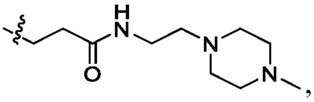
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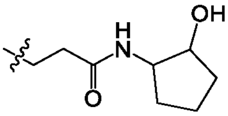
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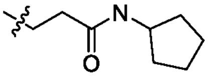
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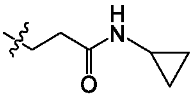
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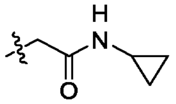
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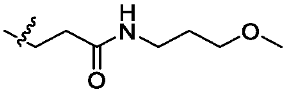
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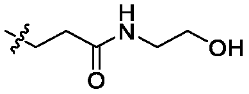
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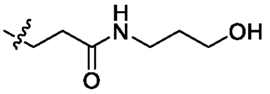
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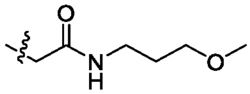
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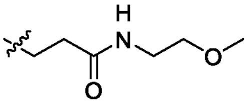
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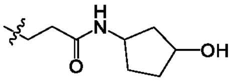
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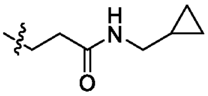
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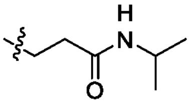
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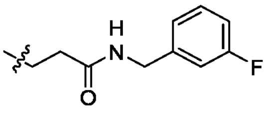
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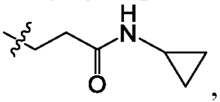
38. The compound of claim 35 or 36, wherein R^5 is $-CONR^{3a}R^{3b}$, $CH_2CONR^{5a}R^{5b}$ or $-CH_2CH_2CONR^{5a}R^{5b}$, R^{5a} is hydrogen or methyl; and R^{5b} is selected from cycloalkyl, such as cycloalkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, and cyclododecyl groups; said cycloalkyl is optionally substituted with OH, $-CH_3$, $-OCH_3$; preferably R^5 is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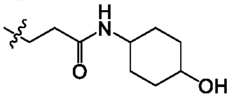
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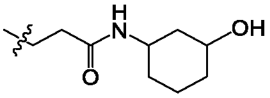
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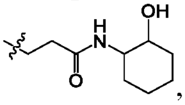
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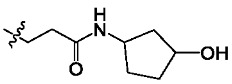
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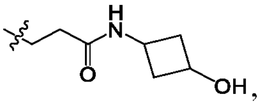
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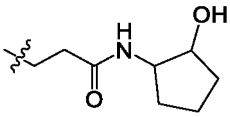
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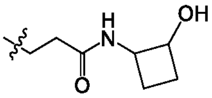
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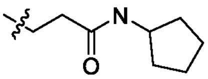
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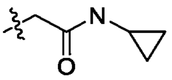
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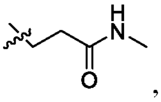
39. The compound of claim 35 or 36, wherein R^5 is $-CONR^{5a}R^{5b}$, $CH_2CONR^{5a}R^{5b}$ or $-CH_2CH_2CONR^{5a}R^{5b}$, R^{5a} is hydrogen or methyl; and R^{5b} is selected from $-C_{1-8}$alkyl, cycloalkyl or $-C_{1-8}$alkyl-heterocyclyl, said $-C_{1-8}$alkyl, cycloalkyl or $-C_{1-8}$alkyl-heterocyclyl is optionally substituted with at least one substituents R^{5e}, R^{5e} is selected from cycloalkyl, $-C_{1-8}$alkyl, $-CH_2OH$ or OR^{5f}, OR^{5f} is selected from hydrogen or $-C_{1-8}$alkyl. For example, R^5 is selected from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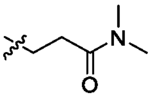
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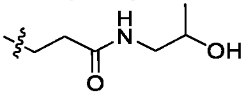
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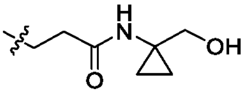
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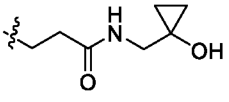
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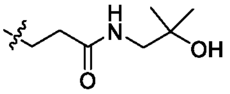
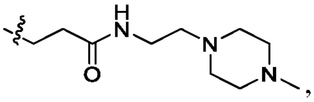
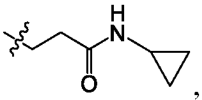
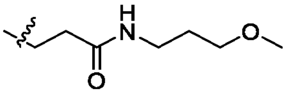
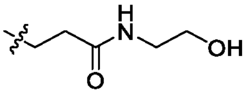
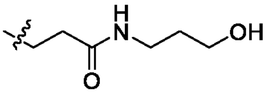
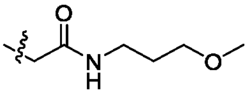
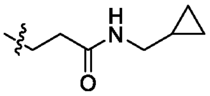
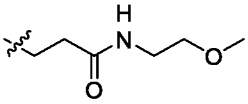
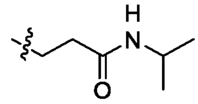
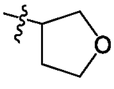
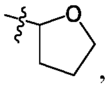
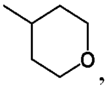
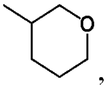
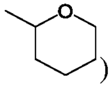
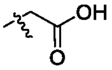
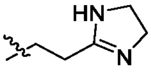
, , , ,

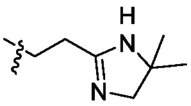
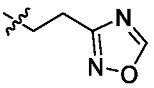
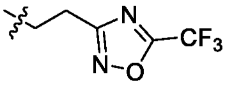
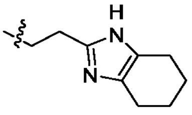
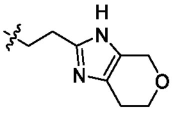
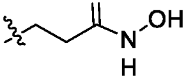
, , , ,

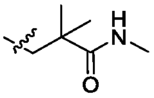
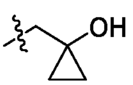
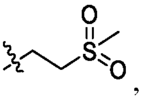
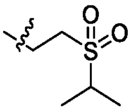
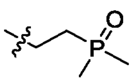
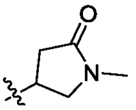
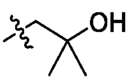
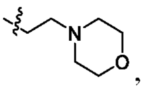
 or .

