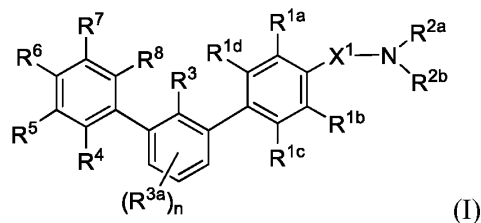


WHAT IS CLAIMED IS:

- 1 1. A compound of Formula (I):



- 2
- 3 or a pharmaceutically acceptable salt thereof, or a prodrug or bioisostere thereof; wherein:
- 4 R^{1a} , R^{1b} , R^{1c} and R^{1d} are each independently selected from the group consisting of H, F, Cl, C_{1-3}
- 5 alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy and CN;
- 6 X^1 is C_{1-3} alkylene, optionally substituted with one or two C_{1-2} alkyl or CO_2H ;
- 7 R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_{1-8} alkyl, C_{1-8}
- 8 haloalkyl, $-Y$, $-X^2-C(O)_2R^a$, $-X^2-OR^a$, $-X^2-NR^aR^b$, $-X^2-CONR^aR^b$, $-X^2-SO_2R^a$,
- 9 $-X^2-SO_2NR^aR^b$, $-X^2-SO_3R^a$ and $-X^2-Y$ wherein each X^2 is C_{1-6} alkylene and any C_{1-8}
- 10 alkyl or C_{1-6} alkylene, is optionally further substituted with one or two members
- 11 independently selected from OH, SO_2NH_2 , $CONH_2$, $C(O)NHOH$, PO_3H_2 , $COO-C_{1-8}alkyl$
- 12 or CO_2H , and each Y is selected from the group consisting of C_{3-6} cycloalkyl, C_{4-8}
- 13 heterocyclyl and 5- to 6-membered heteroaryl, each of which is optionally further
- 14 substituted with one to four substituents independently selected from the group consisting
- 15 of oxo, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4}
- 16 hydroxyalkoxy, SO_2NH_2 , $CONH_2$, $C(O)NHOH$, PO_3H_2 , $COO-C_{1-8}alkyl$, and CO_2H ;
- 17 or R^{2a} and R^{2b} are combined to form a 4- to 8-membered ring or spirocyclic ring, optionally
- 18 having one or two additional ring vertices selected from O, N or S;
- 19 or R^{1a} and R^{2a} or X^1 are combined to form a 5- to 7-membered ring;
- 20 or R^{1b} and R^{2b} or X^1 are combined to form a 5- to 7-membered ring;
- 21 wherein the rings formed by combining R^{2a} and R^{2b} , R^{1a} and R^{2a} or X^1 , or R^{1b} and R^{2b} or
- 22 X^1 , are substituted with 0 to 4 substituents independently selected from the group
- 23 consisting of oxo, C_{1-8} alkyl, C_{1-8} haloalkyl, $-X^3-C(O)_2R^a$, $-X^3-OR^a$, $-X^3-NR^aR^b$,

