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- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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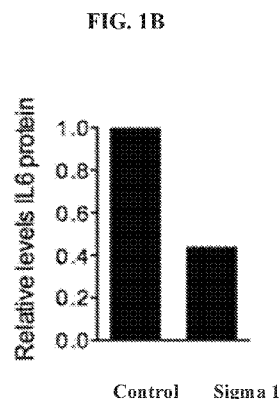
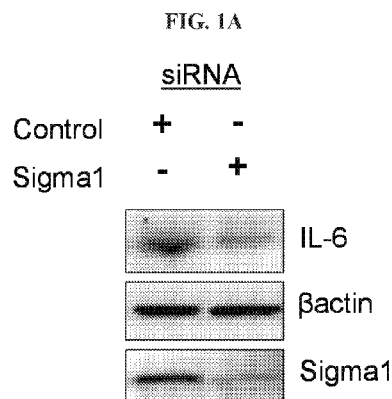
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(54) **Title:** METHODS OF MODULATING LEVELS OF IL-6 AND PD-L1



(57) **Abstract:** Embodiments described herein provide methods of treating various diseases or disorders using Sigma1 modulating compounds alone or in combination with other therapeutic agents.

METHODS OF MODULATING LEVELS OF IL-6 AND PD-L1

CROSS-REFERENCE TO RELATED APPLICATIONS

5 The present application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application No. 62/269,269, filed December 18, 2015, which application is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

10 Interleukin 6 (IL-6) is an interleukin that acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine. IL-6 is secreted by T cells and macrophages to stimulate immune response, normally for infections and tissue damage such as burns. IL-6 mediated signaling also stimulates inflammatory and auto-immune processes in many diseases, such as diabetes, atherosclerosis, depression, lupus, rheumatoid arthritis, and/or a wide range of cancers. Secretion
15 of IL-6 by cancer cells is believed to promote tumor growth. When IL-6 binds to a IL-6 receptor, the protein complex associates with the transmembrane protein glycoprotein 130 (gp130 or IL-6 β) to induce cellular signaling.

Programmed death ligand 1 (PD-L1) is a transmembrane protein that is involved with suppressing the immune system. Normally, the human immune system reacts to antigens by
20 upregulating the proliferation of CD8⁺ T cells specific to those antigens. When PD-L1 binds to the PD-1 receptor on activated T and B cells, an inhibitory signal is produced, which both reduces the proliferation of the antigen specific CD8⁺ T cells and also induces apoptosis in currently activated cells. PD-L1 signaling is involved in disease states, such as cancer (where upregulation of PD-L1 by tumors may allow the tumor to evade the host immune system and
25 enjoy aggressive growth) and infection (where pathogen-induced up-regulation of PD-L1 may allow pathogens to sequester host immune response during both acute and chronic infection).

Since IL-6 and PD-L1 have been implicated in a variety of disorders, several therapeutic strategies have been designed to inhibit IL-6 and/or PD-L1 activity. Murine, chimeric, and other non-human anti-IL-6, anti-PD-1, and/or anti-PD-L1 antibodies have been developed. However,
30 they may be limited in their potency, effectiveness, may often trigger an unacceptable immune response (*i.e.*, immunogenicity) and/or require a high dosage (See, Trikha et al., 2003, Clin. Can.

Res. 9:4653-4665, herein incorporated by reference in its entirety). For example, antibodies containing non-human portions often give rise to an immune response in humans. Accordingly, repeated antibody administration is unsuitable, because therapy and immune complex mediated clearance of antibodies from circulation can reduce the potency/effectiveness of the antibody.

5 Serum sickness and anaphylaxis are two exemplary conditions that may be caused by repeat administration of antibodies having non-human portions.

Accordingly, there is a need for new methods of regulating IL-6, PD-1, and/or PD-L1 expression for a wide range of diseases, including many types of cancer, autoimmune disease, and/or infection. Such methods should render therapeutic treatments more tolerable for human
10 patients and require a smaller therapeutic agent dosage as compared to conventional treatments. Additionally, such novel methods should be available for use alone or in combination with antibody treatments, wherein the combination treatment has improved efficacy above either treatment alone. The present disclosure satisfies these needs as well as others.

15 BRIEF SUMMARY OF THE INVENTION

The present invention provides, in certain aspects, methods of treating conditions related to IL-6-, PD-1-, and/or PD-L1-mediated signaling by administering Signal modulators.

This application incorporates the disclosure of U.S. Patent Application Publication No. 2015/0166472 by reference in its entirety.

20 The present disclosure provides methods of preventing, treating, or ameliorating at least one disorder or disease that is mediated via IL-6 and/or gp130 signaling in a subject, the method comprising administering to the subject at least one compound of the invention.

The present disclosure further provides methods of enhancing an IL-6-mediated immune response in a subject, the method comprising administering to the subject at least one compound
25 of the invention:

In certain embodiments, the present disclosure provides methods of decreasing IL-6 and/or gp130-mediated signaling in a subject, the method comprising administering to the subject at least one compound of the invention.

In certain embodiments, the present disclosure provides methods of preventing, treating,
30 or ameliorating at least one disorder or disease that is mediated via PD-L1 signaling in a subject, the method comprising administering to the subject at least one compound of the invention.

In certain embodiments, the present disclosure provides methods of decreasing PD-L1-mediated signaling in a subject, the method comprising administering to the subject at least one compound of the invention.

5 In certain embodiments, the present disclosure provides methods of treating cancer in a subject, the methods comprising administering to a subject, in a cancer sample of whom at least one selected from the group consisting of PD-1 and PD-L1 is detected, at least one compound of the invention. In other embodiments, the methods further comprise detecting whether PD-1 or PD-L1 is present in a cancer sample from the subject. In yet other embodiments, the methods comprise counseling a subject, in a cancer sample of whom at least one selected from the group
10 consisting of PD-1 and PD-L1 is detected, to be administered at least one compound of the invention.

In certain embodiments, the at least one disorder or disease is an autoimmune disease, inflammation, or cancer.

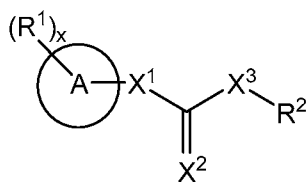
In certain embodiments, the at least one disorder or disease comprises an autoimmune
15 disease. In other embodiments, the autoimmune disease is at least one selected from the group consisting of: asthma, Sjogren's syndrome, multiple sclerosis, systemic lupus erythematosus, Graves' disease, Hashimoto's disease, Castleman's disease, psoriasis, psoriatic arthropathy, ankylosing spondylitis, inflammatory bowel disease (IBD), polymyalgia rheumatica, giant cell arteritis, autoimmune vasculitis, graft versus host disease (GVHD), adult onset Still's disease,
20 rheumatoid arthritis, systemic juvenile idiopathic arthritis, obesity, diabetes, asthma, multiple sclerosis, Alzheimer's disease, cerebrovascular disease, fever, acute phase response, allergies, chronic prostatitis, glomerulonephritis, pelvic inflammatory disease, reperfusion injury, and transplant rejection.

In certain embodiments, the at least one disorder or disease is inflammation. In other
25 embodiments, the inflammation is acute and/or chronic inflammation.

In certain embodiments, the at least one disorder or disease comprises cancer. In other
embodiments, the cancer is at least one selected from the group consisting of bladder cancer, brain cancer, bone cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, head and neck cancer, kidney cancer, large intestine cancer, liver cancer, lung
30 cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin cancer, soft tissue cancer, and testicular cancer.

In certain embodiments, the at least one disorder or disease comprises a B-cell proliferative disorder. In other embodiments, the B-cell proliferative disorder is at least one selected from the group consisting of follicular lymphoma, chronic lymphocytic leukemia, acute lymphoblastic leukemia, hairy cell leukemia, B cell lymphoma, T cell lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, Wiskott-Aldrich syndrome, post-transplant lymphoproliferative disorder, and autoimmune lymphoproliferative syndrome.

In certain embodiments, at least one compound of the invention is selected from the group consisting of:



(i) a compound of Formula (I): (I), wherein in (I):

ring A is a monocyclic or bicyclic aryl or a monocyclic or bicyclic heteroaryl ring, and wherein the aryl or heteroaryl ring is optionally substituted with 0-4 R^1 groups;

each occurrence of R^1 is independently selected from the group consisting of $-\text{C}_1\text{-C}_6$ alkyl, $-\text{C}_1\text{-C}_6$ fluoroalkyl, $-\text{C}_1\text{-C}_6$ heteroalkyl, F, Cl, Br, I, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}^3$, $-\text{SR}^3$, $-\text{S}(=\text{O})\text{R}^3$, $-\text{S}(=\text{O})_2\text{R}^3$, $-\text{NHS}(=\text{O})_2\text{R}^3$, $-\text{C}(=\text{O})\text{R}^3$, $-\text{OC}(=\text{O})\text{R}^3$, $-\text{CO}_2\text{R}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{CH}(\text{R}^3)_2$, $-\text{N}(\text{R}^3)_2$, $-\text{C}(=\text{O})\text{N}(\text{R}^3)_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^3)_2$, $-\text{NHC}(=\text{O})\text{NH}(\text{R}^3)$, $-\text{NHC}(=\text{O})\text{R}^3$, $-\text{NHC}(=\text{O})\text{OR}^3$, $-\text{C}(\text{OH})(\text{R}^3)_2$, and $-\text{C}(\text{NH}_2)(\text{R}^3)_2$;

each occurrence of R^2 is independently selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ heteroalkyl, and $-\text{C}_1\text{-C}_3$ alkyl- $(\text{C}_3\text{-C}_6$ cycloalkyl), wherein the alkyl, heteroalkyl or cycloalkyl group is optionally substituted with 0-5 R^1 groups, or X^3 and R^2 combine to form a $(\text{C}_3\text{-C}_7)$ heterocycloalkyl group, optionally substituted with 0-2 R^1 groups;

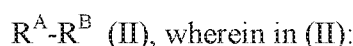
each occurrence of R^3 is independently selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ heteroalkyl, aryl, and $-\text{C}_1\text{-C}_3$ alkyl- $(\text{C}_3\text{-C}_6$ cycloalkyl), wherein the alkyl, heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

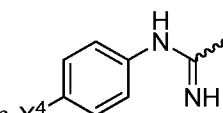
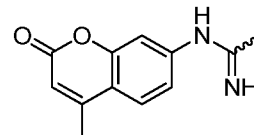
X^1 is $-\text{CH}_2-$, $-\text{S}-$, $-\text{O}-$ or $-(\text{NR}^2)-$;

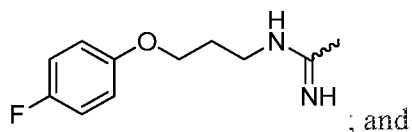
X^2 is $=\text{CH}_2$, $=\text{S}$, $=\text{O}$ or $=\text{NR}^2$; and

X^3 is $-\text{S}-$, $-\text{O}-$, or $-\text{NR}^2-$; and

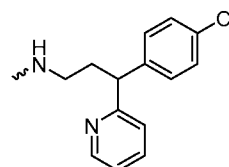
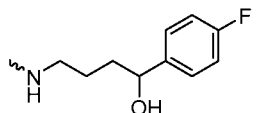
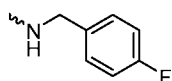
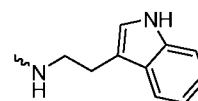
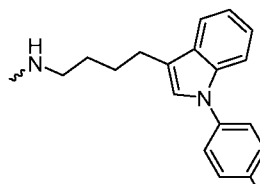
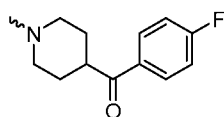
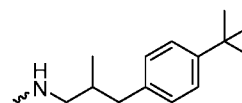
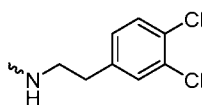
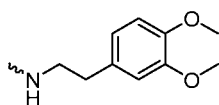
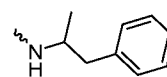
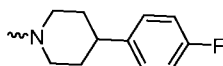
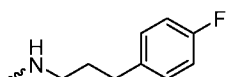
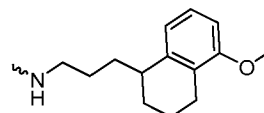
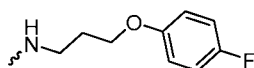
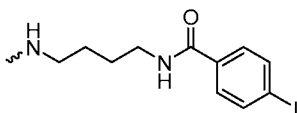
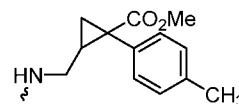
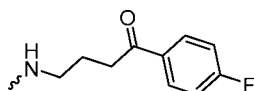
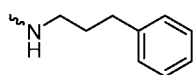
(ii) a compound of Formula (II):



R^A is selected from the group consisting of , , and



R^B is selected from the group consisting of:



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a pharmaceutically acceptable salt or solvate thereof, a *N*-oxide thereof, and any combinations thereof.

In certain embodiments, in the compound of Formula (I):

each occurrence of R^1 is independently selected from the group consisting of $-C_1-C_2$ alkyl, $-C_1-C_2$ fluoroalkyl, $-C_1-C_2$ heteroalkyl, F, Cl, Br, I, $-CN$, $-NO_2$, $-OR^3$, $-SR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-NHS(=O)_2R^3$, $-C(=O)R^3$, $-OC(=O)R^3$, $-CO_2R^3$, $-OCO_2R^3$, $-CH(R^3)_2$, $-N(R^3)_2$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$, $-NHC(=O)NH(R^3)$, $-NHC(=O)R^3$, $-$

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$\text{NHC}(=\text{O})\text{OR}^3$, $-\text{C}(\text{OH})(\text{R}^3)_2$, and $-\text{C}(\text{NH}_2)(\text{R}^3)_2$;

each occurrence of R^2 is independently selected from the group consisting of H, C_1 - C_3 alkyl, and

C_1 - C_3 heteroalkyl, wherein the alkyl, heteroalkyl or cycloalkyl group is optionally

substituted with 0-2 R^1 groups, or X^3 and R^2 combine to form a (C_3 - C_7) heterocycloalkyl

5 group, optionally substituted with 0-2 R^1 groups; and

each occurrence of R^3 is independently selected from the group consisting of H, C_1 - C_2 alkyl, and

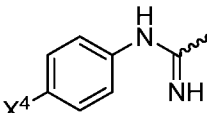
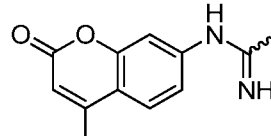
C_1 - C_2 heteroalkyl, aryl, wherein the alkyl, heteroalkyl, aryl, or cycloalkyl group is

optionally substituted with 0-2 groups.

In certain embodiments, the at least one compound is a compound of Formula (I-A), or a

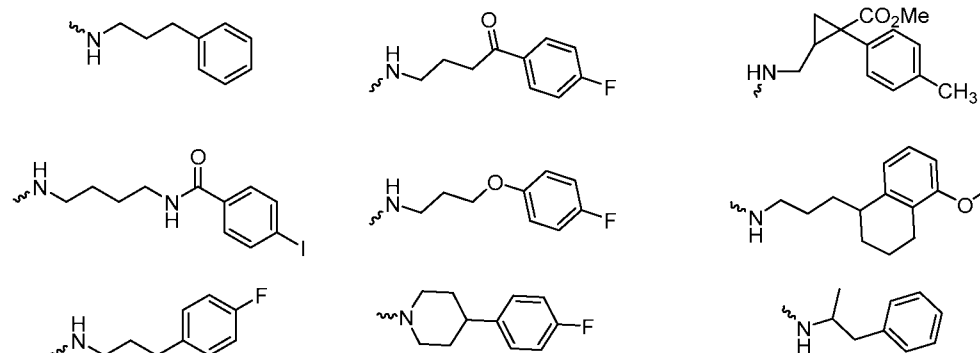
10 pharmaceutically acceptable salt or solvate thereof:

$\text{R}^A\text{-R}^B$ (I-A), wherein in (I-A):

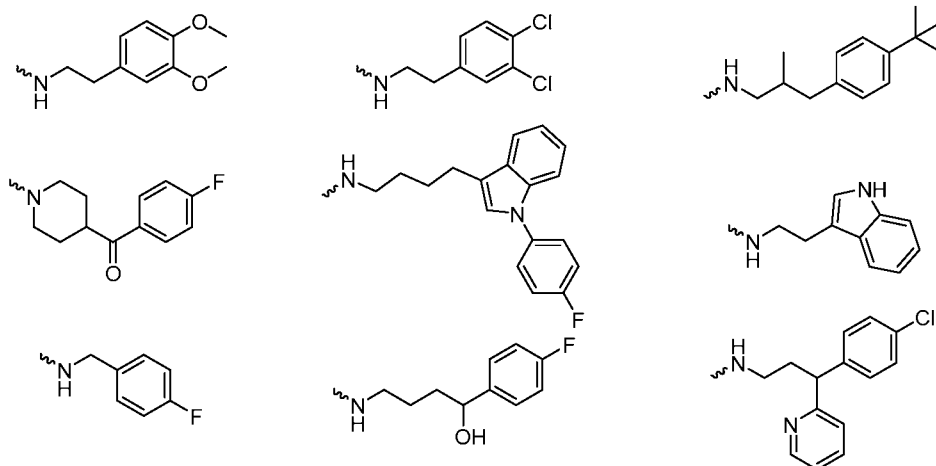
R^A is selected from the group consisting of  and  ;

X^4 is selected from the group consisting of OMe, F, Cl, Br, and I; and

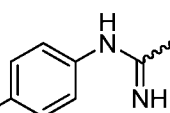
R^B is selected from the group consisting of:

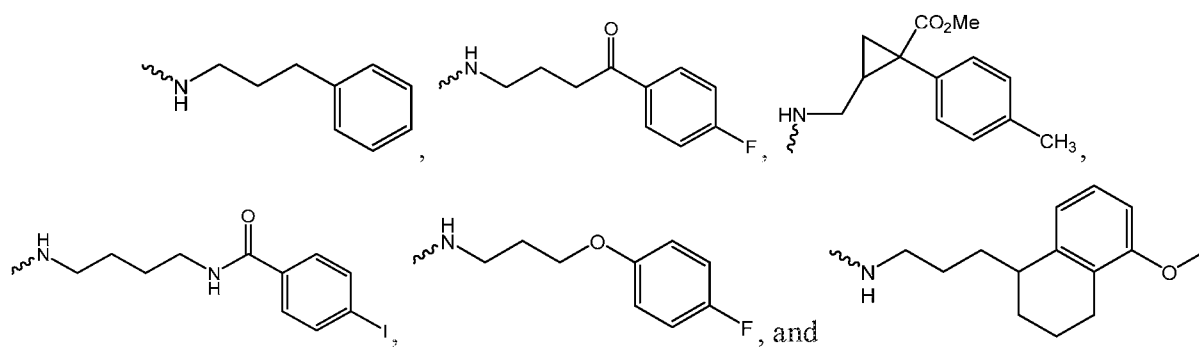


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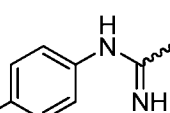


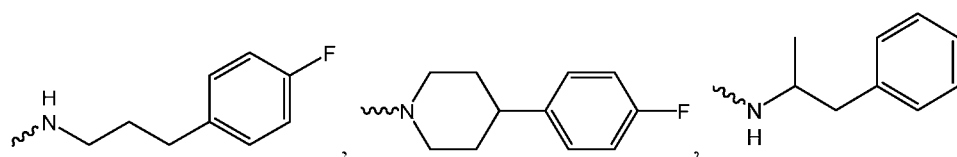
In certain embodiments, in the compound of formula (I-A):

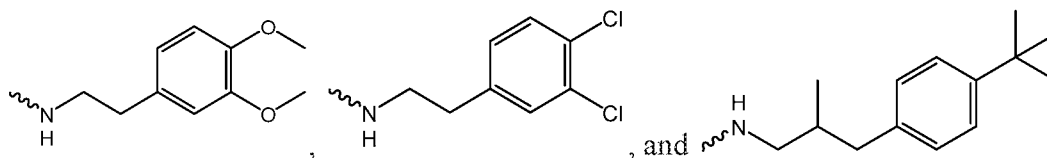
R^A is X^4 -; X^4 is selected from the group consisting of F, Cl, Br, and I; and R^B is selected from the group consisting of:



In certain embodiments, in the compound of formula (I-A):

R^A is X^4 -; X^4 is selected from the group consisting of F, Cl, Br, and I; and R^B is selected from the group consisting of:

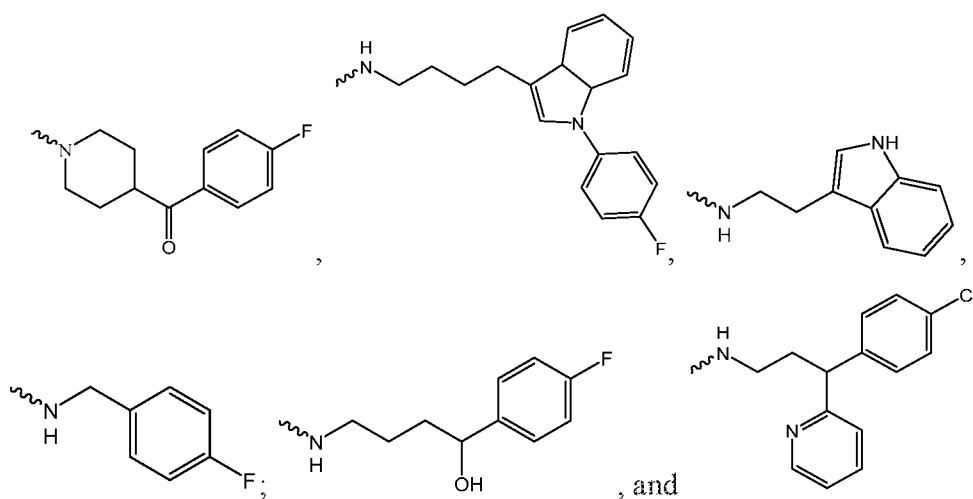




In certain embodiments, in the compound of formula (I-A):

R^A is ; X^4 is selected from the group consisting of F, Cl, Br, and I; and R^B is selected from the group consisting of:

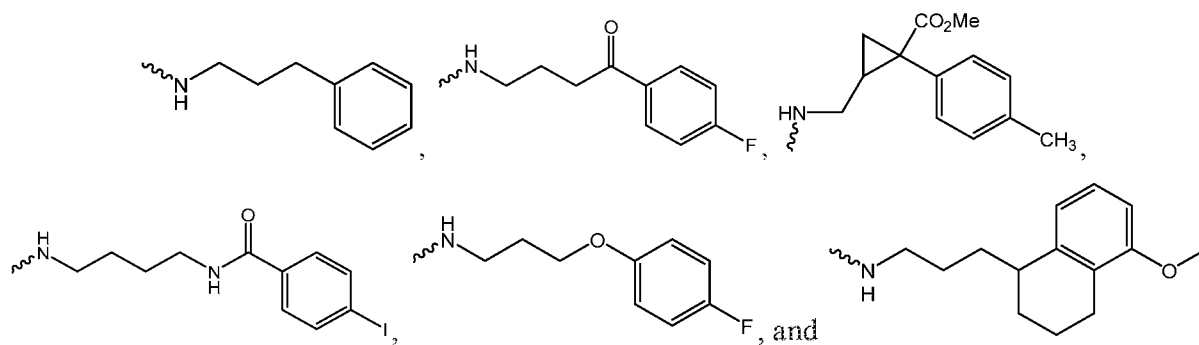
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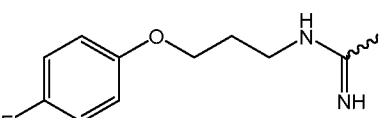
In certain embodiments, in the compound of formula (II):

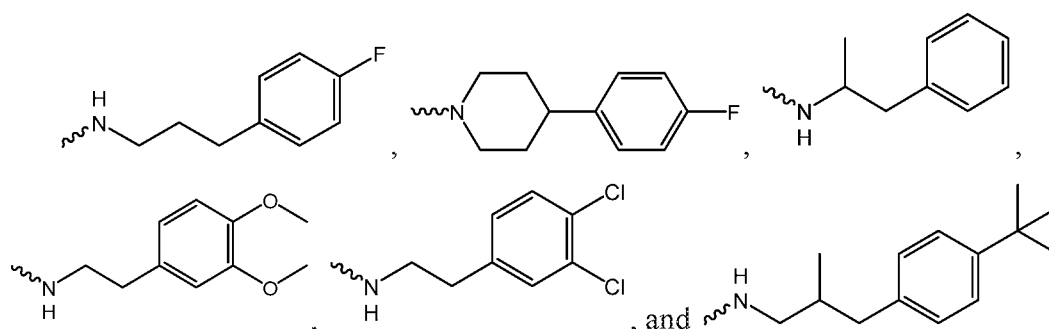
R^A is ; and R^B is selected from the group consisting of:

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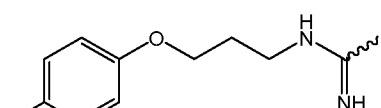


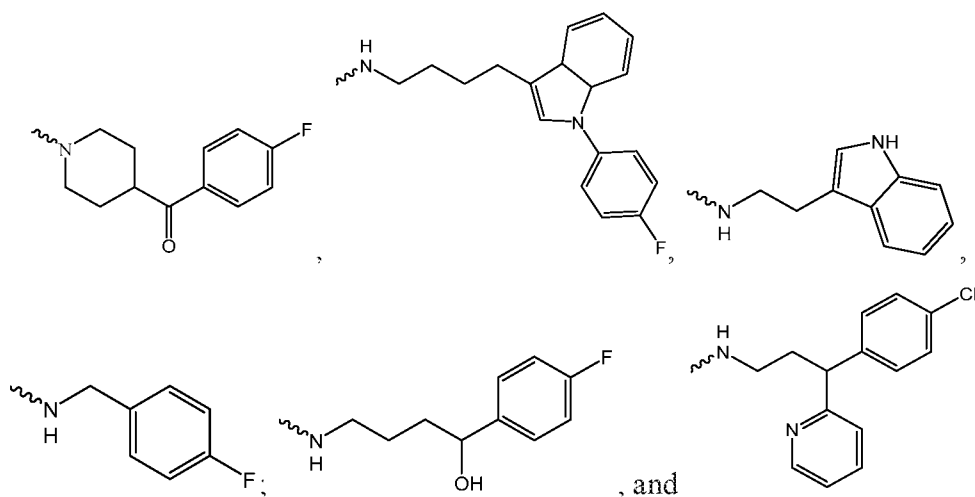
In certain embodiments, in the compound of formula (II):

R^A is ; and R^B is selected from the group consisting of:

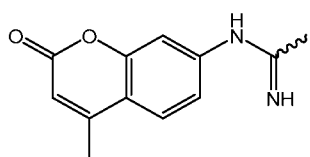


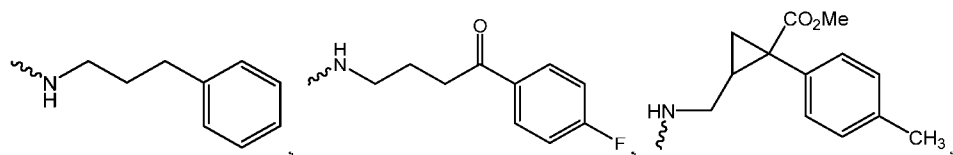
In certain embodiments, in the compound of formula (II):

5 R^A is ; and R^B is selected from the group consisting of:

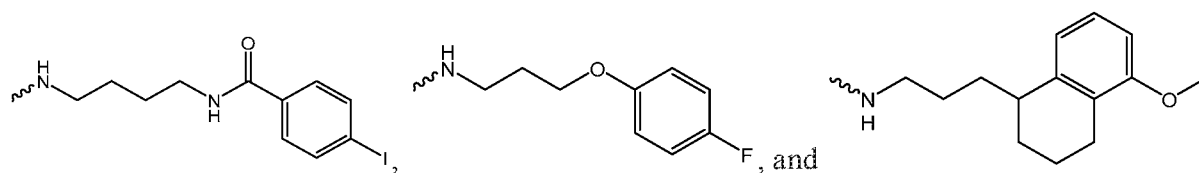


In certain embodiments, in the compound of formula (I-A):

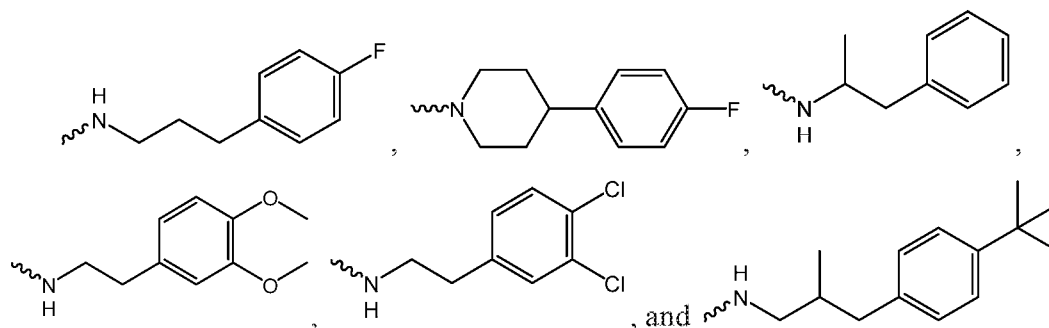
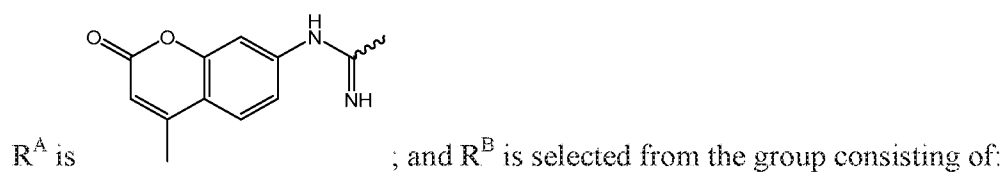
R^A is ; and R^B is selected from the group consisting of:



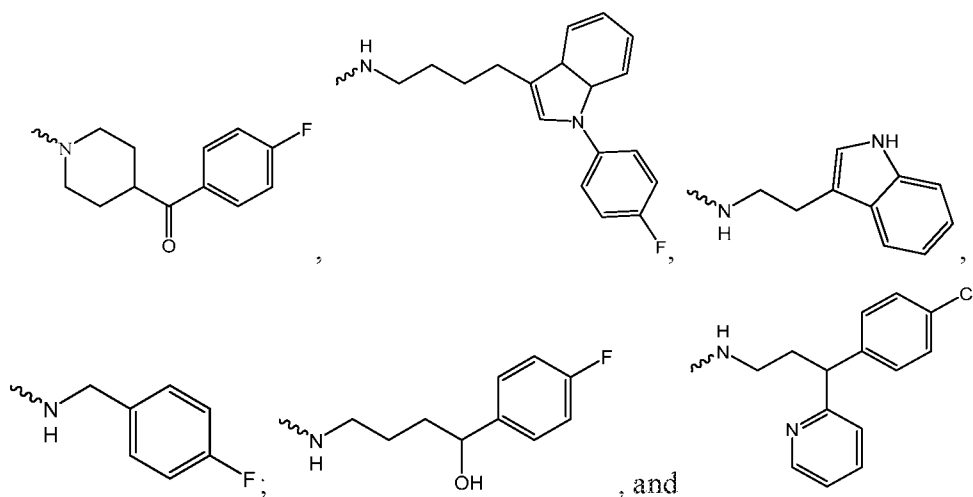
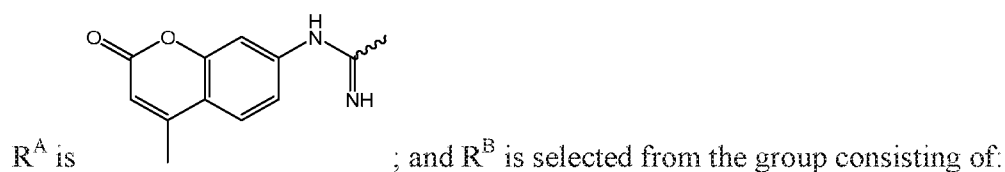
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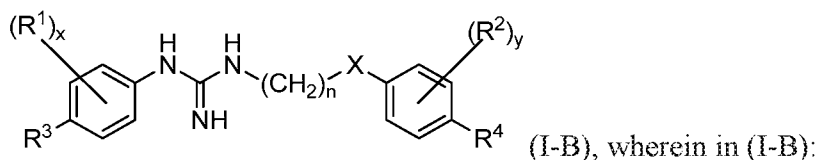
In certain embodiments, in the compound of formula (I-A):



In certain embodiments, in the compound of formula (I-A):



In certain embodiments, the at least one compound is a compound of formula (I-B), or a pharmaceutically acceptable salt or solvate thereof:



each occurrence of R^1 and R^2 is independently selected from the group consisting of $-C_1-C_6$

alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ heteroalkyl, F, Cl, Br, I, $-CN$, $-NO_2$, $-OR^5$, $-SR^5$, $-$

$S(=O)R^5$, $-S(=O)_2R^5$, $-NHS(=O)_2R^5$, $-C(=O)R^5$, $-OC(=O)R^5$, $-CO_2R^5$, $-OCO_2R^5$, $-$

5 $CH(R^5)_2$, $-N(R^5)_2$, $-C(=O)N(R^5)_2$, $-OC(=O)N(R^5)_2$, $-NHC(=O)NH(R^5)$, $-NHC(=O)R^5$, $-$
 $NHC(=O)OR^5$, $-C(OH)(R^5)_2$, and $-C(NH_2)(R^5)_2$;

R^3 is selected from the group consisting of $-C_1-C_6$ alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ alkoxy, F, Cl, Br, and I;

R^4 is selected from the group consisting of $-C_1-C_6$ alkyl, $-C_1-C_6$ alkoxy, F, Cl, Br, and I;

10 each occurrence of R^5 is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, aryl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl, heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

X is selected from the group consisting of CH_2 , $C=O$, and O;

n is an integer from 1-3;

15 x is an integer from 0-4; and

y is an integer from 0-4.

In certain embodiments, the at least one compound is selected from the group consisting of: 1-(3-(4-fluorophenoxy)propyl)-3-(4-iodophenyl)guanidine (Compound A), 1-(3-(4-fluorophenoxy)propyl)-3-(4-methoxyphenyl)guanidine (Compound B), 1-(n-propyl)-3-(4-iodophenyl)guanidine (Compound C), 1-(n-propyl)-3-(4-methoxyphenyl)guanidine (Compound D), 1,3-bis(3-(4-fluorophenoxy)propyl)guanidine (Compound E), 1-(3-(4-fluorophenoxy)propyl)-3-(4-trifluoromethylphenyl)guanidine (Compound F), 1-(3-(4-fluorophenoxy)propyl)-3-(4-chlorophenyl)guanidine (Compound G), and 1-(3-(4-fluorophenoxy)propyl)-3-(4-methoxy-1,2-oxo-2H-chromen-7-yl)guanidine (Compound H), or a pharmaceutically acceptable salt or solvate thereof, and any combinations thereof.

In certain embodiments, the methods described herein further comprise administering to the subject an anti-PD-1 compound and/or an anti-PD-L1 compound. In other embodiments, the anti-PD-1 compound is an antibody. In yet other embodiments, the anti-PD-L1 compound is an antibody.

