[0009] EP_2 and EP_4 are highly expressed in endometriosis and there is data that suggests that EP_2/EP_4 inhibition may serve as nonsteroidal therapy for endometriosis (Arosh J.A. *et al., Proc. Natl. Acad. Sci. U.S.A.* **2015**, 112, p. 9716-9721).

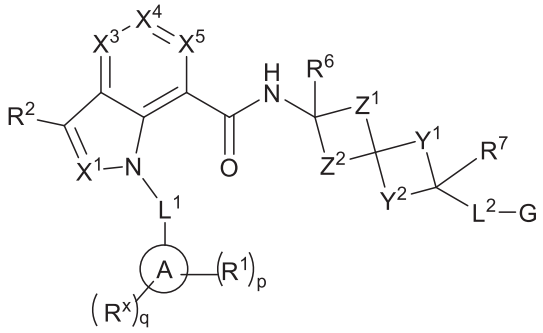
[00010] The EP_4 pathway is also implicated in vascular disease. The EP_4 antagonist ONO-AE3-208 was found to decrease vascular inflammation and to reduce the incidence and severity of abdominal aortic aneurism in the angiotensin II mouse model (Cao R. *et al., Am J Pathol* **2012** 181, p. 313-321). EP_4 overexpression has been associated with enhanced inflammatory reaction in atherosclerotic plaques and EP_4 antagonism has been suggested as a therapy for atherosclerosis and the prevention of acute ischemic syndromes (Cipollone F. *et al., Aterioscleroosis, Thrombosis, and Vascular Biology* **2005**, 25, p. 1925-1931).

[00011] There remains a need to provide novel classes of compounds that are useful in the treatment of EP2 and EP4 receptor-mediated diseases. Such classes of compounds have the potential to be useful in the treatment of inflammatory disease, autoimmune disease, neurodegenerative disease, cardiovascular disease and cancer.

SUMMARY

[00012] Provided herein are compounds of Formula (I) or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, single stereoisomer, mixture of stereoisomers, racemic mixture of stereoisomers, or prodrug thereof. In certain examples, the compounds are modulators of both the EP_2 and EP_4 receptors. In certain examples, the compounds are useful as potent and selective antagonists of both the EP_2 and EP_4 receptors, and in this regard, will confer therapeutic benefits associated with the selective blockade of PGE_2-mediated signaling.

[00013] In certain examples, provided herein are compound having the Formula (I), or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, or prodrug thereof:



Formula (I)

wherein:

X^1 is N or CH;

X^3 is N or CR^3;

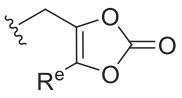
each R^{11} is independently alkyl, deuterated alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one, two, or three groups selected from halogen, alkyl, and haloalkyl;

Y^1 and Y^2 are each independently a bond or $-(CR^a_2)_n-$, provided that Y^1 and Y^2 are not both a bond;

Z^1 and Z^2 are each $-CR^a_2-$;

L^2 is $-(CR^c_2)_m-$;

G is $-C(O)OR^{12}$, $-C(O)NHOH$, $-SO_3H$, $-SO_2NH_2$, $-SO_2NHR^d$, $-SO_2NHC(O)R^d$, $-NHC(O)NHSO_2R^d$, -1*H*-tetrazolyl, $-P(O)(OH)_2$, -1,2,4-oxadiazol-5(4*H*)-one, -tetrazol-5(4*H*)-one, or $-C(O)NHSO_2R^d$;

R^{12} is selected from hydrogen, C_1-C_6 alkyl, aryl, aralkyl, $CH(R^{13})OC(=O)R^{14}$, $CH(R^{13})OC(=O)OR^{14}$ and a (5-alkyl-2-oxo-1,3-dioxolen-4-yl)methyl group having the following formula:  wherein R^e is C_1-C_6 alkyl;

R^{13} is hydrogen or C_1-C_6 alkyl;

R^{14} is C_1-C_6 alkyl or C_3-C_6 –cycloalkyl;

each R^a is independently hydrogen, deuterium, optionally deuterated alkyl, halogen, or haloalkyl;

each R^b is independently hydrogen, deuterium, optionally alkyl or haloalkyl, or two R^bs, together with the carbon atom to which they are attached, form optionally cycloalkyl or heterocyclyl;

each R^c is independently hydrogen or halogen;

R^d is alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

m is 0, 1, or 2;

each n is independently 1, 2, or 3;

p is 1 or 2;

q is 0, 1, or 2; and

t is 1, 2 or 3.

[00014] In one example, the compound provided herein is a compound of Formula (I). In one example, the compound provided herein is a pharmaceutically acceptable salt of the compound of Formula (I). In one example, provided herein is a solvate of the compound of Formula (I). In one example, provided herein is a solvate of the pharmaceutically acceptable salt of the compound of Formula (I). In one example, provided herein is a hydrate of the compound of Formula (I). In one example, provided herein is an isotopic variant of the

compound of Formula (I). In one example, provided herein is a deuterated compound of Formula (I). In one example, provided herein is a prodrug of the compound of Formula (I).

[00015] Also provided are pharmaceutical compositions formulated for administration by an appropriate route and formulations comprising effective concentrations of one or more of the compounds provided herein, or pharmaceutically acceptable salts, solvates, solvates of pharmaceutically acceptable salts, hydrates, and prodrugs thereof and optionally comprising at least one pharmaceutically acceptable carrier.

[00016] In certain examples, the compounds are useful for the treatment, prevention or amelioration of cancer, arthritis, pain, endometriosis, neurodegenerative disease, and cardiovascular disease.

