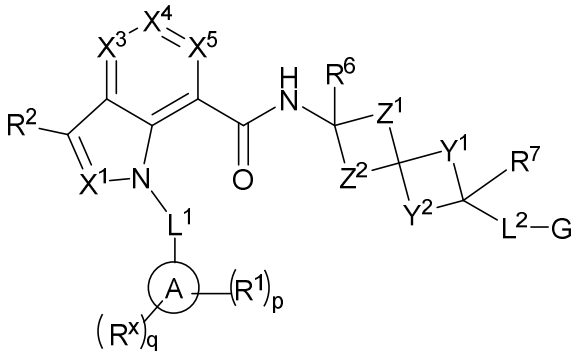
[00020] In another example, the present disclosure provides a method of treating arthritis or inflammatory pain in a patient comprising administering to the patient a compound or pharmaceutical composition as described herein.

[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, or isotopic variant 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;

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, or isotopic variant 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, or isotopic variant 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, or isotopic variant 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, or isotopic variant 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.

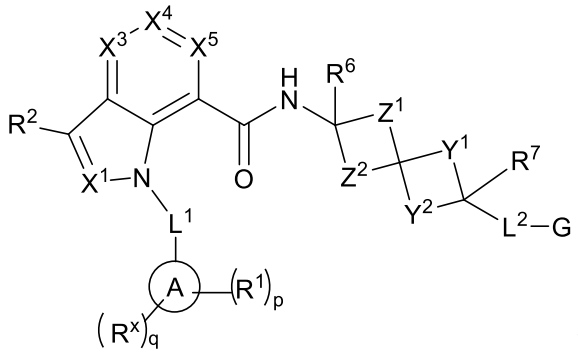
BRIEF DESCRIPTION OF THE DRAWINGS

[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

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, or isotopic variant 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;

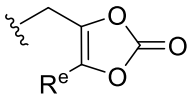
each R^{11} is independently alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl;

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, or isotopic variant 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, or isotopic variant 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

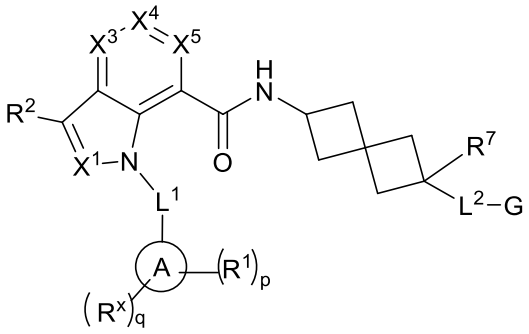
R^8 and R^9, together with the atom or atoms to which they are attached, form a heterocyclyl optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl;

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.

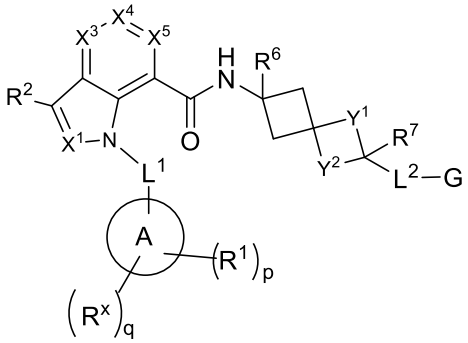
4. The compound of claim 3 having the Formula (II):



(II)

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

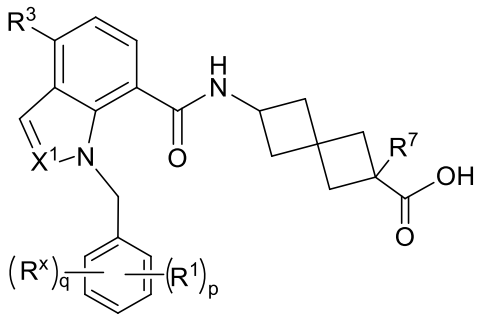
each R^{11} is independently alkyl, deuterated alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, alkyl, and haloalkyl.

