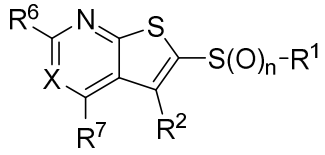
15-PGDH expression in the protection of thrombin-mediated cell death. It is well known that 15-PGDH is responsible for the inactivation of prostaglandin E2 (PGE_2), which is a downstream product of COX-2 metabolism. PGE_2 has been shown to be beneficial in a variety of biological processes, such as hair density, dermal wound healing, and bone formation.

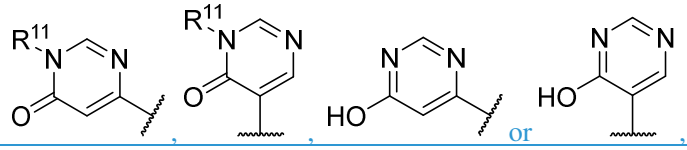
SUMMARY

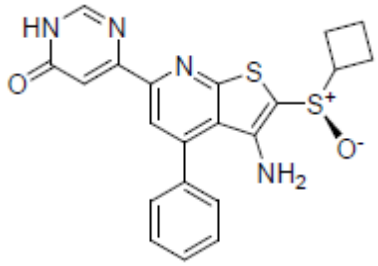
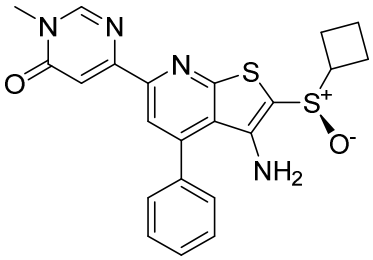
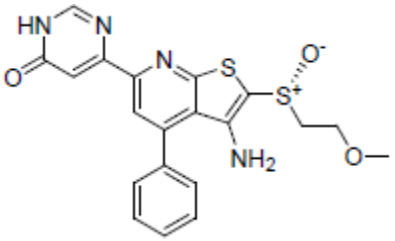
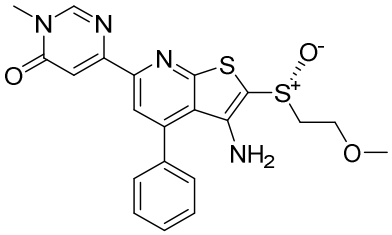
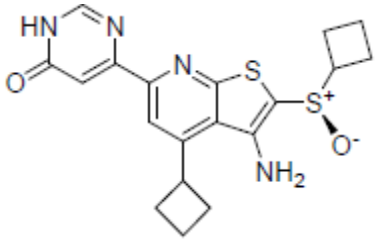
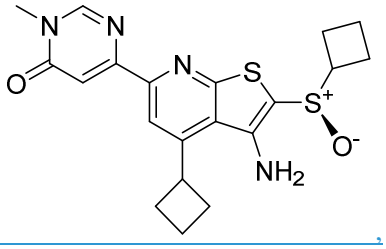
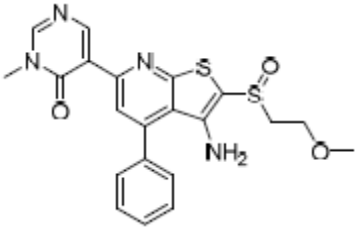
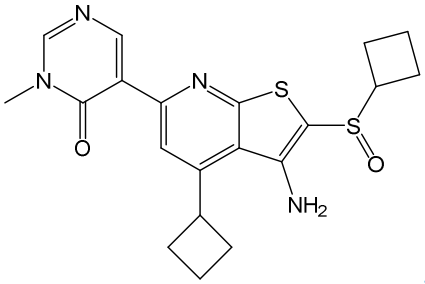
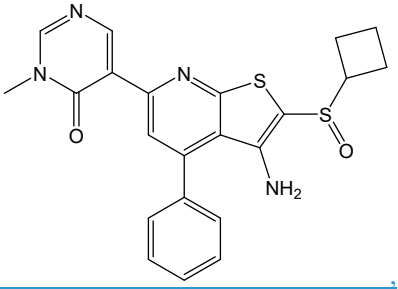
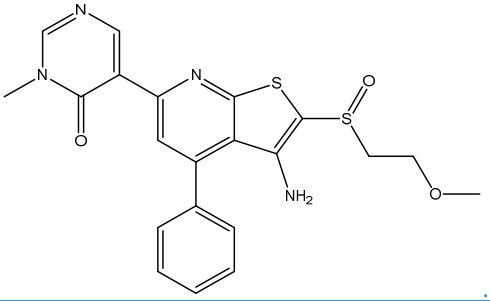
[0005] ~~Embodiment~~Examples described herein relate to compounds and methods of modulating short chain dehydrogenase (SCD) (*e.g.,* 15-PGDH) activities, modulating tissue prostaglandin levels, and/or treating diseases, disorders, or conditions in which it is desired to modulate SCD (*e.g.,* 15-PGDH) activity and/or prostaglandin levels.

[0005a] In one aspect, the present disclosure refers to a compound of formula (I):



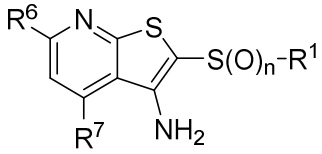
(I)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein: R^1 is alkyl, haloalkyl, cycloalkyl, alkylene-cycloalkyl, alkylene-alkoxy, heterocyclyl, or alkylene-heterocyclyl; R^2 is $–NH_2$, CN, or $–NHC(O)(C_1\text{-}C_6$ alkyl); R^6 is  , each of which is optionally substituted with one or more R^3; R^7 is alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl, -C(O)O-alkyl, or -C(O)NR^5-alkyl, each of which is optionally substituted with one or more R^4; R^3 is -OH, -O-alkeylene-OH, -O-alkeylene-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(alkylene-OH), -$N(R^5)$(alkylene-O-alkyl), alkyl, -alkylene-OH, haloalkyl, cycloalkyl, heterocyclyl, -C(O)$N(R^5)_2$, -C(O)$N(R^5)$(alkylene-OH), -C(O)-alkyl, -C(O)O-alkyl, or -$S(O)_m$-alkyl, wherein the cycloalkyl and the heterocyclyl is each optionally substituted with R^{10}; R^4 is oxo, halogen, -CN, -$N(R^5)_2$, -OH, -O-alkylene-OH, -$S(O)_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, -alkylene-O-alkyl, alkoxy, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8, wherein when R^4 is oxo and R^7 is aryl or heteroaryl, oxo does not violate the valency of the aryl or the heteroaryl; each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -C(O)O-alkyl, -alkylene-COOH, or -$S(O)_m$-alkyl; R^8 is halogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy; R^9 is H or C_1-C_6 alkyl; R^{10} is –OH, halogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy; R^{11} is H or C_1-C_6 alkyl; X is N or CH; m is 0, 1, or 2; and n is 0, 1, or 2; wherein the compound is not:

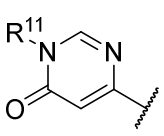
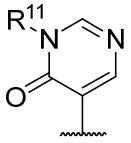
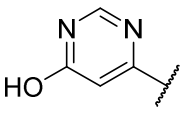
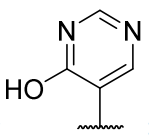











and .

[0005b] In another aspect, the present disclosure refers to a compound of formula (II):

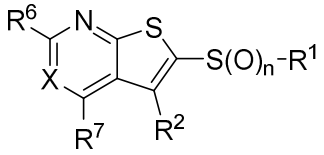


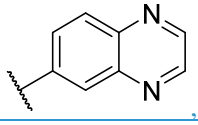
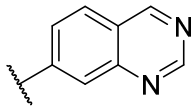
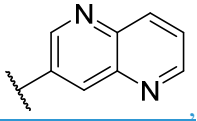
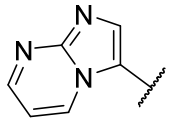
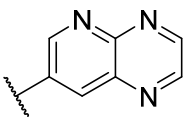
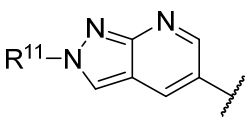
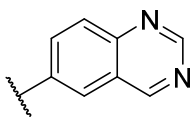
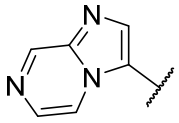
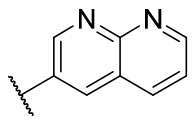
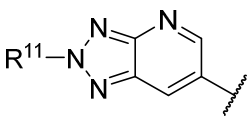
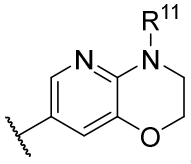
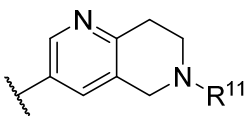
(II) or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein: R^1 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or -(C_1-C_3 alkylene)-(C_1-C_3 alkoxy); R^6 is

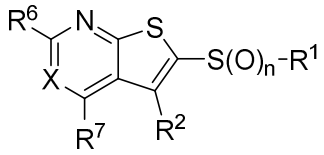
or ; R^7 is a linear or branched, non-cyclic C_1-C_6 alkyl; R^{11} is H or C_1-C_6 alkyl; and n is 0, 1, or 2.

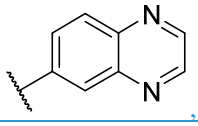
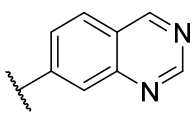
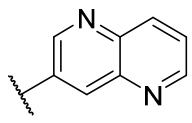
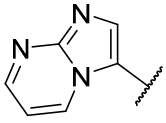
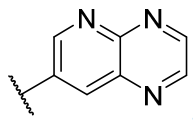
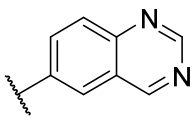
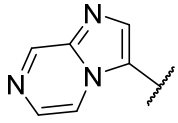
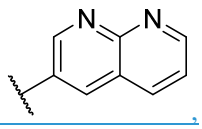
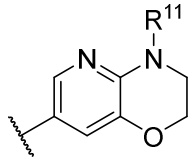
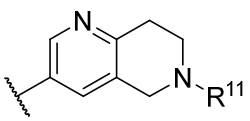
[0005c] In another aspect, the present disclosure refers to a compound of formula (III):

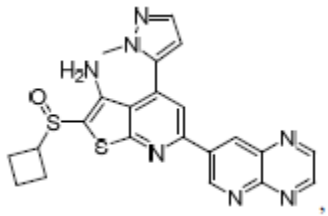
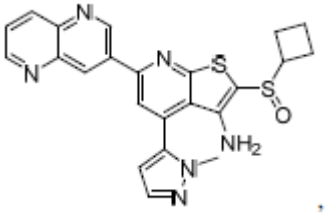
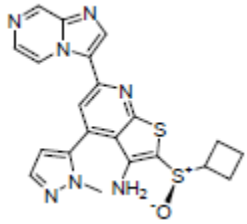


(III) or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein: R^1 is alkyl, haloalkyl, cycloalkyl, alkylene-cycloalkyl, alkylene-alkoxy, heterocyclyl, or alkylene-heterocyclyl; R^2 is $-NH_2$, CN, or $-NHC(O)(C_1\text{-}C_6$ alkyl); R^6 is , , , , , , , , , , , or ; R^7 is alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl, -C(O)O-alkyl, or $-C(O)NR^5$-alkyl, each of which is optionally substituted with one or more R^4; R^4 is oxo, halogen, -CN, $-N(R^5)_2$, -OH, -O-alkylene-OH, $-S(O)_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, -alkylene-O-alkyl, alkoxy, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8, wherein when R^4 is oxo and R^7 is aryl or heteroaryl, oxo does not violate the valency of the aryl or the heteroaryl; each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -C(O)O-alkyl, -alkylene-COOH, or $-S(O)_m$-alkyl; R^8 is halogen, $C_1\text{-}C_6$ alkyl, or $C_1\text{-}C_6$ alkoxy; R^9 is H or $C_1\text{-}C_6$ alkyl; R^{11} is H or $C_1\text{-}C_6$ alkyl; X is N or CH; m is 0, 1, or 2; and n is 0, 1, or 2.

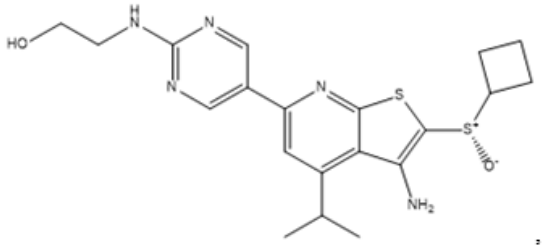
[0005d] In another aspect, the present disclosure refers to a compound of formula (IV):

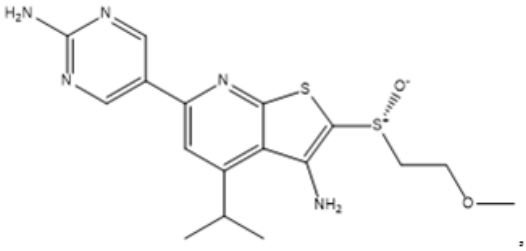
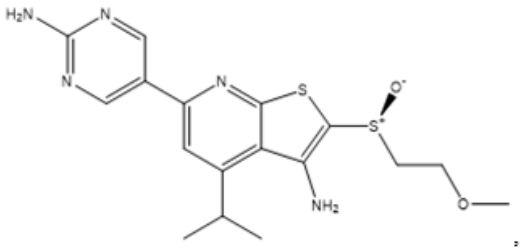


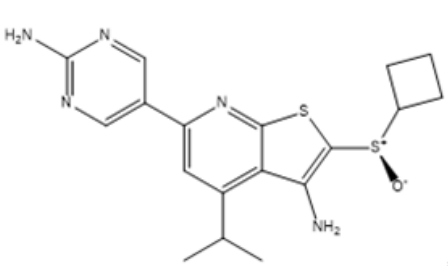
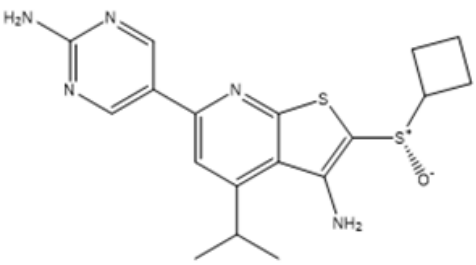
(IV) or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein: R^1 is alkyl, haloalkyl, cycloalkyl, alkylene-cycloalkyl, alkylene-alkoxy, heterocyclyl, or alkylene-heterocyclyl; R^2 is $-NH_2$, CN, or $-NHC(O)(C_1\text{-}C_6$ alkyl); R^6 is , , , , , , , , , or ;

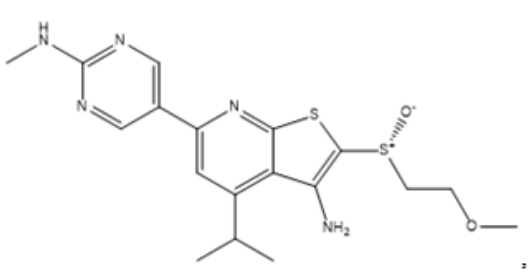
R^7 is alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl, -C(O)O-alkyl, or -C(O)NR^5-alkyl, each of which is optionally substituted with one or more R^4; R^4 is oxo, halogen, -CN, -$N(R^5)_2$, -OH, -O-alkylene-OH, -$S(O)_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, -alkylene-O-alkyl, alkoxy, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8, wherein when R^4 is oxo and R^7 is aryl or heteroaryl, oxo does not violate the valency of the aryl or the heteroaryl; each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -C(O)O-alkyl, -alkylene-COOH, or -$S(O)_m$-alkyl; R^8 is halogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy; R^9 is H or C_1-C_6 alkyl; R^{11} is H or C_1-C_6 alkyl; X is N or CH; m is 0, 1, or 2; and n is 0, 1, or 2; wherein the compound is not , , and .

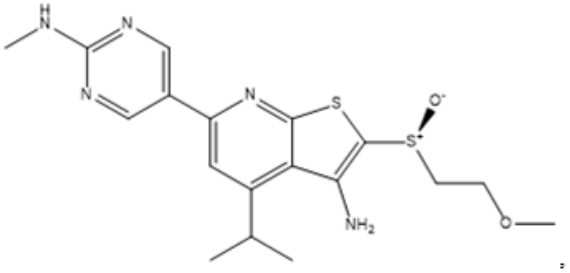
[0005e] In another aspect, the present disclosure refers to a compound selected from:

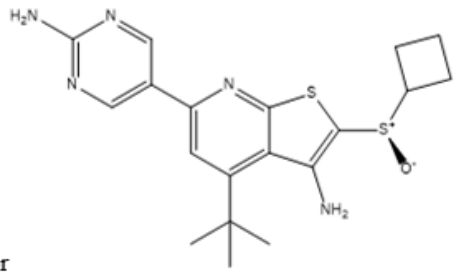
,

, ,

, .







or

or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

[0005f] In another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as disclosed herein and a pharmaceutically acceptable excipient or a carrier.

[0005g] In another aspect, the present disclosure refers to a compound as disclosed herein as a short chain dehydrogenase inhibitor for inhibiting the activity of a short chain dehydrogenase enzyme.

[0005h] In another aspect, the present disclosure refers to a compound as disclosed herein as a 15-PGDH inhibitor for inhibiting the activity of a 15-PGDH enzyme.

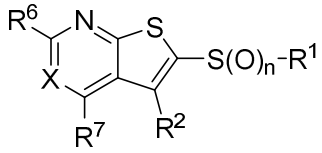
[0005i] In another aspect, the present disclosure refers to the use of the compound as disclosed herein in the manufacture of a medicament for inhibiting the activity of a short chain dehydrogenase enzyme, wherein: the compound inhibits the enzymatic activity of recombinant 15-PGDH at an IC_{50} of less than 1 µM, or preferably at an IC_{50} of less than 250 nM, or more preferably at an IC_{50} of less than 50 nM, or more preferably at an IC_{50} of less than 10 nM, or more preferably at an IC_{50} of less than 5 nM at a recombinant 15-PGDH concentration of about 5 nM to about 10 nM; wherein the compound is to be administered to a tissue of a subject at an amount effective to increase prostaglandin levels in the tissue;the compound is provided in a topical composition; the compound is to be applied to skin of a subject to promote and/or stimulate pigmentation of the skin and/or hair growth and/or inhibiting hair loss, and/or treat skin damage or inflammation; the compound is to be administered to a subject to promote wound healing, tissue repair, and/or tissue regeneration; the compound is to be administered to a subject to treat at least one of oral ulcers, gum disease, colitis, ulcerative colitis, gastrointestinal ulcers, inflammatory bowel disease, vascular insufficiency, Raynaud's disease, Buerger's disease, diabetic neuropathy, pulmonary artery hypertension, cardiovascular disease, and renal disease; the compound is to be administered to a subject in combination with a prostanoid agonist for the purpose of enhancing the therapeutic effect of the agonist in prostaglandin responsive conditions; the compound is to be administered to tissue of the subject to increase tissue stem cells; the compound is to be administered to a tissue graft donor, bone marrow graft donor, and/or a hematopoietic stem cell donor to increase the fitness of a donor tissue graft, a donor bone marrow graft, and/or a donor hematopoietic stem cell graft; the compound is to be administered to bone marrow of a subject to increase stem cells in the subject; the compound is to be administered to bone marrow of a subject to increase the fitness of the marrow as a donor graft; the compound is to be administered to a preparation of hematopoietic stem cells of a subject to increase the fitness of the stem cell preparation as a donor graft; the compound is to be administered to a preparation of peripheral blood hematopoietic stem cells of a subject to increase the fitness of the stem cell preparation as a donor graft; the compound is to be administered to a preparation of umbilical

