

the inhibition of the Adenosine 2b receptor (A2bR) results in synergistic induction of Th1 cytokine production (*e.g.*, IFN- γ , IL-2, TNF and GM-CSF), in human PBMCs, as described in Examples 15, 18-23, 27, and 29.

As further described herein, the inventors have also demonstrated that murine
5 colon carcinoma tumor growth and melanoma tumor growth was reduced in GPR174-deficient mice treated with an anti-GITR antibody (*i.e.*, a Treg attenuating agent) as compared to wild-type mice, as described in Examples 24 and 25.

As further described herein, the inventors have determined that cancer cell-derived exosomes stimulate GPR174 and inhibition of GPR174 in the presence of cancer cell-derived exosomes enhances Th1 cytokine levels, thereby stimulating and/or amplifying the
10 immune system as described in Example 26.

In summary, as demonstrated herein, GPR174 is an immune system-restricted Gas-coupled GPCR and PS exposed on liposomes and cellular membranes stimulates GPR174, supporting a model of active GPR174-mediated immune suppression in the tumor
15 microenvironment. Under conditions where both PS/lysoPS and adenosine are present, inhibition of both axes is necessary for effective restoration of T cell function. As further demonstrated herein, GPR174-deficiency enhances anti-tumor immune responses in mice.

Therefore, in one example, the present disclosure provides methods and compositions for stimulating and/or amplifying an immune response (*e.g.* for treating cancer)
20 by administering to a subject suffering from, or at risk of developing cancer or cancer metastasis, a therapeutically effective amount of an inhibitor of GPR174-mediated signaling as a single agent or optionally in combination with an inhibitor of ATP-Adenosine-A2aR-or A2bR-mediated signaling (such as an A2aR antagonist, an A2bR antagonist and/or a CD73 inhibitor and/or a CD38 inhibitor and/or a CD39 inhibitor, and/or a Treg attenuating agent, or
25 a combination thereof), thereby stimulating and/or amplifying an immune response in a mammalian subject in need thereof. In some examples, the methods comprise administering to a subject suffering from cancer an inhibitor of GPR174 and an A2aR antagonist. In some examples, the methods comprise administering to a subject suffering from cancer an inhibitor of GPR174 and an A2bR antagonist. In some examples, the methods comprise administering
30 to a subject suffering from cancer an inhibitor of GPR174 and an A2aR/A2bR antagonist. In some examples, the methods comprise administering to a subject suffering from cancer an inhibitor of GPR174 and a CD73 inhibitor. In some

examples, the methods comprise administering to a subject suffering from cancer an inhibitor of GPR174 and a CD38 inhibitor. In some examples, the methods comprise administering to a subject suffering from cancer an inhibitor of GPR174 and a CD39 inhibitor. In some examples, the methods comprise administering to a subject suffering from cancer an inhibitor of GPR174 and a Treg attenuating agent. In some examples, the methods comprise administering to a subject suffering from cancer an inhibitor of GPR174 and an A2aR antagonist and optionally at least one or more of an A2bR antagonist, a CD73 inhibitor, a CD38 inhibitor, a CD39 inhibitor and a Treg attenuating agent. In some examples, the A2aR antagonist is a small molecule. In some examples, the A2aR antagonist is an antibody. In some examples, the A2aR antagonist is a peptide- or a nucleotide/nucleic acid-based molecule. In some examples, the A2bR antagonist is a small molecule. In some examples, the A2bR antagonist is an antibody. In some examples, the A2bR antagonist is a peptide- or a nucleotide/nucleic acid-based molecule. In some examples, the CD38 inhibitor is a small molecule. In some examples, the CD38 inhibitor is an antibody. In some examples, the CD38 antagonist is a peptide- or a nucleotide/nucleic acid-based molecule. In some examples, the CD39 inhibitor is a small molecule. In some examples, the CD39 inhibitor is an antibody. In some examples, the CD39 antagonist is a peptide- or a nucleotide/nucleic acid-based molecule. In some examples, the CD73 inhibitor is a small molecule. In some examples, the CD73 inhibitor is an antibody. In some examples, the CD73 antagonist is a peptide- or a nucleotide/nucleic acid-based molecule. In some examples, the Treg attenuating agent is a small molecule. In some examples, the Treg attenuating agent is an antibody. In some examples, the Treg attenuating agent is a peptide or a nucleotide/nucleic acid-based molecule. In some examples, the GPR174 inhibitor is a small molecule. In some examples, the GPR174 inhibitor is an antibody. In some examples of the method, the GPR174 inhibitor, and at least one or more of the A2aR antagonist, the A2bR antagonist, the CD38 inhibitor, the CD39 inhibitor, the CD73 inhibitor and the Treg attenuating agent are administered simultaneously (*e.g.*, co-administered separately or together), or sequentially in any order, provided the effects of the first administered inhibitor remain present at the time of the second (and optionally third) administered inhibitor or attenuating agent.