In certain embodiments, the methods described herein further comprise administering to the subject one or more anti-IL-6 and/or gp130 compounds. In certain embodiments, the methods described herein further comprise administering to the subject an effective amount of at least one immune system modulator. In certain embodiments, the methods described herein further
 5 comprise administering to the subject one or more compounds that block the activity of PD-1 and/or PD-L1.

In certain embodiments, the anti-IL-6 and/or gp130 compound(s) comprise(s) a IL-6 receptor antagonist. In other embodiments, the anti-IL-6 and/or gp130 compound(s) comprise(s) a IL-6 binding compound. In yet other embodiments, the anti-IL-6 and/or gp130 compound(s)
 10 comprise(s) a gp130 antagonist. In yet other embodiments, the one or more anti-IL-6 compound(s) comprise(s) tocilizumab, siltuximab, sarilumab, olokizumab, elsilimomab, ALD518/BMS-94529, sirukumab, CPSI-2364, ARGX-109, FE301, or FM101, or any combination thereof.

In certain embodiments, the at least one immune system modulator modulates the
 15 interactions of T and/or B cells with Sigma1 modulators. In other embodiments, the at least one immune system modulator is at least one selected from the group consisting of blockers of ICOS-ICOS-L, IL-10, IL-24 IL-21, adenosine 2a, arginase, IDO1, CD40-CD40L, CD134-CD134L, CD137-CD137L, CTLA4, PD-1, PD-L1/PD-L2, TIM3, LAG3, TGF- β or activate toll-like receptors, IL-2, and STING.

In certain embodiments, the at least one compound that blocks the activity of PD-1 and/or
 20 PD-L1 is selected from the group consisting of nivolumab, pembrolizumab, pidilizumab (CT-011), BMS-936559, avelumab (MSB0010718C), durvalumab (MEDI4736), MEDI0680, B7-DC-Ig (AMP224), atezolizumab (MPDL3280A), CX-072, REGN2810, TSR-042, STI-1014, STI-1110, or any combinations thereof.

In certain embodiments, the subject is a subject in need thereof. In other embodiments,
 25 the subject is a mammal. In yet other embodiments, the mammal is a human.

BRIEF DESCRIPTION OF THE FIGURES

FIGs. 1A and 1B depict reduced levels of IL-6 due to RNAi of Sigma1. FIG. 1A depicts
 30 an illustrative western blot of IL-6, beta-actin, and Sigma1 with and without the RNAi of Sigma1. Both Sigma1 and IL-6 expression levels were reduced with the RNAi of Sigma1. FIG.

1B depicts the relative levels of the IL-6 protein shown in FIG. 1A.

FIGs. 2A, 2B, 2C depict reduced levels of PD-L1 due to exposure to the Sigma1 modulator IPAG. FIG. 2A depicts a western blot of PD-L1 and Vinculin with and without treatment with IPAG. PD-L1 expression levels were reduced with exposure to IPAG. FIG. 2B depicts the relative levels of the PD-L1 protein shown in FIG. 2A. FIG. 2C depicts the fluorescence activity of Jurkat NFAT-luciferase cells, where disruption of the Sigma1 receptor-ligand interaction induces luciferase activity, when exposed to IPAG.

FIG. 3A depicts protein levels of PD-L1, beta-actin, and Sigma1 under certain conditions as described elsewhere herein. FIG. 3B depicts a graph illustrating the protein levels of PD-L1 under the conditions used to generate the data illustrated in FIG. 3A.

FIG. 4A depicts the protein levels of PD-L1 under certain conditions as described elsewhere herein.

FIG. 4B depicts a graph illustrating the protein levels of PD-L1 under certain conditions as described elsewhere herein.

FIG. 5 depicts the effects of Compound G on tumor growth in immune competent animals (left panel) as compared to immune deficient animals (right panel).

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred methods and materials are described. As used herein, each of the following terms has the meaning associated with it in this section.

The articles “a” and “an” are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

The term “abnormal,” when used in the context of organisms, tissues, cells or components thereof, refers to those organisms, tissues, cells or components thereof that differ in

at least one observable or detectable characteristic (*e.g.*, age, phenotype, treatment, time of day, etc.) from those organisms, tissues, cells or components thereof that display the “normal” (expected) respective characteristic. Characteristics that are normal or expected for one cell or tissue type might be abnormal for a different cell or tissue type.

5 “About” as used herein when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of $\pm 10\%$, $\pm 5\%$, $\pm 1\%$, or $\pm 0.1\%$ from the specified value, or as such variations are appropriate to perform the disclosed methods.

A disease or disorder is “alleviated” if the severity of a symptom, phenotype, tumor size, 10 and the like of the disease or disorder is reduced or the conditions is considered to be improved.

As used herein, the term “BD1047” refers to N’-[2-(3,4-dichlorophenyl)ethyl]-N,N,N’-trimethylethane-1,2-diamine, or a pharmaceutically acceptable salt or solvate thereof.

As used herein, the term “BD1063” refers to 1-[2-(3,4-dichlorophenyl)ethyl]-4-methyl piperazine, or a pharmaceutically acceptable salt or solvate thereof.

15 As used herein, the term “composition” or “pharmaceutical composition” refers to a mixture of at least one compound useful within the disclosure with a pharmaceutically acceptable carrier. The pharmaceutical composition facilitates administration of the compound to a patient or subject. Multiple techniques of administering a compound exist in the art including, but not limited to, intravenous, oral, aerosol, parenteral, ophthalmic, sublingual, pulmonary and 20 topical administration. The compounds can also be a pharmaceutically acceptable salt of the compounds described herein.

As used herein, the term “E64d” refers to (2S,3S)-trans-epoxysuccinyl-L-leucylamido-3-methylbutane ethyl ester, or a pharmaceutically acceptable salt or solvate thereof.

As used herein, the terms “effective amount,” “pharmaceutically effective amount” and 25 “therapeutically effective amount” refer to a nontoxic but sufficient amount of an agent to provide the desired biological result. In certain embodiments, the phrase “effective amount” or “therapeutically effective amount,” as used herein, refers to an amount that is sufficient or effective to prevent or treat (delay or prevent the onset of, prevent the progression of, inhibit, decrease or reverse) a disease or condition associated with the Sigma1 receptor, including 30 alleviating symptoms of such diseases. That result may be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system.

As used herein, the term “haloperidol” refers to 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidyl]-1-(4-fluorophenyl)-butan-1-one, or a pharmaceutically acceptable salt or solvate thereof.

As used herein, the phrase “in need thereof” means that the subject has been identified or suspected as having a need for the particular method or treatment. In certain embodiments, the identification can be by any means of diagnosis. In any of the methods and treatments described herein, the subject can be in need thereof.

As used herein, the term “IPAG” refers to 1-(4-iodophenyl)-3-(2-adamantyl)guanidine, or a pharmaceutically acceptable salt or solvate thereof.

The terms “patient,” “subject,” “individual,” and the like are used interchangeably herein, and refer to any animal, or cells thereof whether *in vitro* or *in situ*, amenable to the methods described herein. In certain embodiments, the patient, subject or individual is a human. In certain embodiments, the subject is a dog, cat, or horse.

As used herein, the term “PB28” refers to 1-cyclohexyl-4-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)propyl]piperazine, or a pharmaceutically acceptable salt or solvate thereof.

As used herein, the term “methyladenine” refers to 3-methyladenine, or a pharmaceutically acceptable salt or solvate thereof.

As used herein, the term “NE100” refers to 4-methoxy-3-(2-phenylethoxy)-N,N-dipropylbenzeneethanamine, or a pharmaceutically acceptable salt or solvate thereof.

As used herein, the term “pharmaceutically acceptable” refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively non-toxic, *i.e.*, the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

As used herein, the term “(+)-pentazocine” refers to (+)-[2S-(2,6,11R*)]-1,2,3,4,5,6-hexahydro-6,1-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol, or a pharmaceutically acceptable salt or solvate thereof.

As used herein, the term “pharmaceutically acceptable carrier” means a pharmaceutically acceptable material, composition or carrier, such as a liquid or solid filler, stabilizer, dispersing agent, suspending agent, diluent, excipient, thickening agent, solvent or encapsulating material, involved in carrying or transporting a compound useful within the disclosure within or to the

patient such that it may perform its intended function. Typically, such constructs are carried or transported from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation, including the compound useful within the disclosure, and not injurious to the patient. Some examples of materials that may serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; surface active agents; alginic acid; pyrogen-free water; isotonic saline; Ringer’s solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

As used herein, “pharmaceutically acceptable carrier” also includes any and all coatings, antibacterial and antifungal agents, and absorption delaying agents, and the like that are compatible with the activity of the compound useful within the disclosure, and are physiologically acceptable to the patient. Supplementary active compounds may also be incorporated into the compositions. The “pharmaceutically acceptable carrier” may further include a pharmaceutically acceptable salt of the compound useful within the disclosure. Other additional ingredients that may be included in the pharmaceutical compositions used in the practice of the disclosure are known in the art and described, for example in Remington’s Pharmaceutical Sciences (Genaro, Ed., Mack Publishing Co., 1985, Easton, Pa.), which is incorporated herein by reference.

As used herein, the language “pharmaceutically acceptable salt” refers to a salt of the administered compounds prepared from pharmaceutically acceptable non-toxic acids, including inorganic acids, organic acids, solvates, hydrates, or clathrates thereof. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, acetic, hexafluorophosphoric, citric, gluconic, benzoic, propionic, butyric, sulfosalicylic, maleic, lauric, malic, fumaric, succinic, tartaric, amsonic, pamoic, p-toluenesulfonic, and mesylic. Appropriate organic acids may be selected, for example, from aliphatic, aromatic, carboxylic and sulfonic

classes of organic acids, examples of which are formic, acetic, propionic, succinic, camphorsulfonic, citric, fumaric, gluconic, isethionic, lactic, malic, mucic, tartaric, para-toluenesulfonic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic (besylate), stearic, sulfanilic, alginic, galacturonic, and the like. Furthermore, pharmaceutically acceptable salts include, by way of non-limiting example, alkaline earth metal salts (e.g., calcium or magnesium), alkali metal salts (e.g., sodium-dependent or potassium), and ammonium salts.

As used herein, the term "PRE084" refers to 2-morpholin-4-ylethyl 1-phenyl cyclohexane-1-carboxylate, or a pharmaceutically acceptable salt or solvate thereof.

As used herein, the term "rimcazole" refers to 9-{3-[(3R,5S)-3,5-dimethylpiperazin-1-yl]propyl}-9H-carbazole, or a pharmaceutically acceptable salt or solvate thereof.

As used herein, the term "Sigma1" or "Sigma 1" refers to the Sigma1 receptor (Sigma1), Sigma1 receptor gene (SIGMAR1), Sigma1 receptor protein, and any splice variant thereof or any isoform thereof.

As used herein, a "Sigma1 modulator" refers to a compound, or solvate or salt thereof, that binds to the Sigma1 receptor and modifies the activity or biological function of the receptor as compared to the activity or biological function of the receptor in the absence of the modulator. The modulator may be a receptor agonist, which is able to activate the receptor and cause a biological response that is enhanced over the baseline activity of the unbound receptor. The modulator may be a partial agonist, which does not activate the receptor thoroughly and causes a biological response that is smaller in magnitude compared to those of full agonists. The modulator may be an antagonist, which binds to the receptor but does not activate it, resulting in receptor blockage and inhibiting the binding of other agonists. An antagonist does not diminish the baseline intracellular response in the absence of an agonist. The modulator may be an inverse agonistic, which reduces the activity of the receptor by inhibiting its constitutive activity. In certain embodiments, the modulator is a specific modulator to Sigma1. In certain embodiments, the Sigma1 modulator possesses a binding affinity (K_d) for Sigma1 of less than about 100 nM and has an *in vivo* effect of restoring a normal immune system profile.

As used herein, the term "(+)-SKF10047" refers to [2S-(2a,6a,11R*)]-1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazocin-8-ol, or a pharmaceutically

acceptable salt or solvate thereof.

As used herein, the term “tamoxifen” refers to (Z)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-N,N-dimethylethanamine, or a pharmaceutically acceptable salt or solvate thereof.

5 A “therapeutic” treatment is a treatment administered to a subject who exhibits signs of pathology, for the purpose of diminishing or eliminating those signs.

As used herein, the term “treatment” or “treating” is defined as the application or administration of a therapeutic agent or mixture of agents, *e.g.*, a compound disclosed herein (alone or in combination with another pharmaceutical agent), to a patient, or application or
10 administration of a therapeutic agent or mixture of agents to a tissue or cell line from a patient (*e.g.*, for diagnosis or *ex vivo* applications), who has a condition contemplated herein, a symptom of a condition contemplated herein or the potential to develop a condition contemplated herein, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect a condition contemplated herein, the symptoms of a condition contemplated
15 herein or the potential to develop a condition contemplated herein. Such treatments may be specifically tailored or modified, based on knowledge obtained from the field of pharmacogenomics.

As used herein, the term “alkyl,” by itself or as part of another substituent means, unless otherwise stated, a straight or branched chain hydrocarbon having the number of carbon atoms
20 designated (*i.e.* C₁₋₆ means one to six carbon atoms) and including straight, branched chain, or cyclic substituent groups. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, hexyl, and cyclopropylmethyl. In certain embodiments, a (C₁-C₆) alkyl is ethyl, methyl, isopropyl, isobutyl, n-pentyl, n-hexyl and cyclopropylmethyl.

As used herein, the term “substituted alkyl” means alkyl as defined above, substituted by
25 one, two or three substituents selected from the group consisting of halogen, –OH, alkoxy, –NH₂, –N(CH₃)₂, –C(=O)OH, trifluoromethyl, –CN, –C(=O)O(C₁-C₄)alkyl, –C(=O)NH₂, –SO₂NH₂, –C(=NH)NH₂, and –NO₂, preferably containing one or two substituents selected from halogen, –OH, alkoxy, –NH₂, trifluoromethyl, –N(CH₃)₂, and –C(=O)OH, more preferably selected from halogen, alkoxy and –OH. Examples of substituted alkyls include, but are not limited to, 2,2-
30 difluoropropyl, 2-carboxycyclopentyl and 3-chloropropyl.

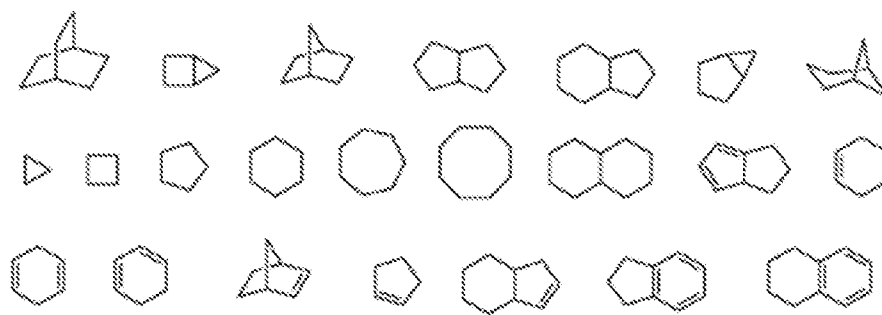
As used herein, the term “heteroalkyl” by itself or in combination with another term

means, unless otherwise stated, a stable straight or branched chain alkyl group consisting of the stated number of carbon atoms and one or two heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may be optionally oxidized and the nitrogen heteroatom may be optionally quaternized. The heteroatom(s) may be placed at any position of the heteroalkyl group, including between the rest of the heteroalkyl group and the fragment to which it is attached, as well as attached to the most distal carbon atom in the heteroalkyl group. Examples include: $-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{OH}$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, and $-\text{CH}_2\text{CH}_2-\text{S}(=\text{O})-\text{CH}_3$. Up to two heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$, or $-\text{CH}_2-\text{CH}_2-\text{S}-\text{S}-\text{CH}_3$.

As used herein, the term “alkoxy” employed alone or in combination with other terms means, unless otherwise stated, an alkyl group having the designated number of carbon atoms, as defined above, connected to the rest of the molecule via an oxygen atom, such as, for example, methoxy, ethoxy, 1-propoxy, 2-propoxy (isopropoxy) and the higher homologs and isomers. In certain embodiments, the alkoxy is $\text{C}_1\text{-C}_3$ alkoxy, such as ethoxy and methoxy.

As used herein, the term “halo” or “halogen” alone or as part of another substituent means, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom, preferably, fluorine, chlorine, or bromine, more preferably, fluorine or chlorine.

As used herein, the term “cycloalkyl” refers to a mono cyclic or polycyclic non-aromatic radical, wherein each of the atoms forming the ring (*i.e.* skeletal atoms) is a carbon atom. In one embodiment, the cycloalkyl group is saturated or partially unsaturated. In other embodiments, the cycloalkyl group is fused with an aromatic ring. Cycloalkyl groups include groups having from 3 to 10 ring atoms. Illustrative examples of cycloalkyl groups include, but are not limited to, the following moieties:

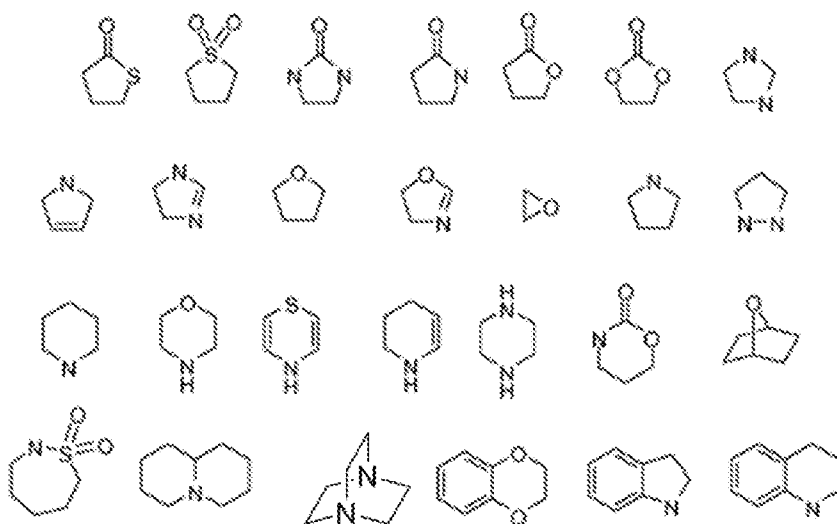


Monocyclic cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Dicyclic cycloalkyls include, but are not

limited to, tetrahydronaphthyl, indanyl, and tetrahydropentalene. Polycyclic cycloalkyls include adamantane and norbornane. The term cycloalkyl includes “unsaturated nonaromatic carbocyclyl” or “nonaromatic unsaturated carbocyclyl” groups, both of which refer to a nonaromatic carbocycle as defined herein, which contains at least one carbon carbon double bond or one carbon carbon triple bond.

As used herein, the term “heterocycloalkyl” or “heterocyclyl” refers to a heteroalicyclic group containing one to four ring heteroatoms each selected from O, S and N. In one embodiment, each heterocycloalkyl group has from 4 to 10 atoms in its ring system, with the proviso that the ring of said group does not contain two adjacent O or S atoms. In other embodiments, the heterocycloalkyl group is fused with an aromatic ring. In one embodiment, the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen atom may be optionally quaternized. The heterocyclic system may be attached, unless otherwise stated, at any heteroatom or carbon atom that affords a stable structure. A heterocycle may be aromatic or non-aromatic in nature. In one embodiment, the heterocycle is a heteroaryl.

An example of a 3-membered heterocycloalkyl group includes, and is not limited to, aziridine. Examples of 4-membered heterocycloalkyl groups include, and are not limited to, azetidine and a beta lactam. Examples of 5-membered heterocycloalkyl groups include, and are not limited to, pyrrolidine, oxazolidine and thiazolidinedione. Examples of 6-membered heterocycloalkyl groups include, and are not limited to, piperidine, morpholine and piperazine. Other non-limiting examples of heterocycloalkyl groups are:



Examples of non-aromatic heterocycles include monocyclic groups such as aziridine,

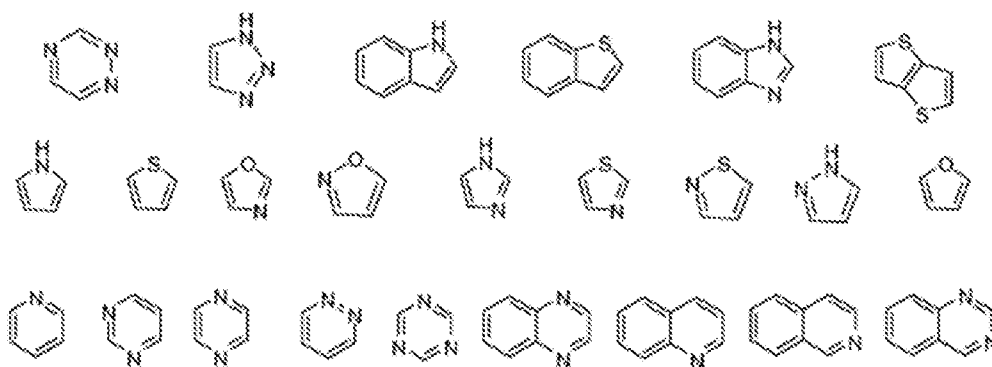
oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, pyrazolidine, imidazoline, dioxolane, sulfolane, 2,3-dihydrofuran, 2,5-dihydrofuran, tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydropyridine, 1,4-dihydropyridine, piperazine, morpholine, thiomorpholine, pyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dioxane, 1,3-dioxane, homopiperazine, homopiperidine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethyleneoxide.

As used herein, the term “aromatic” refers to a carbocycle or heterocycle with one or more polyunsaturated rings and having aromatic character, *i.e.* having $(4n+2)$ delocalized (π) electrons, where n is an integer.

As used herein, the term “aryl,” employed alone or in combination with other terms, means, unless otherwise stated, a carbocyclic aromatic system containing one or more rings (such as one, two or three rings), wherein such rings may also be attached together in a pendent manner, such as a biphenyl, or may be fused, such as naphthalene. Examples of aryl groups include phenyl, anthracyl, and naphthyl. Preferred examples are phenyl and naphthyl, most preferred is phenyl.

As used herein, the term “aryl-(C₁-C₃)alkyl” means a functional group wherein a one- to three-carbon alkylene chain is attached to an aryl group, *e.g.*, $-\text{CH}_2\text{CH}_2\text{-phenyl}$. Preferred is aryl- $\text{CH}_2\text{-}$ and aryl- $\text{CH}(\text{CH}_3)\text{-}$. The term “substituted aryl-(C₁-C₃)alkyl” means an aryl-(C₁-C₃)alkyl functional group in which the aryl group is substituted. Preferred is substituted aryl(CH_2)-. Similarly, the term “heteroaryl-(C₁-C₃)alkyl” means a functional group wherein a one to three carbon alkylene chain is attached to a heteroaryl group, *e.g.*, $-\text{CH}_2\text{CH}_2\text{-pyridyl}$. Preferred is heteroaryl-(CH_2)-. The term “substituted heteroaryl-(C₁-C₃)alkyl” means a heteroaryl-(C₁-C₃)alkyl functional group in which the heteroaryl group is substituted. Preferred is substituted heteroaryl-(CH_2)-.

As used herein, the term “heteroaryl” or “heteroaromatic” refers to a heterocycle having aromatic character. A polycyclic heteroaryl may include one or more rings that are partially saturated. Examples include the following moieties:



Examples of heteroaryl groups also include pyridyl, pyrazinyl, pyrimidinyl (particularly 2- and 4-pyrimidinyl), pyridazinyl, thienyl, furyl, pyrrolyl (particularly 2-pyrrolyl), imidazolyl, thiazolyl, oxazolyl, pyrazolyl (particularly 3- and 5-pyrazolyl), isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,3,4-thiadiazolyl and 1,3,4-oxadiazolyl. Examples of polycyclic heterocycles and heteroaryls include indolyl (particularly 3-, 4-, 5-, 6- and 7-indolyl), indolinyl, quinolyl, tetrahydroquinolyl, isoquinolyl (particularly 1- and 5-isoquinolyl), 1,2,3,4-tetrahydroisoquinolyl, cinnolinyl, quinoxaliny (particularly 2- and 5-quinoxaliny), quinazolinyl, phthalazinyl, 1,8-naphthyridinyl, 1,4-benzodioxanyl, coumarin, dihydrocoumarin, 1,5-naphthyridinyl, benzofuryl (particularly 3-, 4-, 5-, 6- and 7-benzofuryl), 2,3-dihydrobenzofuryl, 1,2-benzisoxazolyl, benzothienyl (particularly 3-, 4-, 5-, 6-, and 7-benzothienyl), benzoxazolyl, benzothiazolyl (particularly 2-benzothiazolyl and 5-benzothiazolyl), purinyl, benzimidazolyl (particularly 2-benzimidazolyl), benzotriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrrolizidinyl, and quinolizidinyl.

As used herein, the term “substituted” means that an atom or group of atoms has replaced hydrogen as the substituent attached to another group. The term “substituted” further refers to any level of substitution, namely mono-, di-, tri-, tetra-, or penta-substitution, where such substitution is permitted. The substituents are independently selected, and substitution may be at any chemically accessible position. In one embodiment, the substituents vary in number between one and four. In other embodiments, the substituents vary in number between one and three. In yet another embodiment, the substituents vary in number between one and two.

As used herein, the term “optionally substituted” means that the referenced group may be substituted or unsubstituted. In certain embodiments, the referenced group is optionally substituted with zero substituents, *i.e.*, the referenced group is unsubstituted. In other embodiments, the referenced group is optionally substituted with one or more additional group(s)

individually and independently selected from groups described herein.

In certain embodiments, the substituents are independently selected from the group consisting of oxo, halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NH}(\text{CH}_3)$, $-\text{N}(\text{CH}_3)_2$, alkyl (including straight chain, branched and/or unsaturated alkyl), substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, fluoro alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkoxy, fluoroalkoxy, $-\text{S-alkyl}$, $\text{S}(=\text{O})_2\text{alkyl}$, $-\text{C}(=\text{O})\text{NH}[\text{substituted or unsubstituted alkyl, or substituted or unsubstituted phenyl}]$, $-\text{C}(=\text{O})\text{N}[\text{H or alkyl}]_2$, $-\text{OC}(=\text{O})\text{N}[\text{substituted or unsubstituted alkyl}]_2$, $-\text{NHC}(=\text{O})\text{NH}[\text{substituted or unsubstituted alkyl, or substituted or unsubstituted phenyl}]$, $-\text{NHC}(=\text{O})\text{alkyl}$, $-\text{N}[\text{substituted or unsubstituted alkyl}]\text{C}(=\text{O})[\text{substituted or unsubstituted alkyl}]$, $-\text{NHC}(=\text{O})[\text{substituted or unsubstituted alkyl}]$, $-\text{C}(\text{OH})[\text{substituted or unsubstituted alkyl}]_2$, and $-\text{C}(\text{NH}_2)[\text{substituted or unsubstituted alkyl}]_2$. In other embodiments, by way of example, an optional substituent is selected from oxo, fluorine, chlorine, bromine, iodine, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NH}(\text{CH}_3)$, $-\text{N}(\text{CH}_3)_2$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}(\text{CH}_3)_2$, $-\text{OCF}_3$, $-\text{OCH}_2\text{CF}_3$, $-\text{S}(=\text{O})_2-\text{CH}_3$, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})-\text{NHCH}_3$, $-\text{NHC}(=\text{O})\text{NHCH}_3$, $-\text{C}(=\text{O})\text{CH}_3$, and $-\text{C}(=\text{O})\text{OH}$. In yet one embodiment, the substituents are independently selected from the group consisting of C_{1-6} alkyl, $-\text{OH}$, C_{1-6} alkoxy, halo, amino, acetamido, oxo and nitro. In yet another embodiment, the substituents are independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, halo, acetamido, and nitro. As used herein, where a substituent is an alkyl or alkoxy group, the carbon chain may be branched, straight or cyclic. In certain embodiments, the chain is straight.

Ranges: various aspects of the disclosure can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the disclosure. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range and also the endpoints of the range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed sub-ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. This applies regardless of the breadth of the range.

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure provides, in certain aspects, compounds that are useful in the treatment of Sigma receptor-related diseases and disorders, either alone or in combination with at least one additional therapeutic agent.

The present disclosure further provides, in certain aspects, methods of preventing, treating, and/or ameliorating disorders or diseases in a subject that are mediated by IL-6 and/or gp130 using compounds that bind to and modulate the activity of the Sigma receptor. In certain embodiments, the method comprising administering one or more compounds contemplated herein, alone or in combination with an additional therapeutic agent to the subject. In certain embodiments, the Sigma modulator is a Sigma antagonist, inverse agonist or agonist. In certain
10 embodiments, the Sigma modulator is a Sigma antagonist. In certain embodiments, the Sigma receptor is a Sigma₁ receptor. In certain embodiments, the method comprises administering therapeutically effective amount(s) of one or more compounds described herein, alone or in combination with an additional therapeutic agent, to the subject.

In some embodiment, the IL-6- and/or gp130-mediated disease or disorder comprises at
15 least one selected from the group consisting of cancer, autoimmune disease, and infection, such as, but not limited to leukemia, acute leukemia, acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, B-cell, T-cell or FAB ALL, acute myeloid leukemia (AML), acute myelogenous leukemia, chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodysplastic syndrome (MDS), a lymphoma, Hodgkin's disease, a
20 malignant lymphoma, non-Hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, Kaposi's sarcoma, colorectal carcinoma, pancreatic carcinoma, nasopharyngeal carcinoma, malignant histiocytosis, paraneoplastic syndrome/hypercalcemia of malignancy, solid tumors, bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head cancer, neck cancer, hereditary nonpolyposis cancer, Hodgkin's lymphoma, liver cancer, lung cancer, non-small cell
25 lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, testicular cancer, adenocarcinomas, sarcomas, malignant melanoma, hemangioma, metastatic disease, cancer related bone resorption, cancer related bone pain, rheumatoid arthritis, juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, gastric ulcer, seronegative arthropathies, osteoarthritis, osteolysis, inflammatory
30 bowel disease, ulcerative colitis, systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, antiphospholipid syndrome, iridocyclitis/uveitis/optic neuritis, idiopathic

pulmonary fibrosis, systemic vasculitis/wegener's granulomatosis, sarcoidosis, orchitis/vasectomy reversal procedures, allergic/atopic diseases, asthma, allergic rhinitis, eczema, allergic contact dermatitis, allergic conjunctivitis, hypersensitivity pneumonitis, transplants, organ transplant rejection, graft-versus-host disease, systemic inflammatory response syndrome, sepsis syndrome, gram positive sepsis, gram negative sepsis, culture negative sepsis, fungal sepsis, neutropenic fever, urosepsis, meningococcemia, trauma/hemorrhage, burns, ionizing radiation exposure, acute pancreatitis, adult respiratory distress syndrome, rheumatoid arthritis, alcohol-induced hepatitis, chronic inflammatory pathologies, sarcoidosis, Crohn's pathology, sickle cell anemia, diabetes, nephrosis, atopic diseases, hypersensitivity reactions, allergic rhinitis, hay fever, perennial rhinitis, conjunctivitis, endometriosis, asthma, urticaria, systemic anaphylaxis, dermatitis, pernicious anemia, hemolytic disease, thrombocytopenia, graft rejection of any organ or tissue, kidney transplant rejection, heart transplant rejection, liver transplant rejection, pancreas transplant rejection, lung transplant rejection, bone marrow transplant (BMT) rejection, skin allograft rejection, cartilage transplant rejection, bone graft rejection, small bowel transplant rejection, fetal thymus implant rejection, parathyroid transplant rejection, xenograft rejection of any organ or tissue, allograft rejection, anti-receptor hypersensitivity reactions, Graves disease, Raynaud's disease, type B insulin-resistant diabetes, asthma, myasthenia gravis, antibody-mediated cytotoxicity, type III hypersensitivity reactions, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome, antiphospholipid syndrome, pemphigus, scleroderma, mixed connective tissue disease, idiopathic Addison's disease, diabetes mellitus, chronic active hepatitis, primary biliary cirrhosis, vitiligo, vasculitis, post-MI cardiomyopathy syndrome, type IV hypersensitivity, contact dermatitis, hypersensitivity pneumonitis, allograft rejection, granulomas due to intracellular organisms, drug sensitivity, metabolic/idiopathic, Wilson's disease, hemochromatosis, alpha-1-antitrypsin deficiency, diabetic retinopathy, Hashimoto's thyroiditis, osteoporosis, hypothalamic-pituitary-adrenal axis evaluation, primary biliary cirrhosis, thyroiditis, encephalomyelitis, cachexia, cystic fibrosis, neonatal chronic lung disease, chronic obstructive pulmonary disease (COPD), familial hemophagocytic lymphohistiocytosis, dermatologic conditions, psoriasis, alopecia, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, hemodialysis, uremia, toxicity, preeclampsia, acute or chronic bacterial

infection, acute and chronic parasitic or infectious processes, including bacterial, viral and fungal infections, HIV infection/HIV neuropathy, meningitis, hepatitis (e.g., A, B or C, or the like), septic arthritis, peritonitis, pneumonia, epiglottitis, *E. coli* 0157:h7, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, malaria, dengue hemorrhagic fever, leishmaniasis, leprosy, toxic shock syndrome, streptococcal myositis, gas gangrene, *Mycobacterium tuberculosis*, *Mycobacterium avium* intracellulare, *Pneumocystis carinii* pneumonia, pelvic inflammatory disease, orchitis/epididymitis, *Legionella*, Lyme disease, influenza A, Epstein-Barr virus, viral-associated hemaphagocytic syndrome, viral encephalitis/aseptic meningitis, and the like.

The present disclosure further provides, in certain aspects, methods of preventing, treating, and/or ameliorating disorders or diseases mediated by PD-L1 using compounds that bind to and modulate the activity of the Sigma receptor. In certain embodiments, the method comprises administering one or more compounds contemplated herein, alone or in combination with an additional therapeutic agent, to the subject. In certain embodiments, the Sigma modulator of the invention is a Sigma antagonist, inverse agonist or agonist. In other embodiments, the Sigma modulator of the invention is a Sigma antagonist. In yet another embodiment, the Sigma receptor is a Sigma1 receptor (also known as Sigma1). In certain embodiments, the method comprises administering therapeutically effective amount(s) of one or more compounds described herein, alone or in combination with an additional therapeutic agent, to the subject.