cord blood stem cells to increase the fitness of the stem cell preparation as a donor graft; the compound is to be administered to a preparation of umbilical cord blood stem cells to decrease the number of units of umbilical cord blood required for transplantation; the compound is to be administered to a subject to mitigate tissue graft rejection; the compound is to be administered to a subject to enhance tissue and/or bone marrow graft engraftment; the compound is to be administered to a subject to enhance bone marrow graft engraftment, following treatment of the subject or the marrow of the subject with radiation therapy, chemotherapy, or immunosuppressive therapy; the compound is to be administered to a subject to enhance engraftment of a progenitor stem cell graft, hematopoietic stem cell graft, or an umbilical cord blood stem cell graft; the compound is to be administered to a subject to enhance engraftment of a hematopoietic stem cell graft, or an umbilical cord stem cell graft, following treatment of the subject or the marrow of the subject with radiation therapy, chemotherapy, or immunosuppressive therapy; the compound is to be administered to a subject in order to decrease the number of units of umbilical cord blood required for transplantation into the subject; the compound is to be administered to a recipient of a tissue graft transplant, bone marrow transplant, and/or hematopoietic stem cell transplant, or of an umbilical cord stem cell transplant, in order to decrease the administration of other treatments or growth factors; the compound is to be administered to a subject or to a tissue graft of a subject to mitigate graft rejection; the compound is to be administered to a subject or to a tissue graft of a subject to enhance graft engraftment; the compound is to be administered to a subject or to a tissue graft of a subject to enhance graft engraftment following treatment of the subject or the marrow of the subject with radiation therapy, chemotherapy, or immunosuppressive therapy; the compound is to be administered to a subject or to the bone marrow of a subject to confer resistance to toxic or lethal effects of exposure to radiation; the compound is to be administered to a subject or to the bone marrow of a subject to confer resistance to the toxic effect of Cytoxan, the toxic effect of fludarabine, the toxic effect of chemotherapy, or the toxic effect of immunosuppressive therapy; the compound is to be administered to a subject or to the bone marrow of a subject to decrease infection; the compound is to be administered to a subject to increase neutrophil counts following a hematopoietic cell transplant with bone marrow, hematopoetic stem cells, or umbilical cord blood; the compound is to be administered to a subject to increase neutrophil counts in a subject with neutropia following chemotherapy administration or radiation therapy; the compound is to be administered to a subject to increase neutrophil counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, neutropenia due to other bone marrow diseases, drug induced neutropenia, autoimmune neutropenia, idiopathic neutropenia, or neutropenia following viral infections; the compound is to be administered to a subject to increase neutrophil counts in a subject with neutropia; the compound is to be administered to a subject to increase platelet counts following a hematopoetic cell transplant with bone marrow, hematopoetic stem cells, or umbilical cord blood; the compound is to be administered to a subject to increase platelet counts in a subject with thrombocytopenia following chemotherapy administration or radiation therapy; the compound is to be administered to a subject to increase platelet counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, thrombocytopenia due to other bone marrow diseases, drug induced thrombocytopenia, autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura, idiopathic thrombocytopenia, or thrombocytopenia following viral infections; the compound is to be administered to a subject to increase platelet counts in a subject with thrombocytopenia; the compound is to be administered to a subject to increase red blood cell counts, or hematocrit, or hemoglobin level, following a hematopoetic cell transplant with bone marrow, hematopoetic stem cells, or umbilical cord blood; the compound is to be administered to a subject to increase red blood cell counts, or hematocrit, or hemoglobin level in a subject with anemia following chemotherapy administration or radiation therapy; the compound is to be administered to a subject to increase red blood cell counts, or hematocrit, or hemoglobin level counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, anemia due to other disorder of bone marrow, drug induced anemia, immune mediated anemias, anemia of chronic disease, anemia following viral infections, or anemia of unknown cause; the compound is to be administered to a subject to increase red blood cell counts, or hematocrit, or hemoglobin level in a subject with anemia; the compound is to be administered to a subject to increase bone marrow stem cells, following a hematopoetic cell transplant with bone marrow, hematopoetic stem cells, or umbilical cord blood; the compound is to be administered to a subject to increase bone marrow stem cells in a subject following chemotherapy administration or radiation therapy; the compound is to be administered to a subject to increase bone marrow stem cells in a subject with aplastic anemia, myelodysplasia,

myelofibrosis, other disorder of bone marrow, drug induced cytopenias, immune cytopenias, cytopenias following viral infections, or cytopenias; the compound is to be administered to a subject to increase responsiveness to cytokines in the presence of cytopenias, with cytopenias including any of: neutropenia, thrombocytopenia, lymphocytopenia and anemia; and with cytokines having increased responsiveness potentiated by the 15-PGDH inhibitor including any of: G-CSF, GM-CSF, EPO, IL-3, IL-6, TPO, TPO-RA (thrombopoietin receptor agonist), and SCF; the compound is to be administered to a subject or the bone marrow of a subject to decrease pulmonary toxicity from radiation; the compound is to be administered to a subject to increase bone density, treat osteoporosis, promote healing of fractures, or promote healing after bone surgery or joint replacement; the compound is to be administered to a subject to promote healing of bone to bone implants, bone to artificial implants, dental implants, and bone grafts; the compound is to be administered to a subject or to the intestine of a subject to increase stem cells in the intestine; the compound is to be administered to a subject or to intestine of a subject to increase stem cells in the intestine and confer resistance to toxic or lethal effects of exposure to radiation or the toxic, lethal, or mucositis effects resultant from treatment with chemotherapy; the compound is to be administered to a subject or to the intestines of a subject to confer resistance to toxic or lethal effects of exposure to radiation or the toxic, lethal, or mucositis effects resultant from treatment with chemotherapy; the compound is to be administered to a subject or to intestine of a subject as a treatment for colitis, ulcerative colitis, or inflammatory bowel disease; the compound is to be administered to a subject to increase liver regeneration following liver surgery, following live liver donation, following liver transplantation, or following liver injury by toxins; the compound is to be administered to a subject to promote recovery from or resistance to liver toxins, including acetaminophen and related compounds; the compound is to be administered to a subject to treat erectile dysfunction; or the compound is to be administered to inhibit at least one of the growth, proliferation, or metastasis of 15-PGDH expressing cancers.

[0005i] In another aspect, the present disclosure refers to a compound as disclosed herein for use in therapy.

[0006] In ~~embodiment~~examples, the modulator of SCD can be an SCD inhibitor that can be administered to tissue or blood of a subject at an amount effective to inhibit the activity of a short chain dehydrogenase enzyme. The SCD inhibitor can be a 15-PGDH inhibitor that can be administered to tissue or blood of a subject at an amount effective to increase prostaglandin levels in the tissue or blood. The 15-PGDH inhibitor can include a compound having a structure of formula (I):

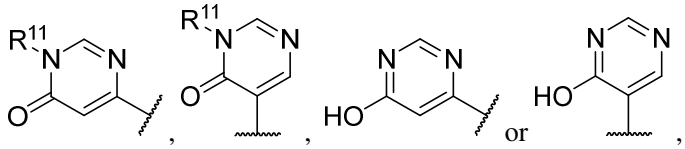


(I)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is alkyl, haloalkyl, cycloalkyl, alkylene-cycloalkyl, alkylene-alkoxy, heterocyclyl, or alkylene-heterocyclyl;

R^2 is $–NH_2$, CN, or $–NHC(O)(C_1\text{-}C_6$ alkyl);

R^6 is , each of which is optionally substituted with one or more R^3;

R^7 is alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl, -C(O)O-alkyl, or -C(O)NR^5-alkyl, each of which is optionally substituted with one or more R^4;

R^3 is -OH, -O-alkeylene-OH, -O-alkeylene-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(alkylene-OH), -$N(R^5)$(alkylene-O-alkyl), alkyl, -alkylene-OH, haloalkyl, cycloalkyl, heterocyclyl, -$C(O)N(R^5)_2$, -$C(O)N(R^5)$(alkylene-OH), -C(O)-alkyl, -C(O)O-alkyl, or -$S(O)_m$-alkyl, wherein the cycloalkyl and the heterocyclyl is each optionally substituted with R^{10};

R^4 is oxo, halogen, -CN, -$N(R^5)_2$, -OH, -O-alkylene-OH, -$S(O)_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, -alkylene-O-alkyl, alkoxy, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8, wherein when R^4 is oxo and R^7 is aryl or heteroaryl, oxo does not violate the valency of the aryl or the heteroaryl;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -C(O)O-alkyl, -alkylene-COOH, or -$S(O)_m$-alkyl;

R^8 is halogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy;

R^9 is H or C_1-C_6 alkyl;

R^{10} is –OH, halogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy;

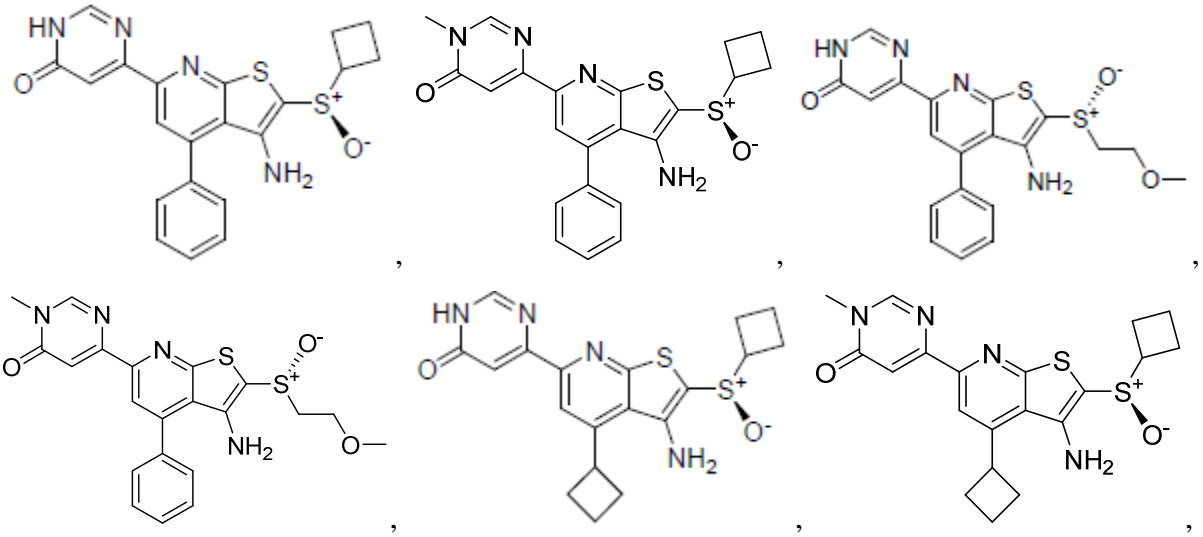
R^{11} is H or C_1-C_6 alkyl;

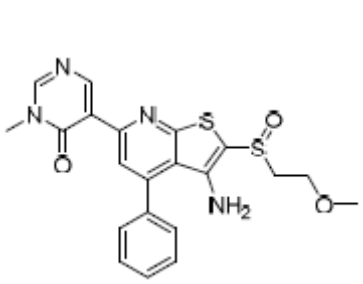
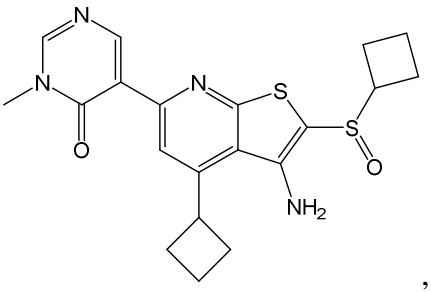
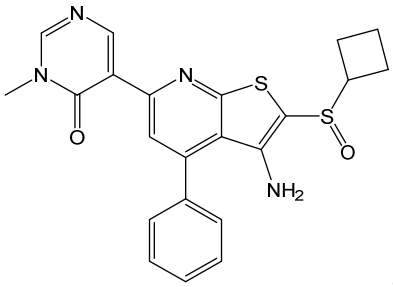
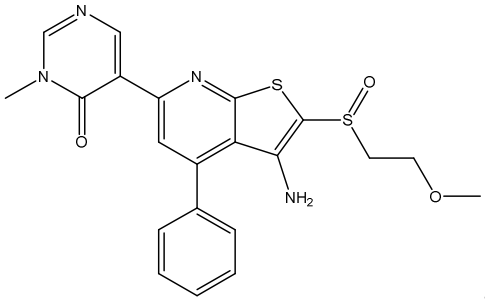
X is N or CH;

m is 0, 1, or 2; and

n is 0, 1, or 2.

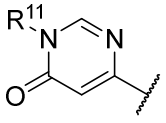
[0007] In ~~embodiment~~examples, the compound of formula (I) is not:




,

,

, and

.

[0008] In ~~embodiment~~examples of compounds of formula (I), R^1 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or -(C_1-C_3 alkylene)-(C_1-C_3 alkoxy). In ~~embodiment~~examples, R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -$(CH_2)_p$-cyclopropyl, -$(CH_2)_p$-cyclobutyl, -$(CH_2)_p$-cyclopentyl, -$(CH_2)_p$-cyclohexyl, or -$(CH_2)_p$-OCH_3; wherein p is 1, 2, or 3.

[0009] In ~~embodiment~~examples of compounds of formula (I), R^2 is NH_2.

[0010] In ~~embodiment~~examples of compounds of formula (I), R^6 is .

[0011] In ~~embodiment~~examples of compounds of formula (I), R^{11} is H or methyl.

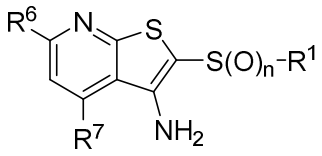
[0012] In ~~embodiment~~examples of compounds of formula (I), R^7 is phenyl, alkyl, or cycloalkyl, each of which is optionally substituted with one or more R^4.

[0013] In ~~embodiment~~examples of compounds of formula (I), R^7 is a linear or branched, non-cyclic C_1-C_6 alkyl. In ~~embodiment~~examples, R^7 is methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *s*-butyl, or *t*-butyl. In ~~embodiment~~examples, R^7 is *i*-propyl.

[0014] In ~~embodiment~~examples of compounds of formula (I), X is CH.

[0015] In ~~embodiment~~examples of compounds of formula (I), n is 1.

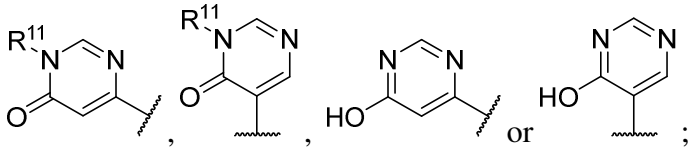
[0016] The present disclosure also relates to compounds of formula (II):



(II)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or -(C_1-C_3 alkylene)-(C_1-C_3 alkoxy);

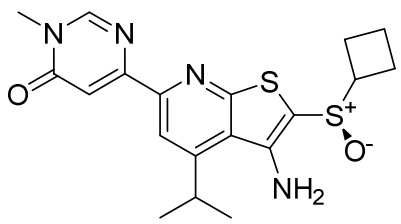
R^6 is ;

R^7 is a linear or branched, non-cyclic C_1-C_6 alkyl;

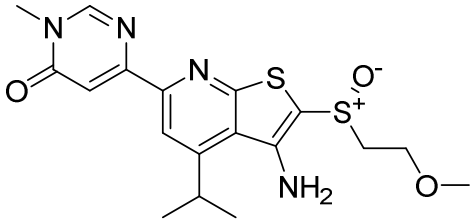
R^{11} is H or C_1-C_6 alkyl; and

n is 0, 1, or 2.

[0017] In ~~embodiment~~examples of compounds of formula (I) or (II), the compound is selected from:

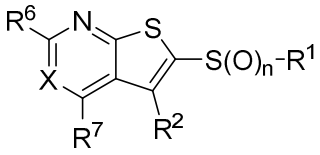


or



, or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

[0018] The present disclosure also relates to compounds of formula (III):

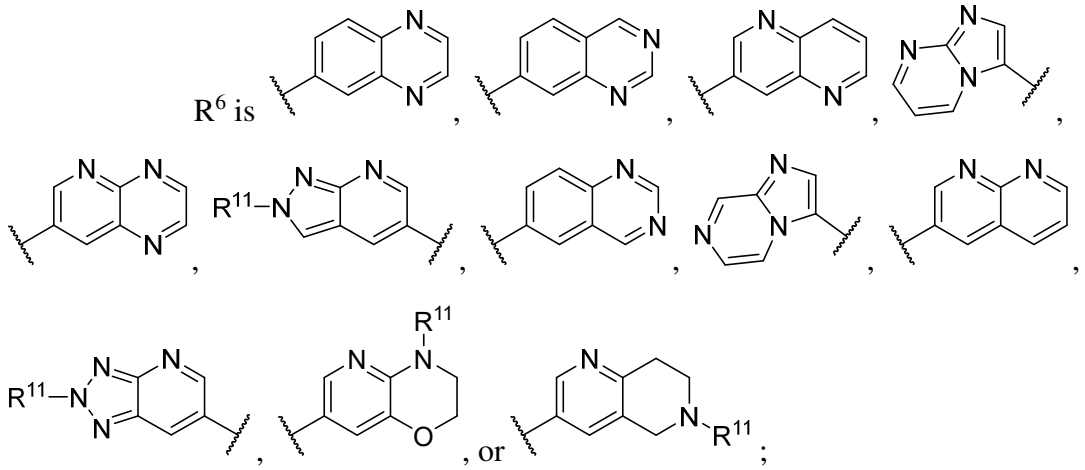


(III)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is alkyl, haloalkyl, cycloalkyl, alkylene-cycloalkyl, alkylene-alkoxy, heterocyclyl, or alkylene-heterocyclyl;

R^2 is $–NH_2$, CN, or –NHC(O)(C_1-C_6 alkyl);

R^6 is 

R^7 is alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl, -C(O)O-alkyl, or -C(O)NR^5-alkyl, each of which is optionally substituted with one or more R^4;

R^4 is oxo, halogen, -CN, -$N(R^5)_2$, -OH, -O-alkylene-OH, -$S(O)_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, -alkylene-O-alkyl, alkoxy, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8, wherein when R^4 is oxo and R^7 is aryl or heteroaryl, oxo does not violate the valency of the aryl or the heteroaryl;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -C(O)O-alkyl, -alkylene-COOH, or -$S(O)_m$-alkyl;

R^8 is halogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy;

R^9 is H or C_1-C_6 alkyl;

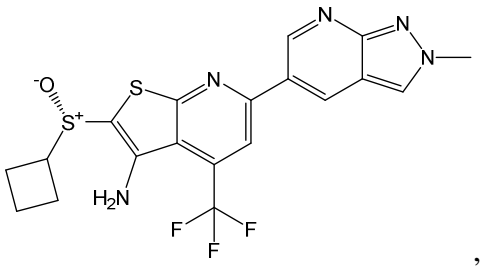
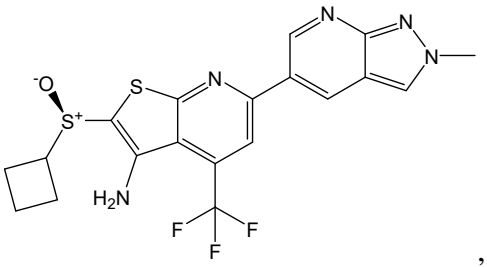
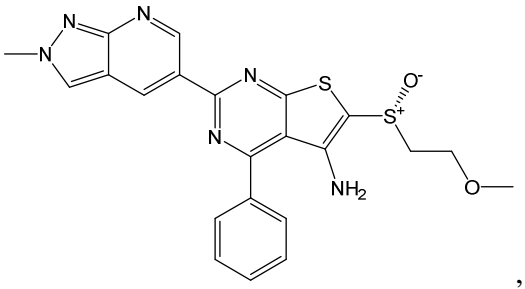
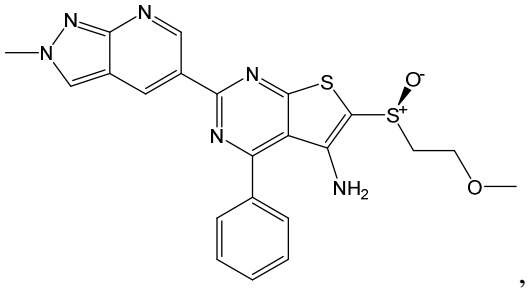
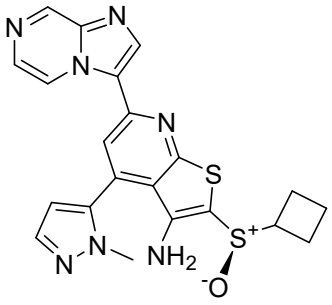
R^{11} is H or C_1-C_6 alkyl;

X is N or CH;

m is 0, 1, or 2; and

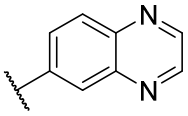
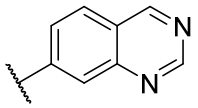
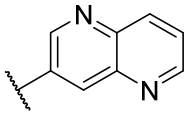
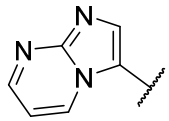
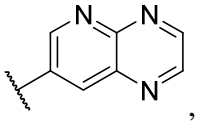
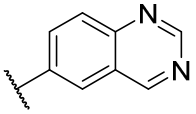
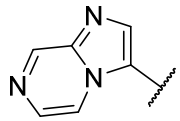
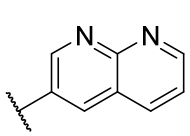
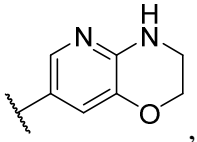
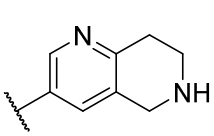
n is 0, 1, or 2.