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, or isotopic variant 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, or isotopic variant 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, or isotopic variant thereof, wherein q is 0 or 1.

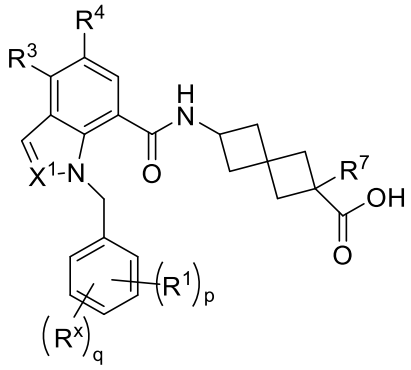
13. The compound of claim 1 having the Formula (V):



(V)

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

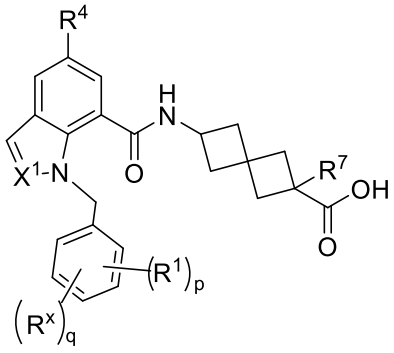
14. The compound of claim 1 having the Formula (Va):



(Va)

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

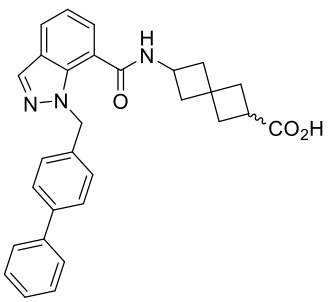