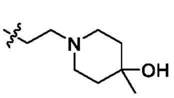
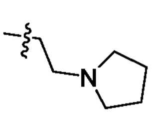
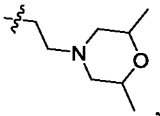
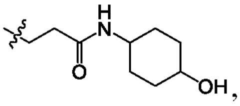
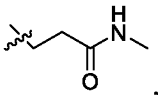
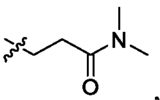
40. The compound of claim 35 or 36, wherein R^5 is $-CONR^{5a}R^{5b}$, $CH_2CONR^{5a}R^{5b}$ or $-CH_2CH_2CONR^{5a}R^{5b}$, R^{5a} is hydrogen or methyl; and R^{5b} is heterocyclyl (such as , , , , ) or aryl (such as phenyl), said heterocyclyl or aryl is optionally substituted with at least one substituents R^{5e} selected from halogen, $-C_{1-8}alkyl$ or $-OR^{5f}$; R^{5f} is each independently hydrogen or $-C_{1-8}alkyl$.

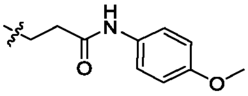
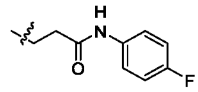
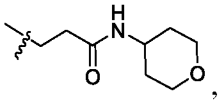
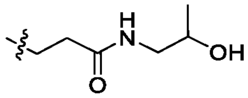
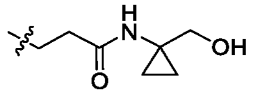
41. The compound of claim 30, wherein R^5 is selected from $-CONR^{5a}R^{5b}$, $CH_2CONR^{5a}R^{5b}$, $-CH_2CH_2CONR^{5a}R^{5b}$, wherein R^{5a} and R^{5b} together with the nitrogen atom to which they are attached, form a 4- to 7-membered ring, said ring comprising 0, 1 or 2 additional heteroatoms independently selected from nitrogen, oxygen or optionally oxidized sulfur as ring member (s), said ring is optionally substituted with at least one substituents R^{5e}; R^{5e} is each independently halogen, $-C_{1-8}alkyl$, $-OR^{5f}$, R^{5f} is each independently hydrogen or $-C_{1-8}alkyl$.

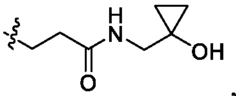
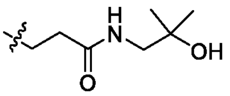
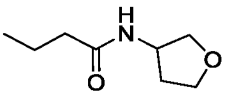
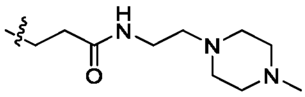
42. The compound of any claims 1-41, wherein R^5 is selected from methyl, ethyl, propyl, butyl, pentyl or hexyl, $-CH_2OH$, $-C_2H_4OH$, $C_2H_4NHCH_3$, $-C_2H_4OCH_3$, , ,

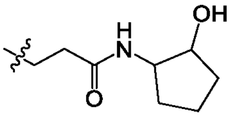
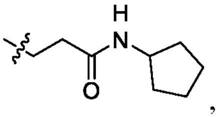
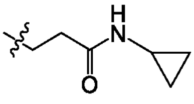
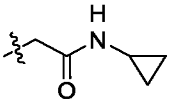
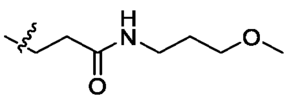
, , , , , ,

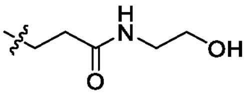
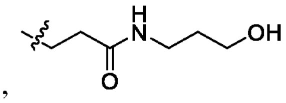
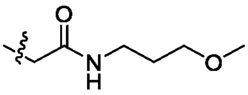
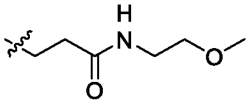
, , , , , , , ,

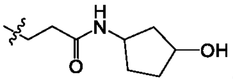
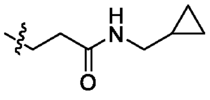
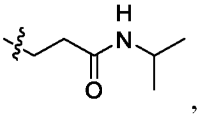
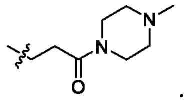
, , , , , ,

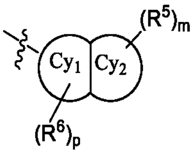
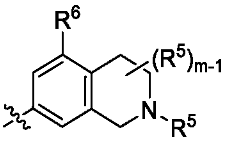
, , , , ,

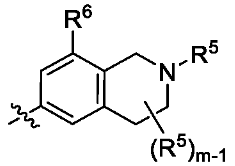
, , , ,

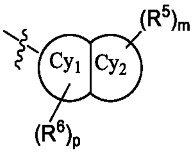
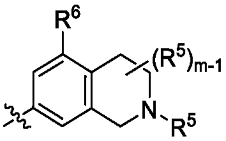
, , , , ,

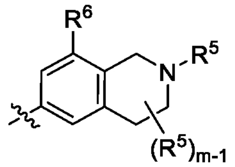
, , , ,

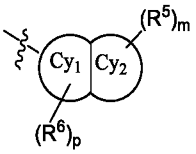
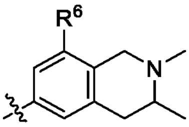
, , , .