[00017] In an example, the present disclosure provides a method for the treatment of cancer in a patient comprising administering to the patient a compound or pharmaceutical composition as described herein. In some examples, the cancer is selected from glioblastoma bone cancer, head and neck cancer, melanoma, basal cell carcinoma, squamous cell carcinoma, adenocarcinoma, oral cancer, esophageal cancer, gastric cancer, intestinal cancer, colon cancer, bladder cancer, hepatocellular carcinoma, renal cell carcinoma, pancreatic cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer, and prostate cancer. In some examples, the cancer is selected from colon cancer, bladder cancer, hepatocellular carcinoma, pancreatic cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer and prostate cancer.

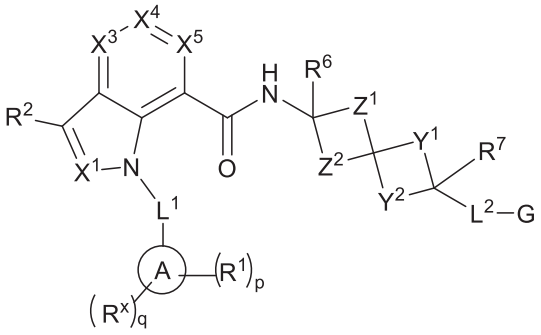
[00018] In another example, the present disclosure provides a compound or pharmaceutical composition (e.g., as described herein) for use in the treatment of cancer. In some examples, the cancer is selected from glioblastoma bone cancer, head and neck cancer, melanoma, basal cell carcinoma, squamous cell carcinoma, adenocarcinoma, oral cancer, esophageal cancer, gastric cancer, intestinal cancer, colon cancer, bladder cancer, hepatocellular carcinoma, renal cell carcinoma, pancreatic cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer, and prostate cancer. In some examples, the cancer is selected from colon cancer, bladder cancer, hepatocellular carcinoma, pancreatic cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer and prostate cancer.

[00019] In another example, the present disclosure provides a method of treating a neurodegenerative disease in a patient comprising administering to the patient a compound or pharmaceutical composition as described herein. In some examples, the neurodegenerative disease is selected from epilepsy, Alzheimer’s disease (AD), Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS) and traumatic brain injury (TBI).

[00020] In another example, the present disclosure provides a method of treating arthritis or inflammatory pain in a patient comprising administering to the patient a compound or pharmaceutical composition as described herein.

[00021] In certain examples, the compounds are useful as pharmaceutically acceptable compositions and useful in the treatment of various diseases; in particular cancer, both alone or in combination with radiation, antibodies to cytotoxic t-lymphocyte antigen 4 (i.e. anti-CTLA4 agents such as ipilimumab, or the like), antibodies to programmed death-ligand 1 (i.e. anti-PD-L1 agents such as atezolizumab, avelumab, or the like), antibodies to programmed cell death protein 1 (i.e. anti-PD-1 agents such as nivolumab, pembrolizumab, or the like), activators of stimulator of interferon genes pathway (i.e. STING activators such as ADU-S100, MK-1454, or the like) and cytotoxic agents (i.e. alkylating agents such as cisplatin, dacarbazine, chlorambucil, or the like; anti-metabolites such as methotrexate, fludarabine, gemcitabine, or the like; anti-microtubule agents such as vinblastine, paclitaxel, or the like; topoisomerase inhibitors such as topotecan, doxorubicin, or the like; and others). Also provided herein are processes for the preparation of the compounds of this intervention, as well as for the preparation of intermediates useful for the synthesis of the compounds of Formula (I).

[00021a]In one aspect, the present disclosure refers to a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof:



Formula (I)

wherein:

X^1 is N;

X^3 is CR^3;

X^4 is CR^4;

X^5 is CR^5;

L^1 is $-CR^b{}_2-$;

Ring A is aryl;

R^1 is aryl optionally substituted with one, two, or three R^y;

each R^y is independently alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, halogen, $-OR^8$, $-NR^8R^9$, -CN, $-C(O)R^{11}$, $-C(O)NR^8R^9$, $-NR^8C(O)R^{11}$, $-NR^8C(O)OR^9$, $-NR^{10}C(O)NR^8R^9$, $-OC(O)NR^8R^9$, $-S(O)_2R^{11}$, $-S(O)R^{11}$, $-SR^8$, $-S(O)_2NR^8R^9$,
$-S(O)NR^8R^9$, $-NR^8S(O)R^{11}$, $-NR^8S(O)_2R^{11}$, or $-NR^{10}S(O)_2NR^8R^9$; wherein the alkyl is optionally substituted with $-OR^8$ or $-NR^8R^9$ and wherein the cycloalkyl and heterocyclyl are optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl;

each R^x is independently halogen, methyl, C_1haloalkyl, or -CN;

R^2, R^3, R^4, and R^5 are each independently hydrogen, alkyl, halogen, $-OR^8$, $-NR^8R^9$, $-SR^8$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, -CN, cycloalkyl, or haloalkyl;

R^6 is hydrogen, alkyl, or haloalkyl;

R^7 is hydrogen, halogen, alkyl, alkoxy, haloalkoxy, hydroxyl, or haloalkyl;

each R^8 and each R^9 are independently hydrogen, alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl; or

R^8 and R^9, together with the atom or atoms to which they are attached, form a heterocyclyl optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl;

each R^{10} is independently hydrogen or alkyl;

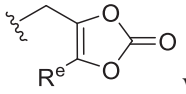
each R^{11} is independently alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl;

Y^1 and Y^2 are each independently a bond or $-(CR^a_2)_n-$, provided that Y^1 and Y^2 are not both a bond;

Z^1 and Z^2 are each $-CR^a_2-$;

L^2 is $-(CR^c_2)_m-$;