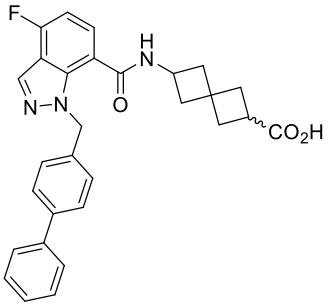
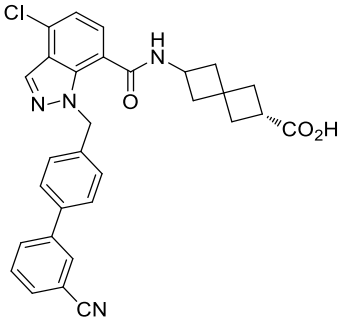
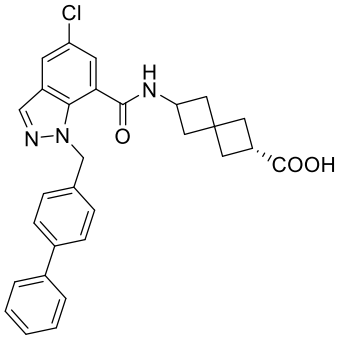
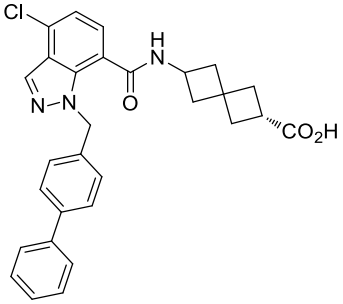
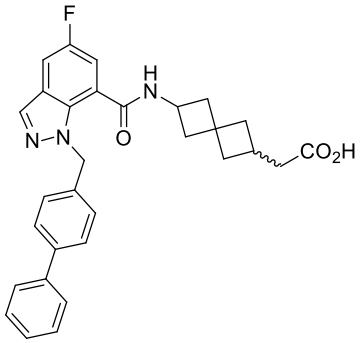
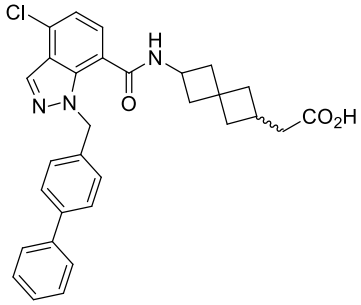
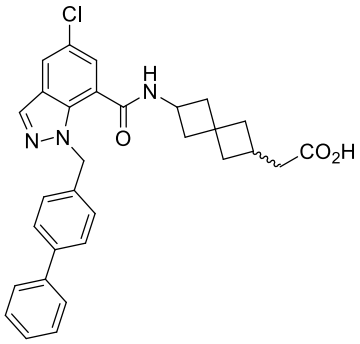
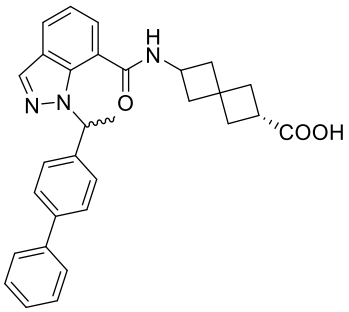
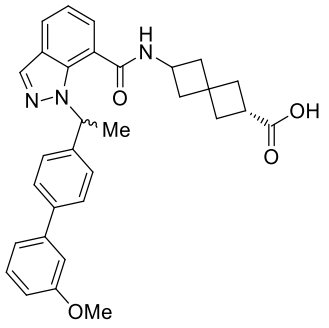
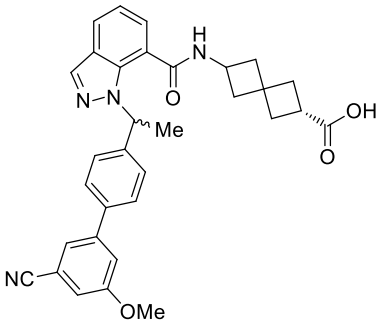
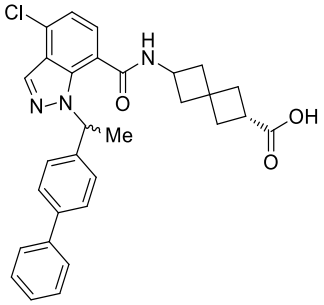
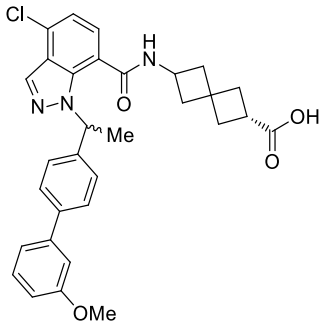
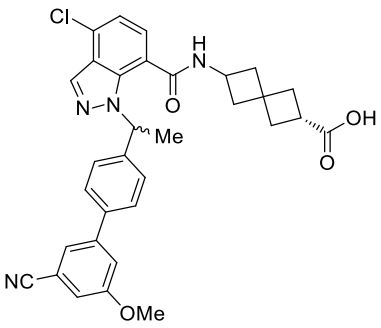
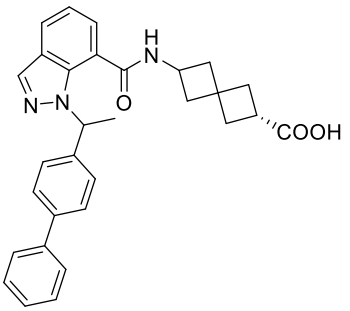
15. The compound of claim 1 having the Formula (Vb):

