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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
03 October 2019 (03.10.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/191707 A1

(51) International Patent Classification:
C07D 413/14 (2006.01) *A61P 37/00* (2006.01)
A61K 31/423 (2006.01)

(21) International Application Number:
PCT/US2019/025036

(22) International Filing Date:
29 March 2019 (29.03.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/650,821 30 March 2018 (30.03.2018) US
62/687,964 21 June 2018 (21.06.2018) US

(71) Applicant: **INCYTE CORPORATION** [US/US]; 1801 Augustine Cut-Off, Wilmington, Delaware 19803 (US).

(72) Inventors: **WU, Liangxing**; 1801 Augustine Cut-Off, Wilmington, Delaware 19803 (US). **LI, Jingwei**; 1801 Augustine Cut-Off, Wilmington, Delaware 19803 (US). **YAO, Wenqing**; 1801 Augustine Cut-Off, Wilmington, Delaware 19803 (US).

(74) Agent: **BOYLE, Craig D.** et al.; P.O. Box 1022, Minneapolis, Minnesota 55440-1022 (US).

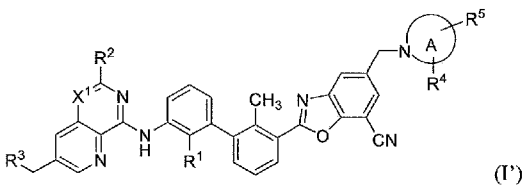
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, 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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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

(54) Title: HETEROCYCLIC COMPOUNDS AS IMMUNOMODULATORS



(I')

(57) Abstract: Disclosed are compounds of Formula (I'), methods of using the compounds as immunomodulators, and pharmaceutical compositions comprising such compounds. The compounds are useful in treating, preventing or ameliorating diseases or disorders such as cancer or infections.

WO 2019/191707 A1

HETEROCYCLIC COMPOUNDS AS IMMUNOMODULATORS

The present application claims the benefit of U.S. Provisional Application No. 62/650,821, filed March 30, 2018; and U.S. Provisional Application No. 62/687,964, filed June 21, 2018, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present application is concerned with pharmaceutically active compounds. The disclosure provides compounds as well as their compositions and methods of use. The compounds modulate PD-1/PD-L1 protein/protein interaction and are useful in the treatment of various diseases including infectious diseases and cancer.

BACKGROUND OF THE INVENTION

The immune system plays an important role in controlling and eradicating diseases such as cancer. However, cancer cells often develop strategies to evade or to suppress the immune system in order to favor their growth. One such mechanism is altering the expression of co-stimulatory and co-inhibitory molecules expressed on immune cells (Postow et al, J. Clinical Oncology 2015, 1-9). Blocking the signaling of an inhibitory immune checkpoint, such as PD-1, has proven to be a promising and effective treatment modality.

Programmed cell death-1 (PD-1), also known as CD279, is a cell surface receptor expressed on activated T cells, natural killer T cells, B cells, and macrophages (Greenwald et al, Annu. Rev. Immunol 2005, 23:515–548; Okazaki and Honjo, Trends Immunol 2006, (4):195-201). It functions as an intrinsic negative feedback system to prevent the activation of T-cells, which in turn reduces autoimmunity and promotes self-tolerance. In addition, PD-1 is also known to play a critical role in the suppression of antigen-specific T cell response in diseases like cancer and viral infection (Sharpe et al, *Nat Immunol* 2007 8, 239–245; Postow et al, J. Clinical Oncol 2015, 1-9).

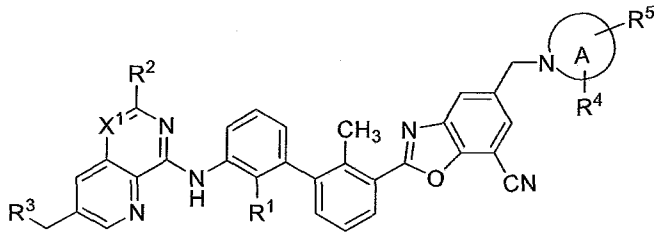
The structure of PD-1 consists of an extracellular immunoglobulin variable-like domain followed by a transmembrane region and an intracellular domain (Parry et al, Mol Cell Biol 2005, 9543–9553). The intracellular domain contains two phosphorylation sites located in an immunoreceptor tyrosine-based inhibitory motif and an immunoreceptor tyrosine-based switch motif, which suggests that PD-1 negatively regulates T cell receptor-mediated signals. PD-1 has

two ligands, PD-L1 and PD-L2 (Parry et al, Mol Cell Biol 2005, 9543–9553; Latchman et al, Nat Immunol 2001, 2, 261–268), and they differ in their expression patterns. PD-L1 protein is upregulated on macrophages and dendritic cells in response to lipopolysaccharide and GM-CSF treatment, and on T cells and B cells upon T cell receptor and B cell receptor signaling. PD-L1 is also highly expressed on almost all tumor cells, and the expression is further increased after IFN-γ treatment (Iwai et al, PNAS2002, 99(19):12293-7; Blank et al, Cancer Res 2004, 64(3):1140-5). In fact, tumor PD-L1 expression status has been shown to be prognostic in multiple tumor types (Wang et al, Eur J Surg Oncol 2015; Huang et al, Oncol Rep 2015; Sabatier et al, Oncotarget 2015, 6(7): 5449–5464). PD-L2 expression, in contrast, is more restricted and is expressed mainly by dendritic cells (Nakae et al, J Immunol 2006, 177:566-73). Ligation of PD-1 with its ligands PD-L1 and PD-L2 on T cells delivers a signal that inhibits IL-2 and IFN-γ production, as well as cell proliferation induced upon T cell receptor activation (Carter et al, Eur J Immunol 2002, 32(3):634-43; Freeman et al, J Exp Med 2000, 192(7):1027-34). The mechanism involves recruitment of SHP-2 or SHP-1 phosphatases to inhibit T cell receptor signaling such as Syk and Lck phosphorylation (Sharpe et al, Nat Immunol 2007, 8, 239–245). Activation of the PD-1 signaling axis also attenuates PKC-θ activation loop phosphorylation, which is necessary for the activation of NF-κB and AP1 pathways, and for cytokine production such as IL-2, IFN-γ and TNF (Sharpe et al, Nat Immunol 2007, 8, 239–245; Carter et al, Eur J Immunol 2002, 32(3):634-43; Freeman et al, J Exp Med 2000, 192(7):1027-34).

Several lines of evidence from preclinical animal studies indicate that PD-1 and its ligands negatively regulate immune responses. PD-1-deficient mice have been shown to develop lupus-like glomerulonephritis and dilated cardiomyopathy (Nishimura et al, Immunity 1999, 11:141–151; Nishimura et al, Science 2001, 291:319–322). Using an LCMV model of chronic infection, it has been shown that PD-1/PD-L1 interaction inhibits activation, expansion and acquisition of effector functions of virus-specific CD8 T cells (Barber et al, Nature 2006, 439, 682-7). Together, these data support the development of a therapeutic approach to block the PD-1-mediated inhibitory signaling cascade in order to augment or "rescue" T cell response. Accordingly, there is a need for new compounds that block PD-1/PD-L1 protein/protein interaction.

SUMMARY

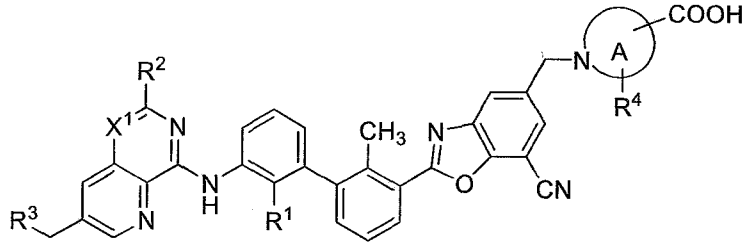
The present disclosure provides, *inter alia*, a compound of Formula (I')



(I')

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein constituent variables are defined herein.

The present disclosure also provides a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein constituent variables are defined herein.

The present disclosure further provides a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt or a stereoisomer thereof, and one or more pharmaceutically acceptable excipient or carrier.

The present disclosure further provides methods of inhibiting PD-1/PD-L1 interaction, said method comprising administering to a patient a compound disclosed herein, or a pharmaceutically acceptable salt or a stereoisomer thereof.

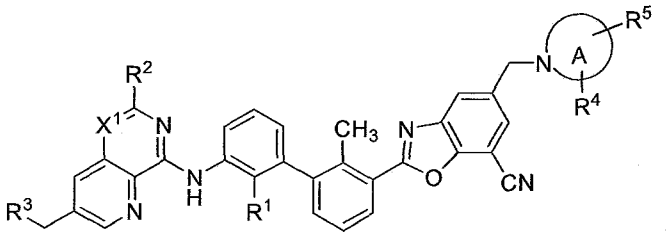
The present disclosure further provides methods of treating a disease or disorder associated with inhibition of PD-1/PD-L1 interaction, said method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of disclosed herein, or a pharmaceutically acceptable salt or a stereoisomer thereof.

The present disclosure further provides methods of enhancing, stimulating and/or increasing the immune response in a patient, said method comprising administering to the patient in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or a stereoisomer thereof.

DETAILED DESCRIPTION

I. Compounds

The present disclosure provides, *inter alia*, compounds of Formula (I'):



(I')

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

ring A is azetidinyl, pyrrolidinyl or piperidinyl;

X^1 is CH or N;

R^1 is methyl or halo;

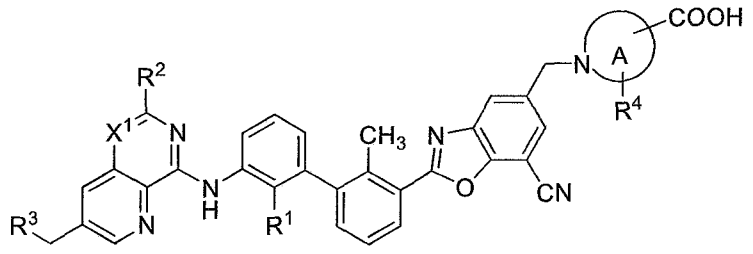
R^2 is C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-2} alkyl-, OH, NH_2, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, 4- to 6-membered heterocycloalkyl or 4- to 6-membered heterocycloalkyl-C_{1-2} alkyl-, wherein the 4- to 6-membered heterocycloalkyl and 4- to 6-membered heterocycloalkyl-C_{1-2} alkyl- each has one or two heteroatoms as ring members selected from O and N, and wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-2} alkyl-, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, 4- to 6-membered heterocycloalkyl and 4- to 6-membered heterocycloalkyl-C_{1-2} alkyl- of R^2 are each optionally substituted with 1 or 2 substituents independently selected from halo, CN and OH;

R^3 is selected from (R)-3-hydroxy-3-methylpyrrolidin-1-yl, (S)-3-hydroxy-3-methylpyrrolidin-1-yl, (R)-3-hydroxypyrrolidin-1-yl, (S)-3-hydroxypyrrolidin-1-yl, (R)-2-hydroxy-2-methyl-ethylamino, (S)-2-hydroxy-2-methyl-ethylamino, (R)-2-hydroxy-1-methyl-ethylamino and (S)-2-hydroxy-1-methyl-ethylamino; and

R^4 is H or C_{1-3} alkyl; and

R^5 is C(O)OH, C(O)N(CH_3)$_2$, C(O)NH(CH_3), or C(O)NH(CH_2)$_2$C(O)OH.

In some embodiments, provided herein are compounds of Formula (I):



(I)

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

ring A is azetidinyl, pyrrolidinyl or piperidinyl;

X^1 is CH or N;

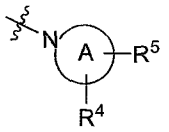
R^1 is methyl or halo;

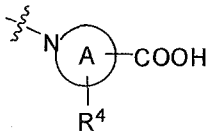
R^2 is C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-2} alkyl-, OH, NH_2, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, 4- to 6-membered heterocycloalkyl or 4- to 6-membered heterocycloalkyl-C_{1-2} alkyl-, wherein the 4- to 6-membered heterocycloalkyl and 4- to 6-membered heterocycloalkyl-C_{1-2} alkyl- each has one or two heteroatoms as ring members selected from O and N, and wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-2} alkyl-, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, 4- to 6-membered heterocycloalkyl and 4- to 6-membered heterocycloalkyl-C_{1-2} alkyl- of R^2 are each optionally substituted with 1 or 2 substituents independently selected from halo, CN and OH;

R^3 is selected from (R)-3-hydroxy-3-methylpyrrolidin-1-yl, (S)-3-hydroxy-3-methylpyrrolidin-1-yl, (R)-3-hydroxypyrrolidin-1-yl, (S)-3-hydroxypyrrolidin-1-yl, (R)-2-hydroxy-2-methyl-ethylamino, (S)-2-hydroxy-2-methyl-ethylamino, (R)-2-hydroxy-1-methyl-ethylamino and (S)-2-hydroxy-1-methyl-ethylamino; and

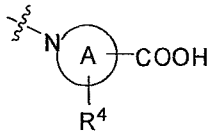
R^4 is H or C_{1-3} alkyl.

In some embodiments, ring A is pyrrolidinyl. In some embodiments, ring A is piperidinyl. In other embodiments, ring A is piperidinyl.

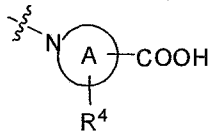
In some embodiments, the moiety  is selected from 4-carboxypiperidin-1-yl, 3-carboxypyrrolidin-1-yl, 3-methyl-3-carboxypyrrolidin-1-yl, 4-(N,N-dimethylaminocarbonyl)piperidin-1-yl, 4-(N-methylaminocarbonyl)piperidin-1-yl, and 4-(2-carboxyethylaminocarbonyl)piperidin-1-yl, wherein the wavy line indicates the point of attachment to the rest of the molecule.



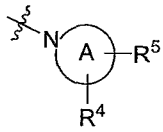
In some embodiments, the moiety is selected from 4-carboxypiperidin-1-yl, 3-carboxypyrrolidin-1-yl, and 3-methyl-3-carboxypyrrolidin-1-yl, wherein the wavy line indicates the point of attachment to the rest of the molecule.



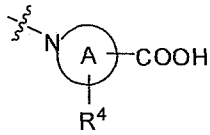
In some embodiments, the moiety is 4-carboxypiperidin-1-yl, wherein the wavy line indicates the point of attachment to the rest of the molecule.



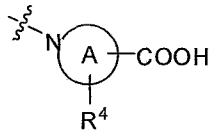
In some embodiments, the moiety is 3-carboxypyrrolidin-1-yl, wherein the wavy line indicates the point of attachment to the rest of the molecule. In some embodiments, the 3-carboxypyrrolidin-1-yl is (R)-3-carboxypyrrolidin-1-yl. In some embodiments, the 3-carboxypyrrolidin-1-yl is (S)-3-carboxypyrrolidin-1-yl.



In some embodiments, the moiety is selected from 4-(N,N-dimethylaminocarbonyl)piperidin-1-yl, 4-(N-methylaminocarbonyl)piperidin-1-yl, and 4-(2-carboxyethylaminocarbonyl)piperidin-1-yl, wherein the wavy line indicates the point of attachment to the rest of the molecule.



In some embodiments, the moiety is 3-methyl-3-carboxypyrrolidin-1-yl, wherein the wavy line indicates the point of attachment to the rest of the molecule. In some embodiments, the 3-methyl-3-carboxypyrrolidin-1-yl is (R)-3-methyl-3-carboxypyrrolidin-1-yl. In some embodiments, the 3-methyl-3-carboxypyrrolidin-1-yl is (S)-3-methyl-3-carboxypyrrolidin-1-yl.



In some embodiments, the moiety is selected from 4-carboxypiperidin-1-yl, (R)-3-carboxypyrrolidin-1-yl, (S)-3-carboxypyrrolidin-1-yl, (R)-3-methyl-3-

carboxypyrrolidin-1-yl and (S)-3-methyl-3-carboxypyrrolidin-1-yl, wherein the wavy line indicates the point of attachment to the rest of the molecule.

In some embodiments, X^1 is N. In some embodiments, X^1 is CH.

In some embodiments, R^1 is CH_3 or Cl. In some embodiments, R^1 is CH_3. In some embodiments, R^1 is halo (e.g., F, Cl, or Br). In some embodiments, R^1 is Cl.

In some embodiments, R^2 is C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-2} alkyl-, OH, NH_2, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, 1-azetidinyl, azetidin-1-ylmethyl, 1-pyrrolidinyl, pyrrolidin-1-ylmethyl, 1-piperidinyl, or piperidin-1-ylmethyl, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-2} alkyl-, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, 1-azetidinyl, azetidin-1-ylmethyl, 1-pyrrolidinyl, pyrrolidin-1-ylmethyl, 1-piperidinyl and piperidin-1-ylmethyl of R^2 are each optionally substituted with 1 or 2 substituents independently selected from halo, CN and OH.

In some embodiments, R^2 is C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, OH, NH_2, -NH-C_{1-4} alkyl, or -N(C_{1-4} alkyl)$_2$, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, -NH-C_{1-4} alkyl, and -N(C_{1-4} alkyl)$_2$ of R^2 are each optionally substituted with 1 or 2 substituents independently selected from halo, CN and OH.

In some embodiments, R^2 is C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-2} alkyl-, 1-azetidinyl, azetidin-1-ylmethyl, 1-pyrrolidinyl, pyrrolidin-1-ylmethyl, 1-piperidinyl, or piperidin-1-ylmethyl, wherein the C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-2} alkyl-, 1-azetidinyl, azetidin-1-ylmethyl, 1-pyrrolidinyl, pyrrolidin-1-ylmethyl, 1-piperidinyl and piperidin-1-ylmethyl of R^2 are each optionally substituted with 1 or 2 substituents independently selected from halo, CN and OH.

In some embodiments, R^2 is methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, CHF_2, CFH_2, OCF_3, $OCHF_2$, OCH_2F, cyclopropyl, cyclobutyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclohexylmethyl, OH, NH_2, $NHCH_3$, $N(CH_3)_2$, 1-azetidinyl, azetidin-1-ylmethyl, 1-pyrrolidinyl, pyrrolidin-1-ylmethyl, 1-piperidinyl or piperidin-1-ylmethyl, wherein the methyl, ethyl, isopropyl, methoxy, ethoxy, cyclopropyl, cyclobutyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclohexylmethyl, $NHCH_3$, $N(CH_3)_2$, 1-azetidinyl, azetidin-1-ylmethyl, 1-pyrrolidinyl, pyrrolidin-1-ylmethyl, 1-piperidinyl and piperidin-1-ylmethyl of R^2 are each optionally substituted with 1 or 2 substituents independently selected from F, Cl, Br, CN and OH.

In some embodiments, R^2 is methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, CHF_2, CFH_2, OCF_3, $OCHF_2$, OCH_2F, OH, NH_2, $NHCH_3$, or $N(CH_3)_2$, wherein the methyl, ethyl,

isopropyl, methoxy, ethoxy, $NHCH_3$, and $N(CH_3)_2$ of R^2 are each optionally substituted with 1 or 2 substituents independently selected from F, Cl, Br, CN and OH.

In some embodiments, R^2 is cyclopropyl, cyclobutyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclohexylmethyl, 1-azetidinyl, azetidin-1-ylmethyl, 1-pyrrolidinyl, pyrrolidin-1-ylmethyl, 1-piperidinyl or piperidin-1-ylmethyl, wherein the cyclopropyl, cyclobutyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclohexylmethyl, 1-azetidinyl, azetidin-1-ylmethyl, 1-pyrrolidinyl, pyrrolidin-1-ylmethyl, 1-piperidinyl and piperidin-1-ylmethyl of R^2 are each optionally substituted with 1 or 2 substituents independently selected from F, Cl, Br, CN and OH.

In some embodiments, R^2 is CH_3, CF_3, CHF_2, $CH(CH_3)_2$, NH_2, cyclopropyl, or CH_2OH.

In some embodiments, R^2 is C_{1-4} alkyl or C_{1-4} haloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from F, Cl, Br, CN and OH.

In some embodiments, R^2 is C_{1-4} alkyl or C_{1-4} haloalkyl. In some embodiments, R^2 is CH_3, CF_3, CHF_2 or $CH(CH_3)_2$. In some embodiments, R^2 is C_{1-4} alkyl such as CH_3 and $CH(CH_3)_2$. In some embodiments, R^2 is CH_3. In some embodiments, R^2 is $CH(CH_3)_2$. In some embodiments, R^2 is C_{1-4} haloalkyl such as CF_3, CHF_2, and CH_2F. In some embodiments, R^2 is C_{1-4} haloalkyl such as CF_3 and CHF_2. In some embodiments, R^2 is CF_3. In some embodiments, R^2 is CHF_2. In some embodiments, R^2 is CH_2F.

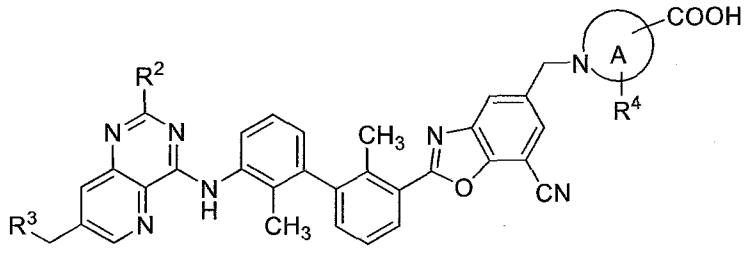
In some embodiments, R^2 is NH_2, $NHCH_3$, or $N(CH_3)_2$, wherein the $NHCH_3$ and $N(CH_3)_2$ of R^2 are each optionally substituted with 1 or 2 substituents independently selected from F, Cl, Br, CN and OH. In some embodiments, R^2 is NH_2.

In some embodiments, R^2 is cyclopropyl, cyclobutyl, or cyclohexyl, wherein the cyclopropyl, cyclobutyl, and cyclohexyl of R^2 are each optionally substituted with 1 or 2 substituents independently selected from F, Cl, Br, CN and OH. In some embodiments, R^2 is cyclopropyl optionally substituted with 1 or 2 substituents independently selected from F, Cl, Br, CN and OH. In some embodiments, R^2 is cyclopropyl.

In some embodiments, R^3 is (R)-3-hydroxy-3-methylpyrrolidin-1-yl or (S)-3-hydroxy-3-methylpyrrolidin-1-yl. In some embodiments, R^3 is (R)-3-hydroxypyrrolidin-1-yl or (S)-3-hydroxypyrrolidin-1-yl. In some embodiments, R^3 is (R)-2-hydroxy-2-methyl-ethylamino or (S)-2-hydroxy-2-methyl-ethylamino. In some embodiments, R^3 is (R)-2-hydroxy-1-methyl-ethylamino or (S)-2-hydroxy-1-methyl-ethylamino.

In some embodiments, R^4 is H or CH_3. In some embodiments, R^4 is H. In some embodiments, R^4 is C_{1-3} alkyl such as CH_3.

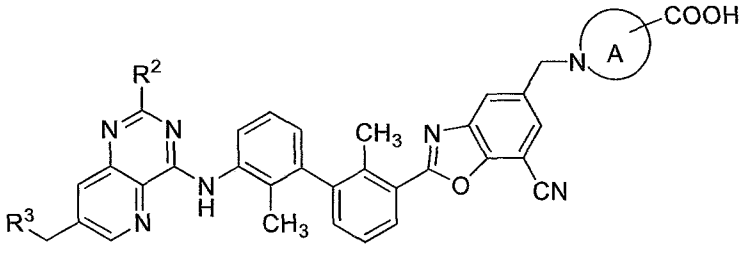
In some embodiments, the compound provided herein is a compound of Formula II:



(II)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2, R^3, R^4 and ring A are as described herein.