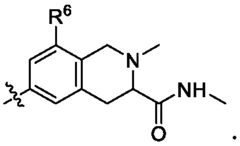
43. The compound of claim 28, wherein  is  or

, m=2, 3 or 4, R^5 is each independently halogen, $-C_{1-8}$alkyl, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, cycloalkyl, $-C_{1-8}$alkyl-cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo, -CN, $-NO_2$, $-OR^{5a}$, $-SO_2R^{5a}$, $-SO_2NR^{5a}R^{5b}$, $-POR^{5a}R^{5b}$, $-COR^{5a}$, $-CO_2R^{5a}$, $-CONR^{5a}R^{5b}$, $-C (=NR^{5a})NR^{5b}R^{5c}$, $-CH_2CONR^{5a}R^{5b}$, $-CH_2CH_2CONR^{5a}R^{5b}$, $-CH_2CH_2CH_2CONR^{5a}R^{5b}$, $-NR^{5a}R^{5b}$, $-CH_2NR^{5a}R^{5b}$, $-CH_2 CH_2NR^{5a}R^{5b}$, $-CH_2CH_2CH_2NR^{5a}R^{5b}$, $-NR^{5a}COR^{5b}$, $-NR^{5a}CONR^{5b}R^{5c}$, $-NR^{5a}CO_2R^{5b}$, $-NR^{5a}SONR^{5b}R^{5c}$, $-NR^{5a}SO_2NR^{5b}R^{5c}$, or $-NR^{5a}SO_2R^{5b}$, each of said $-C_{1-8}$alkyl, $-C_{2-8}$alkenyl, $-C_{2-8}$alkynyl, cycloalkyl, $-C_{1-8}$alkyl-cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with at least one substituents R^{5d}; R^6, R^{5a}, R^{5b}, R^{5c} and R^{5d} are defined for Formula (I).

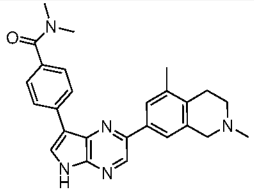
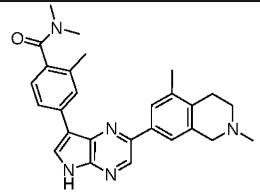
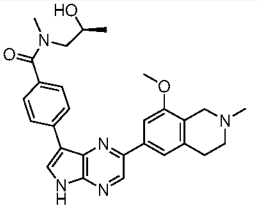
44. The compound of claim 43, wherein  is  or

, m=2, R^5 is each independently $-C_{1-8}$alkyl or $-CONR^{5a}R^{5b}$, R^{5b} and R^{5d} are hydrogen or $-C_{1-8}$alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl or hexyl); R^6 is selected from $-C_{1-8}$alkyl, $-OR^{6a}$ or $-NR^{6a}R^{6b,}$ said $-C_{1-8}$alkyl is optionally substituted with at least one substituents R^{6d}, R^{6a} and R^{6b} are each hydrogen or $-C_{1-8}$alkyl; R^{6d} is each independently hydrogen, halogen or $-C_{1-8}$alkyl; preferably R^6 is selected from $-CH_3$, $-OCH_3$, $-NHCH_3$, $-CHF_2$, or $-C (CH_3)_2OH$.

45. The compound of claim 44, wherein  is  or

 ; R^6 is selected from $-CH_3$, $-OCH_3$, $-NHCH_3$, $-CHF_2$, or $-C (CH_3)_2OH$.

