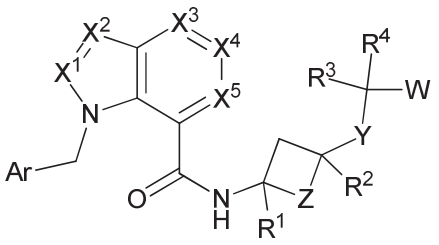
proliferation and activation of cyototoxic Teff cells, and kyneurenine, the product of the IDO and TDO enzymes, is essential for the proliferation and activation of immunosuppressive Treg cells (Dounay et al., J. Med. Chem. 2015, 58, p. 8762), inhibition of the IDO and/or TDO activity represents a promising avenue for the treatment of various cancers (Jochems et al., Oncotarget 2016, 7, p. 37762). In fact, increased overall response rate in patients with advanced stage IIIB or IV melanoma have been reported with epacadostat, a potent and selective IDO inhibitor from Incyte, when used in combination with pembrolizumab. In light of all these observations and studies, it is therefore reasonable that antagonism of EP4 would represent a rational and efficacious approach for the treatment of advanced cancer, both as a single agent and in combination with other anti-cancer therapies.

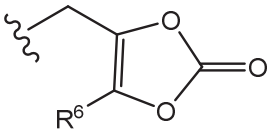
SUMMARY OF THE DISCLOSURE

[006] Some examples provided herein describe compounds of Formula I, which are potent and selective antagonists of the EP4 receptor, pharmaceutically acceptable salts of Formula I, pharmaceutically acceptable compositions comprising such compounds, and the use of such compounds in the treatment of various diseases that may be ameliorated with the blockade of PGE2-mediated signaling, in particular cancer. For the treatment of cancer, compounds of Formula I, in some instances, are used alone or in combination with other cancer therapies, for example, 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) or 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). Other examples provided herein describe processes for the preparation of the compounds of Formula I, as well as for the preparation of intermediates used in the synthesis of the compounds described herein.

[007] Some aspects provided herein describe compounds of Formula I:



I



wherein R^6 is C_1-C_6 alkyl;

R^7 is hydrogen or C_1-C_6 alkyl;

R^8 is C_1-C_6 alkyl or C_3-C_6 -cycloalkyl;

R^a is selected from: (a) H, (b) C_1-C_6 alkyl, (c) halogen, (d) aryl, (e) OR^b, (f) cyano, (g) heteroaryl, (h) C_3-C_6 cycloalkyl, and (i) C_1-C_6 haloalkyl;

$R^{a'}$ is selected from: (a) cyano, (b) C_1-C_6 alkyl, (c) halogen, (d) aryl, (e) OR^b, (f) heteroaryl, (g) C_3-C_6 cycloalkyl, and (h) C_1-C_6 haloalkyl;

R^b and R^c are independently selected from: (a) H, (b) C_1-C_6 alkyl, (c) aryl, (d) heteroaryl, (e) C_3-C_6 cycloalkyl, (f) C_2-C_6 heterocycle, or (g) C_1-C_6 haloalkyl; or

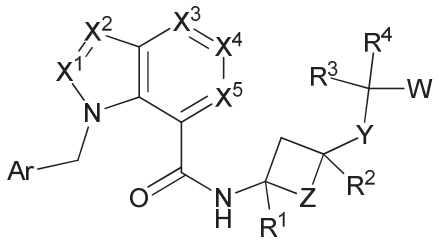
R^b and R^c taken together with the N to which they are both attached form a 3- to 6-membered heterocycle optionally having an additional heteroatom selected from N, O and S;

m is 0, 1, or 2;

n is 1, 2 or 3; and

p is 1, 2 or 3.

[008] Some aspects provided herein describe compounds of Formula I:



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;

wherein

Ar is an aryl or a heteroaryl, wherein said aryl and said heteroaryl are each optionally substituted with 1 to 3 substituents independently selected from: (a) C_1-C_6 alkyl, (b) C_3-C_7 cycloalkyl, (c) heterocycle, (d) aryl, (e) heteroaryl, (f) halogen, (g) CN, (h) OR^b, (i) $N(R^b)C(=O)R^c$, (j) $C(=O)N(R^b)(R^c)$, (k) $S(=O)_mR^b$, (l) $S(=O)_2N(R^b)(R^c)$, (m) $N(R^b)S(=O)_2R^c$, (n) SF_5, and (o) C_1-C_6 haloalkyl;

W is selected from: (a) $C(=O)OR^5$, (b) C(=O)NHOH, (c) $S(=O)_2NHR^b$, (d) $S(=O)_2NHC(=O)R^b$, (e) $NHC(=O)NHSO_2R^b$, (f) 1*H*-tetrazole, (g) 1,2,4-oxadiazol-

R^b and R^c are independently selected from: (a) H, (b) C_1-C_6 alkyl, (c) aryl, (d) heteroaryl, (e) C_3-C_6 cycloalkyl, or (f) C_1-C_6 haloalkyl; or

R^b and R^c taken together with the N to which they are both attached form a 3- to 6-membered heterocycle optionally having an additional heteroatom selected from N, O and S;

m is 0, 1, or 2;

n is 1, 2 or 3; and

p is 1, 2 or 3.