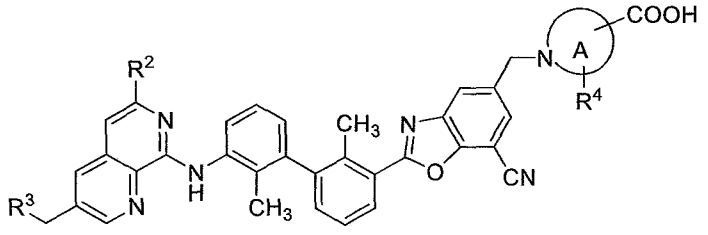
In some embodiments, the compound provided herein is a compound of Formula III:



(III)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2, R^3, and ring A are as described herein.

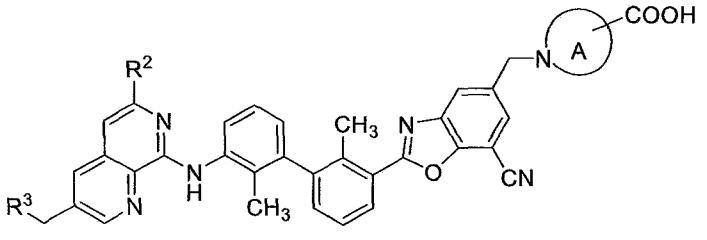
In some embodiments, the compound provided herein is a compound of Formula IV:



(IV)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2, R^3, R^4, and ring A are as described herein.

In some embodiments, the compound provided herein is a compound of Formula V:



(V)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2, R^3, and ring A are as described herein.

In some embodiments, the compound is selected from:

1-((7-cyano-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

1-((7-cyano-2-(3'-(7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

1-((7-cyano-2-(3'-(7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

1-((7-cyano-2-(3'-(7-((1-hydroxypropan-2-ylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

1-((7-cyano-2-(3'-(7-((2-hydroxypropylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

1-((7-cyano-2-(3'-(7-((-3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid;

1-((7-cyano-2-(3'-(7-((-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid;

1-((7-cyano-2-(3'-(7-((-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid;

1-((7-cyano-2-(3'-(7-((-1-hydroxypropan-2-ylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid;

1-((7-cyano-2-(3'-(7-((-2-hydroxypropylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid;

1-((7-cyano-2-(3'-(7-((-3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid;

1-((7-cyano-2-(3'-(7-((-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid;

1-((7-cyano-2-(3'-(7-((-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid;

1-((7-cyano-2-(3'-(7-((-1-hydroxypropan-2-ylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid;

1-((7-cyano-2-(3'-(7-((-2-hydroxypropylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid;

1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((-3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid;

1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((-3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid;

1-((7-cyano-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

1-((7-cyano-2-(3'-(7-((-3-hydroxypyrrolidin-1-yl)methyl)-2-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid; and

1-((7-cyano-2-(3'-(7-((-3-hydroxypyrrolidin-1-yl)methyl)-2-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid,

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In some embodiments, the compound is selected from:

1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid;

1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid;

1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-4-methylpiperidine-4-carboxylic acid;

1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-N,N-dimethylpiperidine-4-carboxamide;

1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-N-methylpiperidine-4-carboxamide;

3-(1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxamido)propanoic acid;

1-((7-cyano-2-(3'-(2-cyclopropyl-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid;

1-((2-(3'-(2-amino-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)-7-cyanobenzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

1-((7-cyano-2-(3'-(2-(hydroxymethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

1-((7-cyano-2-(3'-(3-((3-hydroxypyrrolidin-1-yl)methyl)-6-methyl-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid; and

1-((7-cyano-2-(3'-(6-(difluoromethyl)-3-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid,

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In some embodiments, the compound is selected from the examples provided herein.

It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment (while the embodiments are intended to be combined as if written in multiply dependent form). Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination. Thus, it is contemplated as features described as embodiments of the compounds of Formula (I) can be combined in any suitable combination.

At various places in the present specification, certain features of the compounds are disclosed in groups or in ranges. It is specifically intended that such a disclosure include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose (without limitation) methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl and C_6 alkyl.

The term "n-membered," where n is an integer, typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

At various places in the present specification, variables defining divalent linking groups may be described. It is specifically intended that each linking substituent include both the forward and backward forms of the linking substituent. For example, -NR(CR'R")$_n$- includes both -NR(CR'R")$_n$- and -(CR'R")$_n$NR- and is intended to disclose each of the forms individually. Where the structure requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists "alkyl" or "aryl" then it is understood that the "alkyl" or "aryl" represents a linking alkylene group or arylene group, respectively.

The term "substituted" means that an atom or group of atoms formally replaces hydrogen as a "substituent" attached to another group. The term "substituted", unless otherwise indicated, refers to any level of substitution, *e.g.*, mono-, di-, tri-, tetra- or penta-substitution, where such substitution is permitted. The substituents are independently selected, and substitution may be at any chemically accessible position. It is to be understood that substitution at a given atom is limited by valency. It is to be understood that substitution at a given atom results in a chemically stable molecule. The phrase "optionally substituted" means unsubstituted or substituted. The term "substituted" means that a hydrogen atom is removed and replaced by a substituent. A single divalent substituent, *e.g.*, oxo, can replace two hydrogen atoms.

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_{1-4}, C_{1-6} and the like.

The term "alkyl" employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chained or branched. The term "C_{n-m} alkyl", refers to an alkyl group having n to m carbon atoms. An alkyl group formally corresponds to an alkane with one C-H bond replaced by the point of attachment of the alkyl group to the remainder of the compound. In some embodiments, the alkyl group contains from 1 to 6 carbon atoms, from 1 to 4 carbon atoms, from 1 to 3 carbon atoms, or 1 to 2 carbon atoms. Examples of alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, isobutyl, *sec*-butyl; higher homologs such as 2-methyl-1-butyl, *n*-pentyl, 3-pentyl, *n*-hexyl, 1,2,2-trimethylpropyl and the like.

The term "alkenyl" employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or more double carbon-carbon bonds. An alkenyl group formally corresponds to an alkene with one C-H bond replaced by the point of attachment of the alkenyl group to the remainder of the compound. The term "C_{n-m} alkenyl" refers to an alkenyl group having n to m carbons. In some embodiments, the alkenyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms. Example alkenyl groups include, but are not limited to, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl and the like.

The term "alkynyl" employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or more triple carbon-carbon bonds. An alkynyl group formally corresponds to an alkyne with one C-H bond replaced by the point of attachment of the alkyl group to the remainder of the compound. The term "C_{n-m} alkynyl" refers to an alkynyl group having n to m carbons. Example

alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl and the like. In some embodiments, the alkynyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms.

The term "alkylene", employed alone or in combination with other terms, refers to a divalent alkyl linking group. An alkylene group formally corresponds to an alkane with two C-H bond replaced by points of attachment of the alkylene group to the remainder of the compound. The term "C_{n-m} alkylene" refers to an alkylene group having n to m carbon atoms. Examples of alkylene groups include, but are not limited to, ethan-1,2-diyl, propan-1,3-diyl, propan-1,2-diyl, butan-1,4-diyl, butan-1,3-diyl, butan-1,2-diyl, 2-methyl-propan-1,3-diyl and the like.

The term "alkoxy", employed alone or in combination with other terms, refers to a group of formula -O-alkyl, wherein the alkyl group is as defined above. The term "C_{n-m} alkoxy" refers to an alkoxy group, the alkyl group of which has n to m carbons. Example alkoxy groups include methoxy, ethoxy, propoxy (*e.g.*, *n*-propoxy and isopropoxy), *t*-butoxy and the like. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

The term "amino" refers to a group of formula $-NH_2$.

The term "carbamyl" refers to a group of formula $-C(O)NH_2$.

The term "carbonyl", employed alone or in combination with other terms, refers to a -C(=O)- group, which also may be written as C(O).

The term "cyano" or "nitrile" refers to a group of formula $-C\equiv N$, which also may be written as -CN.

The terms "halo" or "halogen", used alone or in combination with other terms, refers to fluoro, chloro, bromo and iodo. In some embodiments, "halo" refers to a halogen atom selected from F, Cl, or Br. In some embodiments, halo groups are F.

The term "haloalkyl" as used herein refers to an alkyl group in which one or more of the hydrogen atoms has been replaced by a halogen atom. The term "C_{n-m} haloalkyl" refers to a C_{n-m} alkyl group having n to m carbon atoms and from at least one up to {2(n to m)+1} halogen atoms, which may either be the same or different. In some embodiments, the halogen atoms are fluoro atoms. In some embodiments, the haloalkyl group has 1 to 6 or 1 to 4 carbon atoms. Example haloalkyl groups include CF_3, C_2F_5, CHF_2, CCl_3, $CHCl_2$, C_2Cl_5 and the like. In some embodiments, the haloalkyl group is a fluoroalkyl group.

The term "haloalkoxy", employed alone or in combination with other terms, refers to a group of formula -O-haloalkyl, wherein the haloalkyl group is as defined above. The term "C_{n-m} haloalkoxy" refers to a haloalkoxy group, the haloalkyl group of which has n to m carbons.

Example haloalkoxy groups include trifluoromethoxy and the like. In some embodiments, the haloalkoxy group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

The term "oxo" refers to an oxygen atom as a divalent substituent, forming a carbonyl group when attached to carbon, or attached to a heteroatom forming a sulfoxide or sulfone group, or an *N*-oxide group. In some embodiments, heterocyclic groups may be optionally substituted by 1 or 2 oxo (=O) substituents.

The term "sulfido" refers to a sulfur atom as a divalent substituent, forming a thiocarbonyl group (C=S) when attached to carbon.

The term "aromatic" refers to a carbocycle or heterocycle having one or more polyunsaturated rings having aromatic character (*i.e.*, having (4n + 2) delocalized π (pi) electrons where n is an integer).

The term "aryl," employed alone or in combination with other terms, refers to an aromatic hydrocarbon group, which may be monocyclic or polycyclic (*e.g.*, having 2 fused rings). The term "C_{n-m} aryl" refers to an aryl group having from n to m ring carbon atoms. Aryl groups include, *e.g.*, phenyl, naphthyl, indanyl, indenyl and the like. In some embodiments, aryl groups have from 6 to about 10 carbon atoms. In some embodiments aryl groups have 6 carbon atoms. In some embodiments aryl groups have 10 carbon atoms. In some embodiments, the aryl group is phenyl. In some embodiments, the aryl group is naphthyl.

The term "heteroatom" used herein is meant to include boron, phosphorus, sulfur, oxygen and nitrogen.

The term "heteroaryl" or "heteroaromatic," employed alone or in combination with other terms, refers to a monocyclic or polycyclic aromatic heterocycle having at least one heteroatom ring member selected from boron, phosphorus, sulfur, oxygen and nitrogen. In some embodiments, the heteroaryl ring has 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, any ring-forming N in a heteroaryl moiety can be an N-oxide. In some embodiments, the heteroaryl has 5-14 ring atoms including carbon atoms and 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl has 5-14, or 5-10 ring atoms including carbon atoms and 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl has 5-6 ring atoms and 1 or 2 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl is a five-membered or six-membered heteroaryl ring. In other embodiments, the heteroaryl is an eight-membered, nine-membered or ten-membered fused

bicyclic heteroaryl ring. Example heteroaryl groups include, but are not limited to, pyridinyl (pyridyl), pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, azolyl, oxazolyl, thiazolyl, imidazolyl, furanyl, thiophenyl, quinolinyl, isoquinolinyl, naphthyridinyl (including 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3- and 2,6-naphthyridine), indolyl, benzothiophenyl, benzofuranyl, benzisoxazolyl, imidazo[1,2-*b*]thiazolyl, purinyl, and the like.

A five-membered heteroaryl ring is a heteroaryl group having five ring atoms wherein one or more (*e.g.*, 1, 2 or 3) ring atoms are independently selected from N, O and S. Exemplary five-membered ring heteroaryls include thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl and 1,3,4-oxadiazolyl.

A six-membered heteroaryl ring is a heteroaryl group having six ring atoms wherein one or more (*e.g.*, 1, 2 or 3) ring atoms are independently selected from N, O and S. Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

The term "cycloalkyl," employed alone or in combination with other terms, refers to a non-aromatic hydrocarbon ring system (monocyclic, bicyclic or polycyclic), including cyclized alkyl and alkenyl groups. The term "C_{n-m} cycloalkyl" refers to a cycloalkyl that has n to m ring member carbon atoms. Cycloalkyl groups can include mono- or polycyclic (*e.g.*, having 2, 3 or 4 fused rings) groups and spirocycles. Cycloalkyl groups can have 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 ring-forming carbons (C_{3-14}). In some embodiments, the cycloalkyl group has 3 to 14 members, 3 to 10 members, 3 to 6 ring members, 3 to 5 ring members, or 3 to 4 ring members. In some embodiments, the cycloalkyl group is monocyclic. In some embodiments, the cycloalkyl group is monocyclic or bicyclic. In some embodiments, the cycloalkyl group is a C_{3-6} monocyclic cycloalkyl group. Ring-forming carbon atoms of a cycloalkyl group can be optionally oxidized to form an oxo or sulfido group. Cycloalkyl groups also include cycloalkylidenes. In some embodiments, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the cycloalkyl ring, *e.g.*, benzo or thienyl derivatives of cyclopentane, cyclohexane and the like. A cycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl,

norpinyl, norcarnyl, bicyclo[1.1.1]pentanyl, bicyclo[2.1.1]hexanyl, and the like. In some embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

The term "heterocycloalkyl," employed alone or in combination with other terms, refers to a non-aromatic ring or ring system, which may optionally contain one or more alkenylene groups as part of the ring structure, which has at least one heteroatom ring member independently selected from boron, nitrogen, sulfur oxygen and phosphorus, and which has 4-14 ring members, 4-10 ring members, 4-7 ring members, or 4-6 ring members. Included within the term "heterocycloalkyl" are monocyclic 4-, 5-, 6- and 7-membered heterocycloalkyl groups. Heterocycloalkyl groups can include mono- or bicyclic or polycyclic (*e.g.*, having two or three fused or bridged rings) ring systems or spirorcycles. In some embodiments, the heterocycloalkyl group is a monocyclic group having 1, 2 or 3 heteroatoms independently selected from nitrogen, sulfur and oxygen. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally oxidized to form an oxo or sulfido group or other oxidized linkage (*e.g.*, C(O), S(O), C(S) or $S(O)_2$, *N*-oxide *etc.*) or a nitrogen atom can be quaternized. The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double bonds. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the heterocycloalkyl ring, *e.g.*, benzo or thienyl derivatives of piperidine, morpholine, azepine, *etc.* A heterocycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. Examples of heterocycloalkyl groups include azetidinyl, azepanyl, dihydrobenzofuranyl, dihydrofuranyl, dihydropyranyl, morpholino, 3-oxa-9-azaspiro[5.5]undecanyl, 1-oxa-8-azaspiro[4.5]decanyl, piperidinyl, piperazinyl, oxopiperazinyl, pyranyl, pyrrolidinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydropyranyl, 1,2,3,4-tetrahydroquinolinyl, tropanyl, 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridinyl, and thiomorpholino.

At certain places, the definitions or embodiments refer to specific rings (*e.g.*, an azetidine ring, a pyridine ring, *etc.*). Unless otherwise indicated, these rings can be attached to any ring member provided that the valency of the atom is not exceeded. For example, an azetidine ring may be attached at any position of the ring, whereas an azetidin-3-yl ring is attached at the 3-position.

The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. *Cis* and *trans* geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. One method includes fractional recrystallization using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, *e.g.*, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β-camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α-methylbenzylamine (*e.g.*, *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, *N*-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane and the like.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (*e.g.*, dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

In some embodiments, the compounds of the invention have the (*R*)-configuration. In other embodiments, the compounds have the (*S*)-configuration. In compounds with more than one chiral centers, each of the chiral centers in the compound may be independently (*R*) or (*S*), unless otherwise indicated.

Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide - imidic acid pairs, lactam – lactim pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a

heterocyclic system, *e.g.*, 1*H*- and 3*H*-imidazole, 1*H*-, 2*H*- and 4*H*- 1,2,4-triazole, 1*H*- and 2*H*-isoindole and 1*H*- and 2*H*-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium. One or more constituent atoms of the compounds of the invention can be replaced or substituted with isotopes of the atoms in natural or non-natural abundance. In some embodiments, the compound includes at least one deuterium atom. For example, one or more hydrogen atoms in a compound of the present disclosure can be replaced or substituted by deuterium. In some embodiments, the compound includes two or more deuterium atoms. In some embodiments, the compound includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 deuterium atoms. Synthetic methods for including isotopes into organic compounds are known in the art.

The term, "compound," as used herein is meant to include all stereoisomers, geometric isomers, tautomers and isotopes of the structures depicted. The term is also meant to refer to compounds of the inventions, regardless of how they are prepared, e.g., synthetically, through biological process (e.g., metabolism or enzyme conversion), or a combination thereof.

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (*e.g.*, hydrates and solvates) or can be isolated. When in the solid state, the compounds described herein and salts thereof may occur in various forms and may, *e.g.*, take the form of solvates, including hydrates. The compounds may be in any solid state form, such as a polymorph or solvate, so unless clearly indicated otherwise, reference in the specification to compounds and salts thereof should be understood as encompassing any solid state form of the compound.

In some embodiments, the compounds of the invention, or salts thereof, are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, *e.g.*, a composition enriched in the compounds of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds of the invention, or salt thereof.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The expressions, "ambient temperature" and "room temperature," as used herein, are understood in the art, and refer generally to a temperature, *e.g.*, a reaction temperature, that is about the temperature of the room in which the reaction is carried out, *e.g.*, a temperature from about 20 °C to about 30 °C.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. The term "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the non-toxic salts of the parent compound formed, *e.g.*, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (*e.g.*, methanol, ethanol, iso-propanol or butanol) or acetonitrile (MeCN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th Ed., (Mack Publishing Company, Easton, 1985), p. 1418, Berge *et al.*, *J. Pharm. Sci.*, 1977, *66*(1), 1-19 and in Stahl *et al.*, *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, (Wiley, 2002). In some embodiments, the compounds described herein include the N-oxide forms.

II. Synthesis

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

The reactions for preparing compounds of the invention 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 (reactants), the intermediates or products at the temperatures at which the reactions are carried out, *e.g.*, temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups is described, *e.g.*, in Kocienski, *Protecting Groups*, (Thieme, 2007); Robertson, *Protecting Group Chemistry*, (Oxford University Press, 2000); Smith *et al.*, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th Ed. (Wiley, 2007); Peturssion *et al.*, "Protecting Groups in Carbohydrate Chemistry," *J. Chem. Educ.*, 1997, *74*(11), 1297; and Wuts *et al.*, *Protective Groups in Organic Synthesis*, 4th Ed., (Wiley, 2006).

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (*e.g.*, ^{1}H or ^{13}C), infrared spectroscopy, spectrophotometry (*e.g.*, UV-visible), mass spectrometry or by chromatographic methods such as high performance liquid chromatography (HPLC) or thin layer chromatography (TLC).

III. Uses of the Compounds

Compounds of the present disclosure can inhibit the activity of PD-1/PD-L1 protein/protein interaction and, thus, are useful in treating diseases and disorders associated with activity of PD-1 and the diseases and disorders associated with PD-L1 including its interaction with other proteins such as PD-1 and B7-1 (CD80). In certain embodiments, the compounds of the present disclosure, or pharmaceutically acceptable salts or stereoisomers thereof, are useful for therapeutic administration to enhance, stimulate and/or increase immunity in cancer, chronic infection or sepsis, including enhancement of response to vaccination. In some embodiments, the present disclosure provides a method for inhibiting the PD-1/PD-L1 protein/protein interaction. The method includes administering to an individual or a patient a compound of Formula (I) or of any of the formulas as described herein, or of a compound as recited in any of

the claims and described herein, or a pharmaceutically acceptable salt or a stereoisomer thereof. The compounds of the present disclosure can be used alone, in combination with other agents or therapies or as an adjuvant or neoadjuvant for the treatment of diseases or disorders, including cancer or infection diseases. For the uses described herein, any of the compounds of the disclosure, including any of the embodiments thereof, may be used.

The compounds of the present disclosure inhibit the PD-1/PD-L1 protein/protein interaction, resulting in a PD-1 pathway blockade. The blockade of PD-1 can enhance the immune response to cancerous cells and infectious diseases in mammals, including humans. In some embodiments, the present disclosure provides treatment of an individual or a patient *in vivo* using a compound of Formula (I) or a salt or stereoisomer thereof such that growth of cancerous tumors is inhibited. A compound of Formula (I) or of any of the formulas as described herein, or a compound as recited in any of the claims and described herein, or a salt or stereoisomer thereof, can be used to inhibit the growth of cancerous tumors. Alternatively, a compound of Formula (I) or of any of the formulas as described herein, or a compound as recited in any of the claims and described herein, or a salt or stereoisomer thereof, can be used in conjunction with other agents or standard cancer treatments, as described below. In one embodiment, the present disclosure provides a method for inhibiting growth of tumor cells *in vitro*. The method includes contacting the tumor cells *in vitro* with a compound of Formula (I) or of any of the formulas as described herein, or of a compound as recited in any of the claims and described herein, or of a salt or stereoisomer thereof. In another embodiment, the present disclosure provides a method for inhibiting growth of tumor cells in an individual or a patient. The method includes administering to the individual or patient in need thereof a therapeutically effective amount of a compound of Formula (I) or of any of the formulas as described herein, or of a compound as recited in any of the claims and described herein, or a salt or a stereoisomer thereof.

In some embodiments, provided herein is a method for treating cancer. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a salt thereof. Examples of cancers include those whose growth may be inhibited using compounds of the disclosure and cancers typically responsive to immunotherapy.

In some embodiments, the present disclosure provides a method of enhancing, stimulating and/or increasing the immune response in a patient. The method includes administering to the patient in need thereof a therapeutically effective amount of a compound of

Formula (I) or any of the formulas as described herein, a compound or composition as recited in any of the claims and described herein, or a salt thereof.

Examples of cancers that are treatable using the compounds of the present disclosure include, but are not limited to, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, endometrial cancer, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or urethra, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T -cell lymphoma, environmentally induced cancers including those induced by asbestos, and combinations of said cancers. The compounds of the present disclosure are also useful for the treatment of metastatic cancers, especially metastatic cancers that express PD-L1.

In some embodiments, cancers treatable with compounds of the present disclosure include melanoma (e.g., metastatic malignant melanoma, cutaneous melanoma), renal cancer (e.g. clear cell carcinoma), prostate cancer (e.g. hormone refractory prostate adenocarcinoma), breast cancer (e.g., breast invasive carcinoma), colon cancer, lung cancer (e.g. non-small cell lung cancer and small cell lung cancer), squamous cell head and neck cancer (e.g., squamous cell carcinoma of the head and neck), urothelial cancer (e.g., bladder cancer, nonmuscle invasive bladder cancer (NMIBC)) and cancers with high microsatellite instability (MSI^{high}). Additionally, the disclosure includes refractory or recurrent malignancies whose growth may be inhibited using the compounds of the disclosure.

In some embodiments, cancers that are treatable using the compounds of the present disclosure include, but are not limited to, solid tumors (*e.g.*, prostate cancer, colon cancer, esophageal cancer, endometrial cancer, ovarian cancer, uterine cancer, renal cancer, hepatic cancer, pancreatic cancer, gastric cancer, breast cancer, lung cancer, cancers of the head and neck, thyroid cancer, glioblastoma, sarcoma, bladder cancer, etc.), hematological cancers (*e.g.*,

lymphoma, leukemia such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), DLBCL, mantle cell lymphoma, Non-Hodgkin lymphoma (including relapsed or refractory NHL and recurrent follicular), Hodgkin lymphoma or multiple myeloma) and combinations of said cancers.