[0019] In ~~embodiment~~examples of the compounds of formula (III), the compound is not:


,

,

,

,

and .

[0020] In ~~embodiment~~examples of compounds of formula (III), R^1 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or -(C_1-C_3 alkylene)-(C_1-C_3 alkoxy). In ~~embodiment~~examples, R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -$(CH_2)_p$-cyclopropyl, -$(CH_2)_p$-cyclobutyl, -$(CH_2)_p$-cyclopentyl, -$(CH_2)_p$-cyclohexyl, or -$(CH_2)_p$-OCH_3; wherein p is 1, 2, or 3.

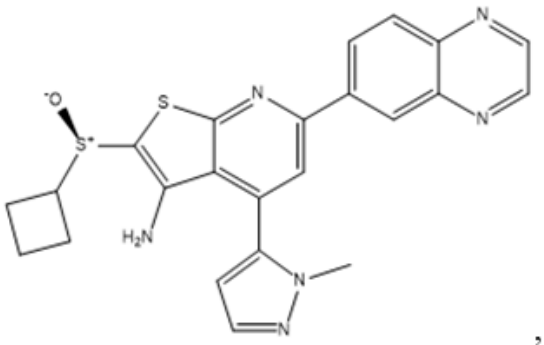
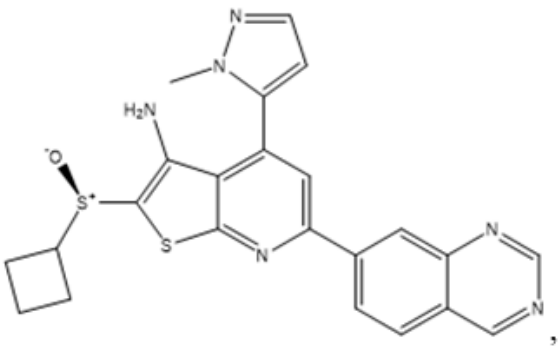
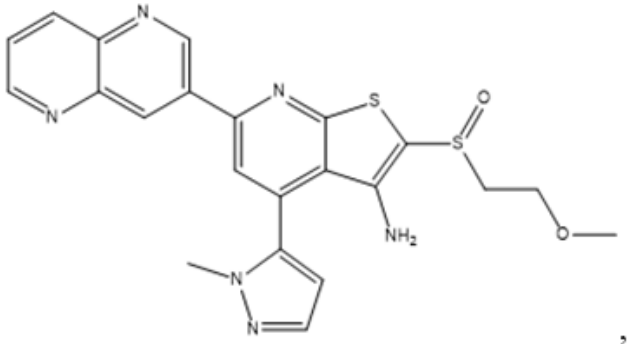
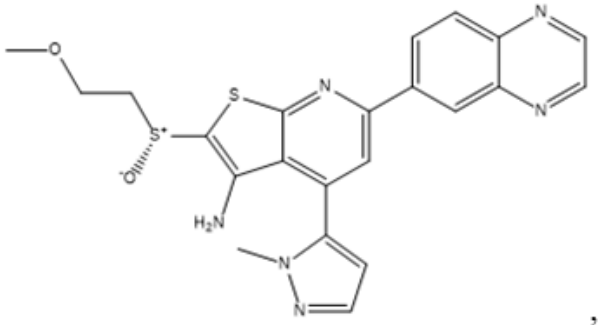
[0021] In ~~embodiment~~examples of compounds of formula (III), R^2 is NH_2 or -CN.

[0022] In ~~embodiment~~examples of compounds of formula (III), R^6 is , , , , , , , , , or .

[0023] In ~~embodiment~~examples of compounds of formula (III), R^7 is alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl, each of which is optionally substituted with one or more R^4.

[0024] In ~~embodiment~~examples of compounds of formula (III), n is 1.

[0025] In ~~embodiment~~examples of compounds of formula (III), the compound is selected from:

, , , ,

[0029] In ~~embodiment~~examples, the compound or 15-PGDH inhibitor of the present disclosure can inhibit the enzymatic activity of recombinant 15-PGDH at an IC_{50} of less than or equal to 1 μM, an IC_{50} of less than or equal to 250 nM, an IC_{50} of less than or equal to 50 nM, an IC_{50} of less than or equal to 10 nM, an IC_{50} of less than or equal to 5 nM, an IC_{50} of about 2.5 nM to about 10 nM, or an IC_{50} of less than or equal to about 2.5 nM, at a 15-PGDH concentration of about 1 nM to about 10 nM.

[0030] In ~~embodiment~~examples, the compound or 15-PGDH inhibitor of the present disclosure can inhibit the enzymatic activity of recombinant 15-PGDH at an IC_{50} of less than or equal to 1 μM, an IC_{50} of less than or equal to 250 nM, an IC_{50} of less than or equal to 50 nM, an IC_{50} of less than or equal to 10 nM, an IC_{50} of less than or equal to 5 nM, at an IC_{50} of about 2.5 nM to about 10 nM, or an IC_{50} of less than or equal to about 2.5 nM, at a 15-PGDH concentration of about 0.5 nM to about 5 nM.

[0031] In ~~embodiment~~examples, the compound or 15-PGDH inhibitor of the present disclosure can inhibit the enzymatic activity of recombinant 15-PGDH at an IC_{50} of less than or equal to 1 μM, an IC_{50} of less than or equal to 250 nM, an IC_{50} of less than or equal to 50 nM, an IC_{50} of less than or equal to 10 nM, an IC_{50} of less than or equal to 5 nM, at an IC_{50} of about 2.5 nM to about 10 nM, or an IC_{50} of less than about or equal to 2.5 nM, at a 15-PGDH concentration of about 1 nM to about 2 nM. In ~~embodiment~~examples, the compound or 15-PGDH inhibitor of the present disclosure can inhibit the enzymatic activity of recombinant 15-PGDH at an IC_{50} of less than about 2.5 nM, at a 15-PGDH concentration of about 1 nM to about 2 nM.

[0032] The 15-PGDH inhibitor of the present disclosure can be provided in a topical composition that can be applied to skin of a subject to promote and/or stimulate pigmentation of the skin and/or hair growth and/or inhibiting hair loss, and/or treat skin damage or inflammation.

[0033] The 15-PGDH inhibitor of the present disclosure can also be administered to a subject to promote wound healing, tissue repair, and/or tissue regeneration and/or engraftment or regeneration of a tissue graft.

[0034] In ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a subject to treat at least one of oral ulcers, gum disease, colitis, ulcerative colitis, gastrointestinal ulcers, inflammatory bowel disease, vascular insufficiency, Raynaud's

disease, Buerger's disease, diabetic neuropathy, pulmonary artery hypertension, cardiovascular disease, and renal disease.

[0035] In another ~~embodiment~~example, the 15-PGDH inhibitor of the present disclosure can be administered to a subject in combination with a prostanoid agonist for the purpose of enhancing the therapeutic effect of the agonist in prostaglandin responsive conditions.

[0036] In ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a subject and/or tissue of the subject to increase tissue stem cells. For example, the 15-PGDH inhibitor can be administered to bone marrow of a subject to increase stem cells in the subject.

[0037] In still other ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a tissue graft donor, bone marrow graft donor, and/or a hematopoietic stem cell donor, and/or a tissue graft, and/or a bone marrow graft, and/or a hematopoietic stem cell graft, to increase the fitness of a donor tissue graft, a donor bone marrow graft, and/or a donor hematopoietic stem cell graft. In ~~embodiment~~examples, the 15-PGDH inhibitor is administered ex vivo to a tissue graft, and/or a bone marrow graft, and/or a hematopoietic stem cell graft. For example, the 15-PGDH inhibitor can be administered to a subject, and/or bone marrow of a subject to increase the fitness of the marrow as a donor graft, and/or to a preparation of hematopoietic stem cells of a subject to increase the fitness of the stem cell preparation as a donor graft, and/or to a preparation of peripheral blood hematopoietic stem cells of a subject to increase the fitness of the stem cell preparation as a donor graft, and/or to a preparation of umbilical cord blood stem cells to increase the fitness of the stem cell preparation as a donor graft, and/or to a preparation of umbilical cord blood stem cells to decrease the number of units of umbilical cord blood required for transplantation.

[0038] In ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a subject to mitigate tissue graft rejection, to enhance tissue and/or bone marrow graft engraftment, to enhance bone marrow graft engraftment, following treatment of the subject or the marrow of the subject with radiation therapy, chemotherapy, or immunosuppressive therapy, to enhance engraftment of a progenitor stem cell graft, hematopoietic stem cell graft, or an umbilical cord blood stem cell graft, to enhance engraftment of a hematopoietic stem cell

graft, or an umbilical cord stem cell graft, following treatment of the subject or the marrow of the subject with radiation therapy, chemotherapy, or immunosuppressive therapy, and/or in order to decrease the number of units of umbilical cord blood required for transplantation into the subject.

[0039] In ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a recipient of a tissue graft transplant, bone marrow transplant, and/or hematopoietic stem cell transplant, or of an umbilical cord stem cell transplant, in order to decrease the administration of other treatments or growth factors.

[0040] In ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a subject or to a tissue graft of a subject to mitigate graft rejection, to enhance graft engraftment, and/or to enhance graft engraftment following treatment of the subject or the marrow of the subject with radiation therapy, chemotherapy, or immunosuppressive therapy.

[0041] In ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a subject or to the bone marrow of a subject to confer resistance to toxic or lethal effects of exposure to radiation, to confer resistance to the toxic effect of Cytoxan, the toxic effect of fludarabine, the toxic effect of chemotherapy, or the toxic effect of immunosuppressive therapy, to decrease pulmonary toxicity from radiation, and/or to decrease infection.

[0042] In still other ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a subject to increase neutrophil counts following a hematopoietic cell transplant with bone marrow, hematopoietic stem cells, or umbilical cord blood, to increase neutrophil counts in a subject with neutropia following chemotherapy administration or radiation therapy, to increase neutrophil counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, neutropenia due to other bone marrow diseases, drug induced neutropenia, autoimmune neutropenia, idiopathic neutropenia, or neutropenia following viral infections, to increase neutrophil counts in a subject with neutropia, to increase platelet counts following a hematopoietic cell transplant with bone marrow, hematopoietic stem cells, or umbilical cord blood, to increase platelet counts in a subject with thrombocytopenia following chemotherapy administration or radiation therapy, to increase platelet counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, thrombocytopenia due to other bone marrow diseases, drug induced thrombocytopenia, autoimmune thrombocytopenia, idiopathic thrombocytopenic

purpura, idiopathic thrombocytopenia, or thrombocytopenia following viral infections, to increase platelet counts in a subject with thrombocytopenia, to increase red blood cell counts, or hematocrit, or hemoglobin level, following a hematopoietic cell transplant with bone marrow, hematopoietic stem cells, or umbilical cord blood, to increase red blood cell counts, or hematocrit, or hemoglobin level in a subject with anemia following chemotherapy administration or radiation therapy, to increase red blood cell counts, or hematocrit, or hemoglobin level counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, anemia due to other disorder of bone marrow, drug induced anemia, immune mediated anemias, anemia of chronic disease, anemia following viral infections, or anemia of unknown cause, to increase red blood cell counts, or hematocrit, or hemoglobin level in a subject with anemia, to increase bone marrow stem cells, following a hematopoietic cell transplant with bone marrow, hematopoietic stem cells, or umbilical cord blood, to increase bone marrow stem cells in a subject following chemotherapy administration or radiation therapy, and/or to increase bone marrow stem cells in a subject with aplastic anemia, myelodysplasia, myelofibrosis, other disorder of bone marrow, drug induced cytopenias, immune cytopenias, cytopenias following viral infections, or cytopenias.

[0043] In ~~embodiment~~examples, the administration of a 15-PGDH inhibitor of the present disclosure can be used to modulate hematopoietic stem cells and hematopoiesis. For a 15-PGDH inhibitor can be administered alone or in combination with a cytokine to a subject in need thereof to increase and/or mobilize hematopoietic stem cells and/or neutrophils in the blood, marrow, and/or tissue of the subject.

[0044] In ~~embodiment~~examples, the administration of a 15-PGDH inhibitor of the present disclosure can be in combination with G-CSF for the purpose of increasing neutrophils.

[0045] In ~~embodiment~~examples, the administration of a 15-PGDH inhibitor of the present disclosure can be in combination with a hematopoietic cytokine for the purpose of increasing neutrophils.

[0046] In still other ~~embodiment~~examples, the administration of a 15-PGDH inhibitor of the present disclosure can be in combination with G-CSF for the purpose of increasing numbers of and/or of mobilizing peripheral blood hematopoietic stem cells.

[0047] In ~~embodiment~~examples, the administration of a 15-PGDH inhibitor of the present disclosure can be in combination with a hemopoietic cytokine for the purpose of increasing numbers of and/or of mobilizing peripheral blood hematopoietic stem cells.

[0048] In ~~embodiment~~examples, the administration of a 15-PGDH inhibitor of the present disclosure can be in combination with a second agent, including Plerixafor, for the purpose of increasing numbers of and/or of mobilizing peripheral blood hematopoietic stem cells.

[0049] In ~~embodiment~~examples, the administration of a 15-PGDH inhibitor of the present disclosure can be in combination with G-CSF for the purpose of increasing numbers of and/or of mobilizing peripheral blood hematopoietic stem cells for use in hematopoietic stem cell transplantation.

[0050] In still other ~~embodiment~~examples, the administration of a 15-PGDH inhibitor of the present disclosure can be in combination with a hemopoietic cytokine for the purpose of increasing numbers of and/or of mobilizing peripheral blood hematopoietic stem cells for use in hematopoietic stem cell transplantation.

[0051] In ~~embodiment~~examples, the administration of a 15-PGDH inhibitor of the present disclosure can be in combination with a second agent, including Plerixafor, for the purpose of increasing numbers of and/or of mobilizing peripheral blood hematopoietic stem cells for use in hematopoietic stem cell transplantation.

[0052] In still other ~~embodiment~~examples, the administration of a 15-PGDH inhibitor of the present disclosure can be in combination with G-CSF for the purpose of increasing numbers of hematopoietic stem cells in blood or bone marrow.

[0053] In ~~embodiment~~examples, the administration of a 15-PGDH inhibitor of the present disclosure can be in combination with a hemopoietic cytokine for the purpose of increasing numbers of hematopoietic stem cells in blood or bone marrow.

[0054] In ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a subject and/or tissue of the subject to increase tissue stem cells. For example, the 15-PGDH inhibitor can be administered to bone marrow of a subject to increase stem cells in the subject.

[0055] In ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a recipient of a tissue graft transplant, bone marrow transplant, and/or hematopoietic stem cell transplant, or of an umbilical cord stem cell transplant, in order to decrease the administration of other treatments or growth factors.

[0056] In still other ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a subject to increase neutrophil counts following a hematopoietic cell transplant with bone marrow, hematopoietic stem cells, or umbilical cord blood, to increase neutrophil counts in a subject with neutropia following chemotherapy administration or radiation therapy, to increase neutrophil counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, neutropenia due to other bone marrow diseases, drug induced neutropenia, autoimmune neutropenia, idiopathic neutropenia, or neutropenia following viral infections, to increase neutrophil counts in a subject with neutropia, to increase platelet counts following a hematopoietic cell transplant with bone marrow, hematopoietic stem cells, or umbilical cord blood, to increase platelet counts in a subject with thrombocytopenia following chemotherapy administration or radiation therapy, to increase platelet counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, thrombocytopenia due to other bone marrow diseases, drug induced thrombocytopenia, autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura, idiopathic thrombocytopenia, or thrombocytopenia following viral infections, to increase platelet counts in a subject with thrombocytopenia, to increase red blood cell counts, or hematocrit, or hemoglobin level, following a hematopoietic cell transplant with bone marrow, hematopoietic stem cells, or umbilical cord blood, to increase red blood cell counts, or hematocrit, or hemoglobin level in a subject with anemia following chemotherapy administration or radiation therapy, to increase red blood cell counts, or hematocrit, or hemoglobin level counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, anemia due to other disorder of bone marrow, drug induced anemia, immune mediated anemias, anemia of chronic disease, anemia following viral infections, or anemia of unknown cause, to increase red blood cell counts, or hematocrit, or hemoglobin level in a subject with anemia, to increase bone marrow stem cells, following a hematopoietic cell transplant with bone marrow, hematopoietic stem cells, or umbilical cord blood, to increase bone marrow stem cells in a subject following chemotherapy

administration or radiation therapy, and/or to increase bone marrow stem cells in a subject with aplastic anemia, myelodysplasia, myelofibrosis, other disorder of bone marrow, drug induced cytopenias, immune cytopenias, cytopenias following viral infections, or cytopenias.

[0057] In ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a subject to increase responsiveness to cytokines in the presence of cytopenias, with cytopenias including any of: neutropenia, thrombocytopenia, lymphocytopenia and anemia; and with cytokines having increased responsiveness potentiated by the 15-PGDH inhibitor including any of: G-CSF, GM-CSF, EPO, IL-3, IL-6, TPO, TPO-RA (thrombopoietin receptor agonist), and SCF.

[0058] In ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a subject to increase bone density, treat osteoporosis, promote healing of fractures, or promote healing after bone surgery or joint replacement and/or to promote healing of bone to bone implants, bone to artificial implants, dental implants, and bone grafts.

[0059] In ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a subject or to the intestine of a subject to increase stem cells or cell proliferation in the intestine and/or and confer resistance to toxic or lethal effects of exposure to radiation or the toxic, lethal, or mucositis effects resultant from treatment with chemotherapy.

[0060] In ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a subject or to intestine of a subject as a treatment for colitis, ulcerative colitis, or inflammatory bowel disease.

[0061] In ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a subject to increase liver regeneration following liver surgery, following live liver donation, following liver transplantation, or following liver injury by toxins and/or to promote recovery from or resistance to liver toxins, including acetaminophen and related compounds.

[0062] In still other ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a subject to treat erectile dysfunction.

[0063] In yet other ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to inhibit at least one of the growth, proliferation, or metastasis of 15-PGDH expressing cancers.

[0064] Still other ~~embodiment~~examples described herein relate to a method of treating a subject in need of cell therapy. The method includes administering to the subject a therapeutically effective amount of a preparation comprising human hematopoietic stem cell administered a 15-PGDH inhibitor described herein and/or a therapeutic composition comprising human hematopoietic stem cells and a 15-PGDH inhibitor described herein.

[0065] In ~~embodiment~~examples, the subject has received human hematopoietic stem cells and/or has received the preparation and/or the therapeutic composition.

[0066] In ~~embodiment~~examples, the subject has acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), juvenile myelomonocytic leukemia, Hodgkin`s lymphoma, non-Hodgkin`s lymphoma, multiple myeloma, severe aplastic anemia, Fanconi`s anemia, paroxysmal nocturnal hemoglobinuria (PNH), pure red cell aplasia, amegakaryocytosis/congenital thrombocytopenia, severe combined immunodeficiency syndrome (SCID), Wiskott-Aldrich syndrome, beta-thalassemia major, sickle cell disease, Hurler`s syndrome, adrenoleukodystrophy, metachromatic leukodystrophy, myelodysplasia, refractory anemia, chronic myelomonocytic leukemia, agnogenic myeloid metaplasia, familial erythrophagocytic lymphohistiocytosis, solid tumors, chronic granulomatous disease, mucopolysaccharidoses, or Diamond Blackfan anemia.

[0067] Other ~~embodiment~~examples relate to a method of treating a subject having at least one symptom associated with an ischemic tissue or a tissue damaged by ischemia. The method includes administering to the subject a therapeutically effective amount of a preparation comprising human hematopoietic stem cell administered a 15-PGDH inhibitor described herein and/or a therapeutic composition comprising human hematopoietic stem cells and a 15-PGDH inhibitor described herein.