[009] In some examples, Ar is an aryl or a heteroaryl, wherein said aryl and said heteroaryl are each optionally substituted with 1 to 3 substituents independently selected from the group consisting of:

(a) C_1-C_6 alkyl,

(b) C_3-C_7 cycloalkyl,

(c) heterocycle,

(d) aryl,

(e) heteroaryl,

(f) halogen,

(g) CN,

(h) OR^b,

(i) $N(R^b)C(=O)R^c$,

(j) $C(=O)N(R^b)(R^c)$,

(k) $S(=O)_mR^b$,

(l) $S(=O)_2N(R^b)(R^c)$,

(m) $N(R^b)S(=O)_2R^c$,

(n) SF_5 and

(o) C_1-C_6 haloalkyl.

[0010] In some examples, W is selected from the group consisting of:

(a) CO_2H,

(b) C(=O)NHOH,

(c) $S(=O)_2NHR^b$,

(d) $S(=O)_2NHC(=O)R^b$,

(e) $NHC(=O)NHSO_2R^b$,

(f) 1*H*-tetrazole,

(g) 1,2,4-oxadiazol-5(4*H*)one,

(h) 1,2,4-thiadiazol-5(4*H*)one,

(i) 1,2,4-oxadiazole-5(4*H*)-thione,

(j) 1,2,4-triazole-5(4*H*)-one,

(k) tetrazol-5(4*H*)-one, and

(l) $C(=O)NHS(=O)_2R^b$.

[0011] In some examples, X^1, X^2, X^3, X^4, and X^5 are each independently N or CR^a, wherein not more than 2 of X^1, X^2, X^3, X^4, and X^5 are N.

[0012] In some examples, Y is selected from: (a) a bond, (b) $(CH_2)_n$ wherein 1 to 4 hydrogen atoms may be replaced by $R^{a'}$, (c) O, and (d) NR^b.

[0013] In some examples, Z is $(CH_2)_n$, wherein 1 to 4 hydrogen atoms may be replaced by $R^{a'}$.

[0014] In some examples, R^1 and R^2 are independently selected from:

(a) H,

(b) C_1-C_6 alkyl,

(c) C_3-C_6 cycloalkyl, and

(d) C_1-C_6 haloalkyl.

[0015] In some examples, R^1 and R^2 are not both H.

[0016] In some examples, R^1 and R^2 taken together represent $-(CH_2)_n-$, $-(CH_2)_nO(CH_2)_p-$, $-(CH_2)_nNR^b(CH_2)_p-$ or $-(CH_2)_nS(=O)_m(CH_2)_p-$.

[0017] In some examples, R^3 and R^4 are independently selected from the group consisting of:

(a) H,

(b) C_1-C_6 alkyl,

(c) C_3-C_6 cycloalkyl,

(d) aryl,

(e) heteroaryl,

(f) halogen, and

(g) C_1-C_6 haloalkyl.

[0018] In some examples, R^3 and R^4 taken together represent $-(CH_2)_n-$, $-(CH_2)_nO(CH_2)_p-$, $-(CH_2)_nNR^b(CH_2)_p-$ or $-(CH_2)_nS(=O)_m(CH_2)_p-$.

[0019] In some examples, R^3 and R^2 taken together represent $(CH_2)_n$, $(CH_2)_nO(CH_2)_p$, $(CH_2)_nNR^b(CH_2)_p$, or $(CH_2)_nS(=O)_m(CH_2)_p$.

[0020] In some examples, R^a is selected from the group consisting of:

(a) H,

(b) C_1-C_6 alkyl,

(c) halogen,

(d) aryl,

(e) OR^b,

(f) cyano,

(g) heteroaryl,

(h) C_3-C_6 cycloalkyl, and

(i) C_1-C_6 haloalkyl.

[0021] In some examples, $R^{a'}$ is selected from the group consisting of:

(a) cyano,

(b) C_1-C_6 alkyl,

(c) halogen,

(d) aryl,

(e) OR^b,

(f) heteroaryl,

(g) C_3-C_6 cycloalkyl, and

(h) C_1-C_6 haloalkyl.

[0022] In some examples, R^b and R^c are independently selected from the group consisting of:

(a) H,

(b) C_1-C_6 alkyl,

(c) aryl,

(d) heteroaryl,

(e) C_3-C_6 cycloalkyl, and

(f) C_1-C_6 haloalkyl.

[0023] In some examples, R^b and R^c taken together with the N to which they are both attached form a 3- to 6-membered heterocycle optionally having an additional heteroatom selected from N, O and S.

[0024] In some examples, m is 0, 1, or 2.

[0025] In some examples, n is 1, 2 or 3.

[0026] In some examples, p is 1, 2 or 3.