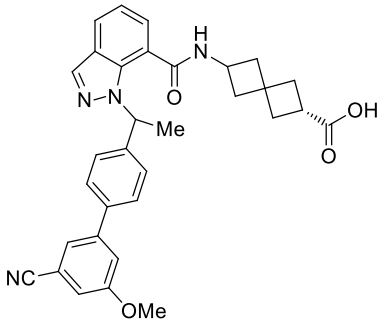
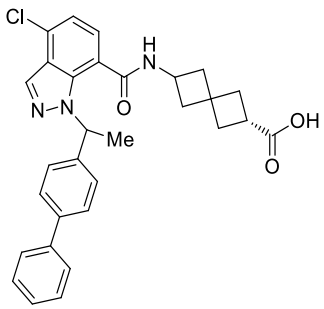
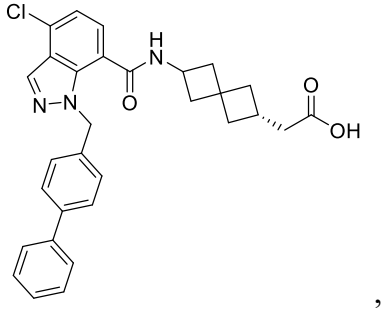
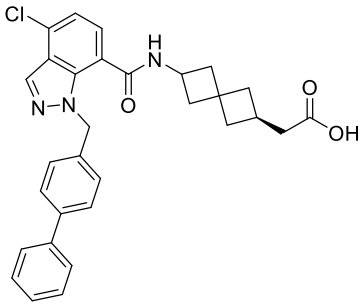
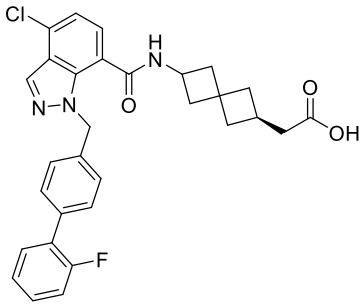
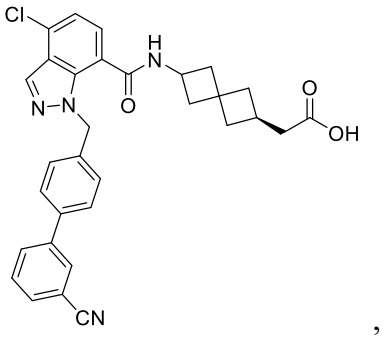
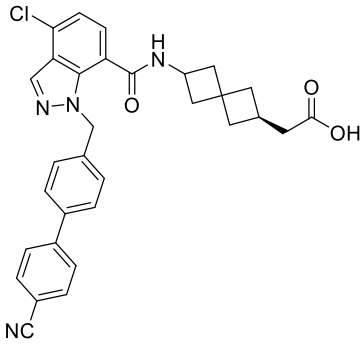
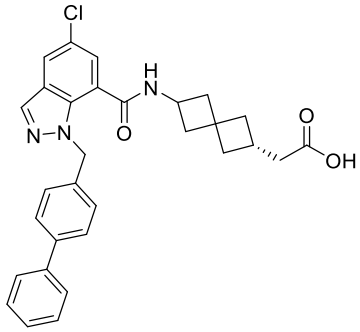
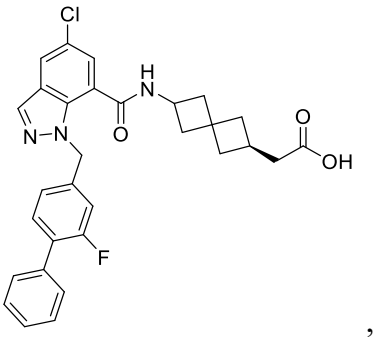
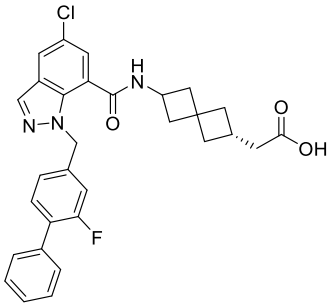
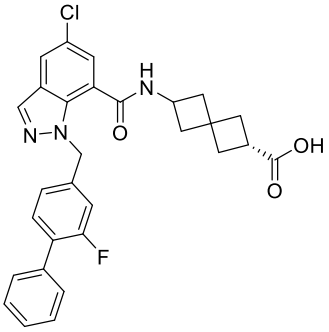
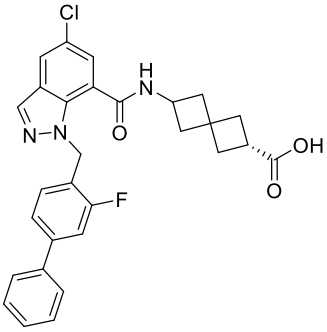
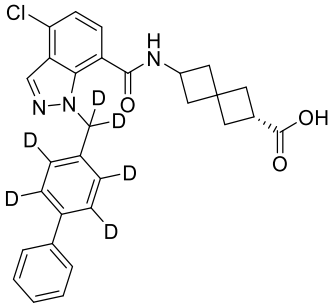
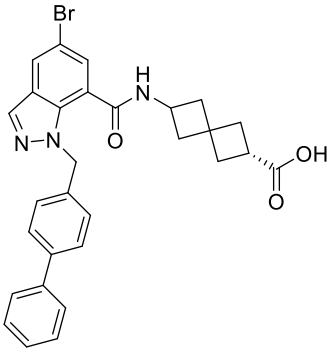
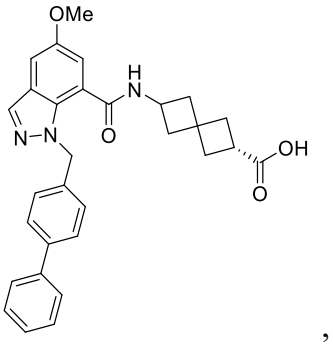