[0068] In ~~embodiment~~examples, the ischemia can be associated with at least one of acute coronary syndrome, acute lung injury (ALI), acute myocardial infarction (AMI), acute respiratory distress syndrome (ARDS), arterial occlusive disease, arteriosclerosis, articular cartilage defect, aseptic

systemic inflammation, atherosclerotic cardiovascular disease, autoimmune disease, bone fracture, bone fracture, brain edema, brain hypoperfusion, Buerger`s disease, burns, cancer, cardiovascular disease, cartilage damage, cerebral infarct, cerebral ischemia, cerebral stroke, cerebrovascular disease, chemotherapy-induced neuropathy, chronic infection, chronic mesenteric ischemia, claudication, congestive heart failure, connective tissue damage, contusion, coronary artery disease (CAD), critical limb ischemia (CLI), Crohn`s disease, deep vein thrombosis, deep wound, delayed ulcer healing, delayed wound-healing, diabetes (type I and type II), diabetic neuropathy, diabetes induced ischemia, disseminated intravascular coagulation (DIC), embolic brain ischemia, graft- versus-host disease, hereditary hemorrhagic telengiectasiaischemic vascular disease, hyperoxic injury, hypoxia, inflammation, inflammatory bowel disease, inflammatory disease, injured tendons, intermittent claudication, intestinal ischemia, ischemia, ischemic brain disease, ischemic heart disease, ischemic peripheral vascular disease, ischemic placenta, ischemic renal disease, ischemic vascular disease, ischemic-reperfusion injury, laceration, left main coronary artery disease, limb ischemia, lower extremity ischemia, myocardial infarction, myocardial ischemia, organ ischemia, osteoarthritis, osteoporosis, osteosarcoma, Parkinson`s disease, peripheral arterial disease (PAD), peripheral artery disease, peripheral ischemia, peripheral neuropathy, peripheral vascular disease, pre-cancer, pulmonary edema, pulmonary embolism, remodeling disorder, renal ischemia, retinal ischemia, retinopathy, sepsis, skin ulcers, solid organ transplantation, spinal cord injury, stroke, subchondral-bone cyst, thrombosis, thrombotic brain ischemia, tissue ischemia, transient ischemic attack (TIA), traumatic brain injury, ulcerative colitis, vascular disease of the kidney, vascular inflammatory conditions, von Hippel-Lindau syndrome, and wounds to tissues or organs.

[0069] Other ~~embodiment~~examples relate to methods for treating and/or preventing fibrosis and various fibrotic diseases, disorders or conditions by administration of 15-PGDH inhibitors. In ~~embodiment~~examples, a 15-PGDH inhibitor described herein can be administered to a subject in need thereof to decrease fibrotic symptoms, such as collagen deposition, inflammatory cytokine expression, and inflammatory cell infiltration, and treat and/or prevent various fibrotic diseases, disorders, and conditions characterized, in whole or in part, by the excess production of fibrous

material, including excess production of fibrotic material within the extracellular matrix, or the replacement of normal tissue elements by abnormal, non-functional, and/or excessive accumulation of matrix-associated components.

[0070] Fibrotic diseases, disorders and conditions characterized, in whole or in part, by excess production of fibrotic material can include systemic sclerosis, multifocal fibrosclerosis, nephrogenic systemic fibrosis, scleroderma(including morphea, generalized morphea, or linear scleroderma), sclerodermatous graft-vs-host-disease, kidney fibrosis (including glomerular sclerosis, renal tubulointerstitial fibrosis, progressive renal disease or diabetic nephropathy), cardiac fibrosis (*e.g.,* myocardial fibrosis), pulmonary fibrosis (*e.g.,* glomerulosclerosis pulmonary fibrosis, idiopathic pulmonary fibrosis, silicosis, asbestosis, interstitial lung disease, interstitial fibrotic lung disease, and chemotherapy/radiation induced pulmonary fibrosis), oral fibrosis, endomyocardial fibrosis, deltoid fibrosis, pancreatitis, inflammatory bowel disease, Crohn's disease, nodular fascilitis, eosinophilic fasciitis, general fibrosis syndrome characterized by replacement of normal muscle tissue by fibrous tissue in varying degrees, retroperitoneal fibrosis, liver fibrosis, liver cirrhosis, chronic renal failure; myelofibrosis (bone marrow fibrosis), drug induced ergotism, glioblastoma in Li-Fraumeni syndrome, sporadic glioblastoma, myeloid leukemia, acute myelogenous leukemia, myelodysplastic syndrome, myeloproliferative syndrome, gynecological cancer, Kaposi's sarcoma, Hansen's disease, collagenous colitis, acute fibrosis, organ specific fibrosis, and the like.

[0071] In ~~embodiment~~examples, a method of treating or preventing a fibrotic disease, disorder or condition includes administering to a subject in need thereof a therapeutically effect amount of a 15-PGDH inhibitor of the present disclosure.

[0072] In ~~embodiment~~examples, the 15-PGDH inhibitors of the present disclosure can be used to treat or prevent lung fibrosis. Lung fibrosis, which can be treated, can be selected from the group consisting of pulmonary fibrosis, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), asthma, idiopathic pulmonary fibrosis, sarcoidosis, cystic fibrosis, familial pulmonary fibrosis, silicosis, asbestosis, coal worker's pneumoconiosis, carbon pneumoconiosis, hypersensitivity pneumonitides, pulmonary fibrosis caused by inhalation of inorganic dust, pulmonary fibrosis caused by an infectious agent, pulmonary fibrosis caused by inhalation of

noxious gases, aerosols, chemical dusts, fumes or vapors, drug-induced interstitial lung disease, or pulmonary hypertension, and combinations thereof.

[0073] In ~~embodiment~~examples, the 15-PGDH inhibitors of the present disclosure can be used to treat or prevent kidney fibrosis. The kidney fibrosis can result from dialysis following kidney failure, catheter placement, a nephropathy, glomerulosclerosis, glomerulonephritis, chronic renal insufficiency, acute kidney injury, end stage renal disease or renal failure, or combinations thereof.

[0074] In ~~embodiment~~examples, the 15-PGDH inhibitors of the present disclosure can be used to treat or prevent liver fibrosis. The liver fibrosis can result from a chronic liver disease, viral induced hepatic cirrhosis, hepatitis B virus infection, hepatitis C virus infection, hepatitis D virus infection, schistosomiasis, primary biliary cirrhosis, alcoholic liver disease or non-alcoholic steatohepatitis (NASH), NASH associated cirrhosis obesity, diabetes, protein malnutrition, coronary artery disease, auto-immune hepatitis, cystic fibrosis, alpha-1-antitrypsin deficiency, primary biliary cirrhosis, drug reaction and exposure to toxins, or combinations thereof.

[0075] In ~~embodiment~~examples, the 15-PGDH inhibitors of the present disclosure can be used to treat or prevent heart fibrosis, for example, cardiac fibrosis and endomyocardial fibrosis.

[0076] In ~~embodiment~~examples, the 15-PGDH inhibitors of the present disclosure can be used to treat or prevent systemic sclerosis.

[0077] In ~~embodiment~~examples, the 15-PGDH inhibitors of the present disclosure can be used to treat or prevent fibrotic diseases, disorders or conditions caused by post-surgical adhesion formation.

[0078] In ~~embodiment~~examples, the 15-PGDH inhibitors of the present disclosure can be used for reducing or preventing scar formation in a subject.

[0079] In ~~embodiment~~examples, the 15-PGDH inhibitors of the present disclosure can be used to reduce or prevent scar formation on skin or scleroderma.

[0080] In various ~~embodiment~~examples, the 15-PGDH inhibitors of the present disclosure can be administered at a therapeutically effective amount such that at least one symptom or feature of a fibrotic disease, disorder or condition, or other related diseases, disorders or conditions, is reduced in intensity, severity, or frequency, or has delayed onset.

[0081] In ~~embodiment~~examples, the 15-PGDH inhibitors of the present disclosure can be used in a method for decreasing or reducing collagen secretion or collagen deposition in a tissue or organ, such as the lung, the liver, the intestines, the colon, the skin or the heart, of a subject. The method can include administering a therapeutically effective amount of the 15-PGDH inhibitors to the subject in need thereof. The subject can have or be at risk of an excessive collagen secretion or collagen deposition in the tissue or organ, such as the kidney, the lung, the liver, the intestines, the colon, the skin or the heart. Usually, the excessive collagen secretion or collagen deposition in an organ results from an injury or an insult. Such injury and insult can be organ-specific. The 15-PGDH inhibitors can be administered over a sufficient period of time to decrease or reduce the level of collagen deposition in the tissue or organ, completely or partially. A sufficient period of time can be during one week, or between 1 week to 1 month, or between 1 to 2 months, or 2 months or more. For chronic condition, the15-PGDH inhibitors can be advantageously administered for life time period.

[0082] Other ~~embodiment~~examples described herein relate to the use of 15-PGDH inhibitors of the present disclosure in combination with corticosteroids or TNF inhibitors to treat inflammation, reduce aberrant activity of the immune system, and/or promote wound healing in a subject in need thereof. It was found that corticosteroids administered to a subject can induce 15-PGDH expression in tissue of the subject. Administration of a 15-PGDH inhibitor in combination with a corticosteroid was found to enhance anti-inflammatory and/or immunosuppressive effects of the corticosteroid while attenuating corticosteroid induced adverse and/or cytotoxic effects. Treatment of inflammatory, disorders, immune disorders, and/or wounds by administration of 15-PGDH inhibitors in combination with corticosteroids can increase therapeutic efficacy and can allow the corticosteroids to be administered, in some instances, at lower dosages to achieve similar effects, and, in other instances, at higher dosages and for prolonged periods of times with attenuated and/or reduced adverse or cytotoxic effects.

[0083] In ~~embodiment~~examples, the inflammatory and/or immune disease or disorder treated with the combination of 15-PGDH inhibitor of the present disclosure and a corticosteroid or TNF inhibitor can include intestinal, gastrointestinal, or bowel disorders. As described below, it was found that inhibitors of short-chain dehydrogenase activity, such as 15-PGDH inhibitors, can be

administered to a subject in need thereof alone or in combination with corticosteroids and tumor necrosis factor (TNF)-alpha antagonists to treat intestinal, gastrointestinal, or bowel disorders, such as oral ulcers, gum disease, gastritis, colitis, ulcerative colitis, gastric ulcers, inflammatory bowel disease, and Crohn's disease.

[0084] In ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be used as a glucocorticoid sensitizer to treat glucocorticoid insensitivity, restore corticosteroid sensitivity, enhance glucocorticoid sensitivity, and/or reverse the glucocorticoid insensitivity in a subject experiencing corticosteroid dependence or corticoid resistance or unresponsiveness or intolerance to corticosteroids. For example, the 15-PGDH inhibitor can be administered to a subject in combination with the corticosteroid to treat glucocorticoid insensitivity, restore corticosteroid sensitivity, enhance glucocorticoid sensitivity, and/or reverse the glucocorticoid insensitivity in a subject experiencing corticosteroid dependence or corticoid resistance or unresponsiveness or intolerance to corticosteroids.

[0085] The 15-PGDH inhibitor of the present disclosure can also be administered in combination with a corticosteroid or TNF inhibitor to a subject to promote wound healing, tissue repair, and/or tissue regeneration and/or engraftment or regeneration of a tissue graft.

[0086] In ~~embodiment~~examples, the 15-PGDH inhibitor of the present disclosure can be administered to a subject at an amount effective to increase prostaglandin levels in the subject and attenuate corticosteroid induced adverse and/or cytotoxic effects.

DETAILED DESCRIPTION

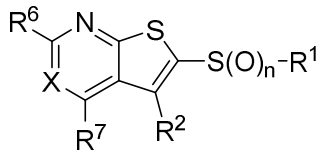
Definitions

[0087] While the following terms are believed to be well understood by one of ordinary skill in the art, the following definitions are set forth to facilitate explanation of the presently disclosed subject matter.

[0088] As used herein, the verb "comprise" as is used in this description and in the claims and its conjugations are used in its non-limiting sense to mean that items following the word are included, but items not specifically mentioned are not excluded. The present invention may

What is claimed:

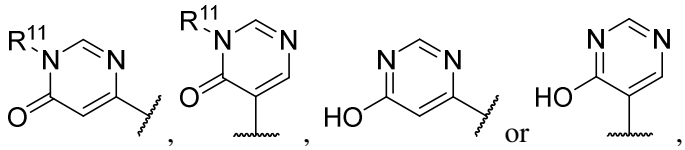
1. A compound of formula (I):


(I)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is alkyl, haloalkyl, cycloalkyl, alkylene-cycloalkyl, alkylene-alkoxy, heterocyclyl, or alkylene-heterocyclyl;

R^2 is $–NH_2$, CN, or $–NHC(O)(C_1\text{-}C_6$ alkyl);

R^6 is , each of which is optionally substituted with one or more R^3;

R^7 is alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl, -C(O)O-alkyl, or -C(O)NR^5-alkyl, each of which is optionally substituted with one or more R^4;

R^3 is -OH, -O-alkeylene-OH, -O-alkeylene-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(alkylene-OH), -$N(R^5)$(alkylene-O-alkyl), alkyl, -alkylene-OH, haloalkyl, cycloalkyl, heterocyclyl, -$C(O)N(R^5)_2$, -$C(O)N(R^5)$(alkylene-OH), -C(O)-alkyl, -C(O)O-alkyl, or -$S(O)_m$-alkyl, wherein the cycloalkyl and the heterocyclyl is each optionally substituted with R^{10};

R^4 is oxo, halogen, -CN, -$N(R^5)_2$, -OH, -O-alkylene-OH, -$S(O)_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, -alkylene-O-alkyl, alkoxy, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8, wherein when R^4 is oxo and R^7 is aryl or heteroaryl, oxo does not violate the valency of the aryl or the heteroaryl;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -C(O)O-alkyl, -alkylene-COOH, or -$S(O)_m$-alkyl;

R^8 is halogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy;

R^9 is H or C_1-C_6 alkyl;

R^{10} is –OH, halogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy;

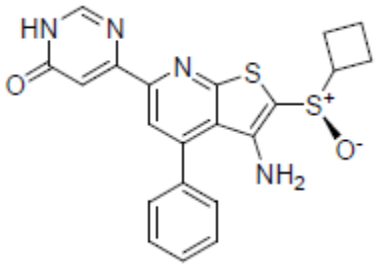
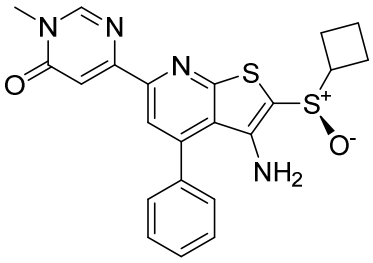
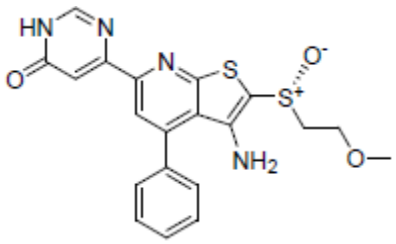
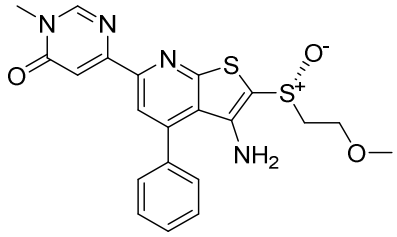
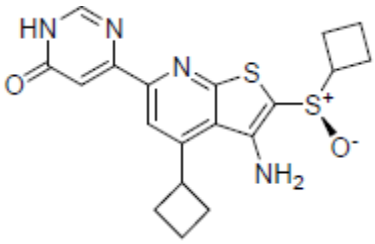
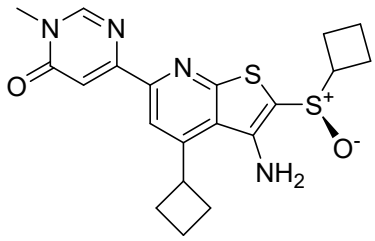
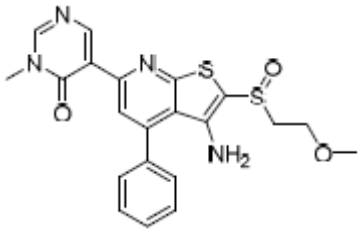
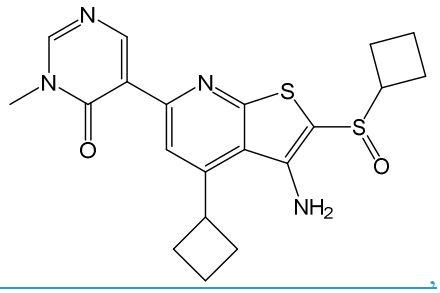
R^{11} is H or C_1-C_6 alkyl;

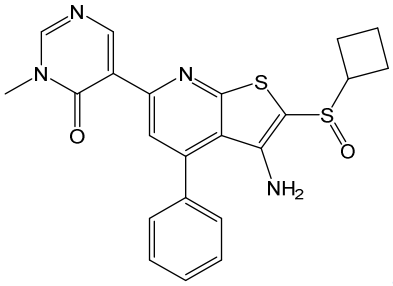
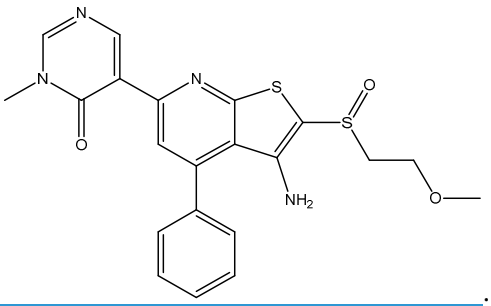
X is N or CH;

m is 0, 1, or 2; and

n is 0, 1, or 2;

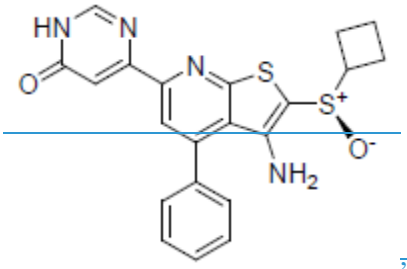
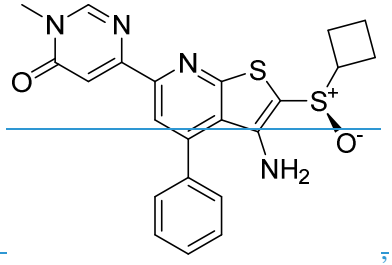
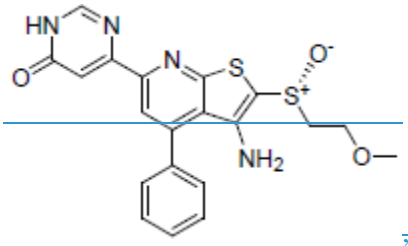
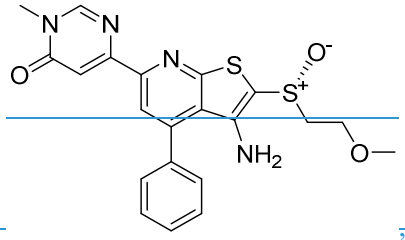
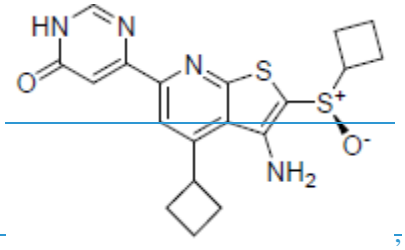
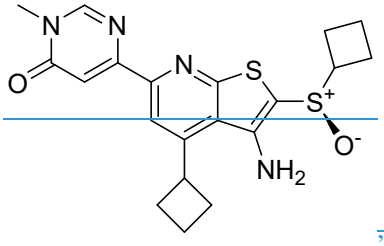
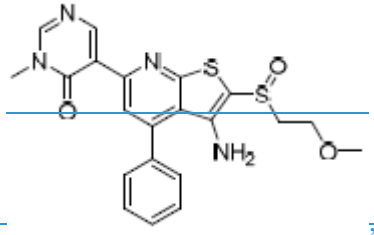
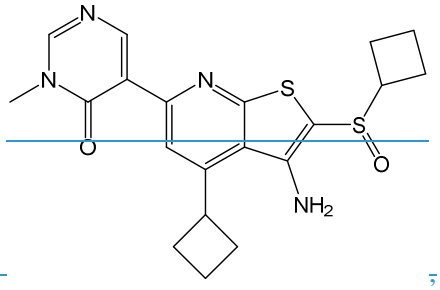
wherein the compound is not:

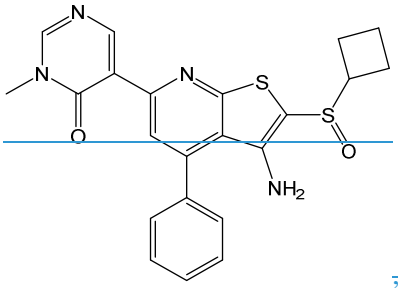









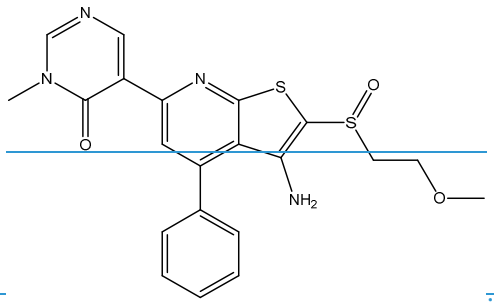



, and .