G is $-C(O)OR^{12}$, -C(O)NHOH, $-SO_3H$, $-SO_2NH_2$, $-SO_2NHR^d$, $-SO_2NHC(O)R^d$, $-NHC(O)NHSO_2R^d$, -1*H*-tetrazolyl, $-P(O)(OH)_2$, -1,2,4-oxadiazol-5(4*H*)-one, -tetrazol-5(4*H*)-one, or $-C(O)NHSO_2R^d$;

R^{12} is selected from H, C_1-C_6 alkyl, aryl, aralkyl, $CH(R^{13})OC(=O)R^{14}$, $CH(R^{13})OC(=O)OR^{14}$ and a (5-alkyl-2-oxo-1,3-dioxolen-4-yl)methyl group having the following formula:  wherein R^e is C_1-C_6 alkyl;

R^{13} is hydrogen or C_1-C_6 alkyl;

R^{14} is C_1-C_6 alkyl or C_3-C_6 –cycloalkyl;

each R^a is independently hydrogen, alkyl, halogen, or haloalkyl;

each R^b is independently hydrogen, alkyl, or haloalkyl, or

two R^bs, together with the carbon atom to which they are attached, form a cycloalkyl or a heterocyclyl;

each R^c is independently hydrogen or halogen;

R^d is alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

m is 0, 1, or 2;

each n is independently 1, 2, or 3;

p is 1; and

q is 0, 1, or 2.

[00021b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the compound as described herein, or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof, and a pharmaceutically acceptable carrier.

[00021c] In another aspect, the present disclosure refers to a use of the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof as described herein, in the manufacture of a medicament for the treatment of an EP4-mediated cancer in a patient, wherein the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant or prodrug thereof is to be administered to a patient.

[00021d] In yet another aspect, the present disclosure refers to the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof as described herein, or the pharmaceutical composition as described herein for use in therapy.

[00022] These and other examples of the subject matter described herein will become evident upon reference to the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[00023] FIG. 1 depicts animal tumor growth delay in syngeneic CT26 colon carcinoma mouse model. CT26 tumor bearing mice treated p.o., b.i.d with 50 mg/kg of one of the compounds of Formula (I) (Compound A) for 14 days resulted in a statistically significant (p=0.02) reduction

in tumor size compared to animals treated with vehicle or an internal EP4 selective compound (Compound B).

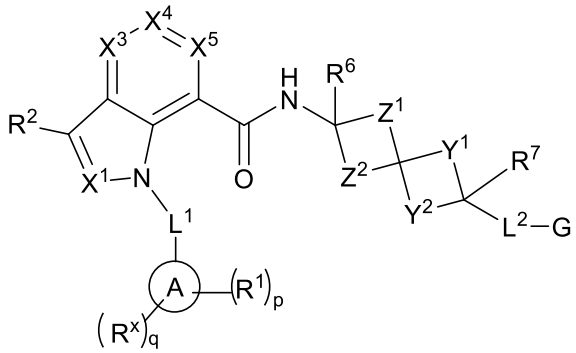
[00024] FIG. 2A-C depict Spider plots of individual CT26 tumor bearing mice treated with one of the compounds of Formula (I) (Compound A) for 14 days (FIG. 2B) which also demonstrate significant tumor growth inhibition compared to animals treated with vehicle (FIG. 2A) or an internal EP4 selective compound Compound B (FIG. 2C).

[00025] FIG 3 depicts animal tumor growth delay in syngeneic CT26 colon carcinoma mouse model. CT26 tumor bearing mice treated p.o., b.i.d with 30 mg/kg of one of the compounds of Formula (I) (Compound A-1) for 14 days resulted in a statistically significant ($p=0.008$) reduction in tumor size compared to animals treated with vehicle or an internal EP4 selective compound (Compound B).

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof:



Formula (I)

wherein:

X^1 is N;

X^3 is CR^3;

X^4 is CR^4;

X^5 is CR^5;

L^1 is $-CR^b{}_2-$;

Ring A is aryl;

R^1 is aryl optionally substituted with one, two, or three R^y;

each R^y is independently alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, halogen, $-OR^8$, $-NR^8R^9$, -CN, $-C(O)R^{11}$, $-C(O)NR^8R^9$, $-NR^8C(O)R^{11}$, $-NR^8C(O)OR^9$, $-NR^{10}C(O)NR^8R^9$, $-OC(O)NR^8R^9$, $-S(O)_2R^{11}$, $-S(O)R^{11}$, $-SR^8$, $-S(O)_2NR^8R^9$, $-S(O)NR^8R^9$, $-NR^8S(O)R^{11}$, $-NR^8S(O)_2R^{11}$, or $-NR^{10}S(O)_2NR^8R^9$; wherein the alkyl is optionally substituted with $-OR^8$ or $-NR^8R^9$ and wherein the cycloalkyl and heterocyclyl are optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl;

each R^x is independently halogen, methyl, C_1haloalkyl, or -CN;

R^2, R^3, R^4, and R^5 are each independently hydrogen, alkyl, halogen, $-OR^8$, $-NR^8R^9$, $-SR^8$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, -CN, cycloalkyl, or haloalkyl;

R^6 is hydrogen, alkyl, or haloalkyl;

R^7 is hydrogen, halogen, alkyl, alkoxy, haloalkoxy, hydroxyl, or haloalkyl;

each R^8 and each R^9 are independently hydrogen, alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl; or

R^8 and R^9, together with the atom or atoms to which they are attached, form a heterocyclyl optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl;

each R^{10} is independently hydrogen or alkyl;

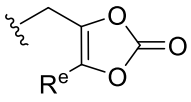
each R^{11} is independently alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl;

Y^1 and Y^2 are each independently a bond or $-(CR^a_2)_n-$, provided that Y^1 and Y^2 are not both a bond;