In some embodiments, cancers that are treatable using the compounds of the present disclosure include, but are not limited to, cholangiocarcinoma, bile duct cancer, biliary tract cancer, triple negative breast cancer, rhabdomyosarcoma, small cell lung cancer, leiomyosarcoma, hepatocellular carcinoma, Ewing's sarcoma, brain cancer, brain tumor, astrocytoma, neuroblastoma, neurofibroma, basal cell carcinoma, chondrosarcoma, epithelioid sarcoma, eye cancer, Fallopian tube cancer, gastrointestinal cancer, gastrointestinal stromal tumors, hairy cell leukemia, intestinal cancer, islet cell cancer, oral cancer, mouth cancer, throat cancer, laryngeal cancer, lip cancer, mesothelioma, neck cancer, nasal cavity cancer, ocular cancer, ocular melanoma, pelvic cancer, rectal cancer, renal cell carcinoma, salivary gland cancer, sinus cancer, spinal cancer, tongue cancer, tubular carcinoma, urethral cancer, and ureteral cancer.

In some embodiments, the compounds of the present disclosure can be used to treat sickle cell disease and sickle cell anemia.

In some embodiments, diseases and indications that are treatable using the compounds of the present disclosure include, but are not limited to hematological cancers, sarcomas, lung cancers, gastrointestinal cancers, genitourinary tract cancers, liver cancers, bone cancers, nervous system cancers, gynecological cancers, and skin cancers.

Exemplary hematological cancers include lymphomas and leukemias such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, Non-Hodgkin lymphoma (including relapsed or refractory NHL and recurrent follicular), Hodgkin lymphoma, myeloproliferative diseases (e.g., primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocytosis (ET)), myelodysplasia syndrome (MDS), T-cell acute lymphoblastic lymphoma (T-ALL) and multiple myeloma (MM).

Exemplary sarcomas include chondrosarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, angiosarcoma, fibrosarcoma, liposarcoma, myxoma, rhabdomyoma, rhabdosarcoma, fibroma, lipoma, harmatoma, and teratoma.

Exemplary lung cancers include non-small cell lung cancer (NSCLC) (e.g., squamous cell NSCLC), small cell lung cancer, bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, chondromatous hamartoma, and mesothelioma.

Exemplary gastrointestinal cancers include cancers of the esophagus (carcinoma, squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma, adenocarcinoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), and colorectal cancer (e.g., colorectal adenocarcinoma).

Exemplary genitourinary tract cancers include cancers of the kidney (adenocarcinoma, Wilm's tumor [nephroblastoma]), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), and testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma). In some embodiments, the cancer is a urological cancer (e.g., papilliary kidney carcinoma, testicular germ cell cancer, chromophobe renal cell carcinoma, clear cell renal carcinoma, or prostate adenocarcinoma).

Exemplary liver cancers include hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, and hemangioma.

Exemplary bone cancers include, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, and giant cell tumors

Exemplary nervous system cancers include cancers of the skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, meduoblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma, glioblastoma multiform, oligodendroglioma,

schwannoma, retinoblastoma, congenital tumors), and spinal cord (neurofibroma, meningioma, glioma, sarcoma), as well as neuroblastoma and Lhermitte-Duclos disease.

Exemplary gynecological cancers include cancers of the uterus (endometrial carcinoma), cervix (cervical carcinoma, pre -tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, serous adenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), and fallopian tubes (carcinoma).

Exemplary skin cancers include melanoma, basal cell carcinoma, squamous cell carcinoma (e.g., cutaneous squamous cell carcinoma), Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, and keloids. In some embodiments, diseases and indications that are treatable using the compounds of the present disclosure include, but are not limited to, sickle cell disease (e.g., sickle cell anemia), triple-negative breast cancer (TNBC), myelodysplastic syndromes, testicular cancer, bile duct cancer, esophageal cancer, and urothelial carcinoma.

PD-1 pathway blockade with compounds of the present disclosure can also be used for treating infections such as viral, bacteria, fungus and parasite infections. The present disclosure provides a method for treating infections such as viral infections. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, a salt thereof. Examples of viruses causing infections treatable by methods of the present disclosure include, but are not limit to, human immunodeficiency virus, human papillomavirus, influenza, hepatitis A, B, C or D viruses, adenovirus, poxvirus, herpes simplex viruses, human cytomegalovirus, severe acute respiratory syndrome virus, ebola virus, and measles virus. In some embodiments, viruses causing infections treatable by methods of the present disclosure include, but are not limit to, hepatitis (A, B, or C), herpes virus (e.g., VZV, HSV-1, HAV-6, HSV-II, and CMV, Epstein Barr virus), adenovirus, influenza virus, flaviviruses, echovirus, rhinovirus, coxsackie virus, cornovirus, respiratory syncytial virus, mumpsvirus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus, tuberculosis and arboviral encephalitis virus.

The present disclosure provides a method for treating bacterial infections. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a salt thereof. Non-limiting examples of pathogenic bacteria causing infections treatable by methods of the disclosure include chlamydia, rickettsial bacteria, mycobacteria, staphylococci, streptococci, pneumonococci, meningococci and conococci, klebsiella, proteus, serratia, pseudomonas, legionella, diphtheria, salmonella, bacilli, cholera, tetanus, botulism, anthrax, plague, leptospirosis, and Lyme's disease bacteria.

The present disclosure provides a method for treating fungus infections. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a salt thereof. Non-limiting examples of pathogenic fungi causing infections treatable by methods of the disclosure include Candida (albicans, krusei, glabrata, tropicalis, etc.), Cryptococcus neoformans, Aspergillus (fumigatus, niger, etc.), Genus Mucorales (mucor, absidia, rhizophus), Sporothrix schenkii, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Coccidioides immitis and Histoplasma capsulatum.

The present disclosure provides a method for treating parasite infections. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a salt thereof. Non-limiting examples of pathogenic parasites causing infections treatable by methods of the disclosure include Entamoeba histolytica, Balantidium coli, Naegleriafowleri, Acanthamoeba sp., Giardia lambia, Cryptosporidium sp., Pneumocystis carinii, Plasmodium vivax, Babesia microti, Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondi, and Nippostrongylus brasiliensis.

The present disclosure provides a method for treating neurodegenerative diseases or disorders. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a salt thereof. Non-limiting examples of neurodegenerative diseases or disorders include Alzheimer's disease, Parkinson's disease, Huntington's disease, prion disease, Motor neurone diseases, Spinocerebellar ataxia and Spinal muscular atrophy.

It is believed that compounds of Formula (I), or any of the embodiments thereof, may possess satisfactory pharmacological profile and promising biopharmaceutical properties, such as toxicological profile, metabolism and pharmacokinetic properties, solubility, and permeability. It will be understood that determination of appropriate biopharmaceutical properties is within the knowledge of a person skilled in the art, *e.g.*, determination of cytotoxicity in cells or inhibition of certain targets or channels to determine potential toxicity.

The terms "individual" or "patient," used interchangeably, refer to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

The phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

As used herein, the term "treating" or "treatment" refers to one or more of (1) inhibiting the disease; *e.g.*, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, arresting further development of the pathology and/or symptomatology); and (2) ameliorating the disease; *e.g.*, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

In some embodiments, the compounds of the invention are useful in preventing or reducing the risk of developing any of the diseases referred to herein; *e.g.*, preventing or reducing the risk of developing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease.

Combination Therapies

Cancer cell growth and survival can be impacted by dysfunction in multiple biological pathways. Thus, it may be useful to combine inhibitors of different mechanisms, such as enzyme inhibitors, signal transduction inhibitors, inhibitors of chromatin dynamics or modulators of immune responses, to treat such conditions. Targeting more than one signaling pathway (or more than one biological molecule involved in a given signaling pathway) may reduce the likelihood of drug-resistance arising in a cell population, or reduce the toxicity of treatment.

The compounds of the present disclosure can be used in combination with one or more other therapies for the treatment of diseases, such as cancer or infections. Examples of diseases and indications treatable with combination therapies include those as described herein. Examples of cancers include solid tumors and non-solid tumors, such as liquid tumors, blood cancers. Examples of infections include viral infections, bacterial infections, fungus infections or parasite infections. For example, the compounds of the present disclosure can be combined with one or more inhibitors of the following kinases for the treatment of cancer: Akt1, Akt2, Akt3, BCL2, CDK, TGF-βR, PKA, PKG, PKC, CaM-kinase, phosphorylase kinase, MEKK, ERK, MAPK, mTOR, EGFR, HER2, HER3, HER4, INS-R, IDH2, IGF-1R, IR-R, PDGFαR, PDGFβR, PI3K (alpha, beta, gamma, delta, and multiple or selective), CSF1R, KIT, FLK-II, KDR/FLK-1, FLK-4, flt-1, FGFR1, FGFR2, FGFR3, FGFR4, c-Met, PARP, Ron, Sea, TRKA, TRKB, TRKC, TAM kinases (Axl, Mer, Tyro3), FLT3, VEGFR/Flt2, Flt4, EphA1, EphA2, EphA3, EphB2, EphB4, Tie2, Src, Fyn, Lck, Fgr, Btk, Fak, SYK, FRK, JAK, ABL, ALK and B-Raf. In some embodiments, the compounds of the present disclosure can be combined with one or more of the following inhibitors for the treatment of cancer or infections. Non-limiting examples of inhibitors that can be combined with the compounds of the present disclosure for treatment of cancer and infections include an FGFR inhibitor (FGFR1, FGFR2, FGFR3 or FGFR4, e.g., pemigatinib (INCY54828), INCB62079), a JAK inhibitor (JAK1 and/or JAK2, e.g., ruxolitinib, baricitinib or itacitinib (INCB39110)), an IDO inhibitor (e.g., epacadostat, NLG919, or BMS-986205, MK7162), an LSD1 inhibitor (e.g., INCB59872 and INCB60003), a TDO inhibitor, a PI3K-delta inhibitor (e.g., Parsaclisib (INCB50465) and INCB50797), a PI3K-gamma inhibitor such as PI3K-gamma selective inhibitor, a Pim inhibitor (e.g., INCB53914), an EGFR inhibitor (also known as ErB-1 or HER-1; e.g. erlotinib, gefitinib, vandetanib, orsimertinib, cetuximab, necitumumab, or panitumumab), a VEGFR inhibitor or pathway blocker (e.g. bevacizumab, pazopanib, sunitinib, sorafenib, axitinib, regorafenib, ponatinib, cabozantinib, axitinib, vandetanib, ramucirumab, lenvatinib, ziv-aflibercept), a PARP inhibitor (e.g. olaparib, rucaparib, veliparib, talazoparib, or niraparib), a CSF1R inhibitor, a TAM receptor tyrosine kinases (Tyro-3, Axl, and Mer), an adenosine receptor antagonist (e.g., A2a/A2b receptor antagonist), an HPK1 inhibitor, a chemokine receptor inhibitor (e.g. CCR2 or CCR5 inhibitor), a SHP1/2 phosphatase inhibitor, a histone deacetylase inhibitor (HDAC) such as an HDAC8 inhibitor, an angiogenesis inhibitor, an interleukin receptor inhibitor, bromo and extra terminal family members inhibitors (for example, bromodomain inhibitors or BET inhibitors such as INCB54329 and INCB57643), an arginase inhibitor (INCB001158), a PARP inhibitor

(such as rucaparib or olaparib), sitravatinib, a B-Raf inhibitor-MEK inhibitor combination (such as encorafenib plus binimetinib, dabrafenib plus trametinib, or cobimetinib plus vemurafenib), and an adenosine receptor antagonist or combinations thereof.

In some embodiments, the compounds of the present disclosure can be combined with a TLR7 agonist (e.g., imiquimod).

The compounds of the present disclosure can further be used in combination with other methods of treating cancers, for example by chemotherapy, irradiation therapy, tumor-targeted therapy, adjuvant therapy, immunotherapy or surgery. Examples of immunotherapy include cytokine treatment (e.g., interferons, GM-CSF, G-CSF, IL-2), CRS-207 immunotherapy, cancer vaccine, monoclonal antibody, bispecific or multi-specific antibody, antibody drug conjugate, adoptive T cell transfer, Toll receptor agonists, STING agonists, RIG-I agonists, oncolytic virotherapy and immunomodulating small molecules, including thalidomide or JAK1/2 inhibitor, PI3Kδ inhibitor and the like. The compounds can be administered in combination with one or more anti-cancer drugs, such as a chemotherapeutic agent. Examples of chemotherapeutics include any of: abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, anastrozole, arsenic trioxide, asparaginase, azacitidine, bevacizumab, bexarotene, baricitinib, bleomycin, , bortezomib, busulfan intravenous, busulfan oral, calusterone, capecitabine, carboplatin, carmustine, cetuximab, chlorambucil, cisplatin, cladribine, clofarabine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, dalteparin sodium, dasatinib, daunorubicin, decitabine, denileukin, denileukin diftitox, dexrazoxane, docetaxel, doxorubicin, dromostanolone propionate, eculizumab, epirubicin, erlotinib, estramustine, etoposide phosphate, etoposide, exemestane, fentanyl citrate, filgrastim, floxuridine, fludarabine, fluorouracil, fulvestrant, gefitinib, gemcitabine, gemtuzumab ozogamicin, goserelin acetate, histrelin acetate, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib mesylate, interferon alfa 2a, irinotecan, lapatinib ditosylate, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, mechlorethamine, megestrol acetate, melphalan, mercaptopurine, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone phenpropionate, nelarabine, nofetumomab, oxaliplatin, paclitaxel, pamidronate, panitumumab, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, procarbazine, quinacrine, rasburicase, rituximab, ruxolitinib, sorafenib, streptozocin, sunitinib, sunitinib maleate, tamoxifen, temozolomide, teniposide, testolactone, thalidomide, thioguanine, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, vorinostat and zoledronate.

Other anti-cancer agent(s) include antibody therapeutics such as trastuzumab (Herceptin), antibodies to costimulatory molecules such as CTLA-4 (e.g., ipilimumab), 4-1BB (e.g. urelumab, utomilumab), antibodies to PD-1 and PD-L1, or antibodies to cytokines (IL-10, TGF-β, etc.). Examples of antibodies to PD-1 and/or PD-L1 that can be combined with compounds of the present disclosure for the treatment of cancer or infections such as viral, bacteria, fungus and parasite infections include, but are not limited to nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab and SHR-1210.

Compounds of the present disclosure can be used in combination with one or more immune checkpoint inhibitors for the treatment of diseases, such as cancer or infections. Exemplary immune checkpoint inhibitors include inhibitors against immune checkpoint molecules such as CBL-B, CD27, CD28, CD40, CD122, CD96, CD73, CD47, OX40, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM, arginase, CD137 (also known as 4-1BB), ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, LAG3, TIM3, TIGIT, CD112R, VISTA, PD-1, PD-L1 and PD-L2. In some embodiments, the immune checkpoint molecule is a stimulatory checkpoint molecule selected from CD27, CD28, CD40, ICOS, OX40, GITR and CD137. In some embodiments, the immune checkpoint molecule is an inhibitory checkpoint molecule selected from A2AR, B7-H3, B7-H4, BTLA, CTLA-4, IDO, KIR, LAG3, PD-1, TIM3, and VISTA. In some embodiments, the compounds provided herein can be used in combination with one or more agents selected from KIR inhibitors, TIGIT inhibitors, LAIR1 inhibitors, CD160 inhibitors, 2B4 inhibitors and TGFR beta inhibitors.

In some embodiments, the inhibitor of an immune checkpoint molecule is anti-PD1 antibody, anti-PD-L1 antibody, or anti-CTLA-4 antibody.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-1, e.g., an anti-PD-1 monoclonal antibody. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab, pembrolizumab (also known as MK-3475), pidilizumab, SHR-1210, PDR001, or AMP-224. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab or pembrolizumab. In some embodiments, the anti-PD1 antibody is pembrolizumab.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-L1, e.g., an anti-PD-L1 monoclonal antibody. In some embodiments, the anti-PD-L1 monoclonal antibody is BMS-935559, MEDI4736, MPDL3280A (also known as RG7446), or MSB0010718C. In some embodiments, the anti-PD-L1 monoclonal antibody is MPDL3280A or MEDI4736.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CTLA-4, e.g., an anti-CTLA-4 antibody. In some embodiments, the anti-CTLA-4 antibody is ipilimumab or tremelimumab.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of LAG3, e.g., an anti-LAG3 antibody. In some embodiments, the anti-LAG3 antibody is BMS-986016, LAG525 or INCAGN2385.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of TIM3, e.g., an anti-TIM3 antibody. In some embodiments, the anti-TIM3 antibody is INCAGN2390, MBG453, or TSR-022.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of GITR, e.g., an anti-GITR antibody. In some embodiments, the anti-GITR antibody is TRX518, MK-4166, INCAGN1876, MK-1248, AMG228, BMS-986156, GWN323, or MEDI1873.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of OX40, e.g., an anti-OX40 antibody or OX40L fusion protein. In some embodiments, the anti-OX40 antibody is MEDI0562, MOXR-0916, PF-04518600, GSK3174998, or BMS-986178. In some embodiments, the OX40L fusion protein is MEDI6383.

The compounds of the present disclosure can further be used in combination with one or more anti-inflammatory agents, steroids, immunosuppressants or therapeutic antibodies.

The compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be combined with another immunogenic agent, such as cancerous cells, purified tumor antigens (including recombinant proteins, peptides, and carbohydrate molecules), cells, and cells transfected with genes encoding immune stimulating cytokines. Non-limiting examples of tumor vaccines that can be used include peptides of melanoma antigens, such as peptides of gp100, MAGE antigens, Trp-2, MARTI and/or tyrosinase, or tumor cells transfected to express the cytokine GM-CSF.

The compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be used in combination with a vaccination protocol for the treatment of cancer. In some embodiments, the tumor cells are transduced to express GM-CSF. In some embodiments, tumor vaccines include the proteins from viruses implicated in human cancers such as Human Papilloma Viruses (HPV), Hepatitis Viruses (HBV and HCV) and Kaposi's Herpes Sarcoma Virus (KHSV). In some embodiments, the compounds of the present disclosure can be used in combination with tumor specific antigen such as heat shock proteins isolated from tumor tissue itself. In some embodiments, the

compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be combined with dendritic cells immunization to activate potent anti-tumor responses.

The compounds of the present disclosure can be used in combination with bispecific macrocyclic peptides that target Fe alpha or Fe gamma receptor-expressing effectors cells to tumor cells. The compounds of the present disclosure can also be combined with macrocyclic peptides that activate host immune responsiveness.

The compounds of the present disclosure can be used in combination with bone marrow transplant for the treatment of a variety of tumors of hematopoietic origin.

The compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be used in combination with vaccines, to stimulate the immune response to pathogens, toxins, and self antigens. Examples of pathogens for which this therapeutic approach may be particularly useful, include pathogens for which there is currently no effective vaccine, or pathogens for which conventional vaccines are less than completely effective. These include, but are not limited to, HIV, Hepatitis (A, B, & C), Influenza, Herpes, Giardia, Malaria, Leishmania, Staphylococcus aureus, Pseudomonas Aeruginosa.

Viruses causing infections treatable by methods of the present disclosure include, but are not limit to human papillomavirus, influenza, hepatitis A, B, C or D viruses, adenovirus, poxvirus, herpes simplex viruses, human cytomegalovirus, severe acute respiratory syndrome virus, ebola virus, measles virus, herpes virus (e.g., VZV, HSV-1, HAV-6, HSV-II, and CMV, Epstein Barr virus), flaviviruses, echovirus, rhinovirus, coxsackie virus, cornovirus, respiratory syncytial virus, mumpsvirus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus and arboviral encephalitis virus.

Pathogenic bacteria causing infections treatable by methods of the disclosure include, but are not limited to, chlamydia, rickettsial bacteria, mycobacteria, staphylococci, streptococci, pneumonococci, meningococci and conococci, klebsiella, proteus, serratia, pseudomonas, legionella, diphtheria, salmonella, bacilli, cholera, tetanus, botulism, anthrax, plague, leptospirosis, and Lyme's disease bacteria.

Pathogenic fungi causing infections treatable by methods of the disclosure include, but are not limited to, Candida (albicans, krusei, glabrata, tropicalis, etc.), Cryptococcus neoformans, Aspergillus (fumigatus, niger, etc.), Genus Mucorales (mucor, absidia, rhizophus), Sporothrix

schenkii, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Coccidioides immitis and Histoplasma capsulatum.

Pathogenic parasites causing infections treatable by methods of the disclosure include, but are not limited to, Entamoeba histolytica, Balantidium coli, Naegleriafowleri, Acanthamoeba sp., Giardia lambia, Cryptosporidium sp., Pneumocystis carinii, Plasmodium vivax, Babesia microti, Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondi, and Nippostrongylus brasiliensis.

When more than one pharmaceutical agent is administered to a patient, they can be administered simultaneously, separately, sequentially, or in combination (*e.g.*, for more than two agents).

IV. Formulation, Dosage Forms and Administration

When employed as pharmaceuticals, the compounds of the present disclosure can be administered in the form of pharmaceutical compositions. Thus the present disclosure provides a composition comprising a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt thereof, or any of the embodiments thereof, and at least one pharmaceutically acceptable carrier or excipient. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is indicated and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (*e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, *e.g.*, intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, *e.g.*, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, the compound of the present disclosure or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers or excipients. In some

embodiments, the composition is suitable for topical administration. In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, *e.g.*, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, *e.g.*, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, *e.g.*, about 40 mesh.

The compounds of the invention may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compounds of the invention can be prepared by processes known in the art see, *e.g.*, WO 2002/000196.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

In some embodiments, the pharmaceutical composition comprises silicified microcrystalline cellulose (SMCC) and at least one compound described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the silicified microcrystalline cellulose comprises about 98% microcrystalline cellulose and about 2% silicon dioxide w/w.

In some embodiments, the composition is a sustained release composition comprising at least one compound described herein, or a pharmaceutically acceptable salt thereof, and at least

one pharmaceutically acceptable carrier or excipient. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and at least one component selected from microcrystalline cellulose, lactose monohydrate, hydroxypropyl methylcellulose and polyethylene oxide. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose, lactose monohydrate and hydroxypropyl methylcellulose. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose, lactose monohydrate and polyethylene oxide. In some embodiments, the composition further comprises magnesium stearate or silicon dioxide. In some embodiments, the microcrystalline cellulose is Avicel PH102™. In some embodiments, the lactose monohydrate is Fast-flo 316™. In some embodiments, the hydroxypropyl methylcellulose is hydroxypropyl methylcellulose 2208 K4M (*e.g.*, Methocel K4 M Premier™) and/or hydroxypropyl methylcellulose 2208 K100LV (*e.g.*, Methocel K00LV™). In some embodiments, the polyethylene oxide is polyethylene oxide WSR 1105 (*e.g.*, Polyox WSR 1105™).

In some embodiments, a wet granulation process is used to produce the composition. In some embodiments, a dry granulation process is used to produce the composition.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 1,000 mg (1 g), more usually about 100 mg to about 500 mg, of the active ingredient. In some embodiments, each dosage contains about 10 mg of the active ingredient. In some embodiments, each dosage contains about 50 mg of the active ingredient. In some embodiments, each dosage contains about 25 mg of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The components used to formulate the pharmaceutical compositions are of high purity and are substantially free of potentially harmful contaminants (*e.g.*, at least National Food grade, generally at least analytical grade, and more typically at least pharmaceutical grade). Particularly for human consumption, the composition is preferably manufactured or formulated under Good Manufacturing Practice standards as defined in the applicable regulations of the U.S. Food and Drug Administration. For example, suitable formulations may be sterile and/or substantially isotonic and/or in full compliance with all Good Manufacturing Practice regulations of the U.S. Food and Drug Administration.

The active compound may be effective over a wide dosage range and is generally administered in a therapeutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms and the like.

The therapeutic dosage of a compound of the present invention can vary according to, *e.g.*, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 μg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from in vitro or animal model test systems.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, *e.g.*, about 0.1 to about 1000 mg of the active ingredient of the present invention.