In certain embodiments, the PD-L1-mediated disease or disorder comprises at least one selected from the group consisting of cancer, autoimmune disease and infection, such as, but not limited to, leukemia, acute leukemia, acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, B-cell, T-cell or FAB ALL, acute myeloid leukemia (AML), acute myelogenous leukemia, chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodysplastic syndrome (MDS), a lymphoma, Hodgkin's disease, a malignant lymphoma, non-Hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, Kaposi's sarcoma, colorectal carcinoma, pancreatic carcinoma, nasopharyngeal carcinoma, malignant histiocytosis, paraneoplastic syndrome/hypercalcemia of malignancy, solid tumors, bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head cancer, neck cancer, hereditary nonpolyposis cancer, Hodgkin's lymphoma, liver cancer, lung cancer, non-small cell lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, testicular cancer,

adenocarcinomas, sarcomas, malignant melanoma, hemangioma, metastatic disease, cancer related bone resorption, cancer related bone pain, rheumatoid arthritis, juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, gastric ulcer, seronegative arthropathies, osteoarthritis, osteolysis, inflammatory bowel disease, ulcerative colitis, systemic lupus erythematosus, cutaneous lupus erythematosus, lupus nephritis, antiphospholipid syndrome, iridocyclitis/uveitis/optic neuritis, idiopathic pulmonary fibrosis, systemic vasculitis/wegener's granulomatosis, sarcoidosis, orchitis/vasectomy reversal procedures, allergic/atopic diseases, asthma, allergic rhinitis, eczema, allergic contact dermatitis, allergic conjunctivitis, hypersensitivity pneumonitis, transplants, organ transplant rejection, graft-versus-host disease, systemic inflammatory response syndrome, sepsis syndrome, gram positive sepsis, gram negative sepsis, culture negative sepsis, fungal sepsis, neutropenic fever, urosepsis, meningococemia, trauma/hemorrhage, burns, ionizing radiation exposure, acute pancreatitis, adult respiratory distress syndrome, rheumatoid arthritis, alcohol-induced hepatitis, chronic inflammatory pathologies, sarcoidosis, Crohn's pathology, sickle cell anemia, diabetes, nephrosis, atopic diseases, hypersensitivity reactions, allergic rhinitis, hay fever, perennial rhinitis, conjunctivitis, endometriosis, asthma, urticaria, systemic anaphylaxis, dermatitis, pernicious anemia, hemolytic disease, thrombocytopenia, graft rejection of any organ or tissue, kidney transplant rejection, heart transplant rejection, liver transplant rejection, pancreas transplant rejection, lung transplant rejection, bone marrow transplant (BMT) rejection, skin allograft rejection, cartilage transplant rejection, bone graft rejection, small bowel transplant rejection, fetal thymus implant rejection, parathyroid transplant rejection, xenograft rejection of any organ or tissue, allograft rejection, anti-receptor hypersensitivity reactions, Graves disease, Raynaud's disease, type B insulin-resistant diabetes, asthma, myasthenia gravis, antibody-mediated cytotoxicity, type III hypersensitivity reactions, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome, antiphospholipid syndrome, pemphigus, scleroderma, mixed connective tissue disease, idiopathic Addison's disease, diabetes mellitus, chronic active hepatitis, primary biliary cirrhosis, vitiligo, vasculitis, post-MI cardiomyopathy syndrome, type IV hypersensitivity, contact dermatitis, hypersensitivity pneumonitis, allograft rejection, granulomas due to intracellular organisms, drug sensitivity, metabolic/idiopathic, Wilson's disease, hemochromatosis, alpha-1-

antitrypsin deficiency, diabetic retinopathy, Hashimoto's thyroiditis, osteoporosis, hypothalamic-pituitary-adrenal axis evaluation, primary biliary cirrhosis, thyroiditis, encephalomyelitis, cachexia, cystic fibrosis, neonatal chronic lung disease, chronic obstructive pulmonary disease (COPD), familial hemophagocytic lymphohistiocytosis, dermatologic conditions, psoriasis, alopecia, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, hemodialysis, uremia, toxicity, preeclampsia, acute or chronic bacterial infection, acute and chronic parasitic or infectious processes, including bacterial, viral and fungal infections, HIV infection/HIV neuropathy, meningitis, hepatitis (e.g., A, B or C, or the like), septic arthritis, peritonitis, pneumonia, epiglottitis, *E. coli* 0157:h7, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura, malaria, dengue hemorrhagic fever, leishmaniasis, leprosy, toxic shock syndrome, streptococcal myositis, gas gangrene, *Mycobacterium tuberculosis*, *Mycobacterium avium* intracellulare, *Pneumocystis carinii* pneumonia, pelvic inflammatory disease, orchitis/epididymitis, *Legionella*, Lyme disease, influenza A, Epstein-Barr virus, viral-associated hemophagocytic syndrome, viral encephalitis/aseptic meningitis, and the like.

In certain embodiments, the invention provides methods of treating cancer in a subject. In certain embodiments, the methods comprise detecting whether PD-1 or PD-L1 is present in a cancer sample from the subject. In certain embodiments, the methods comprise administering to the subject in which cancer sample PD-1 or PD-L1 is detected one or more compounds, compositions or therapeutic agents described herein, or any combination thereof. In certain embodiments, the method comprising administering therapeutically effective amount(s) of one or more compounds described herein, alone or in combination with an additional therapeutic agent, to the subject.

PD-1 and/or PD-L1 can be detected using any method known in the art and/or described herein. The detection can be based upon protein or mRNA levels of PD-L1. For example, the PD-L1 IHC 22C3 PHARMDX™ immunohistochemistry companion diagnostic test can be used to detect PD-L1. This particular test is already used, for example, as a companion diagnostic in the use of pembrolizumab. This is just one non-limiting example of how PD-L1 can be detected, and any other known test can be used. In certain embodiments, prior to the administration of one or more compounds, compositions or therapeutic agents described herein, or any combination thereof, a tumor sample for a subject can be analyzed for the expression of PD-L1. If the tumor sample is found to have PD-L1 present, the subject can be treated with the compounds and

compositions described herein. However, in certain embodiments, the subject is treated with any of the compounds described herein even if PD-L1 is not present. In certain embodiments, the subject is not treated with any of the compounds described herein if PD-L1 is not detected in the sample.

5 In certain embodiments, compounds that can be used in the methods described herein include the compounds, or pharmaceutically acceptable salts thereof, of Formula (I), Formula (I-A), Formula (I-B), and Formula (II) as described herein, and/or species thereof, as well as any compound known to be a Sigma1 antagonist, agonist or inverse agonist, such as but not limited to haloperidol, IPAG, PB28, rimcazone, BD1063, BD1047, PRE084, NE100, (+)-SKF10047, (+)-
10 pentazocine, and any combinations thereof.

Without wishing to be limited by theory, protein homeostasis / “proteostasis” (*i.e.*, maintenance of proper protein synthesis, processing, folding, transport, assembly, and degradation) modulating properties of the compounds of the invention allow them to be used in the treatment of any disease in which protein homeostasis is disrupted (*e.g.*, neurodegenerative
15 diseases) or in which this process plays an important role, which in some cases be a key or crucial role (*e.g.*, cancer). In certain embodiments, the compound of the invention crosses the blood-brain barrier. In certain embodiments, the compound of the invention does not cross the blood-brain barrier.

In certain embodiments, the invention provides compositions comprising at least one
20 compound described herein. In other embodiments, the composition further comprises at least one additional therapeutic agent. In yet other embodiments, the composition is administered with or in timing proximity to an additional therapeutic agent. Accordingly, in certain embodiments, compositions are provided comprising a Sigma1 receptor-modulating compound and at least one additional therapeutic agent. In one embodiment, the additional therapeutic agent targets the
25 UPR and/or autophagic survival pathway. In other embodiments, the additional therapeutic agent binds to and modulates the Sigma1 receptor. In yet another embodiment, the additional therapeutic agent is a chemotherapeutic and/or hormone therapy agent. In certain embodiments, the additional therapeutic binds to IL-6. In certain embodiments, the additional therapeutic inhibits the activity of IL-6. In certain embodiments, the additional therapeutic enhances the
30 activity of IL-6. As discussed herein, IL-6 acts through its binding to IL-6R. Therefore, a composition provided herein can also comprise or be administered with an additional therapeutic

agent that acts on IL-6R. In certain embodiments, the additional therapeutic binds to IL-6R and blocks its activity. In certain embodiments, the additional therapeutic binds to PD-L1 and blocks its activity. In certain embodiments, the additional therapeutic inhibits the activity of PD-L1. As discussed herein, PD-L1 acts through its binding to PD-1. Therefore, a composition provided

5 herein can also comprise or be administered with an additional therapeutic agent that acts on PD-1. In certain embodiments, the additional therapeutic binds to PD-1 and blocks its activity. In certain embodiments, the additional therapeutic inhibits the activity of PD-1. In certain embodiments, the additional therapeutic is an antibody. In certain embodiments, the additional therapeutic is an anti-PD-1 antibody. In certain embodiments, the additional therapeutic is an

10 anti-PD-L1 antibody. In certain embodiments, the additional therapeutic is an anti-IL-6 antibody. The antibody can be any suitable therapeutic antibody for the subject. In certain embodiments, the antibody is a chimeric antibody, a murine antibody, a human antibody, a humanized antibody, and the like.

In certain embodiments, the antibody comprises nivolumab (OPDIVO[®]), pembrolizumab

15 (KEYTRUDA[®]), pidilizumab (CT-011, Curetech Bio), avelumab (MSB0010718C, Merck KGaA), durvalumab (MEDI4736, Medimmune), MEDI0680 (Medimmune), B7-DC-Ig (AMP224, GlaxoSmithKline), BMS-936559, atezolizumab (MPDL3280A, Genentech), CX-072 (CytomX Therapeutics), REGN2810 (Regeneron), TSR-042 (Tesaro, Inc.), STI-1014 (Sorrento Therapeutics), STI-1110 (Sorrento Therapeutics), sirukumab (CNTO 136, Janssen

20 Pharmaceuticals), siltuximab (SYLVANT[®]), olokizumab (UCB), clazakizumab (ALD518, Alder Biopharmaceuticals), gerilimumab (ARGX-109, RuiYi/arGEN-X), sarilumab (REGN88/SAR153191, Regeneron), PF-04236921 (Pfizer), anti-IL-6R nanobody (ALX-0061, Ablynx), and tocilizumab (ACTEMRA[®]).

Examples of additional therapeutic agents contemplated within the invention also

25 include, but are not limited to, growth factor receptor inhibitors, monoclonal antibodies against growth factor receptors (*e.g.*, trastuzumab), hormone receptor antagonists (*e.g.*, androgen receptor inhibitors), autophagy modulators (such as rapamycin and its analogs or “rapalogs”), ER stress response inhibitors, proteasome inhibitors, protein translation inhibitors (*e.g.*, MAPK-interacting Ser/Thr kinase 1 (MNK1) inhibitors), p97/VCP inhibitors (*e.g.*, DBE-Q and

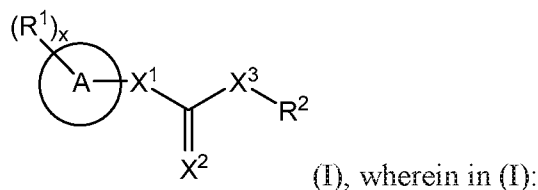
30 derivatives thereof; Chou *et al.*, 2011, PNAS U S A 108(12):4834-9), DNA repair inhibitors (*e.g.*, olaparib), and combinations thereof.

Non-limiting examples of additional therapeutic agents contemplated within the disclosure include octapeptide, somatostatin, analoguem, lanreotide, angiopeptin, dermopeptin, octreotide, pegvisomant, 3-methyladenine, chloroquine, hydroxychloroquine, wortmannin, eeyarestatin I, salubrinal, versipelostatin, 2H-isoindole-2-carboxylic acid, 4-fluoro-1,3-dihydro-
 5 (2R,6S,12Z,13aS,14aR,16aS)-14a-[[[(cyclopropyl-sulfonyl)amino]carbonyl]-6-[[[(1,1-dimethyl ethoxy)carbonyl]amino]-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-5,16-dioxocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-2-yl ester (Danoprevir), adamantane-acetyl-(6-aminohexanoyl)3-(leuciny)3-vinyl-(methyl)-sulfone, N-acetyl-L-leucyl-L-leucyl-L-methional, N-[(phenylmethoxy)carbonyl]-L-leucyl-N-[(1S)-1-formyl-3-methylbutyl]-
 10 L-leucinamide, (2R,3S,4R)-3-hydroxy-2-[(1S)-1-hydroxy-2-methylpropyl]-4-methyl-5-oxo-2-pyrrolidinecarboxy-N-acetyl-L-cysteine thioester, N-[N-(N-acetyl-L-leucyl)-L-leucyl]-L-norleucine, lactacystin, 4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride, (S)-1-carboxy-2-phenyl]-carbamoyl-Arg-Val-arginal, bovine pancreatic trypsin inhibitor, [(2S,2R)-3-amino-2-hydroxy-4-phenylbutanoyl]-L-leucine, N-[(S)-1-carboxy-isopentyl]-carbamoyl-alpha-(2-imino
 15 hexahydro-4-(S)-pyrimidyl]-L-glycyl-L-phenylalaninal, ethylenediamine-tetraacetic acid disodium salt dehydrate, acetyl-leucyl-leucyl-arginal, isovaleryl-Val-Val-AHMHA-Ala-AHMHA where AHMHA is (3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid, N-alpha-L-rhamnopyranosyloxy-(hydroxyphosphinyl)-L-leucyl-L-tryptophan, phenylmethanesulfonyl fluoride, bortezomib, carfilzomib, ONX 0912, NPI-0052, CEP-18770, MLN9708, disulfiram,
 20 epigallocatechin-3-gallate, salinosporamide A, PI3K inhibitors, lapatinib, rapamycin and rapalogs, heat shock protein (HSP) inhibitors (*e.g.*, geldanamycin and derivatives such as 17-AAG), androgen receptor inhibitors (*e.g.*, MDV3100, ARN-509), and conjugation products of Sigma1 ligands with targeting components such as Herceptin/trastuzumab (*e.g.*, trastuzumab-
 25 (Herceptin) linked to the cytotoxin mertansine–Niculescu-Duvaz, 2010, *Curr. Opin. Mol. Ther.* 12(3):350-60).

Compounds

The compounds described herein may be synthesized using techniques well-known in the art of organic synthesis. The starting materials and intermediates required for the synthesis may
 30 be obtained from commercial sources or synthesized according to methods known to those skilled in the art or as described herein.

In certain embodiments, the compound of the invention is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



- ring A is a monocyclic or bicyclic aryl or a monocyclic or bicyclic heteroaryl
 5 ring, and wherein the aryl or heteroaryl ring is optionally substituted with 0-4 R^1 groups;
 each occurrence of R^1 is independently selected from the group consisting of $-C_1$ - C_6 alkyl, $-C_1$ - C_6 fluoroalkyl, $-C_1$ - C_6 heteroalkyl, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-OR^3$, $-SR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-NHS(=O)_2R^3$, $-C(=O)R^3$, $-OC(=O)R^3$, $-CO_2R^3$, $-OCO_2R^3$, $-CH(R^3)_2$, $-N(R^3)_2$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$, $-NHC(=O)NH(R^3)$, $-NHC(=O)R^3$, $-NHC(=O)OR^3$, $-C(OH)(R^3)_2$, and $-C(NH_2)(R^3)_2$;

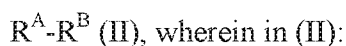
- each occurrence of R^2 is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, and $-C_1$ - C_3 alkyl- $(C_3$ - C_6 cycloalkyl), wherein the alkyl, heteroalkyl or cycloalkyl group is optionally substituted with 0-5 R^1 groups, or X^3 and R^2 combine to form a $(C_3$ - $C_7)$ heterocycloalkyl group, optionally substituted with 0-2 R^1 groups;
 15 each occurrence of R^3 is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, aryl, and $-C_1$ - C_3 alkyl- $(C_3$ - C_6 cycloalkyl), wherein the alkyl, heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

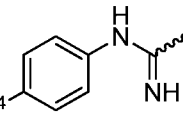
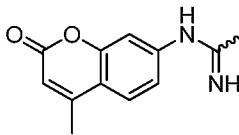
- X^1 is $-CH_2-$, $-S-$, $-O-$ or $-(NR^2)-$;
 X^2 is $=CH_2$, $=S$, $=O$ or $=NR^2$; and
 20 X^3 is $-S-$, $-O-$, or $-NR^2-$.

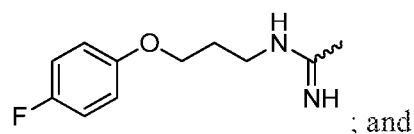
In certain embodiments, ring A is a monocyclic aryl or monocyclic heteroaryl ring optionally substituted with 0-4 R^1 groups. In certain embodiments, ring A is unsubstituted. In certain embodiments, ring A is phenyl or substituted phenyl.

In certain embodiments, X^1 and X^3 are both $-NH-$, and X^2 is NH .

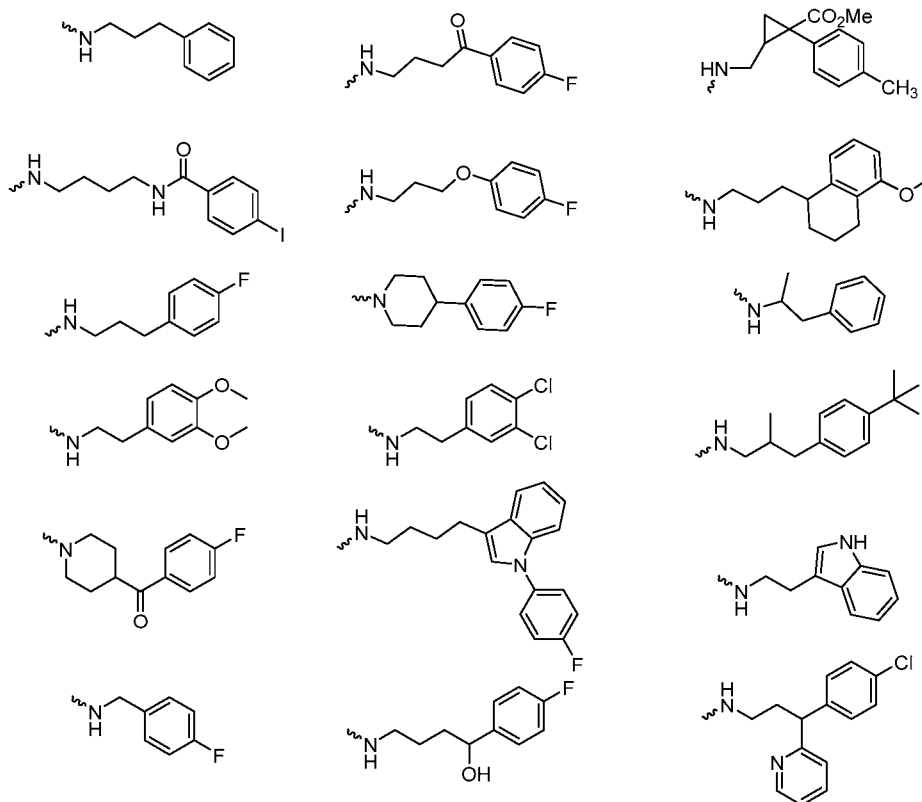
- 25 In certain embodiments, the compound of the invention is a compound of formula (II), or a pharmaceutically acceptable salt or solvate thereof:



R^A is selected from the group consisting of X^4 -, , and

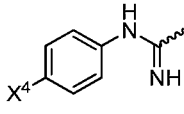
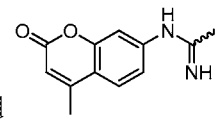


R^B is selected from the group consisting of:



5 In certain embodiments, the compound of the invention is a compound of formula (I-A), or a pharmaceutically acceptable salt or solvate thereof:

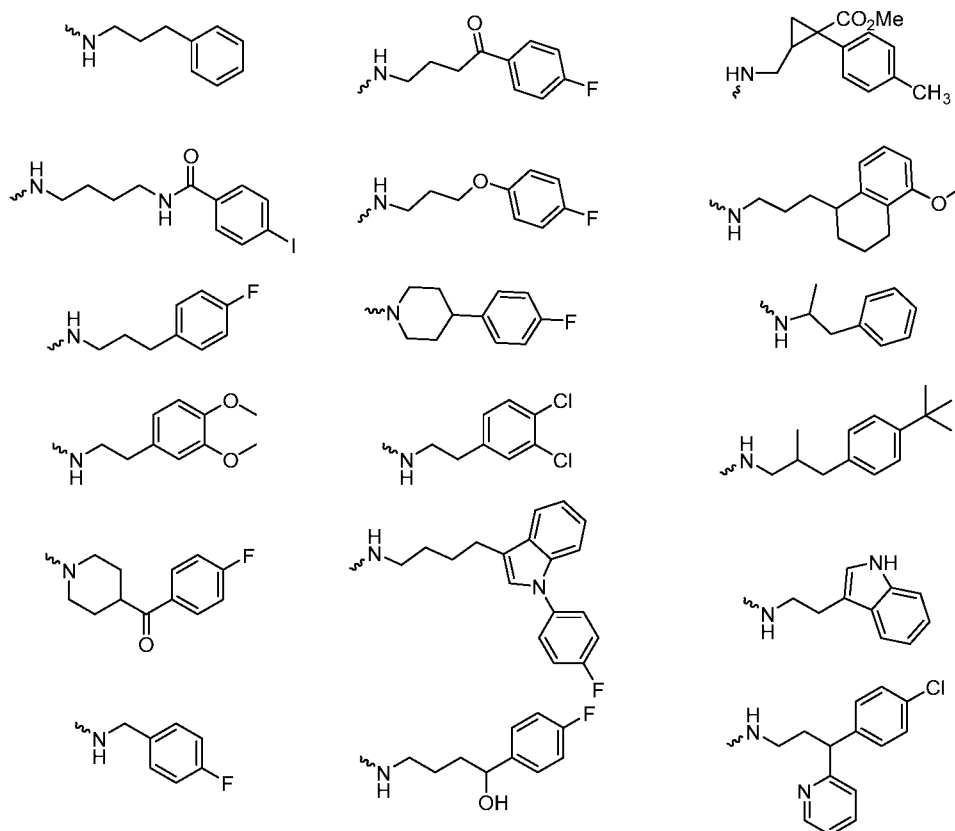
R^A - R^B (I-A), wherein in (I-A):

R^A is selected from the group consisting of X^4 - and ;

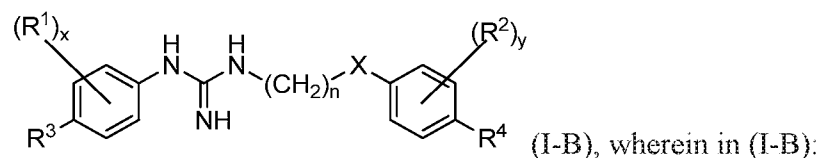
X^4 is selected from the group consisting of OMe, F, Cl, Br, and I; and

R^B is selected from the group consisting of:

10



In certain embodiments, the compound of the invention is a compound of formula (I-B), or a pharmaceutically acceptable salt or solvate thereof:



5 each occurrence of R^1 and R^2 is independently selected from the group consisting of $-C_1-C_6$ alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ heteroalkyl, F, Cl, Br, I, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}^5$, $-\text{SR}^5$, $-\text{S}(=\text{O})\text{R}^5$, $-\text{S}(=\text{O})_2\text{R}^5$, $-\text{NHS}(=\text{O})_2\text{R}^5$, $-\text{C}(=\text{O})\text{R}^5$, $-\text{OC}(=\text{O})\text{R}^5$, $-\text{CO}_2\text{R}^5$, $-\text{OCO}_2\text{R}^5$, $-\text{CH}(\text{R}^5)_2$, $-\text{N}(\text{R}^5)_2$, $-\text{C}(=\text{O})\text{N}(\text{R}^5)_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^5)_2$, $-\text{NHC}(=\text{O})\text{NH}(\text{R}^5)$, $-\text{NHC}(=\text{O})\text{R}^5$, $-\text{NHC}(=\text{O})\text{OR}^5$, $-\text{C}(\text{OH})(\text{R}^5)_2$, and $-\text{C}(\text{NH}_2)(\text{R}^5)_2$;

10 R^3 is selected from the group consisting of $-C_1-C_6$ alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ alkoxy, F, Cl, Br, and I;

R^4 is selected from the group consisting of $-C_1-C_6$ alkyl, $-C_1-C_6$ alkoxy, F, Cl, Br, and I;

each occurrence of R^5 is independently selected from the group consisting of H,

C₁-C₆ alkyl, C₁-C₆ heteroalkyl, aryl, and -C₁-C₃ alkyl-(C₃-C₆ cycloalkyl), wherein the alkyl, heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

X is selected from the group consisting of CH₂, C=O, and O;

n is an integer from 1-3;

5 x is an integer from 0-4; and

y is an integer from 0-4.

In certain embodiments, the compound is selected from the group consisting of: 1-(3-(4-fluorophenoxy)propyl)-3-(4-iodophenyl)guanidine (Compound A); 1-(3-(4-fluorophenoxy)propyl)-3-(4-methoxyphenyl)guanidine (Compound B); 1-(n-propyl)-3-(4-iodophenyl)guanidine (Compound C); 1-(n-propyl)-3-(4-methoxyphenyl)guanidine (Compound D); 1,3-bis(3-(4-fluorophenoxy)propyl)guanidine (Compound E); 1-(3-(4-fluorophenoxy)propyl)-3-(4-trifluoromethylphenyl)guanidine (Compound F); 1-(3-(4-fluorophenoxy)propyl)-3-(4-chlorophenyl)guanidine (Compound G); 1-(3-(4-fluorophenoxy)propyl)-3-(4-methyl-2-oxo-2H-chromen-7-yl)guanidine (Compound H); or a pharmaceutically acceptable salt of any of the foregoing; and any combinations thereof.

The compound, or any pharmaceutically acceptable salt thereof, can include any of those described in U.S. Patent Application Publication No. 2015/0166472, which is hereby incorporated by reference in its entirety.

The compounds can be prepared according to any method known in the art. Methods of synthesis are, for example, described in U.S. Patent Application Publication No. 2015/0166472, which is hereby incorporated by reference in its entirety. The methods of synthesis described therein are non-limiting.

The compounds of the invention may possess one or more stereocenters, and each stereocenter may exist independently in either the (R) or (S)-configuration. In certain embodiments, compounds described herein are present in optically active or racemic forms. It is to be understood that the compounds described herein encompass racemic, optically active, regioisomeric and stereoisomeric forms, or combinations thereof that possess the therapeutically useful properties described herein. Preparation of optically active forms is achieved in any suitable manner, including by way of non-limiting example, by resolution of the racemic form with recrystallization techniques, synthesis from optically-active starting materials, chiral synthesis, or chromatographic separation using a chiral stationary phase. In one embodiment, a

mixture of one or more isomer is utilized as the therapeutic compound described herein. In other embodiments, compounds described herein contain one or more chiral centers. These compounds are prepared by any means, including stereoselective synthesis, enantioselective synthesis and/or separation of a mixture of enantiomers and/or diastereomers. Resolution of compounds and isomers thereof is achieved by any means including, by way of non-limiting example, chemical processes, enzymatic processes, fractional crystallization, distillation, and chromatography.

The methods and formulations described herein include the use of N-oxides (if appropriate), crystalline forms (also known as polymorphs), solvates, amorphous phases, and/or pharmaceutically acceptable salts of compounds having the structure of any compound of the invention, as well as metabolites and active metabolites of these compounds having the same type of activity. Solvates include water, ether (*e.g.*, tetrahydrofuran, methyl tert-butyl ether) or alcohol (*e.g.*, ethanol) solvates, acetates and the like. In one embodiment, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents, such as water and ethanol. In other embodiments, the compounds described herein exist in unsolvated form.

In certain embodiments, the compounds may exist as tautomers. All tautomers are included within the scope of the compounds described herein.

In certain embodiments, compounds described herein are prepared as prodrugs. A “prodrug” refers to an agent that is converted into the active moiety *in vivo*.

In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically active form of the compound. In certain embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically or therapeutically active form of the compound.

Compounds described herein also include isotopically labeled compounds, wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds described herein include and are not limited to ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{36}Cl , ^{18}F , ^{123}I , ^{125}I , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , and ^{35}S . In one embodiment, isotopically labeled compounds are useful in drug and/or substrate tissue distribution studies. In other embodiments, substitution with heavier isotopes such as deuterium affords greater metabolic stability (for example, increased *in vivo* half-life or reduced dosage requirements). In yet another embodiment, substitution with positron emitting isotopes, such as

^{11}C , ^{18}F , ^{15}O and ^{13}N , is useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds are prepared by any suitable method or by processes using an appropriate isotopically labeled reagent in place of the non-labeled reagent otherwise employed.

5 In certain embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Methods of Treating

10 The invention further provides methods of treating, ameliorating and/or preventing a IL-6 and/or PD-L1 related disorder or disease in a subject. In certain embodiments, the method comprises administering to the subject a therapeutic (pharmaceutical) composition comprising one or more compounds, or pharmaceutically acceptable salts or solvents thereof, as described herein. In certain embodiments, the disease or disorder comprises at least one selected from the group consisting of cancer, immune related disorders, infection, neuropathic pain, depression,
15 substance abuse, epilepsy, psychosis, Alzheimer's disease, Parkinson's disease, and combinations thereof. In certain embodiments, the cancer is at least one selected from the group consisting of prostate cancer, breast cancer, renal cancer, pancreas cancer, colon cancer, skin cancer, lung cancer, bone cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach
20 cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the
25 penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma,
30 epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, and combinations thereof.

The invention further provides methods of treating, ameliorating and/or preventing a IL-6 and/or PD-L1 related disorder or disease in a subject. In certain embodiments, the method comprises administering to the subject a therapeutic composition comprising a Sigma1 modulating compound, or a pharmaceutically acceptable salt thereof, such as those described
5 herein, and further administering to the subject a therapeutic agent that inhibits the ubiquitin proteasome system (UPS) and/or autophagic survival pathways. In certain embodiments, the Sigma1 modulating compound is a compound of the invention.

In certain embodiments, administering the Sigma1 modulating compound to the subject allows for administering a lower dose of the therapeutic agent that inhibits the ubiquitin
10 proteasome system (UPS) and/or autophagic survival pathways, as compared to the dose of the therapeutic agent alone that is required to achieve similar results in treating, ameliorating or preventing the IL-6 and/or PD-L1 related disorder or disease in the subject. In other embodiments, the Sigma1 modulating compound and the therapeutic agent are co-administered to the subject.

15 In certain embodiments, the Sigma1 modulating compound and the therapeutic agent are co-formulated and/or co-administered to the subject.

In certain embodiments, the subject is a mammal. In certain embodiments, the mammal is a human. In certain embodiments, the subject is a subject in need thereof.

The compounds described herein can also be used in combination with one or more
20 additional compounds or therapeutic agents. These additional compounds may comprise compounds of the present disclosure and/or therapeutic agents known to treat, prevent, or reduce the symptoms or effects of IL-6, PD-1, and/or PD-L1 related disorder or disease. Such compounds include, but are not limited to, hormone receptor antagonists, autophagy inhibitors, ER stress response inhibitors, protein translation inhibitors, DNA repair inhibitors, anti-IL-6
25 and/or gp130 compounds, PD-1 inhibitors, PD-L1 inhibitors, immune system modulators, and proteasome inhibitors. Non-limiting examples of these are described herein.

In non-limiting examples, the compounds, or pharmaceutically acceptable salts thereof, may be used in combination with one or more therapeutic agents (or a salt, solvate or prodrug thereof) selected from the group consisting of hormone receptor antagonists, including but are
30 not limited to octapeptide, somatostatin, analoguem, lanreotide, angiopeptin, dermopeptin, octreotide, pegvisomant, tamoxifen, lasofoxifene, raloxifene, RAD1901, enzalutamide, ARN-

509, ARN-810, galeterone, ODM-201, ORM-15341, and ARV-330; autophagy inhibitors, including but are not limited to 3-methyladenine, chloroquine, hydroxychloroquine, and wortmannin; ER stress response inhibitors, including but are not limited to eeyarestatin I, salubrinol, and versipelostatin; anti-IL-6 and/or gp130 compounds, including but are not limited to tocilizumab, siltuximab, sarilumab, olokizumab, elsilimomab, ALD518/BMS-94529, sirukumab, CPSI-2364, ARGX-109, FE301, and FM101; anti-PD-1 and/or anti-PD-L1 compounds, including but are not limited to nivolumab, pembrolizumab, pidilizumab, avelumab, durvalumab, MEDI0680, BMS-936559, AMP224, atezolizumab, CX-072, REGN2810, TSR-042, STI-1014, STI-1110; immune system modulators, including but are not limited to blockers of ICOS-ICOS-L, IL-10, IL-24 IL-21, adenosine A2a, arginase, IDO1, CD40-CD40L, CD134-CD134L, CD137-CD137L, CTLA4, OX40/OX40L, PD-1, PD-L1/PD-L2, TIM3, LAG3, TGF- β or activate toll-like receptors, IL-2, and STING; proteasome inhibitors, including but are not limited to 2H-isoinidole-2-carboxylic acid, 4-fluoro-1,3-dihydro-(2R,6S,12Z,13aS,14aR,16aS)-14a-[[[(cyclopropylsulfonyl)amino]carbonyl]-6-[[[(1,1-dimethylethoxy)carbonyl]amino]-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-5,16-dioxocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-2-yl ester (Danoprevir), adamantane-acetyl-(6-aminohexanoyl)3-(leucyl)3-vinyl-(methyl)-sulfone, N-acetyl-L-leucyl-L-leucyl-L-methionine, N-[(phenylmethoxy)carbonyl]-L-leucyl-N-[(1S)-1-formyl-3-methylbutyl]-L-leucinamide, (2R,3S,4R)-3-hydroxy-2-[(1S)-1-hydroxy-2-methylpropyl]-4-methyl-5-oxo-2-pyrrolidinecarboxy-N-acetyl-L-cysteine thioester, N-[N-(N-acetyl-L-leucyl)-L-leucyl]-L-norleucine, lactacystin, 4-(2-aminoethyl)benzenesulfonyl fluoride hydrochloride, (S)-1-carboxy-2-phenyl]-carbamoyl-arg-val-arginal, bovine pancreatic trypsin inhibitor, [(2S,2R)-3-amino-2-hydroxy-4-phenylbutanoyl]-L-leucine, N-[(S)-1-carboxy-isopentyl]-carbamoyl- α -(2-imino-6-hydroxy-4-(S)-pyrimidinyl)-L-glycyl-L-phenylalaninal, ethylenediamine-tetraacetic acid disodium salt hydrate, acetyl-leucyl-leucyl-arginal, isovaleryl-val-val-AHMHA-ala-AHMHA where AHMHA is (3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid, N- α -L-rhamnopyranosyloxy(hydroxyphosphinyl)-L-leucyl-L-tryptophan, phenylmethanesulfonyl fluoride, bortezomib, carfilzomib, ONX 0912, NPI-0052, CEP-18770, MLN9708, disulfiram, epigallocatechin-3-gallate, and salinosporamide A; and p97/VCP inhibitors, including but not limited to DBeQ and derivatives thereof. In certain embodiments, In certain embodiments, the additional therapeutic is nivolumab, pembrolizumab, pidilizumab, avelumab, durvalumab, MEDI0680, AMP224, atezolizumab, CX-072, REGN2810,

TSR-042, STI-1014, STI-1110, sirukumab, siltuximab, olokizumab, clazakizumab, gerilimumab, sarilumab, PF-04236921, ALX-0061, and tocilizumab. The compounds described herein can be administered with one or more than one additional therapeutic. The additional therapeutic can be administered simultaneously or sequentially with a compound, or
5 pharmaceutically acceptable salt thereof, provided herein. In certain embodiments, the additional therapeutic is administered before or after a compound described herein. The combination can be provided a synergistic effect.

Administration/Dosing

The regimen of administration may affect what constitutes an effective amount. The
10 therapeutic formulations may be administered to the subject either prior to or after the onset of a IL-6 and/or PD-L1 related disorder or disease. Further, several divided dosages, as well as staggered dosages may be administered daily or sequentially, or the dose may be continuously infused, or may be a bolus injection. Further, the dosages of the therapeutic formulations may be proportionally increased or decreased as indicated by the exigencies of the therapeutic or
15 prophylactic situation.