Z^1 and Z^2 are each $-CR^a_2-$;

L^2 is $-(CR^c_2)_m-$;

G is $-C(O)OR^{12}$, $-C(O)NHOH$, $-SO_3H$, $-SO_2NH_2$, $-SO_2NHR^d$, $-SO_2NHC(O)R^d$, $-NHC(O)NHSO_2R^d$, -1*H*-tetrazolyl, $-P(O)(OH)_2$, -1,2,4-oxadiazol-5(4*H*)-one, -tetrazol-5(4*H*)-one, or $-C(O)NHSO_2R^d$;

R^{12} is selected from H, C_1-C_6 alkyl, aryl, aralkyl, $CH(R^{13})OC(=O)R^{14}$, $CH(R^{13})OC(=O)OR^{14}$ and a (5-alkyl-2-oxo-1,3-dioxolen-4-yl)methyl group having the following formula:  wherein R^e is C_1-C_6 alkyl;

R^{13} is hydrogen or C_1-C_6 alkyl;

R^{14} is C_1-C_6 alkyl or C_3-C_6 –cycloalkyl;

each R^a is independently hydrogen, alkyl, halogen, or haloalkyl;

each R^b is independently hydrogen, alkyl, or haloalkyl, or

two R^bs, together with the carbon atom to which they are attached, form a cycloalkyl or a heterocyclyl;

each R^c is independently hydrogen or halogen;

R^d is alkyl, haloalkyl, cycloalkyl, aryl, or heteroaryl;

m is 0, 1, or 2;

each n is independently 1, 2, or 3;

p is 1; and

q is 0, 1, or 2.

2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof, wherein:

R^2, R^3, R^4, and R^5 are each independently hydrogen, alkyl, halogen, $-OR^8$, -CN, cycloalkyl, or haloalkyl; each R^b is independently hydrogen, deuterium, optionally deuterated alkyl or haloalkyl, or two R^bs, together with the carbon atom to which they are attached, form optionally deuterated cycloalkyl; and

each R^8 is independently hydrogen, alkyl, deuterated alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl.

3. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof, wherein:

each R^y is independently alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, halogen, $-OR^8$, $-NR^8R^9$, -CN, $-C(O)R^{11}$, $-C(O)NR^8R^9$, $-NR^8C(O)R^{11}$, $-NR^8C(O)OR^9$, $-NR^{10}C(O)NR^8R^9$, $-OC(O)NR^8R^9$, $-S(O)_2R^{11}$, $-S(O)R^{11}$, $-SR^8$, $-S(O)_2NR^8R^9$, $-NR^8S(O)_2R^{11}$, or $-NR^{10}S(O)_2NR^8R^9$ wherein alkyl is optionally substituted with $-OR^8$ or $-NR^8R^9$ and wherein cycloalkyl and heterocyclyl are optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl;

each R^8 and each R^9 are independently hydrogen, alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl; or

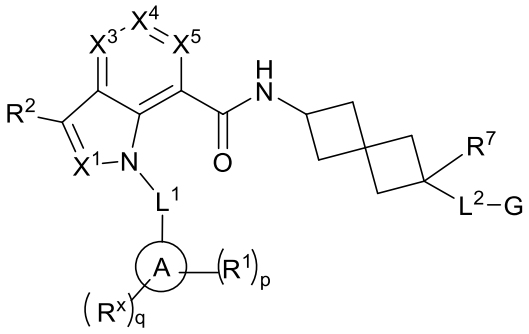
R^8 and R^9, together with the atom or atoms to which they are attached, form a heterocyclyl optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl;

each R^{10} is independently hydrogen or alkyl;

each R^{11} is independently alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl; and

each R^b is independently hydrogen or deuterium.

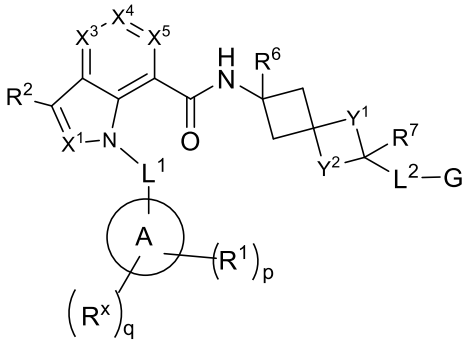
4. The compound of claim 3 having the Formula (II):



(II)

or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof, wherein L^1 is $-CR^b_2-$ and each R^b is independently hydrogen or deuterium.

5. The compound of claim 3 having the Formula (IIc):



(IIc)

or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof, wherein L^1 is $-CR^b_2-$ and each R^b is independently hydrogen or deuterium.

6. The compound of claim 5, or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof, wherein:

R^3, R^4, and R^5 are each independently hydrogen, alkyl, halogen, $-OR^8$, $-NR^8R^9$, $-SR^8$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, -CN, cycloalkyl, or haloalkyl; and

each R^8 and each R^9 are independently hydrogen, deuterium, alkyl, deuterated alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl; or

R^8 and R^9, together with the atom or atoms to which they are attached, form a heterocyclyl optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl; and

each R^{11} is independently alkyl, deuterated alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl.

7. The compound of claim 6, or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof, wherein:

one of R^3, R^4, and R^5 is alkyl, halogen, $-OR^8$, $-NR^8R^9$, $-SR^8$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, -CN, cycloalkyl, or haloalkyl and the remainder of R^3, R^4, and R^5, when present, are hydrogen.

8. The compound of claim 7, or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof, wherein one of R^3 or R^4 is halogen and the other of R^3 and R^4, when present, is hydrogen and R^5, when present, is hydrogen.