24 $-X^3-\text{CONR}^a\text{R}^b$, $-X^3-\text{SO}_2\text{R}^a$, $-X^3-\text{SO}_2\text{NR}^a\text{R}^b$, and $-X^3-\text{SO}_3\text{R}^a$; wherein X^3 is a bond
 25 or C_{1-6} alkylene;
 26 R^3 is selected from the group consisting of H, F, Cl, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3}
 27 haloalkoxy, C_{2-3} alkenyl and CN;
 28 the subscript n is 0, 1 or 2;
 29 each R^{3a} is independently selected from the group consisting of F, Cl, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3}
 30 haloalkyl, C_{1-3} haloalkoxy, C_{2-3} alkenyl and CN;
 31 each of R^4 , R^6 , R^7 and R^8 is independently selected from the group consisting of H, halogen, CN,
 32 C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, $-\text{Y}^1$, $-\text{X}^4-\text{C}(\text{O})_2\text{R}^a$,
 33 $-\text{X}^4-\text{OR}^a$, $-\text{X}^4-\text{NR}^a\text{R}^b$, $-\text{X}^4-\text{CONR}^a\text{R}^b$, $-\text{X}^4-\text{SO}_2\text{R}^a$, $-\text{X}^4-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{X}^4-\text{SO}_3\text{R}^a$, $-\text{O}-\text{X}^4-\text{Y}^1$
 34 and $-\text{X}^4-\text{Y}^1$ wherein each X^4 is a bond or C_{1-6} alkylene and is optionally further
 35 substituted with OH, SO_2NH_2 , CONH_2 , $\text{C}(\text{O})\text{NHOH}$, PO_3H_2 , $\text{COO}-\text{C}_{1-8}$ alkyl or CO_2H ,
 36 and each Y^1 is selected from the group consisting of C_{3-6} cycloalkyl, C_{4-8} heterocyclyl and
 37 5- to 6-membered heteroaryl, each of which is optionally further substituted with one to
 38 four substituents independently selected from the group consisting of oxo, OH, C_{1-4} alkyl,
 39 C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkoxy,
 40 SO_2NH_2 , CONH_2 , $\text{C}(\text{O})\text{NHOH}$, PO_3H_2 , $\text{COO}-\text{C}_{1-8}$ alkyl, and CO_2H ;
 41 R^5 is a member selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl,
 42 C_{1-6} hydroxyalkyl, $-\text{Y}^2$, $-\text{X}^5-\text{C}(\text{O})_2\text{R}^a$, $-\text{X}^5-\text{OR}^a$, $-\text{X}^5-\text{NR}^a\text{R}^b$, $-\text{X}^5-\text{CONR}^a\text{R}^b$, $-\text{X}^5-\text{SO}_2\text{R}^a$,
 43 $-\text{X}^5-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{X}^5-\text{SO}_3\text{R}^a$, $-\text{X}^5-\text{Y}^2$, $-\text{O}-\text{X}^5-\text{Y}^2$ and $-\text{A}-\text{Z}$, wherein each X^5 is a bond or
 44 C_{1-6} alkylene and is optionally further substituted with OH, SO_2NH_2 , CONH_2 ,
 45 $\text{C}(\text{O})\text{NHOH}$, PO_3H_2 , $\text{COO}-\text{C}_{1-8}$ alkyl or CO_2H , and each Y^2 is selected from the group
 46 consisting of C_{3-6} cycloalkyl, C_{4-8} heterocyclyl, C_{7-9} spiroheterocyclyl, and 5- to 6-
 47 membered heteroaryl, each of which is optionally further substituted with one to four
 48 substituents independently selected from the group consisting of oxo, halogen, OH, C_{1-4}
 49 alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} hydroxyalkoxy,
 50 SO_2NH_2 , CONH_2 , $\text{C}(\text{O})\text{NHOH}$, PO_3H_2 , $\text{COO}-\text{C}_{1-8}$ alkyl, and CO_2H ;
 51 wherein
 52 A is a member selected from the group consisting of a bond, $-\text{O}-$ and $-\text{N}(\text{R}^a)-$;
 53 Z is selected from the group consisting of:

54 i) a monocyclic 5- or 6-membered heteroaryl ring, optionally substituted
 55 with one to three R^c;
 56 ii) phenyl, optionally substituted with one to three R^c; and
 57 iii) a 5- or 6-membered non-aromatic heterocyclic ring, optionally substituted
 58 with one to three R^c;
 59 and when A is -O- or -N(R^a)-, then Z is other than phenyl;
 60 and two of R⁴, R⁵, R⁶, R⁷ and R⁸ on adjacent carbon atoms are optionally combined to form a 5-
 61 or 6-membered non-aromatic heterocyclic ring having one or two ring vertices selected
 62 from the group consisting of O, -N(R^b)- and =N-; wherein said non-aromatic heterocyclic
 63 ring is optionally substituted with oxo and optionally with from one to four R^c;
 64 and at least one of R⁴, R⁵, R⁶, R⁷ and R⁸ is other than H;
 65 each R^a is independently selected from the group consisting of H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆
 66 haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkylene-CO₂H, C₁₋₆ alkylene-COO-C₁₋₈alkyl, C₁₋₆
 67 alkylene-SO₃H;
 68 each R^b is independently selected from the group consisting of H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆
 69 haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkylene-CO₂H, C₁₋₆ alkylene-SO₃H and C₁₋₆
 70 alkylene-Y³, wherein Y³ is C₃₋₆ cycloalkyl or C₄₋₈ heterocyclyl, and each R^b is optionally
 71 further substituted with one or two members independently selected from oxo, OH,
 72 SO₂NH₂, CONH₂, C(O)NHOH, PO₃H₂, COO-C₁₋₈alkyl and CO₂H;
 73 and R^a and R^b, when attached to the same nitrogen atom, are optionally combined to form a 4- to
 74 8-membered ring or spirocyclic ring, optionally substituted with halogen, OH, SO₂NH₂,
 75 CONH₂, C(O)NHOH, PO₃H₂, COO-C₁₋₈alkyl or CO₂H;
 76 each R^c is independently selected from the group consisting of H, halogen, CN, C₁₋₆ alkyl, C₁₋₆
 77 haloalkyl, -Y⁴, -X⁶-C(O)₂R^a, -X⁶-OR^a, -X⁶-NR^aR^b, -X⁶-CONR^aR^b, -X⁶-SO₂R^a,
 78 -X⁶-SO₂NR^aR^b, -X⁶-SO₃R^a, and -N(R^a)-X⁶-C(O)₂R^a, wherein each X⁶ is a bond or C₁₋₆
 79 alkylene, and each Y⁴ is selected from the group consisting of C₃₋₆ cycloalkyl and C₄₋₈
 80 heterocyclyl; and optionally two R^c on adjacent ring vertices are combined to form a
 81 fused 5- or 6-membered heterocyclic ring.