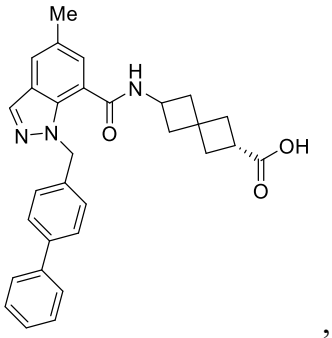
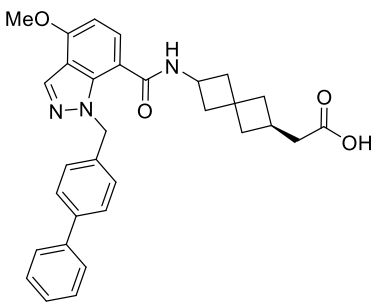
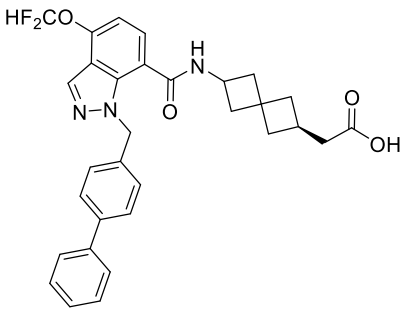
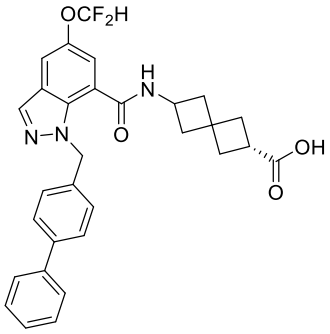
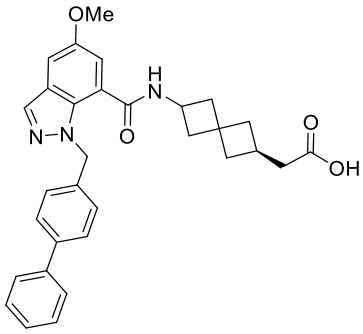
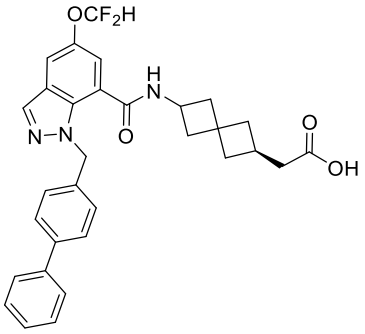
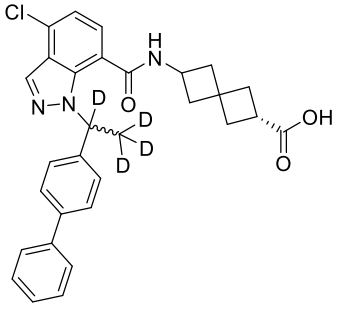
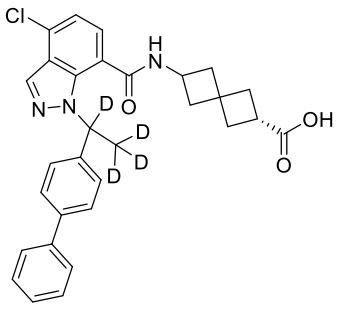