9. The compound of claim 8, or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof, wherein:

R^1 is aryl optionally deuterated and optionally substituted with one or two R^y;

each R^y is independently alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, halogen, $-OR^8$, $-NR^8R^9$, -CN, $-C(O)R^{11}$, $-C(O)NR^8R^9$, $-NR^8C(O)R^{11}$, $-NR^8C(O)OR^9$, $-NR^{10}C(O)NR^8R^9$, $-OC(O)NR^8R^9$, $-S(O)_2R^{11}$, $-S(O)R^{11}$, $-SR^8$, $-S(O)_2NR^8R^9$,

$-S(O)NR^8R^9$, $-NR^8S(O)R^{11}$, $-NR^8S(O)_2R^{11}$, or $-NR^{10}S(O)_2NR^8R^9$; wherein alkyl is optionally substituted with $-OR^8$ or $-NR^8R^9$ and wherein cycloalkyl and heterocyclyl are

optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl;

each R^8 and each R^9 are independently hydrogen, deuterium, alkyl, deuterated alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl; or

R^8 and R^9, together with the atom or atoms to which they are attached, form a heterocyclyl optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl;

each R^{10} is independently hydrogen, deuterium, alkyl or deuterated alkyl; and

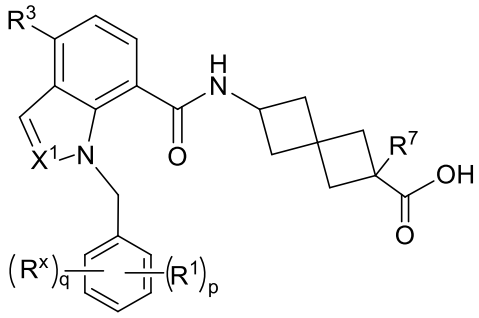
each R^{11} is independently alkyl, deuterated alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl.

10. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant or prodrug thereof, wherein Ring A is phenyl and R^1 is phenyl.

11. The compound of claim 10, or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof, wherein R^7 is hydrogen or deuterium.

12. The compound of claim 11, or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof, wherein q is 0 or 1.

13. The compound of claim 1 having the Formula (V):

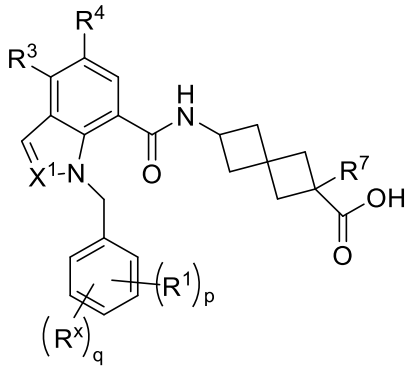


(V)

or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic

variant, or prodrug thereof; wherein p is 1 and R^1 is phenyl optionally substituted with one, two, or three R^y.

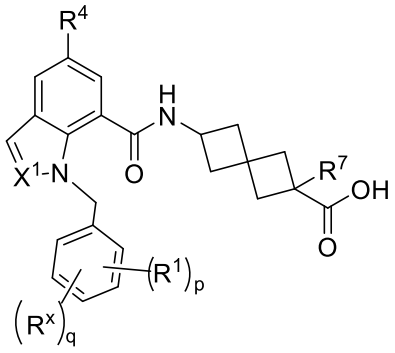
14. The compound of claim 1 having the Formula (Va):



(Va)

or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof; wherein p is 1 and R^1 is phenyl optionally substituted with one, two, or three R^y.