The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into

the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face mask, tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

Topical formulations can contain one or more conventional carriers. In some embodiments, ointments can contain water and one or more hydrophobic carriers selected from, *e.g.*, liquid paraffin, polyoxyethylene alkyl ether, propylene glycol, white Vaseline, and the like. Carrier compositions of creams can be based on water in combination with glycerol and one or more other components, *e.g.*, glycerinemonostearate, PEG-glycerinemonostearate and cetylstearyl alcohol. Gels can be formulated using isopropyl alcohol and water, suitably in combination with other components such as, *e.g.*, glycerol, hydroxyethyl cellulose, and the like. In some embodiments, topical formulations contain at least about 0.1, at least about 0.25, at least about 0.5, at least about 1, at least about 2 or at least about 5 wt % of the compound of the invention. The topical formulations can be suitably packaged in tubes of, *e.g.*, 100 g which are optionally associated with instructions for the treatment of the select indication, *e.g.*, psoriasis or other skin condition.

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an

amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of a compound of the present invention can vary according to, *e.g.*, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 μg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

V. Labeled Compounds and Assay Methods

The compounds of the present disclosure can further be useful in investigations of biological processes in normal and abnormal tissues. Thus, another aspect of the present invention relates to labeled compounds of the invention (radio-labeled, fluorescent-labeled, *etc.*) that would be useful not only in imaging techniques but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating PD-1 or PD-L1 protein in tissue samples, including human, and

for identifying PD-L1 ligands by inhibition binding of a labeled compound. Accordingly, the present invention includes PD-1/PD-L1 binding assays that contain such labeled compounds.

The present invention further includes isotopically-substituted compounds of the disclosure. An "isotopically-substituted" compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having the same atomic number but a different atomic mass or mass number, e.g., a different atomic mass or mass number from the atomic mass or mass number typically found in nature (*i.e.*, naturally occurring). It is to be understood that a "radio-labeled" compound is a compound that has incorporated at least one isotope that is radioactive (e.g., radionuclide). Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I and ^{131}I. The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* PD-L1 protein labeling and competition assays, compounds that incorporate ^{3}H, ^{14}C, ^{82}Br, ^{125}I, ^{131}I, ^{35}S or will generally be most useful. For radio-imaging applications ^{11}C, ^{18}F, ^{125}I, ^{123}I, ^{124}I, ^{131}I, ^{75}Br, ^{76}Br or ^{77}Br will generally be most useful.

In some embodiments the radionuclide is selected from the group consisting of ^{3}H, ^{14}C, ^{125}I, ^{35}S and ^{82}Br. Synthetic methods for incorporating radio-isotopes into organic compounds are known in the art.

Specifically, a labeled compound of the invention can be used in a screening assay to identify and/or evaluate compounds. For example, a newly synthesized or identified compound (*i.e.*, test compound) which is labeled can be evaluated for its ability to bind a PD-L1 protein by monitoring its concentration variation when contacting with the PD-L1 protein, through tracking of the labeling. For example, a test compound (labeled) can be evaluated for its ability to reduce binding of another compound which is known to bind to a PD-L1 protein (*i.e.*, standard compound). Accordingly, the ability of a test compound to compete with the standard compound for binding to the PD-L1 protein directly correlates to its binding affinity. Conversely, in some other screening assays, the standard compound is labeled and test compounds are unlabeled. Accordingly, the concentration of the labeled standard compound is monitored in order to evaluate the competition between the standard compound and the test compound, and the relative binding affinity of the test compound is thus ascertained.

VI. Kits

The present disclosure also includes pharmaceutical kits useful, *e.g.*, in the treatment or prevention of diseases or disorders associated with the activity of PD-L1 including its interaction with other proteins such as PD-1 and B7-1 (CD80), such as cancer or infections, which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or any of the embodiments thereof. Such kits can further include one or more of various conventional pharmaceutical kit components, such as, *e.g.*, containers with one or more pharmaceutically acceptable carriers, additional containers, *etc.*, as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

The following abbreviations may be used herein: aq. (aqueous); br (broad); d (doublet); dd (doublet of doublets); DCM (dichloromethane); DMF (*N*, *N*-dimethylformamide); Et (ethyl); EtOAc (ethyl acetate); g (gram(s)); h (hour(s)); HPLC (high performance liquid chromatography); Hz (hertz); J (coupling constant); LCMS (liquid chromatography – mass spectrometry); m (multiplet); M (molar); MS (Mass spectrometry); Me (methyl); MeCN (acetonitrile); MeOH (methanol); mg (milligram(s)); min. (minutes(s)); mL (milliliter(s)); mmol (millimole(s)); nM (nanomolar); NMR (nuclear magnetic resonance spectroscopy); Ph (phenyl); r.t. (room temperature), s (singlet); t (triplet or tertiary); TBS (tert-butyldimethylsilyl); tert (tertiary); tt (triplet of triplets); TFA (trifluoroacetic acid); THF (tetrahydrofuran); μg (microgram(s)); μL (microliter(s)); μM (micromolar); wt % (weight percent).

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results. The compounds of the Examples have been found to inhibit the activity of PD-1/PD-L1 protein/protein interaction according to at least one assay described herein.

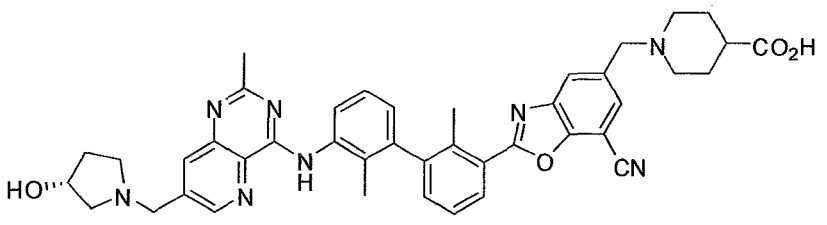
EXAMPLES

Experimental procedures for compounds of the invention are provided below. Open Access Preparative LCMS Purification of some of the compounds prepared was performed on Waters mass directed fractionation systems. The basic equipment setup, protocols and control

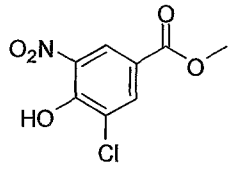
software for the operation of these systems have been described in detail in literature. *See, e.g.*, Blom, "Two-Pump At Column Dilution Configuration for Preparative LC-MS", K. Blom, *J. Combi. Chem.*, **2002**, *4*, 295-301; Blom *et al.*, "Optimizing Preparative LC-MS Configurations and Methods for Parallel Synthesis Purification", *J. Combi. Chem.*, **2003**, *5*, 670-83; and Blom *et al.*, "Preparative LC-MS Purification: Improved Compound Specific Method Optimization", *J. Combi. Chem.*, **2004**, *6*, 874-883.

Example 1

(*R*)-1-((7-cyano-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

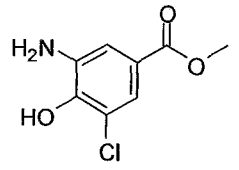


Step 1: methyl 3-chloro-4-hydroxy-5-nitrobenzoate



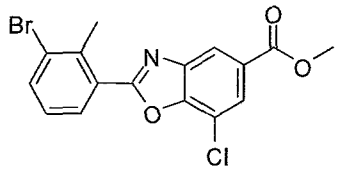
To a solution of methyl 3-chloro-4-hydroxybenzoate (Alfa Aesar, #A512389: 10.0 g, 53.6 mmol) in acetic acid (20.0 mL) was added a mixture of acetic acid (20.0 mL) and nitric acid (4.72 mL, 112 mmol) dropwise at 0 °C. Then the ice bath was removed and the thick mixture was stirred at room temperature for 2 hrs. Then an equal volume of water was added to the reaction suspension at 0 °C. The mixture was filtered and washed with cold water. A yellow solid was obtained as the desired product without further purification. LC-MS calculated for $C_8H_7ClNO_5$ $(M+H)^+$: m/z = 232.0; found 232.0.

Step 2: methyl 3-amino-5-chloro-4-hydroxybenzoate



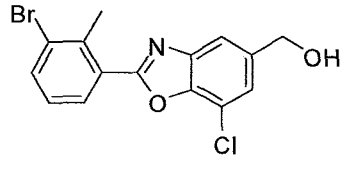
Methyl 3-chloro-4-hydroxy-5-nitrobenzoate (2.08 g, 8.98 mmol) was hydrogenated under ambient pressure of hydrogen using palladium on carbon (10 wt%, 0.57 g, 0.539 mmol) in ethyl acetate (15 mL) for 1 h. The resulting suspension was filtered through a pad of Celite and washed with EtOAc and the solvent was removed under reduced pressure to give a crude product, which was purified by column chromatography (eluting with MeOH/DCM 0%-10%). LC-MS calculated for $C_8H_9ClNO_3$ $(M+H)^+$: m/z = 202.0; found 202.0.

Step 3: methyl 2-(3-bromo-2-methylphenyl)-7-chlorobenzo[d]oxazole-5-carboxylate



A mixture of methyl 3-amino-5-chloro-4-hydroxybenzoate (1.04 g, 5.16 mmol), 3-bromo-2-methylbenzaldehyde (AstaTech, #52940: 0.98 g, 4.92 mmol) in EtOH (25 ml) was placed in a vial and stirred at room temperature for 1 h. The mixture was then concentrated. The residue was redissovled in methylene chloride (25 mL) and dichlorodicyanoquinone (1.12 g, 4.92 mmol) was added. The mixture was stirred at room temperature for 30 min. The reaction was diluted with methylene chloride and washed with an aqueous $Na_2S_2O_3$ solution and $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$, filtered and the filtrate was concentrated. The crude residue was used directly without further purification. LC-MS calculated for $C_{16}H_{12}BrClNO_3$ $(M+H)^+$: m/z = 380.0; found 379.9.

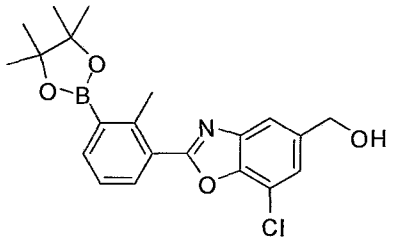
Step 4: (2-(3-bromo-2-methylphenyl)-7-chlorobenzo[d]oxazol-5-yl)methanol



To a solution of methyl 2-(3-bromo-2-methylphenyl)-7-chlorobenzo[d]oxazole-5-carboxylate (395.0 mg, 1.04 mmol) in DCM (10.0 ml) was added diisobutylaluminum hydride in DCM (1.0 M, 2.08 ml, 2.08 mmol) dropwise at -78 °C. The mixture was slowly warmed up to 0 °C. Then the mixture was quenched with EtOAc and DCM, followed by aqueous Rochell's salt solution. The mixture was stirred vigorously at room temperature for 1 h. The organic phase was separated and dried over $MgSO_4$ before filtering through a short

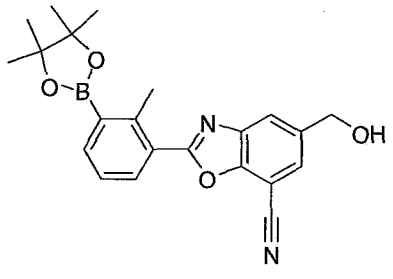
pad of Celite to remove solids. The filtrate was concentrated and purified by column chromatography (eluting with MeOH/DCM, 0-5%). LC-MS calculated for $C_{15}H_{12}BrClNO_2$ $(M+H)^+$: m/z = 352.0; found 352.0.

Step 5: (7-chloro-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzo[d]oxazol-5-yl)methanol



A mixture of (2-(3-bromo-2-methylphenyl)-7-chlorobenzo[d]oxazol-5-yl)methanol (113 mg, 0.322 mmol), bis(pinacolato)diboron (98 mg, 0.386 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (26.3 mg, 0.032 mmol) and anhydrous potassium acetate (79 mg, 0.804 mmol) in 1,4-dioxane (3.5 mL) was purged with nitrogen and stirred at 110 °C for 2 h. The crude was diluted with DCM, and then filtered through Celite. The filtrate was concentrated. The residue was purified by flash chromatography (eluting with EtOAc/Hexanes, 0-40%). LC-MS calculated for $C_{21}H_{24}BClNO_4$ $(M+H)^+$: m/z = 400.2; found 400.2.

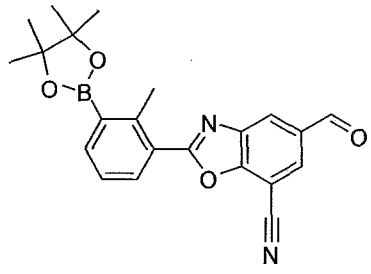
Step 6: 5-(hydroxymethyl)-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzo[d]oxazole-7-carbonitrile



A stirred mixture of (7-chloro-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzo[d]oxazol-5-yl)methanol (1.08 g, 2.63 mmol), zinc cyanide (0.253 g, 2.11 mmol) and methanesulfonato(2-di-t-butylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (0.171 g, 0.211 mmol) in THF (5.27 ml) and water (5.27 ml) at r.t. was degassed and refilled with N_2 three times. It was heated at 90 °C overnight. The reaction mixture was diluted with THF while hot. It was cooled to r.t. and

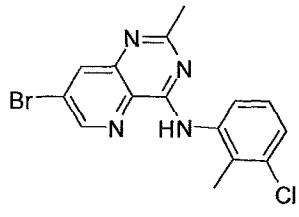
filtered to remove insoluble solid. The filtrate was concentrated *in vacuo*. Acetonitrile was then added. The resulting slurry was filtered and washed with acetonitrile. The solid was collected and used directly in the next step without further purification. LC-MS calculated for $C_{22}H_{24}BN_2O_4$ $(M+H)^+$: m/z = 391.2; found: 391.2.

Step 7: 5-formyl-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzo[d]oxazole-7-carbonitrile



To a solution of 5-(hydroxymethyl)-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzo[d]oxazole-7-carbonitrile (1.51 g, 3.68 mmol) in DCM (16.4 mL) and DMF (2.0 ml) was added Dess-Martin periodinane (2.49 g, 5.70 mmol). The mixture was stirred at r.t. for 3 h. The crude mixture was quenched with saturated $Na_2S_2O_3$ and saturated $NaHCO_3$. The mixture was extracted with DCM three times. The organic phase was combined, dried and filtered. The filtrate was concentrated. Diethyl ether was added to the residue to form slurry, which was filtered to give the desired aldehyde. LCMS calculated for $C_{22}H_{22}BN_2O_4$ $(M+H)+$: m/z = 389.2; found 389.2.

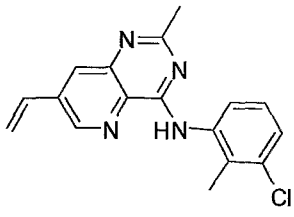
Step 8: 7-bromo-N-(3-chloro-2-methylphenyl)-2-methylpyrido[3,2-d]pyrimidin-4-amine



To a mixture of 7-bromo-2-methylpyrido[3,2-d]pyrimidin-4-ol (Combi-Blocks, cat#ST-6117: 175 mg, 0.729 mmol), benzyltriethylammonium chloride (332 mg, 1.46 mmol) and N,N-diethylaniline (174 µl, 1.09 mmol) in acetonitrile (3.6 ml) was added phosphoryl chloride (408 µl, 4.37 mmol). The mixture was stirred at 90 °C for 2 h. Then the reaction was cooled to r.t. The volatiles were removed under reduced pressure. The residue was used directly.

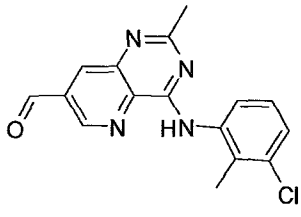
To the residue above in 2-propanol (3.6 ml) was added 3-chloro-2-methylaniline (113 mg, 0.800 mmol) and methanesulfonic acid (47.2 µl, 0.727 mmol). The mixture was stirred at 80 °C for 2 h. Then the reaction was cooled to r.t. The mixture was carefully quenched by $NaHCO_3$ aq. solution, extracted with DCM. The combined DCM solutions were dried over $MgSO_4$ and filtered. The filtrate was concentrated. The residue was purified by flash chromatography (0-70% EtOAc/hexanes). LC-MS calculated for $C_{15}H_{13}BrClN_4$ $(M+H)^+$: m/z = 363.0; found 363.0.

Step 9: N-(3-chloro-2-methylphenyl)-2-methyl-7-vinylpyrido[3,2-d]pyrimidin-4-amine



A mixture of 7-bromo-N-(3-chloro-2-methylphenyl)-2-methylpyrido[3,2-d]pyrimidin-4-amine (250 mg, 0.687 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (159 mg, 1.03 mmol), tetrakis(triphenylphosphine) palladium(0) (79 mg, 0.069 mmol) and potassium phosphate (365 mg, 1.72 mmol) in tert-butanol (3.4 ml) and water (3.4 ml) was purged with N_2 and sealed. The resulting mixture was stirred at 100 °C for 3 h. The reaction mixture was cooled then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was used directly in the next step without further purification. LC-MS calculated for $C_{17}H_{16}ClN_4$ $(M+H)^+$: m/z = 311.2; found 311.2.

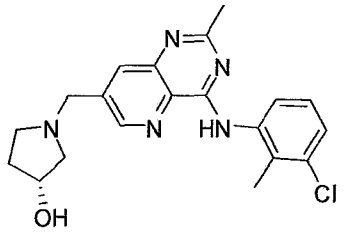
Step 10: 4-(3-chloro-2-methylphenylamino)-2-methylpyrido[3,2-d]pyrimidine-7-carbaldehyde



A vial was charged with N-(3-chloro-2-methylphenyl)-2-methyl-7-vinylpyrido[3,2-d]pyrimidin-4-amine (214 mg, 0.689 mmol), THF (5.5 ml) , a stir bar and water (1.4 ml). To this solution was added sodium periodate (736 mg, 3.44 mmol) followed by osmium tetroxide (4% w/w in water, 270 µl, 0.034 mmol). After stirring at r.t. for 1 h, the reaction

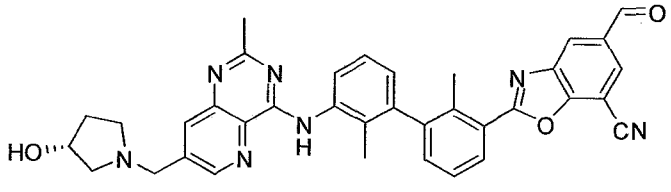
was quenched with a saturated aqueous solution of sodium thiosulfate. The mixture was then extracted with DCM, and the combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was used directly in the next step without further purification. LC-MS calculated for $C_{16}H_{14}ClN_4O$ $(M+H)^+$: m/z = 313.1; found 313.1.

Step 11: (R)-1-((4-(3-chloro-2-methylphenylamino)-2-methylpyrido[3,2-d]pyrimidin-7-yl)methyl)pyrrolidin-3-ol



A mixture of 4-((3-chloro-2-methylphenyl)amino)-2-methylpyrido[3,2-d]pyrimidine-7-carbaldehyde (215 mg, 0.687 mmol) and (*R*)-pyrrolidin-3-ol (71.9 mg, 0.825 mmol) in DCM (4.6 ml) was stirred at r.t. for 30 min. Then sodium triacetoxyborohydride (219 mg, 1.03 mmol) was added. The mixture was further stirred at r.t. for 1 h. The reaction was quenched with NH_4OH aq. solution, extracted by DCM. The organic phase was combined and dried over MgSO4. After filtration, the DCM solution was concentrated and the residue was purified by flash chromatography (0-12% MeOH/DCM) to give the desired product. LC-MS calculated for $C_{20}H_{23}ClN_5O$ $(M+H)^+$: m/z = 384.2; found 384.2.

Step 12: (R)-5-formyl-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile



A mixture of (R)-1-((4-((3-chloro-2-methylphenyl)amino)-2-methylpyrido[3,2-d]pyrimidin-7-yl)methyl)pyrrolidin-3-ol (229 mg, 0.597 mmol), 5-formyl-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzo[d]oxazole-7-carbonitrile (*Step 7*: 255 mg, 0.657 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (47.0 mg, 0.060 mmol) and potassium phosphate (317 mg, 1.493 mmol) in water (1.0 ml) and 1,4-dioxane (5.0 ml) was purged with

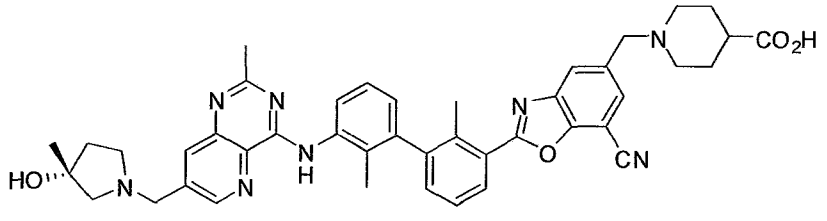
N_2 and then sealed. The reaction was stirred at 100 °C for 2 h. The reaction was cooled to room temperature. The reaction mixture was diluted with DCM and H_2O. The layers were separated. The aqueous layer was extracted with DCM three times. The organic layer was dried over $MgSO_4$, filtered and concentrated to give a crude residue, which was used directly in the next step without further purification. LC-MS calculated for $C_{36}H_{32}N_7O_3$ $(M+H)^+$: m/z = 610.3; found 610.4.

Step 13: (R)-1-((7-cyano-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

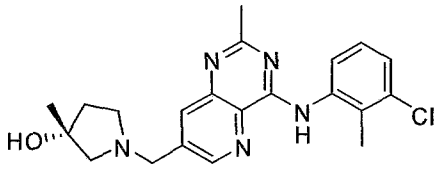
A mixture of (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile (16 mg, 0.026 mmol) and tert-butyl piperidine-4-carboxylate (9.7 mg, 0.052 mmol) in DCM (500 µL) was stirred at r.t. for 2 h. Then sodium triacetoxyborohydride (16.7 mg, 0.079 mmol) was added. The mixture was further stirred at r.t. for 1 h. The reaction was treated with trifluoroacetic acid (404 µL, 5.25 mmol) and stirred at r.t. for 30 min. After evaporating the volatiles, the residue was diluted in MeOH then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired TFA salt. LC-MS calculated for $C_{42}H_{43}N_8O_4$ $(M+H)^+$: m/z = 723.3; found 723.3. ^1H NMR (500 MHz, DMSO) δ 9.08 (s, 1H), 8.38 (d, J = 9.5 Hz, 2H), 8.19 (d, J = 7.1 Hz, 1H), 8.10 (s, 1H), 7.65 – 7.55 (m, 2H), 7.48 (d, J = 6.8 Hz, 1H), 7.42 (t, J = 7.7 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 4.72 (s, 2H), 4.59 – 4.41 (m, 3H), 3.76 – 3.20 (m, 6H), 3.09 – 2.90 (m, 2H), 2.56 (s, 3H), 2.49 (s, 3H), 2.48 (s, 1H), 2.39 – 2.25 (m, 1H), 2.14 – 2.02 (m, 2H), 1.96 (s, 3H), 1.96 – 1.86 (m, 1H), 1.80 – 1.68 (m, 2H).

Example 2

(R)-1-((7-cyano-2-(3'-(7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

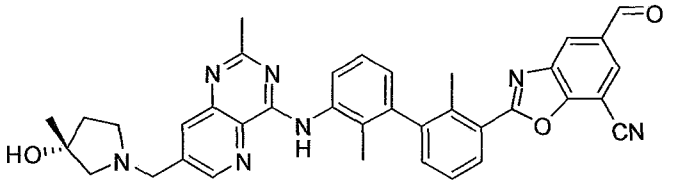


Step 1: (R)-1-((4-(3-chloro-2-methylphenylamino)-2-methylpyrido[3,2-d]pyrimidin-7-yl)methyl)-3-methylpyrrolidin-3-ol



This compound was prepared using similar procedures as described for *Example 1, Step 11* with (*R*)-3-methylpyrrolidin-3-ol replacing (*R*)-pyrrolidin-3-ol. LC-MS calculated for $C_{21}H_{25}ClN_5O$ $(M+H)^+$: m/z = 398.2; found 398.2.