46. The compound of claim 1, selected from: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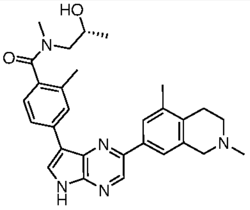	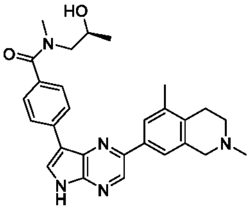	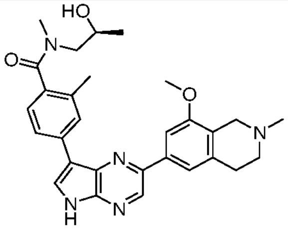
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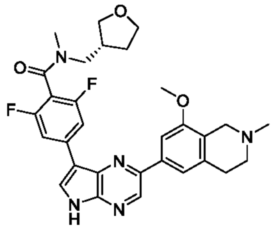	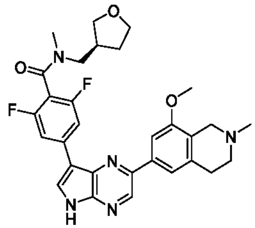	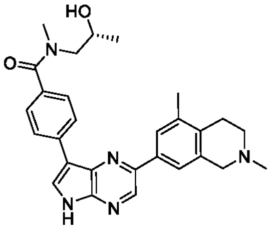
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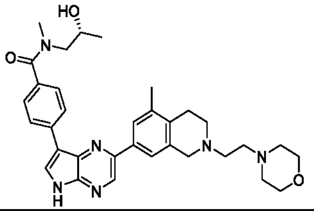	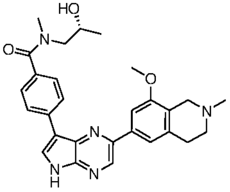	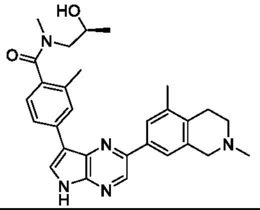
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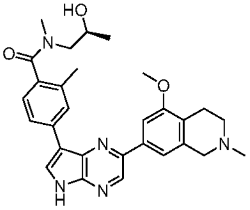	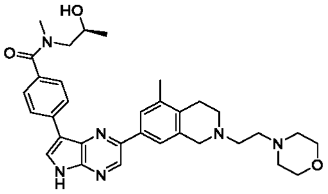	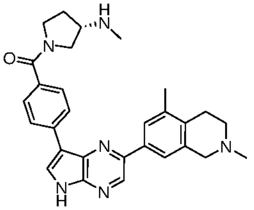
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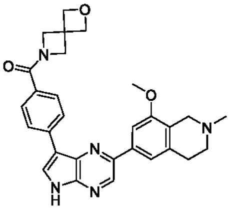	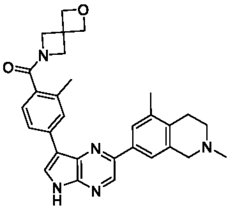	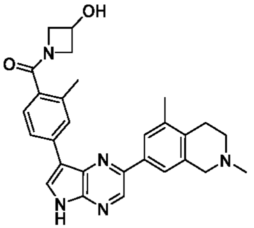
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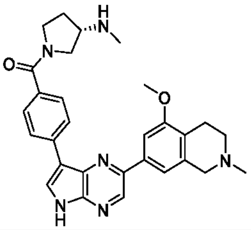	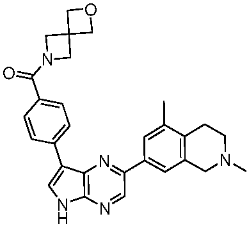	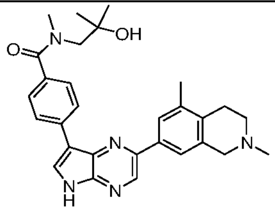
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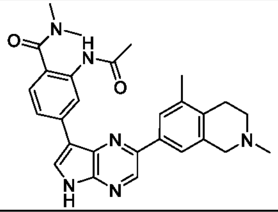	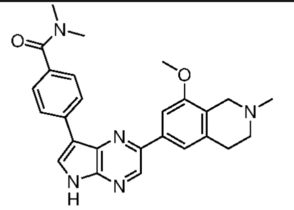	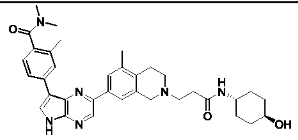
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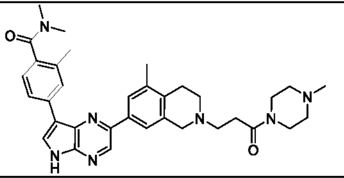	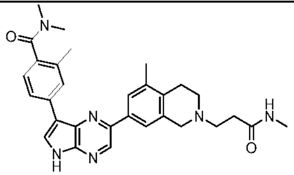	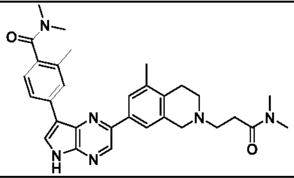
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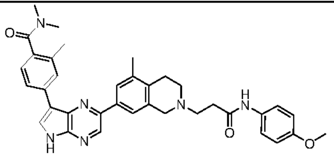	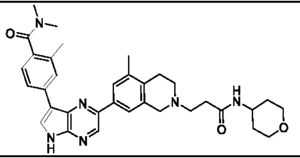	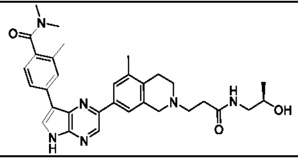