1 **2.** The compound of claim 1, or a pharmaceutically acceptable salt thereof
 2 wherein R⁵ is -A-Z.

1 **3.** The compound of claim 1, or a pharmaceutically acceptable salt thereof
2 wherein R^5 is $-O-X^5-Y^2$.

1 **4.** The compound of claim 1, or a pharmaceutically acceptable salt thereof
2 wherein R^5 is $-A-Z$, A is a bond, and Z is phenyl, optionally substituted with one to three R^c .

1 **5.** The compound of claim 1, or a pharmaceutically acceptable salt thereof
2 wherein X^1 is $-CH_2-$.

1 **6.** The compound of claim 1, or a pharmaceutically acceptable salt thereof
2 wherein R^{1c} , R^7 and R^8 are H, and R^3 is selected from the group consisting of F, Cl, CH_3 , CF_3
3 and OCH_3 .

1 **7.** The compound of claim 1, or a pharmaceutically acceptable salt thereof
2 wherein a ring is formed between one pair of R^4 and R^5 , R^5 and R^6 , R^{1b} and R^{2b} , or R^{1a} and R^{2a} .

1 **8.** The compound of claim 1, or a pharmaceutically acceptable salt thereof
2 wherein R^5 is $-A-Z$, and Z is selected from the group consisting of piperidinyl, imidazolyl and
3 pyridinyl.

1 **9.** The compound of claim 1, or a pharmaceutically acceptable salt thereof
2 wherein n is 0.

1 **10.** The compound of claim 1, or a pharmaceutically acceptable salt thereof
2 wherein R^4 is selected from the group consisting of F, Cl, CH_3 , CF_3 and OCH_3 .

1 **11.** The compound of claim 1, or a pharmaceutically acceptable salt thereof
2 wherein the group R^{1a} is OCH_3 and R^{1b} is F.

1 **12.** The compound of claim 1, or a pharmaceutically acceptable salt thereof
2 wherein R^{2a} and R^{2b} are each H.

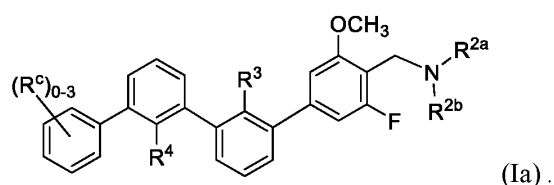
1 **13.** The compound of any one of claims 1 to 3, or a pharmaceutically
2 acceptable salt thereof wherein R^{2a} and R^{2b} are combined to form a 4- to 8-membered ring or

3 spirocyclic ring, optionally having one or two additional ring vertices selected from O, N or S;
 4 wherein said ring or spirocyclic ring is substituted with 0 to 4 substituents independently selected
 5 from the group consisting of oxo, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₁₋₈ hydroxyalkyl, -X²-C(O)₂R^a,
 6 -X²-OR^a, -X²-NR^aR^b, -X²-CONR^aR^b, -X²-SO₂R^a, -X²-SO₂NR^aR^b, and -X²-SO₃R^a; wherein X² is
 7 a bond or C₁₋₆ alkylene.