Step 2: (R)-5-formyl-2-(3'-(7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile



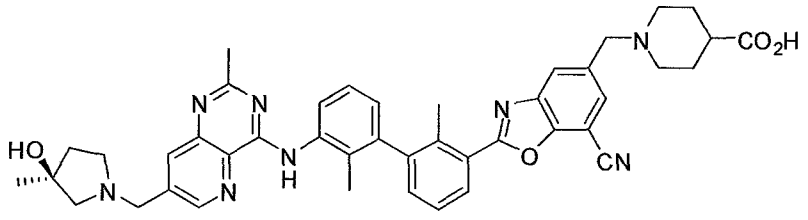
This compound was prepared using similar procedures as described for *Example 1, Step 12* with (*R*)-1-((4-(3-chloro-2-methylphenylamino)-2-methylpyrido[3,2-d]pyrimidin-7-yl)methyl)-3-methylpyrrolidin-3-ol (*Step 1*) replacing (*R*)-1-((4-(3-chloro-2-methylphenylamino)-2-methylpyrido[3,2-d]pyrimidin-7-yl)methyl)pyrrolidin-3-ol in. LC-MS calculated for $C_{37}H_{34}N_7O_3$ $(M+H)^+$: m/z = 624.3; found 624.3.

Step 3: (R)-1-((7-cyano-2-(3'-(7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

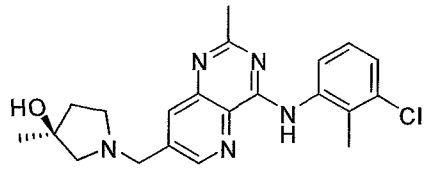
This compound was prepared using similar procedures as described for *Example 1, Step 13* with (*R*)-5-formyl-2-(3'-(7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile (*Step 2*) replacing (*R*)-5-formyl-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{43}H_{45}N_8O_4$ $(M+H)^+$: m/z = 737.4; found 737.4.

Example 3

(S)-1-((7-cyano-2-(3'-(7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

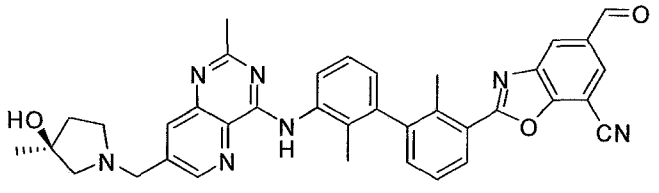


Step 1: (S)-1-((4-(3-chloro-2-methylphenylamino)-2-methylpyrido[3,2-d]pyrimidin-7-yl)methyl)-3-methylpyrrolidin-3-ol



This compound was prepared using similar procedures as described for *Example 1, Step 11* with (*S*)-3-methylpyrrolidin-3-ol replacing (*R*)-pyrrolidin-3-ol. LC-MS calculated for $C_{21}H_{25}ClN_5O$ $(M+H)^+$: m/z = 398.2; found 398.2.

Step 2: (S)-5-formyl-2-(3'-(7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile



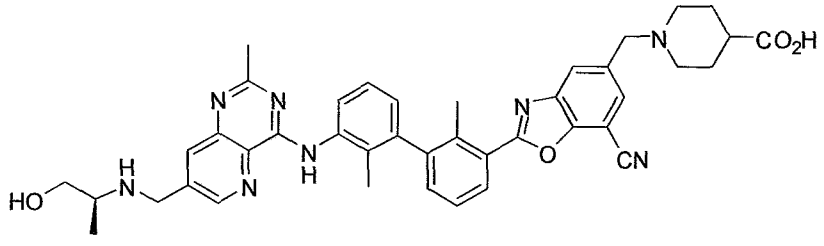
This compound was prepared using similar procedures as described for *Example 1, Step 12* with (*S*)-1-((4-(3-chloro-2-methylphenylamino)-2-methylpyrido[3,2-d]pyrimidin-7-yl)methyl)-3-methylpyrrolidin-3-ol (*Step 1*) replacing (*R*)-1-((4-(3-chloro-2-methylphenylamino)-2-methylpyrido[3,2-d]pyrimidin-7-yl)methyl)pyrrolidin-3-ol. LC-MS calculated for $C_{37}H_{34}N_7O_3$ $(M+H)^+$: m/z = 624.3; found 624.3.

Step 3: (S)-1-((7-cyano-2-(3'-(7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido [3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

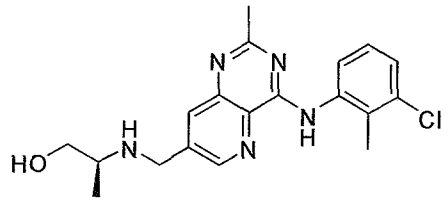
This compound was prepared using similar procedures as described for *Example 1, Step 13* with (*S*)-5-formyl-2-(3'-(7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile (*Step 2*) replacing (*R*)-5-formyl-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{43}H_{45}N_8O_4$ $(M+H)^+$: m/z = 737.4; found 737.4.

Example 4

(S)-1-((7-cyano-2-(3'-(7-((1-hydroxypropan-2-ylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

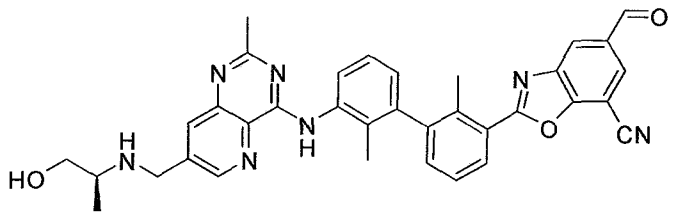


Step 1: (S)-2-((4-(3-chloro-2-methylphenylamino)-2-methylpyrido[3,2-d]pyrimidin-7-yl)methylamino)propan-1-ol



This compound was prepared using similar procedures as described for *Example 1, Step 11* with (S)-2-aminopropan-1-ol replacing (*R*)-pyrrolidin-3-ol. LC-MS calculated for $C_{19}H_{23}ClN_5O$ $(M+H)^+$: m/z = 372.2; found 372.2.

Step 2: (S)-5-formyl-2-(3'-(7-((1-hydroxypropan-2-ylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile



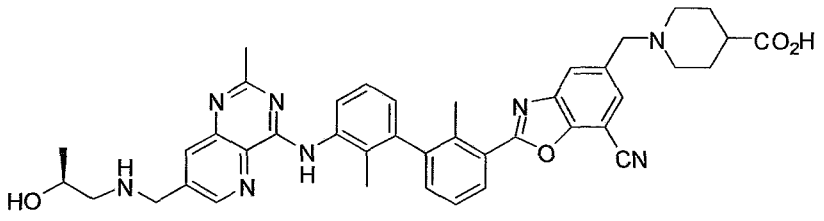
This compound was prepared using similar procedures as described for *Example 1, Step 12* with (*S*)-2-((4-(3-chloro-2-methylphenylamino)-2-methylpyrido[3,2-d]pyrimidin-7-yl)methylamino)propan-1-ol (*Step 1*) replacing (*R*)-1-((4-(3-chloro-2-methylphenylamino)-2-methylpyrido[3,2-d]pyrimidin-7-yl)methyl)pyrrolidin-3-ol. LC-MS calculated for $C_{35}H_{32}N_7O_3$ $(M+H)^+$: m/z = 598.3; found 598.3.

Step 3: (S)-1-((7-cyano-2-(3'-(7-((1-hydroxypropan-2-ylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

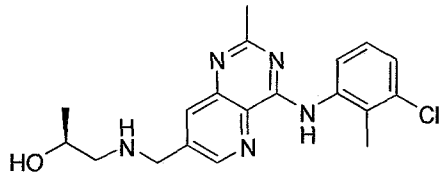
This compound was prepared using similar procedures as described for *Example 1, Step 13* with (*S*)-5-formyl-2-(3'-(7-((1-hydroxypropan-2-ylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile (*Step 2*) replacing (*R*)-5-formyl-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{41}H_{43}N_8O_4$ $(M+H)^+$: m/z = 711.3; found 711.3.

Example 5

(S)-1-((7-cyano-2-(3'-(7-((2-hydroxypropylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

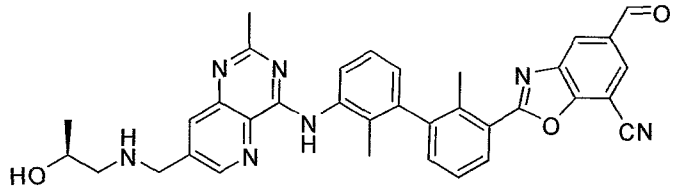


Step 1: (S)-1-((4-(3-chloro-2-methylphenylamino)-2-methylpyrido[3,2-d]pyrimidin-7-yl)methylamino)propan-2-ol



This compound was prepared using similar procedures as described for *Example 1, Step 11* with (*S*)-1-aminopropan-2-ol replacing (*R*)-pyrrolidin-3-ol. LC-MS calculated for $C_{19}H_{23}ClN_5O$ $(M+H)^+$: m/z = 372.2; found 372.2.

Step 2: (S)-5-formyl-2-(3'-(7-((2-hydroxypropylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile



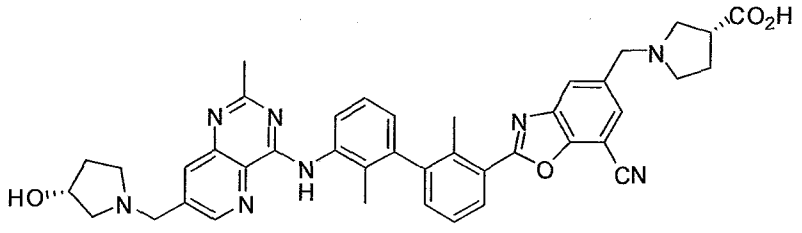
This compound was prepared using similar procedures as described for *Example 1, Step 12* with (*S*)-1-((4-(3-chloro-2-methylphenylamino)-2-methylpyrido[3,2-d]pyrimidin-7-yl)methylamino)propan-2-ol (*Step 1*) replacing (*R*)-1-((4-(3-chloro-2-methylphenylamino)-2-methylpyrido[3,2-d]pyrimidin-7-yl)methyl)pyrrolidin-3-ol. LC-MS calculated for $C_{35}H_{32}N_7O_3$ $(M+H)^+$: m/z = 598.3; found 598.3.

Step 3: (S)-1-((7-cyano-2-(3'-(7-((2-hydroxypropylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

This compound was prepared using similar procedures as described for *Example 1, Step 13* with (*S*)-5-formyl-2-(3'-(7-((2-hydroxypropylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile (*Step 2*) replacing (*R*)-5-formyl-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{41}H_{43}N_8O_4$ $(M+H)^+$: m/z = 711.3; found 711.3.

Example 6

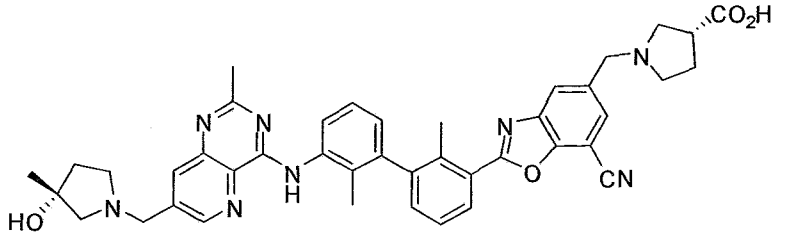
(R)-1-((7-cyano-2-(3'-(7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid



A mixture of (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile (*Example 1, Step 12*: 16 mg, 0.026 mmol), (*R*)-pyrrolidine-3-carboxylic acid (6.0 mg, 0.052 mmol) and triethylamine (7.3 μL, 0.052 mmol) in DCM (500 μL) was stirred at r.t. for 2 h. Then sodium triacetoxyborohydride (16.69 mg, 0.079 mmol) was added. The mixture was further stirred at r.t. for 1 h. The reaction mixture was diluted in MeOH then purified by prep-HPLC (pH = 2, acetonitrile/ water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{41}H_{41}N_8O_4$ $(M+H)^+$: m/z = 709.3; found 709.3.

Example 7

(R)-1-((7-cyano-2-(3'-(7-(((R)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid

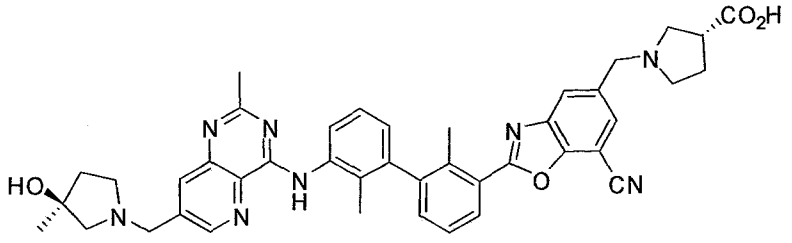


This compound was prepared using similar procedures as described for *Example 6* with (*R*)-5-formyl-2-(3'-(7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile (*Example 2, Step 2*) replacing (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was

diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{42}H_{43}N_8O_4$ $(M+H)^+$: m/z = 723.3; found 723.3.

Example 8

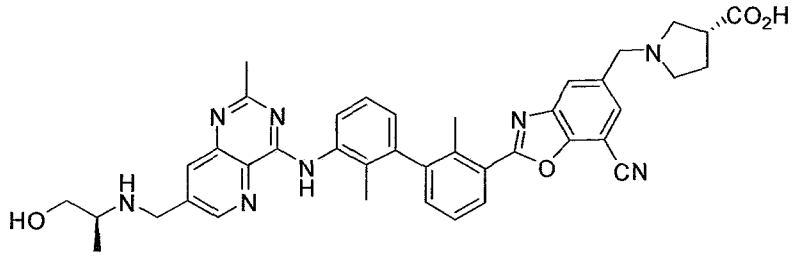
(R)-1-((7-cyano-2-(3'-(7-(((S)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid



This compound was prepared using similar procedures as described for *Example 6* with (*S*)-5-formyl-2-(3'-(7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile (*Example 3, Step 2*) replacing (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{42}H_{43}N_8O_4$ $(M+H)^+$: m/z = 723.3; found 723.3.

Example 9

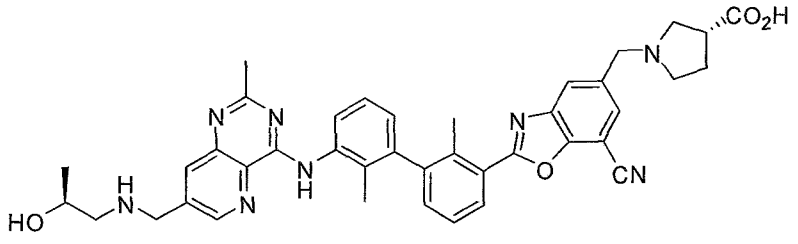
(R)-1-((7-cyano-2-(3'-(7-(((S)-1-hydroxypropan-2-ylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid



This compound was prepared using similar procedures as described for *Example 6* with (*S*)-5-formyl-2-(3'-(7-((1-hydroxypropan-2-ylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile (*Example 4, Step 2*) replacing (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{40}H_{41}N_8O_4$ $(M+H)^+$: m/z = 697.3; found 697.3.

Example 10

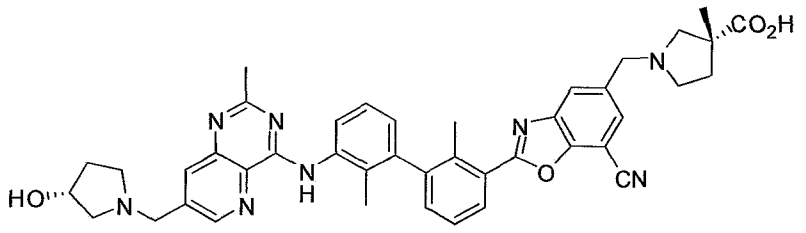
(R)-1-((7-cyano-2-(3'-(7-(((S)-2-hydroxypropylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid



This compound was prepared using similar procedures as described for *Example 6* with (*S*)-5-formyl-2-(3'-(7-((2-hydroxypropylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile (*Example 5, Step 2*) replacing (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{40}H_{41}N_8O_4$ $(M+H)^+$: m/z = 697.3; found 697.3.

Example 11

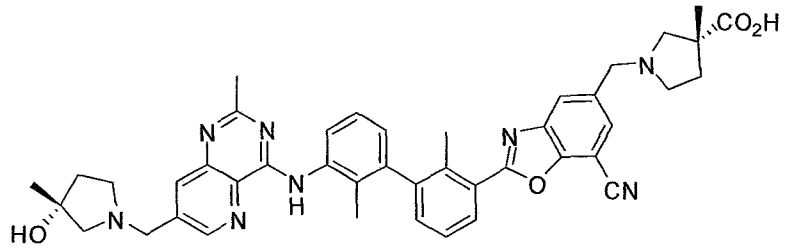
(R)-1-((7-cyano-2-(3'-(7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid



A mixture of (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile (*Example 1, Step 12*: 16 mg, 0.026 mmol), (*R*)-3-methylpyrrolidine-3-carboxylic acid (6.8 mg, 0.052 mmol) and triethylamine (7.3 μL, 0.052 mmol) in DCM (500 μL) was stirred at r.t. for 2 h. Then sodium triacetoxyborohydride (16.7 mg, 0.079 mmol) was added. The mixture was further stirred at r.t. for 1 h. The reaction mixture was diluted in MeOH then purified by prep-HPLC (pH = 2, acetonitrile/ water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{42}H_{43}N_8O_4$ $(M+H)^+$: m/z = 723.3; found 723.3. ^{1}H NMR (600 MHz, DMSO) δ 9.87 (s, 1H), 8.77 (d, *J* = 1.7 Hz, 1H), 8.15 (d, *J* = 7.3 Hz, 1H), 8.10 (s, 1H), 7.95 (s, 1H), 7.90 – 7.81 (m, 2H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 6.9 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.3 Hz, 1H), 4.21 (dt, *J* = 6.3, 3.6 Hz, 1H), 3.87 – 3.80 (m, 1H), 3.79 – 3.72 (m, 2H), 3.72 – 3.66 (m, 1H), 2.92 (d, *J* = 9.1 Hz, 1H), 2.71 (dd, *J* = 9.6, 6.1 Hz, 1H), 2.65 (q, *J* = 8.0 Hz, 1H), 2.62 – 2.54 (m, 2H), 2.48 – 2.46 (m, 6H), 2.46 – 2.43 (m, 1H), 2.38 (dd, *J* = 9.6, 3.5 Hz, 1H), 2.33 – 2.26 (m, 2H), 2.05 – 1.99 (m, 1H), 1.98 (s, 3H), 1.60 – 1.50 (m, 2H), 1.24 (s, 3H).

Example 12

(R)-1-((7-cyano-2-(3'-(7-(((R)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid

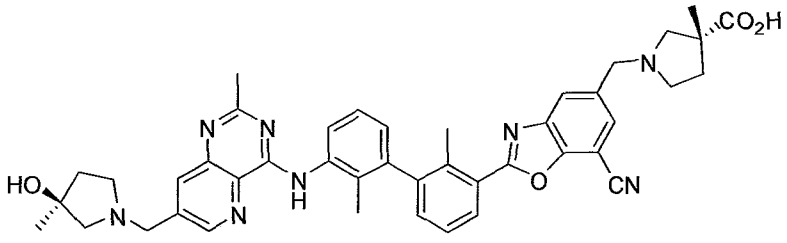


This compound was prepared using similar procedures as described for *Example 11* with (*R*)-5-formyl-2-(3'-(7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile (*Example*

2, Step 2) replacing (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{43}H_{45}N_8O_4$ $(M+H)^+$: m/z = 737.4; found 737.4.

Example 13

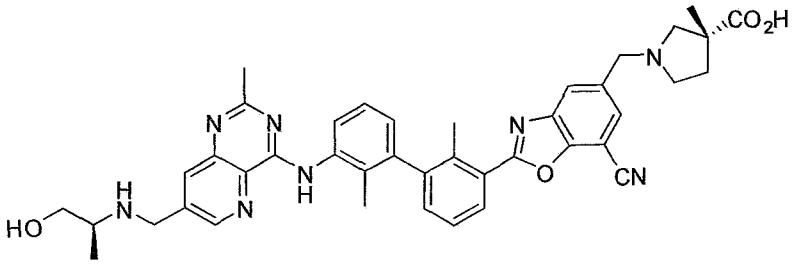
(R)-1-((7-cyano-2-(3'-(7-(((S)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid



This compound was prepared using similar procedures as described for *Example 11* with (*S*)-5-formyl-2-(3'-(7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile (*Example 3, Step 2*) replacing (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{43}H_{45}N_8O_4$ $(M+H)^+$: m/z = 737.4; found 737.4.

Example 14

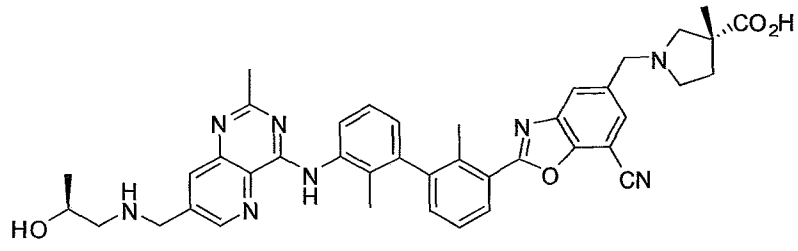
(R)-1-((7-cyano-2-(3'-(7-(((S)-1-hydroxypropan-2-ylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid



This compound was prepared using similar procedures as described for *Example 11* with (*S*)-5-formyl-2-(3'-(7-((1-hydroxypropan-2-ylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile (*Example 4, Step 2*) replacing (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{41}H_{43}N_8O_4$ $(M+H)^+$: m/z = 711.3; found 711.3.

Example 15

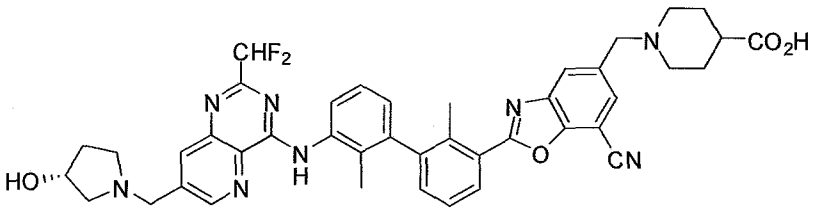
(R)-1-((7-cyano-2-(3'-(7-(((S)-2-hydroxypropylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid



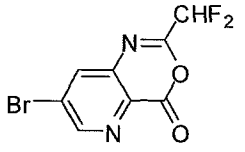
This compound was prepared using similar procedures as described for *Example 11* with (*S*)-5-formyl-2-(3'-(7-((2-hydroxypropylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile (*Example 5, Step 2*) replacing (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{41}H_{43}N_8O_4$ $(M+H)^+$: m/z = 711.3; found 711.3.

Example 16

(R)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

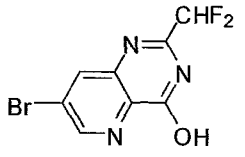


Step 1: 7-bromo-2-(difluoromethyl)-4H-pyrido[3,2-d][1,3]oxazin-4-one



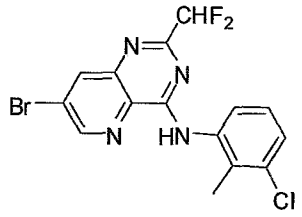
A mixture of 3-amino-5-bromopicolinic acid (PharmBlock cat#PB0554: 645 mg, 2.97 mmol) and 2,2-difluoroacetic anhydride (4.14 g, 23.8 mmol) was stirred at 60 °C for 3 h. After cooling to r.t., the volatiles were removed by rotavap and high vacuum pump. The residue was used directly for next step. LC-MS calculated for $C_8H_4BrF_2N_2O_2$ $(M+H)^+$: m/z = 276.9; found 277.0.