[0027] In some examples, Ar is phenyl optionally substituted with 1 to 3 substituents independently selected from:

(a) halogen,

(b) cyano,

(c) C_1-C_6 alkyl,

(d) SF_5,

(e) C_1-C_6 haloalkyl,

(f) OR^b wherein R^b is C_1-C_6 alkyl, aryl, heteroaryl, C_3-C_6 cycloalkyl or C_1-C_6 haloalkyl,

(g) heterocycle,

(h) aryl, and

(i) heteroaryl.

[0028] In some examples, Ar is phenyl optionally substituted with 1 to 3 substituents independently selected from:

(a) halogen,

(b) cyano,

(c) C_1-C_6 alkyl,

(d) SF_5, and

(e) C_1-C_6 haloalkyl.

[0029] In some examples, each of X^1, X^2, X^3, X^4 and X^5 is independently C-R^a. In some examples, one of X^1, X^2, X^3, X^4 and X^5 is N, and the others are each independently C-R^a. In some examples, each of X^1, X^2, X^3, X^4 and X^5 is independently C-R^a. In some examples, R^a is H or a halogen atom.

[0030] In some examples, W is selected from the group consisting of: (a) CO_2H and (b) 1*H*-tetrazole.

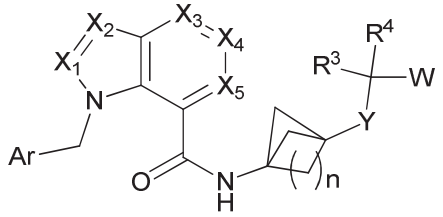
[0031] In some examples, Z is -CH_2-.

[0032] In some examples, Y is a bond or -CH_2-.

[0033] In some examples, R^1 and R^2 taken together represent -CH_2- or -CH_2CH_2-.

[0034] In some examples, Y is -CH_2-, and R^3 and R^2 taken together represent -CH_2- or -CH_2CH_2-.

[0035] Some examples provided herein describe a compound of Formula I having the structure of Formula Ia:



Ia

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.

[0036] In some examples, Ar is phenyl optionally substituted with 1 to 3 substituents independently selected from:

(a) halogen,

(b) cyano,

(c) C_1-C_6 alkyl,

(d) SF_5,

(e) C_1-C_6 haloalkyl,

(f) OR^b wherein R^b is C_1-C_6 alkyl, aryl, heteroaryl, C_3-C_6 cycloalkyl or C_1-C_6 haloalkyl,

(g) heterocycle,

(h) aryl, and

(i) heteroaryl.

[0037] In some examples, Ar is phenyl optionally substituted with 1 to 3 substituents independently selected from:

(a) halogen,

(b) cyano,

(c) C_1-C_6 alkyl,

(d) SF_5, and

(e) C_1-C_6 haloalkyl.

[0038] In some examples, each X^1, X^2, X^3, X^4 and X^5 is independently C-R^a. In some examples, one of X^1, X^2, X^3, X^4 and X^5 is N, and the others are each independently C-R^a.

[0039] In some examples, W is selected from the group consisting of: (a) CO_2H and (b) 1*H*-tetrazole.

[0040] In some examples, Y is a bond or -CH_2-.

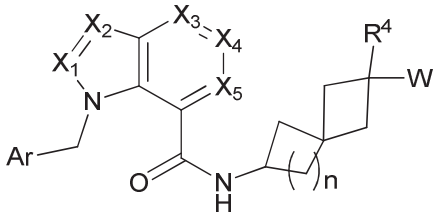
[0041] In some examples, n is 1 or 2.

[0042] In some examples, R^3 and R^4 are independently selected from the group consisting of: (a) H, (b) C_1-C_3 alkyl, and (c) C_1-C_3 haloalkyl.

[0043] In some examples, R^a is selected from the group consisting of H and halogen.

[0044] In some examples, Y is a bond, and n is 1.

[0045] Some examples provided herein describe a compound of Formula I having the structure of Formula Ib:



Ib

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.

[0046] In some examples, Ar is phenyl optionally substituted with 1 to 3 substituents independently selected from:

(a) halogen,

(b) cyano,

(c) C_1-C_6 alkyl,

(d) SF_5,

(e) C_1-C_6 haloalkyl,

(f) OR^b wherein R^b is C_1-C_6 alkyl, aryl, heteroaryl, C_3-C_6 cycloalkyl or C_1-C_6 haloalkyl,

(g) heterocycle,

(h) aryl, and

(i) heteroaryl.

[0047] In some examples, Ar is phenyl optionally substituted with 1 to 3 substituents independently selected from:

(a) halogen,

(b) cyano,

(c) C_1-C_6 alkyl,

(d) SF_5, and

(e) C_1-C_6 haloalkyl.

[0048] In some examples, each X^1, X^2, X^3, X^4 and X^5 is independently C-R^a, or one of X^1, X^2, X^3, X^4 and X^5 is N, and the others are each independently C-R^a.

[0049] In some examples, W is selected from the group consisting of: (a) CO_2H and (b) 1*H*-tetrazole.

