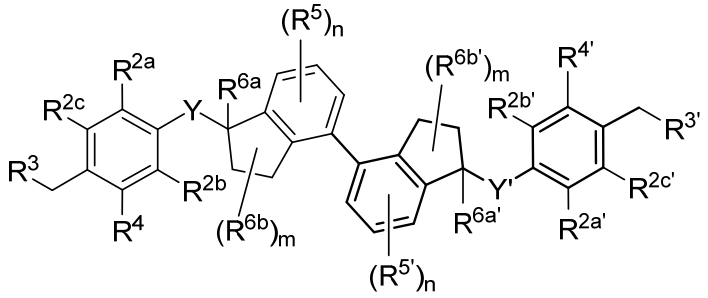
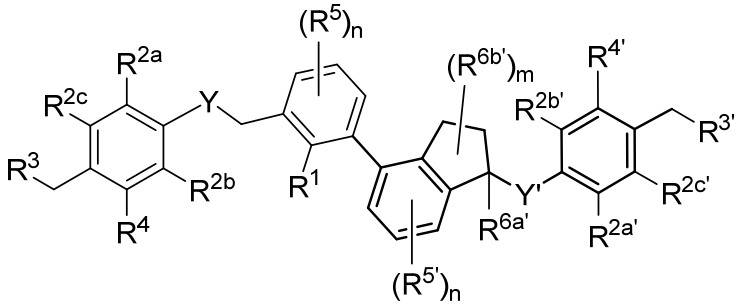
CLAIMS:

1. A compound represented by Formula (I) or Formula (II):



(I)



(II)

or a pharmaceutically acceptable salt, solvate, or hydrate thereof, wherein

Y and Y' are each independently selected from the group consisting of O, NH and N(C_{1-4} alkyl);

R^1 is independently selected from the group consisting of H, halogen, CN, C_{1-4} alkyl, C_{1-4} haloalkyl, –O-C_{1-4} alkyl and –O-C_{1-4} haloalkyl;

each R^{2a}, R^{2b}, R^{2c}, $R^{2a'}$, $R^{2b'}$ and $R^{2c'}$ is independently selected from the group consisting of H, halogen, -CN, -R^a, -CO_2R^b, -$CONR^bR^c$, -$OC(O)NR^bR^c$, -$NR^cC(O)R^b$, -$NR^cC(O)_2R^a$, -NR^b-$C(O)NR^bR^c$, -NR^bR^c, -OR^b, -X^1-OR^b, -X^1-NR^bR^c, -X^1-CO_2R^b, -SF_5, and -$S(O)_2NR^bR^c$, wherein each X^1 is a C_{1-4} alkylene; each R^b and R^c is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O and S, and optionally substituted with oxo; each R^a is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, and C_{1-8} haloalkyl;

R^3 and $R^{3'}$ are each independently selected from the group consisting of $-NR^dR^e$ and 4- to 12-membered monocyclic, bicyclic or spirocyclic non-aromatic heterocyclic ring, optionally substituted with 1 to 6 R^{3a}; wherein

R^d is selected from the group consisting of H, C_{1-8} haloalkyl and C_{1-8} alkyl;