Administration of the compositions of the present disclosure to a patient, such as a mammal, such as a human, may be carried out using known procedures, at dosages and for periods of time effective to treat Signal receptor-related disorders or diseases in the patient. An effective amount of the therapeutic compound necessary to achieve a therapeutic effect may vary
20 according to factors such as the state of the disease or disorder in the patient; the age, sex, and weight of the patient; and the ability of the therapeutic compound to treat Signal receptor-related disorders or diseases in the patient. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily, or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic
25 situation. A non-limiting example of an effective dose range for a therapeutic compound of the invention is from about 1 and 5,000 mg/kg of body weight/per day. One of ordinary skill in the art would be able to study the relevant factors and make the determination regarding the effective amount of the therapeutic compound without undue experimentation.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this
30 disclosure may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of

administration, without being toxic to the patient.

In particular, the selected dosage level depends upon a variety of factors including the activity of the particular compound employed, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds or materials used in combination with the compound, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A medical doctor, *e.g.*, physician or veterinarian, having ordinary skill in the art may readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In particular embodiments, it may be advantageous to formulate the compound in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the patients to be treated; each unit containing a predetermined quantity of therapeutic compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the therapeutic compound and the particular therapeutic effect to be achieved, and/or (b) the limitations inherent in the art of compounding/formulating such a therapeutic compound for the treatment of Sigma receptor-related disorders or diseases in a patient.

In certain embodiments, the compositions of the invention are formulated using one or more pharmaceutically acceptable excipients or carriers. In certain embodiments, the pharmaceutical compositions of the invention comprise a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier.

The carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms may be achieved by various antibacterial and antifungal agents, for example,

parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, may be included in the composition. Prolonged absorption of the injectable compositions may be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

Pharmaceutical compositions can include effective amounts of one or more compound(s) described herein together with, for example, pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or other carriers. Such compositions may include diluents of various buffer content (*e.g.*, TRIS or other amines, carbonates, phosphates, amino acids, for example, glycineamide hydrochloride (especially in the physiological pH range), N-glycylglycine, sodium or potassium phosphate (dibasic, tribasic), *etc.* or TRIS-HCl or acetate), pH and ionic strength; additives such as detergents and solubilizing agents (*e.g.*, surfactants such as Pluronics, Tween 20, Tween 80 (Polysorbate 80), Cremophor, polyols such as polyethylene glycol, propylene glycol, *etc.*), anti-oxidants (*e.g.*, ascorbic acid, sodium metabisulfite), preservatives (*e.g.*, Thimersol, benzyl alcohol, parabens, *etc.*) and bulking substances (*e.g.*, sugars such as sucrose, lactose, mannitol, polymers such as polyvinylpyrrolidones or dextran, *etc.*); and/or incorporation of the material into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, *etc.* or into liposomes. Hyaluronic acid may also be used. Such compositions can be employed to influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of a compound described herein. See, *e.g.*, Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, Pa. 18042) pages 1435-1712, which are herein incorporated by reference. The compositions can, for example, be prepared in liquid form, or can be in dried powder, such as lyophilized form. Particular methods of administering such compositions are described elsewhere herein.

Where a buffer is to be included in the formulations described herein, the buffer can be selected from the group consisting of sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginine, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate, and tris(hydroxymethyl)-aminomethane, or mixtures thereof. The buffer can also be glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, and sodium phosphate or mixtures thereof.

Where a pharmaceutically acceptable preservative is to be included in a formulation of

one of the compounds described herein, the preservative can be selected from the group consisting of phenol, m-cresol, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, 2-phenoxyethanol, butyl p-hydroxybenzoate, 2-phenylethanol, benzyl alcohol, chlorobutanol, and thiomerosal, or mixtures thereof. The preservative can also be phenol or m-cresol.

5 The preservative is present in a concentration from about 0.1 mg/ml to about 50 mg/ml, in a concentration from about 0.1 mg/ml to about 25 mg/ml, or in a concentration from about 0.1 mg/ml to about 10 mg/ml. The use of a preservative in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: The Science and Practice of Pharmacy, 19th edition, 1995. The formulation may further comprise a chelating
10 agent where the chelating agent may be selected from the group consisting of salts of ethlenediaminetetraacetic acid (EDTA), citric acid, and aspartic acid, and mixtures thereof. The chelating agent can be present in a concentration from 0.1 mg/ml to 5 mg/ml, from 0.1 mg/ml to 2 mg/ml or from 2 mg/ml to 5 mg/ml. The use of a chelating agent in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to
15 Remington: The Science and Practice of Pharmacy, 19th edition, 1995.

 The formulation of the compounds described herein may further comprise a stabilizer selected from the group consisting of high molecular weight polymers and low molecular compounds where such stabilizers include, but are not limited to, polyethylene glycol (*e.g.* PEG 3350), polyvinylalcohol (PVA), polyvinylpyrrolidone, carboxymethylcellulose, different salts
20 (*e.g.* sodium chloride), L-glycine, L-histidine, imidazole, arginine, lysine, isoleucine, aspartic acid, tryptophan, and threonine or any mixture thereof. The stabilizer can also be L-histidine, imidazole or arginine. The high molecular weight polymer can be present in a concentration from 0.1 mg/ml to 50 mg/ml, from 0.1 mg/ml to 5 mg/ml, from 5 mg/ml to 10 mg/ml, from 10 mg/ml to 20 mg/ml, from 20 mg/ml to 30 mg/ml or from 30 mg/ml to 50 mg/ml. The low
25 molecular weight compound can be present in a concentration from 0.1 mg/ml to 50 mg/ml, from 0.1 mg/ml to 5 mg/ml, from 5 mg/ml to 10 mg/ml, from 10 mg/ml to 20 mg/ml, from 20 mg/ml to 30 mg/ml or from 30 mg/ml to 50 mg/ml. The use of a stabilizer in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: The Science and Practice of Pharmacy, 19th edition, 1995.

30 The formulation of the compounds described herein may further include a surfactant. In certain embodiments, the surfactant may be selected from the group consisting of a detergent,

ethoxylated castor oil, polyglycolized glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, such as 188 and 407, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives such as alkylated and alkoxyated derivatives (tweens, *e.g.* Tween-20, or Tween-80), monoglycerides or ethoxylated derivatives thereof, diglycerides or

5 polyoxyethylene derivatives thereof, glycerol, cholic acid or derivatives thereof, lecithins, alcohols and phospholipids, glycerophospholipids (lecithins, kephalins, phosphatidyl serine), glyceroglycolipids (galactopyransoide), sphingophospholipids (sphingomyelin), and sphingoglycolipids (ceramides, gangliosides), DSS (docusate sodium, docusate calcium, docusate potassium, SDS (sodium dodecyl sulfate or sodium lauryl sulfate), dipalmitoyl

10 phosphatidic acid, sodium caprylate, bile acids and salts thereof and glycine or taurine conjugates, ursodeoxycholic acid, sodium cholate, sodium deoxycholate, sodium taurocholate, sodium glycocholate, N-Hexadecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate, anionic (alkyl-aryl-sulphonates) monovalent surfactants, palmitoyl lysophosphatidyl-L-serine, lysophospholipids (*e.g.* 1-acyl-sn-glycero-3-phosphate esters of ethanolamine, choline, serine or

15 threonine), alkyl, alkoxyl (alkyl ester), alkoxy (alkyl ether)-derivatives of lysophosphatidyl and phosphatidylcholines, *e.g.* lauroyl and myristoyl derivatives of lysophosphatidylcholine, dipalmitoylphosphatidylcholine, and modifications of the polar head group, that is cholines, ethanolamines, phosphatidic acid, serines, threonines, glycerol, inositol, and the postively charged DODAC, DOTMA, DCP, BISHOP, lysophosphatidylserine and

20 lysophosphatidylthreonine, zwitterionic surfactants (*e.g.* N-alkyl-N,N-dimethylammonio-1-propanesulfonates, 3-cholamido-1-propyldimethylammonio-1-propanesulfonate, dodecylphosphocholine, myristoyl lysophosphatidylcholine, hen egg lysolecithin), cationic surfactants (quarternary ammonium bases) (*e.g.* cetyl-trimethylammonium bromide, cetylpyridinium chloride), non-ionic surfactants, polyethyleneoxide/polypropyleneoxide block

25 copolymers (Pluronics/Tetronics, Triton X-100, Dodecyl β -D-glucopyranoside) or polymeric surfactants (Tween-40, Tween-80, Brij-35), fusidic acid derivatives—(*e.g.* sodium tauro-dihydrofusidate *etc.*), long-chain fatty acids and salts thereof C6-C12 (*e.g.* oleic acid and caprylic acid), acylcarnitines and derivatives, N $_{\alpha}$ -acylated derivatives of lysine, arginine or histidine, or side-chain acylated derivatives of lysine or arginine, N $_{\alpha}$ -acylated derivatives of dipeptides

30 comprising any combination of lysine, arginine or histidine and a neutral or acidic amino acid, N $_{\alpha}$ -acylated derivative of a tripeptide comprising any combination of a neutral amino acid and

two charged amino acids, or the surfactant may be selected from the group of imidazoline derivatives, or mixtures thereof. The use of a surfactant in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: The Science and Practice of Pharmacy, 19th edition, 1995.

Pharmaceutically acceptable sweeteners can be part of the formulation of the compounds described herein. Pharmaceutically acceptable sweeteners include at least one intense sweetener such as saccharin, sodium or calcium saccharin, aspartame, acesulfame potassium, sodium cyclamate, alitame, a dihydrochalcone sweetener, monellin, stevioside or sucralose (4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose), saccharin, sodium or calcium saccharin, and optionally a bulk sweetener such as sorbitol, mannitol, fructose, sucrose, maltose, isomalt, glucose, hydrogenated glucose syrup, xylitol, caramel, and honey. Intense sweeteners are conveniently employed in low concentrations. For example, in the case of sodium saccharin, the concentration may range from 0.04% to 0.1% (w/v) based on the total volume of the final formulation, or is about 0.06% in the low-dosage formulations and about 0.08% in the high-dosage ones. The bulk sweetener can effectively be used in larger quantities ranging from about 10% to about 35%, or from about 10% to 15% (w/v).

The formulations of the compounds described herein may be prepared by conventional techniques, *e.g.* as described in Remington's Pharmaceutical Sciences, 1985 or in Remington: The Science and Practice of Pharmacy, 19th edition, 1995, where such conventional techniques of the pharmaceutical industry involve dissolving and mixing the ingredients as appropriate to give the desired end product.

The phrase "pharmaceutically acceptable" or "therapeutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and preferably do not typically produce an allergic or similar untoward reaction, such as gastric upset, dizziness and the like, when administered to a human. As used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a State government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia (*e.g.*, Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985)) for use in animals, and more particularly in humans.

In certain embodiments, the compositions of the invention are administered to the patient in dosages that range from one to five times per day or more. In other embodiments, the

compositions of the invention are administered to the patient in range of dosages that include, but are not limited to, once every day, every two, days, every three days to once a week, and once every two weeks. It is readily apparent to one skilled in the art that the frequency of administration of the various combination compositions of the invention varies from individual to individual depending on many factors including, but not limited to, age, disease or disorder to be treated, gender, overall health, and other factors. Thus, the disclosure should not be construed to be limited to any particular dosage regime and the precise dosage and composition to be administered to any patient is determined by the attending physical taking all other factors about the patient into account.

Compounds of the invention for administration may be in the range of from about 1 μ g to about 10,000 mg, about 20 μ g to about 9,500 mg, about 40 μ g to about 9,000 mg, about 75 μ g to about 8,500 mg, about 150 μ g to about 7,500 mg, about 200 μ g to about 7,000 mg, about 3050 μ g to about 6,000 mg, about 500 μ g to about 5,000 mg, about 750 μ g to about 4,000 mg, about 1 mg to about 3,000 mg, about 10 mg to about 2,500 mg, about 20 mg to about 2,000 mg, about 25 mg to about 1,500 mg, about 30 mg to about 1,000 mg, about 40 mg to about 900 mg, about 50 mg to about 800 mg, about 60 mg to about 750 mg, about 70 mg to about 600 mg, about 80 mg to about 500 mg, and any and all whole or partial increments therebetween.

In certain embodiments, the dose of a compound of the invention is from about 1 mg and about 2,500 mg. In certain embodiments, a dose of a compound of the invention used in compositions described herein is less than about 10,000 mg, or less than about 8,000 mg, or less than about 6,000 mg, or less than about 5,000 mg, or less than about 3,000 mg, or less than about 2,000 mg, or less than about 1,000 mg, or less than about 500 mg, or less than about 200 mg, or less than about 50 mg. Similarly, in certain embodiments, a dose of a second compound as described herein is less than about 1,000 mg, or less than about 800 mg, or less than about 600 mg, or less than about 500 mg, or less than about 400 mg, or less than about 300 mg, or less than about 200 mg, or less than about 100 mg, or less than about 50 mg, or less than about 40 mg, or less than about 30 mg, or less than about 25 mg, or less than about 20 mg, or less than about 15 mg, or less than about 10 mg, or less than about 5 mg, or less than about 2 mg, or less than about 1 mg, or less than about 0.5 mg, and any and all whole or partial increments thereof.

In certain embodiments, the present disclosure provides packaged pharmaceutical compositions comprising a container holding a therapeutically effective amount of at least one

compound of the invention, alone or in combination with a second pharmaceutical agent; and instructions for using the at least one compound to treat, prevent, or reduce one or more symptoms of Sigma receptor-related disorders or diseases in a patient.

Formulations may be employed in admixtures with conventional excipients, *i.e.*,
5 pharmaceutically acceptable organic or inorganic carrier substances suitable for oral, parenteral, nasal, intravenous, subcutaneous, enteral, or any other suitable mode of administration, known to the art. The pharmaceutical preparations may be sterilized and if desired mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, coloring, flavoring and/or aromatic substances and the like.
10 They may also be combined where desired with other active agents, *e.g.*, other analgesic agents.

Routes of administration of any of the compositions of the invention include oral, nasal, rectal, intravaginal, parenteral, buccal, sublingual or topical. The compounds for use in the disclosure may be formulated for administration by any suitable route, such as for oral or parenteral, for example, transdermal, transmucosal (*e.g.*, sublingual, lingual, (trans)buccal,
15 (trans)urethral, vaginal (*e.g.*, trans- and perivaginally), (intra)nasal and (trans)rectal), intravesical, intrapulmonary, intraduodenal, intragastrical, intrathecal, subcutaneous, intramuscular, intradermal, intra-arterial, intravenous, intrabronchial, inhalation, and topical administration.

Suitable compositions and dosage forms include, for example, tablets, capsules, caplets,
20 pills, gel caps, troches, dispersions, suspensions, solutions, syrups, granules, beads, transdermal patches, gels, powders, pellets, magmas, lozenges, creams, pastes, plasters, lotions, discs, suppositories, liquid sprays for nasal or oral administration, dry powder or aerosolized formulations for inhalation, compositions and formulations for intravesical administration and the like. It should be understood that the formulations and compositions that would be useful in
25 the present disclosure are not limited to the particular formulations and compositions that are described herein.

For oral application, particularly suitable are tablets, dragees, liquids, drops, suppositories, or capsules, caplets and gelcaps. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or
30 more agents selected from the group consisting of inert, non-toxic pharmaceutically excipients that are suitable for the manufacture of tablets. Such excipients include, for example an inert

diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay the release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent.

For oral administration, the compounds of the invention may be in the form of tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, polyvinylpyrrolidone, hydroxypropylcellulose or hydroxypropylmethyl cellulose); fillers (*e.g.*, cornstarch, lactose, microcrystalline cellulose or calcium phosphate); lubricants (*e.g.*, magnesium stearate, talc, or silica); disintegrates (*e.g.*, sodium starch glycollate); or wetting agents (*e.g.*, sodium lauryl sulphate). If desired, the tablets may be coated using suitable methods and coating materials such as OPADRY® film coating systems available from Colorcon, West Point, Pa. (*e.g.*, OPADRY® OY Type, OYC Type, Organic Enteric OY-P Type, Aqueous Enteric OY-A Type, OY-PM Type and OPADRY® White, 32K18400). Liquid preparation for oral administration may be in the form of solutions, syrups or suspensions. The liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agent (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters or ethyl alcohol); and preservatives (*e.g.*, methyl or propyl p-hydroxy benzoates or sorbic acid).

Granulating techniques are well known in the pharmaceutical art for modifying starting powders or other particulate materials of an active ingredient. The powders are typically mixed with a binder material into larger permanent free-flowing agglomerates or granules referred to as a “granulation.” For example, solvent-using “wet” granulation processes are generally characterized in that the powders are combined with a binder material and moistened with water or an organic solvent under conditions resulting in the formation of a wet granulated mass from which the solvent must then be evaporated.

Melt granulation generally consists in the use of materials that are solid or semi-solid at room temperature (*i.e.* having a relatively low softening or melting point range) to promote granulation of powdered or other materials, essentially in the absence of added water or other liquid solvents. The low melting solids, when heated to a temperature in the melting point range,

liquefy to act as a binder or granulating medium. The liquefied solid spreads itself over the surface of powdered materials with which it is contacted, and on cooling, forms a solid granulated mass in which the initial materials are bound together. The resulting melt granulation may then be provided to a tablet press or be encapsulated for preparing the oral dosage form.

- 5 Melt granulation improves the dissolution rate and bioavailability of an active (*i.e.* drug) by forming a solid dispersion or solid solution.

U.S. Pat. No. 5,169,645 discloses directly compressible wax-containing granules having improved flow properties. The granules are obtained when waxes are admixed in the melt with certain flow improving additives, followed by cooling and granulation of the admixture. In some
10 cases, only the wax itself melts in the melt combination of the wax(es) and additives(s), and in other cases both the wax(es) and the additives(s) melt.

The present disclosure also includes a multi-layer tablet comprising a layer providing for the delayed release of one or more compounds of the invention, and a further layer providing for the immediate release of a medication for treatment of the disease or disorder. Using a wax/pH-
15 sensitive polymer mix, a gastric insoluble composition may be obtained in which the active ingredient is entrapped, ensuring its delayed release.

For parenteral administration, the compounds of the invention may be formulated for injection or infusion, for example, intravenous, intramuscular or subcutaneous injection or infusion, or for administration in a bolus dose and/or continuous infusion. Suspensions, solutions
20 or emulsions in an oily or aqueous vehicle, optionally containing other formulatory agents such as suspending, stabilizing and/or dispersing agents may be used.

Additional dosage forms of this disclosure include dosage forms as described in U.S. Pat. Nos. 6,340,475; 6,488,962; 6,451,808; 5,972,389; 5,582,837; and 5,007,790. Additional dosage forms of this disclosure also include dosage forms as described in U.S. Patent Application
25 Publications Nos. 20030147952; 20030104062; 20030104053; 20030044466; 20030039688; and 20020051820. Additional dosage forms of this disclosure also include dosage forms as described in PCT Application Publications Nos. WO 03/35041; WO 03/35040; WO 03/35029; WO 03/35177; WO 03/35039; WO 02/96404; WO 02/32416; WO 01/97783; WO 01/56544; WO 01/32217; WO 98/55107; WO 98/11879; WO 97/47285; WO 93/18755; and WO 90/11757.

30 In certain embodiments, the formulations of the present disclosure may be, but are not limited to, short-term, rapid-offset, as well as controlled, for example, sustained release, delayed

release and pulsatile release formulations.

The term sustained release is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that may, although not necessarily, result in substantially constant blood levels of a drug over an extended
5 time period. The period of time may be as long as a month or more and should be a release that is longer than the same amount of agent administered in bolus form.

For sustained release, the compounds may be formulated with a suitable polymer or hydrophobic material that provides sustained release properties to the compounds. As such, the compounds for use the method of the invention may be administered in the form of
10 microparticles, for example, by injection or in the form of wafers or discs by implantation.

In certain embodiments, the compounds of the invention are administered to a patient, alone or in combination with another pharmaceutical agent, using a sustained release formulation.

The term delayed release is used herein in its conventional sense to refer to a drug
15 formulation that provides for an initial release of the drug after some delay following drug administration and that may, although not necessarily, include a delay of from about 10 minutes up to about 12 hours.

The term pulsatile release is used herein in its conventional sense to refer to a drug formulation that provides release of the drug in such a way as to produce pulsed plasma profiles
20 of the drug after drug administration.

The term immediate release is used in its conventional sense to refer to a drug formulation that provides for release of the drug immediately after drug administration.

As used herein, short-term refers to any period of time up to and including about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1
25 hour, about 40 minutes, about 20 minutes, or about 10 minutes and any or all whole or partial increments thereof after drug administration after drug administration.

As used herein, rapid-offset refers to any period of time up to and including about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 40 minutes, about 20 minutes, or about 10 minutes, and any and all whole or
30 partial increments thereof after drug administration.

The therapeutically effective amount or dose of a compound of the present disclosure

depends on the age, sex and weight of the patient, the current medical condition of the patient and the progression of Sigma receptor-related disorders or diseases in the patient being treated. The skilled artisan is able to determine appropriate dosages depending on these and other factors.

A suitable dose of a compound of the present disclosure may be in the range of from
5 about 0.01 mg to about 5,000 mg per day, such as from about 0.1 mg to about 1,000 mg, for example, from about 1 mg to about 500 mg, such as about 5 mg to about 250 mg per day. The dose may be administered in a single dosage or in multiple dosages, for example from 1 to 4 or more times per day. When multiple dosages are used, the amount of each dosage may be the same or different. For example, a dose of 1 mg per day may be administered as two 0.5 mg
10 doses, with about a 12-hour interval between doses.

It is understood that the amount of compound dosed per day may be administered, in non-limiting examples, every day, every other day, every 2 days, every 3 days, every 4 days, or every 5 days. For example, with every other day administration, a 5 mg per day dose may be initiated on Monday with a first subsequent 5 mg per day dose administered on Wednesday, a second
15 subsequent 5 mg per day dose administered on Friday, and so on.

In the case wherein the patient's status does improve, upon the doctor's discretion the administration of a compound or composition is optionally given continuously; alternatively, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). The length of the drug holiday optionally varies between 2
20 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, or 365 days. The dose reduction during a drug holiday includes from 10%-100%, including, by way of example only, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%,
25 80%, 85%, 90%, 95%, or 100%.

Once improvement of the patient's conditions has occurred, a maintenance dose may be administered if necessary. In certain embodiments, patients require intermittent treatment on a long-term basis upon any recurrence of symptoms.

The compounds, or pharmaceutically acceptable salts thereof, may be formulated in unit
30 dosage form. The term "unit dosage form" refers to physically discrete units suitable as unitary dosage for patients undergoing treatment, with each unit containing a predetermined quantity of

active material calculated to produce the desired therapeutic effect, optionally in association with a suitable pharmaceutical carrier. The unit dosage form may be for a single daily dose or one of multiple daily doses (*e.g.*, about 1 to 4 or more times per day). When multiple daily doses are used, the unit dosage form may be the same or different for each dose. The unit dosage form may also comprise one or more additional therapeutics, such as, but not limited to, those described herein.

Toxicity and therapeutic efficacy of such therapeutic regimens are optionally determined in cell cultures or experimental animals, including, but not limited to, the determination of the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index, which is expressed as the ratio between LD₅₀ and ED₅₀. The data obtained from cell culture assays and animal studies are optionally used in formulating a range of dosage for use in human. The dosage optionally varies within this range depending upon the dosage form employed and the route of administration utilized.

Those skilled in the art recognizes, or is able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures, embodiments, claims, and examples described herein. Such equivalents were considered to be within the scope of this disclosure and covered by the claims appended hereto. For example, it should be understood, that modifications in reaction conditions, including but not limited to reaction times, reaction size/volume, and experimental reagents, such as solvents, catalysts, pressures, atmospheric conditions, *e.g.*, nitrogen atmosphere, and reducing/oxidizing agents, with art-recognized alternatives and using no more than routine experimentation, are within the scope of the present application.

It is to be understood that wherever values and ranges are provided herein, all values and ranges encompassed by these values and ranges, are meant to be encompassed within the scope of the present disclosure. Moreover, all values that fall within these ranges, as well as the upper or lower limits of a range of values, are also contemplated by the present application.

The following examples further illustrate aspects of the present disclosure. However, they are in no way a limitation of the teachings or disclosure of the present disclosure as set forth herein.

EXAMPLES

The disclosure is further described in detail by reference to the following experimental examples. These examples are provided for purposes of illustration only, and are not intended to be limiting unless otherwise specified. Thus, the disclosure should in no way be construed as being limited to the following examples, but rather, should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

Example 1: Reduction in IL-6 protein levels by RNAi of Signal

Production of the Signal protein was inhibited by RNA interference (RNAi), and then levels of IL-6 were measured to determine if a lower expression levels of Signal resulted in lower expression of IL-6.

Methods:

Protein lysates were prepared from MDA-468 cells. 10 cm plates were seeded to 50-60% confluent the day before the transfection. 32 μ L of Signal siRNA + 600 μ L OPTIMEM were combined, mixed through pipetting and incubated 10 minutes at room temperature (RT). During the 10 minute incubation, media was replaced in plate with 10 mL fresh media. To that tube of siRNA and OPTIMEM, 35 μ L of interferin were added, and the system was vortexed immediately for 20 seconds, and incubated for 20 minutes at RT. The entire volume was added to the plate. The system was incubated for 2 days. On third day, plates were split so that cells were 50-60% confluent. On the following day, the procedure was repeated with a second Signal SiRNA transfection. After the next 2 days, the cells were harvested, lysed, and run on gel to confirm Signal knockdown.

Cells were rinsed with Ca/Mg-free PBS and detached using 2 mM EDTA in Ca/Mg-free PBS. Cells were spun for 4 minutes at 14,000 rpm at 4 °C. PBS was aspirated and pellets were re-spun. Pellets were snap-frozen on dry ice. The pellets were lysed using RIPA + 10% glycerol + Protease inhibitor cocktail + Phosphatase inhibitor cocktail + EDTA. Lysis consisted of pipetting up and down 20 times, rotating the tubes at 4 °C for 30 minutes then centrifuged for 15 minutes at 14,000 rpm at 4 °C. The lysates were aliquoted into 30 μ L volumes and stored at -80 °C.

To each tube of 30 μ L lysate, 15 μ L 4x loading buffer, 5.5 μ L DTT and 1 μ L BME were added. 12 μ L were loaded into each well of a 10% gel, gel was run for 30 minutes at 90 mV then

increase to 11 mV for 60 minutes. Gel was transferred to membrane for 90 minutes at 200 mA. Membrane was blocked for 30 minutes using 5% non-fat dry milk in 1x TBST. IL-6 was detected by a two night, overnight incubation in anti-IL-6 (Cell Signaling 12153, 1:500 in 5% BSA in TBST). Anti-Rabbit HRP was used as a secondary antibody (Cell Signaling 7074 1:2000 in 5% non-fat dry milk in TBST) and HRP-beta actin was used as a loading control (Cell Signaling 47778, 2:1000 in 5% non-fat dry milk in TBST). Protein levels were measured using ImageJ, IL-6 expression was normalized to beta actin.

Results:

Surprisingly and unexpectedly, RNAi of Sigma1 reduced levels of IL-6 but not the control beta-actin. In FIG. 1A, the protein bands for IL-6, beta-actin, and Sigma1 are illustrated. The left column is the control RNAi, while the right column used the Sigma1 RNAi construct. In the Sigma1 RNAi experiment, both Sigma1 and IL-6 expression levels were reduced, while the beta-actin expression levels remained unchanged. The decrease in levels of the IL-6 protein shown in FIG. 1A is quantitated in FIG. 1B. The control expression levels of IL-6 were set to 1.0. The RNAi of Sigma1 reduced IL-6 expression to about 0.45. This demonstrates that the modulation of Sigma1 can be used to control the expression of IL-6, which can be used to treat various disorders as described herein.

Example 2: Reduction in PD-L1 expression in prostate cancer cells by administration of Sigma1 modulator

Production of the Sigma1 protein was inhibited by the Sigma1 inhibitor 1-(4-iodophenyl)-3-(2-adamantyl)guanidine (IPAG), and then levels of PD-L1 were measured to determine if a lower expression levels of Sigma1 resulted in lower expression of PD-L1. A Jurkat cell Nuclear Factor of Activated T Cells (NFAT) assay was also performed to confirm IPAG was inhibition of the Sigma1 receptor.

Methods:

PC3 (AR⁺ PCa) cells were treated with 10 μ M of IPAG for 16 hours. PC3 (AR⁺ PCa) cells were seeded 24h prior to treatment with dimethyl sulfoxide (DMSO) or 10 μ M IPAG for 16h.

Cells were rinsed with Ca/Mg-free PBS and detached using 2 mM EDTA in Ca/Mg-free PBS. Cells were spun for 4 minutes at 14,000 rpm at 4 °C. PBS was aspirated and pellets were re-spun. Pellets were snap-frozen on dry ice. The pellets were lysed using RIPA + 10% glycerol

+ Protease inhibitor cocktail + Phosphatase inhibitor cocktail. Lysis consisted of pipetting up and down 20 times, rotating the tubes at 4 °C for 30 minutes then centrifuged for 15 minutes at 14,000 rpm at 4 °C. The lysates were aliquoted into 30 µL volumes and stored at -80 °C.

To each tube of 30 µL lysate, 15 µL 4x loading buffer, 5.5 µL DTT and 1 µL BME were added. 12 µL were loaded into each well of a 10% gel, gel was run for 30 minutes at 90 mV then increase to 11 mV for 60 minutes. Gel was transferred to membrane for 90 minutes at 200 mA. Membrane was blocked for 30 minutes using 5% non-fat dry milk in 1x TBST. Programmed death-ligand 1 (PD-L1) was detected by an overnight incubation in anti-PD-L1 (Abcam ab174838, 1:1000 in 5% non-fat dry milk in TBST). Anti-rabbit HRP was used as a secondary antibody (Cell Signaling 7074 1:2000 in 5% non-fat dry milk in TBST). Vinculin was used as a loading control (Sigma Aldrich V9131 1:1000 in 5% non-fat dry milk in TBST) with anti-mouse HRP as a secondary (Cell Signaling 7076 1:2000 in 5% non-fat dry milk in TBST). Protein levels were measured using ImageJ, PD-L1 expression was normalized to Vinculin.

The Jurkat NFAT Luciferase Assay utilized the Promega PD1/PD-L1 Blockade Assay Kit (CS187111). 10,000 PC3 cells/well were plated on Wallac B&W 96-well Isoplate (with white wells and bottom and black matrix) in complete culture medium, *i.e.*, RPMI-1640 supplemented with 5% fetal bovine serum (FBS). The next day, PC3 cells were treated with 10µM IPAG for 16 hours. After 16 hour treatment, the IPAG containing culture medium was removed and treated PC3 cells were washed with complete medium. Subsequently, 10,000 Jurkat (*NFAT-luciferase*) cells were added to wells in complete culture medium. Six hours later, Promega Bio-Glo reagent was added to each well. After 5 minutes, the plate was read with a GloMax plate reader.

Results:

Surprisingly, IPAG reduced levels of PD-L1 but not control Vinculin. In FIG. 2A, the protein bands for PD-L1 and the control Vinculin are shown. The left column is the control treatment (DMSO), while the right column is the 10 µM IPAG treatment. IPAG greatly reduces expression of PD-L1, but not the control. The decrease in expression of the PD-L1 protein is quantitated in FIG. 2B. The control expression levels of PD-L1 are set to 1.0. The exposure to IPAG reduced PD-L1 expression to less than 0.1. In FIG. 2C, exposure of Jurkat *NFAT-luciferase* cells to IPAG (right bar) greatly increases the luciferase signal compared to the no IPAG exposure (left bar), indicating that IPAG is inhibiting the Sigma1 pathway in the Jurkat

cells. This demonstrates that the modulation of Sigma1 can be used to control the expression of PD-L1, which can be used to treat various disorders as described herein.

Example 3: Reduction in PD-L1 protein levels in breast cancer cells by RNAi of Sigma1

5 Production of the Sigma1 protein was inhibited by RNA interference (RNAi) or Sigma1 modulator, and then levels of PD-L1 were measured to determine if a lower expression levels of Sigma1 resulted in lower expression of PD-L1.

Methods:

10 Protein lysates were prepared from MDA-231 cells. 10 cm plates were seeded to 50-60% confluent the day before the transfection. 32 μ L of Sigma1 siRNA + 600 μ L OPTIMEM were combined, mixed through pipetting and incubated 10 minutes at room temperature (RT). During the 10 minute incubation, media was replaced in plate with 10 mL fresh media. To that tube of siRNA and OPTIMEM, 35 μ L of interferin were added, and the system was vortexed immediately for 20 seconds, and incubated for 20 minutes at RT. The entire volume was added to the plate. The system was incubated for 2 days. On third day, plates were split so that cells were 50-60% confluent. On the following day, the procedure was repeated with a second Sigma1 SiRNA transfection. After the next 2 days, the cells were harvested, lysed, and run on gel to confirm Sigma1 knockdown.

20 Cells were rinsed with Ca/Mg-free PBS and detached using 2 mM EDTA in Ca/Mg-free PBS. Cells were spun for 4 minutes at 14,000 rpm at 4 °C. PBS was aspirated and pellets were respun. Pellets were snap-frozen on dry ice. The pellets were lysed using RIPA + 10% glycerol + Protease inhibitor cocktail + Phosphatase inhibitor cocktail + EDTA. Lysis comprised pipetting up and down 20 times, rotating the tubes at 4 °C for 30 minutes then centrifuged for 15 minutes at 14,000 rpm at 4 °C. The lysates were aliquoted into 30 μ L volumes and stored at -80 °C.

25 To each tube of 30 μ L lysate, 15 μ L 4x loading buffer, 5.5 μ L DTT and 1 μ L BME were added. 12 μ L were loaded into each well of a 10% gel, gel was run for 30 minutes at 90 mV then increase to 11 mV for 60 minutes. Gel was transferred to membrane for 90 minutes at 200 mA. Membrane was blocked for 30 minutes using 5% non-fat dry milk in 1x TBST. PD-L1 was detected by a two night, overnight incubation in anti-PD-L1 (Cell Signaling 15165, 1:500 in 5% BSA in TBST). Anti-Rabbit HRP was used as a secondary antibody (Cell Signaling 7074 1:2000 in 5% non-fat dry milk in TBST) and HRP-beta actin was used as a loading control (Cell

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Signaling 47778, 2:1000 in 5% non-fat dry milk in TBST). Protein levels were measured using ImageJ, PD-L1 expression was normalized to beta actin.

Results:

Surprisingly and unexpectedly, RNAi of Sigma1 reduced levels of PD-L1 but not the control beta-actin. In FIG. 3A, the protein bands for PD-L1, beta-actin, and Sigma1 are illustrated. The left column is the control RNAi, while the right column used the Sigma1 RNAi construct. In the Sigma1 RNAi experiment, both Sigma1 and PD-L1 expression levels were reduced, while the beta-actin expression levels remained unchanged. The decrease in levels of the PD-L1 protein shown in FIG. 3A is quantitated in FIG. 3B. The control expression levels of PD-L1 were set to 1.0. The RNAi of Sigma1 reduced PD-L1 expression to about 0.36. This demonstrates that the modulation of Sigma1 can be used to control the expression of PD-L1, which can be used to treat various disorders as described herein.

Example 4: Reduction in PD-L1 expression in breast cancer cells by administration of Sigma1 modulator

Production of the Sigma1 protein was inhibited by the Sigma1 inhibitor 1-(4-iodophenyl)-3-(2-adamantyl)guanidine (IPAG) or activated by the Sigma1 agonist 1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-(3-phenylpropyl)-piperazine dihydrochloride (SA4503), and then levels of PD-L1 were measured to determine if a lower expression levels of Sigma1 resulted in lower expression of PD-L1.