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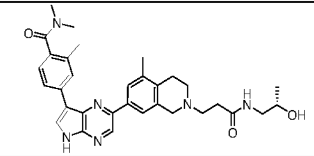	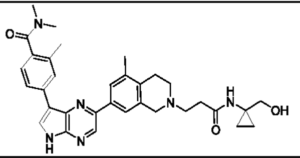	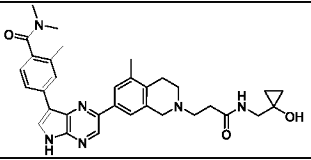
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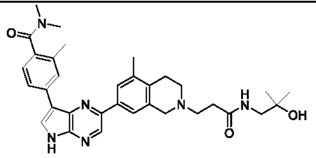	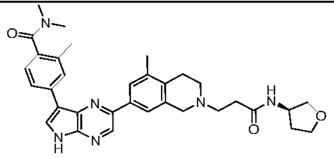	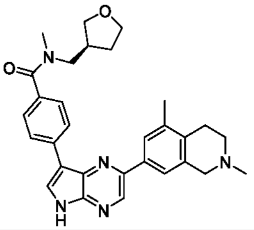
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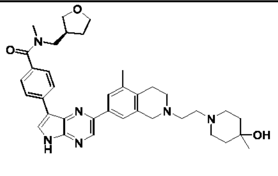	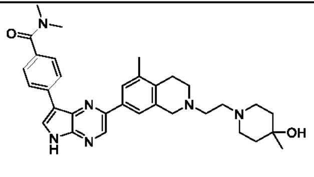	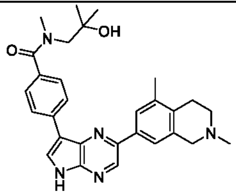
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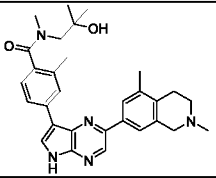	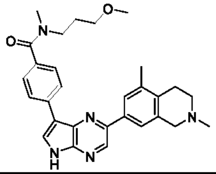	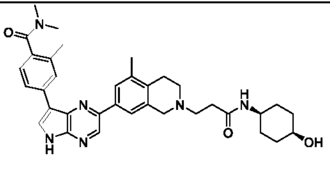
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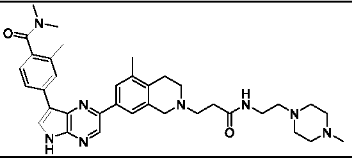	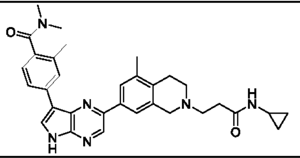	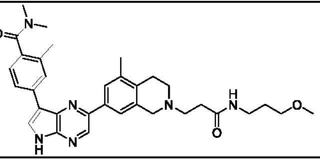
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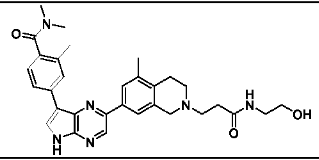	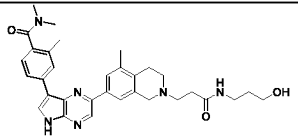	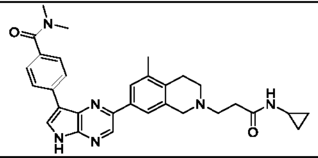
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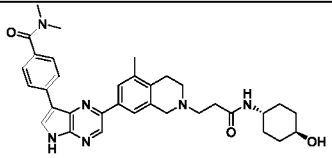	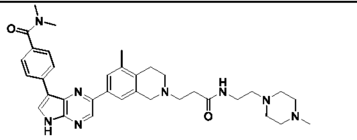	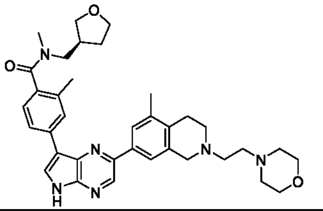
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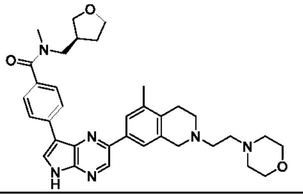	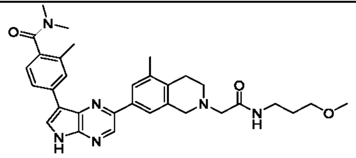	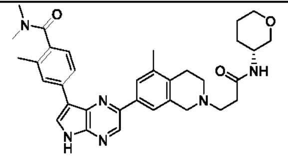
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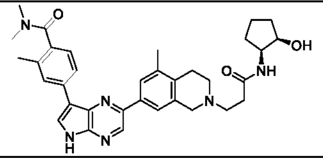	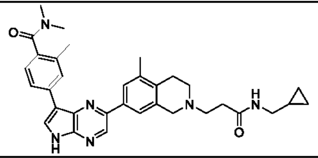	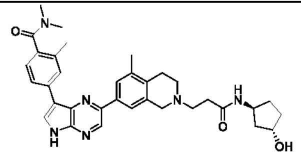
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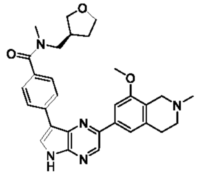	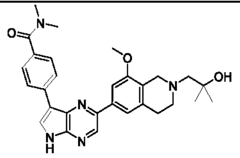	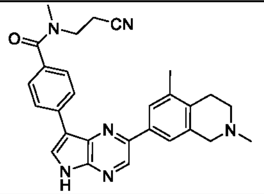