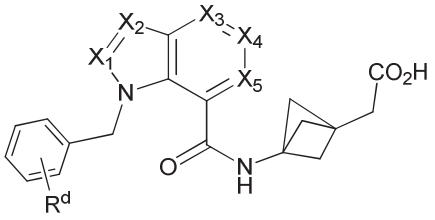
[0050] In some examples, n is 1 or 2.

[0051] In some examples, R^4 is selected from the group consisting of: (a) H, (b) C_1-C_3, and (c) C_1-C_3 haloalkyl.

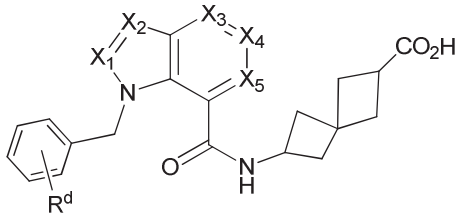
[0052] In some examples, R^a is selected from the group consisting of H and halogen.

[0053] In some examples, n is 1.

[0054] Some examples provided herein describe a compound of Formula I having the Formula Ic or Id:



Ic



Id

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.

[0055] In some examples, each X^1, X^2, X^3, X^4 and X^5 is independently C-R^a.

[0056] In some examples, one of X^1, X^2, X^3, X^4 and X^5 is N, and the others are each independently C-R^a.

[0057] In some examples, R^a is selected from the group consisting of H and halogen.

[0058] In some examples, R^d is selected from:

(a) CN,

(b) C_1-C_3 alkyl,

(c) SF_5,

(d) C_1-C_3 haloalkyl,

(e) OR^b wherein R^b is C_1-C_6 alkyl, aryl, heteroaryl, C_3-C_6 cycloalkyl or C_1-C_6 haloalkyl,

(f) heterocycle,

(g) aryl, and

(h) heteroaryl.

[0059] In some examples, R^d is selected from the group consisting of: (a) CN, (b) C_1-C_3 alkyl, (c) SF_5, and (d) C_1-C_3 haloalkyl.

[0060] In some examples, each X^1, X^2, X^3, X^4 and X^5 is CH; or one of X^1, X^2, X^3, X^4 and X^5 is C-R^a and the others are CH, and R^a is halogen.

[0061] In some examples, the compound is selected from:

2-(3-(1-(4-cyanobenzyl)-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl)acetic acid;

2-(3-(1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl)acetic acid;

6-(1-((4-(pentafluorothiol)phenyl)methyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*R*)-6-(1-((4-(pentafluorothiol)phenyl)methyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*S*)-6-(1-((4-(pentafluorothiol)phenyl)methyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

6-(1-(4-(difluoromethyl)benzyl)-4-fluoro-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*R*)-6-(1-(4-(difluoromethyl)benzyl)-4-fluoro-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*S*)-6-(1-(4-(difluoromethyl)benzyl)-4-fluoro-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

2-(3-(1-(4-(difluoromethyl)benzyl)-4-fluoro-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl)acetic acid;

2-(3-(5-fluoro-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl)acetic acid;

2-(3-(1-([1,1'-biphenyl]-4-ylmethyl)-1*H*-indole-7-carboxamido)bicyclo[1.1.1] pentan-1-yl)acetic acid;

2-(3-(1-([1,1'-biphenyl]-4-ylmethyl)-4-fluoro-1*H*-indole-7-carboxamido)bicyclo[1.1.1] pentan-1-yl)acetic acid;

2-(3-(1-([1,1'-biphenyl]-4-ylmethyl)-1*H*-indazole-7-carboxamido)bicyclo[1.1.1] pentan-1-yl)acetic acid;

2-(3-(1-(4-(trifluoromethoxy)benzyl)-1*H*-indazole-7-carboxamido)bicyclo[1.1.1] pentan-1-yl)acetic acid;

2-(3-(4-fluoro-1-(4-iodobenzyl)-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl) acetic acid;

2-(3-(4-fluoro-1-(4-(pyridine-4-yl)benzyl)-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl) acetic acid; and

2-(3-(4-fluoro-1-(4-morpholinobenzyl)-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl) acetic acid;

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.

[0062] Some examples provided herein describe pharmaceutical compositions comprising a compound of any of Formula I, Ia, Ib, Ic, or Id, 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 of any of the foregoing, and a pharmaceutically acceptable carrier.

[0063] Some examples provided herein describe methods for the treatment of cancer comprising administering to a patient in need thereof a compound of any of Formula I, Ia, Ib, Ic, or Id, 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 of any of the foregoing, or a pharmaceutical composition comprising any of Formula I, Ia, Ib, Ic, or Id, or a pharmaceutically acceptable salt of any of the foregoing.

[0063a] In one aspect, provided herein is the compound or the pharmaceutical composition as described herein for use in therapy.

[0063b] In one aspect, provided herein are uses of the compound or the pharmaceutical composition as described herein in the manufacture of a medicament of the treatment of cancer, wherein the medicament is to be administered to a patient in need thereof.

[0064] In some examples, the cancer is selected from the group consisting of 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.

[0065] In some examples, the treatment further comprises an additional agent selected from an anti-PD-1 antibody and an anti-PD-L1 antibody.