R^e is selected from H, -C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, -X^2-CO_2R^g, -X^2-$CONR^gR^h$, and -X^2-$CONHSO_2R^g$, -X^2-$SO_2NR^gR^h$, -X^2-SO_3R^g, -X^2-$B(OH)_2$, -X^2-PO_3H_2, -X^2-C(O)NHOH, -X^2-NR^gR^h, -C(O)R^g, C_{3-10} cycloalkyl, -C_{3-10} cycloalkyl-$COOR^g$, -C_{3-10} cycloalkyl-OR^g, C_{4-8} heterocyclyl, -C_{4-8} heterocyclyl-$COOR^g$, -C_{4-8} heterocyclyl-OR^g, -X^2-C_{4-8} heterocyclyl, -C(=O)O-X^2-C_{4-8} heterocyclyl, -X^2-C_{3-10} cycloalkyl, C_{5-10} heteroaryl, -X^2-C_{5-10} heteroaryl, -X^2-C_{6-10} aryl, -X^2- (C=O)-C_{6-10} aryl, -CO_2-X^2-O_2C-C_{1-8} alkyl, -X^2-NH(C=O)-C_{2-8} alkenyl , -X^2-NH(C=O)-C_{1-8} alkyl, -X^2-NH(C=O)-C_{2-8} alkynyl, -X^2- (C=O)-NH-X^2-$COOR^g$, and -X^2-(C=O)-NH-X^2-OR^g optionally substituted with CO_2H; wherein the alkyl or alkylene portions of R^e are optionally further substituted with from 1 to 3 substituents independently selected from OH, COOH, SO_2NH_2, $CONH_2$, C(O)NHOH, COO-C_{1-8} alkyl, and PO_3H_2; the C_{5-10} heteroaryl and the C_{6-10} aryl portions of R^e are optionally substituted with 1 to 3 substituents independently selected from OH, $B(OH)_2$, COOH, NH_2, SO_2NH_2, $CONH_2$, C(O)NHOH, PO_3H_2, COO-C_{1-8}alkyl, C_{1-4}alkyl, C_{1-4}alkylene-OH, C_{1-4}alkylene-SO_2NH_2, C_{1-4}alkylene $CONH_2$, C_{1-4}alkylene-C(O)NHOH, C_{1-4}alkylene- PO_3H_2, and C_{1-4}alkylene-COOH; and the C_{4-8} heterocyclyl and C_{3-10} cycloalkyl portions of R^e are optionally substituted with 1 to 4 R^w substituents;

or

R^e combined with the N to which it is attached is a mono-amino acid, di- or tri-peptide comprising natural amino acids and non-natural amino acids, wherein the non-natural amino acids have an alpha carbon substituent selected from the group consisting of C_{2-4} hydroxyalkyl, C_{1-3} alkyl-guanidinyl, and C_{1-4} alkyl-heteroaryl, and wherein the alpha carbon of each natural or non-natural amino acid is optionally further substituted with a methyl group, and the terminal moiety of the

mono-, di-, or tri-peptide is selected from the group consisting of C(O)OH, C(O)O-C_{1-6} alkyl, $C(O)NH_2$ and PO_3H_2;

each R^{3a} is independently selected from the group consisting of halogen, -CN, oxo, -R^f, -CO_2R^g, -$CONR^gR^h$, -$CONHC_{1-6}$ alkyl-OH, -$C(O)R^g$, -$OC(O)R^g$, -$OC(O)NR^gR^h$, -$NR^gC(O)R^h$, -$NR^gC(O)_2R^h$, -CONHOH, -PO_3H_2, -NR^g-X^2-$C(O)_2R^h$, -$NR^gC(O)NR^gR^h$, -NR^gR^h, -OR^g, -$S(O)_2NR^gR^h$, -O-X^2-OR^g, -O-X^2-NR^gR^h, -O-X^2-CO_2R^g, -O-X^2-$CONR^gR^h$, -X^2-OR^g, -X^2-NR^gR^h, -X^2-CO_2R^g, -X^2-$CONR^gR^h$, -X^2- $CONHSO_2R^g$ and SF_5; wherein X^2 is C_{1-6} alkylene and is optionally further substituted with OH, NH_2, SO_2NH_2, $CONH_2$, C(O)NHOH, PO_3H_2, COO-C_{1-8}alkyl or CO_2H, wherein each R^g and R^h is independently selected from hydrogen, C_{1-8} alkyl optionally substituted with 1 to 2 substituents selected from OH, NH_2, SO_2NH_2, $CONH_2$, C(O)NHOH, PO_3H_2, COO-C_{1-8}alkyl and CO_2H, and C_{1-8} haloalkyl optionally substituted with 1 to 2 substituents selected from OH, NH_2, SO_2NH_2, $CONH_2$, C(O)NHOH, PO_3H_2, COO-C_{1-8}alkyl and CO_2H, or when attached to the same nitrogen atom R^g and R^h can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and optionally substituted with oxo; each R^f is independently selected from the group consisting of –OH, C_{1-8} alkyl, C_{2-8} alkenyl, and C_{1-8} haloalkyl each of which may be optionally substituted with OH, NH_2, SO_2NH_2, $CONH_2$, C(O)NHOH, PO_3H_2, COO-C_{1-8}alkyl or CO_2H;

each R^w substituent is independently selected from C_{1-4} alkyl, C_{1-4} alkylene-OH, C_{1-4} alkylene-COOH, C_{1-4} alkylene-SO_2NH_2, C_{1-4} alkylene-$CONH_2$, C_{1-4} alkylene-C(O)NHOH, C_{1-4} alkylene-PO_3H, OH, COO-C_{1-8} alkyl, COOH, SO_2NH_2, $CONH_2$, C(O)NHOH, PO_3H_2 and oxo;