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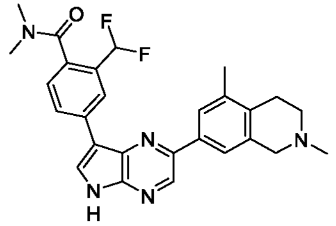	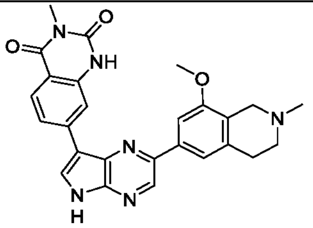	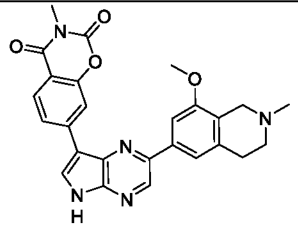
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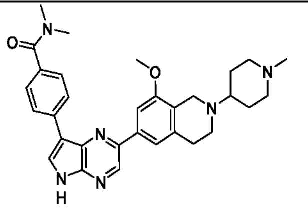	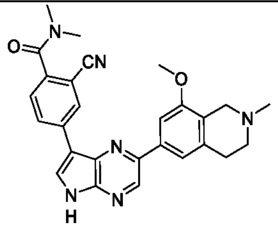	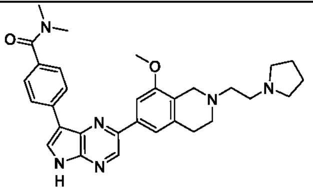
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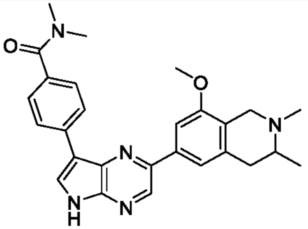	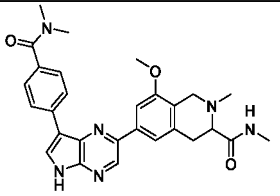	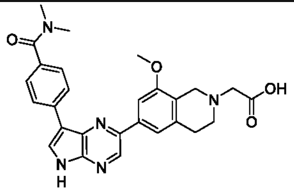
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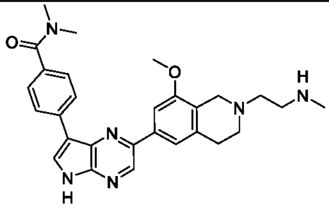	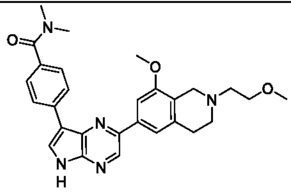	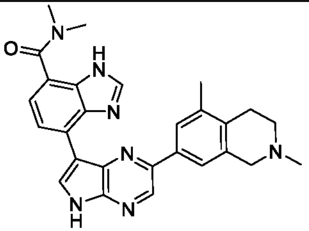
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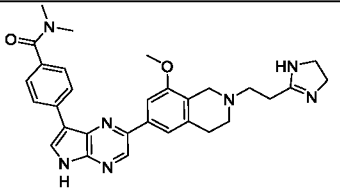	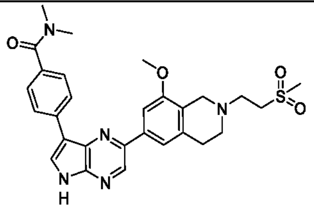	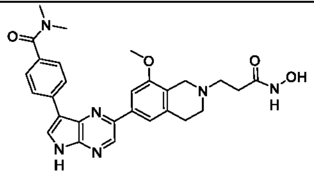
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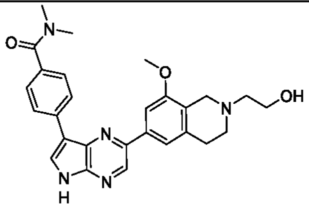	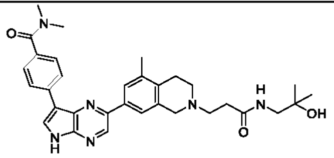	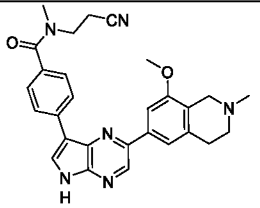
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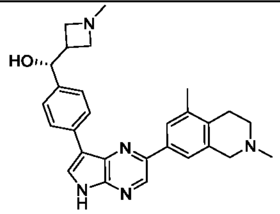	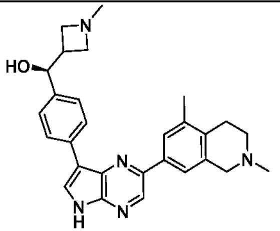	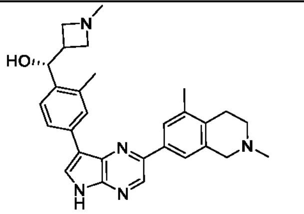
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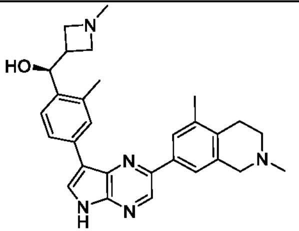	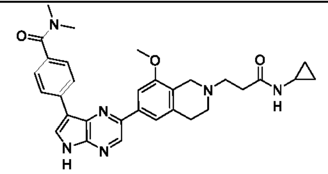	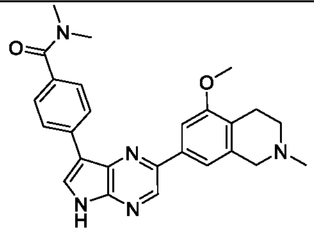
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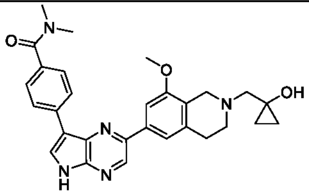	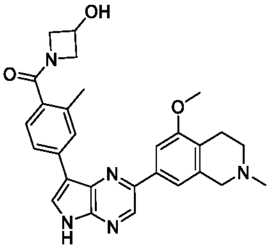	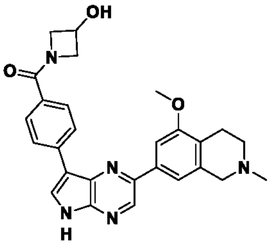