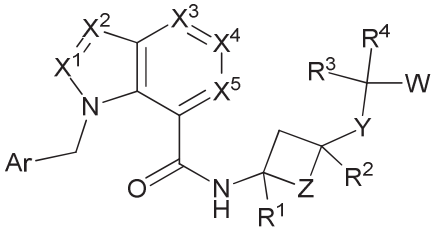
BRIEF DESCRIPTION OF THE DRAWINGS

[0066] FIGURES 1A and 1B illustrate the effect of Compound A on tumor volume in a murine colon cancer model.

DETAILED DESCRIPTION OF THE INVENTION

[0067] Provided herein in some embodiments are selective EP4 receptor antagonists and compositions comprising these compounds (i.e., the selective EP4 receptor antagonists). The compounds and compositions are useful for the treatment of cancer.

[0068] Some embodiments provided herein describe compounds of Formula I:



I

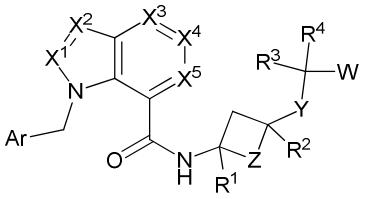
or a pharmaceutically acceptable salt, solvate, solvate of the salt, or prodrug thereof.

[0069] In certain embodiments, provided herein are compounds of Formula I:

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula I:



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, wherein:

Ar is an aryl or a heteroaryl, wherein said aryl and said heteroaryl are each optionally substituted with 1 to 3 substituents independently selected from:

(a) C_1-C_6 alkyl,

(b) C_3-C_7 cycloalkyl,

(c) heterocycle,

(d) aryl,

(e) heteroaryl,

(f) halogen,

(g) CN,

(h) OR^b,

(i) $N(R^b)C(=O)R^c$,

(j) $C(=O)N(R^b)(R^c)$,

(k) $S(=O)_mR^b$,

(l) $S(=O)_2N(R^b)(R^c)$,

(m) $N(R^b)S(=O)_2R^c$,

(n) SF_5; and

(o) C_1-C_6 haloalkyl

W is selected from:

(a) $C(=O)OR^5$,

(b) C(=O)NHOH,

(c) $S(=O)_2NHR^b$,

(d) $S(=O)_2NHC(=O)R^b$,

(e) $NHC(=O)NHSO_2R^b$,

(f) 1*H*-tetrazole,

(g) 1,2,4-oxadiazol-5(4*H*)one,

(h) 1,2,4-thiadiazol-5(4*H*)one,

(i) 1,2,4-oxadiazole-5(4*H*)-thione,

(j) 1,2,4-triazole-5(4*H*)-one,

(k) tetrazol-5(4*H*)-one, and

(l) $C(=O)NHS(=O)_2R^b$;

X^1, X^2, X^3, X^4, and X^5 are each independently N or CR^a, wherein not more than 2 of X^1, X^2, X^3, X^4, and X^5 are N;

Y is selected from:

(a) a bond,

(b) $(CH_2)_n$ wherein 1 to 4 hydrogen atoms may be replaced by $R^{a'}$,

(c) O, and

(d) NR^b;

Z is $(CH_2)_n$, wherein 1 to 4 hydrogen atoms may be replaced by $R^{a'}$;

R^1 and R^2 are independently selected from:

(a) H,

(b) C_1-C_6 alkyl,

(c) C_3-C_6 cycloalkyl, and

(d) C_1-C_6 haloalkyl;

wherein R^2 is not H; or

R^1 and R^2 taken together represent $-(CH_2)_n-$, $-(CH_2)_nO(CH_2)_p-$, $-(CH_2)_nNR^b(CH_2)_p-$ or $-(CH_2)_nS(=O)_m(CH_2)_p-$;

R^3 and R^4 are independently selected from:

(a) H,

(b) C_1-C_6 alkyl,

(c) C_3-C_6 cycloalkyl,

(d) aryl,

(e) heteroaryl,

(f) halogen,

(g) C_1-C_6 haloalkyl; or

R^3 and R^4 taken together represent $-(CH_2)_n-$, $-(CH_2)_nO(CH_2)_p-$, $-(CH_2)_nNR^b(CH_2)_p-$ or $-(CH_2)_nS(=O)_m(CH_2)_p-$;

or R^1, R^2, R^3 and R^4 above are selected as follows:

R^1 is selected from H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and C_1-C_6 haloalkyl;

R^3 and R^2 taken together represent $(CH_2)_n$, $(CH_2)_nO(CH_2)_p$, $(CH_2)_nNR^b(CH_2)_p$, or $(CH_2)_nS(=O)_m(CH_2)_p$; and

R^4 is selected from H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, heteroaryl, halogen and C_1-C_6 haloalkyl;