Methods:

MDA231 (triple negative breast cancer) cells that are PD-L1 positive were treated with 10 μ M of IPAG, 20 μ M of SA4503, or the combination of both for 16 hours. MDA231 cells were seeded 24h prior to treatment with dimethyl sulfoxide (DMSO) or 10 μ M IPAG, 20 μ M of SA4503, or the combination of both for 16h.

Results:

Unexpectedly, IPAG reduced levels of PD-L1 but not control Vinculin, and the Sigma1 agonist SA4503 reversed IPAG-mediated PD-L1 inhibition. Together, this indicates that IPAG inhibition of PD-L1 is Sigma1-dependent. In FIG. 4A, the protein bands for PD-L1 and the control Vinculin are shown. The left column is the control treatment (DMSO), while the right columns are the 10 μ M IPAG treatment, followed by 20 μ M of SA4503 or the combination of

both. IPAG greatly reduces expression of PD-L1, but not the control. IPAG-mediated PD-L1 inhibition is reversed by the addition of SA4503. The decrease in expression of the PD-L1 protein is quantitated in FIG. 4B. The control expression levels of PD-L1 are set to 1.0. The exposure to IPAG reduced PD-L1 expression to approximately 0.5. The exposure to IPAG plus SA4503 increased PD-L1 expression to approximately 1.35, indicating that a Sigma1 agonist (SA4503) can reverse PD-L1 inhibition by a Sigma1 inhibitor (IPAG). This demonstrates that the modulation of Sigma1 can be used to control the expression of PD-L1, which can be used to treat various disorders as described herein.

Example 5: Reduction in tumor growth in PD-L1-dependent breast cancer cells by administration of Sigma1 modulator.

Sigma1 protein was inhibited by the Sigma1 inhibitor, Compound G, and then tumor growth inhibition was measured to determine if Sigma1 inhibition delayed tumor growth in a PD-L1 positive triple negative breast cancer cell line (MDA231).

Methods:

MDA-MB-231 human breast carcinoma cell lines were obtained from the American Type Culture Collection (Manassas, VA) and maintained according to the supplier's instructions. Cells were harvested at the exponential phase of growth for injection into the mammary fat pads of mice. NOD *scid* (NOD/SCID) and BalbC mice were purchased from Jackson Laboratory. Eight week old female mice were injected unilaterally with 2.5×10^6 cells in 200 μ L of 50:50 Matrigel/Collagen I into the fourth abdominal fat pad by subcutaneous injection at the base of the nipple. Tumor growth was monitored externally using vernier calipers for up to 2 weeks and animals sacrificed when tumors reached 10% of body weight. Control (DMSO) and drug (Compound G) were formulated in 0.5% Tween polysorbate 80/1% sodium carboxymethyl cellulose in phosphate buffered saline (PBS) and administered by oral gavage.

Results:

Unexpectedly, Compound G inhibited tumor growth in BalbC and not NOD/SCID mice, indicating that Sigma1 inhibition requires mice to have an intact immune system (BalbC) to stimulate an anti-tumor response through PD-L1 downregulation. In FIG. 5, tumor growth inhibition in immune-competent mice (BalbC) are shown on the left while tumor growth inhibition in immune-deficient mice (NOD/SCID) are shown on the right. Mice were treated with

either control (DMSO) or 30 mg/kg of Compound G. Compound G greatly reduced tumor growth in immune-competent mice, indicating that Sigma1 inhibition of PD-L1 results in potent anti-tumor immune activity. This demonstrates that the modulation of Sigma1 can be used to control the expression of PD-L1 and stimulate an anti-tumor immune response, which can be used to treat various disorders as described herein.

Example 6: Reduction of IL-6 and PD-L1 expression in cancer patients by treatment with Sigma1 modulators

A pharmaceutical composition described in Example 2 and the PD-L1 inhibitor atezolizumab (MPDL3280A) are administered to human non-small cell lung cancer (NSCLC) patients orally in combination with chemotherapy. Patients are monitored for tumor regression as well as levels of IL-6 and PD-L1 expression in whole blood and tumor biopsies. Patients are given the treatment combination for standard treatment cycles 4-6 cycles. After 6 months from start of the treatment, the tumors in patients receiving the combination treatment are measured and/or evaluated. The combination therapy shrinks tumors in the majority of patients. Levels of IL-6 and/or PD-L1 are decreased after administration of the combination.

Example 7: Combination of Compound used in Example 2 and anti-PD-1 antibodies shrink tumor size in lung cancer patients and increase survival in lung cancer patients

Patients are administered a combination, either simultaneously or sequentially, of the compound used in Example 2 and an anti-PD-1 antibody to a human with non-small cell lung cancer (NSCLC). The patients are previously treated with chemotherapy, or not previously treated with chemotherapy. Patients are monitored for tumor regression and survival. Tumor size and median survival are evaluated in the patients. Tumors are found to have been reduced in size as compared to a regimen without the compound of Example 2. The median survival increases as compared to a regimen without the compound of Example 2. as compared to a regimen without the compound of Example 2, this result is replicated regardless of the anti-PD-1 antibody that is used.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present specification,

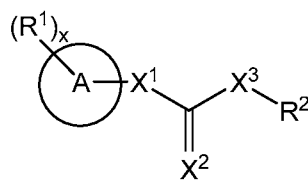
including definitions, will control. While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such embodiments
5 and equivalent variations.

CLAIMS

What is claimed is:

1. A method of treating cancer in a subject, the method comprising administering to a subject, in a cancer sample of whom at least one selected from the group consisting of PD-1 and PD-L1 is detected, at least one compound selected from the group consisting of:

(i) a compound of Formula (I):



ring A is a monocyclic or bicyclic aryl or a monocyclic or bicyclic heteroaryl ring, and wherein the aryl or heteroaryl ring is optionally substituted with 0-4 R^1 groups;

each occurrence of R^1 is independently selected from the group consisting of $\text{---C}_1\text{---C}_6$

alkyl, $\text{---C}_1\text{---C}_6$ fluoroalkyl, $\text{---C}_1\text{---C}_6$ heteroalkyl, F, Cl, Br, I, ---CN , ---NO_2 , ---OR^3 , ---SR^3 , ---S(=O)R^3 , $\text{---S(=O)}_2\text{R}^3$, $\text{---NHS(=O)}_2\text{R}^3$, ---C(=O)R^3 , ---OC(=O)R^3 , $\text{---CO}_2\text{R}^3$, $\text{---OCO}_2\text{R}^3$, $\text{---CH(R}^3\text{)}_2$, $\text{---N(R}^3\text{)}_2$, $\text{---C(=O)N(R}^3\text{)}_2$, $\text{---OC(=O)N(R}^3\text{)}_2$, $\text{---NHC(=O)NH(R}^3\text{)}$, ---NHC(=O)R^3 , ---NHC(=O)OR^3 , $\text{---C(OH)(R}^3\text{)}_2$, and $\text{---C(NH}_2\text{)(R}^3\text{)}_2$;

each occurrence of R^2 is independently selected from the group consisting of H, $\text{C}_1\text{---C}_6$

alkyl, $\text{C}_1\text{---C}_6$ heteroalkyl, and $\text{---C}_1\text{---C}_3$ alkyl- $\text{(C}_3\text{---C}_6$ cycloalkyl), wherein the alkyl, heteroalkyl or cycloalkyl group is optionally substituted with 0-5 R^1 groups, or X^3 and R^2 combine to form a $\text{(C}_3\text{---C}_7\text{)}$ heterocycloalkyl group, optionally substituted with 0-2 R^1 groups;

each occurrence of R^3 is independently selected from the group consisting of H, $\text{C}_1\text{---C}_6$

alkyl, $\text{C}_1\text{---C}_6$ heteroalkyl, aryl, and $\text{---C}_1\text{---C}_3$ alkyl- $\text{(C}_3\text{---C}_6$ cycloalkyl), wherein the alkyl, heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

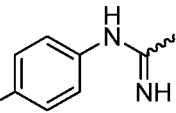
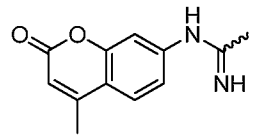
X^1 is $\text{---CH}_2\text{---}$, ---S--- , ---O--- or $\text{---(NR}^2\text{)---}$;

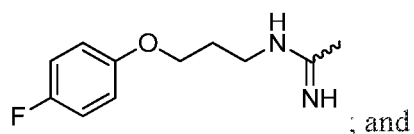
X^2 is =CH_2 , =S , =O or =NR^2 ; and

X^3 is ---S--- , ---O--- , or $\text{---NR}^2\text{---}$; and

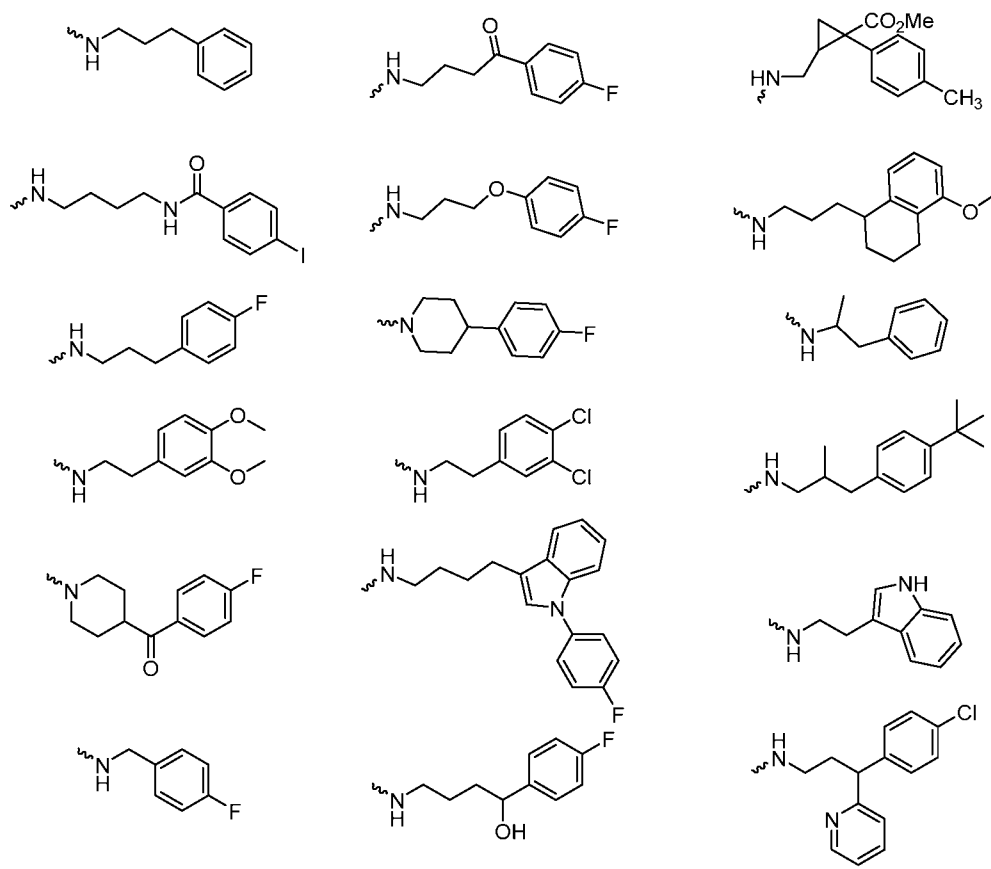
(ii) a compound of Formula (II):

$\text{R}^A\text{---R}^B$ (II), wherein in (II):

R^A is selected from the group consisting of X^4 -, , and



R^B is selected from the group consisting of:

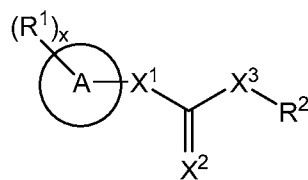


a pharmaceutically acceptable salt or solvate thereof, a *N*-oxide thereof, and any combinations thereof.

2. The method of claim 1, further comprising administering to the subject at least one selected from the group consisting of an anti-PD-1 compound and an anti-PD-L1 compound.

3. The method of claim 2, wherein the anti-PD-1 compound is an antibody.

4. The method of claim 2, wherein the anti-PD-L1 compound is an antibody.
5. A method of preventing, treating, or ameliorating at least one disorder or disease that is mediated via IL-6 and/or pg130 signaling in a subject, the method comprising administering to the subject at least one compound selected from the group consisting of:
- (i) a compound of Formula (I):



(I), wherein in (I):

ring A is a monocyclic or bicyclic aryl or a monocyclic or bicyclic heteroaryl ring, and

wherein the aryl or heteroaryl ring is optionally substituted with 0-4 R^1 groups;

each occurrence of R^1 is independently selected from the group consisting of $-\text{C}_1\text{-C}_6$

alkyl, $-\text{C}_1\text{-C}_6$ fluoroalkyl, $-\text{C}_1\text{-C}_6$ heteroalkyl, F, Cl, Br, I, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}^3$, $-\text{SR}^3$,

$-\text{S}(=\text{O})\text{R}^3$, $-\text{S}(=\text{O})_2\text{R}^3$, $-\text{NHS}(=\text{O})_2\text{R}^3$, $-\text{C}(=\text{O})\text{R}^3$, $-\text{OC}(=\text{O})\text{R}^3$, $-\text{CO}_2\text{R}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{CH}(\text{R}^3)_2$, $-\text{N}(\text{R}^3)_2$, $-\text{C}(=\text{O})\text{N}(\text{R}^3)_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^3)_2$, $-\text{NHC}(=\text{O})\text{NH}(\text{R}^3)$, $-\text{NHC}(=\text{O})\text{R}^3$, $-\text{NHC}(=\text{O})\text{OR}^3$, $-\text{C}(\text{OH})(\text{R}^3)_2$, and $-\text{C}(\text{NH}_2)(\text{R}^3)_2$;

each occurrence of R^2 is independently selected from the group consisting of H, $\text{C}_1\text{-C}_6$

alkyl, $\text{C}_1\text{-C}_6$ heteroalkyl, and $-\text{C}_1\text{-C}_3$ alkyl- $(\text{C}_3\text{-C}_6$ cycloalkyl), wherein the alkyl,

heteroalkyl or cycloalkyl group is optionally substituted with 0-5 R^1 groups, or X^3

and R^2 combine to form a $(\text{C}_3\text{-C}_7)$ heterocycloalkyl group, optionally substituted with 0-2 R^1 groups;

each occurrence of R^3 is independently selected from the group consisting of H, $\text{C}_1\text{-C}_6$

alkyl, $\text{C}_1\text{-C}_6$ heteroalkyl, aryl, and $-\text{C}_1\text{-C}_3$ alkyl- $(\text{C}_3\text{-C}_6$ cycloalkyl), wherein the alkyl,

heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

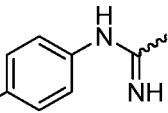
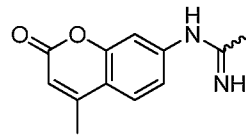
X^1 is $-\text{CH}_2-$, $-\text{S}-$, $-\text{O}-$ or $-(\text{NR}^2)-$;

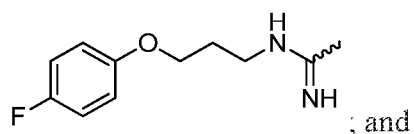
X^2 is $=\text{CH}_2$, $=\text{S}$, $=\text{O}$ or $=\text{NR}^2$; and

X^3 is $-\text{S}-$, $-\text{O}-$, or $-\text{NR}^2-$; and

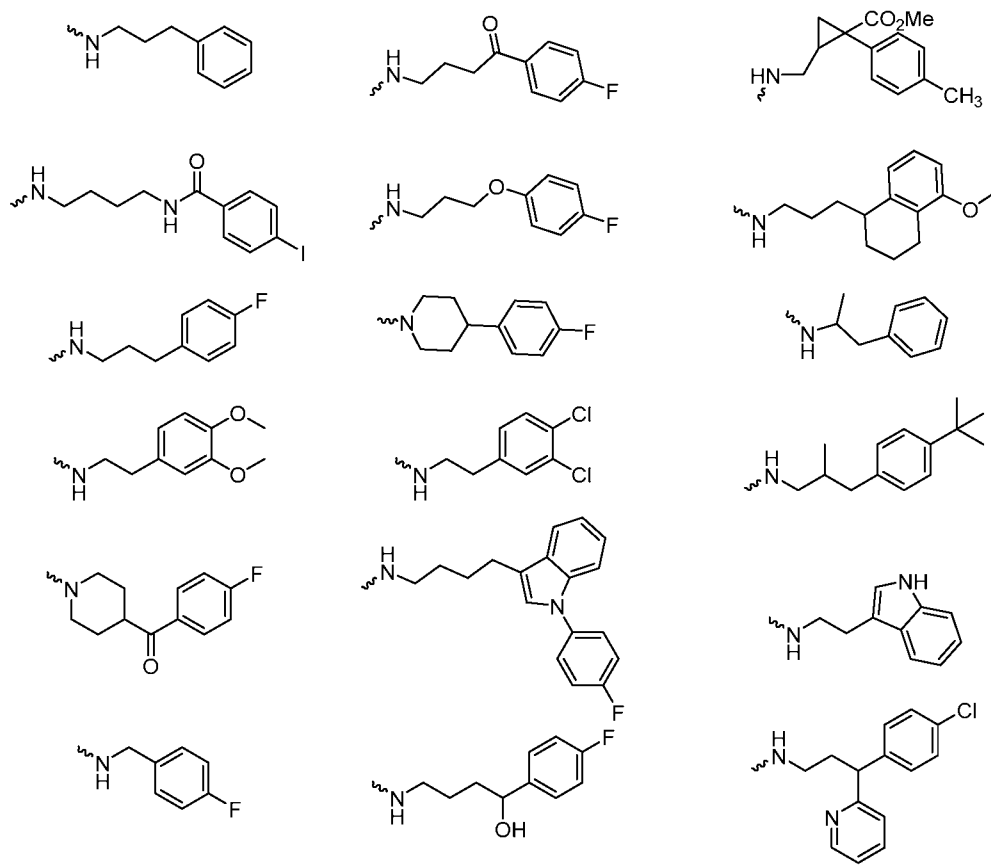
- (ii) a compound of Formula (II):

$\text{R}^A\text{-R}^B$ (II), wherein in (II):

R^A is selected from the group consisting of X^4 -, , and



R^B is selected from the group consisting of:



a pharmaceutically acceptable salt or solvate thereof, a *N*-oxide thereof, and any combinations thereof.

6. The method of claim 5, wherein the at least one disorder or disease comprises an autoimmune disease.

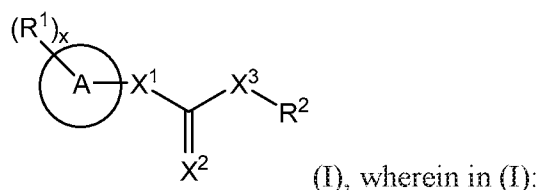
7. The method of claim 6, wherein the autoimmune disease is at least one selected from the group consisting of: asthma, Sjogren's syndrome, multiple sclerosis, systemic lupus

erythematosus, Graves' disease, Hashimoto's disease, Castleman's disease, psoriasis, psoriatic arthropathy, ankylosing spondylitis, inflammatory bowel disease (IBD), polymyalgia rheumatica, giant cell arteritis, autoimmune vasculitis, graft versus host disease (GVHD), adult onset Still's disease, rheumatoid arthritis, systemic juvenile idiopathic arthritis, obesity, diabetes, asthma, multiple sclerosis, Alzheimer's disease, cerebrovascular disease, fever, acute phase response, allergies, chronic prostatitis, glomerulonephritis, pelvic inflammatory disease, reperfusion injury, and transplant rejection.

8. The method of claim 5, wherein the at least one disorder or disease comprises inflammation.
9. The method of claim 8, wherein the inflammation is acute and/or chronic inflammation.
10. The method of claim 5, wherein the at least one disorder or disease comprises cancer.
11. The method of claim 10, wherein the cancer is at least one selected from the group consisting of bladder cancer, brain cancer, bone cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, head and neck cancer, kidney cancer, large intestine cancer, liver cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin cancer, soft tissue cancer, and testicular cancer.
12. The method of claim 5, wherein the at least one disorder or disease comprises a B-cell proliferative disorder.
13. The method of claim 12, wherein the B-cell proliferative disorder is at least one selected from the group consisting of follicular lymphoma, chronic lymphocytic leukemia, acute lymphoblastic leukemia, hairy cell leukemia, B cell lymphoma, T cell lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, Wiskott-Aldrich syndrome, post-transplant lymphoproliferative disorder, and autoimmune lymphoproliferative syndrome.
14. A method of enhancing an IL-6 mediated immune response in a subject, the method

comprising administering to the subject at least one compound selected from the group consisting of:

(i) a compound of Formula (I):



ring A is a monocyclic or bicyclic aryl or a monocyclic or bicyclic heteroaryl ring, and

wherein the aryl or heteroaryl ring is optionally substituted with 0-4 R^1 groups;

each occurrence of R^1 is independently selected from the group consisting of $-C_1-C_6$

alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ heteroalkyl, F, Cl, Br, I, $-CN$, $-NO_2$, $-OR^3$, $-SR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-NHS(=O)_2R^3$, $-C(=O)R^3$, $-OC(=O)R^3$, $-CO_2R^3$, $-OCO_2R^3$, $-CH(R^3)_2$, $-N(R^3)_2$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$, $-NHC(=O)NH(R^3)$, $-NHC(=O)R^3$, $-NHC(=O)OR^3$, $-C(OH)(R^3)_2$, and $-C(NH_2)(R^3)_2$;

each occurrence of R^2 is independently selected from the group consisting of H, C_1-C_6

alkyl, C_1-C_6 heteroalkyl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl, heteroalkyl or cycloalkyl group is optionally substituted with 0-5 R^1 groups, or X^3 and R^2 combine to form a (C_3-C_7) heterocycloalkyl group, optionally substituted with 0-2 R^1 groups;

each occurrence of R^3 is independently selected from the group consisting of H, C_1-C_6

alkyl, C_1-C_6 heteroalkyl, aryl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl, heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

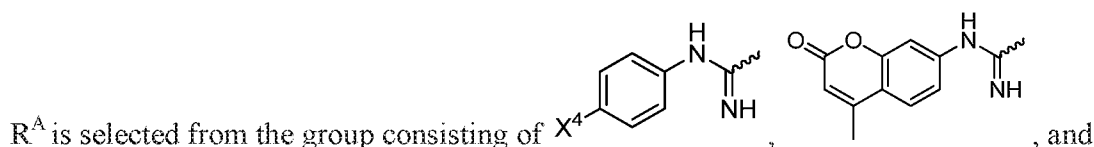
X^1 is $-CH_2-$, $-S-$, $-O-$ or $-(NR^2)-$;

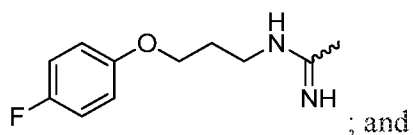
X^2 is $=CH_2$, $=S$, $=O$ or $=NR^2$; and

X^3 is $-S-$, $-O-$, or $-(NR^2)-$; and

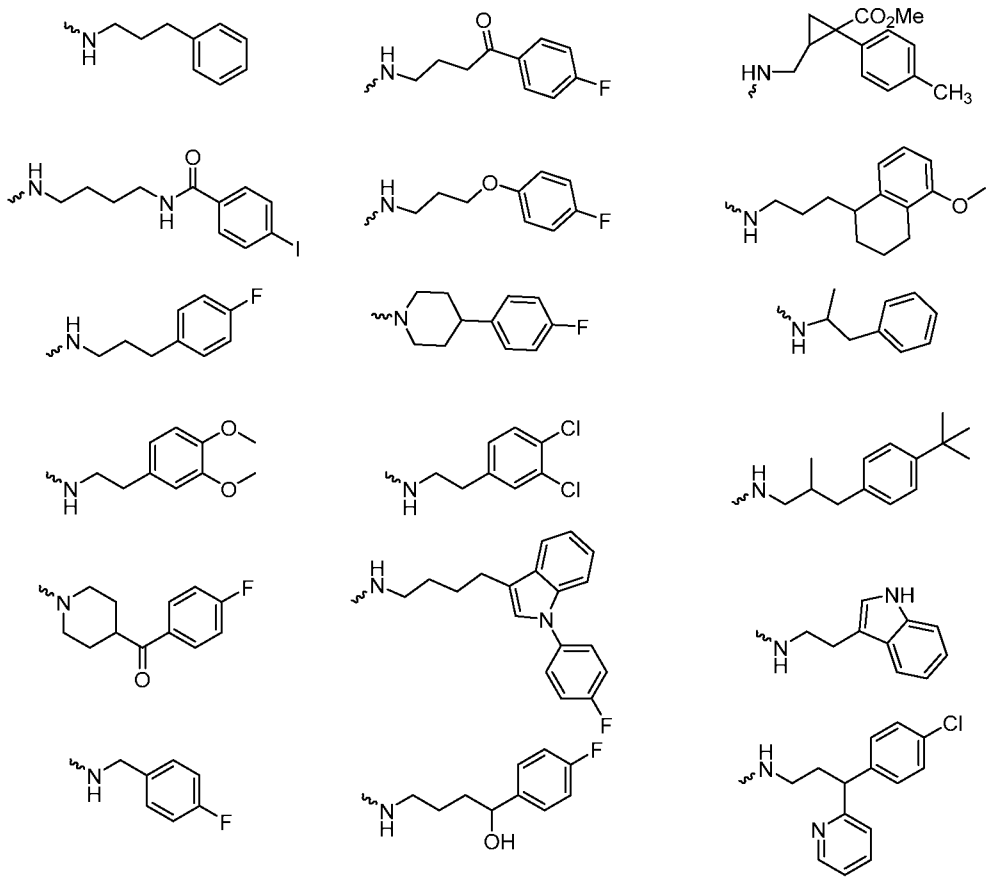
(ii) a compound of Formula (II):

R^A-R^B (II), wherein in (II):





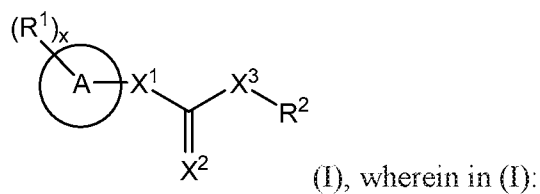
R^B is selected from the group consisting of:



a pharmaceutically acceptable salt or solvate thereof, a *N*-oxide thereof, and any combinations thereof.

15. A method of decreasing IL-6 and/or gp130-mediated signaling in a subject, the method comprising administering to the subject at least one compound selected from the group consisting of:

(i) a compound of Formula (I):



ring A is a monocyclic or bicyclic aryl or a monocyclic or bicyclic heteroaryl ring, and

wherein the aryl or heteroaryl ring is optionally substituted with 0-4 R^1 groups;

each occurrence of R^1 is independently selected from the group consisting of $-C_1-C_6$

alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ heteroalkyl, F, Cl, Br, I, $-CN$, $-NO_2$, $-OR^3$, $-SR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-NHS(=O)_2R^3$, $-C(=O)R^3$, $-OC(=O)R^3$, $-CO_2R^3$, $-OCO_2R^3$, $-CH(R^3)_2$, $-N(R^3)_2$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$, $-NHC(=O)NH(R^3)$, $-NHC(=O)R^3$, $-NHC(=O)OR^3$, $-C(OH)(R^3)_2$, and $-C(NH_2)(R^3)_2$;

each occurrence of R^2 is independently selected from the group consisting of H, C_1-C_6

alkyl, C_1-C_6 heteroalkyl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl,

heteroalkyl or cycloalkyl group is optionally substituted with 0-5 R^1 groups, or X^3

and R^2 combine to form a (C_3-C_7) heterocycloalkyl group, optionally substituted with 0-2 R^1 groups;

each occurrence of R^3 is independently selected from the group consisting of H, C_1-C_6

alkyl, C_1-C_6 heteroalkyl, aryl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl,

heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

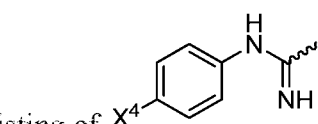
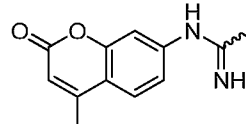
X^1 is $-CH_2-$, $-S-$, $-O-$ or $-(NR^2)-$;

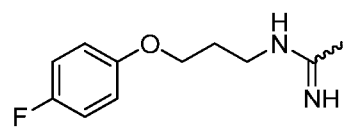
X^2 is $=CH_2$, $=S$, $=O$ or $=NR^2$; and

X^3 is $-S-$, $-O-$, or $-(NR^2)-$; and

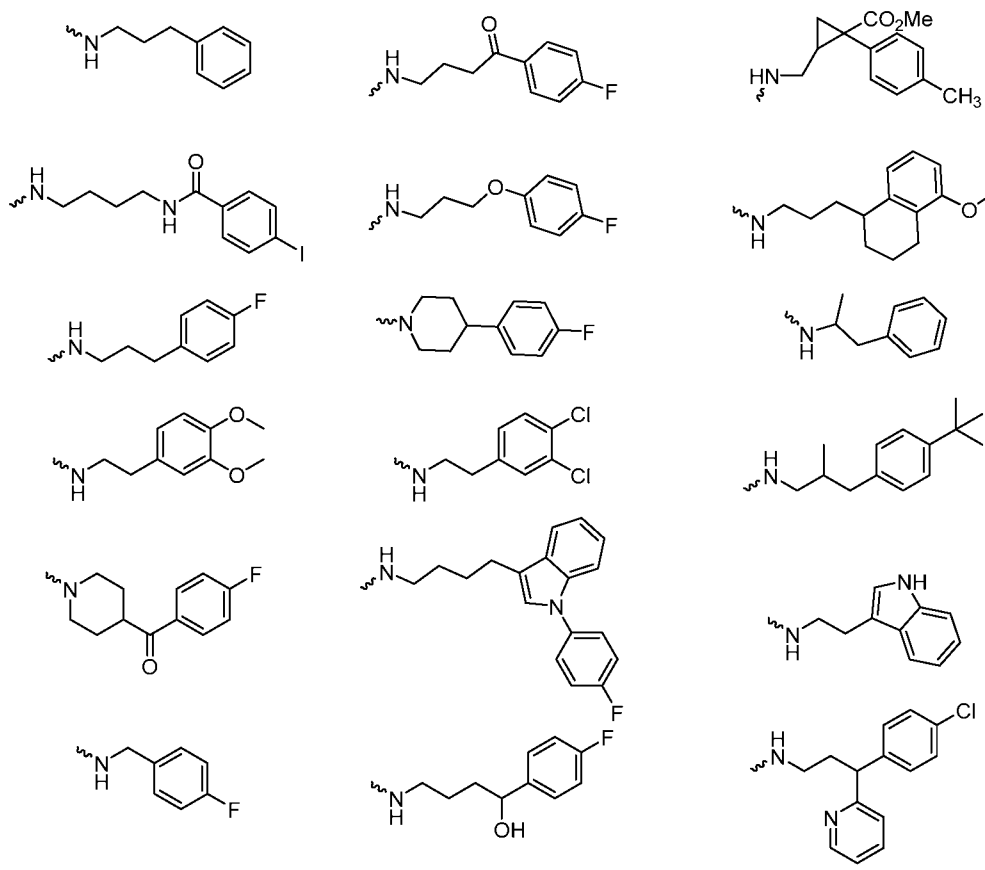
(ii) a compound of Formula (II):

R^A-R^B (II), wherein in (II):

R^A is selected from the group consisting of X^4 , , and

; and

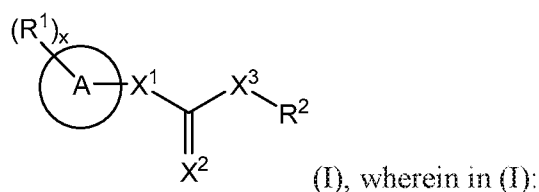
R^B is selected from the group consisting of:



a pharmaceutically acceptable salt or solvate thereof, a *N*-oxide thereof, and any combinations thereof.

16. A method of preventing, treating, or ameliorating at least one disorder or disease that is mediated via PD-L1 signaling in a subject, the method comprising administering to the subject at least one compound selected from the group consisting of:

(i) a compound of Formula (I):



ring A is a monocyclic or bicyclic aryl or a monocyclic or bicyclic heteroaryl ring, and wherein the aryl or heteroaryl ring is optionally substituted with 0-4 R^1 groups; each occurrence of R^1 is independently selected from the group consisting of $-C_1-C_6$ alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ heteroalkyl, F, Cl, Br, I, $-CN$, $-NO_2$, $-OR^3$, $-SR^3$,

$-\text{S}(=\text{O})\text{R}^3$, $-\text{S}(=\text{O})_2\text{R}^3$, $-\text{NHS}(=\text{O})_2\text{R}^3$, $-\text{C}(=\text{O})\text{R}^3$, $-\text{OC}(=\text{O})\text{R}^3$, $-\text{CO}_2\text{R}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{CH}(\text{R}^3)_2$, $-\text{N}(\text{R}^3)_2$, $-\text{C}(=\text{O})\text{N}(\text{R}^3)_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^3)_2$, $-\text{NHC}(=\text{O})\text{NH}(\text{R}^3)$, $-\text{NHC}(=\text{O})\text{R}^3$, $-\text{NHC}(=\text{O})\text{OR}^3$, $-\text{C}(\text{OH})(\text{R}^3)_2$, and $-\text{C}(\text{NH}_2)(\text{R}^3)_2$;

each occurrence of R^2 is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, and $-\text{C}_1$ - C_3 alkyl- $(\text{C}_3$ - C_6 cycloalkyl), wherein the alkyl, heteroalkyl or cycloalkyl group is optionally substituted with 0-5 R^1 groups, or X^3 and R^2 combine to form a $(\text{C}_3$ - $\text{C}_7)$ heterocycloalkyl group, optionally substituted with 0-2 R^1 groups;

each occurrence of R^3 is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, aryl, and $-\text{C}_1$ - C_3 alkyl- $(\text{C}_3$ - C_6 cycloalkyl), wherein the alkyl, heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

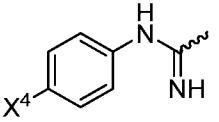
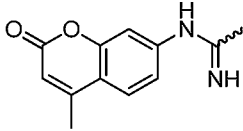
X^1 is $-\text{CH}_2-$, $-\text{S}-$, $-\text{O}-$ or $-(\text{NR}^2)-$;

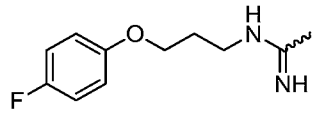
X^2 is $=\text{CH}_2$, $=\text{S}$, $=\text{O}$ or $=\text{NR}^2$; and

X^3 is $-\text{S}-$, $-\text{O}-$, or $-\text{NR}^2-$; and

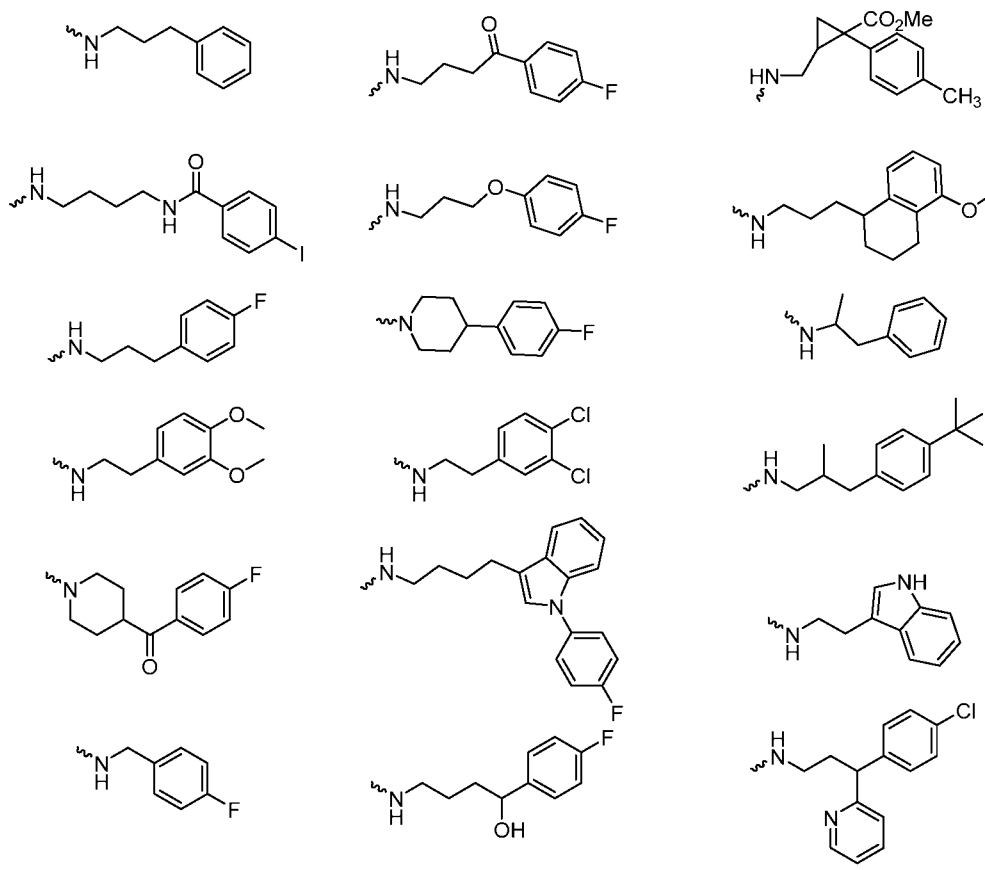
(ii) a compound of Formula (II):

R^A - R^B (II), wherein in (II):

R^A is selected from the group consisting of , , and

; and

R^B is selected from the group consisting of:



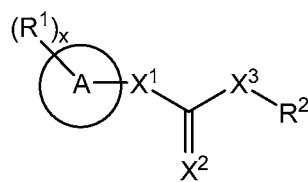
a pharmaceutically acceptable salt or solvate thereof, a *N*-oxide thereof, and any combinations thereof.