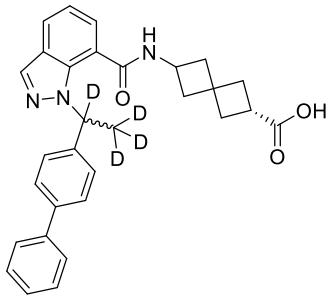
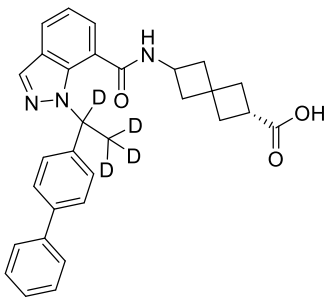
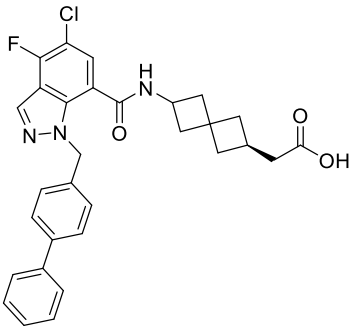
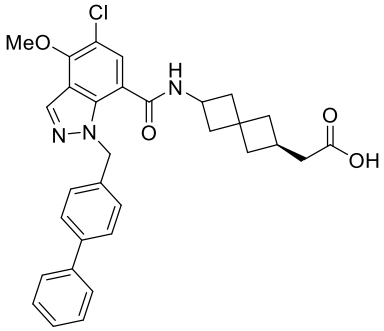
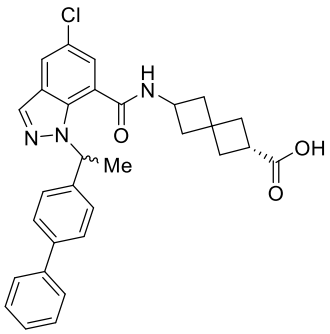
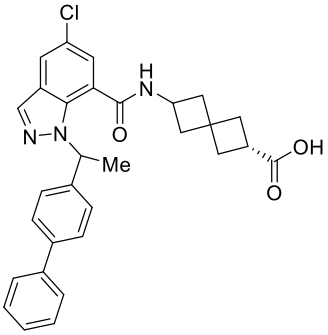
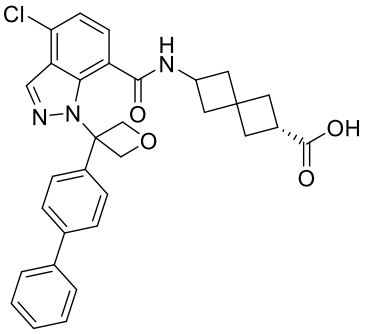
(Vb)