R^5 is selected from

(a) H,

(b) C_1-C_6 alkyl,

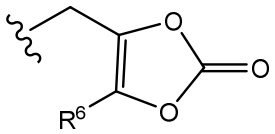
(c) aryl,

(d) aralkyl,

(e) $CH(R^7)OC(=O)R^8$,

(f) $CH(R^7)OC(=O)OR^8$, and

(g) a (5-alkyl-2-oxo-1,3-dioxolen-4-yl)methyl group having the following formula:



wherein R^6 is C_1-C_6 alkyl;

R^7 is hydrogen or C_1-C_6 alkyl;

R^8 is C_1-C_6 alkyl or C_3-C_6 -cycloalkyl;

R^a is selected from:

(a) H,

(b) C_1-C_6 alkyl,

(c) halogen,

(d) aryl,

(e) OR^b,

(f) cyano,

(g) heteroaryl,

(h) C_3-C_6 cycloalkyl, and

(i) C_1-C_6 haloalkyl;

$R^{a'}$ is selected from:

(a) cyano,

(b) C_1-C_6 alkyl,

(c) halogen,

(d) aryl,

(e) OR^b,

(f) heteroaryl,

(g) C_3-C_6 cycloalkyl, and

(h) C_1-C_6 haloalkyl;

R^b and R^c are independently selected from:

(a) H,

(b) C_1-C_6 alkyl,

(c) aryl,

(d) heteroaryl,

(e) C_3-C_6 cycloalkyl, and

(f) C_1-C_6 haloalkyl; or

R^b and R^c taken together with the N to which they are both attached form a 3- to 6-membered heterocycle optionally having an additional heteroatom selected from N, O and S;

m is 0, 1, or 2;

n is 1, 2 or 3; and

p is 1, 2 or 3.

2. A compound of Claim 1 wherein Ar is aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from:

(a) halogen,

(b) cyano,

(c) C_1-C_6 alkyl,

(d) SF_5,

(e) C_1-C_6 haloalkyl,

(f) OR^b wherein R^b is C_1-C_6 alkyl, aryl, heteroaryl, C_3-C_6 cycloalkyl or C_1-C_6 haloalkyl;

(g) heterocycle,

(h) aryl, and

(i) heteroaryl.

3. A compound of Claim 1 or Claim 2 wherein Ar is phenyl.

4. A compound any one of Claims 1 to 3 wherein each of X^1, X^2, X^3, X^4 and X^5 is independently C-R^a, or one of X^1, X^2, X^3, X^4 and X^5 is N, and the others are each independently C-R^a.

5. A compound of Claim 4 wherein each of X^1, X^2, X^3, X^4 and X^5 is independently C-R^a.

6. A compound of any of Claims 1 to 5 wherein R^a is H or a halogen atom.

7. A compound of any of Claims 1 to 6 wherein W is selected from the group consisting of:

(a) CO_2H; and

(b) 1*H*-tetrazole.

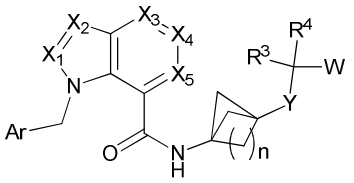
8. A compound of any of Claims 1 to 7 wherein Z is -CH_2-.

9. A compound of any of Claims 1 to 8 wherein Y is a bond or -CH_2-.

10. A compound of any of Claims 1 to 9 wherein R^1 and R^2 taken together represent -CH_2-, -CH_2CH_2- or -$CH_2CH_2CH_2$-.

11. A compound of any of Claims 1 to 8 wherein Y is -CH_2-, and R^3 and R^2 taken together represent -CH_2-, -CH_2CH_2- or -$CH_2CH_2CH_2$-.

12. A compound of Claim 1 having the Formula Ia:



Ia

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, wherein

Ar is phenyl optionally substituted with 1 to 3 substituents independently selected from:

(a) halogen,

(b) cyano,

(c) C_1-C_6 alkyl,

(d) SF_5,

(e) C_1-C_6 haloalkyl,

(f) OR^b wherein R^b is C_1-C_6 alkyl, aryl, heteroaryl, C_3-C_6 cycloalkyl or C_1-C_6 haloalkyl,

(g) heterocycle,

(h) aryl, and

(i) heteroaryl;

each X^1, X^2, X^3, X^4 and X^5 is independently C-R^a, or one of X^1, X^2, X^3, X^4 and X^5 is N, and the others are each independently C-R^a;

W is selected from:

(a) CO_2H and

(b) 1*H*-tetrazole;

Y is a bond or -CH_2-;

n is 1 or 2;

R^3 and R^4 are independently selected:

(a) H,

(b) C_1-C_3 alkyl, and

(c) C_1-C_3 haloalkyl;

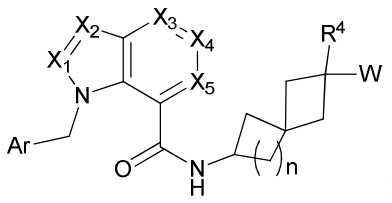
R^a is selected from:

(a) H and

(b) halogen.