17. The method of claim 16, wherein the at least one disorder or disease comprises cancer.

18. The method of claim 19, wherein the cancer is at least one selected from the group consisting of bladder cancer, brain cancer, bone cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, head and neck cancer, kidney cancer, large intestine cancer, liver cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin cancer, soft tissue cancer, and testicular cancer.

19. A method of decreasing PD-L1-mediated signaling in a subject, the method comprising administering to the subject at least one compound selected from the group consisting of:

(i) a compound of Formula (I):



ring A is a monocyclic or bicyclic aryl or a monocyclic or bicyclic heteroaryl ring, and

wherein the aryl or heteroaryl ring is optionally substituted with 0-4 R^1 groups;

each occurrence of R^1 is independently selected from the group consisting of $-C_1-C_6$

alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ heteroalkyl, F, Cl, Br, I, $-CN$, $-NO_2$, $-OR^3$, $-SR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-NHS(=O)_2R^3$, $-C(=O)R^3$, $-OC(=O)R^3$, $-CO_2R^3$, $-OCO_2R^3$, $-CH(R^3)_2$, $-N(R^3)_2$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$, $-NHC(=O)NH(R^3)$, $-NHC(=O)R^3$, $-NHC(=O)OR^3$, $-C(OH)(R^3)_2$, and $-C(NH_2)(R^3)_2$;

each occurrence of R^2 is independently selected from the group consisting of H, C_1-C_6

alkyl, C_1-C_6 heteroalkyl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl,

heteroalkyl or cycloalkyl group is optionally substituted with 0-5 R^1 groups, or X^3

and R^2 combine to form a (C_3-C_7) heterocycloalkyl group, optionally substituted with 0-2 R^1 groups;

each occurrence of R^3 is independently selected from the group consisting of H, C_1-C_6

alkyl, C_1-C_6 heteroalkyl, aryl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl,

heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

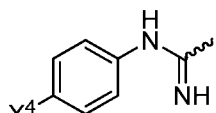
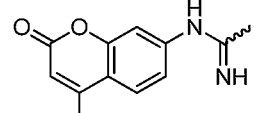
X^1 is $-CH_2-$, $-S-$, $-O-$ or $-(NR^2)-$;

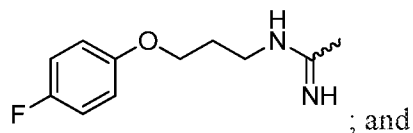
X^2 is $=CH_2$, $=S$, $=O$ or $=NR^2$; and

X^3 is $-S-$, $-O-$, or $-(NR^2)-$; and

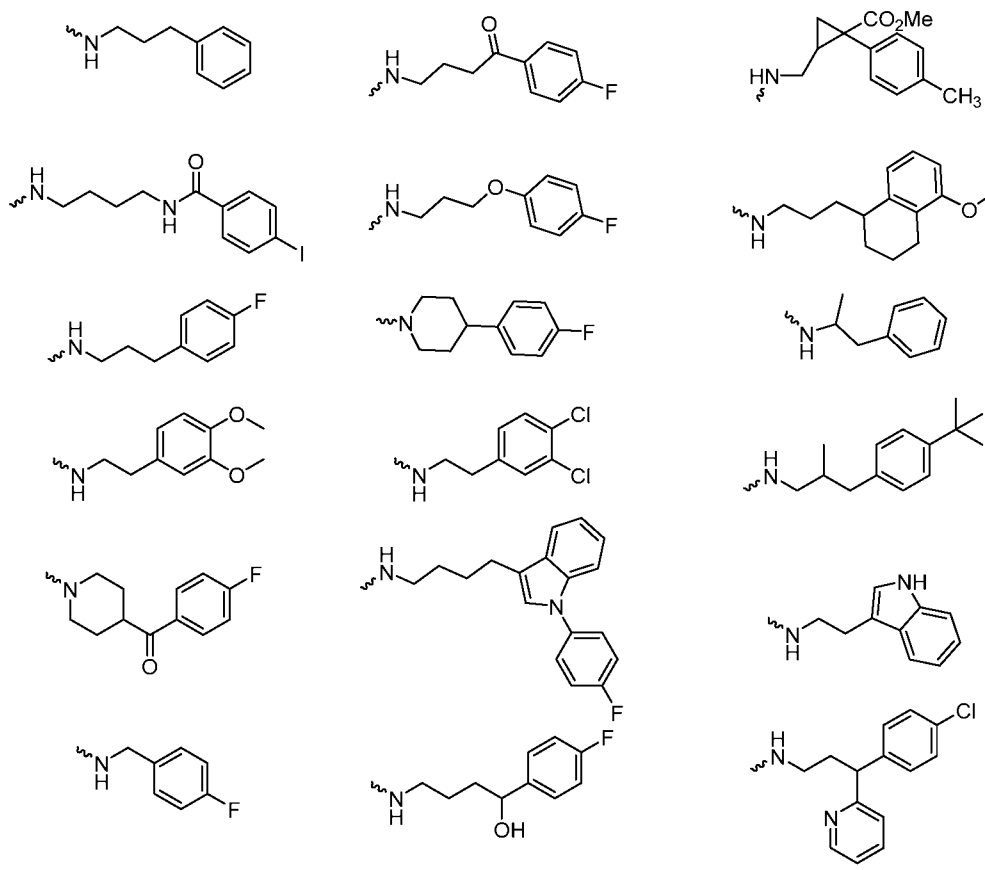
(ii) a compound of Formula (II):

R^A-R^B (II), wherein in (II):

R^A is selected from the group consisting of , , and



R^B is selected from the group consisting of:



a pharmaceutically acceptable salt or solvate thereof, a *N*-oxide thereof, and any combinations thereof.

20. The method of any of claims 1-19, wherein in the compound of Formula (I):

each occurrence of R^1 is independently selected from the group consisting of $-C_1-C_2$ alkyl, $-C_1-C_2$ fluoroalkyl, $-C_1-C_2$ heteroalkyl, F, Cl, Br, I, $-CN$, $-NO_2$, $-OR^3$, $-SR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-NHS(=O)_2R^3$, $-C(=O)R^3$, $-OC(=O)R^3$, $-CO_2R^3$, $-OCO_2R^3$, $-CH(R^3)_2$, $-N(R^3)_2$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$, $-NHC(=O)NH(R^3)$, $-NHC(=O)R^3$, $-NHC(=O)OR^3$, $-C(OH)(R^3)_2$, and $-C(NH_2)(R^3)_2$;

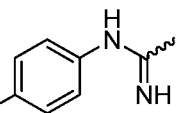
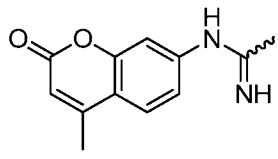
each occurrence of R^2 is independently selected from the group consisting of H, C_1-C_3 alkyl, and C_1-C_3 heteroalkyl, wherein the alkyl, heteroalkyl or cycloalkyl group is optionally substituted with 0-2 R^1 groups, or X^3 and R^2 combine to form a (C_3-C_7) heterocycloalkyl group, optionally substituted with 0-2 R^1 groups; and

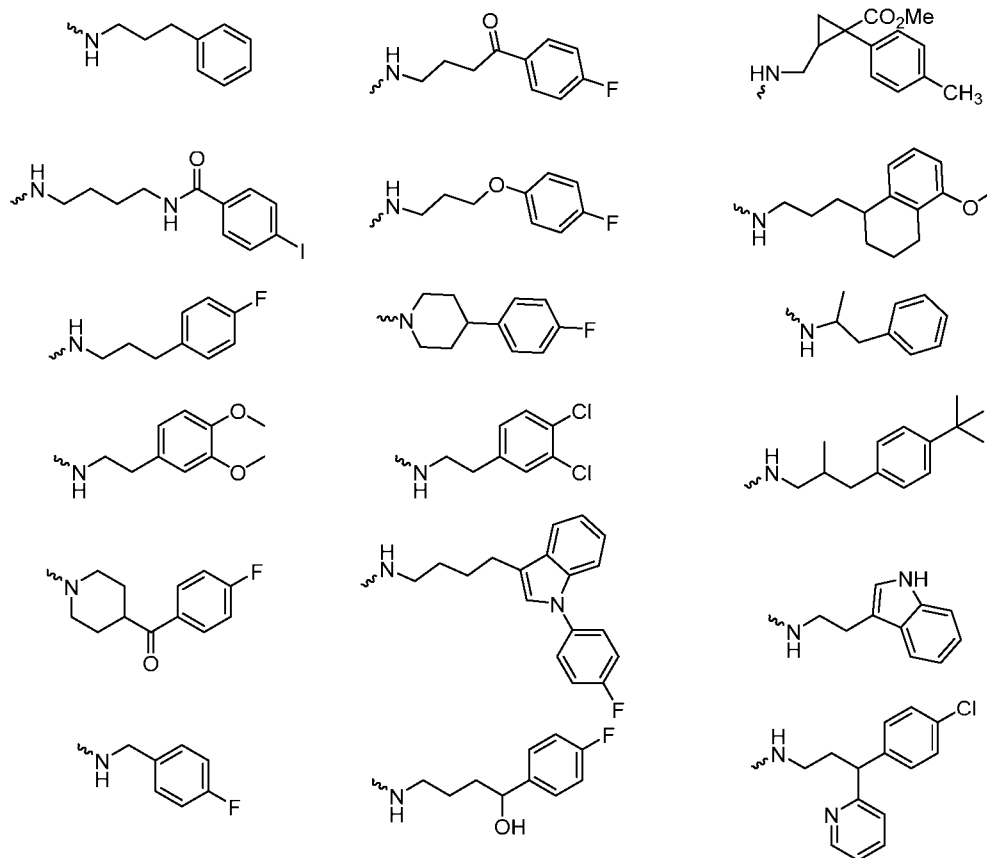
each occurrence of R^3 is independently selected from the group consisting of H, C_1-C_2 alkyl, and C_1-C_2 heteroalkyl, aryl, wherein the alkyl, heteroalkyl, aryl, or cycloalkyl group is

optionally substituted with 0-2 groups.

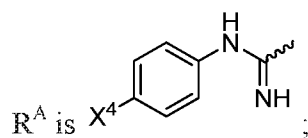
21. The method of any of claims 1-19, wherein the at least one compound is a compound of Formula (I-A), or a pharmaceutically acceptable salt or solvate thereof:

R^A-R^B (I-A), wherein in (I-A):

R^A is selected from the group consisting of X^4 - and  ;
 X^4 is selected from the group consisting of OMe, F, Cl, Br, and I; and
 R^B is selected from the group consisting of:

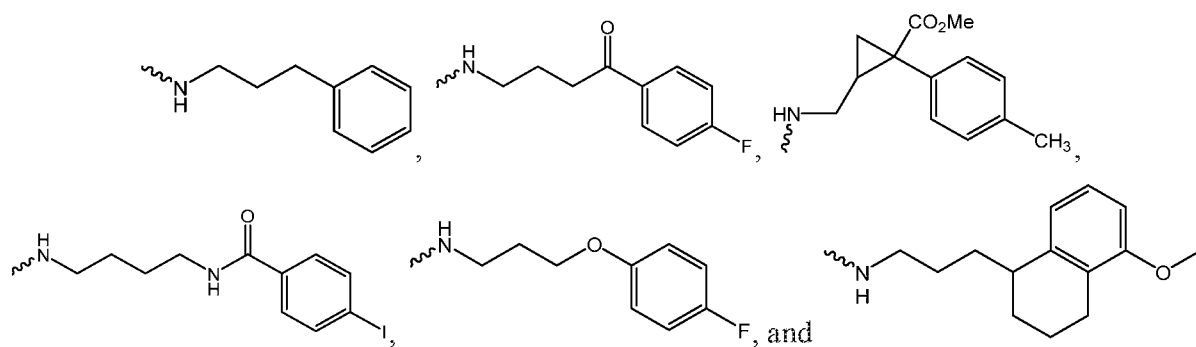


22. The method of claim 21, wherein in the compound of formula (I-A):

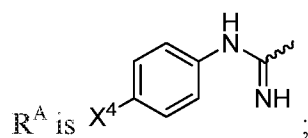


X^4 is selected from the group consisting of F, Cl, Br, and I; and

R^B is selected from the group consisting of:

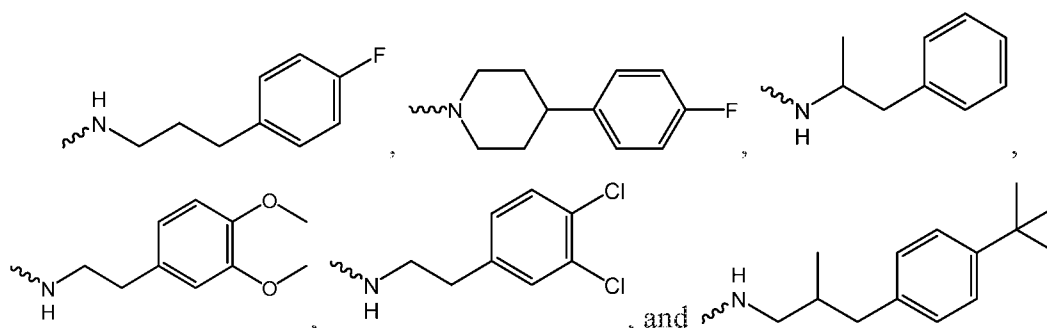


23. The method of claim 21, wherein in the compound of formula (I-A):

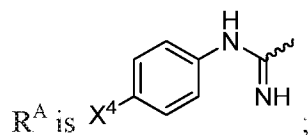


X^4 is selected from the group consisting of F, Cl, Br, and I; and

R^B is selected from the group consisting of:

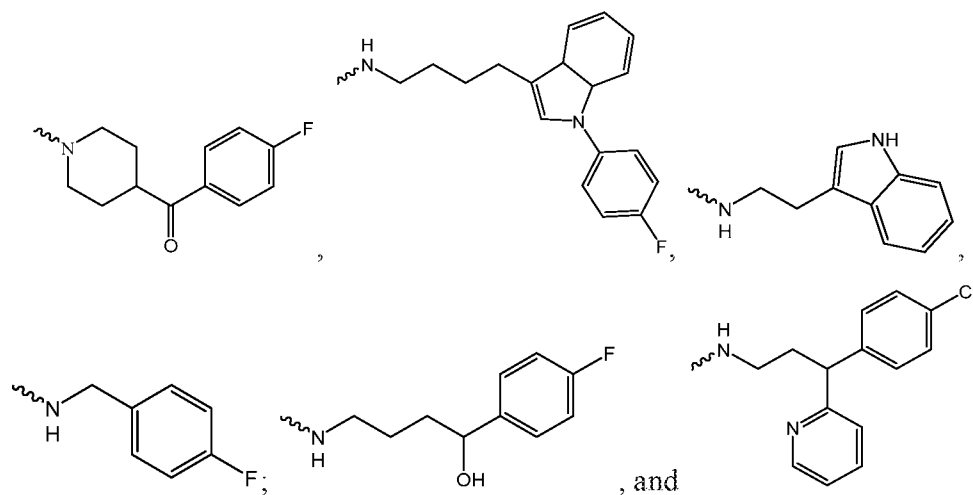


24. The method of claim 21, wherein in the compound of formula (I-A):

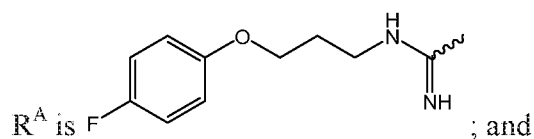


X^4 is selected from the group consisting of F, Cl, Br, and I; and

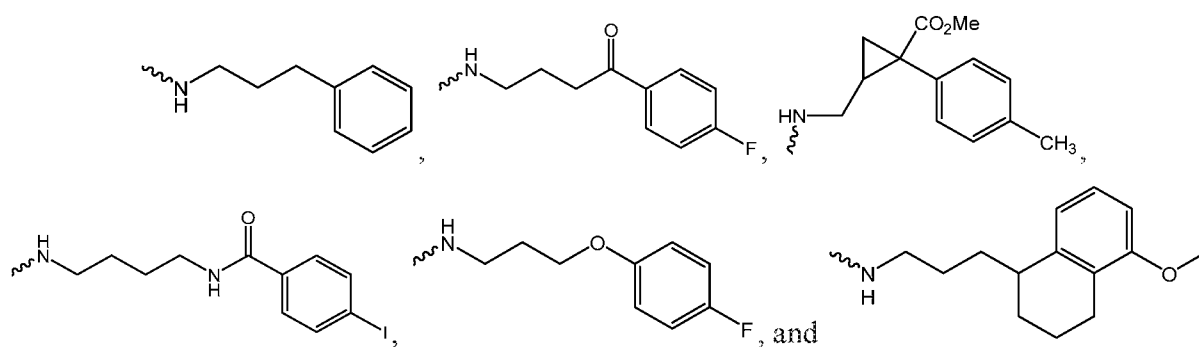
R^B is selected from the group consisting of:



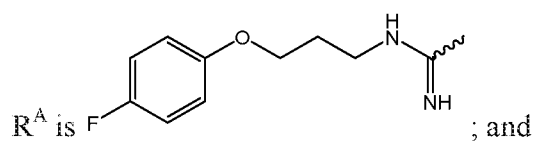
25. The method of any of claims 1-19, wherein in the compound of formula (II):



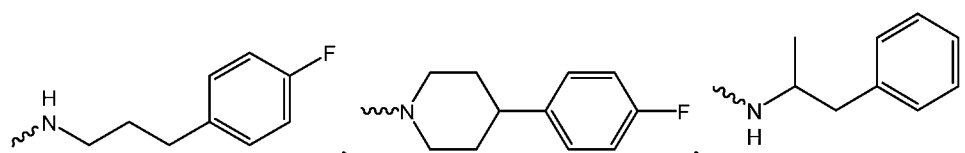
R^B is selected from the group consisting of:

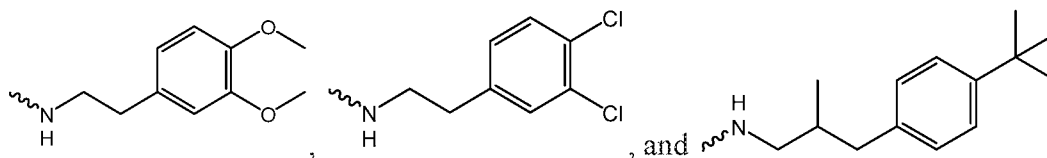


26. The method of any of claims 1-19, wherein in the compound of formula (II):

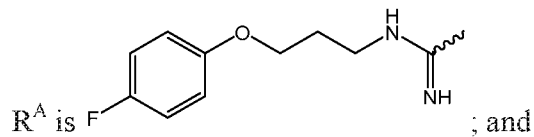


R^B is selected from the group consisting of:

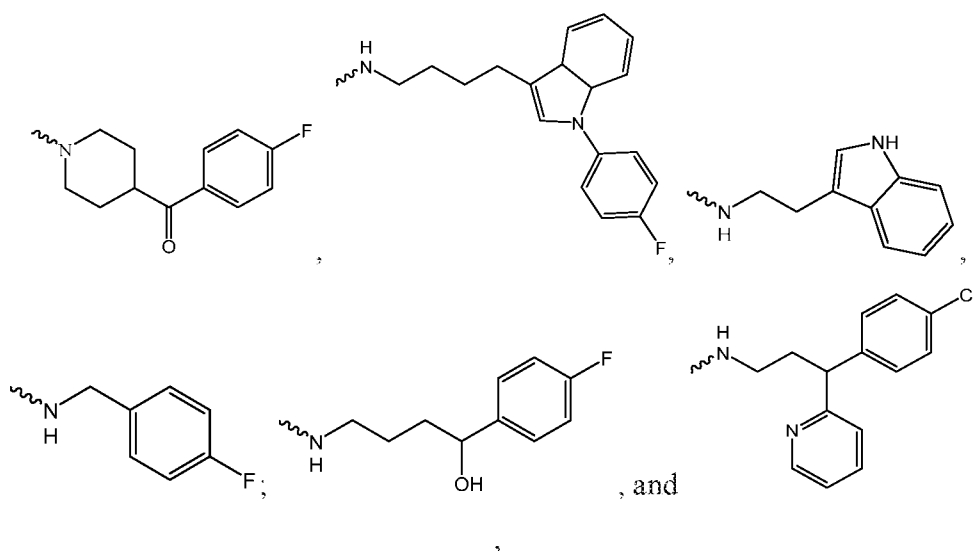




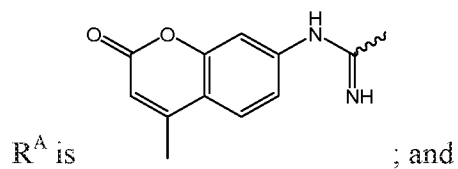
27. The method of any of claims 1-19, wherein in the compound of formula (II):



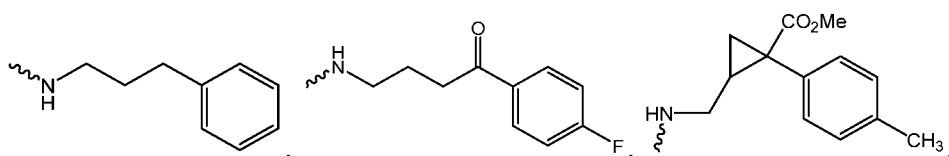
R^B is selected from the group consisting of:

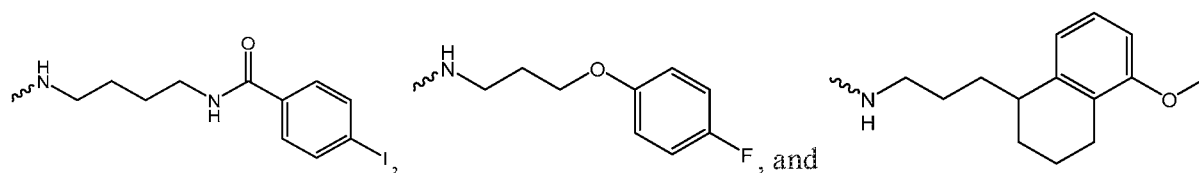


28. The method of claim 21, wherein in the compound of Formula (I-A):

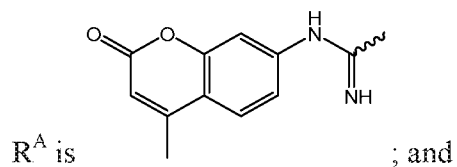


R^B is selected from the group consisting of:

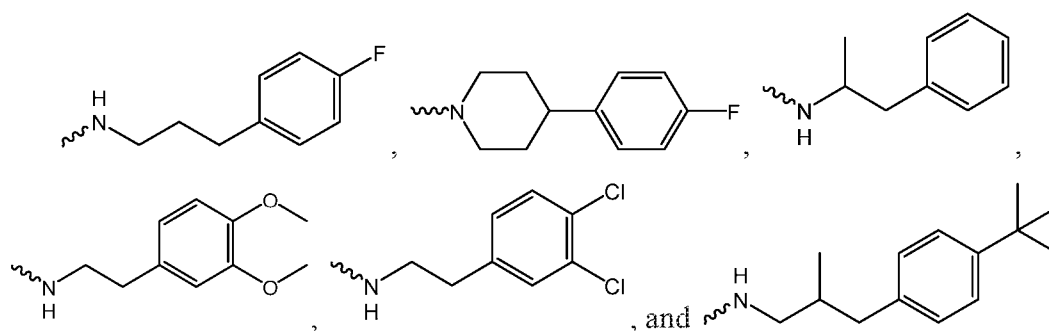




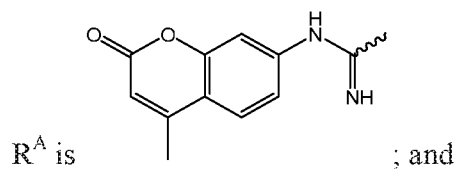
29. The method of claim 21, wherein in the compound of Formula (I-A):



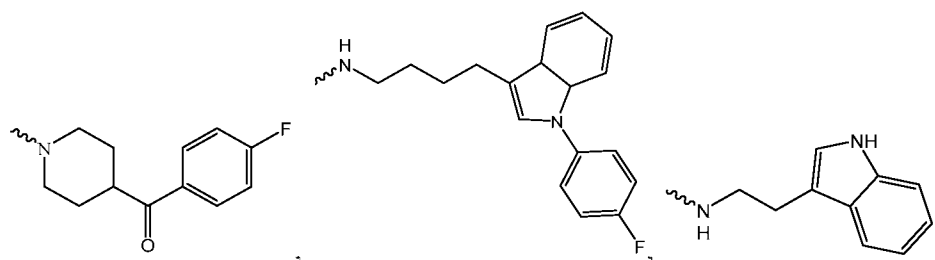
R^B is selected from the group consisting of:

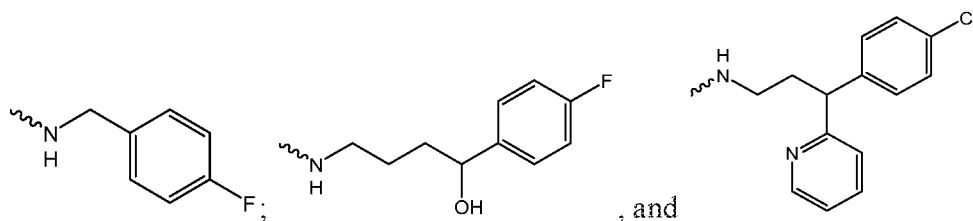


30. The method of claim 21, wherein in the compound of Formula (I-A):

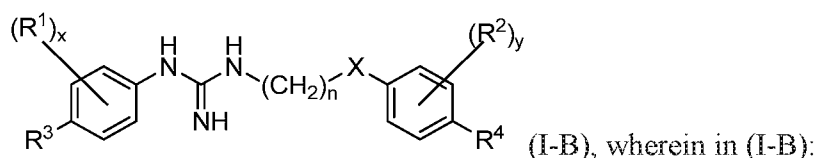


R^B is selected from the group consisting of:





31. The method of any of claims 1-19, wherein the at least one compound is a compound of formula (I-B), or a pharmaceutically acceptable salt or solvate thereof:



each occurrence of R^1 and R^2 is independently selected from the group consisting of $-C_1-C_6$ alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ heteroalkyl, F, Cl, Br, I, $-CN$, $-NO_2$, $-OR^5$, $-SR^5$, $-S(=O)R^5$, $-S(=O)_2R^5$, $-NHS(=O)_2R^5$, $-C(=O)R^5$, $-OC(=O)R^5$, $-CO_2R^5$, $-OCO_2R^5$, $-CH(R^5)_2$, $-N(R^5)_2$, $-C(=O)N(R^5)_2$, $-OC(=O)N(R^5)_2$, $-NHC(=O)NH(R^5)$, $-NHC(=O)R^5$, $-NHC(=O)OR^5$, $-C(OH)(R^5)_2$, and $-C(NH_2)(R^5)_2$;

R^3 is selected from the group consisting of $-C_1-C_6$ alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ alkoxy, F, Cl, Br, and I;

R^4 is selected from the group consisting of $-C_1-C_6$ alkyl, $-C_1-C_6$ alkoxy, F, Cl, Br, and I;

each occurrence of R^5 is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, aryl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl, heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

X is selected from the group consisting of CH_2 , $C=O$, and O;

n is an integer from 1-3;

x is an integer from 0-4; and

y is an integer from 0-4.

32. The method of any of claims 1-19, wherein the at least one compound is selected from the group consisting of:

1-(3-(4-fluorophenoxy)propyl)-3-(4-iodophenyl)guanidine (Compound A),

1-(3-(4-fluorophenoxy)propyl)-3-(4-methoxyphenyl)guanidine (Compound B),

1-(n-propyl)-3-(4-iodophenyl)guanidine (Compound C),
1-(n-propyl)-3-(4-methoxyphenyl)guanidine (Compound D),
1,3-bis(3-(4-fluorophenoxy)propyl)guanidine (Compound E),
1-(3-(4-fluorophenoxy)propyl)-3-(4-trifluoromethylphenyl)guanidine (Compound F),
1-(3-(4-fluorophenoxy)propyl)-3-(4-chlorophenyl)guanidine (Compound G), and
1-(3-(4-fluorophenoxy)propyl)-3-(4-methy 1-2-oxo-2Hchromen-7-yl)guanidine (Compound H),
or a pharmaceutically acceptable salt or solvate thereof, and any combinations thereof.

33. The method of any of claims 1-19, wherein the method further comprises administering to the subject one or more anti-IL-6 and/or gp130 compound(s).

34. The method of any of claims 20-32, wherein the method further comprises administering to the subject one or more anti-IL-6 and/or gp130 compound(s).

34. The method of claim 33, wherein the anti-IL-6 and/or gp130 compound(s) comprise(s) a IL-6 receptor antagonist.

35. The method of claim 33, wherein the anti-IL-6 and/or gp130 compound(s) comprise(s) a IL-6 binding compound.

36. The method of claim 33, wherein the anti-IL-6 and/or gp130 compound(s) comprise(s) a gp130 antagonist.

37. The method of claim 33, wherein the one or more anti-IL-6 compound(s) comprise(s) tocilizumab, siltuximab, sarilumab, olokizumab, elsilimomab, ALD518/BMS-94529, sirukumab, CPSI-2364, ARGX-109, FE301, or FM101, or any combination thereof.

38. The method of any of claims 1-37, wherein the method further comprises administering to the subject an effective amount of at least one immune system modulator.

39. The method of claim 38, wherein the at least one immune system modulator modulates

the interactions of T and/or B cells with Signal modulators.

40. The method of claim 39, wherein the at least one immune system modulator is at least one selected from the group consisting of blockers of ICOS-ICOS-L, IL-10, IL-24 IL-21, adenosine 2a, arginase, IDO1, CD40-CD40L, CD134-CD134L, CD137-CD137L, CTLA4, PD-1, PD-L1/PD-L2, TIM3, LAG3, TGF- β or activate toll-like receptors, IL-2, and STING.

41. The method of any of claims 1-40, further comprising administering to the subject at least one compound that blocks the activity of PD-1 and/or PD-L1.

42. The method of claim 41, wherein the at least one compound that blocks the activity of PD-1 and/or PD-L1 is selected from the group consisting of nivolumab, pembrolizumab, pidilizumab (CT-011), BMS-936559, avelumab (MSB0010718C), durvalumab (MEDI4736), MEDI0680, B7-DC-Ig (AMP224), atezolizumab (MPDL3280A), CX-072, REGN2810, TSR-042, STI-1014, STI-1110, or any combinations thereof.

43. The method of any of claims 1-42, wherein the subject is a subject in need thereof.

44. The method of any of claims 1-43, wherein the subject is a mammal.

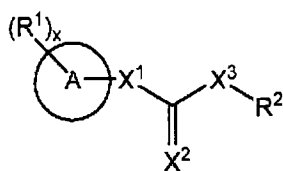
45. The method of claim 44, wherein the mammal is a human.