Step 2: 7-bromo-2-(difluoromethyl)pyrido[3,2-d]pyrimidin-4-ol



A mixture of 7-bromo-2-(difluoromethyl)-4H-pyrido[3,2-d][1,3]oxazin-4-one (801 mg, 2.89 mmol) and ammonium hydroxide aq. soln, (8.0 ml, 28%) in a heavy wall glass tube was sealed and stirred at 85 °C for 2 h. After cooling to r.t., the solution was then evaporated and the residue was rediluted with CH_3CN and toluene. The suspension was evaporated again and the residue was used in the next step without further purification. LC-MS calculated for $C_8H_5BrF_2N_3O$ $(M+H)^+$: m/z = 276.0; found 276.0.

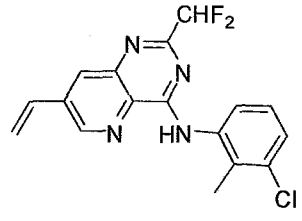
Step 3: 7-bromo-N-(3-chloro-2-methylphenyl)-2-(difluoromethyl)pyrido[3,2-d]pyrimidin-4-amine



To a mixture of 7-bromo-2-(difluoromethyl)pyrido[3,2-d]pyrimidin-4-ol (crude product from *Step 2*: 750 mg, 2.72 mmol), benzyltriethylammonium chloride (1238 mg, 5.43 mmol) and N,N-diethylaniline (648 µl, 4.08 mmol) in acetonitrile (13.6 ml) was added phosphoryl chloride (1.52 ml, 16.3 mmol). The mixture was stirred at 75 °C for 2 h. Then the reaction was cooled to r.t. The volatiles were removed under reduced pressure.

To a solution of 3-chloro-2-methylaniline (409 mg, 2.89 mmol) and 7-bromo-4-chloro-2-(difluoromethyl)pyrido[3,2-d]pyrimidine (the residue above) in 2-propanol (14.4 ml) was added methanesulfonic acid (188 µl, 2.89 mmol). The mixture was stirred at 80 °C for 2 h. Then the reaction was cooled to r.t. The mixture was carefully quenched by $NaHCO_3$ aq solution. The precipitates were filtered, washed by water and dried by air. The solids were used directly for next step. LC-MS calculated for $C_{15}H_{11}BrClF_2N_4$ $(M+H)^+$: m/z = 399.0; found 399.0.

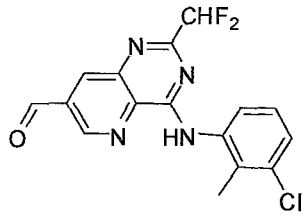
Step 4: N-(3-chloro-2-methylphenyl)-2-(difluoromethyl)-7-vinylpyrido[3,2-d]pyrimidin-4-amine



A mixture of 7-bromo-N-(3-chloro-2-methylphenyl)-2-(difluoromethyl)pyrido[3,2-d]pyrimidin-4-amine (841 mg, 2.10 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (537 µl, 3.16 mmol), tetrakis(triphenylphosphine) palladium(0) (243 mg, 0.21 mmol) and potassium phosphate (1117 mg, 5.26 mmol) in tert-butanol (7.0 ml) and water (7.0 ml) was purged with N_2 and then stirred at 100 °C for 3 h. The reaction was cooled to room temperature. The reaction mixture was diluted with water and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated to give a crude residue, which

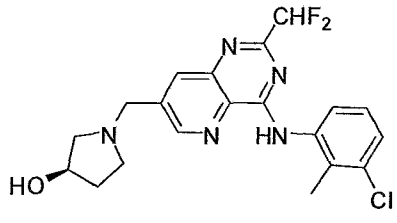
was purified by flash chromatography (0-30% EtOAc/DCM). LC-MS calculated for $C_{17}H_{14}ClF_2N_4$ $(M+H)^+$: m/z = 347.1; found 347.1.

Step 5: 4-(3-chloro-2-methylphenylamino)-2-(difluoromethyl)pyrido[3,2-d]pyrimidine-7-carbaldehyde



A vial was charged with N-(3-chloro-2-methylphenyl)-2-(difluoromethyl)-7-vinylpyrido[3,2-d]pyrimidin-4-amine (195 mg, 0.562 mmol), THF (4.5 ml), a stir bar and water (1.1 ml). To this solution was added sodium periodate (601 mg, 2.81 mmol) followed by osmium tetroxide (4% w/w in water, 221 µl, 0.028 mmol). After stirring at r.t. for 1 h, the reaction was quenched with a saturated aqueous solution of sodium thiosulfate. The mixture was then extracted with DCM, and the combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was used directly in the next step without further purification. LC-MS calculated for $C_{16}H_{12}ClF_2N_4O$ $(M+H)+$: m/z = 349.1; found 349.1.

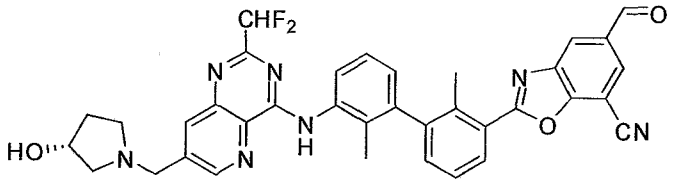
Step 6: (R)-1-((4-(3-chloro-2-methylphenylamino)-2-(difluoromethyl)pyrido[3,2-d]pyrimidin-7-yl)methyl)pyrrolidin-3-ol



A mixture of 4-((3-chloro-2-methylphenyl)amino)-2-(difluoromethyl)pyrido[3,2-d]pyrimidine-7-carbaldehyde (101 mg, 0.290 mmol) and (*R*)-pyrrolidin-3-ol (30.3 mg, 0.348 mmol) in DCM (1931 µl) was stirred at r.t. for 30 min. Then sodium triacetoxyborohydride (92 mg, 0.434 mmol) was added. The mixture was further stirred at r.t. for 1 h. The reaction was quenched with NH_4OH aq. solution and extracted by DCM. The organic phase was combined and dried over $MgSO_4$. After filtration, the DCM solution was concentrated to a

residue, which was purified by flash chromatography (0-12% MeOH/DCM). LC-MS calculated for $C_{20}H_{21}ClF_2N_5O$ $(M+H)^+$: m/z = 420.1; found 420.2.

Step 7: (R)-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)-5-formylbenzo[d]oxazole-7-carbonitrile



A mixture of (*R*)-1-((4-((3-chloro-2-methylphenyl)amino)-2-(difluoromethyl)pyrido[3,2-d]pyrimidin-7-yl)methyl)pyrrolidin-3-ol (34.4 mg, 0.082 mmol), 5-formyl-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzo[d]oxazole-7-carbonitrile (*Example 1, Step 7*: 35 mg, 0.090 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (6.5 mg, 8.2 μmol) and potassium phosphate (43.5 mg, 0.205 mmol) in water (140 μl) and 1,4-dioxane (690 μl) was purged with N_2 and then sealed. The reaction was stirred at 100 °C for 2 h. The reaction was cooled to room temperature. The reaction mixture was diluted with DCM and H_2O. The layers were separated. The aqueous layer was extracted with DCM three times. The organic layer was dried over $MgSO_4$, filtered and concentrated to give a crude residue, which was used directly in the next step without further purification. LC-MS calculated for $C_{36}H_{30}F_2N_7O_3$ $(M+H)^+$: m/z = 646.2; found 646.3.

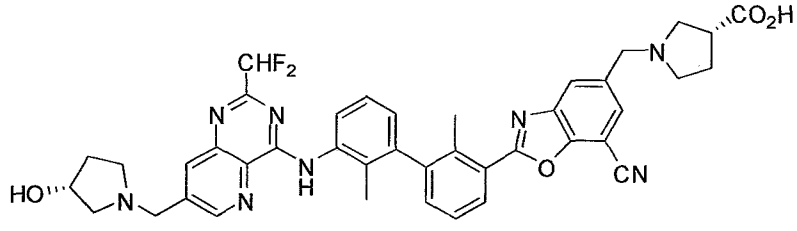
Step 8: (R)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

A mixture of (*R*)-2-(3'-((2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)-5-formylbenzo[d]oxazole-7-carbonitrile (9.5 mg, 0.015 mmol) and tert-butyl piperidine-4-carboxylate (5.45 mg, 0.029 mmol) was stirred at r.t. for 2 h. Then sodium triacetoxyborohydride (9.36 mg, 0.044 mmol) was added. The mixture was stirred at r.t. for 1 h. Then to the mixture was added trifluoroacetic acid (300 μL) and stirred for 30 min. The volatiles were evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS

calculated for $C_{42}H_{41}F_2N_8O_4$ $(M+H)^+$: m/z = 759.3; found 759.6. ^1H NMR (500 MHz, DMSO) δ 10.63 (s, 1H), 9.13 (s, 1H), 8.52 (d, *J* = 2.0 Hz, 1H), 8.39 (d, *J* = 1.6 Hz, 1H), 8.19 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.11 (d, *J* = 2.1 Hz, 1H), 7.64 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.49 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.16 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.74 (t, *J* = 54.5 Hz, 1H), 4.85 – 4.65 (m, 2H), 4.58 – 4.40 (m, 3H), 3.74 – 3.00 (m, 8H), 2.78 – 2.54 (m, 1H), 2.50 (s, 3H), 2.32 – 1.91 (m, 5H), 1.95 (s, 3H), 1.79 – 1.67 (m, 1H).

Example 17

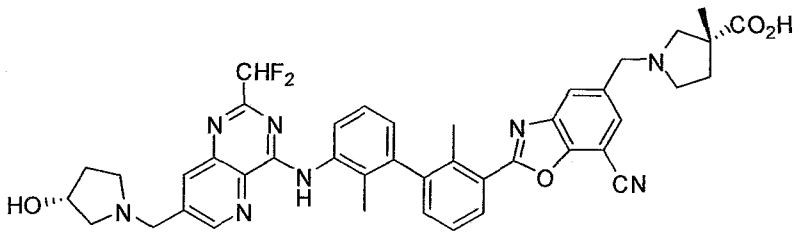
(R)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid



This compound was prepared using similar procedures as described for *Example 6* with (*R*)-2-(3'-((2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)-5-formylbenzo[d]oxazole-7-carbonitrile (*Example 16, Step 7*) replacing (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{41}H_{39}F_2N_8O_4$ $(M+H)^+$: m/z = 745.3; found 745.3.

Example 18

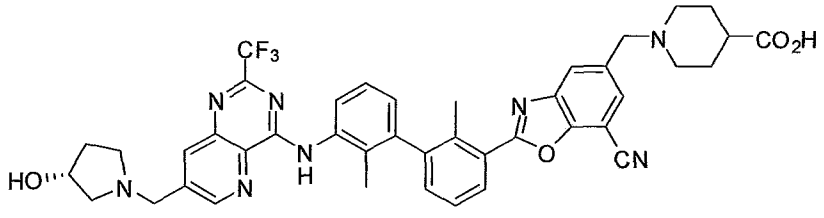
(R)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid



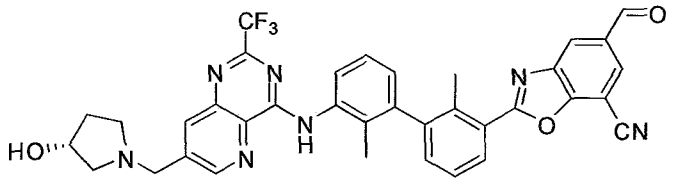
This compound was prepared using similar procedures as described for *Example 11* with (*R*)-2-(3'-((2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)-5-formylbenzo[d]oxazole-7-carbonitrile (*Example 16, Step 7*) replacing (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{42}H_{41}F_2N_8O_4$ $(M+H)^+$: m/z = 759.3; found 759.6.

Example 19

(R)-1-((7-cyano-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid



Step 1: (R)-5-formyl-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile



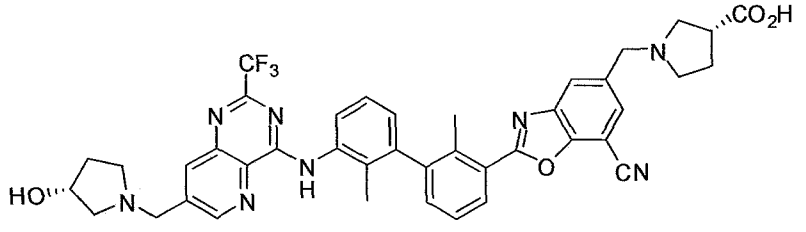
This compound was prepared using similar procedures (*Step 1-7*) as described for *Example 16* with trifluoroacetic anhydride replacing 2,2-difluoroacetic anhydride in *Step 1*. LC-MS calculated for $C_{36}H_{29}F_3N_7O_3$ $(M+H)^+$: m/z = 664.2; found 664.2.

Step 2: (R)-1-((7-cyano-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

This compound was prepared using similar procedures as described for *Example 1, Step 13* with (R)-5-formyl-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile (*Step 1*) replacing (*R*)-5-formyl-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{42}H_{40}F_3N_8O_4$ $(M+H)^+$: m/z = 777.3; found 777.3.

Example 20

(R)-1-((7-cyano-2-(3'-(7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-2-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid

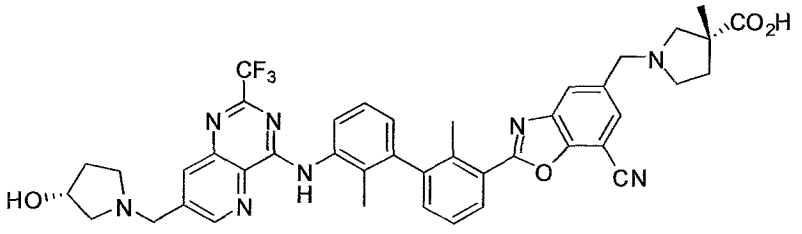


This compound was prepared using similar procedures as described for *Example 6* with (R)-5-formyl-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile (*Example 19, Step 1*) replacing (*R*)-5-formyl-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2,

acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{41}H_{38}F_3N_8O_4$ $(M+H)^+$: m/z = 763.3; found 763.3.

Example 21

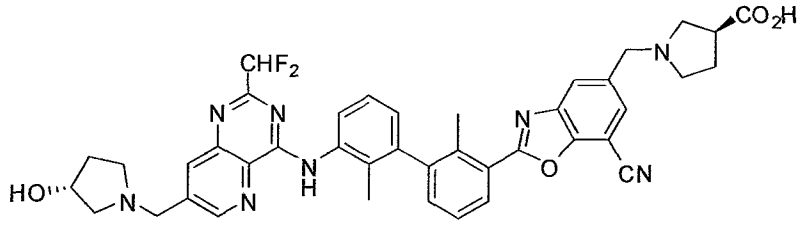
(R)-1-((7-cyano-2-(3'-(7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-2-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid



This compound was prepared using similar procedures as described for *Example 11* with (R)-5-formyl-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile (*Example 19, Step 1*) replacing (*R*)-5-formyl-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{42}H_{40}F_3N_8O_4$ $(M+H)^+$: m/z = 777.3; found 777.3.

Example 22

(S)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid

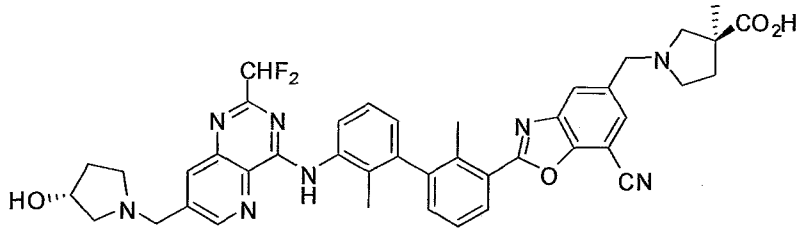


This compound was prepared using similar procedures as described for *Example 6* with (S)-pyrrolidine-3-carboxylic acid replacing (R)-pyrrolidine-3-carboxylic acid and (*R*)-2-(3'-((2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-

yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)-5-formylbenzo[d]oxazole-7-carbonitrile (*Example 16, Step 7*) replacing (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d] pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{41}H_{39}F_2N_8O_4$ $(M+H)^+$: m/z = 745.3; found 745.3.

Example 23

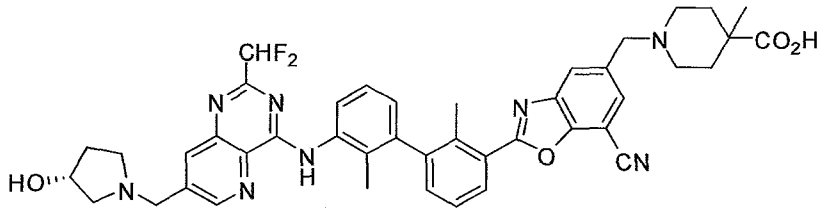
(S)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid



This compound was prepared using similar procedures as described for *Example 6* with (S)-3-methylpyrrolidine-3-carboxylic acid replacing (R)-pyrrolidine-3-carboxylic acid and (*R*)-2-(3'-((2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-yl) amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)-5-formylbenzo[d]oxazole-7-carbonitrile (*Example 16, Step 7*) replacing (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{42}H_{41}F_2N_8O_4$ $(M+H)^+$: m/z = 759.3; found 759.3.

Example 24

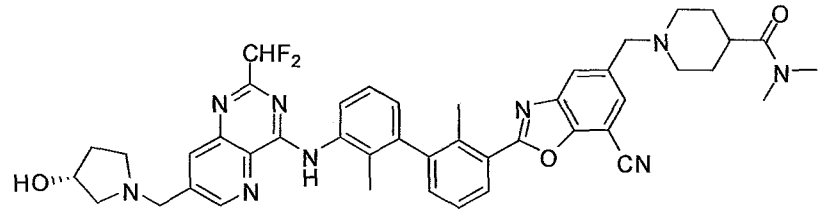
(R)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-4-methylpiperidine-4-carboxylic acid



This compound was prepared using similar procedures as described for *Example 16* with tert-butyl 4-methylpiperidine-4-carboxylate replacing tert-butyl piperidine-4-carboxylate in Step 8. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{43}H_{43}F_2N_8O_4$ $(M+H)^+$: m/z = 773.3; found 773.3.

Example 25

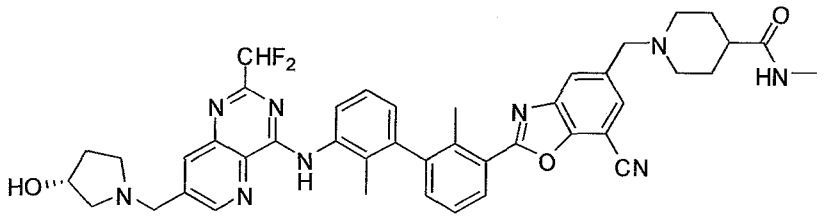
(R)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-N,N-dimethylpiperidine-4-carboxamide



To a solution of (R)-1-((7-cyano-2-(3'-((2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid (Example 16: 7.0 mg, 9.22 μmol), dimethylamine (2.0M in methanol, 0.014 ml) and N,N-diisopropylethylamine (5 μl, 0.028 mmol) in DMF (0.3 ml) was added HATU (7.0 mg, 0.018 mmol). After being stirred at r.t. for 2 h, the reaction mixture was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{44}H_{46}F_2N_9O_3$ $(M+H)^+$: m/z = 786.4; found 786.4.

Example 26

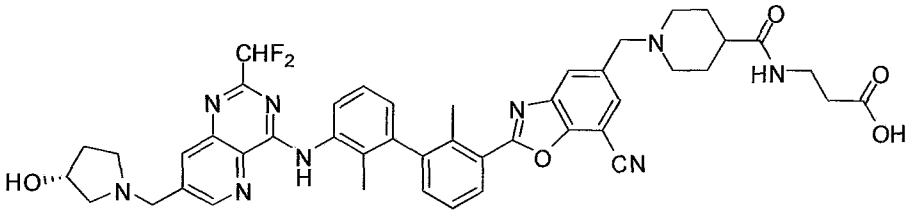
(R)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-N-methylpiperidine-4-carboxamide



This compound was prepared using similar procedures as described for *Example 25* with methylamine solution replacing dimethylamine solution. The reaction mixture was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{43}H_{44}F_2N_9O_3$ $(M+H)^+$: m/z = 772.4; found 772.3.

Example 27

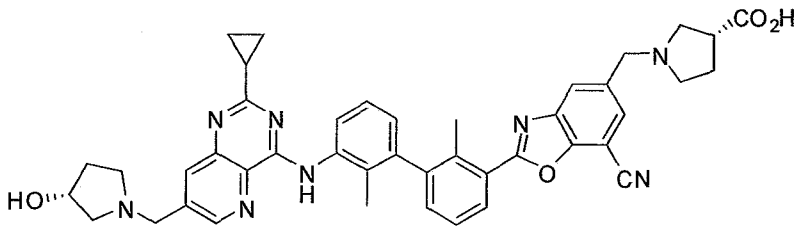
(R)-3-(1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxamido)propanoic acid



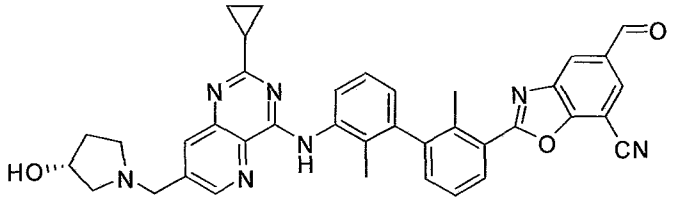
This compound was prepared using similar procedures as described for *Example 25* with *tert*-butyl 3-aminopropanoate replacing dimethylamine solution. After amide bond formation, the reaction mixture was treated with trifluoroacetic acid (0.5 mL) and stirred at r.t. for 1 h. Then the reaction mixture was concentrated, redissovled in MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water +TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{45}H_{46}F_2N_9O_5$ $(M+H)^+$: m/z = 830.4; found 830.3.

Example 28

(R)-1-((7-cyano-2-(3'-(2-cyclopropyl-7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid



Step 1: (R)-2-(3'-(2-cyclopropyl-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)-5-formylbenzo[d]oxazole-7-carbonitrile



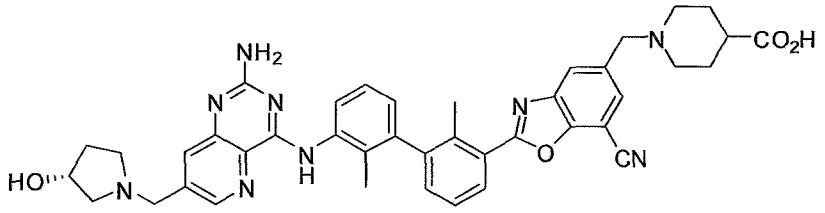
This compound was prepared using similar procedures (*Step 1-7*) as described for *Example 16* with cyclopropanecarboxylic anhydride replacing 2,2-difluoroacetic anhydride in *Step 1*. LC-MS calculated for $C_{38}H_{34}N_7O_3$ $(M+H)^+$: m/z = 636.3; found 636.4.

Step 2: (R)-1-((7-cyano-2-(3'-(2-cyclopropyl-7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid

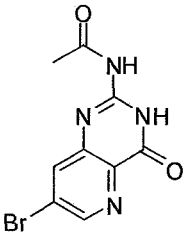
This compound was prepared using similar procedures as described for *Example 6* with (R)-2-(3'-(2-cyclopropyl-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)-5-formylbenzo[d]oxazole-7-carbonitrile (*Step 1*) replacing (*R*)-5-formyl-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{43}H_{43}N_8O_4$ $(M+H)^+$: m/z = 735.3; found 735.3.