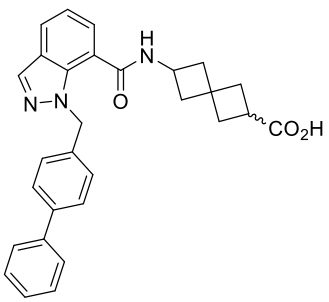
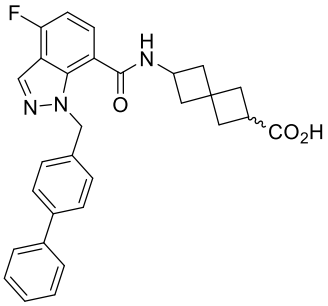
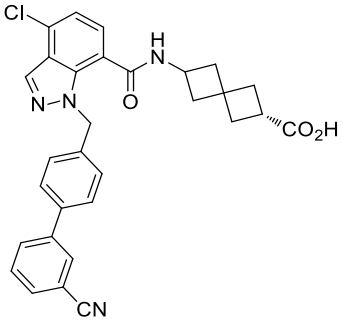
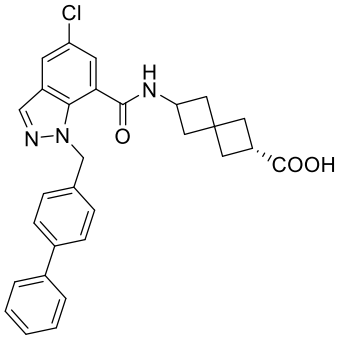
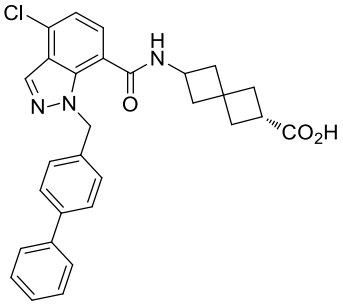
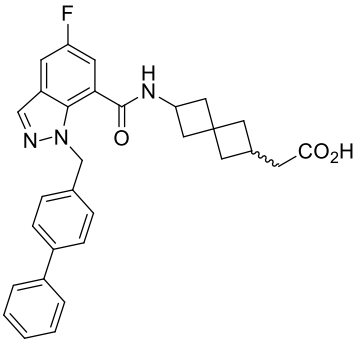
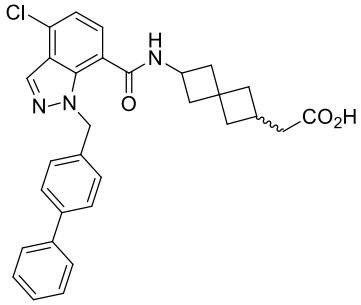
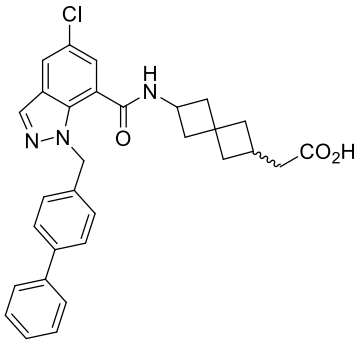
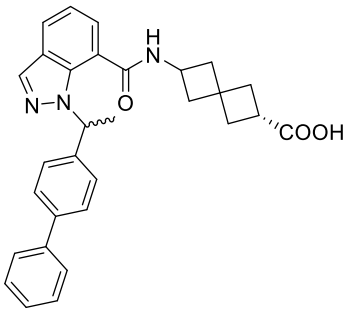
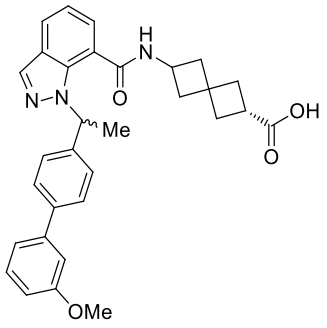
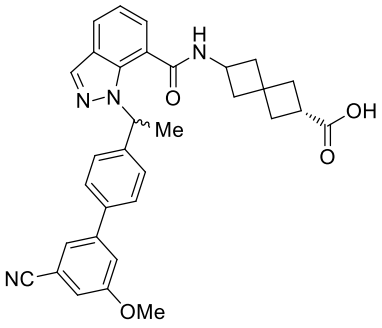
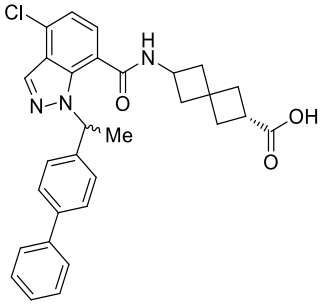
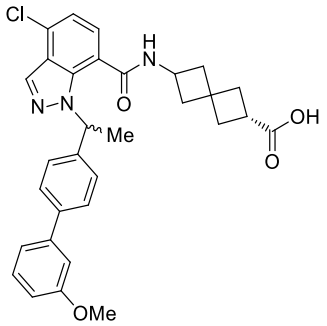
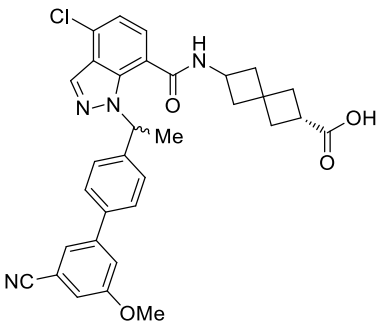
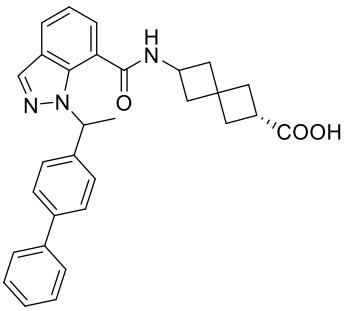
15. The compound of claim 1 having the Formula (Vb):