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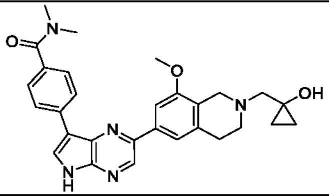	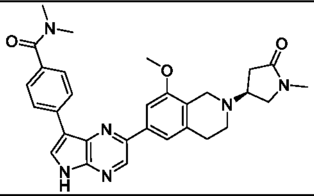	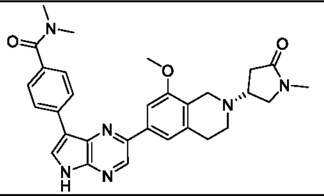
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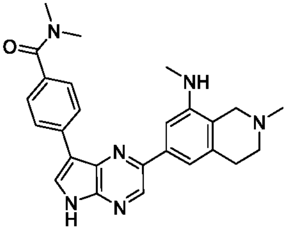	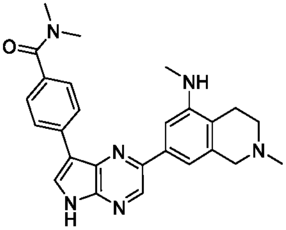	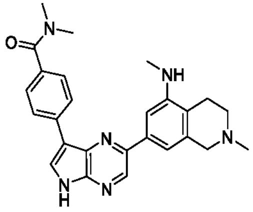
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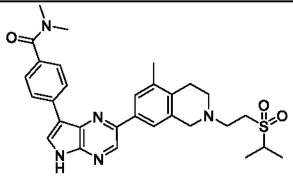	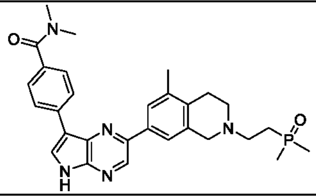	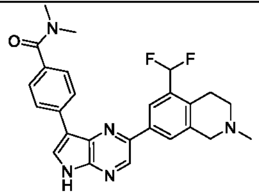
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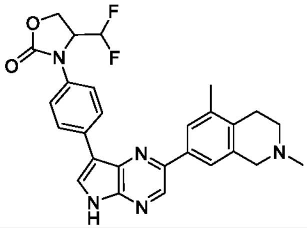	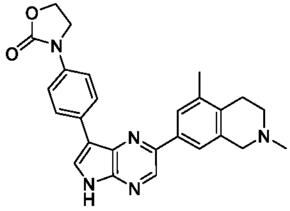	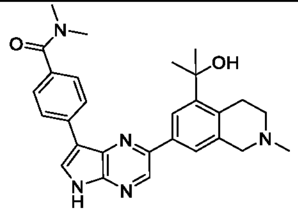
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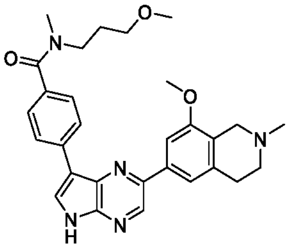	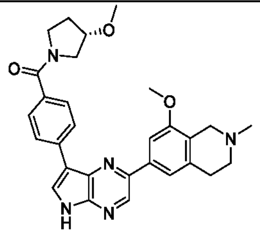	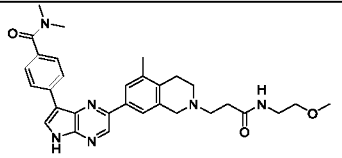
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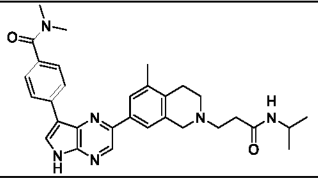	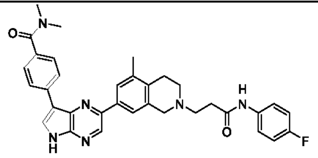	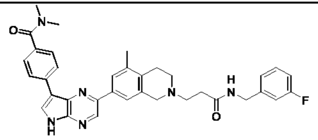
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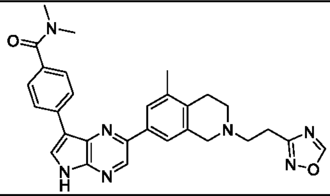	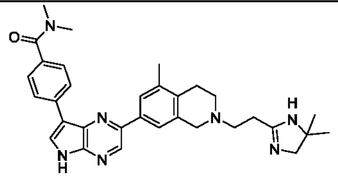	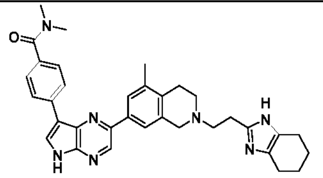
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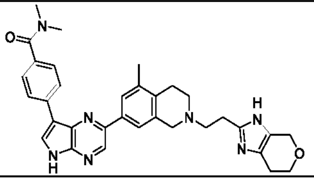	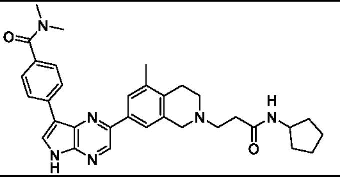	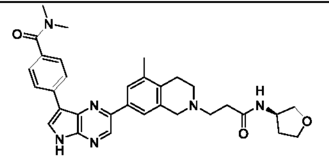
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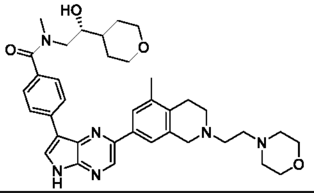	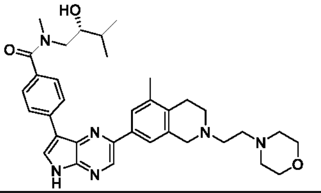	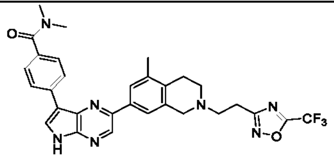
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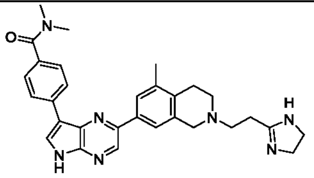	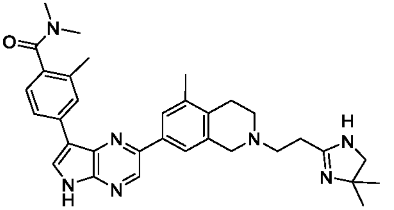	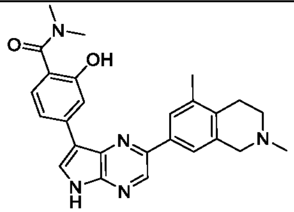
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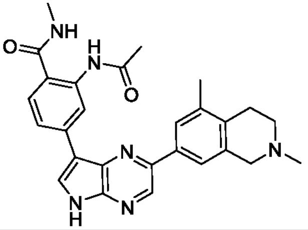	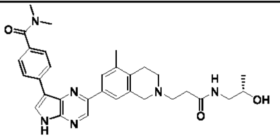	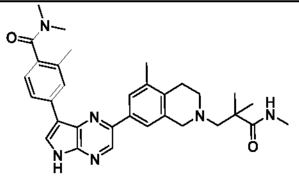
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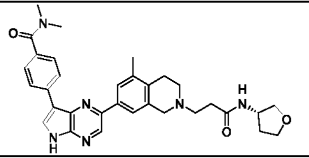	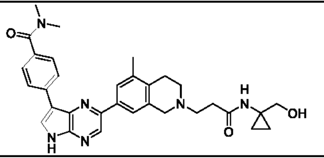	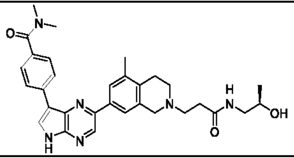
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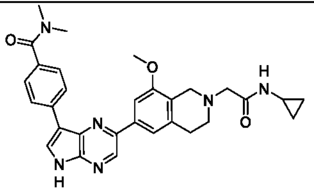	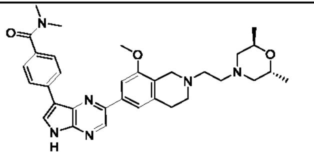	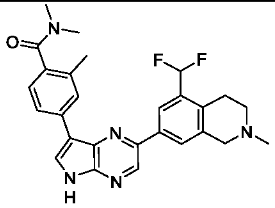
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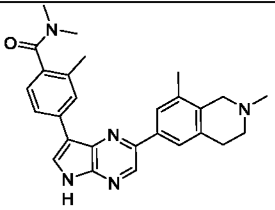	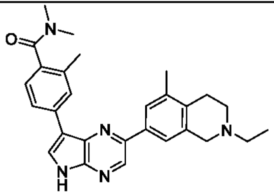	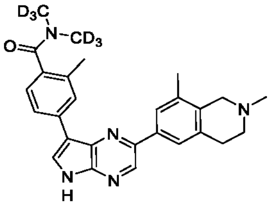
126	127	128