13. A compound of any of Claims 1 to 12 wherein Y is a bond, and n is 1.

14. A compound of Claim 1 having the Formula Ib:



Ib

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, wherein

Ar is phenyl optionally substituted with 1 to 3 substituents independently selected from:

(a) halogen,

(b) cyano,

(c) C_1-C_6 alkyl,

(d) SF_5,

(e) C_1-C_6 haloalkyl,

(f) OR^b wherein R^b is C_1-C_6 alkyl, aryl, heteroaryl, C_3-C_6 cycloalkyl or C_1-C_6 haloalkyl,

(g) heterocycle,

(h) aryl, and

(i) heteroaryl;

each X^1, X^2, X^3, X^4 and X^5 is independently C-R^a, or one of X^1, X^2, X^3, X^4 and X^5 is N, and the others are each independently C-R^a;

W is selected from :

(a) CO_2H and

(b) 1*H*-tetrazole;

n is 1 or 2;

R^4 is selected from :

(a) H,

(b) C_1-C_3 alkyl, and

(c) C_1-C_3 haloalkyl;

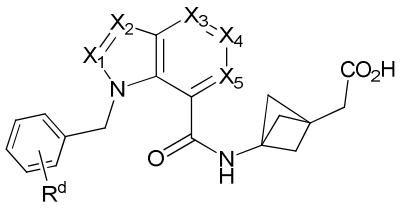
R^a is selected from :

(a)H and

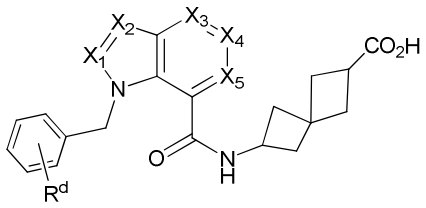
(b) halogen.

15. A compound of Claim 14 wherein n is 1.

16. A compound of Claim 1 having the Formula Ic or Id:



Ic



Id

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, wherein

each X^1, X^2, X^3, X^4 and X^5 is independently C-R^a, or one of X^1, X^2, X^3, X^4 and X^5 is N, and the others are each independently C-R^a;

R^a is selected from :

(a) H and

(b) halogen;

R^d is selected from :

(a) CN,

(b) C_1-C_3 alkyl,

(c) SF_5,

(d) C_1-C_3 haloalkyl,

(e) OR^b wherein R^b is C_1-C_6 alkyl, aryl, heteroaryl, C_3-C_6 cycloalkyl or C_1-C_6 haloalkyl,

(f) heterocycle,

(g) aryl, and

(h) heteroaryl.

17. A compound of any of Claims 1 to 16 wherein each X^1, X^2, X^3, X^4 and X^5 is CH; or one of X^1, X^2, X^3, X^4 and X^5 is C-R^a and the others are CH, and R^a is halogen.

18. A compound of Claim 1 selected from :

2-(3-(1-(4-cyanobenzyl)-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl)acetic acid;

2-(3-(1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl)acetic acid;

2-(3-(1-(4-(trifluoromethyl)benzyl)-1*H*-pyrrolo[3,2-*b*]pyridine-7-carboxamido)bicyclo[1.1.1]pentan-1-yl)acetic acid;

2-(3-(1-(4-(trifluoromethyl)benzyl)-1*H*-pyrrolo[3,2-*c*]pyridine-7-carboxamido)bicyclo[1.1.1]pentan-1-yl)acetic acid;

2-(3-(1-(4-(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-7-carboxamido)bicyclo[1.1.1]pentan-1-yl)acetic acid;

2-(3-(1-(4-(trifluoromethyl)benzyl)-1*H*-indazole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl)acetic acid;

2-(3-(1-((4-(trifluoromethyl)phenyl)methyl-d_2)-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl)acetic acid;

6-(1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*R*)-6-(1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*S*)-6-(1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

6-(1-(4-(trifluoromethyl)benzyl)-1*H*-pyrrolo[3,2-*b*]pyridine-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*R*)-6-(1-(4-(trifluoromethyl)benzyl)-1*H*-pyrrolo[3,2-*b*]pyridine-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*S*)-6-(1-(4-(trifluoromethyl)benzyl)-1*H*-pyrrolo[3,2-*b*]pyridine-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

6-(1-(4-(trifluoromethyl)benzyl)-1*H*-pyrrolo[3,2-*c*]pyridine-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*R*)-6-(1-(4-(trifluoromethyl)benzyl)-1*H*-pyrrolo[3,2-*c*]pyridine-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*S*)-6-(1-(4-(trifluoromethyl)benzyl)-1*H*-pyrrolo[3,2-*c*]pyridine-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

6-(1-(4-(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*R*)-6-(1-(4-(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*S*)-6-(1-(4-(trifluoromethyl)benzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

6-(1-(4-(trifluoromethyl)benzyl)-1*H*-indazole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*R*)-6-(1-(4-(trifluoromethyl)benzyl)-1*H*-indazole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*S*)-6-(1-(4-(trifluoromethyl)benzyl)-1*H*-indazole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

6-(1-(4-(trifluoromethyl)benzyl)-1*H*-benzo[*d*]imidazole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*R*)-6-(1-(4-(trifluoromethyl)benzyl)-1*H*-benzo[*d*]imidazole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*S*)-6-(1-(4-(trifluoromethyl)benzyl)-1*H*-benzo[*d*]imidazole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