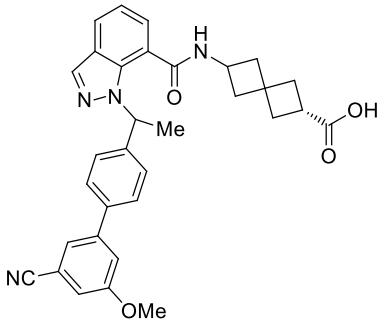
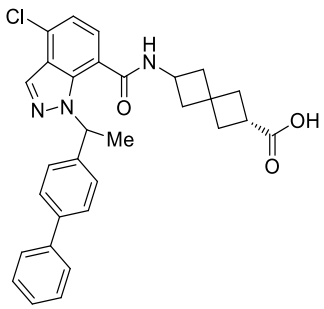
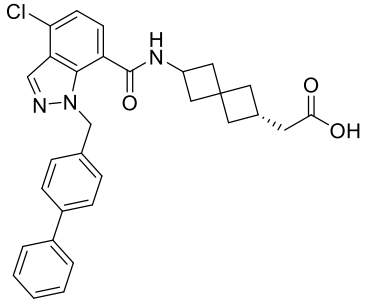
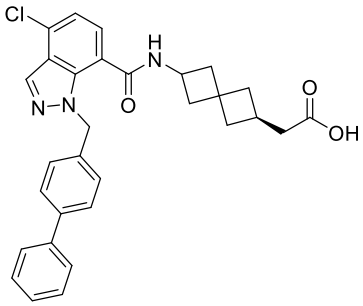
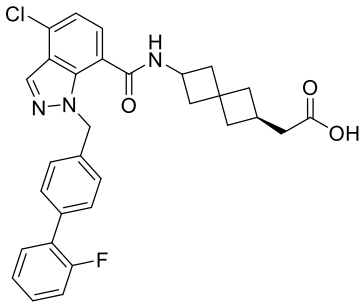
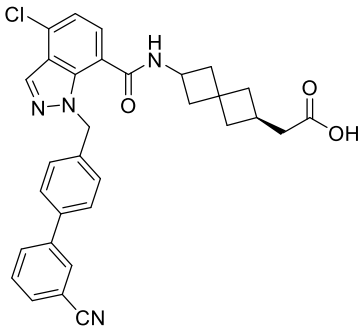
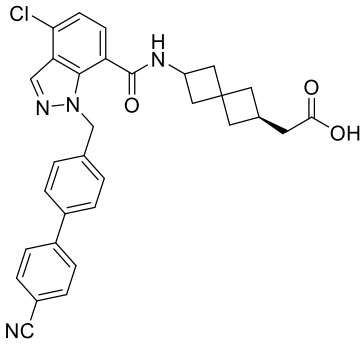
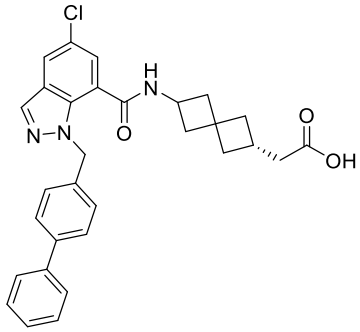
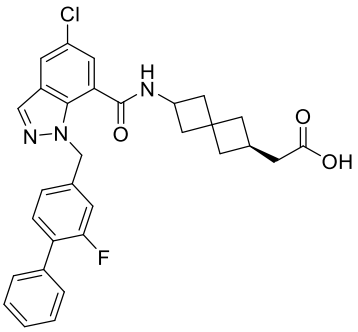
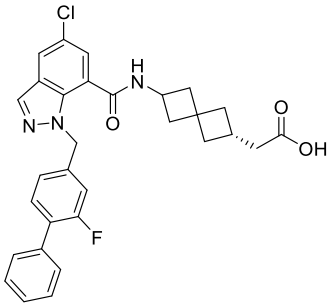
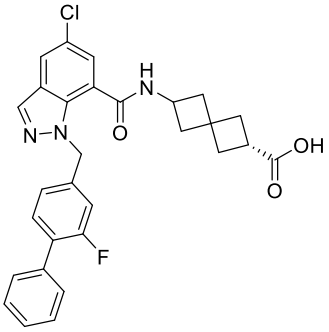
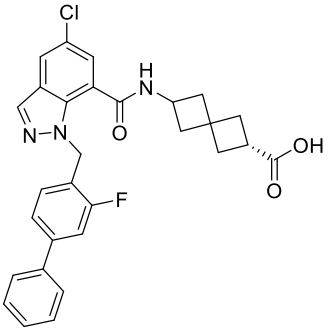
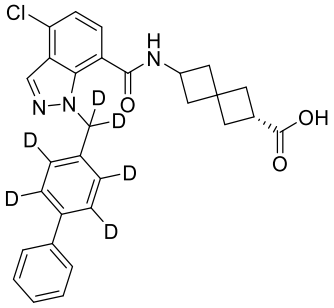
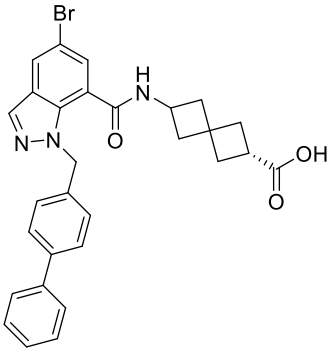
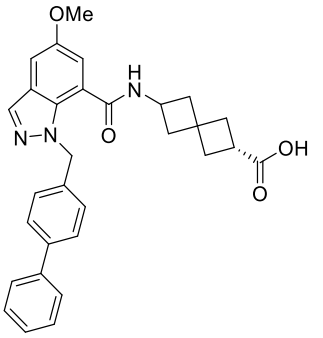