~~2. The compound of claim 1, wherein the compound is not:~~


, 
, 
, 
, 
, 
, 
, 
.



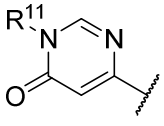


~~, and~~ .

23. The compound of claim 1, wherein R^1 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or -(C_1-C_3 alkylene)-(C_1-C_3 alkoxy).

34. The compound of claim 1 or ~~3~~2, wherein R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -$(CH_2)_p$-cyclopropyl, -$(CH_2)_p$-cyclobutyl, -$(CH_2)_p$-cyclopentyl, -$(CH_2)_p$-cyclohexyl, or -$(CH_2)_p$-OCH_3; wherein p is 1, 2, or 3.

45. The compound of any one of claims 1~~,3, and 4~~ to 3, wherein R^2 is NH_2.

56. The compound of any one of claims 1 ~~and 3-5~~to 4, wherein R^6 is .

~~7~~6. The compound of any one of claims 1 ~~and 3-6~~to 5, wherein R^{11} is H or methyl.

~~8~~7. The compound of any one of claims 1 ~~and 3-7~~to 6, wherein R^7 is phenyl, alkyl, or cycloalkyl, each of which is optionally substituted with one or more R^4.

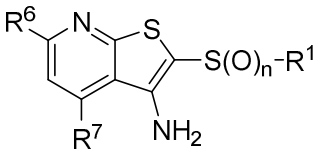
89. The compound of any one of claims 1 ~~and 3-8~~to 7, wherein R^7 is a linear or branched, non-cyclic C_1-C_6 alkyl.

910. The compound of any one of claims 1 ~~and 3-9~~to 8, wherein R^7 is methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *s*-butyl, or *t*-butyl.

~~11~~10. The compound of any one of claims 1 ~~and 3-10~~to 9, wherein X is CH.

~~12~~11. The compound of any one of claims 1 ~~and 3-11~~to 10, wherein n is 1.

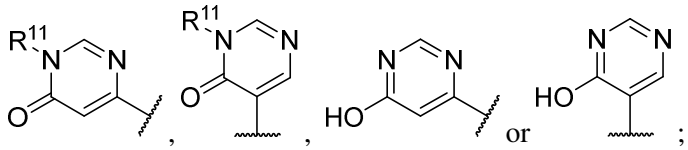
~~13~~12. A compound of formula (II):



(II)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or -(C_1-C_3 alkylene)-(C_1-C_3 alkoxy);

R^6 is 

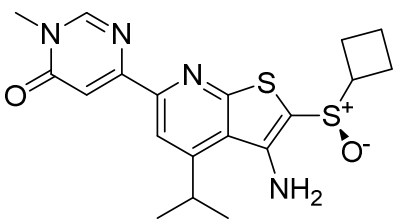
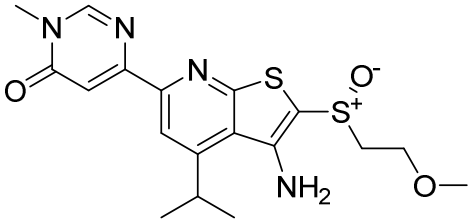
;

R^7 is a linear or branched, non-cyclic C_1-C_6 alkyl;

R^{11} is H or C_1-C_6 alkyl; and

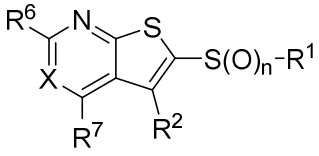
n is 0, 1, or 2.

~~14~~13. The compound of claim 1 or ~~13~~ 12 selected from:

or , or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

~~15~~14. A compound of formula (III):

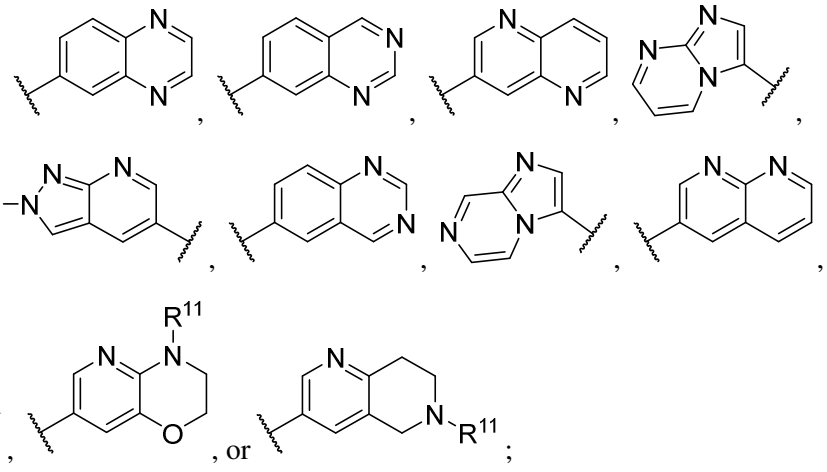


(III)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is alkyl, haloalkyl, cycloalkyl, alkylene-cycloalkyl, alkylene-alkoxy, heterocyclyl, or alkylene-heterocyclyl;

R^2 is $–NH_2$, CN, or $–NHC(O)(C_1\text{-}C_6$ alkyl);

R^6 is 

, or
;

R^7 is alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl,

-C(O)O-alkyl, or -C(O)NR^5-alkyl, each of which is optionally substituted with one or more R^4;

R^4 is oxo, halogen, -CN, -$N(R^5)_2$, -OH, -O-alkylene-OH, -$S(O)_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, -alkylene-O-alkyl, alkoxy, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8, wherein when R^4 is oxo and R^7 is aryl or heteroaryl, oxo does not violate the valency of the aryl or the heteroaryl;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -C(O)O-alkyl, -alkylene-COOH, or -$S(O)_m$-alkyl;

R^8 is halogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy;

R^9 is H or C_1-C_6 alkyl;

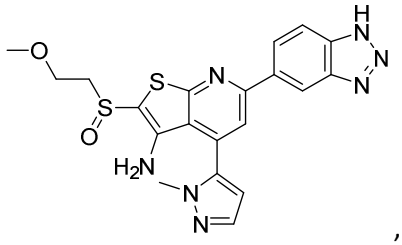
R^{11} is H or C_1-C_6 alkyl;

X is N or CH;

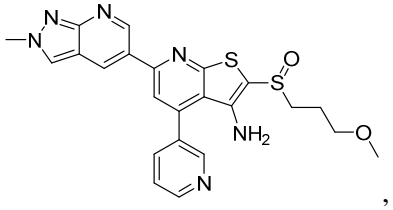
m is 0, 1, or 2; and

n is 0, 1, or 2.

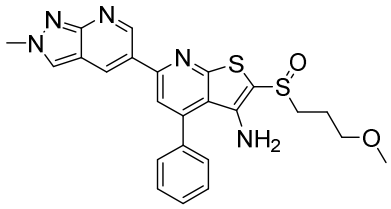
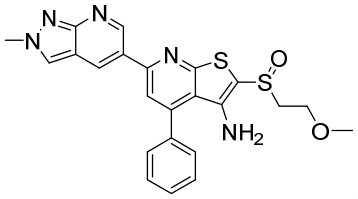
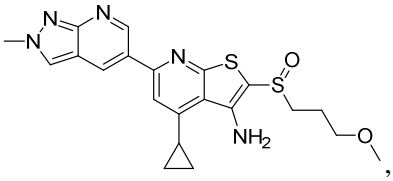
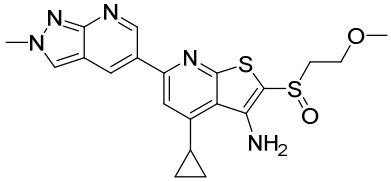
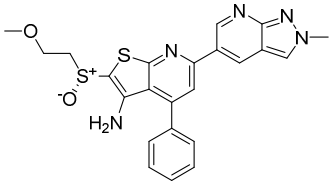
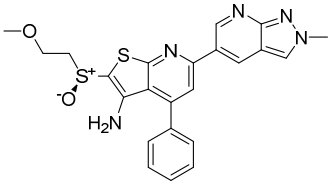
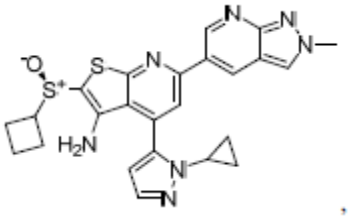
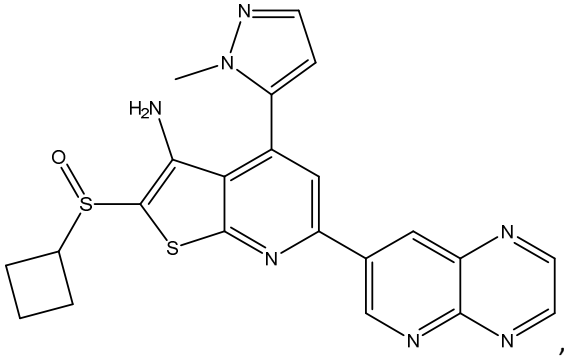
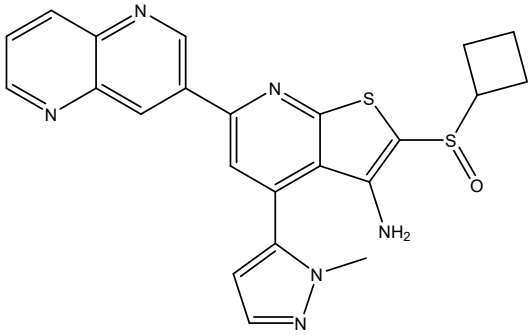
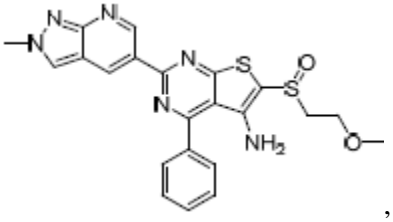
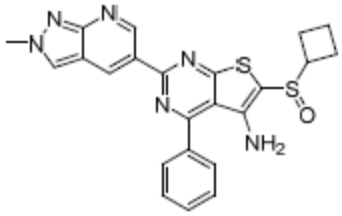
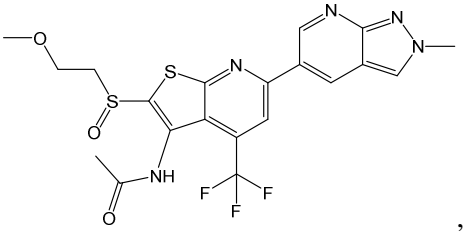
~~16~~15. The compound of claim ~~15~~14, wherein the compound is not:

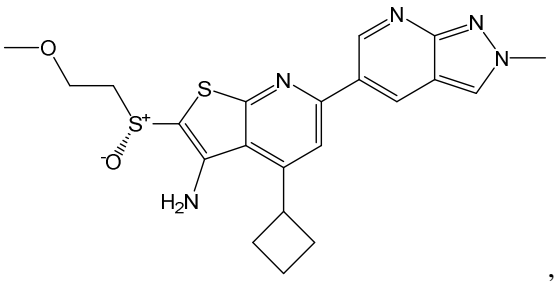
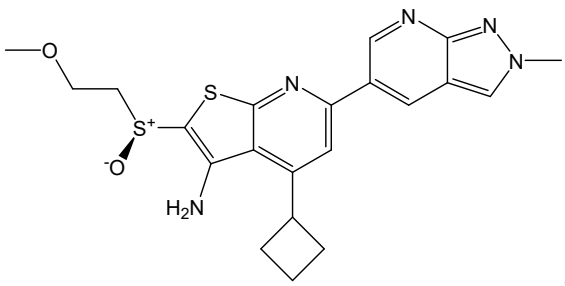
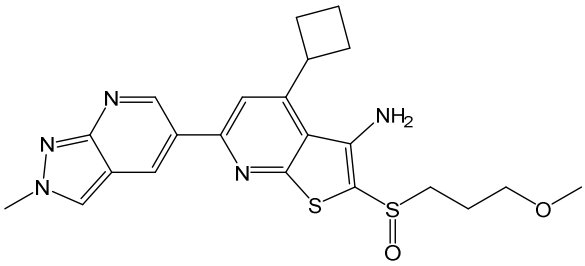
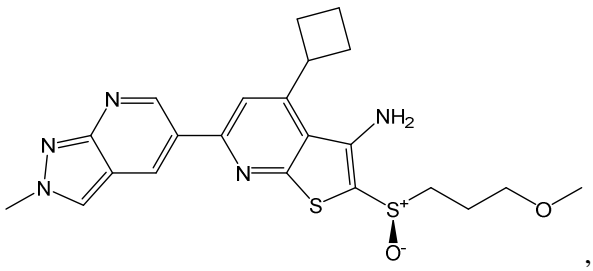
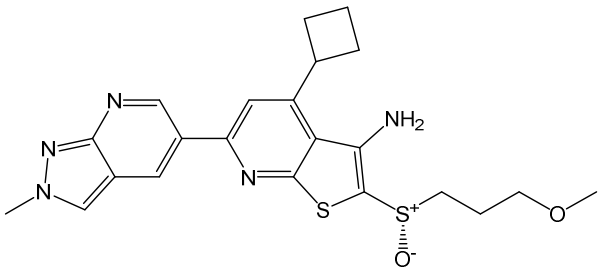
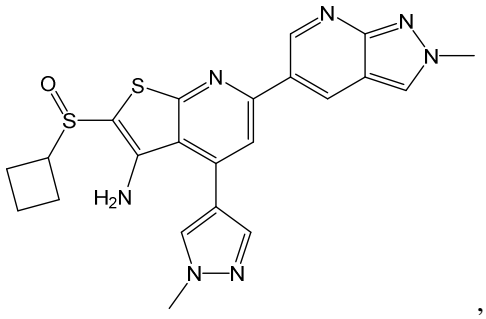
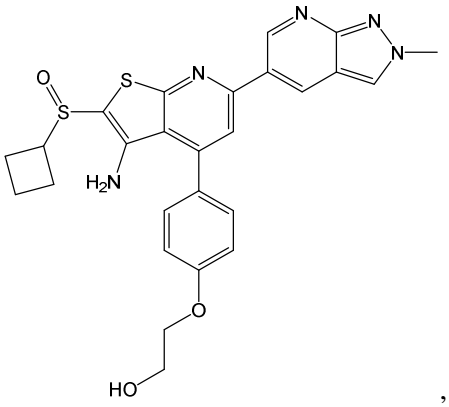
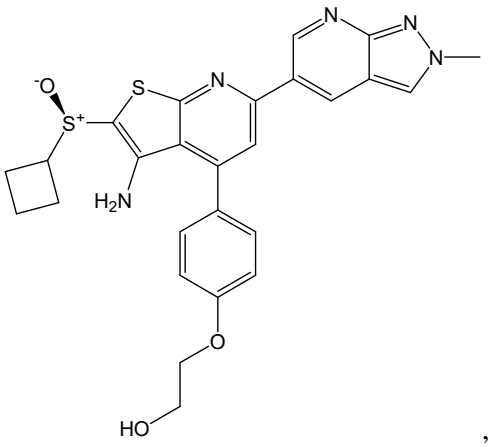


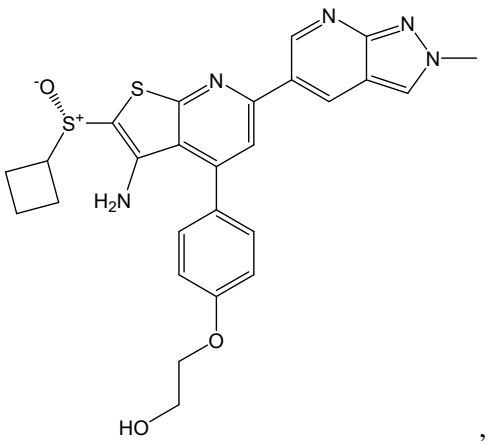
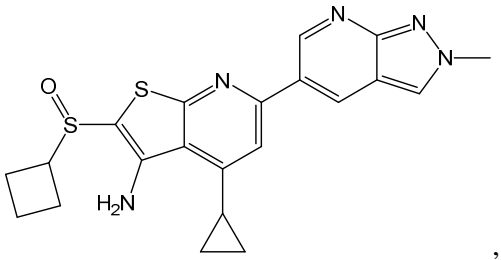
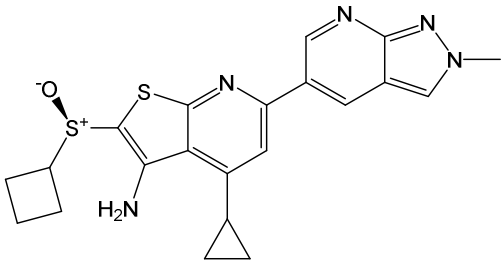
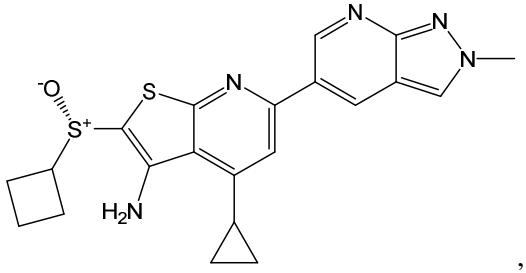
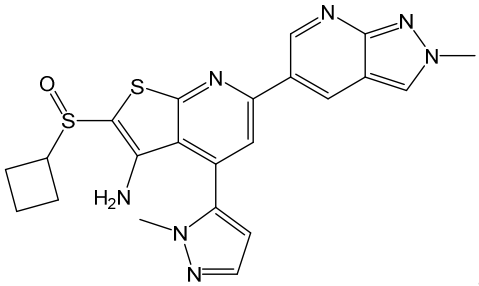
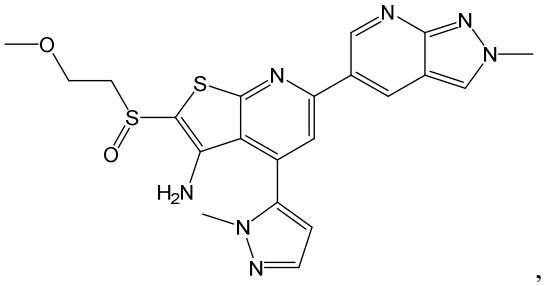
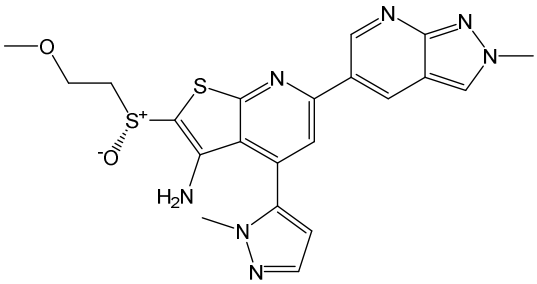
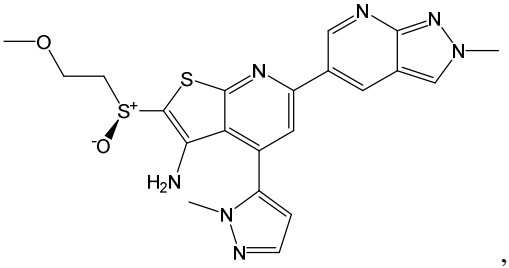
,