R^4 and $R^{4'}$ are each independently selected from the group consisting of O-C_{1-8} alkyl, O-C_{1-8} haloalkyl, C_{6-10} aryl, C_{5-10} heteroaryl, -O-C_{1-4} alkyl-C_{4-7} heterocycloalkyl, -O-C_{1-4} alkyl-C_{6-10}aryl and -O-C_{1-4} alkyl-C_{5-10} heteroaryl, each of which is optionally substituted with 1 to 5 R^{4a};

each R^{4a} is independently selected from the group consisting of halogen, -CN, -R^i, -CO_2R^j, -$CONR^jR^k$, -$C(O)R^j$, -$OC(O)NR^jR^k$, -$NR^jC(O)R^k$, -$NR^jC(O)_2R^i$, -NR^j-$C(O)NR^jR^k$, -NR^jR^k, and -OR^j; wherein

each R^i is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, and C_{1-8} haloalkyl; and optionally when two R^{4a} substituents are on adjacent atoms, they are combined to form a fused five or six-membered carbocyclic or heterocyclic ring optionally substituted with oxo;

each R^j and R^k is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and optionally substituted with oxo;

each n is independently 0, 1, 2 or 3;

each R^5 and $R^{5'}$ is independently selected from the group consisting of halogen, -CN, -R^q, -CO_2R^r, -$CONR^rR^s$, -$C(O)R^r$, -NR^rR^s, and -OR^r, wherein

each R^r and R^s is independently selected from hydrogen, C_{1-4} alkyl, and C_{1-4} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and optionally substituted with oxo; each R^q is independently selected from the group consisting of C_{1-8} alkyl, and C_{1-8} haloalkyl;

R^{6a} and $R^{6a'}$ are each independently selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl;

each m is independently 0, 1, 2, 3 or 4;

each R^{6b} and $R^{6b'}$ is independently selected from the group consisting of F, C_{1-4} alkyl, and C_{1-4} haloalkyl.

2. A compound of claim **1**, wherein said compound is represented by Formula (I).

3. A compound of claim **1**, wherein said compound is represented by Formula (II).

4. A compound of claim **1**, wherein Y and Y' are each independently selected from the group consisting of O and NH.

5. A compound of claim **1**, wherein Y and Y' are each O.

6. A compound of any one of claims **2** or **3**, wherein each subscript m is independently 0 or 1 and each subscript n is independently 0 or 1.

7. A compound of any one of claims **2** or **3**, wherein each R^3 and $R^{3'}$ is independently a 4- to 9-membered monocyclic or spirocyclic non-aromatic heterocyclic ring, optionally substituted with 1 to 4 R^{3a}.

8. A compound of any one of claims **2** or **3**, wherein each R^3 and $R^{3'}$ is independently $-NR^dR^e$.

9. A compound of any one of claims **2** or **3**, wherein R^3 and $R^{3'}$ are each $-NR^dR^e$ and R^e combined with the N to which it is attached is a natural or non-natural amino acid, wherein the non-natural amino acids have an alpha carbon substituent selected from the group consisting of C_{2-4} hydroxyalkyl and C_{1-3} alkyl-guanidinyl, and wherein the alpha carbon of each natural or non-natural amino acid is optionally further substituted with a methyl group, and the terminal moiety is selected from the group consisting of C(O)OH, C(O)O-C_{1-6} alkyl, and $C(O)NH_2$.

10. A compound of any one of claims **2** or **3**, wherein R^3 and $R^{3'}$ are each $-NR^dR^e$ and R^e combined with the N to which it is attached is a natural or non-natural amino acid, wherein the non-natural amino acids have a C_{2-4} hydroxyalkyl alpha carbon wherein the alpha carbon of each natural or non-natural amino acid is further substituted with a methyl group, and the terminal moiety is selected from the group consisting of C(O)OH, C(O)O-C_{1-4} alkyl, and $C(O)NH_2$.