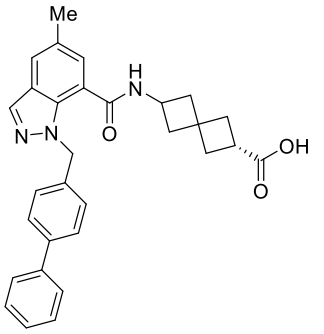
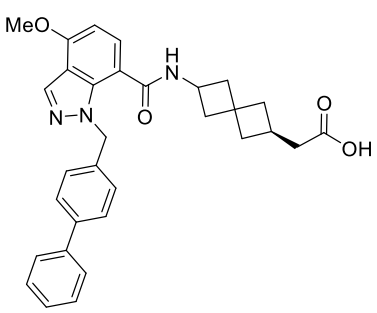
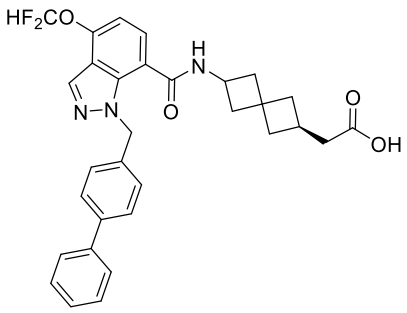
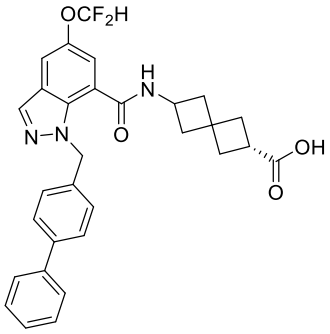
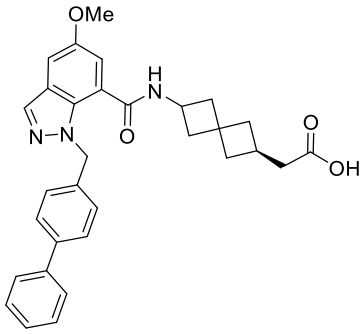
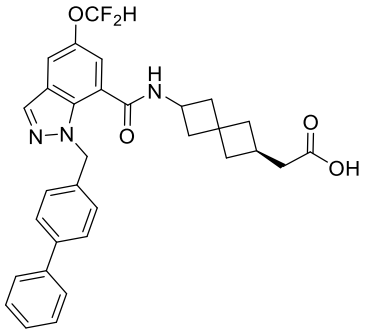
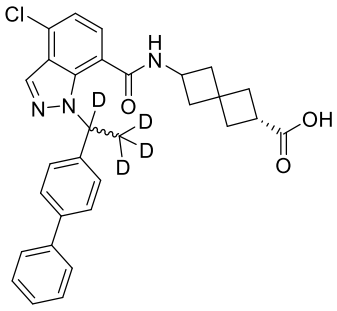
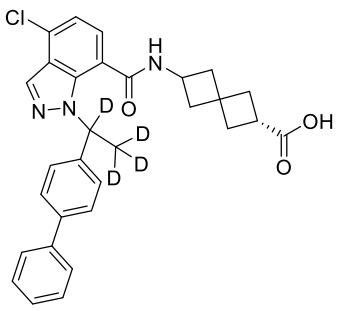
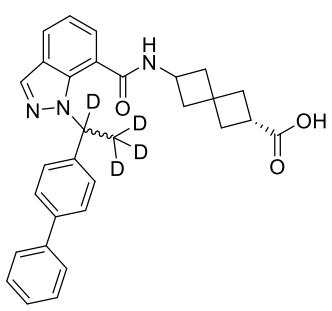
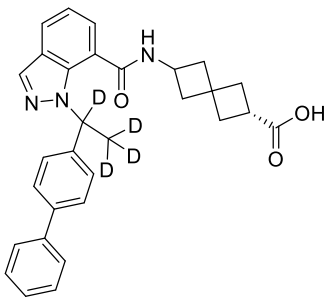
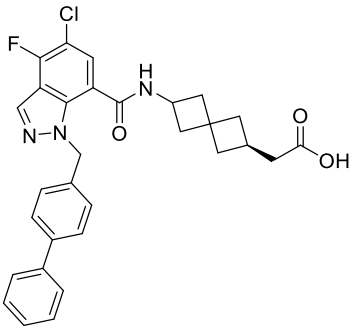
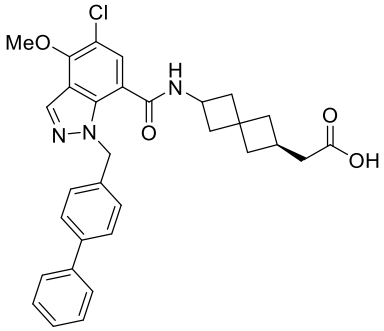
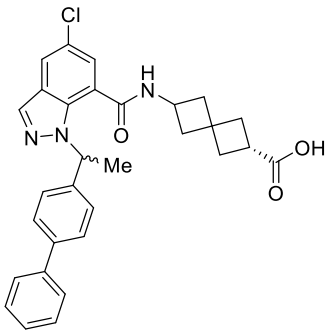
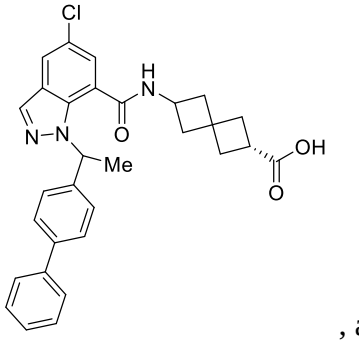
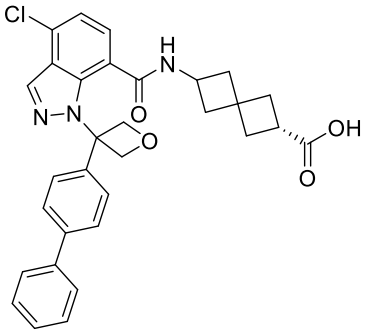
(Vb)

or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof; wherein p is 1 and R^1 is phenyl optionally substituted with one, two, or three R^y.

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


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or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof.

17. A pharmaceutical composition comprising the compound of claim 1, or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof, and a pharmaceutically acceptable carrier.

18. Use of the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant, or prodrug thereof of any one of claims 1 to 16, in the manufacture of a medicament for the treatment of an EP4-mediated cancer in a patient, wherein the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, isotopic variant or prodrug thereof is to be administered to a patient.

19. The use of claim 18, wherein the pharmaceutical composition of claim 17 is to be further administered to the patient.

20. The use of claim 18 or 19, wherein said EP4-mediated cancer is selected from glioblastoma, bone cancer, head and neck cancer, melanoma, basal cell carcinoma, squamous cell carcinoma, adenocarcinoma, oral cancer, esophageal cancer, gastric cancer, intestinal cancer, colon cancer, bladder cancer, hepatocellular carcinoma, renal cell carcinoma, pancreatic cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer and prostate cancer.

21. The use of claim 20, wherein said EP4-mediated cancer is selected from colon cancer, bladder cancer, hepatocellular carcinoma, pancreatic cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer, and prostate cancer.

22. The use of claim 18 or 19, wherein said EP4-mediated cancer is selected from colorectal cancer (CRC), lung cancer, squamous cell carcinoma of the head and neck (SCCHN), bladder cancer, endometrial cancer, and gastric cancer.

23. The use of claim 18 or 19, wherein said EP4-mediated cancer is colorectal cancer (CRC).

24. The compound of Formula (I), or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of

stereoisomers, isotopic variant, or prodrug thereof of any one of claims 1 to 16, or the pharmaceutical composition of claim 17 for use in therapy.