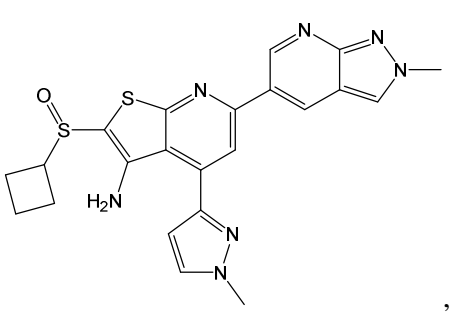
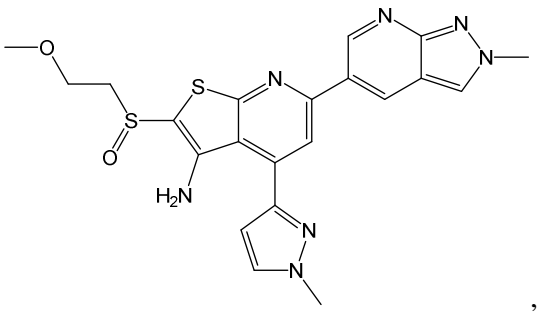
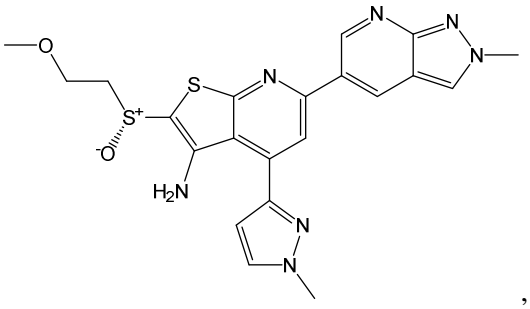
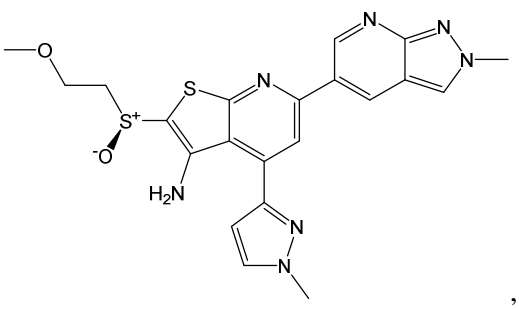
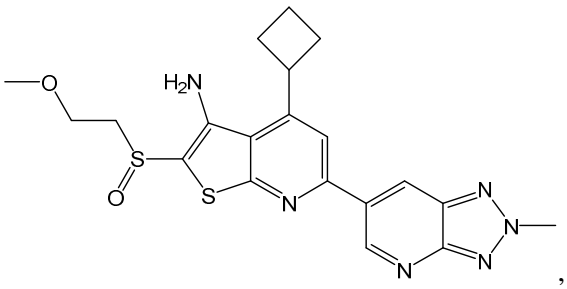
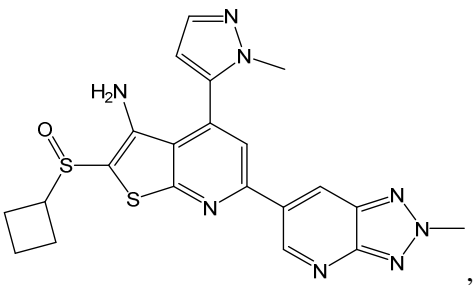
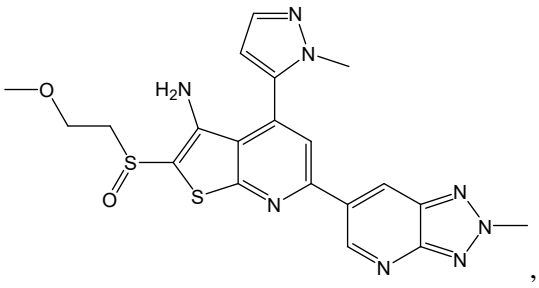
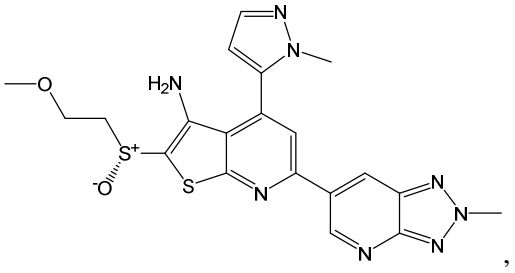
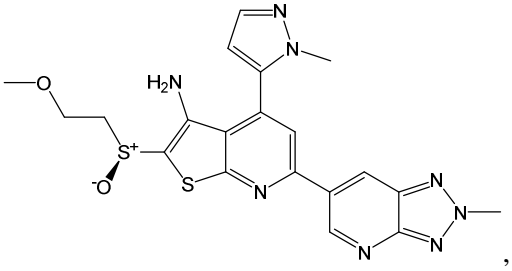
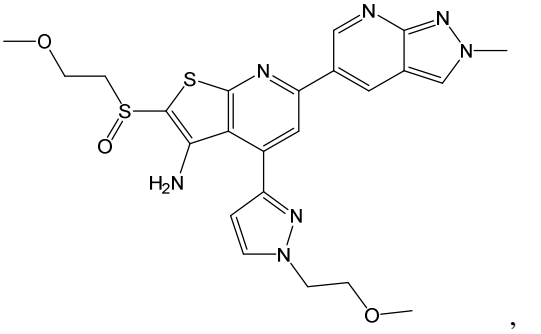


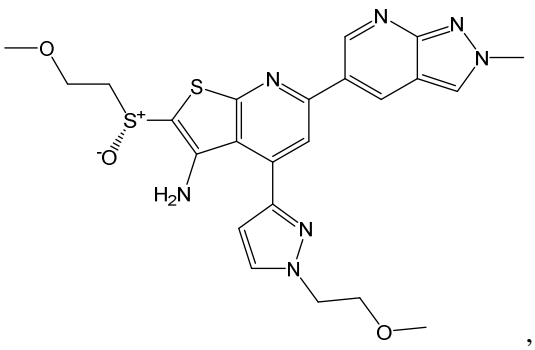
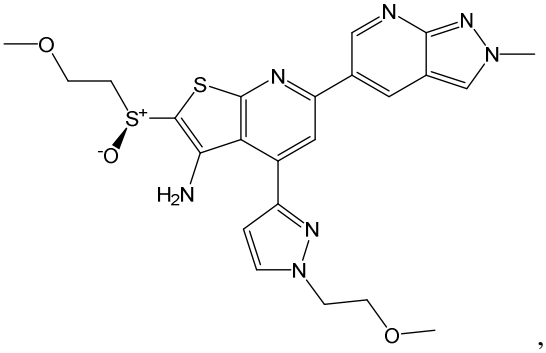
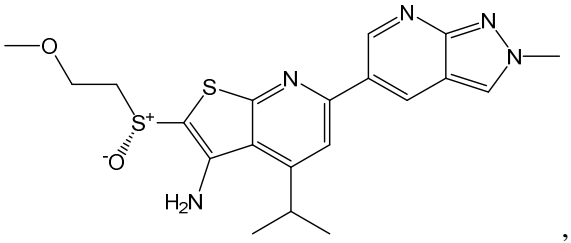
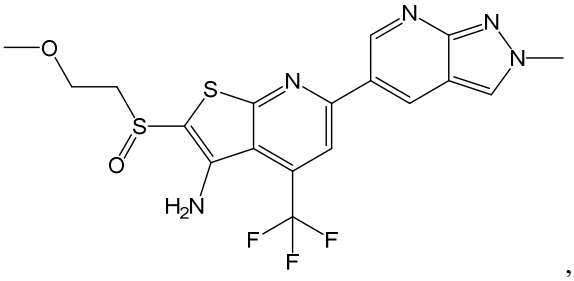
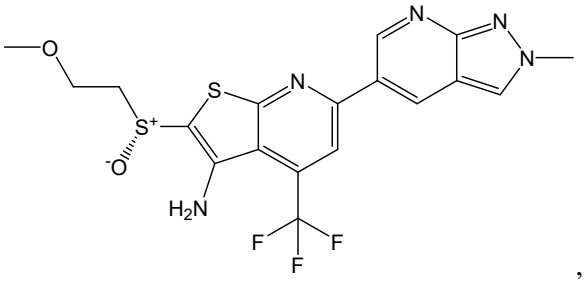
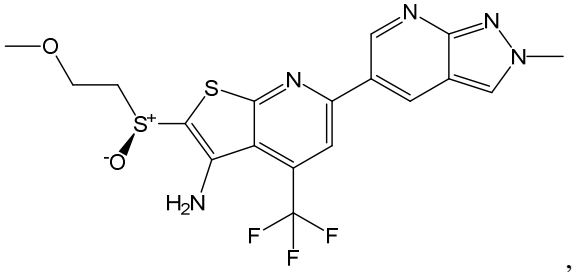
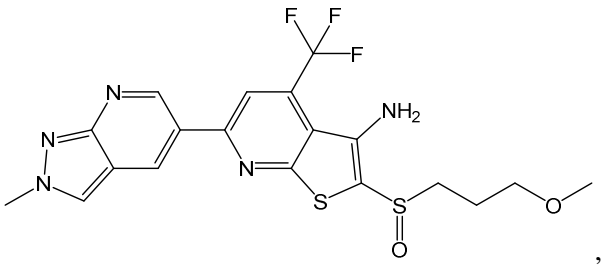
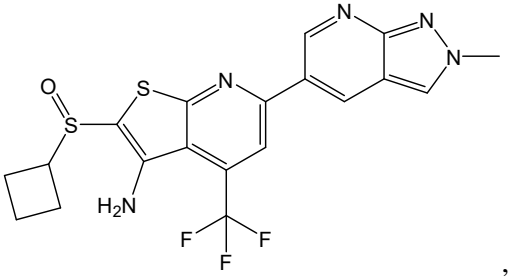
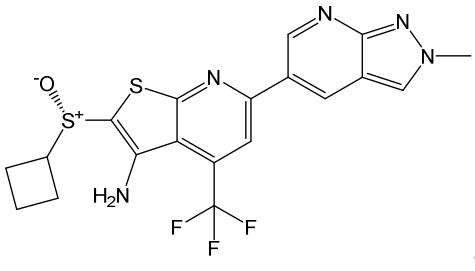
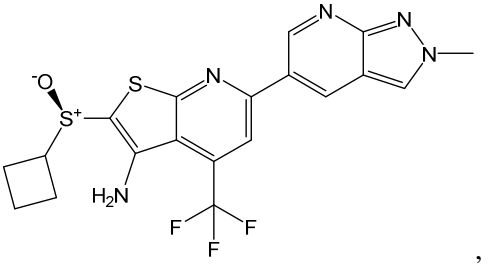
,

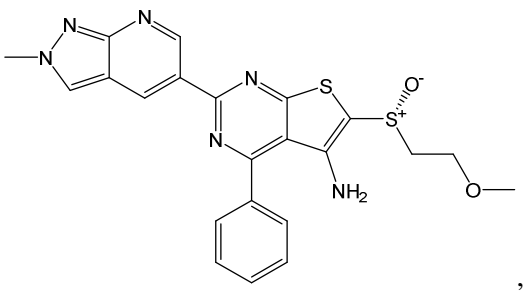
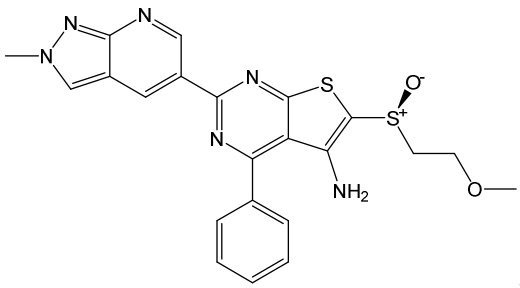
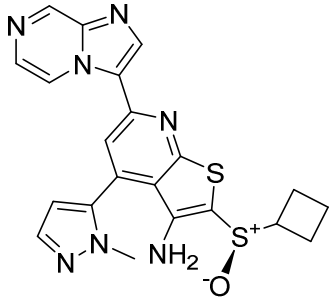

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,


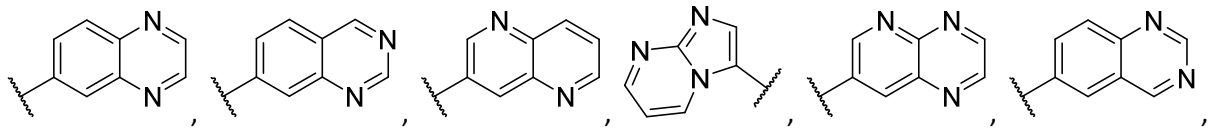


, and

.

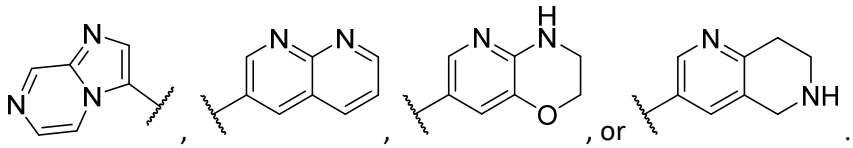
~~17~~16. The compound of claim ~~15~~14, wherein R^1 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or -(C_1-C_3 alkylene)-(C_1-C_3 alkoxy).

~~18~~17. The compound of claim ~~15 or 17~~14 or 16, wherein R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -$(CH_2)_p$-cyclopropyl, -$(CH_2)_p$-cyclobutyl, -$(CH_2)_p$-cyclopentyl, -$(CH_2)_p$-cyclohexyl, or -$(CH_2)_p$-OCH_3; wherein p is 1, 2, or 3.

~~19~~18. The compound of any one of claims ~~15~~14, ~~17~~ 16 and ~~18~~17, wherein R^2 is NH_2 or -CN.

~~20~~19. The compound of any one of claims ~~15~~ 14 and ~~17 19~~16-18, wherein R^6 is

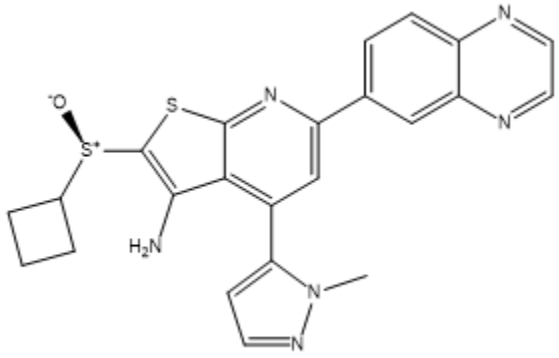


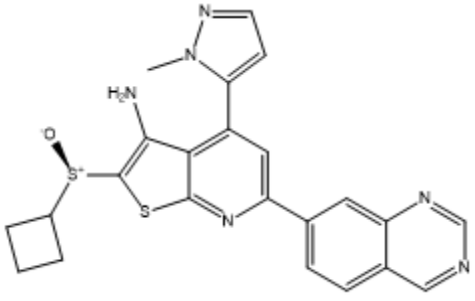


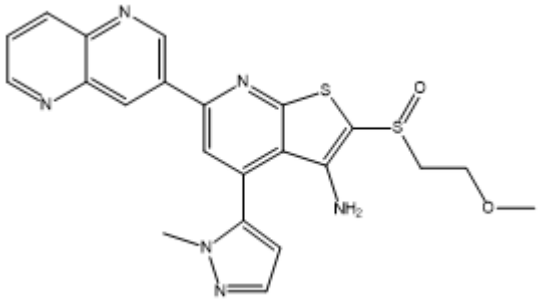
2120. The compound of any one of claims ~~15~~ 14 and ~~17 20~~16-19, wherein R^7 is alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl, each of which is optionally substituted with one or more R^4.

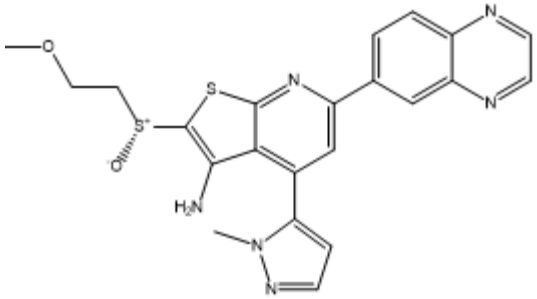
2221. The compound of any one of claims ~~15 and 17 21~~14 and 16-20, wherein n is 1.

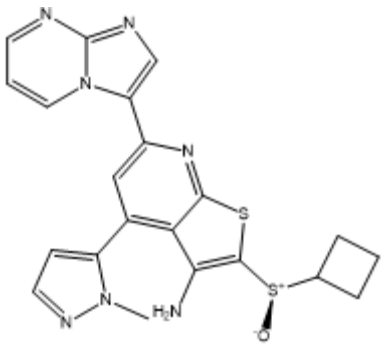
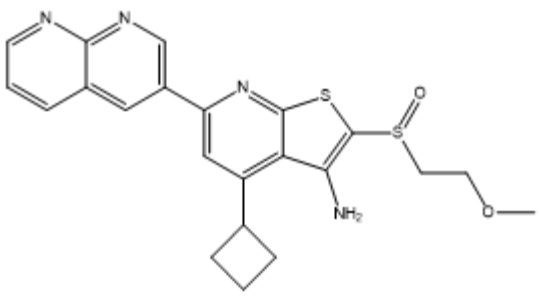
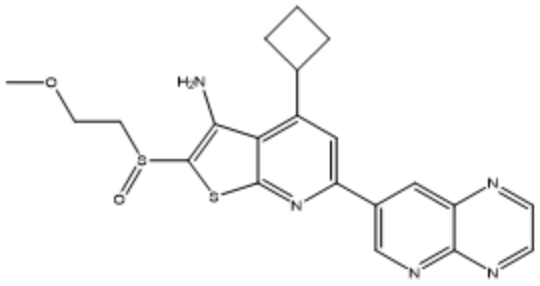
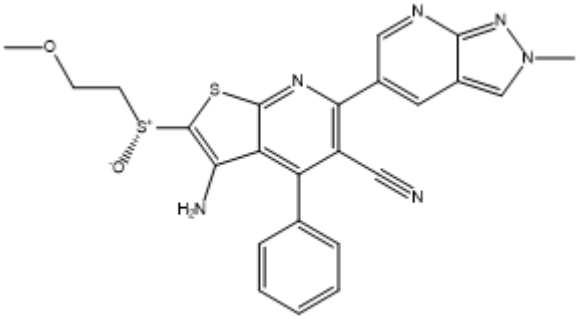
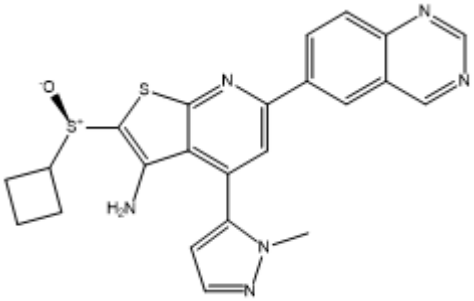
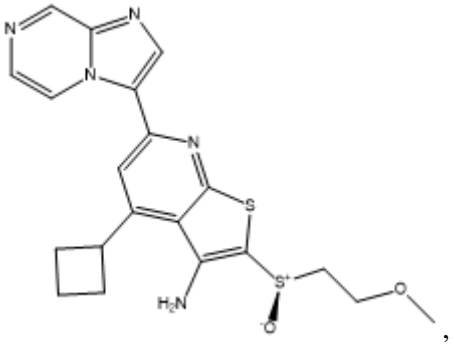
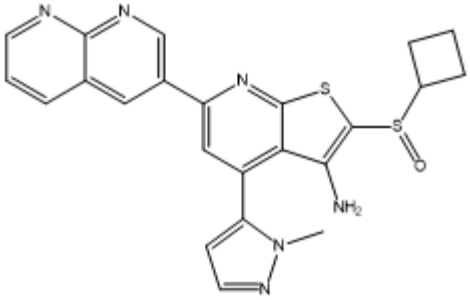
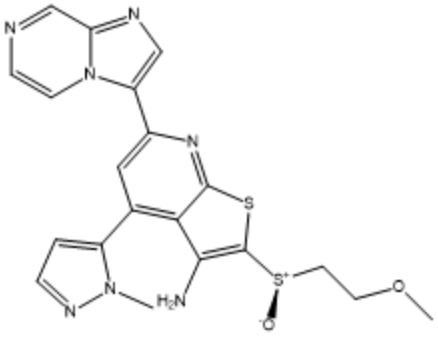
2322. The compound of claim ~~15~~ 14 selected from:

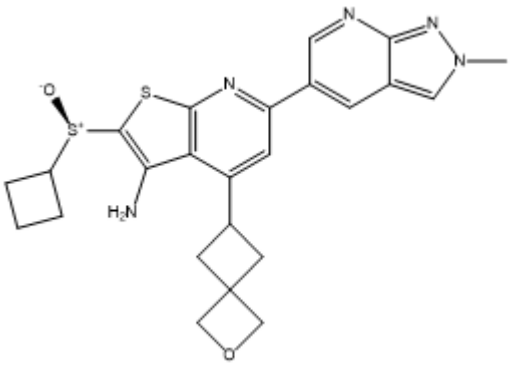
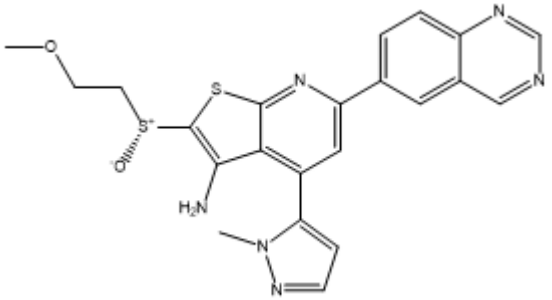
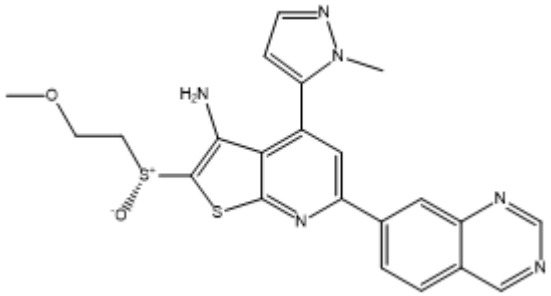
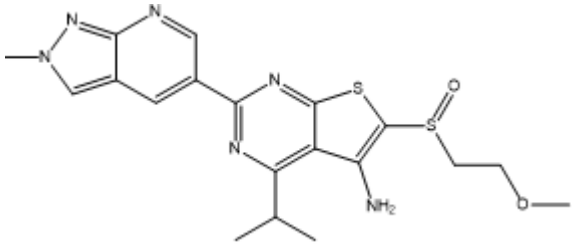
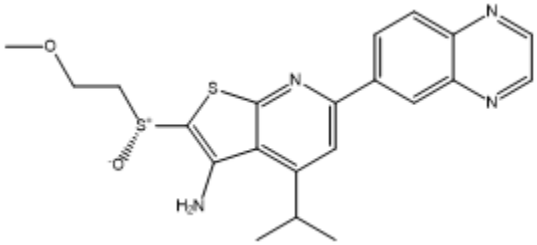
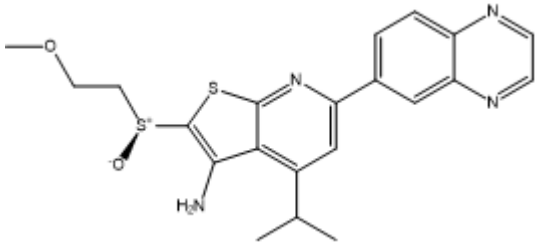
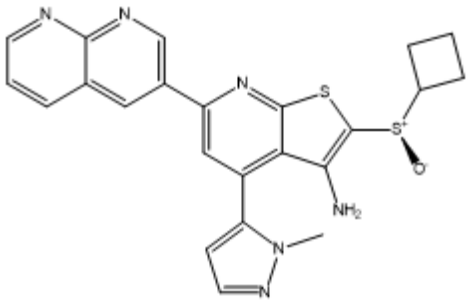
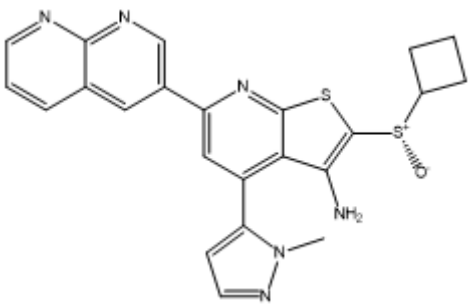
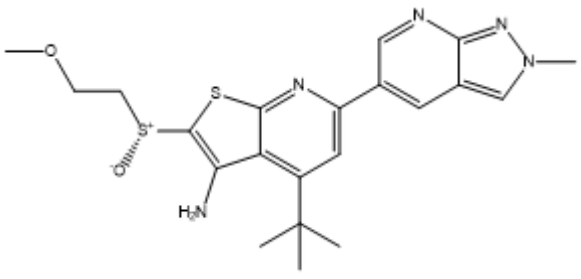
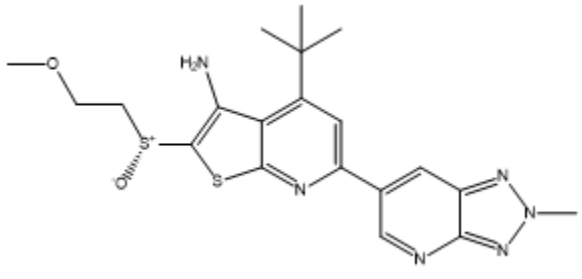


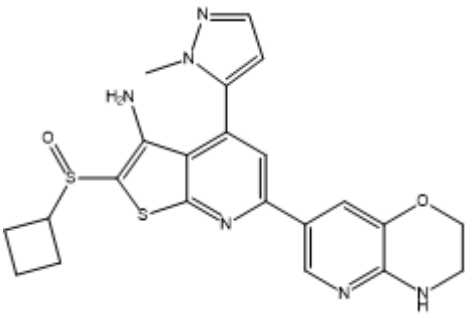
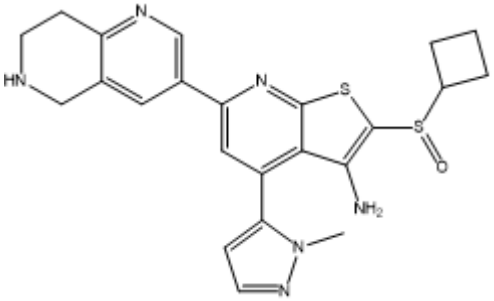
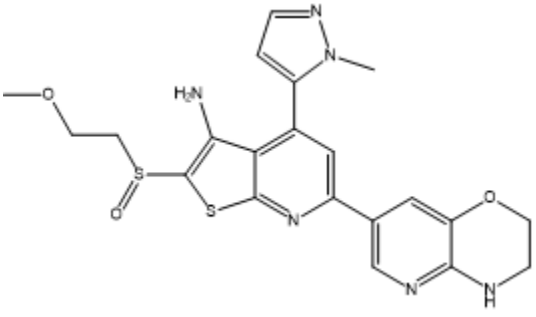




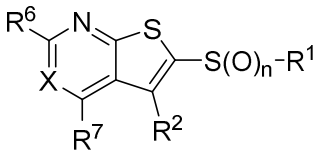



,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,


, 
, or 
, a pharmaceutically acceptable salt, tautomer, or solvate thereof.

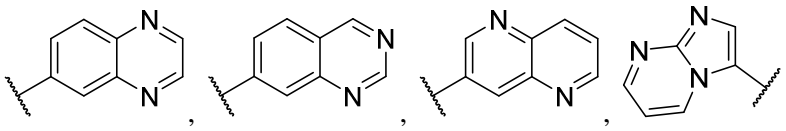
~~24~~23. A compound of formula (IV):

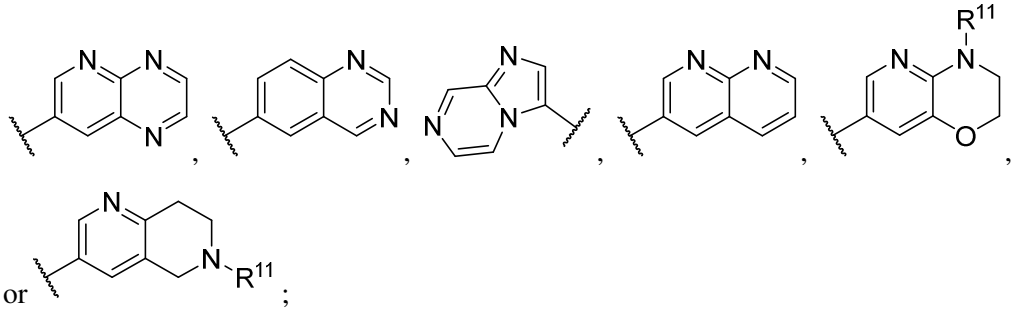

(IV)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is alkyl, haloalkyl, cycloalkyl, alkylene-cycloalkyl, alkylene-alkoxy, heterocyclyl, or alkylene-heterocyclyl;

R^2 is $–NH_2$, CN, or $–NHC(O)(C_1\text{-}C_6$ alkyl);

R^6 is 
,



R^7 is alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl,

-C(O)O-alkyl, or -C(O)NR^5-alkyl, each of which is optionally substituted with one or more R^4;

R^4 is oxo, halogen, -CN, -N(R^5)$_2$, -OH, -O-alkylene-OH, -S(O)$_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, -alkylene-O-alkyl, alkoxy, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8, wherein when R^4 is oxo and R^7 is aryl or heteroaryl, oxo does not violate the valency of the aryl or the heteroaryl;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-N(R^9)$_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -C(O)O-alkyl, -alkylene-COOH, or -S(O)$_m$-alkyl;

R^8 is halogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy;

R^9 is H or C_1-C_6 alkyl;

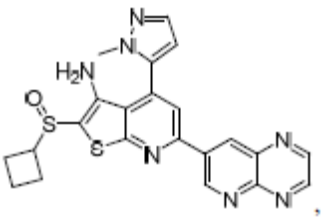
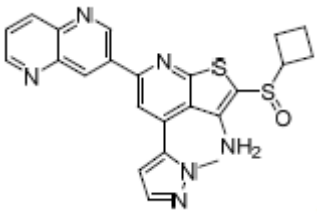
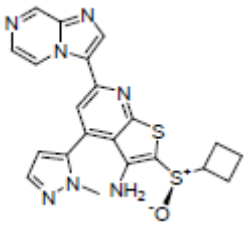
R^{11} is H or C_1-C_6 alkyl;

X is N or CH;

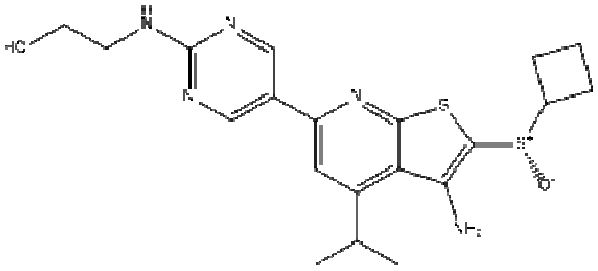
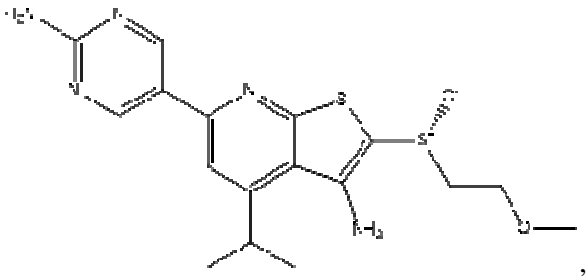
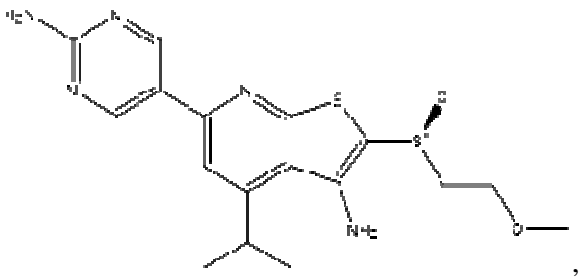
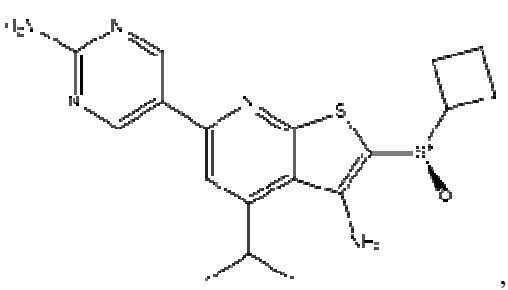
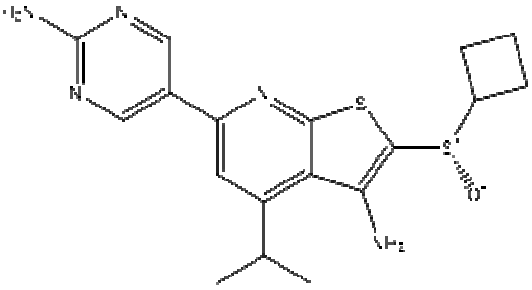
m is 0, 1, or 2; and

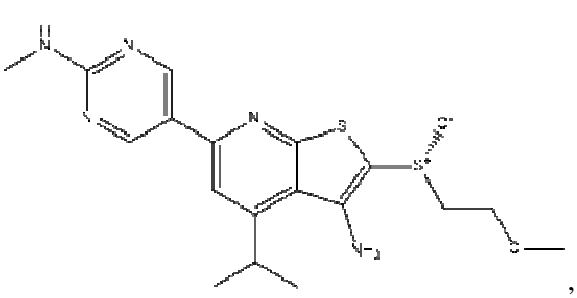
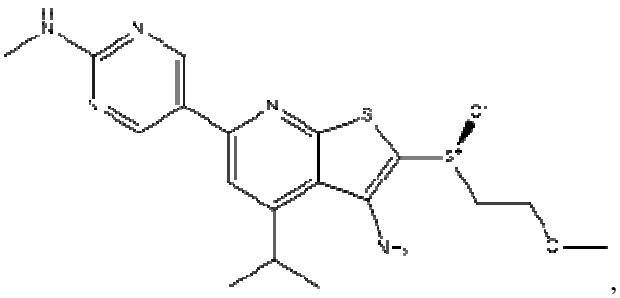
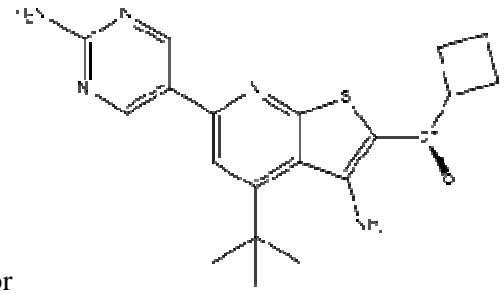
n is 0, 1, or 2;

wherein the compound is not:


,

, and

.

~~25~~24. A compound selected from:


,

,

,

,

,

, , 

or , or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

~~26~~25. A pharmaceutical composition comprising a compound of any one of claims 1 to ~~25~~ 24 and a pharmaceutically acceptable excipient or a carrier.

~~27~~26. ~~Use of a~~A compound of any one of claims 1 to ~~25~~ 24 as a short chain dehydrogenase inhibitor for inhibiting the activity of a short chain dehydrogenase enzyme.

~~28~~27. ~~Use of a~~ A compound of any one of claims 1 to ~~25~~ 24 as a 15-PGDH inhibitor for inhibiting the activity of a 15-PGDH enzyme.

~~29~~28. Use of the compound of any one of claims 1 to 24 in the manufacture of a medicament for inhibiting the activity of a short chain dehydrogenase enzyme~~The use of claims 27 or 28~~, wherein:

the compound inhibits the enzymatic activity of recombinant 15-PGDH at an IC_{50} of less than 1 µM, or preferably at an IC_{50} of less than 250 nM, or more preferably at an IC_{50} of less than 50 nM, or

more preferably at an IC_{50} of less than 10 nM, or more preferably at an IC_{50} of less than 5 nM at a recombinant 15-PGDH concentration of about 5 nM to about 10 nM; .

30. The use of claims 27 or 28, wherein

the compound is to be administered to a tissue of a subject at an amount effective to increase prostaglandin levels in the tissue;.

31. The use of claims 27 or 28, wherein the compound is provided in a topical composition; .

32. The use of claims 27 or 28, wherein the compound is to be applied to skin of a subject to promote and/or stimulate pigmentation of the skin and/or hair growth and/or inhibiting hair loss, and/or treat skin damage or inflammation.;

33. The use of claims 27 or 28, wherein the compound is to be administered to a subject to promote wound healing, tissue repair, and/or tissue regeneration; .

34. The use of claims 27 or 28, wherein the compound is to be administered to a subject to treat at least one of oral ulcers, gum disease, colitis, ulcerative colitis, gastrointestinal ulcers, inflammatory bowel disease, vascular insufficiency, Raynaud's disease, Buerger's disease, diabetic neuropathy, pulmonary artery hypertension, cardiovascular disease, and renal disease.;

35. The use of claims 27 or 28, wherein the compound is to be administered to a subject in combination with a prostanoid agonist for the purpose of enhancing the therapeutic effect of the agonist in prostaglandin responsive conditions.;

36. The use of claims 27 or 28, wherein the compound is to be administered to tissue of the subject to increase tissue stem cells; .

~~37. The use of claims 27 or 28, wherein~~ the compound is to be administered to a tissue graft donor, bone marrow graft donor, and/or a hematopoietic stem cell donor to increase the fitness of a donor tissue graft, a donor bone marrow graft, and/or a donor hematopoietic stem cell graft~~.~~;

~~38. The use of claims 27 or 28, wherein~~ the compound is to be administered to bone marrow of a subject to increase stem cells in the subject;~~.~~

~~39. The use of claims 27 or 28, wherein~~ the compound is to be administered to bone marrow of a subject to increase the fitness of the marrow as a donor graft~~.~~;

~~40. The use of claims 27 or 28, wherein~~ the compound is to be administered to a preparation of hematopoietic stem cells of a subject to increase the fitness of the stem cell preparation as a donor graft; ~~.~~

~~41. The use of claims 27 or 28, wherein~~ the compound is to be administered to a preparation of peripheral blood hematopoietic stem cells of a subject to increase the fitness of the stem cell preparation as a donor graft; ~~.~~

~~42. The use of claims 27 or 28, wherein~~ the compound is to be administered to a preparation of umbilical cord blood stem cells to increase the fitness of the stem cell preparation as a donor graft; ~~.~~

~~43. The use of claims 27 or 28, wherein~~ the compound is to be administered to a preparation of umbilical cord blood stem cells to decrease the number of units of umbilical cord blood required for transplantation; ~~.~~

~~44. The use of claims 27 or 28, wherein~~ the compound is to be administered to a subject to mitigate tissue graft rejection;~~.~~

~~45. The use of claims 27 or 28, wherein~~ the compound is to be administered to a subject to enhance tissue and/or bone marrow graft engraftment; ~~.~~

~~46. The use of claims 27 or 28, wherein~~ the compound is to be administered to a subject to enhance bone marrow graft engraftment, following treatment of the subject or the marrow of the subject with radiation therapy, chemotherapy, or immunosuppressive therapy~~.~~;

~~47. The use of claims 27 or 28, wherein~~ the compound is to be administered to a subject to enhance engraftment of a progenitor stem cell graft, hematopoietic stem cell graft, or an umbilical cord blood stem cell graft;~~.~~

~~48. The use of claims 27 or 28, wherein~~ the compound is to be administered to a subject to enhance engraftment of a hematopoietic stem cell graft, or an umbilical cord stem cell graft, following treatment of the subject or the marrow of the subject with radiation therapy, chemotherapy, or immunosuppressive therapy~~.~~;

~~49. The use of claims 27 or 28, wherein~~ the compound is to be administered to a subject in order to decrease the number of units of umbilical cord blood required for transplantation into the subject~~.~~;

~~50. The use of claims 27 or 28, wherein~~ the compound is to be administered to a recipient of a tissue graft transplant, bone marrow transplant, and/or hematopoietic stem cell transplant, or of an umbilical cord stem cell transplant, in order to decrease the administration of other treatments or growth

factors~~.~~;

~~51. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject or to a tissue graft of a subject to mitigate graft rejection;~~.~~

~~52. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject or to a tissue graft of a subject to enhance graft engraftment;~~.~~

~~53. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject or to a tissue graft of a subject to enhance graft engraftment following treatment of the subject or the marrow of the subject with radiation therapy, chemotherapy, or immunosuppressive therapy;~~.~~