Example 29

(R)-1-((2-(3'-(2-amino-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)-7-cyanobenzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

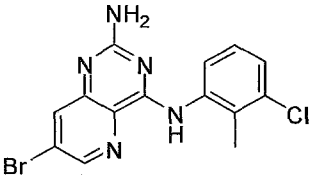


Step 1: N-(7-bromo-4-oxo-3,4-dihydropyrido[3,2-d]pyrimidin-2-yl)acetamide



A mixture of 3-amino-5-bromopicolinamide (1.88 g, 8.70 mmol) and carbamimidic chloride hydrochloride (1.30 g, 11.31 mmol) in sulfolane (5.44 ml) and dimethylsulfone (5.44 ml) was stirred in a sealed vial at 165 °C for 5 h. After cooling to room temperature, the reaction was diluted carefully with water to form a suspension. The precipitate was collected by filtration and washed with water. The solid was dried in the air and used directly without further purification. The mixture of the above solid (685 mg, 2.84 mmol) and acetic anhydride (13.4 ml) was stirred at 115 °C for 8 h. After cooling to room temperature, the mixture was diluted with DCM and washed with water. The organic layer was dried over $MgSO_4$, filtered and concentrated to give a crude material, which was used directly for next step. LC-MS calculated for $C_9H_8BrN_4O_2$ $(M+H)^+$: m/z = 283.0; found 283.0.

Step 2: 7-bromo-N^4-(3-chloro-2-methylphenyl)pyrido[3,2-d]pyrimidine-2,4-diamine

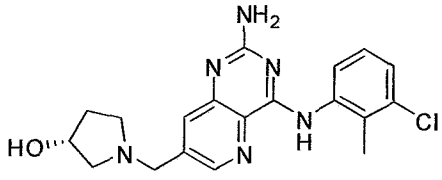


To a mixture of N-(7-bromo-4-oxo-3,4-dihydropyrido[3,2-d]pyrimidin-2-yl)acetamide (201 mg, 0.710 mmol), benzyltriethylammonium chloride (323 mg, 1.420 mmol) and N,N-diethylaniline (169 µl, 1.065 mmol) in acetonitrile (3.5 ml) was added $POCl_3$ (397 µl, 4.26 mmol). The mixture was stirred at 75 °C for 2 h. Then the reaction was cooled to r.t. The volatiles were removed under reduced pressure.

To a solution of 3-chloro-2-methylaniline (100 mg, 0.710 mmol) and N-(7-bromo-4-chloropyrido[3,2-d]pyrimidin-2-yl)acetamide (the residue above) in 2-propanol (3549 µl) was

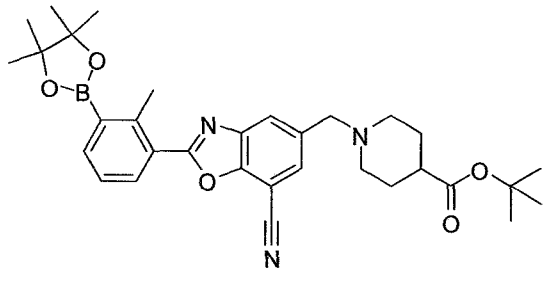
added methanesulfonic acid (46.1 µl, 0.710 mmol). The mixture was stirred at 80 °C for 2 h. Then the reaction was cooled to r.t. The mixture was carefully quenched by $NaHCO_3$ aq solution. The precipitates were filtered, washed by water and dried by air. The solids were used directly for next step. LC-MS calculated for $C_{14}H_{12}BrClN_5$ $(M+H)^+$: m/z = 364.0; found 364.0.

Step 3: (R)-1-((2-amino-4-(3-chloro-2-methylphenylamino)pyrido[3,2-d]pyrimidin-7-yl)methyl)pyrrolidin-3-ol



This compound was prepared using similar procedures (*Step 4-6*) as described for *Example 16* with *7-bromo-N^4-(3-chloro-2-methylphenyl)pyrido[3,2-d]pyrimidine-2,4-diamine* replacing *7-bromo-N-(3-chloro-2-methylphenyl)-2-(difluoromethyl)pyrido[3,2-d]pyrimidin-4-amine* in *Step 4*. LC-MS calculated for $C_{19}H_{22}ClN_6O$ $(M+H)^+$: m/z = 385.2; found 385.2.

Step 4: tert-butyl 1-((7-cyano-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylate



A mixture of 5-formyl-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzo[d]oxazole-7-carbonitrile (Example 1, Step 7: 684 mg, 1.76 mmol) and *tert*-butyl piperidine-4-carboxylate (392 mg, 2.11 mmol) in DCM (7.0 ml) was stirred at r.t. for 2 h. Then sodium triacetoxyborohydride (560 mg, 2.64 mmol) was added. The mixture was further stirred at r.t. for 1 h. The reaction was quenched with NH_4OH aq. solution and extracted by DCM. The organic phase was combined and dried over $MgSO_4$. After filtration, the DCM solution was concentrated to a residue, which was purified by flash

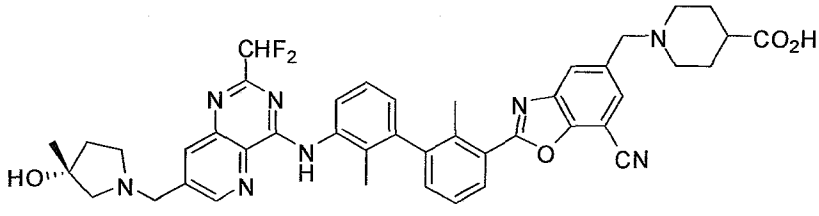
chromatography (0-20% EtOAc/Hexanes). LC-MS calculated for $C_{32}H_{41}BN_3O_5$ $(M+H)^+$: m/z = 558.3; found 558.3.

Step 5: (R)-1-((2-(3'-(2-amino-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)-7-cyanobenzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

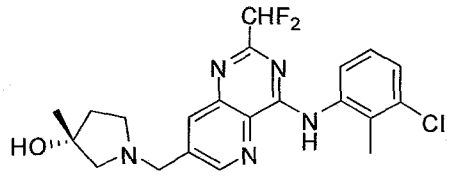
A mixture of (R)-1-((2-amino-4-((3-chloro-2-methylphenyl)amino)pyrido[3,2-d]pyrimidin-7-yl)methyl)pyrrolidin-3-ol (33.9 mg, 0.088 mmol), tert-butyl 1-((7-cyano-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzo[d]oxazol-5-yl)methyl) piperidine-4-carboxylate (54 mg, 0.097 mmol), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (6.9 mg, 8.8 μmol) and potassium phosphate (46.7 mg, 0.22 mmol) in a water (150 μl) and 1,4-dioxane (750 μl) was purged with N_2 and then stirred at 100 °C for 3 h. The reaction was cooled to room temperature. The reaction mixture was diluted with DCM and H_2O. The layers were separated. The aqueous layer was extracted with DCM three times. The organic layer was combined, dried over $MgSO_4$, filtered and concentrated to give a crude residue. The residue was dissolved in DCM (1 mL) and treated with trifluoroacetic acid (1.0 mL). After stirring at r.t. for 30 min, the reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{41}H_{42}N_9O_4$ $(M+H)^+$: m/z = 724.3; found 724.4.

Example 30

(R)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid



Step 1: (R)-1-((4-(3-chloro-2-methylphenylamino)-2-(difluoromethyl)pyrido[3,2-d]pyrimidin-7-yl)methyl)-3-methylpyrrolidin-3-ol



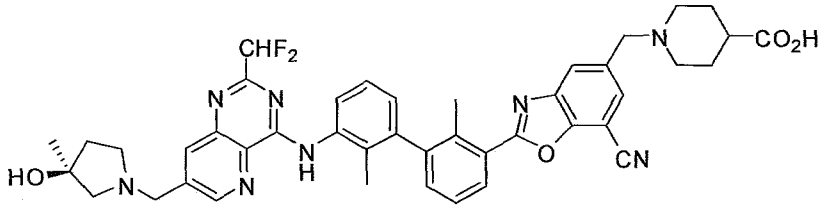
This compound was prepared using similar procedures as described for *Example 16, Step 6* with (*R*)-3-methylpyrrolidin-3-ol replacing (*R*)-pyrrolidin-3-ol. LC-MS calculated for $C_{21}H_{23}ClF_2N_5O$ $(M+H)^+$: m/z = 434.2; found 434.2.

Step 2: (R)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

This compound was prepared using similar procedures as described for *Example 29* with *(R)-1-((4-(3-chloro-2-methylphenylamino)-2-(difluoromethyl)pyrido[3,2-d]pyrimidin-7-yl)methyl)-3-methylpyrrolidin-3-ol* (*Step 1*) replacing *(R)-1-((2-amino-4-(3-chloro-2-methyl phenylamino)pyrido[3,2-d]pyrimidin-7-yl)methyl)pyrrolidin-3-ol* in Step 5. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{43}H_{43}F_2N_8O_4$ $(M+H)^+$: m/z = 773.3; found 773.3.

Example 31

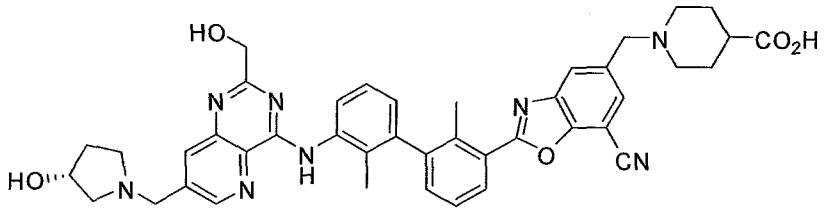
(S)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid



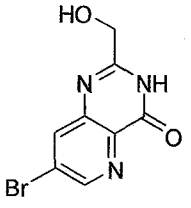
This compound was prepared using similar procedures as described for *Example 30* with (*S*)-3-methylpyrrolidin-3-ol replacing (*R*)-3-methylpyrrolidin-3-ol. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{43}H_{43}F_2N_8O_4$ $(M+H)^+$: m/z = 773.3; found 773.3.

Example 32

(R)-1-((7-cyano-2-(3'-(2-(hydroxymethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid



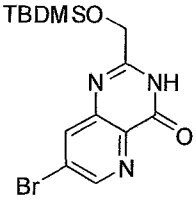
Step 1: 7-bromo-2-(hydroxymethyl)pyrido[3,2-d]pyrimidin-4(3H)-one



To a solution of 3-amino-5-bromopicolinamide (142 mg, 0.657 mmol) in THF was added 2-chloro-2-oxoethyl acetate (90 mg, 0.66 mmol) at 0 °C. The mixture was stirred at r.t. until LCMS showed completion of the reaction. Then water was added slowly to the mixture. The precipitates were filtered and collected, washed by small amount of water and CH_3CN. After air drying, the solid was used directly.

A mixture of the above solid and ammonium hydroxide (aq. soln, 28%, 1.7 ml, 12.04 mmol) in a thick glass tube was stirred at 85 °C for 2 h. After cooling to r.t., the solution was evaporated and the residue was rediluted with CH_3CN and toluene. The suspension was evaporated again and the residue was used for next step without further purification. LC-MS calculated for $C_8H_7BrN_3O_2$ $(M+H)^+$: m/z = 256.0; found 256.1.

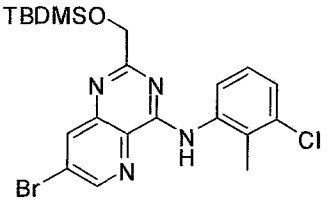
Step 2: 7-bromo-2-((tert-butyldimethylsilyloxy)methyl)pyrido[3,2-d]pyrimidin-4(3H)-one



To a solution of 7-bromo-2-(hydroxymethyl)pyrido[3,2-d]pyrimidin-4(3H)-one (185 mg, 0.722 mmol) and imidazole (73.8 mg, 1.084 mmol) in DMF (4817 µl) was added *tert*-butyldimethylsilyl chloride (120 mg, 0.795 mmol). The mixture was stirred at r.t. for 2 h.

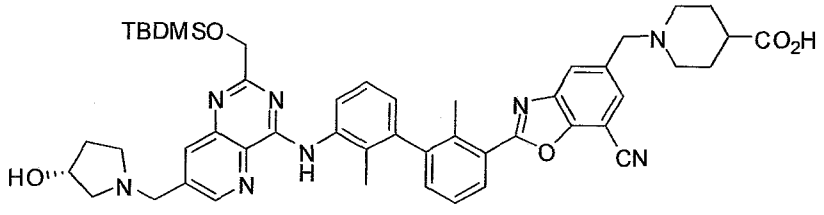
Then the mixture was concentrated and the residue was purified by flash chromatography (0-20% EtOAc/Hexanes) to give the desired product. LC-MS calculated for $C_{14}H_{21}BrN_3O_2Si$ $(M+H)^+$: m/z = 370.1; found 370.1.

Step 3: 7-bromo-2-((tert-butyldimethylsilyloxy)methyl)-N-(3-chloro-2-methylphenyl)pyrido[3,2-d]pyrimidin-4-amine



To a mixture of 7-bromo-2-((tert-butyldimethylsilyloxy)methyl)pyrido[3,2-d]pyrimidin-4(3H)-one (201 mg, 0.54 mmol) and DIEA (190 µl, 1.09 mmol) in DCM (2.2 ml) was added methanesulfonyl chloride (85 µl, 1.09 mmol) at 0 °C. The mixture was stirred at r.t. for 3 h. 3-chloro-2-methylaniline (100 mg, 0.71 mmol) was then added to the mixture and the corresponding mixture was further stirred at r.t. overnight. The mixture was diluted with DCM and then washed by water. The DCM solution was dried over $MgSO_4$ and filtered. The filtrate was concentrated. The residue was purified by flash chromatography (0-40% EtOAc/hexanes). LC-MS calculated for $C_{21}H_{27}BrClN_4OSi$ $(M+H)^+$: m/z = 493.1; found 493.1.

Step 4: (R)-1-((2-(3'-(2-((tert-butyldimethylsilyloxy)methyl)-7-((3-hydroxypyrrolidin-1-yl)methyl) pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)-7-cyanobenzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid



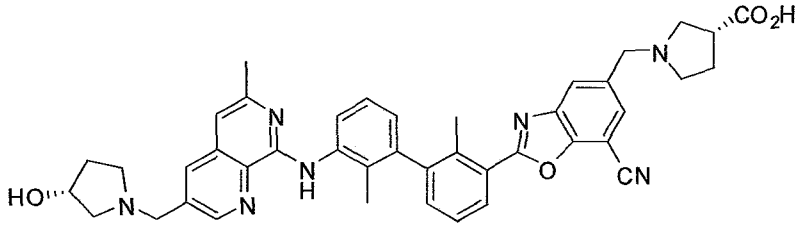
This compound was prepared using similar procedures (Steps 9-13) as described for *Example 1* with 7-bromo-2-((tert-butyldimethylsilyloxy)methyl)-N-(3-chloro-2-methylphenyl)pyrido[3,2-d]pyrimidin-4-amine (*Step 3*) replacing 7-bromo-N-(3-chloro-2-methylphenyl)-2-methylpyrido[3,2-d]pyrimidin-4-amine. After completion, the reaction solution was directly used for next step. LC-MS calculated for $C_{48}H_{57}N_8O_5Si$ $(M+H)^+$: m/z = 853.4; found 853.4.

Step 5: (R)-1-((7-cyano-2-(3'-(2-(hydroxymethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid

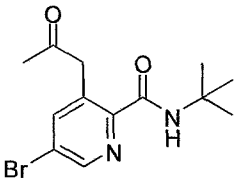
To the above reaction solution (*Step 4*) was added triethylamine trihydrofluoride (411 µl, 60 equiv.) at r.t. The mixture was further stirred at this temperature for 1 h. The reaction mixture was then concentrated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{42}H_{43}N_8O_5$ $(M+H)^+$: m/z = 739.3; found 739.5.

Example 33

(R)-1-((7-cyano-2-(3'-(3-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-6-methyl-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid



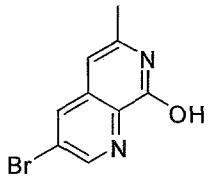
Step 1: 5-bromo-N-tert-butyl-3-(2-oxopropyl)picolinamide



To a solution of diisopropylamine (3.42 ml, 24.0 mmol) in THF (10 mL) was added butyllithium (2.5 M in hexane, 12.79 ml, 32.0 mmol) at -40 °C under N_2 atmosphere. The mixture was stirred at this temperature for 5 min. Then a solution of 5-bromo-N-(tert-butyl)-3-methylpicolinamide (2.71 g, 10.0 mmol) in THF (2 mL) was added. The reaction was stirred at -40 °C for 30 min before warming up to -10 °C. Then the above mixture was added to ethyl acetate (1.17 ml, 12.0 mmol) in THF (6 mL) at -40 °C with stirring. After addition, the reaction was further stirred and slowly warmed up to -10 °C. Then the reaction was quenched by adding aq. NH_4Cl solution. The mixture was then extracted with DCM three times. The organic phase was combined and dried over $MgSO_4$ and filtered. The filtrate was

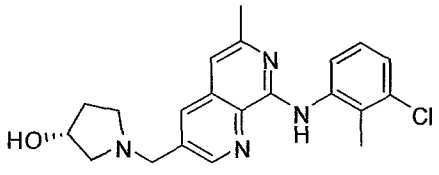
concentrated and the residue was purified by flash chromatography using EtOAc/Hexanes (0-25%) to give the desired product. LC-MS calculated for $C_{13}H_{18}BrN_2O_2$ $(M+H)^+$: m/z = 313.1; found 313.1.

Step 2: 3-bromo-6-methyl-1,7-naphthyridin-8-ol



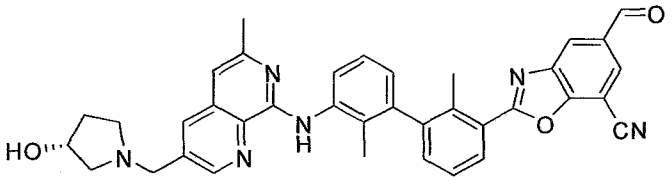
A mixture of 5-bromo-N-(tert-butyl)-3-(2-oxopropyl)picolinamide (716 mg, 2.29 mmol) and ammonium acetate (1762 mg, 22.86 mmol) in acetic acid (1.8 ml) was heated up to 108 °C and stirred at this temperature for 12 h. The reaction was cooled to r.t. Water was added to form a precipitate. The suspension was filtered and the solids were collected to use directly. LC-MS calculated for $C_9H_8BrN_2O$ $(M+H)^+$: m/z = 239.0; found 239.1.

Step 3: (R)-1-((8-(3-chloro-2-methylphenylamino)-6-methyl-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol



This compound was prepared using similar procedures (*Steps 3-6*) as described for *Example 16* with 3-bromo-6-methyl-1,7-naphthyridin-8-ol (*Step 2*) replacing 7-bromo-2-(difluoromethyl)pyrido[3,2-d]pyrimidin-4-ol. LC-MS calculated for $C_{21}H_{24}ClN_4O$ $(M+H)^+$: m/z = 383.2; found 383.3.

Step 4: (R)-5-formyl-2-(3'-(3-((3-hydroxypyrrolidin-1-yl)methyl)-6-methyl-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile



This compound was prepared using similar procedures as described for *Example 1, Step 12* with (R)-1-((8-(3-chloro-2-methylphenylamino)-6-methyl-1,7-naphthyridin-3-

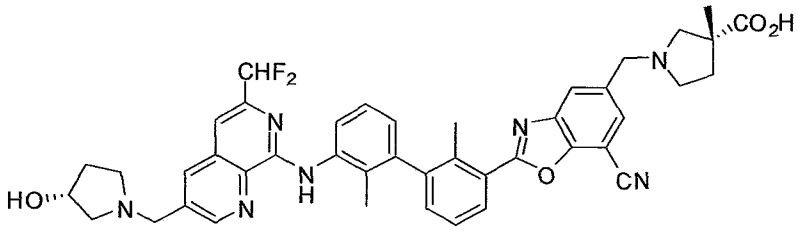
yl)methyl)pyrrolidin-3-ol (*Step 3*) replacing (R)-1-((4-(3-chloro-2-methylphenylamino)-2-methylpyrido[3,2-d]pyrimidin-7-yl)methyl)pyrrolidin-3-ol. LC-MS calculated for $C_{37}H_{33}N_6O_3$ $(M+H)^+$: m/z = 609.3; found 609.4.

Step 5: (R)-1-((7-cyano-2-(3'-(3-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-6-methyl-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid

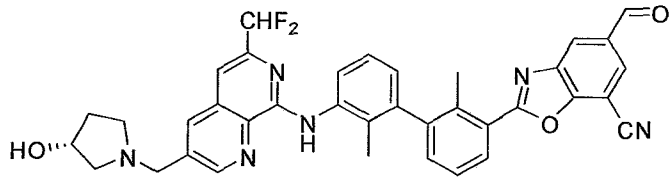
This compound was prepared using similar procedures as described for *Example 6* with (R)-5-formyl-2-(3'-(3-((3-hydroxypyrrolidin-1-yl)methyl)-6-methyl-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazole-7-carbonitrile (*Step 4*) replacing (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{42}H_{42}N_7O_4$ $(M+H)^+$: m/z = 708.3; found 708.3.

Example 34

(R)-1-((7-cyano-2-(3'-(6-(difluoromethyl)-3-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid



Step 1: (R)-2-(3'-(6-(difluoromethyl)-3-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)-5-formylbenzo[d]oxazole-7-carbonitrile



This compound was prepared using similar procedures (*Steps 1-4*) as described for *Example 33* with methyl 2,2-difluoroacetate replacing ethyl acetate. LC-MS calculated for $C_{37}H_{31}F_2N_6O_3$ $(M+H)^+$: m/z = 645.2; found 645.2.

Step 2: (R)-1-((7-cyano-2-(3'-(6-(difluoromethyl)-3-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid

This compound was prepared using similar procedures as described for *Example 11* with *(R)-2-(3'-(6-(difluoromethyl)-3-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)-5-formylbenzo[d]oxazole-7-carbonitrile* (*Step 1*) replacing (*R*)-5-formyl-2-(3'-((7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[d]oxazole-7-carbonitrile. The reaction mixture was evaporated and the residue was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as TFA salt. LC-MS calculated for $C_{43}H_{42}F_2N_7O_4$ $(M+H)^+$: m/z = 758.3; found 758.3.

Example A. Homogeneous Time-Resolved Fluorescence (HTRF) PD-1/PD-L1 Binding Assay

The assays were conducted in a standard black 384-well polystyrene plate with a final volume of 20 µL. Inhibitors were first serially diluted in DMSO and then added to the plate wells before the addition of other reaction components. The final concentration of DMSO in the assay was 1%. The assays were carried out at 25° C in the PBS buffer (pH 7.4) with 0.05% Tween-20 and 0.1% BSA. Recombinant human PD-L1 protein (19-238) with a His-tag at the C-terminus was purchased from AcroBiosystems (PD1-H5229). Recombinant human PD-1 protein (25-167) with Fc tag at the C-terminus was also purchased from AcroBiosystems (PD1-H5257). PD-L1 and PD-1 proteins were diluted in the assay buffer and 10 µL was added to the plate well. Plates were centrifuged and proteins were preincubated with inhibitors for 40 minutes. The incubation was followed by the addition of 10 µL of HTRF detection buffer supplemented with Europium cryptate-labeled anti-human IgG (PerkinElmer-AD0212) specific for Fc and anti-His antibody conjugated to SureLight®-Allophycocyanin (APC, PerkinElmer-AD0059H). After centrifugation, the plate was incubated at 25° C for 60 min. before reading on a PHERAstar FS plate reader (665nm/620nm ratio). Final concentrations in the assay were - 3 nM PD1, 10 nM PD-L1, 1

nM europium anti-human IgG and 20 nM anti-His-Allophycocyanin. IC_{50} determination was performed by fitting the curve of percent control activity versus the log of the inhibitor concentration using the GraphPad Prism 5.0 software.