AMENDED CLAIMS

received by the International Bureau on 10 March 2017 (10.03.2017)

1. (Original) A method of treating cancer in a subject, the method comprising administering to a subject, in a cancer sample of whom at least one selected from the group consisting of PD-1 and PD-L1 is detected, at least one compound selected from the group consisting of:

(i) a compound of Formula (I):



(I), wherein in (I):

ring A is a monocyclic or bicyclic aryl or a monocyclic or bicyclic heteroaryl ring, and wherein the aryl or heteroaryl ring is optionally substituted with 0-4 R^1 groups;

each occurrence of R^1 is independently selected from the group consisting of $-C_1-C_6$ alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ heteroalkyl, F, Cl, Br, I, $-CN$, $-NO_2$, $-OR^3$, $-SR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-NHS(=O)_2R^3$, $-C(=O)R^3$, $-OC(=O)R^3$, $-CO_2R^3$, $-OCO_2R^3$, $-CH(R^3)_2$, $-N(R^3)_2$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$, $-NHC(=O)NH(R^3)$, $-NHC(=O)R^3$, $-NHC(=O)OR^3$, $-C(OH)(R^3)_2$, and $-C(NH_2)(R^3)_2$;

each occurrence of R^2 is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl, heteroalkyl or cycloalkyl group is optionally substituted with 0-5 R^1 groups, or X^3 and R^2 combine to form a (C_3-C_7) heterocycloalkyl group, optionally substituted with 0-2 R^1 groups;

each occurrence of R^3 is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, aryl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl, heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

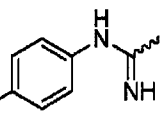
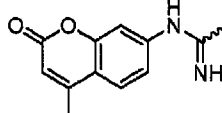
X^1 is $-CH_2-$, $-S-$, $-O-$ or $-(NR^2)-$;

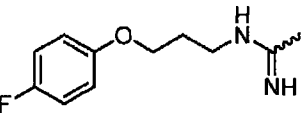
X^2 is $=CH_2$, $=S$, $=O$ or $=NR^2$; and

X^3 is $-S-$, $-O-$, or $-NR^2-$; and

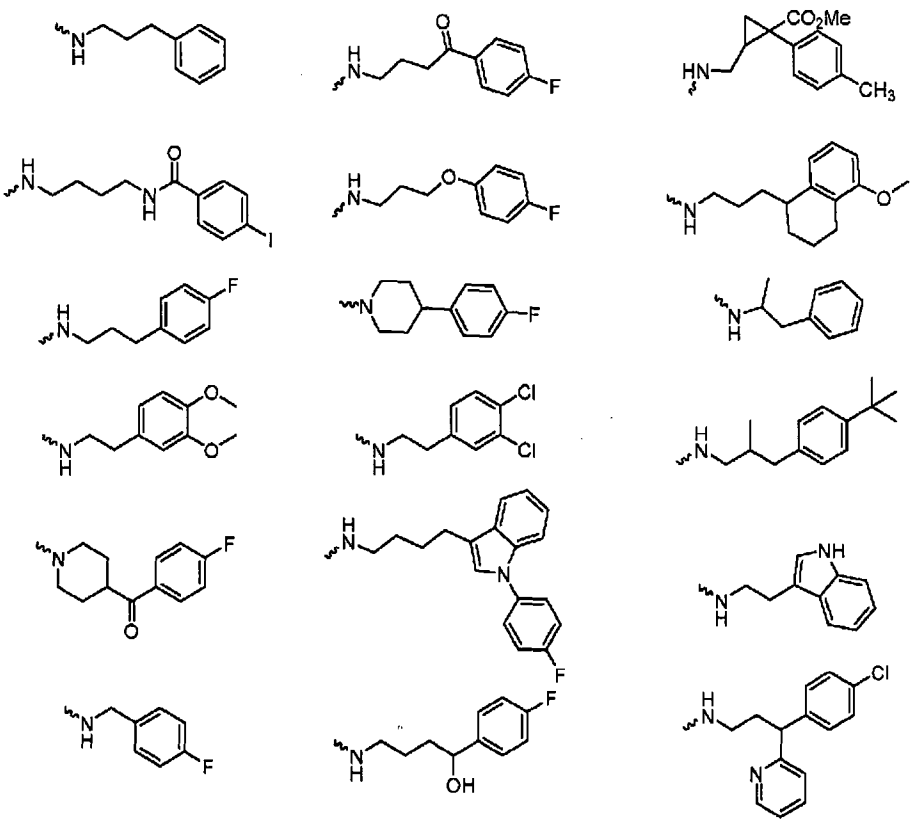
(ii) a compound of Formula (II):

R^A-R^B (II), wherein in (II):

R^A is selected from the group consisting of X^4 , ,

and ; and

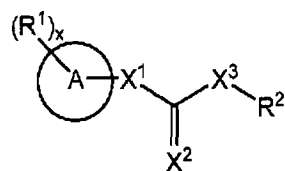
R^B is selected from the group consisting of:



a pharmaceutically acceptable salt or solvate thereof, a *N*-oxide thereof, and any combinations thereof.

2. (Original) The method of claim 1, further comprising administering to the subject at least one selected from the group consisting of an anti-PD-1 compound and an anti-PD-L1 compound.

3. (Original) The method of claim 2, wherein the anti-PD-1 compound is an antibody.
4. (Original) The method of claim 2, wherein the anti-PD-L1 compound is an antibody.
5. (Original) A method of preventing, treating, or ameliorating at least one disorder or disease that is mediated via IL-6 and/or pg130 signaling in a subject, the method comprising administering to the subject at least one compound selected from the group consisting of:
 - (i) a compound of Formula (I):



ring A is a monocyclic or bicyclic aryl or a monocyclic or bicyclic heteroaryl ring, and wherein the aryl or heteroaryl ring is optionally substituted with 0-4 R^1 groups;

each occurrence of R^1 is independently selected from the group consisting of $-C_1-C_6$ alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ heteroalkyl, F, Cl, Br, I, $-CN$, $-NO_2$, $-OR^3$, $-SR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-NHS(=O)_2R^3$, $-C(=O)R^3$, $-OC(=O)R^3$, $-CO_2R^3$, $-OCO_2R^3$, $-CH(R^3)_2$, $-N(R^3)_2$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$, $-NHC(=O)NH(R^3)$, $-NHC(=O)R^3$, $-NHC(=O)OR^3$, $-C(OH)(R^3)_2$, and $-C(NH_2)(R^3)_2$;

each occurrence of R^2 is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl, heteroalkyl or cycloalkyl group is optionally substituted with 0-5 R^1 groups, or X^3 and R^2 combine to form a (C_3-C_7) heterocycloalkyl group, optionally substituted with 0-2 R^1 groups;

each occurrence of R^3 is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, aryl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl, heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

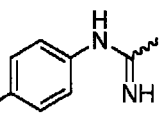
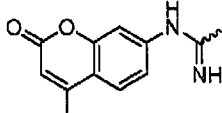
X^1 is $-CH_2-$, $-S-$, $-O-$ or $-(NR^2)-$;

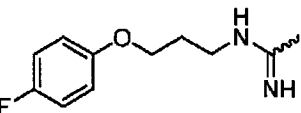
X^2 is $=CH_2$, $=S$, $=O$ or $=NR^2$; and

X^3 is $-S-$, $-O-$, or $-NR^2-$; and

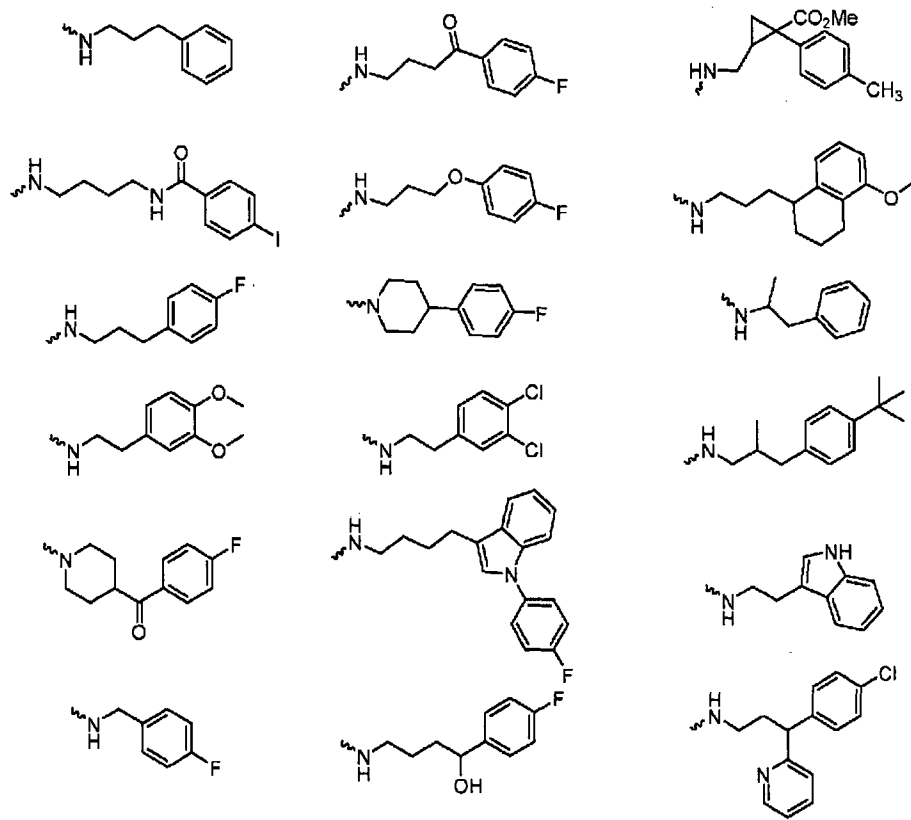
(ii) a compound of Formula (II):

R^A-R^B (II), wherein in (II):

R^A is selected from the group consisting of X^4 , ,

and ; and

R^B is selected from the group consisting of:



a pharmaceutically acceptable salt or solvate thereof, a *N*-oxide thereof, and any combinations thereof.

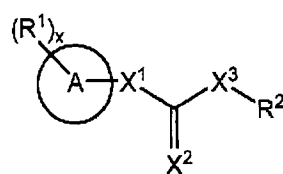
6. (Original) The method of claim 5, wherein the at least one disorder or disease comprises an autoimmune disease.

7. (Original) The method of claim 6, wherein the autoimmune disease is at least one selected from the group consisting of: asthma, Sjogren's syndrome, multiple sclerosis, systemic lupus erythematosus, Graves' disease, Hashimoto's disease, Castleman's disease, psoriasis, psoriatic arthropathy, ankylosing spondylitis, inflammatory bowel disease (IBD), polymyalgia rheumatica, giant cell arteritis, autoimmune vasculitis, graft versus host disease (GVHD), adult onset Still's disease, rheumatoid arthritis, systemic juvenile idiopathic arthritis, obesity, diabetes, asthma, multiple sclerosis, Alzheimer's disease, cerebrovascular disease, fever, acute phase response, allergies, chronic prostatitis, glomerulonephritis, pelvic inflammatory disease, reperfusion injury, and transplant rejection.
8. (Original) The method of claim 5, wherein the at least one disorder or disease comprises inflammation.
9. (Original) The method of claim 8, wherein the inflammation is acute and/or chronic inflammation.
10. (Original) The method of claim 5, wherein the at least one disorder or disease comprises cancer.
11. (Original) The method of claim 10, wherein the cancer is at least one selected from the group consisting of bladder cancer, brain cancer, bone cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, head and neck cancer, kidney cancer, large intestine cancer, liver cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin cancer, soft tissue cancer, and testicular cancer.
12. (Original) The method of claim 5, wherein the at least one disorder or disease comprises a B-cell proliferative disorder.
13. (Original) The method of claim 12, wherein the B-cell proliferative disorder is at least one selected from the group consisting of follicular lymphoma, chronic lymphocytic leukemia, acute lymphoblastic leukemia, hairy cell leukemia, B cell lymphoma, T cell

lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, Wiskott-Aldrich syndrome, post-transplant lymphoproliferative disorder, and autoimmune lymphoproliferative syndrome.

14. (Original) A method of enhancing an IL-6 mediated immune response in a subject, the method comprising administering to the subject at least one compound selected from the group consisting of:

(i) a compound of Formula (I):



ring A is a monocyclic or bicyclic aryl or a monocyclic or bicyclic heteroaryl ring, and wherein the aryl or heteroaryl ring is optionally substituted with 0-4 R^1 groups;

each occurrence of R^1 is independently selected from the group consisting of $-C_1-C_6$ alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ heteroalkyl, F, Cl, Br, I, $-CN$, $-NO_2$, $-OR^3$, $-SR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-NHS(=O)_2R^3$, $-C(=O)R^3$, $-OC(=O)R^3$, $-CO_2R^3$, $-OCO_2R^3$, $-CH(R^3)_2$, $-N(R^3)_2$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$, $-NHC(=O)NH(R^3)$, $-NHC(=O)R^3$, $-NHC(=O)OR^3$, $-C(OH)(R^3)_2$, and $-C(NH_2)(R^3)_2$;

each occurrence of R^2 is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl, heteroalkyl or cycloalkyl group is optionally substituted with 0-5 R^1 groups, or X^3 and R^2 combine to form a (C_3-C_7) heterocycloalkyl group, optionally substituted with 0-2 R^1 groups;

each occurrence of R^3 is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, aryl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl, heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

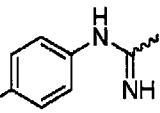
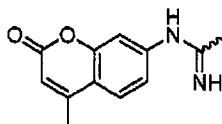
X^1 is $-CH_2-$, $-S-$, $-O-$ or $-(NR^2)-$;

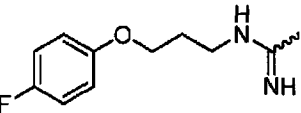
X^2 is $=CH_2$, $=S$, $=O$ or $=NR^2$; and

X^3 is $-S-$, $-O-$, or $-NR^2-$; and

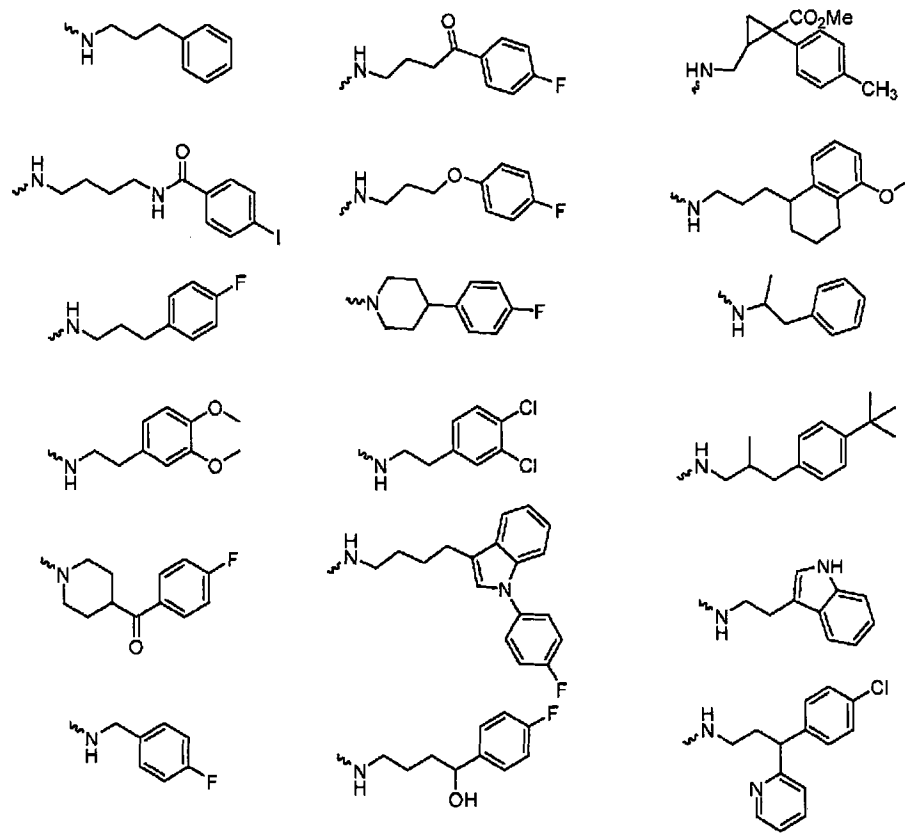
(ii) a compound of Formula (II):

R^A-R^B (II), wherein in (II):

R^A is selected from the group consisting of X^4 , ,

and ; and

R^B is selected from the group consisting of:

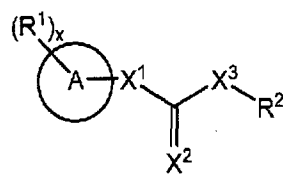


a pharmaceutically acceptable salt or solvate thereof, a *N*-oxide thereof, and any combinations thereof.

15. (Original) A method of decreasing IL-6 and/or gp130-mediated signaling in a subject, the method comprising administering to the subject at least one compound selected from the

group consisting of:

- (i) a compound of Formula (I):



ring A is a monocyclic or bicyclic aryl or a monocyclic or bicyclic heteroaryl ring,
and wherein the aryl or heteroaryl ring is optionally substituted with 0-4 R^1
groups;

each occurrence of R^1 is independently selected from the group consisting of $-C_1-C_6$
alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ heteroalkyl, F, Cl, Br, I, $-CN$, $-NO_2$, $-OR^3$, $-$
 SR^3 , $-S(=O)R^3$, $-S(=O)_2R^3$, $-NHS(=O)_2R^3$, $-C(=O)R^3$, $-OC(=O)R^3$, $-CO_2R^3$, $-$
 OCO_2R^3 , $-CH(R^3)_2$, $-N(R^3)_2$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$, $-$
 $NHC(=O)NH(R^3)$, $-NHC(=O)R^3$, $-NHC(=O)OR^3$, $-C(OH)(R^3)_2$, and $-$
 $C(NH_2)(R^3)_2$;

each occurrence of R^2 is independently selected from the group consisting of H, C_1-C_6
alkyl, C_1-C_6 heteroalkyl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl,
heteroalkyl or cycloalkyl group is optionally substituted with 0-5 R^1 groups, or X^3
and R^2 combine to form a (C_3-C_7) heterocycloalkyl group, optionally substituted
with 0-2 R^1 groups;

each occurrence of R^3 is independently selected from the group consisting of H, C_1-C_6
alkyl, C_1-C_6 heteroalkyl, aryl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the
alkyl, heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

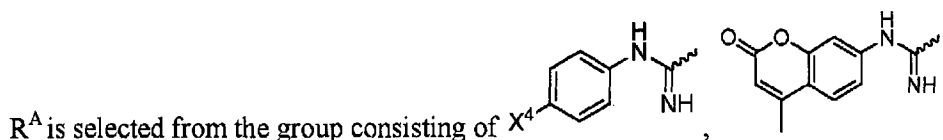
X^1 is $-CH_2-$, $-S-$, $-O-$ or $-(NR^2)-$;

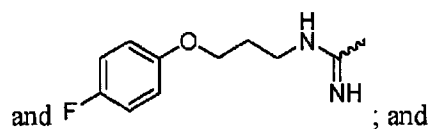
X^2 is $=CH_2$, $=S$, $=O$ or $=NR^2$; and

X^3 is $-S-$, $-O-$, or $-NR^2-$; and

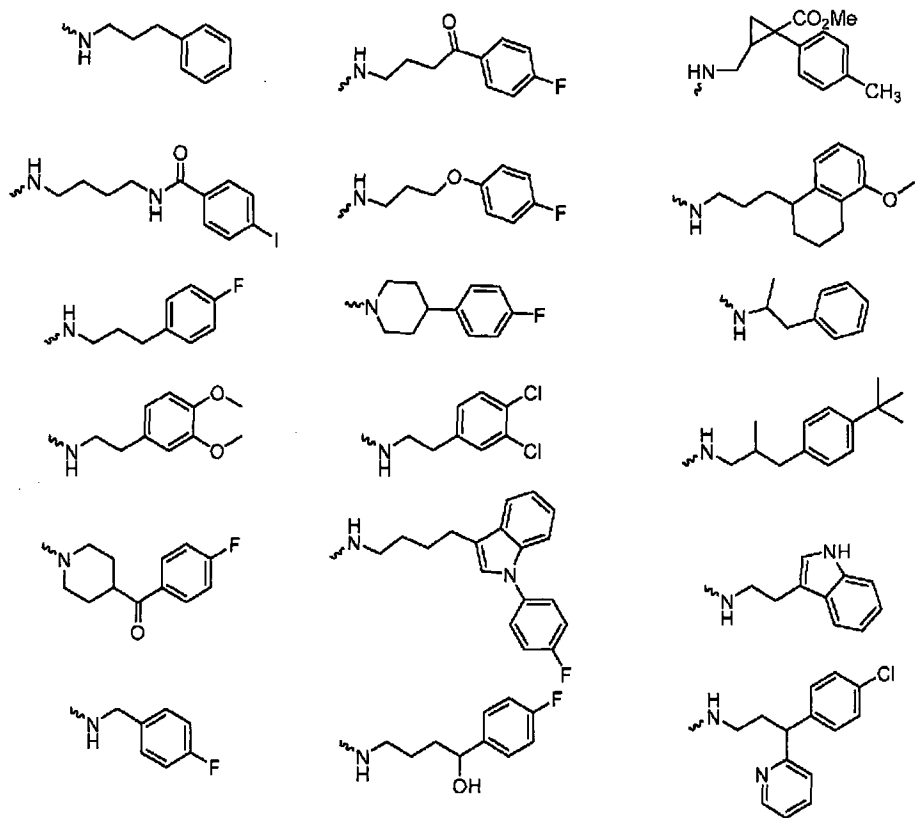
- (ii) a compound of Formula (II):

R^A-R^B (II), wherein in (II):





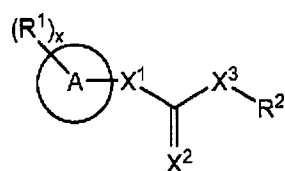
R^B is selected from the group consisting of:



a pharmaceutically acceptable salt or solvate thereof, a *N*-oxide thereof, and any combinations thereof.

16. (Original) A method of preventing, treating, or ameliorating at least one disorder or disease that is mediated via PD-L1 signaling in a subject, the method comprising administering to the subject at least one compound selected from the group consisting of:

(i) a compound of Formula (I):



(I), wherein in (I):

ring A is a monocyclic or bicyclic aryl or a monocyclic or bicyclic heteroaryl ring,

and wherein the aryl or heteroaryl ring is optionally substituted with 0-4 R^1 groups;

each occurrence of R^1 is independently selected from the group consisting of $-C_1-C_6$ alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ heteroalkyl, F, Cl, Br, I, $-CN$, $-NO_2$, $-OR^3$, $-SR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-NHS(=O)_2R^3$, $-C(=O)R^3$, $-OC(=O)R^3$, $-CO_2R^3$, $-OCO_2R^3$, $-CH(R^3)_2$, $-N(R^3)_2$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$, $-NHC(=O)NH(R^3)$, $-NHC(=O)R^3$, $-NHC(=O)OR^3$, $-C(OH)(R^3)_2$, and $-C(NH_2)(R^3)_2$;

each occurrence of R^2 is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl, heteroalkyl or cycloalkyl group is optionally substituted with 0-5 R^1 groups, or X^3 and R^2 combine to form a (C_3-C_7) heterocycloalkyl group, optionally substituted with 0-2 R^1 groups;

each occurrence of R^3 is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, aryl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl, heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

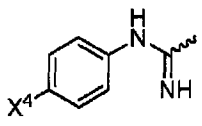
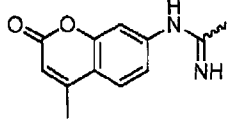
X^1 is $-CH_2-$, $-S-$, $-O-$ or $-(NR^2)-$;

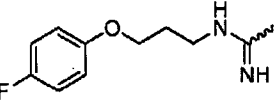
X^2 is $=CH_2$, $=S$, $=O$ or $=NR^2$; and

X^3 is $-S-$, $-O-$, or $-NR^2-$; and

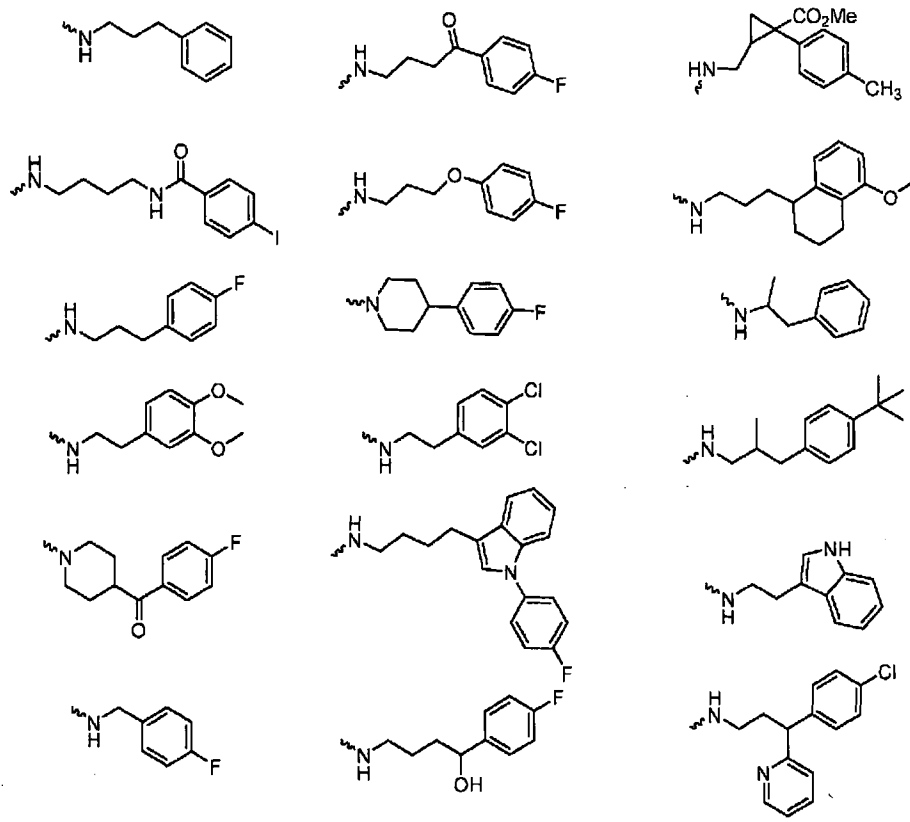
(ii) a compound of Formula (II):

R^A-R^B (II), wherein in (II):

R^A is selected from the group consisting of , ,

and ; and

R^B is selected from the group consisting of:



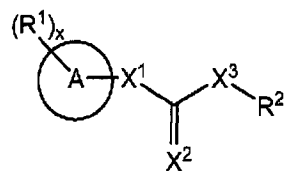
a pharmaceutically acceptable salt or solvate thereof, a *N*-oxide thereof, and any combinations thereof.

17. (Original) The method of claim 16, wherein the at least one disorder or disease comprises cancer.

18. (Original) The method of claim 19, wherein the cancer is at least one selected from the group consisting of bladder cancer, brain cancer, bone cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, head and neck cancer, kidney cancer, large intestine cancer, liver cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin cancer, soft tissue cancer, and testicular cancer.

19. (Original) A method of decreasing PD-L1-mediated signaling in a subject, the method comprising administering to the subject at least one compound selected from the group consisting of:

(i) a compound of Formula (I):



ring A is a monocyclic or bicyclic aryl or a monocyclic or bicyclic heteroaryl ring,
and wherein the aryl or heteroaryl ring is optionally substituted with 0-4 R^1
groups;

each occurrence of R^1 is independently selected from the group consisting of $-C_1-C_6$
alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ heteroalkyl, F, Cl, Br, I, $-CN$, $-NO_2$, $-OR^3$, $-$
 SR^3 , $-S(=O)R^3$, $-S(=O)_2R^3$, $-NHS(=O)_2R^3$, $-C(=O)R^3$, $-OC(=O)R^3$, $-CO_2R^3$, $-$
 OCO_2R^3 , $-CH(R^3)_2$, $-N(R^3)_2$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$, $-$
 $NHC(=O)NH(R^3)$, $-NHC(=O)R^3$, $-NHC(=O)OR^3$, $-C(OH)(R^3)_2$, and $-$
 $C(NH_2)(R^3)_2$;

each occurrence of R^2 is independently selected from the group consisting of H, C_1-C_6
alkyl, C_1-C_6 heteroalkyl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl,
heteroalkyl or cycloalkyl group is optionally substituted with 0-5 R^1 groups, or X^3
and R^2 combine to form a (C_3-C_7) heterocycloalkyl group, optionally substituted
with 0-2 R^1 groups;

each occurrence of R^3 is independently selected from the group consisting of H, C_1-C_6
alkyl, C_1-C_6 heteroalkyl, aryl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the
alkyl, heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

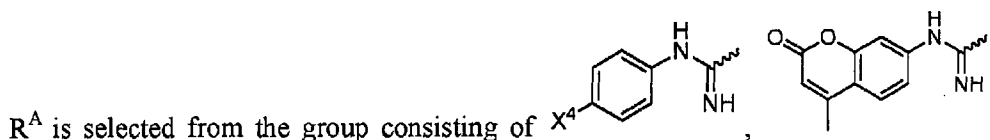
X^1 is $-CH_2-$, $-S-$, $-O-$ or $-(NR^2)-$;

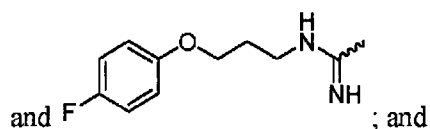
X^2 is $=CH_2$, $=S$, $=O$ or $=NR^2$; and

X^3 is $-S-$, $-O-$, or $-(NR^2)-$; and

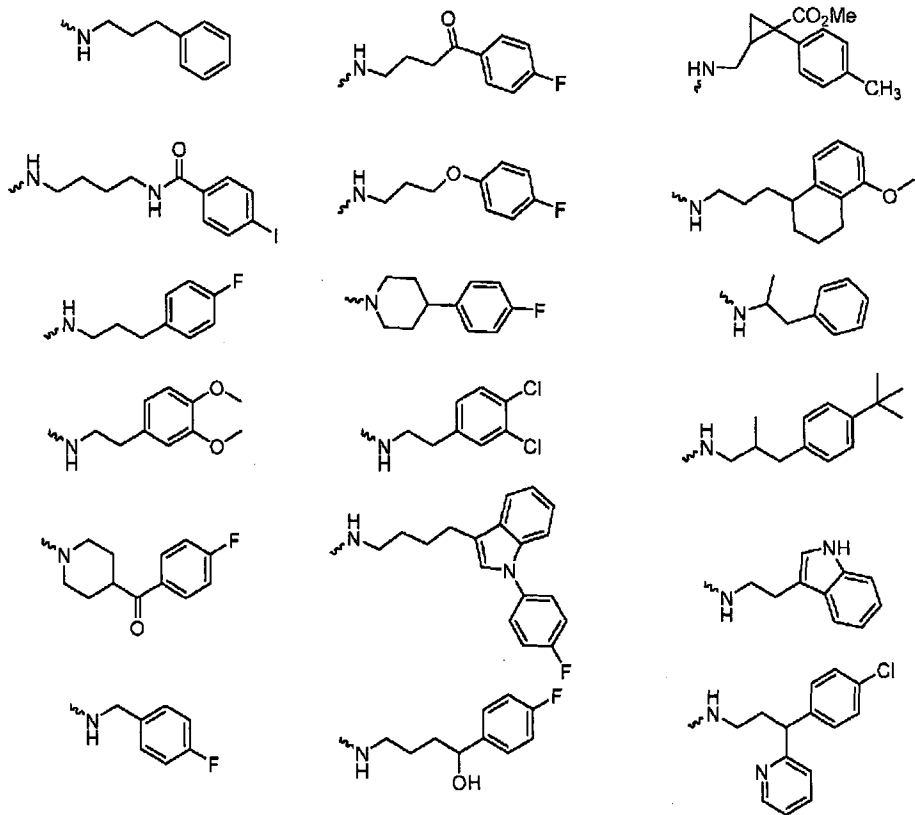
(ii) a compound of Formula (II):

R^A-R^B (II), wherein in (II):





R^B is selected from the group consisting of:



a pharmaceutically acceptable salt or solvate thereof, a *N*-oxide thereof, and any combinations thereof.

20. (Original) The method of any of claims 1-19, wherein in the compound of Formula (I):

each occurrence of R^1 is independently selected from the group consisting of $-C_1-C_2$ alkyl, $-C_1-C_2$ fluoroalkyl, $-C_1-C_2$ heteroalkyl, F, Cl, Br, I, $-CN$, $-NO_2$, $-OR^3$, $-SR^3$, $-S(=O)R^3$, $-S(=O)_2R^3$, $-NHS(=O)_2R^3$, $-C(=O)R^3$, $-OC(=O)R^3$, $-CO_2R^3$, $-OCO_2R^3$, $-CH(R^3)_2$, $-N(R^3)_2$, $-C(=O)N(R^3)_2$, $-OC(=O)N(R^3)_2$, $-NHC(=O)NH(R^3)$, $-NHC(=O)R^3$, $-NHC(=O)OR^3$, $-C(OH)(R^3)_2$, and $-C(NH_2)(R^3)_2$;

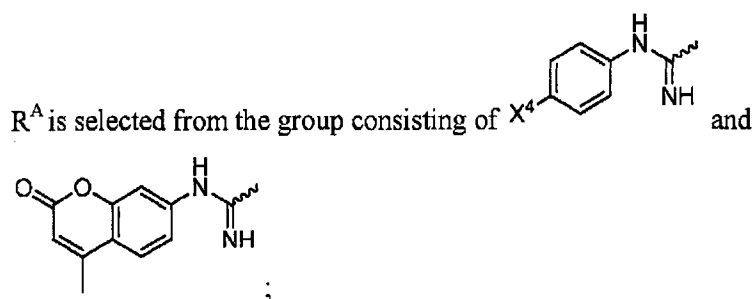
each occurrence of R^2 is independently selected from the group consisting of H, C₁-C₃ alkyl, and C₁-C₃ heteroalkyl, wherein the alkyl, heteroalkyl or cycloalkyl group is optionally

substituted with 0-2 R^1 groups, or X^3 and R^2 combine to form a (C_3 - C_7) heterocycloalkyl group, optionally substituted with 0-2 R^1 groups; and

each occurrence of R^3 is independently selected from the group consisting of H, C_1 - C_2 alkyl, and C_1 - C_2 heteroalkyl, aryl, wherein the alkyl, heteroalkyl, aryl, or cycloalkyl group is optionally substituted with 0-2 groups.