~~54. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject or to the bone marrow of a subject to confer resistance to toxic or lethal effects of exposure to radiation~~.~~;

~~55. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject or to the bone marrow of a subject to confer resistance to the toxic effect of Cytoxan, the toxic effect of fludarabine, the toxic effect of chemotherapy, or the toxic effect of immunosuppressive therapy~~.~~;

~~56. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject or to the bone marrow of a subject to decrease infection;~~.~~

~~57. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase neutrophil counts following a hematopoetic cell transplant with bone marrow, hematopoetic stem cells, or umbilical cord blood;~~.~~

~~58. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase neutrophil counts in a subject with neutropia following chemotherapy administration or radiation therapy~~.~~;

~~59. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase neutrophil counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, neutropenia due to other bone marrow diseases, drug induced neutropenia, autoimmune neutropenia, idiopathic neutropenia, or neutropenia following viral infections~~.~~;

~~60. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase neutrophil counts in a subject with neutropia~~.~~;

~~61. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase platelet counts following a hematopoetic cell transplant with bone marrow, hematopoetic stem cells, or umbilical cord blood~~.~~;

~~62. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase platelet counts in a subject with thrombocytopenia following chemotherapy administration or radiation therapy~~.~~;

~~63. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase platelet counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, thrombocytopenia due to other bone marrow diseases, drug induced thrombocytopenia, autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura, idiopathic thrombocytopenia, or thrombocytopenia following viral infections~~.~~;

~~64. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase platelet counts in a subject with thrombocytopenia~~.~~;

~~65. The use of claims of 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase red blood cell counts, or hematocrit, or hemoglobin level, following a hematopoetic cell transplant with bone marrow, hematopoetic stem cells, or umbilical cord blood~~.~~;

~~66. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase red blood cell counts, or hematocrit, or hemoglobin level in a subject with anemia

following chemotherapy administration or radiation therapy~~.~~;

~~67. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase red blood cell counts, or hematocrit, or hemoglobin level counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, anemia due to other disorder of bone marrow, drug induced anemia, immune mediated anemias, anemia of chronic disease, anemia following viral infections, or anemia of unknown cause~~.~~;

~~68. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase red blood cell counts, or hematocrit, or hemoglobin level in a subject with anemia~~.~~;

~~69. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase bone marrow stem cells, following a hematopoetic cell transplant with bone marrow, hematopoetic stem cells, or umbilical cord blood~~.~~;

~~70. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase bone marrow stem cells in a subject following chemotherapy administration or radiation therapy~~.~~;

~~71. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase bone marrow stem cells in a subject with aplastic anemia, myelodysplasia, myelofibrosis, other disorder of bone marrow, drug induced cytopenias, immune cytopenias, cytopenias following viral infections, or cytopenias~~.~~;

~~72. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase responsiveness to cytokines in the presence of cytopenias, with cytopenias including any of: neutropenia, thrombocytopenia, lymphocytopenia and anemia; and with cytokines having increased responsiveness potentiated by the 15-PGDH inhibitor including any of: G-CSF, GM-CSF, EPO, IL-3, IL-6, TPO, TPO-RA (thrombopoietin receptor agonist), and SCF~~.~~;

~~73. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject or the bone marrow of a subject to decrease pulmonary toxicity from radiation~~.~~;

~~74. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase bone density, treat osteoporosis, promote healing of fractures, or promote healing after bone surgery or joint replacement~~.~~;

~~75. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to promote healing of bone to bone implants, bone to artificial implants, dental implants, and bone grafts~~.~~;

~~76. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject or to the intestine of a subject to increase stem cells in the intestine~~.~~;

~~77. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject or to intestine of a subject to increase stem cells in the intestine and confer resistance to toxic or lethal effects of exposure to radiation or the toxic, lethal, or mucositis effects resultant from treatment with chemotherapy~~.~~;

~~78. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject or to the intestines of a subject to confer resistance to toxic or lethal effects of exposure to radiation or the toxic, lethal, or mucositis effects resultant from treatment with chemotherapy~~.~~;

~~79. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject or to intestine of a subject as a treatment for colitis, ulcerative colitis, or inflammatory bowel disease~~.~~;

~~80. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to increase liver regeneration following liver surgery, following live liver donation, following liver transplantation, or following liver injury by toxins~~.~~;

~~81. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to promote recovery from or resistance to liver toxins, including acetaminophen and related compounds~~.~~;

~~82. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to a subject to treat erectile dysfunction~~.~~; or

~~83. The use of claims 27 or 28, wherein~~ the compound ~~is administered~~is to be administered to inhibit at least one of the growth, proliferation, or metastasis of 15-PGDH expressing cancers.

~~84. A method of treating a subject in need of cell therapy comprising administering to the subject a therapeutically effective amount of a preparation comprising human hematopoietic stem cell administered a compound of any one of claims 1 to 25 and/or a therapeutic composition comprising human hematopoietic stem cells and a compound of any one of claims 1 to 25.~~

~~85. The method of claim 84, further comprising administering of any one of claims 1 to 71 to a subject who has received human hematopoietic stem cells and/or has received the preparation and/or the therapeutic composition.~~

~~86. The method of claim 84, wherein the subject has acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), juvenile myelomonocytic leukemia, Hodgkin`s lymphoma, non-Hodgkin`s lymphoma, multiple myeloma, severe aplastic anemia, Fanconi`s anemia, paroxysmal nocturnal hemoglobinuria (PNH), pure red cell aplasia, amegakaryocytosis/congenital thrombocytopenia, severe combined immunodeficiency syndrome (SCID), Wiskott-Aldrich syndrome, beta-thalassemia major, sickle cell disease, Hurler`s syndrome, adrenoleukodystrophy, metachromatic leukodystrophy, myelodysplasia, refractory anemia, chronic myelomonocytic leukemia, agnogenic myeloid metaplasia, familial erythrophagocytic lymphohistiocytosis, solid tumors, chronic granulomatous disease, mucopolysaccharidoses, or Diamond Blackfan anemia.~~

~~87. A method of treating a subject having at least one symptom associated with an ischemic~~

~~tissue or a tissue damaged by ischemia comprising administering to the subject a therapeutically effective amount of a preparation comprising human hematopoietic stem cell administered a compound of any one of claims 1 to 25 and/or a therapeutic composition comprising human hematopoietic stem cells and a compound of any one of claims 1 to 25.~~

~~88. The method of claim 87, wherein the ischemia is associated with at least one of acute coronary syndrome, acute lung injury (ALI), acute myocardial infarction (AMI), acute respiratory distress syndrome (ARDS), arterial occlusive disease, arteriosclerosis, articular cartilage defect, aseptic systemic inflammation, atherosclerotic cardiovascular disease, autoimmune disease, bone fracture, bone fracture, brain edema, brain hypoperfusion, Buerger`s disease, burns, cancer, cardiovascular disease, cartilage damage, cerebral infarct, cerebral ischemia, cerebral stroke, cerebrovascular disease, chemotherapy-induced neuropathy, chronic infection, chronic mesenteric ischemia, claudication, congestive heart failure, connective tissue damage, contusion, coronary artery disease (CAD), critical limb ischemia (CLI), Crohn`s disease, deep vein thrombosis, deep wound, delayed ulcer healing, delayed wound healing, diabetes (type I and type II), diabetic neuropathy, diabetes induced ischemia, disseminated intravascular coagulation (DIC), embolic brain ischemia, graft-versus-host disease, hereditary hemorrhagic telengiectasiaischemic vascular disease, hyperoxic injury, hypoxia, inflammation, inflammatory bowel disease, inflammatory disease, injured tendons, intermittent claudication, intestinal ischemia, ischemia, ischemic brain disease, ischemic heart disease, ischemic peripheral vascular disease, ischemic placenta, ischemic renal disease, ischemic vascular disease, ischemic-reperfusion injury, laceration, left main coronary artery disease, limb ischemia, lower extremity ischemia, myocardial infarction, myocardial ischemia, organ ischemia, osteoarthritis, osteoporosis, osteosarcoma, Parkinson`s disease, peripheral arterial disease (PAD), peripheral artery disease, peripheral ischemia, peripheral neuropathy, peripheral vascular disease, pre-cancer, pulmonary edema, pulmonary embolism, remodeling disorder, renal ischemia, retinal ischemia, retinopathy, sepsis, skin ulcers, solid organ transplantation, spinal cord injury, stroke, subchondral bone cyst, thrombosis, thrombotic brain ischemia, tissue ischemia, transient isc hemic attack (TIA), traumatic brain injury, ulcerative colitis, vascular disease of the kidney, vascular inflammatory conditions, von Hippel-Lindau syndrome, and wounds to tissues or organs.~~

~~89. A method of increasing neutrophils in a subject in need thereof, the method comprising~~

~~administering to the subject a compound of any one of claims 1 to 25.~~

~~90. The method of claim 89, further comprising administering a hematopoietic cytokine in combination with the compound.~~

~~91. A method increasing numbers of and/or of mobilizing peripheral blood hematopoietic stem cells in a subject in need thereof, the method comprising administering to the subject a compound of any one of claims 1 to 25.~~

~~92. The method of claim 91, further comprising administering G-CSF in combination with the compound.~~

~~93. The method of claim 92, further comprising administering a hematopoietic cytokine in combination with the compound.~~

~~94. The method of claim 93, further comprising administering Plerixafor in combination with the compound.~~

~~95. The method of any of claims 91 to 94, wherein increasing numbers of and/or of mobilizing peripheral blood hematopoietic stem cells is used in hematopoietic stem cell transplantation.~~

~~96. A method of increasing numbers of hematopoietic stem cells in blood or bone marrow, the method comprising: administering to blood or bone marrow of the subject a compound of any one of claims 1 to 25.~~

~~97. The method of claim 96, further comprising administering G-CSF in combination with the compound.~~

~~98. The method of claim 96, further comprising administering a hematopoietic cytokine in combination with the compound.~~

~~99. The method of claim 96, further comprising administering Plerixafor in combination with the compound.~~

~~100. A method of treating or preventing a fibrotic disease, disorder or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 25.~~

~~101. The method of claim 100, wherein the fibrotic disease, disorder or condition is characterized, in whole or in part, by the excess production of fibrous material, including excess production of fibrotic material within the extracellular matrix, or the replacement of normal tissue elements by abnormal, non-functional, and/or excessive accumulation of matrix-associated components.~~

~~102. The method of claim 100, wherein the fibrotic disease, disorder, or condition is selected from the group consisting of systemic sclerosis, multifocal fibrosclerosis, nephrogenic systemic fibrosis, scleroderma, sclerodermatous graft-vs-host disease, kidney fibrosis, glomerular sclerosis, renal tubulointerstitial fibrosis, progressive renal disease or diabetic nephropathy, cardiac fibrosis, pulomanry fibrosis, glomerulosclerosis pulmonary fibrosis, idiopathic pulmonary fibrosis, silicosis, asbestosis, interstitial lung disease, interstitial fibrotic lung disease, chemotherapy/radiation induced pulmonary fibrosis, oral fibrosis, endomyocardial fibrosis, deltoid fibrosis, pancreatitis, inflammatory bowel disease, Crohn's disease, nodular fascilitis, eosinophilic fasciitis, general fibrosis syndrome characterized by replacement of normal muscle tissue by fibrous tissue in varying degrees, retroperitoneal fibrosis, liver~~

~~fibrosis, liver cirrhosis, chronic renal failure; myelofibrosis, bone marrow fibrosis, drug induced ergotism, glioblastoma in Li-Fraumeni syndrome, sporadic glioblastoma, myleoid leukemia, acute myelogenous leukemia, myelodysplastic syndrome, myeloproferative syndrome, gynecological cancer, Kaposi's sarcoma, Hansen's disease, collagenous colitis, acute fibrosis, and organ specific fibrosis.~~

~~103. The method of claim 100, wherein the fibrotic disease, disorder, or condition comprises lung fibrosis.~~

~~104. The method of claim 103, wherein the lung fibrosis is selected from the group consisting of pulmonary fibrosis, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), asthma, idiopathic pulmonary fibrosis, sarcoidosis, cystic fibrosis, familial pulmonary fibrosis, silicosis, asbestosis, coal worker's pneumoconiosis, carbon pneumoconiosis, hypersensitivity pneumonitides, pulmonary fibrosis caused by inhalation of inorganic dust, pulmonary fibrosis caused by an infectious agent, pulmonary fibrosis caused by inhalation of noxious gases, aerosols, chemical dusts, fumes or vapors, drug-induced interstitial lung disease, or pulmonary hypertension, and combinations there.~~

~~105. The method of claim 104, wherein the lung fibrosis is cystic fibrosis.~~

~~106. The method of claim 104, wherein the fibrotic disease, disorder or condition comprises kidney fibrosis.~~

~~107. The method of claim 104, wherein the fibrotic disease, disorder or condition comprises liver fibrosis.~~

~~108. The method of claim 107, wherein the liver fibrosis results from a chronic liver disease, viral induced hepatic cirrhosis, hepatitis B virus infection, hepatitis C virus infection, hepatitis D virus infection, schistosomiasis, primary biliary cirrhosis, alcoholic liver disease or non-alcoholic~~

steatohepatitis (NASH), NASH associated cirrhosis obesity, diabetes, protein malnutrition, coronary artery disease, auto-immune hepatitis, cystic fibrosis, alpha-1-antitrypsin deficiency, primary biliary cirrhosis, drug reaction and exposure to toxins, or combinations thereof.

109. The method of claim 100, wherein the fibrotic disease, disorder or condition comprises heart fibrosis.

110. The method of claim 100, wherein the fibrotic disease, disorder or condition is systemic sclerosis.

111. The method of claim 100, wherein the fibrotic disease, disorder or condition is caused by post-surgical adhesion formation.

112. The method of claim 100, wherein the compound is administered at amount effective to reduce or inhibit collagen deposition, inflammatory cytokine expression, and/or inflammatory cell infiltration in a tissue or organ of the subject being treated.

113. A method of treating intestinal, gastrointestinal, or bowel disorders in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 25 alone or in combination with a corticosteroid and/or a tumor necrosis factor α (TNFα) inhibitor.

114. The method of claim 113, wherein the disorder comprises at least one of oral ulcers, gum disease, gastritis, colitis, ulcerative colitis, gastric ulcers, inflammatory bowel disease, and Crohn's disease.

~~115. The method of claim 113, wherein the disease is inflammatory bowel disease.~~

~~116. The method of claim 113, wherein the corticosteroid induces 15-PGDH expression.~~

~~117. The method of claim 113, wherein the 15-PGDH inhibitor is effective to attenuate corticosteroid induced adverse and/or cytotoxic effects in a subject, or to increase therapeutic efficacy.~~

~~118. The method of claim 113, wherein the corticosteroid is selected from the group consisting of aclovate, alclometasone dipropionate, amcinafel, amcinafide, amcinonide, aristocort A, augmented betamethasone dipropionate, beclamethasone, beclopmethasone dipropionate, betamethasone, betamethasone benzoate, betamethasone 17-benzoate, betamethasone dipropionate, betamethasone sodium phosphate and acetate, betamethasone valerate, betamethasone 17-valerate, chloroprednisone, clobetasol propionate, clobetasone propionate, clocortelone, cordran, corticosterone, cortisol, cortisol acetate, cortisol cypionate, cortisol sodium phosphate, cortisol sodium succinate, cortisone, cortisone acetate, cortodoxone, cyclocort, deflazacort, defluprednate, descinolone, desonide, desowen, desoximetasone, desoxycorticosterone acetate, desoxycorticosterone pivalate, 11-desoxycortisol, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, dichlorisone, diflorasone diacetate, dihydroxycortisone, diprolen, diprolene, diprosone, esters of betamethasone, florone, flucetonide, flucloronide, flucortolone, fludrocortisone, fludrocortisone acetate, flumethalone, flumethasone, flumethasone pivalate, flunisolide, fluocinolone acetonide, fluocinolone acetonide acetate, fluocinonide, fluorametholone, fluorocortisone, fluperolone, fluprednisolone, flurandrenolide, fluroandrenolone acetonide, fluticasone propionate, fuprednisolone, halcinonide, halobetasol propionate, halog, hydrocortamate, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone valerate, hydrocortisone 17-valerate, kenalog, lidex, locold, locorten, maxiflor, medrysone, meprednisone, methylprednisolone, 6.alpha.-methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, methylprednisone, mometasone furoate, paramethasone, paramethasone acetate, prednidone, prednisone, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone sodium succinate, prednisolone tebutate, prednisone, psorcon, synalar, temovate, tetrahydrocortisol, topicort, topicort LP, triamcinolone, triamcinolone acetonide, triamcinolone diacetate,~~

triamcinolone hexacetonide, tridesilone, valisone, and westcort.

119. A method of treating intestinal, gastrointestinal, or bowel disorders in a subject in need thereof, the method comprising:

administering to the subject therapeutically effective amounts of a compound of any one of claims 1 to 25 and a corticosteroid.

120. The method of claim 119, wherein the disorder comprises at least one of oral ulcers, gum disease, gastritis, colitis, ulcerative colitis, gastric ulcers, inflammatory bowel disease, and Crohn's disease.

121. The method of claim 119, wherein the disorder comprises inflammation of the esophagus, inflammation of the glottis, inflammation of the epiglottis, inflammation of the tonsils, inflammation of the oropharynx, eosinophilic esophagitis, gastroesophageal reflux disease (GERD), non-erosive reflux disease (NERD), erosive esophagitis, Barrett's esophagus, eosinophilic gastroenteritis, hypereosinophilic syndrome, corrosive (caustic) chemical esophagitis, radiation-induced esophagitis, chemotherapy-induced esophagitis, transient drug-induced esophagitis, persistent drug-induced esophagitis, Crohn's disease of the esophagus, and pseudomembranous esophagitis.

122. A method of treating inflammation and/or reducing the activity of the immune system in a subject in need thereof, the method comprising:

administering to the subject a therapeutically effective amounts of a compound of any one of claims 1 to 25 and a corticosteroid.

123. The method of claim 122, wherein the inflammation and/or immune system activity is

~~associated with and/or results from atopic dermatitis, psoriasis, eczematous dermatitis, nummular dermatitis, irritant contact dermatitis, allergic contact dermatitis, seborrheic dermatitis, stasis dermatitis, and other steroid responsive dermatoses, acne vulgaris, alopecia, alopecia greata, vitiligo, eczema, xerotic eczema, keratosis pilaris, lichen planus, lichen sclerosus, lichen striatus, lichen simplex chronicus, prurigo nodularis, discoid lupus erythematosus, lymphocytic infiltrate of Jessner/Kanof, lymphacytoma cutis, pyoderma gangrenosum, pruritis ani, sarcoidosis, chondrodermatitis nodularis helices, keloids, hypertrophic scars, pretibial myxedema, other infiltrative dermatological disorders, granuloma annulare, necrobiosis lipoidica diabeticorum, sarcoidosis, other noninfectious granulomas, scleroderma, scleroderma sine scleroderma, systemic lupus erythematosus, systemic vasculitides, leukocytoelastic vasculitis, polyarteritis nodosa, Churg-Strauss syndrome, and rheumatoid vasculitis.~~

~~124. A method for the treatment of glucocorticoid insensitivity, restoring corticosteroid sensitivity, enhancing glucocorticoid sensitivity or reversing the glucocorticoid insensitivity in a subject experiencing corticosteroid dependence or corticoid resistance or unresponsiveness or intolerance to corticosteroids, comprising:~~

~~administering a pharmaceutical composition comprising a compound of any one of claims 1 to 25 in combination with a corticosteroid to the subject exhibiting one or more glucocorticoid insensitivity related conditions, wherein the glucocorticoid insensitivity related conditions comprise a range of immune-inflammatory disorders/diseases treated with steroids when the therapy fails to achieve disease control or is not effective or intolerant or dependent to corticosteroids, and combinations thereof.~~

~~125. The use of claims 27 or 28, the compound being administered *ex vivo* to a tissue graft donor, bone marrow graft donor, and/or a hematopoietic stem cell donor to increase the fitness of a donor tissue graft, a donor bone marrow graft, and/or a donor hematopoietic stem cell graft.~~

29. A compound of any one of claims 1 to 24 for use in therapy.