11. A compound of any one of claims **2** or **3**, wherein each R^{2a}, R^{2b}, R^{2c}, $R^{2a'}$, $R^{2b'}$ and $R^{2c'}$ is independently selected from the group consisting of H, halogen, -CN, -R^a, -CO_2R^b, -$CONR^bR^c$, -NR^bR^c, and -OR^b; wherein each R^b and R^c is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O and S, and optionally substituted with oxo; each R^a is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, and C_{1-8} haloalkyl.

12. A compound of claim **3**, wherein R^1 is H, halogen, CN or C_{1-4} alkyl.

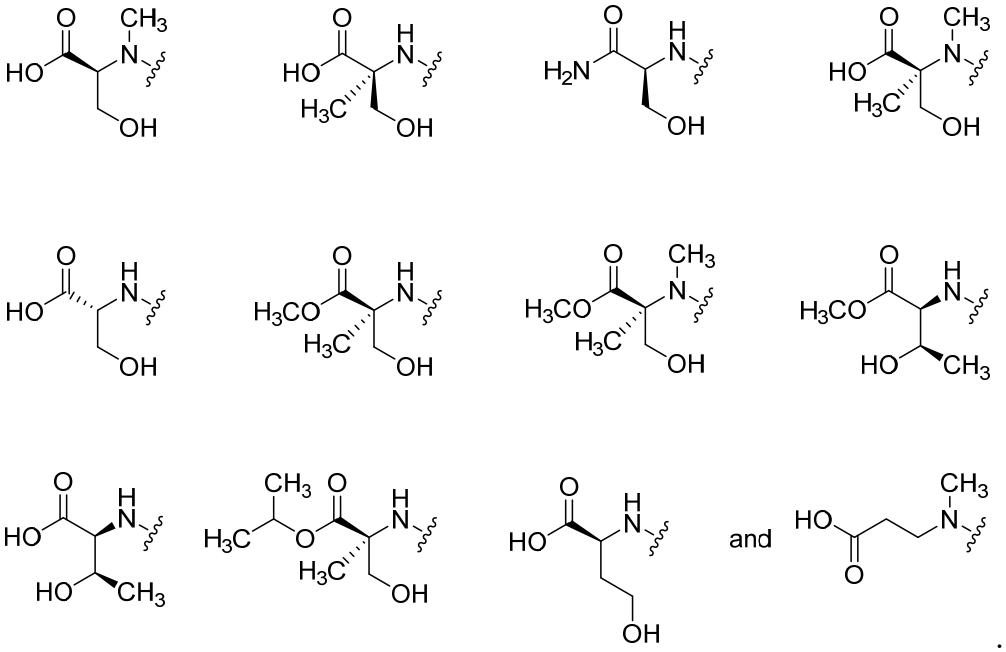
13. A compound of any one of claims **2** or **3**, wherein each R^4 and $R^{4'}$ is independently selected from the group consisting of O-C_{1-8} alkyl, O-C_{1-8} haloalkyl, -O-C_{1-4} alkyl-C_{6-10}aryl and -O-C_{1-4} alkyl-C_{5-10} heteroaryl, each of which is optionally substituted with 1 to 5 R^{4a}.

14. A compound of any one of claims **2** or **3**, wherein each R^4 and $R^{4'}$ is independently selected from the group consisting of O-C_{1-8} alkyl, -O-C_{1-4} alkyl-phenyl and -O-C_{1-4} alkyl-pyridyl, each of which is optionally substituted with 1 to 3 R^{4a}.