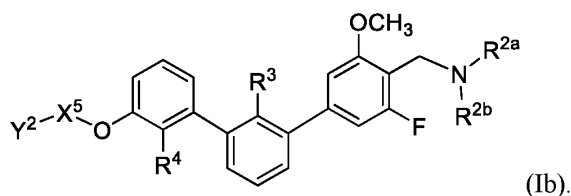
1 **14.** The compound of any one of claims **1** to **3**, or a pharmaceutically
 2 acceptable salt thereof wherein R^{2a} is H or C₁₋₈ alkyl; and R^{2b} is -Y or -X¹-Y.

1 **15.** The compound of claim **14**, or a pharmaceutically acceptable salt thereof
 2 wherein Y is selected from the group consisting of C₃₋₆ cycloalkyl and C₄₋₈ heterocyclyl, each of
 3 which is optionally further substituted with one to four substituents independently selected from
 4 the group consisting of oxo, OH, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ alkoxy, C₁₋₄
 5 haloalkoxy, C₁₋₄ hydroxyalkoxy, SO₂NH₂, CONH₂, C(O)NHOH, PO₃H₂, COO-C₁₋₈alkyl, and
 6 CO₂H.

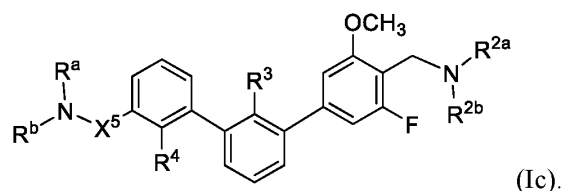
1 **16.** The compound of claim **1**, or a pharmaceutically acceptable salt thereof
 2 having the formula (Ia):



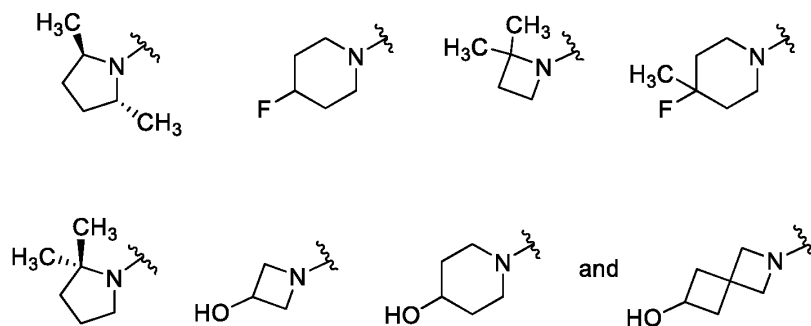
1 **17.** The compound of claim **1**, or a pharmaceutically acceptable salt thereof
 2 having the formula (Ib):



1 **18.** The compound of claim 1, or a pharmaceutically acceptable salt thereof
2 having the formula (Ic):



1 **19.** The compound of claim **17**, or a pharmaceutically acceptable salt thereof
2 wherein Y² is selected from the group consisting of:



1 **20.** The compound of claim 1, or a pharmaceutically acceptable salt thereof,
2 selected from Table 1.

1 **21.** A pharmaceutical composition comprising a compound of any one of
2 claims **1** to **20**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable
3 excipient.

1 **22.** The pharmaceutical composition of claim **21**, further comprising one or
2 more additional therapeutic agents.

1 **23.** The pharmaceutical composition of claim **22**, wherein the one or more
2 additional therapeutic agent is selected from the group consisting of an antimicrobial agent, an
3 antiviral agent, a cytotoxic agent, a gene expression modulatory agent, a chemotherapeutic agent,
4 an anti-cancer agent, an anti-angiogenic agent, an immunotherapeutic agent, an anti-hormonal
5 agent, an anti-fibrotic agent, radiotherapy, a radiotherapeutic agent, an anti-neoplastic agent, and
6 an anti-proliferation agent.

1 **24.** A method of modulating an immune response mediated by the PD-1
2 signaling pathway in a subject, comprising administering to the subject a therapeutically
3 effective amount of a compound of any one of claims **1** to **20**, or a pharmaceutically acceptable
4 salt thereof or a composition of any one of claims **21** to **23**.

1 **25.** A method of enhancing, stimulating, modulating and/or increasing the
2 immune response in a subject in need thereof, comprising administering to the subject a
3 therapeutically effective amount of a compound of any one of claims **1** to **20**, or a
4 pharmaceutically acceptable salt thereof or a composition of any one of claims **21** to **23**.