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

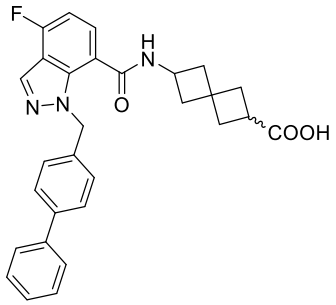
16. The compound of claim 1 wherein the compound is selected from:

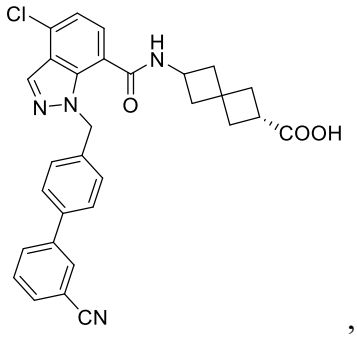

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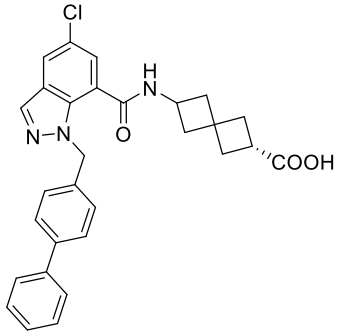

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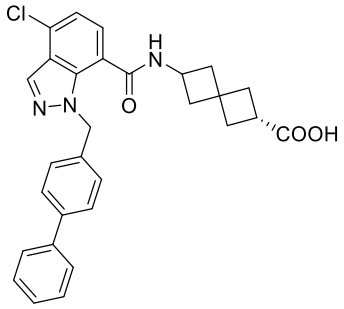

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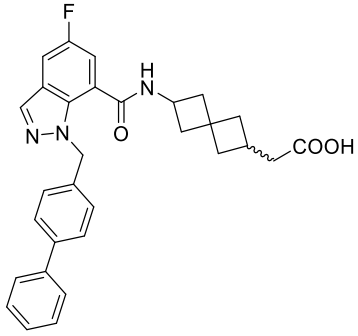
or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, or isotopic variant thereof.

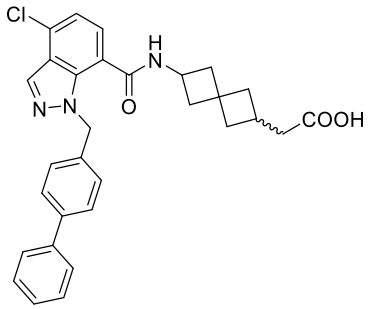
17. The compound of claim 16, wherein the compound is: , or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, or isotopic variant thereof.

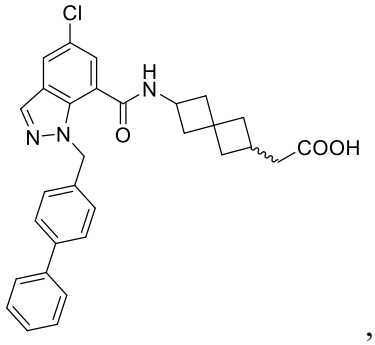
18. The compound of claim 16, wherein the compound is: , or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, or isotopic variant thereof.

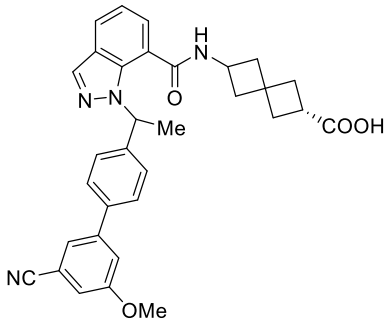
19. The compound of claim 16, wherein the compound is: , or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, or isotopic variant thereof.

20. The compound of claim 16, wherein the compound is: , or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, or isotopic variant thereof.

21. The compound of claim 16, wherein the compound is: , or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, or isotopic variant thereof.

22. The compound of claim 16, wherein the compound is: ,
or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, or isotopic variant thereof.

23. The compound of claim 16, wherein the compound is: ,
or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, or isotopic variant thereof.

24. The compound of claim 16, wherein the compound is: ,
or a pharmaceutically acceptable salt, solvate, solvate of the salt, hydrate, a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers, or isotopic variant thereof.

25. 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, or isotopic variant thereof, and a pharmaceutically acceptable carrier.

26. 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, or isotopic variant 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, or isotopic variant thereof is to be administered to a patient.

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

28. 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.

29. 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.

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

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

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