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47. A pharmaceutical composition comprising the compound of any of claims 1-46 or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

48. A method of treating cancer, comprising administering a subject in need thereof the compound of any of claims 1-46 or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2020/100037

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/00(2006.01)i; C07D 487/00(2006.01)i; C07D 487/04(2006.01)i; C07D 487/02(2006.01)i; A61K 31/517(2006.01)i; A61K 31/519(2006.01)i; A61K 31/437(2006.01)i; A61P 35/00(2006.01)i

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)

C07D; A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNABS, DWPI, SIPOABS, CNTXT, WOXTX, EPTXT, USTXT, CNKI, PUBMED, ISI_Web of Science, Science Direct, STNext: beigene ltd,LI Jing, WANG Zhiwei, XU Sanjia, structure, phenyl, pyrrolo, pyrazin, HPK1 kinase, cancer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	WO 2019167000 A1 (OTSUKA PHARMA. CO., LTD. et al.) 06 September 2019 (2019-09-06) claims 1-37	1-48
X	WO 2006015124 A2 (SGX PHARMACEUTICALS INC. et al.) 09 February 2006 (2006-02-09) paragraphs 0050、0053、0302, Table 16 of the description, claims 31, 38	1-48
X	CN 106336413 A (GUANGDONG DONGYANGGUANG PHARM. CO., LTD.) 18 January 2017 (2017-01-18) claims 1-10	1-48
A	CN 101098872 A (VERTEX PHARM. INC. et al.) 02 January 2008 (2008-01-02) claims 1-46	1-48
A	CN 106432246 A (GUANGDONG DONGYANGGUANG PHARM. CO., LTD.) 22 February 2017 (2017-02-22) claims 1-13	1-48
A	WO 2016164641 A1 (PLEXXIKON INC.) 13 October 2016 (2016-10-13) claims 1-28	1-48

☑ 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	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search **22 September 2020**	Date of mailing of the international search report **10 October 2020**
Name and mailing address of the ISA/CN **National Intellectual Property Administration, PRC** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China**	Authorized officer **JIAO,Shiyong**
Facsimile No. **(86-10)62019451**	Telephone No. **01053961915**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 10239873 B2 (GREEN CROSS CORP.) 26 March 2019 (2019-03-26) claims 1-3	1-48

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.: **48**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claim 48 directs to a method of treating cancer, comprising administering a subject in need thereof the compound of any of claims 1-46 or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof. It does not meet the criteria set out in Rules 39.1(iv) PCT. The search report has been carried out and based on the use of claimed compound in manufacturing medicaments for treating diseases.

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.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2019167000 A1	06 September 2019	TW 202000667 A	01 January 2020
WO 2006015124 A2	09 February 2006	US 2009203687 A1	13 August 2009
		US 7452993 B2	18 November 2008
		EP 2239262 A3	19 October 2011
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		US 2006258662 A1	16 November 2006
		KR 20070089201 A	30 August 2007

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2020/100037

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		CN 101098872 B	05 September 2012
		US 2006122185 A1	08 June 2006
CN 106432246 A	22 February 2017	CN 106432246 B	07 July 2020
WO 2016164641 A1	13 October 2016	US 10160755 B2	25 December 2018
		US 2016326162 A1	10 November 2016
US 10239873 B2	26 March 2019	KR 101660863 B1	28 September 2016
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