3-(3-(1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl)propanoic acid;

3-(3-methyl-3-(1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)cyclobutyl)propanoic acid;

cis-3-(3-methyl-3-(1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)cyclobutyl)propanoic acid;

N-(3-(2-oxo-2-(phenylsulfonamido)ethyl)bicyclo[1.1.1]pentan-1-yl)-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamide;

N-(3-((3-(phenylsulfonyl)ureido)methyl)bicyclo[1.1.1]pentan-1-yl)-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamide;

N-(3-((1*H*-tetrazol-5-yl)methyl)bicyclo[1.1.1]pentan-1-yl)-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamide;

2-(4-(1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)bicyclo[2.1.1]hexan-1-yl)acetic acid;

6-(4-fluoro-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*R*)-6-(4-fluoro-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*S*)-6-(4-fluoro-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

6-(5-fluoro-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*R*)-6-(5-fluoro-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*S*)-6-(5-fluoro-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

6-(5-chloro-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;
(*R*)-6-(5-chloro-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;
(*S*)-6-(5-chloro-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;
6-(6-fluoro-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;
(*R*)-6-(6-fluoro-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;
(*S*)-6-(6-fluoro-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;
6-(1-(4-cyanobenzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;
(*R*)-6-(1-(4-cyanobenzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;
(*S*)-6-(1-(4-cyanobenzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;
6-(1-(4-(difluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;
(*R*)-6-(1-(4-(difluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;
(*S*)-6-(1-(4-(difluoromethyl)benzyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;
2-(4-(1-(4-(difluoromethyl)benzyl)-1*H*-indole-7-carboxamido)bicyclo[2.1.1]hexan-1-yl)acetic acid;
2-(3-(4-fluoro-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl)acetic acid;
2-(4-(4-fluoro-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)bicyclo[2.1.1]hexan-1-yl)acetic acid;
2-(4-(1-((4-(pentafluorothiol)phenyl)methyl)-1*H*-indole-7-carboxamido)bicyclo[2.1.1]hexan-1-yl)acetic acid;
6-(1-((4-(pentafluorothiol)phenyl)methyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;
(*R*)-6-(1-((4-(pentafluorothiol)phenyl)methyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;
(*S*)-6-(1-((4-(pentafluorothiol)phenyl)methyl)-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

6-(1-(4-(difluoromethyl)benzyl)-4-fluoro-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*R*)-6-(1-(4-(difluoromethyl)benzyl)-4-fluoro-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

(*S*)-6-(1-(4-(difluoromethyl)benzyl)-4-fluoro-1*H*-indole-7-carboxamido)spiro[3.3]heptane-2-carboxylic acid;

2-(3-(1-(4-(difluoromethyl)benzyl)-4-fluoro-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl)acetic acid;

2-(3-(5-fluoro-1-(4-(trifluoromethyl)benzyl)-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl)acetic acid;

2-(3-(1-([1,1'-biphenyl]-4-ylmethyl)-1*H*-indole-7-carboxamido)bicyclo[1.1.1] pentan-1-yl)acetic acid;

2-(3-(1-([1,1'-biphenyl]-4-ylmethyl)-4-fluoro-1*H*-indole-7-carboxamido)bicyclo[1.1.1] pentan-1-yl)acetic acid;

2-(3-(1-([1,1'-biphenyl]-4-ylmethyl)-1*H*-indazole-7-carboxamido)bicyclo[1.1.1] pentan-1-yl)acetic acid;

2-(3-(1-(4-(trifluoromethoxy)benzyl)-1*H*-indazole-7-carboxamido)bicyclo[1.1.1] pentan-1-yl)acetic acid;

2-(3-(4-fluoro-1-(4-iodobenzyl)-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl) acetic acid;

2-(3-(4-fluoro-1-(4-(pyridine-4-yl)benzyl)-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl) acetic acid; and

2-(3-(4-fluoro-1-(4-morpholinobenzyl)-1*H*-indole-7-carboxamido)bicyclo[1.1.1]pentan-1-yl) acetic acid;

or a pharmaceutically acceptable salt, solvate, solvate of the salt or prodrug thereof.

19. A pharmaceutical composition comprising a compound of any of Claims 1 to 18, 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, and a pharmaceutically acceptable carrier.

20. Use of a compound of any of Claims 1 to 18 or the pharmaceutical composition of Claim 19 in the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered to a patient in need thereof.

21. The use of Claim 20 wherein said 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.

22. The use of Claim 20 or Claim 21wherein said cancer is selected from colon cancer, bladder cancer, hepatocellular carcinoma, pancreatic cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer, and prostate cancer.

23. The use of any of Claims 20 to 22 wherein the medicament is to be further administered with an additional agent selected from an anti-PD-1 antibody and an anti-PD-L1 antibody.

24. A compound of any of Claims 1 to 18 or the pharmaceutical composition of Claim 19 for use in therapy.