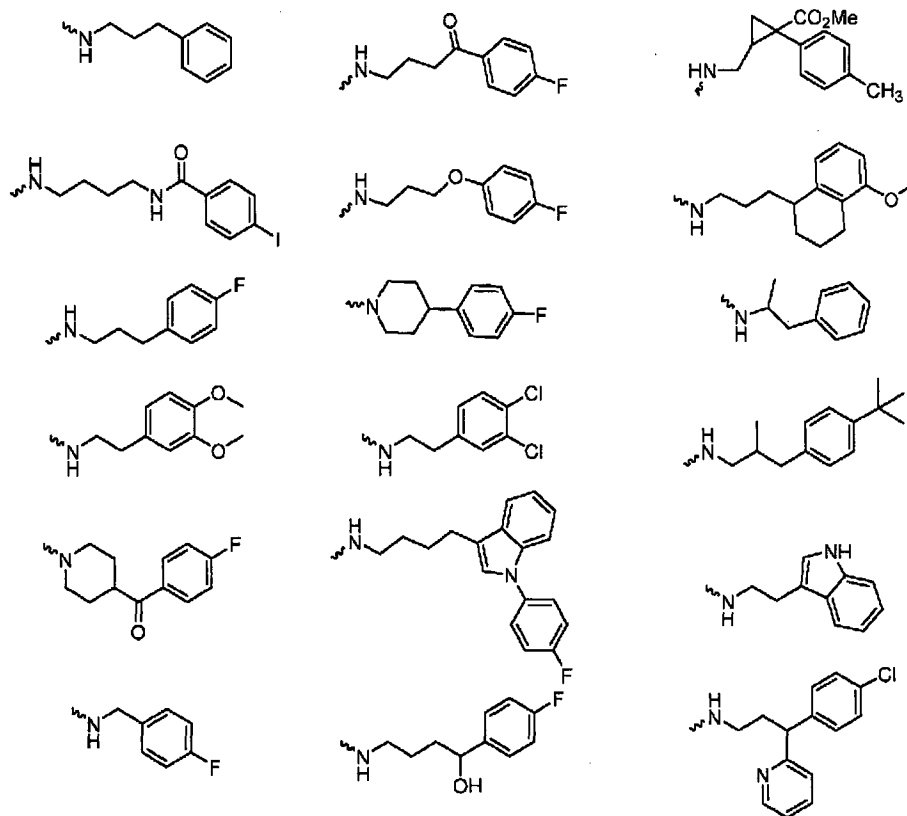
21. (Original) The method of any of claims 1-19, wherein the at least one compound is a compound of Formula (I-A), or a pharmaceutically acceptable salt or solvate thereof:

R^A - R^B (I-A), wherein in (I-A):

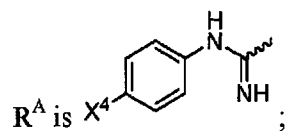


X^4 is selected from the group consisting of OMe, F, Cl, Br, and I; and

R^B is selected from the group consisting of:

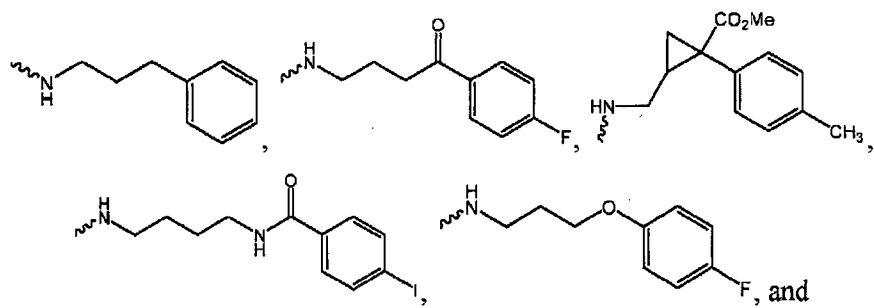


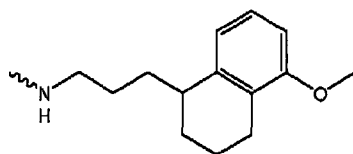
22. (Original) The method of claim 21, wherein in the compound of formula (I-A):



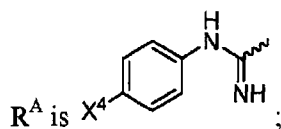
X^4 is selected from the group consisting of F, Cl, Br, and I; and

R^B is selected from the group consisting of:



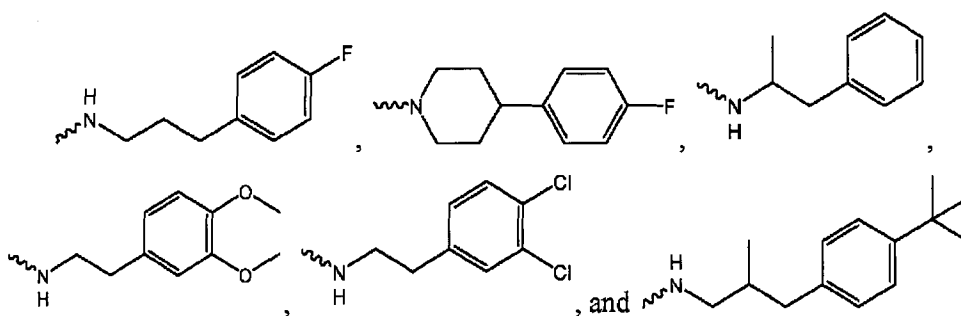


23. (Original) The method of claim 21, wherein in the compound of formula (I-A):

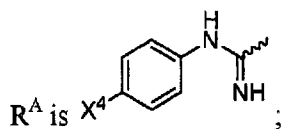


X^4 is selected from the group consisting of F, Cl, Br, and I; and

R^B is selected from the group consisting of:

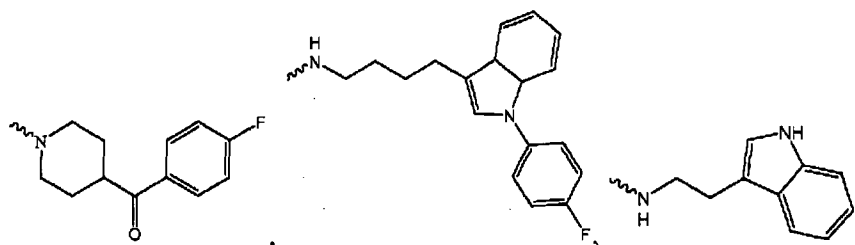


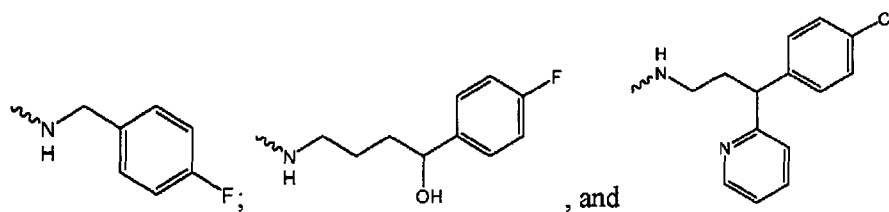
24. (Original) The method of claim 21, wherein in the compound of formula (I-A):



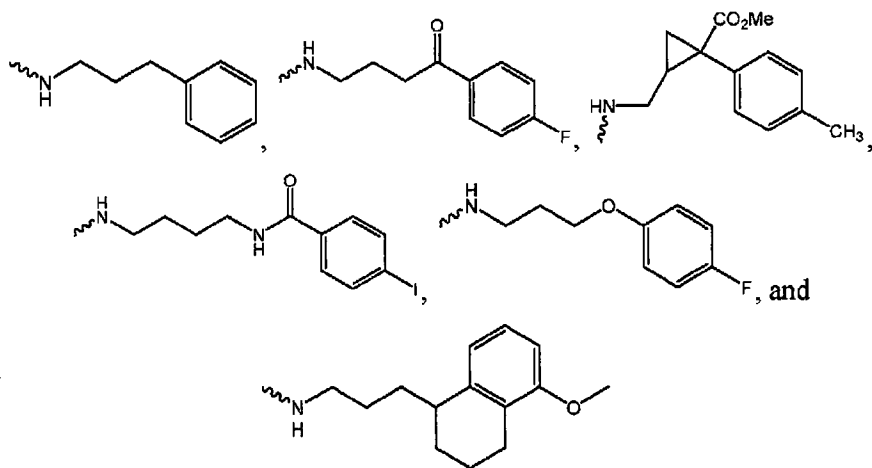
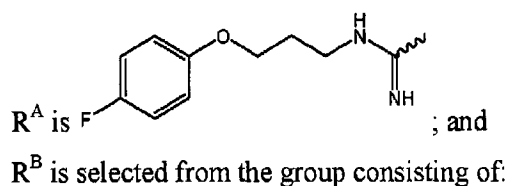
X^4 is selected from the group consisting of F, Cl, Br, and I; and

R^B is selected from the group consisting of:

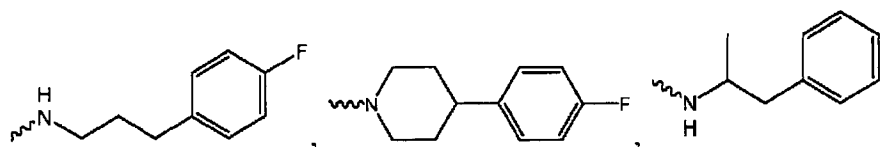
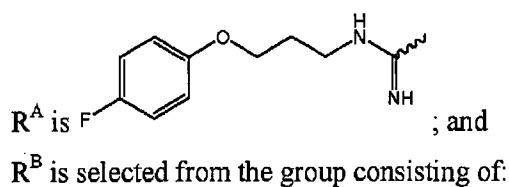


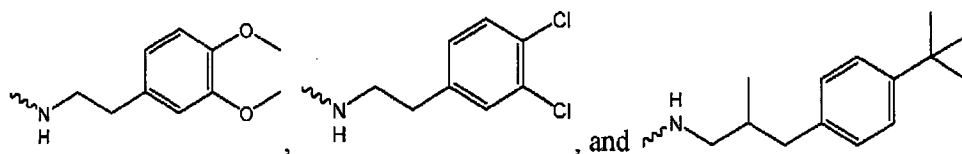


25. (Original) The method of any of claims 1-19, wherein in the compound of formula (II):

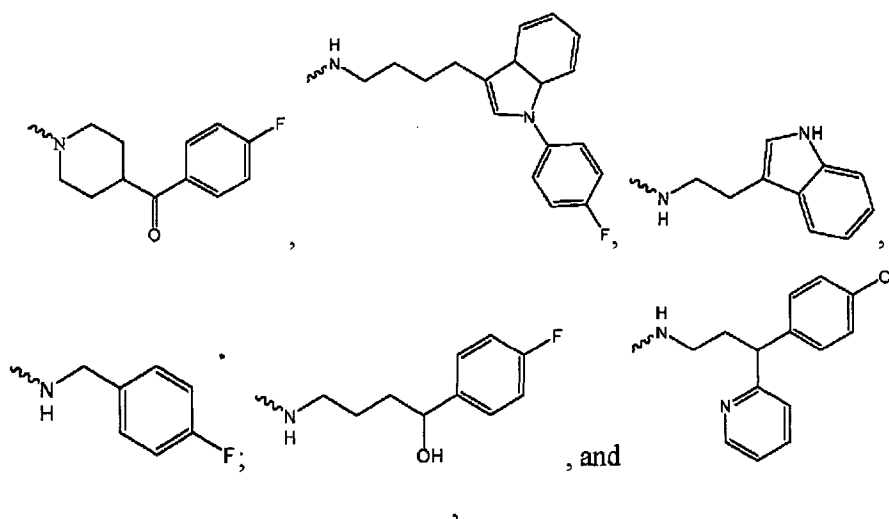
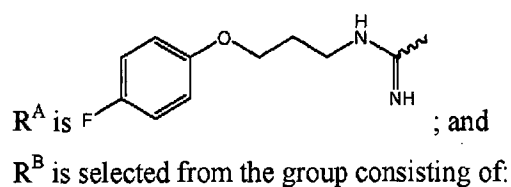


26. (Original) The method of any of claims 1-19, wherein in the compound of formula (II):

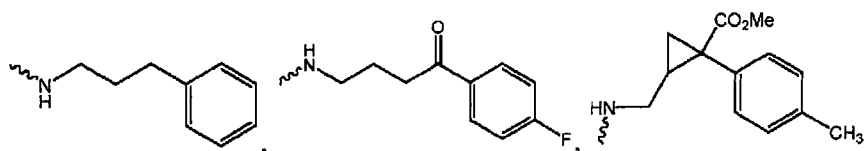
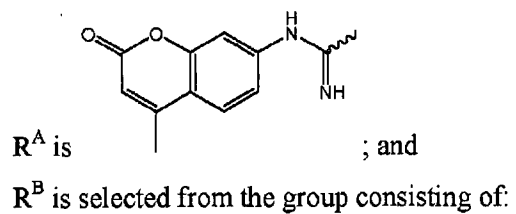


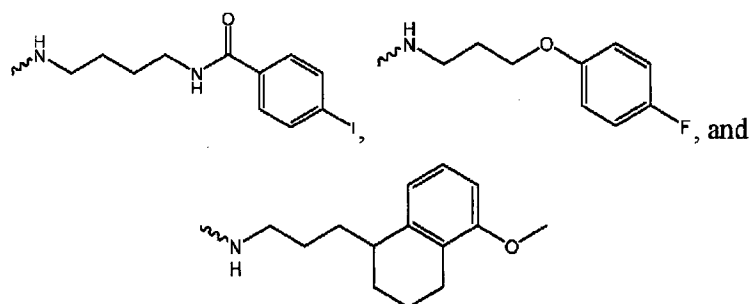


27. (Original) The method of any of claims 1-19, wherein in the compound of formula (II):

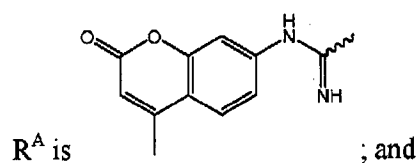


28. (Original) The method of claim 21, wherein in the compound of Formula (I-A):

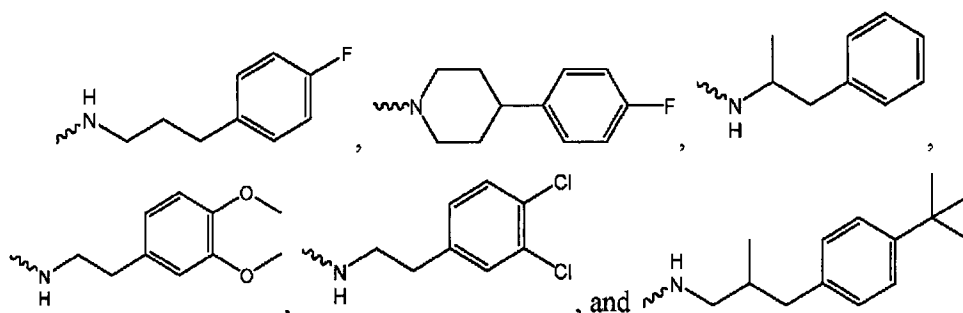




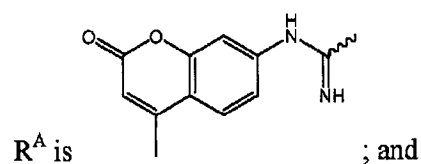
29. (Original) The method of claim 21, wherein in the compound of Formula (I-A):



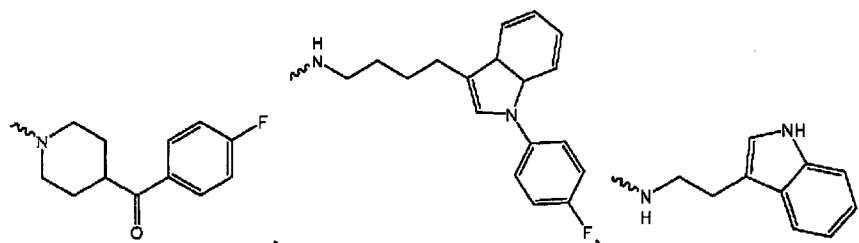
R^B is selected from the group consisting of:

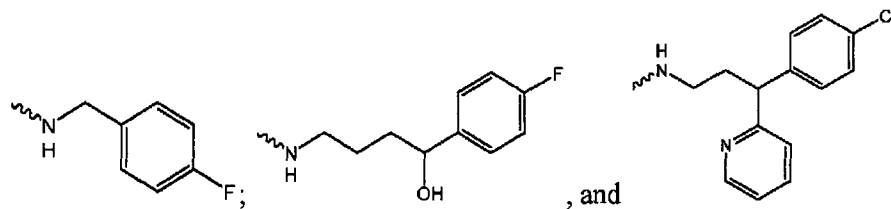


30. (Original) The method of claim 21, wherein in the compound of Formula (I-A):

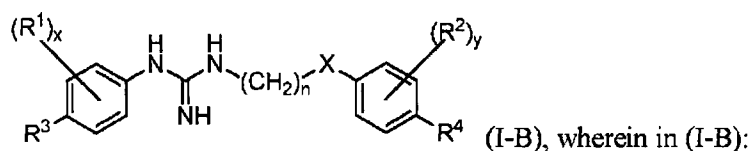


R^B is selected from the group consisting of:





31. (Original) The method of any of claims 1-19, wherein the at least one compound is a compound of formula (I-B), or a pharmaceutically acceptable salt or solvate thereof:



each occurrence of R^1 and R^2 is independently selected from the group consisting of $-C_1-C_6$ alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ heteroalkyl, F, Cl, Br, I, $-CN$, $-NO_2$, $-OR^5$, $-SR^5$, $-S(=O)R^5$, $-S(=O)_2R^5$, $-NHS(=O)_2R^5$, $-C(=O)R^5$, $-OC(=O)R^5$, $-CO_2R^5$, $-OCO_2R^5$, $-CH(R^5)_2$, $-N(R^5)_2$, $-C(=O)N(R^5)_2$, $-OC(=O)N(R^5)_2$, $-NHC(=O)NH(R^5)$, $-NHC(=O)R^5$, $-NHC(=O)OR^5$, $-C(OH)(R^5)_2$, and $-C(NH_2)(R^5)_2$;

R^3 is selected from the group consisting of $-C_1-C_6$ alkyl, $-C_1-C_6$ fluoroalkyl, $-C_1-C_6$ alkoxy, F, Cl, Br, and I;

R^4 is selected from the group consisting of $-C_1-C_6$ alkyl, $-C_1-C_6$ alkoxy, F, Cl, Br, and I;

each occurrence of R^5 is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, aryl, and $-C_1-C_3$ alkyl- $(C_3-C_6$ cycloalkyl), wherein the alkyl, heteroalkyl, aryl, or cycloalkyl group is optionally substituted;

X is selected from the group consisting of CH_2 , $C=O$, and O;

n is an integer from 1-3;

x is an integer from 0-4; and

y is an integer from 0-4.

32. (Original) The method of any of claims 1-19, wherein the at least one compound is selected from the group consisting of:

1-(3-(4-fluorophenoxy)propyl)-3-(4-iodophenyl)guanidine (Compound A),

1-(3-(4-fluorophenoxy)propyl)-3-(4-methoxyphenyl)guanidine (Compound B),
1-(n-propyl)-3-(4-iodophenyl)guanidine (Compound C),
1-(n-propyl)-3-(4-methoxyphenyl)guanidine (Compound D),
1,3-bis(3-(4-fluorophenoxy)propyl)guanidine (Compound E),
1-(3-(4-fluorophenoxy)propyl)-3-(4-trifluoromethylphenyl)guanidine (Compound F),
1-(3-(4-fluorophenoxy)propyl)-3-(4-chlorophenyl)guanidine (Compound G), and
1-(3-(4-fluorophenoxy)propyl)-3-(4-methyl-2-oxo-2H-chromen-7-yl)guanidine (Compound H),
or a pharmaceutically acceptable salt or solvate thereof, and any combinations thereof.

33. (Original) The method of any of claims 1-19, wherein the method further comprises administering to the subject one or more anti-IL-6 and/or gp130 compound(s).

34. (Original) The method of any of claims 20-32, wherein the method further comprises administering to the subject one or more anti-IL-6 and/or gp130 compound(s).

34. (Cancelled)

35. (Original) The method of claim 33, wherein the anti-IL-6 and/or gp130 compound(s) comprise(s) a IL-6 binding compound.

36. (Original) The method of claim 33, wherein the anti-IL-6 and/or gp130 compound(s) comprise(s) a gp130 antagonist.

37. (Original) The method of claim 33, wherein the one or more anti-IL-6 compound(s) comprise(s) tocilizumab, siltuximab, sarilumab, olokizumab, elsilimomab, ALD518/BMS-94529, sirukumab, CPSI-2364, ARGX-109, FE301, or FM101, or any combination thereof.

38. (Original) The method of any of claims 1-37, wherein the method further comprises administering to the subject an effective amount of at least one immune system modulator.

39. (Original) The method of claim 38, wherein the at least one immune system

modulator modulates the interactions of T and/or B cells with Signal modulators.

40. (Original) The method of claim 39, wherein the at least one immune system modulator is at least one selected from the group consisting of blockers of ICOS-ICOS-L, IL-10, IL-24 IL-21, adenosine 2a, arginase, IDO1, CD40-CD40L, CD134-CD134L, CD137-CD137L, CTLA4, PD-1, PD-L1/PD-L2, TIM3, LAG3, TGF- β or activate toll-like receptors, IL-2, and STING.

41. (Original) The method of any of claims 1-40, further comprising administering to the subject at least one compound that blocks the activity of PD-1 and/or PD-L1.

42. (Original) The method of claim 41, wherein the at least one compound that blocks the activity of PD-1 and/or PD-L1 is selected from the group consisting of nivolumab, pembrolizumab, pidilizumab (CT-011), BMS-936559, avelumab (MSB0010718C), durvalumab (MEDI4736), MEDI0680, B7-DC-Ig (AMP224), atezolizumab (MPDL3280A), CX-072, REGN2810, TSR-042, STI-1014, STI-1110, or any combinations thereof.

43. (Original) The method of any of claims 1-42, wherein the subject is a subject in need thereof.

44. (Original) The method of any of claims 1-43, wherein the subject is a mammal.

45. (Original) The method of claim 44, wherein the mammal is a human.

FIG. 1A

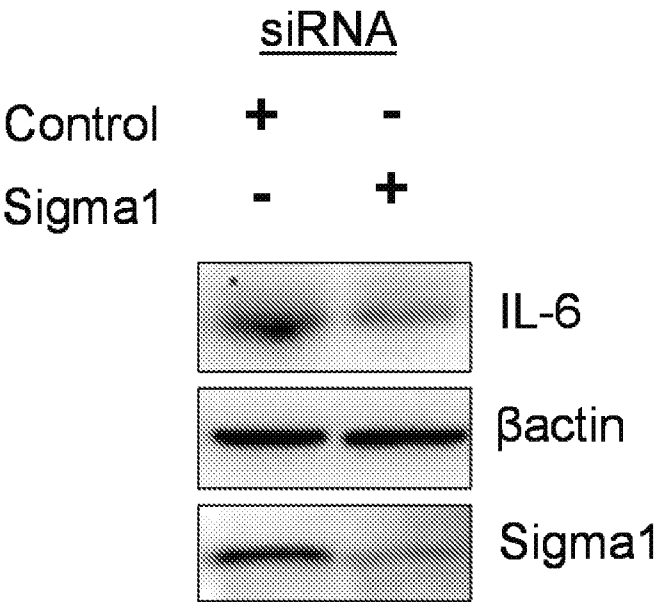


FIG. 1B

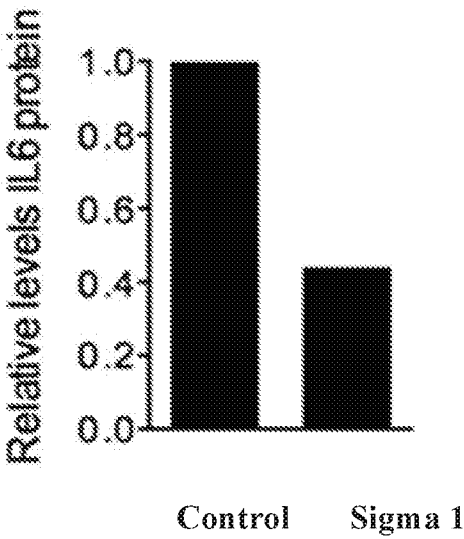


FIG. 2A

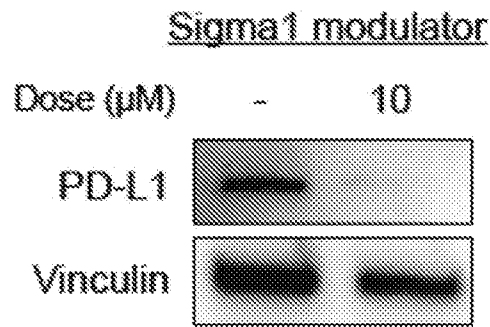


FIG. 2B

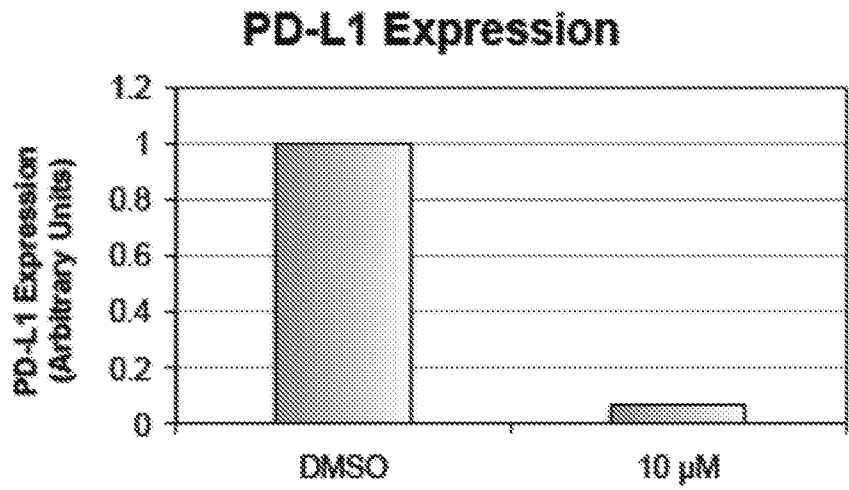


FIG. 2C

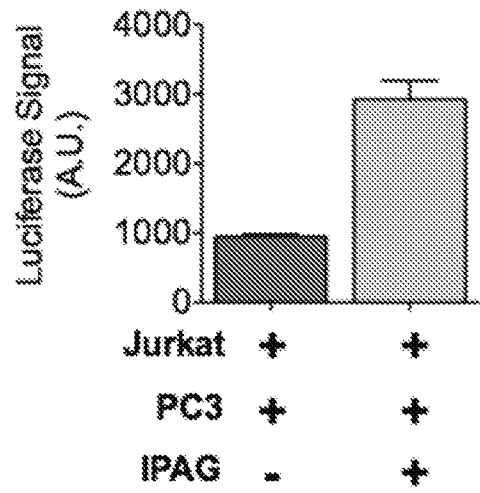


FIG. 3A

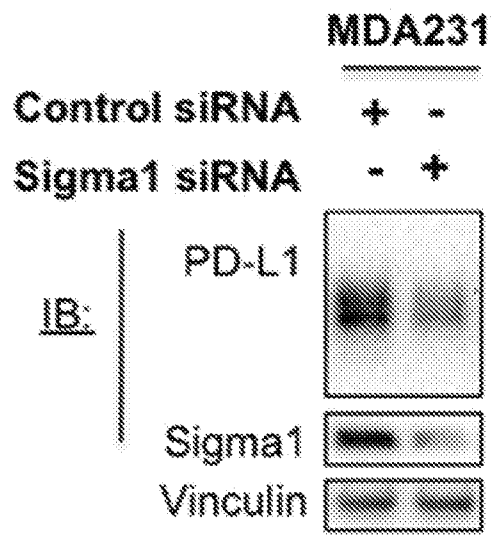


FIG. 3B

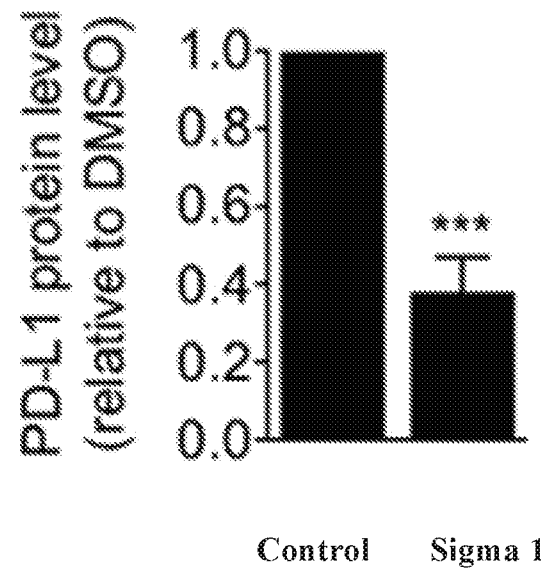


FIG. 4A

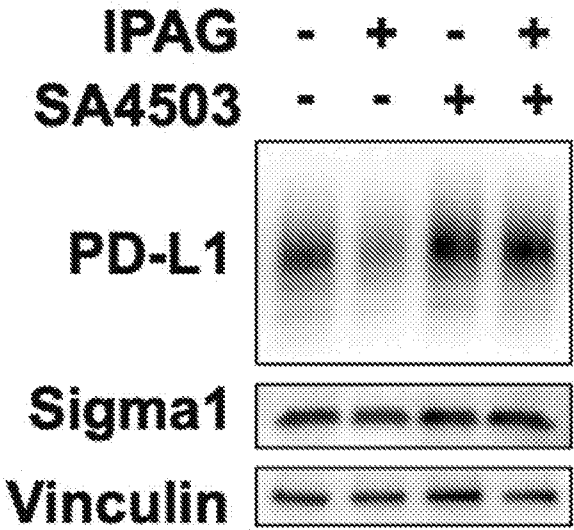


FIG. 4B

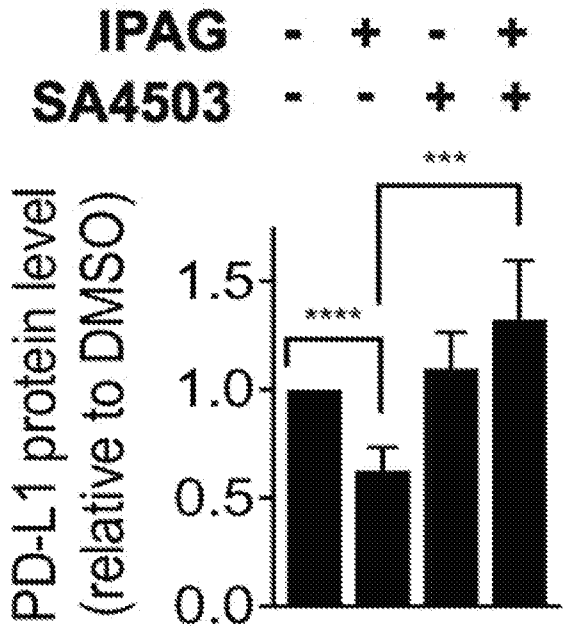
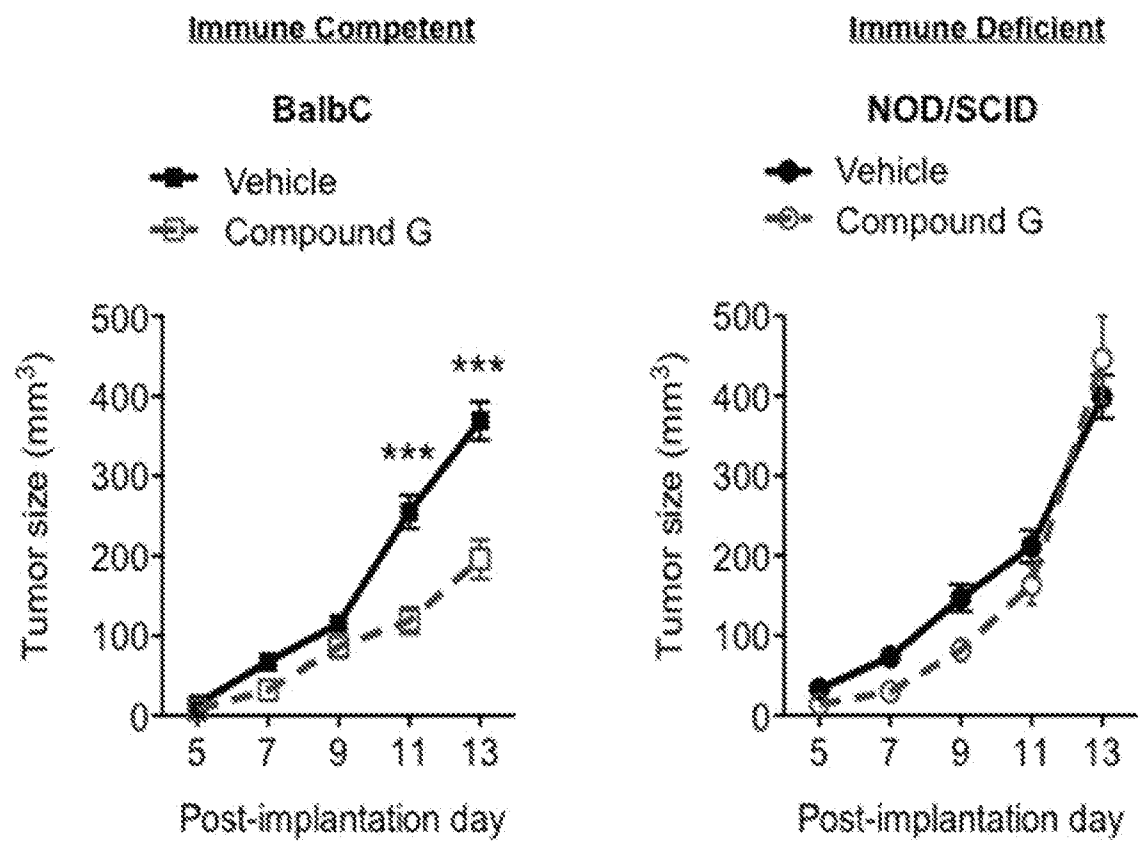


FIG. 5



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/66610

A. CLASSIFICATION OF SUBJECT MATTER
 IPC - A61K 31/366; C07C 279/18 (2016.01)
 CPC - A61K 31/138, 31/155, 31/4035

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2015/0166472 A1 (DREXEL UNIVERSITY) 18 June 2015; paragraphs [0010]-[0017], [0036], [0043]-[0046], [0049], [0051]-[0052], [0054]-[0062], [0069]-[0072], [0318], [0325]	1-19, 20/1-19, 21/1-19, 22/21/1-19, 23/21/1-19, 24/21/1-19, 25/1-19, 26/1-19, 27/1-19, 28/21/1-19, 29/21/1-19, 30/21/1-19, 31/1-19, 32/1-19, 33/1-19, 34B/33/1-19, 35/33/1-19, 36/33/1-19, 37/33/1-19
Y	US 2015/0290207 A1 (INFINITY PHARMACEUTICALS, INC.) 15 October 2015; paragraphs [0025]-[0026], [0028], [0034], [0149], [0160]	1-4, 16-19, 20/1-4, 20/16-19, 21/1-4, 21/16-19, 22/21/1-4, 22/21/16-19, 23/21/1-4, 23/21/16-19, 24/21/1-4, 24/21/16-19, 25/1-4, 25/16-19, 26/1-4, 26/16-19, 27/1-4, 27/16-19, 28/21/1-4, 28/21/16-19, 29/21/1-4, 29/21/16-19, 30/21/1-4, 30/21/16-19, 31/1-4, 31/16-19, 32/1-4, 32/16-19, 33/1-4, 33/16-19, 34B/33/1-4,

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

22 January 2017 (22.01.2017)

Date of mailing of the international search report

16 FEB 2017

Name and mailing address of the ISA/

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 P.O. Box 1450, Alexandria, Virginia 22313-1450
 Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

PCT Helpdesk: 571-272-4300
 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/66610

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 34A and 38-45
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/66610

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TANAKA, T et al., Anti-interleukin-6 receptor antibody, tocilizumab, for the treatment of autoimmune diseases, Federation of European Biochemical Societies Letters 585, pages 3699-3709, 2011; page 3699, column 1, paragraph 1; page 3700, figure 1; page 3701, column 1, paragraph 2; page 3704, column 2, paragraph 3; page 3705, column 2, paragraph 1	34B/33/16-19, 35/33/1-4, 35/33/16-19, 36/33/1-4, 36/33/16-19, 37/33/1-4, 37/33/16-19 5-15, 20/5-15, 21/5-15, 22/21/5-15, 23/21/5-15, 24/21/5-15, 25/5-15, 26/5-15, 27/5-15, 28/21/5-15, 29/21/5-15, 30/21/5-15, 31/5-15, 32/5-15, 33/1-19, 34B/33/1-19, 35/33/1-19, 36/33/1-19, 37/33/1-19
Y	WO 2009/074809 A1 (UNIVERSITY OF DUNDEE) 18 June 2009; page 3, lines 11-22; page 4, lines 1-5, 13-17; page 21, line 31; page 32, lines 22-29, 33-36; page 33, lines 1-2; claim 3	6-9, 12-13, 20/6-9, 20/12-13, 21/6-9, 21/12-13, 22/21/6-9, 22/21/12-13, 23/21/6-9, 23/21/12-13, 24/21/6-9, 24/21/12-13, 25/6-9, 25/12-13, 26/6-9, 26/12-13, 27/6-9, 27/12-13, 28/21/6-9, 28/21/12-13, 29/21/6-9, 29/21/12-13, 30/21/6-9, 30/21/12-13, 31/6-9, 31/12-13, 32/6-9, 32/12-13, 33/6-9, 33/12-13, 34B/33/6-9, 34B/33/12-13, 35/33/6-9, 35/33/12-13, 36/33/6-9, 36/33/12-13, 37/33/6-9, 37/33/12-13