1 **26.** A method of inhibiting growth, proliferation, or metastasis of cancer cells
2 in a subject in need thereof, comprising administering to the subject a therapeutically effective
3 amount of a compound of any one of claims **1** to **20**, or a pharmaceutically acceptable salt
4 thereof or a composition of any one of claims **21** to **23**.

1 **27.** A method of treating a subject suffering from or susceptible to a disease or
2 disorder mediated by the PD-1 signaling pathway, comprising administering to the subject a
3 therapeutically effective amount of a compound of any one of claims **1** to **20**, or a
4 pharmaceutically acceptable salt thereof or a composition of any one of claims **21** to **23**.

1 **28.** The method of any one of claims **24** to **27**, wherein the subject suffers
2 from a disease or disorder selected from the group consisting of an infectious disease, a bacterial
3 infectious disease, a viral infectious disease, a fungal infectious disease, a solid tumor, a
4 hematological malignancy, an immune disorder, an inflammatory disease, and cancer.

1 **29.** The method of claim **27**, wherein the disease or disorder is selected from
2 the group consisting of melanoma, glioblastoma, esophagus tumor, nasopharyngeal carcinoma,
3 uveal melanoma, lymphoma, lymphocytic lymphoma, primary CNS lymphoma, T-cell
4 lymphoma, diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, prostate
5 cancer, castration-resistant prostate cancer, chronic myelocytic leukemia, Kaposi's sarcoma
6 fibrosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma,
7 lymphangiosarcoma, synovioma, , meningioma, leiomyosarcoma, rhabdomyosarcoma, sarcoma
8 of soft tissue, sarcoma, sepsis, biliary tumor, basal cell carcinoma, thymus neoplasm, cancer of
9 the thyroid gland, cancer of the parathyroid gland, uterine cancer, cancer of the adrenal gland,
10 liver infection, Merkel cell carcinoma, nerve tumor, follicle center lymphoma, colon cancer,
11 Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, chronic or acute leukemias including
12 acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic
13 lymphocytic leukemia, multiple myeloma, ovary tumor, myelodysplastic syndrome, cutaneous or
14 intraocular malignant melanoma, renal cell carcinoma, small-cell lung cancer, lung cancer,
15 mesothelioma, breast cancer, squamous non-small cell lung cancer (SCLC), non-squamous
16 NSCLC, colorectal cancer, ovarian cancer, gastric cancer, hepatocellular carcinoma, pancreatic
17 carcinoma, pancreatic cancer, Pancreatic ductal adenocarcinoma, squamous cell carcinoma of the
18 head and neck, cancer of the head or neck, gastrointestinal tract, stomach cancer, HIV, Hepatitis
19 A, Hepatitis B, Hepatitis C, hepatitis D, herpes viruses, papillomaviruses, influenza, bone cancer,
20 skin cancer, rectal cancer, cancer of the anal region, testicular cancer, carcinoma of the fallopian
21 tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina,
22 carcinoma of the vulva, cancer of the esophagus, cancer of the small intestine, cancer of the
23 endocrine system, cancer of the urethra, cancer of the penis, cancer of the bladder, cancer of the
24 kidney, cancer of the ureter, carcinoma of the renal pelvis, neoplasm of the central nervous
25 system (CNS), tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma,
26 epidermoid cancer, abestosis, carcinoma, adenocarcinoma, papillary carcinoma,
27 cystadenocarcinoma, bronchogenic carcinoma, renal cell carcinoma, transitional cell carcinoma,
28 choriocarcinoma, seminoma, embryonal carcinoma, wilm's tumor, pleomorphic adenoma, liver
29 cell papilloma, renal tubular adenoma, cystadenoma, papilloma, adenoma, leiomyoma,
30 rhabdomyoma, hemangioma, lymphangioma, osteoma, chondroma, lipoma and fibroma.

1 **30.** The method of any one of claims **24** to **29**, further comprising
2 administering to the subject a therapeutically effective amount of one or more additional
3 therapeutic agents.

1 **31.** The method of claim **30**, wherein the one or more additional therapeutic
2 agents is selected from the group consisting of an antimicrobial agent, an antiviral agent, a
3 cytotoxic agent, a gene expression modulatory agent, a chemotherapeutic agent, an anti-cancer
4 agent, an anti-angiogenic agent, an immunotherapeutic agent, an anti-hormonal agent, an anti-
5 fibrotic agent, radiotherapy, a radiotherapeutic agent, an anti-neoplastic agent, and an anti-
6 proliferation agent.

7