15. A compound of any one of claims **2** or **3**, wherein each R^{2a}, R^{2b}, R^{2c}, $R^{2a'}$, $R^{2b'}$ and $R^{2c'}$ is independently selected from the group consisting of H, halogen, -CN, -R^a, -CO_2R^b, -$CONR^bR^c$, -NR^bR^c, and -OR^b; wherein each R^b and R^c is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O and S, and optionally substituted with oxo; each R^a is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, and C_{1-8} haloalkyl; each R^3 is –NR^dR^e and R^e combined with the N to which it is attached is a natural or non-natural amino acid, wherein the non-natural amino acids have an

alpha carbon substituent selected from the group consisting of C_{2-4} hydroxyalkyl and C_{1-3} alkyl-guanidinyl, and wherein the alpha carbon of each natural or non-natural amino acid is optionally further substituted with a methyl group, and the terminal moiety is selected from the group consisting of C(O)OH, C(O)O-C_{1-6} alkyl, and $C(O)NH_2$; and each R^4 is selected from the group consisting of O-C_{1-8} alkyl, -O-C_{1-4} alkyl-phenyl and -O-C_{1-4} alkyl-pyridyl, each of which is optionally substituted with 1 to 3 R^{4a}.

16. A compound of claim **1** or claim **15**, wherein each R^3 and $R^{3'}$ is independently selected from the group consisting of



.

17. A compound of claim **1**, selected from the compounds of Table 1 having ++ or +++ activity.

18. A compound of any one of claims **1** to **17**, or a pharmaceutically acceptable salt thereof, wherein the compound is an optically pure or enriched isomer.

19. A pharmaceutical composition comprising a compound of any one of claims **1** to **18**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

20. Use of a compound of any one of claims **1** to **18**, or a pharmaceutically acceptable salt thereof or a composition of claim **19**in the preparation of a medicament for inhibiting growth, proliferation, or metastasis of cancer cells in a subject.

21. Use of a compound of any one of claims **1** to **18**, or a pharmaceutically acceptable salt thereof or a composition of claim **19**in the preparation of a medicament for treating a subject suffering from or susceptible to a disease or disorder mediated by the PD-1 signaling pathway.

22. The use of any one of claims **20** to **21**, wherein the subject suffers from a disease or disorder selected from the group consisting of an infectious disease, a bacterial infectious disease, a viral infectious disease a fungal infectious disease, a solid tumor, a hematological malignancy, an immune disorder, an inflammatory disease, and cancer.

23. The use of claim **21**, wherein the disease or disorder is selected from the group consisting of melanoma, glioblastoma, esophagus tumor, nasopharyngeal carcinoma, uveal melanoma, lymphoma, lymphocytic lymphoma, primary CNS lymphoma, T-cell lymphoma, diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, prostate cancer, castration-resistant prostate cancer, chronic myelocytic leukemia, Kaposi's sarcoma fibrosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma, lymphangiosarcoma, synovioma, , meningioma, leiomyosarcoma, rhabdomyosarcoma, sarcoma of soft tissue, sarcoma, sepsis, biliary tumor, basal cell carcinoma, thymus neoplasm, cancer of the thyroid gland, cancer of the parathyroid gland, uterine cancer, cancer of the adrenal gland, liver infection, Merkel cell carcinoma, nerve tumor, follicle center lymphoma, colon cancer, Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, multiple myeloma, ovary tumor, myelodysplastic syndrome, cutaneous or intraocular malignant melanoma, renal cell carcinoma, small-cell lung cancer, lung cancer, mesothelioma, breast cancer, squamous non-small cell lung cancer (SCLC), non-squamous NSCLC, colorectal cancer, ovarian cancer, gastric cancer, hepatocellular carcinoma, pancreatic carcinoma, pancreatic cancer,

Pancreatic ductal adenocarcinoma, squamous cell carcinoma of the head and neck, cancer of the head or neck, gastrointestinal tract, stomach cancer, HIV, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, herpes viruses, papillomaviruses, influenza, bone cancer, skin cancer, rectal cancer, cancer of the anal region, testicular cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the urethra, cancer of the penis, cancer of the bladder, cancer of the kidney, cancer of the ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, epidermoid cancer, abestosis, carcinoma, adenocarcinoma, papillary carcinoma, cystadenocarcinoma, bronchogenic carcinoma, renal cell carcinoma, transitional cell carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, wilm's tumor, pleomorphic adenoma, liver cell papilloma, renal tubular adenoma, cystadenoma, papilloma, adenoma, leiomyoma, rhabdomyoma, hemangioma, lymphangioma, osteoma, chondroma, lipoma and fibroma.