Example B. Src Homology region 2 Domain-containing Phosphatase (SHP) Assay

U2OS/PD-L1 cells (DiscoveRx Corporation) were maintained in McCoy's 5A medium with addition of 10% FBS, 0.25 μg/ml Puromycin. After removing the culture media, the cell medium was replaced with assay medium (RPMI1640 medium with 1% FBS). The U2OS/PD-L1 cells were then added in 384-well black clear bottom assay plate (CELLCOAT® Tissue Culture Plates, Greiner Bio-One) at 5000 cells per well in 20 μL assay medium. Test compounds were prepared by serial dilution in DMSO and 125 nL compound were first transferred to the 384 REMP plate well (Thermofisher) by ECHO liquid handler (Labcyte) followed with addition of 27.5 μL assay medium. 5 μL/well compounds in the assay medium were transferred to the cell plate with 0.05% DMSO in the final assay at 0.25 μM. Jurkat-PD-1-SHP cells (DiscoveRx Corporation) were cultured in RPMI1640 medium supplemented with 10% FBS, 250 μg/ml Hygromycin B, 500 μg/ml G418. After the replacement of culture media with assay medium, 5,000 Jurkat-PD-1-SHP cells in 20 μL were dispensed into each well. The assay plate was incubated at 37 °C, 5% CO_2 for 2 hours before 2.5 μL PathHunter reagent 1 (DiscoveRx Corporation) were added to each well. The assay plate was shaken for 1 min at 350 rpm in the dark followed with addition of 10 μL PathHunter reagent 2 (DiscoveRx Corporation). Chemiluminescent signal was recorded with TopCount reader (Perkin Elmer) after incubation at room temperature for 1 hour. Wells with DMSO were served as the positive controls and wells containing no cells were used as negative controls. IC_{50} determination was performed by fitting the curve of percentage of control activity versus the log of the compound concentration using the GraphPad Prism 6.0 software.

Example C. Nuclear Factor of Activated T-cells (NFAT) Assay

PD-L1 aAPC/CHO-K1cells (Promega) were maintained in F-12 medium with addition of 10% FBS, 200 μg/ml Hygromycin B, 250 μg/ml Geneticin (G418). Jurkat-PD-1-NFAT effector cells (Promega) were cultured in RPMI 1640 medium supplemented with 10% FBS, 100 μg/ml Hygromycin B, 500 μg/ml G418. The culture media of PD-L1 aAPC/CHO-K1 cells were first replaced with assay medium (RPMI1640 medium with 1%

FBS). The PD-L1 aAPC/CHO-K1cells were then added in a white 384-well white clear bottom assay plate (CELLCOAT® Tissue Culture Plates, Greiner Bio-One) at 8000 per well in 10 μL assay medium. Test compounds were prepared by serial dilution in DMSO and 0.8 μL test compounds in DMSO were first transferred to the 384 REMP plate well (Thermofisher) by PlateMate Plus (Thermofisher) followed with addition of 50 μL plating medium. 5 μL compounds in the assay medium were transferred to the cells with 0.4% DMSO in the final assay at 2 μM. After removing the culture media, 10,000 Jurkat-PD-1-NFAT effector cells in 5μL assay medium was dispensed into each well. The assay plate was incubated at 37 °C, 5% CO_2 for 24 hours. After the assay plate was equilibrated to room temp for 15 minutes, 20μL/well of Bio-Glo™ reagent (Promega) were added. After 8 minutes incubation at room temperature, luminescence was read at with Pherastar microplate reader (BMG Labtech). The fold of induction (FOI) was calculated based on the ratio of luminescence normalized to the DMSO wells within each assay plate. The maximum percentage of induction was reported based on the ratio between the highest FOI of each compound and the maximum FOI of control compound within each assay plate. Wells with DMSO were served as the negative controls and wells containing control compound with the highest FOI were used as positive controls. EC50 determination was performed by fitting the curve of percent control activity versus the log of the compound concentration using the GraphPad Prism 6.0 software.

Example D. PD-L1 Whole Blood Internalization Assay

To determine PD-L1 internalization in human whole blood, normal human blood (Biological Specialty Corp, Colmar. PA) was incubated in the presence or absence of a concentration range of test compounds and 1 ng/ml human interferon γ (R&D Systems Inc. Minn. MN) in a 96 well "2ml Assay Block" (Corning, Corning NY) for 18-20 hours at 37^{0}C. Blood was then stained with PD-L1 (MIH1, eBioscience; or BD Biosciences San Jose, CA), CD14 (Life Technologies, Carlsbad, CA) for 30 minutes in the dark at room temperature. Whole Blood/red cells were lysed/fixed (lysis buffer BD Biosciences) for 5 minutes at 37^{0}C in the dark and then centrifuged at 1600 RPM for 5 minutes. Cells were resuspended in Stain Buffer (BD Bioscience, San Jose, CA) and transferred into 96 well round bottom plates (Corning). Cells were gated on CD14+ (BD Biosciences) and PD-L1 expression determined by mean fluorescence intensity (MFI) (BD LSRFortessa™ X-20). IC_{50} determination was

performed by fitting the curve of compound percent inhibition versus the log of the compound concentration using the GraphPad Prism 7.0 software.

Example E. In Vivo Pharmacokinetics in Rats, Monkeys and Dogs

For in vivo pharmacokinetic experiments, test compounds were administered to male Sprague Dawley rats, male beagle dogs, or male and female Cynomolgus monkeys intravenously or via oral gavage. For IV dosing, test compounds were dosed at 0.5 to 1 mg/kg using a formulation of 10% dimethylacetamide (DMAC) in acidified saline via IV bolus for rat and 5 min or 10 min IV infusion for dog and monkey respectively. For oral dosing, test compounds were dosed at 1.0 to 3.0 mg/kg using 5% DMAC in 0.5% methylcellulose in citrate buffer (pH 3.5). Blood samples were collected at predose and various time points up to 24 hours postdose. All blood samples were collected using EDTA as the anticoagulant and centrifuged to obtain plasma samples. The plasma concentrations of test compounds are determined by LC-MS methods. The measured plasma concentrations are used to calculate PK parameters by standard noncompartmental methods using Phoenix® WinNonlin software program (version 7.0, Pharsight Corporation).

In rats and monkeys, cassette dosing of up to six test compounds were conducted to obtain preliminary PK parameters.

Example F. Results

Compounds of the present disclosure, as exemplified in Examples 1-34, were assessed in each of the HTRF PD-1/PD-L1 binding assay (Example A), SHP assay (Example B), NFAT assay (Example C), and whole blood internalization assay (Example D). The cutoffs for ranges of values observed in each of the assays are shown. The results obtained for the tested compounds are shown in Table 1.

Cutoffs	+	++	+++
HTRF binding assay IC_{50} (nM)	<= 10 nM	> 10 to <= 100	> 100 to <= 500
SHP Assay IC_{50} (nM)	<= 10 nM	> 10 to <= 100	> 100 to <= 500
NFAT assay EC_{50} (nM)	<= 10 nM	> 10 to <= 100	> 100 to <= 500
whole blood internalization assay IC_{50} (nM)	<= 10 nM	> 10 to <= 100	> 100 to <= 500

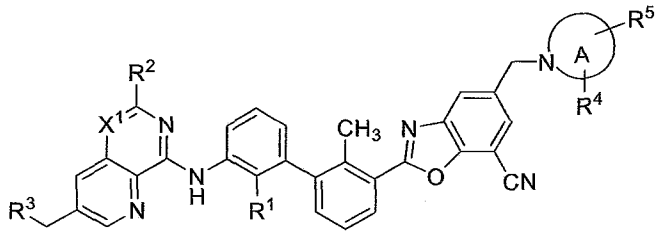
Table 1

Example	HTRF binding IC_{50} (nM)	SHP IC_{50} (nM)	NFAT EC_{50} (nM)	Whole Blood (24HR) IC_{50} (nM)
1	+	+	++	++
2	+	+	++	++
3	+	+	++	++
4	+	+	++	++
5	+	++	++	+++
6	+	+	++	++
7	+	+	++	++
8	+	+	++	++
9	+	+	++	
10	+	+	++	
11	+	+	++	++
12	+	+	++	++
13	+	+	++	++
14	+	+	++	++
15	+	+	++	
16	+	+	+	++
17	+	+	++	++
18	+	+	++	++
19	+	+	++	++
20	+	+	++	++
21	+	+	++	++
22	+		++	++
23	+		+	++
24	+		++	++
25	+		++	++
26	+		+	++
27	+		++	++
28	+	++	++	+++
29	+	+	++	++
30	+	+	+	++
31	+	+	+	++
32	+		++	++
33	+	+	+	++
34	+		+	+++

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including without limitation all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

What is claimed is:

1. A compound of Formula (I'):



(I')

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

ring A is azetidinyl, pyrrolidinyl or piperidinyl;

X^1 is CH or N;

R^1 is methyl or halo;

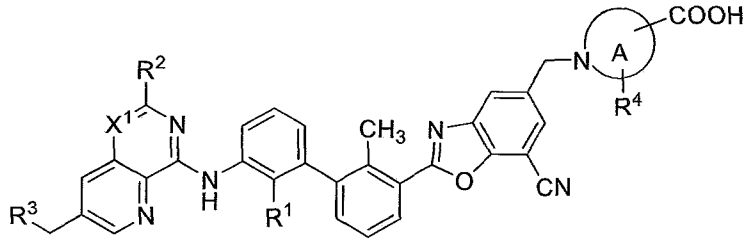
R^2 is C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-2} alkyl-, OH, NH_2, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, 4- to 6-membered heterocycloalkyl or 4- to 6-membered heterocycloalkyl-C_{1-2} alkyl-, wherein the 4- to 6-membered heterocycloalkyl and 4- to 6-membered heterocycloalkyl-C_{1-2} alkyl- each has one or two heteroatoms as ring members selected from O and N, and wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-2} alkyl-, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, 4- to 6-membered heterocycloalkyl and 4- to 6-membered heterocycloalkyl-C_{1-2} alkyl- of R^2 are each optionally substituted with 1 or 2 substituents independently selected from halo, CN and OH;

R^3 is selected from (R)-3-hydroxy-3-methylpyrrolidin-1-yl, (S)-3-hydroxy-3-methylpyrrolidin-1-yl, (R)-3-hydroxypyrrolidin-1-yl, (S)-3-hydroxypyrrolidin-1-yl, (R)-2-hydroxy-2-methyl-ethylamino, (S)-2-hydroxy-2-methyl-ethylamino, (R)-2-hydroxy-1-methyl-ethylamino and (S)-2-hydroxy-1-methyl-ethylamino; and

R^4 is H or C_{1-3} alkyl; and

R^5 is C(O)OH, C(O)N(CH_3)$_2$, C(O)NH(CH_3), or C(O)NH(CH_2)$_2$C(O)OH.

2. A compound of Formula (I):



(I)

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

ring A is azetidinyl, pyrrolidinyl or piperidinyl;

X^1 is CH or N;

R^1 is methyl or halo;

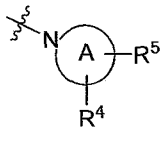
R^2 is C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-2} alkyl-, OH, NH_2, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, 4- to 6-membered heterocycloalkyl or 4- to 6-membered heterocycloalkyl-C_{1-2} alkyl-, wherein the 4- to 6-membered heterocycloalkyl and 4- to 6-membered heterocycloalkyl-C_{1-2} alkyl- each has one or two heteroatoms as ring members selected from O and N, and wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-2} alkyl-, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, 4- to 6-membered heterocycloalkyl and 4- to 6-membered heterocycloalkyl-C_{1-2} alkyl- of R^2 are each optionally substituted with 1 or 2 substituents independently selected from halo, CN and OH;

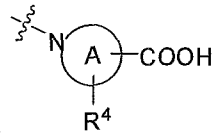
R^3 is selected from (R)-3-hydroxy-3-methylpyrrolidin-1-yl, (S)-3-hydroxy-3-methylpyrrolidin-1-yl, (R)-3-hydroxypyrrolidin-1-yl, (S)-3-hydroxypyrrolidin-1-yl, (R)-2-hydroxy-2-methyl-ethylamino, (S)-2-hydroxy-2-methyl-ethylamino, (R)-2-hydroxy-1-methyl-ethylamino and (S)-2-hydroxy-1-methyl-ethylamino; and

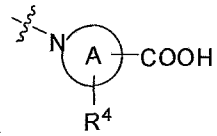
R^4 is H or C_{1-3} alkyl.

3. The compound of claim **1** or **2**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein ring A is pyrrolidinyl.

4. The compound of claim **1** or **2**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein ring A is piperidinyl.

5. The compound of claim **1** or **2**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein  is selected from 4-carboxypiperidin-1-yl, 3-carboxypyrrolidin-1-yl, 3-methyl-3-carboxypyrrolidin-1-yl, 4-(N,N-dimethylaminocarbonyl)piperidin-1-yl, 4-(N-methylaminocarbonyl)piperidin-1-yl, and 4-(2-carboxyethylaminocarbonyl)piperidin-1-yl, wherein the wavy line indicates the point of attachment to the rest of the molecule.

6. The compound of claim **1** or **2**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein  is selected from 4-carboxypiperidin-1-yl, 3-carboxypyrrolidin-1-yl, and 3-methyl-3-carboxypyrrolidin-1-yl, wherein the wavy line indicates the point of attachment to the rest of the molecule.

7. The compound of claim **1** or **2**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein  is selected from 4-carboxypiperidin-1-yl, (R)-3-carboxypyrrolidin-1-yl, (S)-3-carboxypyrrolidin-1-yl, (R)-3-methyl-3-carboxypyrrolidin-1-yl and (S)-3-methyl-3-carboxypyrrolidin-1-yl, wherein the wavy line indicates the point of attachment to the rest of the molecule.

8. The compound of any one of claims **1-7**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 is N.

9. The compound of any one of claims **1-7**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X^1 is CH.

10. The compound of any one of claims **1-9**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^1 is CH_3 or Cl.

11. The compound of any one of claims **1-9**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^1 is CH_3.

12. The compound of any one of claims **1-11**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2 is C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-2} alkyl-, OH, NH_2, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, 1-azetidinyl, azetidin-1-ylmethyl, 1-pyrrolidinyl, pyrrolidin-1-ylmethyl, 1-piperidinyl, or piperidin-1-ylmethyl, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-2} alkyl-, -NH-C_{1-4} alkyl, -N(C_{1-4} alkyl)$_2$, 1-azetidinyl, azetidin-1-ylmethyl, 1-pyrrolidinyl, pyrrolidin-1-

ylmethyl, 1-piperidinyl and piperidin-1-ylmethyl of R^2 are each optionally substituted with 1 or 2 substituents independently selected from halo, CN and OH.

13. The compound of claim **12**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2 is methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, CHF_2, CFH_2, OCF_3, $OCHF_2$, OCH_2F, cyclopropyl, cyclobutyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclohexylmethyl, OH, NH_2, $NHCH_3$, $N(CH_3)_2$, 1-azetidinyl, azetidin-1-ylmethyl, 1-pyrrolidinyl, pyrrolidin-1-ylmethyl, 1-piperidinyl or piperidin-1-ylmethyl, wherein the methyl, ethyl, isopropyl, methoxy, ethoxy, cyclopropyl, cyclobutyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclohexylmethyl, $NHCH_3$, $N(CH_3)_2$, 1-azetidinyl, azetidin-1-ylmethyl, 1-pyrrolidinyl, pyrrolidin-1-ylmethyl, 1-piperidinyl and piperidin-1-ylmethyl of R^2 are each optionally substituted with 1 or 2 substituents independently selected from F, Cl, Br, CN and OH.

14. The compound of any one of claims **1-11**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2 is C_{1-4} alkyl or C_{1-4} haloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from F, Cl, Br, CN and OH.

15. The compound of any one of claims **1-11**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2 is C_{1-4} alkyl or C_{1-4} haloalkyl.

16. The compound of any one of claims **1-11**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2 is CH_3, CF_3, CHF_2, $CH(CH_3)_2$, NH_2, cyclopropyl, or CH_2OH.

17. The compound of any one of claims **1-11**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2 is CH_3, CF_3, CHF_2 or $CH(CH_3)_2$.

18. The compound of any one of claims **1-11**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2 is CH_3.

19. The compound of any one of claims **1-11**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2 is CF_3 or CHF_2.

20. The compound of any one of claims **1-11**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2 is $CH(CH_3)_2$.

21. The compound of any one of claims **1-11**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2 is NH_2.

22. The compound of any one of claims **1-11**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2 is cyclopropyl.

23. The compound of any one of claims **1-11**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^2 is CH_2OH.

24. The compound of any one of claims **1-23**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^3 is (R)-3-hydroxy-3-methylpyrrolidin-1-yl or (S)-3-hydroxy-3-methylpyrrolidin-1-yl.

25. The compound of any one of claims **1-23**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^3 is (R)-3-hydroxypyrrolidin-1-yl or (S)-3-hydroxypyrrolidin-1-yl.

26. The compound of any one of claims **1-23**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^3 is (R)-2-hydroxy-2-methyl-ethylamino or (S)-2-hydroxy-2-methyl-ethylamino.

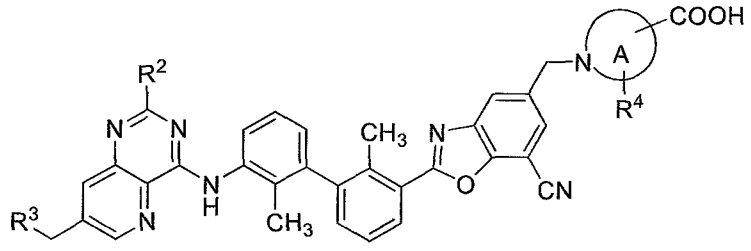
27. The compound of any one of claims **1-23**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^3 is (R)-2-hydroxy-1-methyl-ethylamino or (S)-2-hydroxy-1-methyl-ethylamino.

28. The compound of any one of claims **1-27**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^4 is H or CH_3.

29. The compound of any one of claims **1-27**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^4 is H.

30. The compound of any one of claims **1-27**, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R^4 is CH_3.

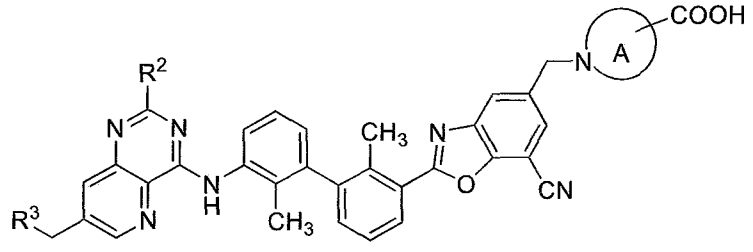
31. The compound of claim **1** having Formula II:



(II)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

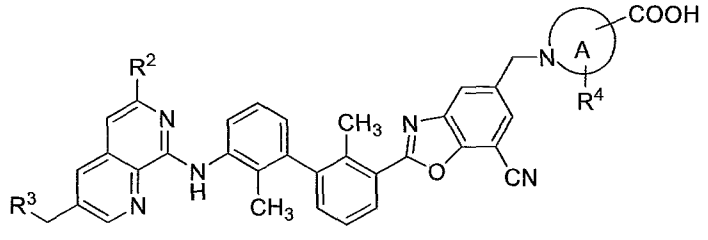
32. The compound of claim **1** having Formula III:



(III)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

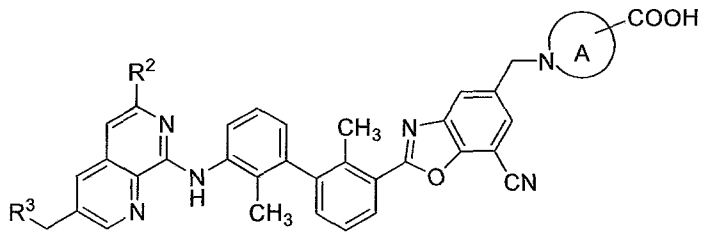
33. The compound of claim **1** having Formula IV:



(IV)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

34. The compound of claim **1** having Formula V:



(V)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

35. The compound of claim **1**, wherein the compound is selected from:

(*R*)-1-((7-cyano-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

(S)-1-((7-cyano-2-(3'-(7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

(S)-1-((7-cyano-2-(3'-(7-((1-hydroxypropan-2-ylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

(S)-1-((7-cyano-2-(3'-(7-((2-hydroxypropylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(7-(((R)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(7-(((S)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(7-(((S)-1-hydroxypropan-2-ylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(7-(((S)-2-hydroxypropylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(7-(((R)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(7-(((S)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(7-(((S)-1-hydroxypropan-2-ylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(7-(((S)-2-hydroxypropylamino)methyl)-2-methylpyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(7-((3-hydroxypyrrolidin-1-yl)methyl)-2-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-2-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid; and

(R)-1-((7-cyano-2-(3'-(7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-2-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid,

or a pharmaceutically acceptable salt or a stereoisomer thereof.

36. The compound of claim 1, wherein the compound is selected from:

(S)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid;

(S)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-4-methylpiperidine-4-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-N,N-dimethylpiperidine-4-carboxamide;

(R)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-N-methylpiperidine-4-carboxamide;

(R)-3-(1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxamido)propanoic acid;

(R)-1-((7-cyano-2-(3'-(2-cyclopropyl-7-(((R)-3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid;

(R)-1-((2-(3'-(2-amino-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)-7-cyanobenzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

(S)-1-((7-cyano-2-(3'-(2-(difluoromethyl)-7-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(2-(hydroxymethyl)-7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)piperidine-4-carboxylic acid;

(R)-1-((7-cyano-2-(3'-(3-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-6-methyl-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)pyrrolidine-3-carboxylic acid; and

(R)-1-((7-cyano-2-(3'-(6-(difluoromethyl)-3-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)benzo[d]oxazol-5-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid,

or a pharmaceutically acceptable salt or a stereoisomer thereof.

37. A pharmaceutical composition comprising a compound of any one of claims **1-36**, or a pharmaceutically acceptable salt or a stereoisomer thereof, and a pharmaceutically acceptable excipient or carrier.

38. A method of inhibiting PD-1/PD-L1 interaction, said method comprising administering to a patient a compound of any one of claims **1-36**, or a pharmaceutically acceptable salt or a stereoisomer thereof.

39. A method of treating a disease or disorder associated with inhibition of PD-1/PD-L1 interaction, said method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of claims **1-36**, or a pharmaceutically acceptable salt or a stereoisomer thereof.

40. The method of claim **39**, wherein the disease or disorder is an infection disease, inflammation, autoimmune disease, cancer, or neurodegenerative disorder

41. A method of enhancing, stimulating and/or increasing the immune response in a patient, said method comprising administering to the patient in need thereof a therapeutically effective amount of a compound of any one of claims **1-36**, or a pharmaceutically acceptable salt or a stereoisomer thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/025036

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/14 A61K31/423 A61P37/00
ADD.

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

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)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/087777 A1 (INCYTE CORP [US]) 26 May 2017 (2017-05-26) page 76; example 15	1-41
X	WO 2018/026971 A1 (ARISING INT LLC [US]) 8 February 2018 (2018-02-08) page 63; example 27	1-41
X,P	WO 2018/119266 A1 (INCYTE CORP [US]) 28 June 2018 (2018-06-28) page 156 - page 172; examples 22-28, 30, 33-35	1-41

☐ 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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 June 2019	03/07/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Lewis, Sara

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/025036

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2017087777 A1	26-05-2017	AU 2016358100 A1	05-07-2018
		CA 3005727 A1	26-05-2017
		CN 109641885 A	16-04-2019
		EA 201891203 A1	28-12-2018
		EP 3377488 A1	26-09-2018
		JP 2018538269 A	27-12-2018
		KR 20180095824 A	28-08-2018
		PH 12018501084 A1	28-01-2019
		SG 11201804152R A	28-06-2018
		TW 201726635 A	01-08-2017
		US 2017145025 A1	25-05-2017
		WO 2017087777 A1	26-05-2017
WO 2018026971 A1	08-02-2018	AU 2017305399 A1	31-01-2019
		CA 3030773 A1	08-02-2018
		CN 109195602 A	11-01-2019
		EP 3493804 A1	12-06-2019
		WO 2018026971 A1	08-02-2018
WO 2018119266 A1	28-06-2018	TW 201835073 A	01-10-2018
		US 2018179197 A1	28-06-2018
		WO 2018119266 A1	28-06-2018