As further described herein in Examples 16 and 17, the inventors have also discovered that phosphatidylserine (PS) is an agonist for GPR174-mediated Gs signaling.

Example 17 provides experimental results demonstrating that apoptotic cells stimulate GPR174 Gs signaling pathway in cells expressing GPR174. As further described in Example 16 and shown in FIGURES 47A-47F, PS-mediated GPR174 Gs signaling is inhibited by representative GPR174 inhibitory compounds 6, 10, 11, 20, 23 and 30 which belong to different chemical classes (*i.e.*, Groups I, II and IV). This data demonstrates that compounds 6, 10, 11, 20, 23, and 30 act as GPR174 antagonists and inhibit PS liposome-mediated cAMP signaling. Thus, PS liposome signaling through GPR174 is inhibited by multiple GPR174 inhibitory small molecule compounds with diverse chemical structures. Accordingly, in one example, the present disclosure provides a method of inhibiting PS-mediated activation of GPR174 Gs signaling in an immune cell expressing GPR174 comprising contacting said immune cell with an inhibitor of GPR174 Gs signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent. In one example, the present disclosure provides a method of stimulating T-cell mediated immunity in a subject suffering from cancer comprising administering a GPR174 inhibitor either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor, and/or a Treg attenuating agent to said subject in an amount effective to stimulate T-cell mediated immunity as described herein.

In one aspect, the present disclosure refers to use of a GPR174 inhibitor and at least one additional agent selected from the group consisting of: i. an adenosine-A2A (A2A) receptor antagonist; ii. an adenosine-A2B (A2B) receptor antagonist; iii. a CD73 inhibitor; iv. a CD38 inhibitor; v. a CD39 inhibitor; and vi. a Treg attenuating agent, in the manufacture of a medicament for treating cancer, wherein the GPR174 inhibitor and the at least one additional agent are to be administered simultaneously, or sequentially in any order, provided that the effects of the first administered inhibitor or antagonist remain present at the time of the second administered inhibitor or antagonist.

In another example, the disclosure provides a method of increasing an anti-tumor immune response in a subject that is currently undergoing, or has undergone treatment with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent, comprising administering an effective amount of a GPR174 inhibitor to stimulate an enhanced anti-tumor immune response in the subject, provided that the use of a CD73 inhibitor is preferably avoided during early tumor formation or in the setting of metastasis due to the fact that it might be preferable to have CD73 remain active in such settings.

In another aspect, the present disclosure refers to use of a GPR174 inhibitor in the manufacture of a medicament for enhancing an anti-tumor immune response in a subject that is currently undergoing treatment with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and a Treg attenuating agent.

In some examples, provided herein is a method of stimulating an immune response in a mammalian patient in need thereof comprising administering to the mammalian patient a small molecule inhibitor of GPR174 signaling, alone or in combination with an inhibitor of ATP-Adenosine-A2aR-or ATP-Adenosine-A2bR-mediated signaling (such as an A2aR antagonist, an A2bR antagonist, and/or a CD73 inhibitor and/or a CD38 inhibitor and/or a CD39 inhibitor) and/or a Treg attenuating agent. In some examples, the GPR174

inhibitor inhibits GPR174-mediated signaling through the Gs alpha subunit of the heterotrimeric G protein that stimulates the 3',5'-cyclic adenosine monophosphate (cAMP)-dependent pathway. The cAMP-dependent pathway (also referred to as Gs signaling or Gs pathway) involves synthesis of the second messenger cAMP, which in turn activates the cAMP-dependent protein kinase (Protein Kinase A or PKA).

In one example, the disclosure provides a pharmaceutical composition comprising a combination of an inhibitor of GPR174 signaling and a least one or more of an adenosine A2A receptor antagonist, an adenosine A2B receptor antagonist, a CD73 inhibitor and/or a CD38 inhibitor and/or a CD39 inhibitor and a pharmaceutically acceptable carrier.

In one example, the disclosure provides a pharmaceutical composition comprising a combination of an inhibitor of GPR174 signaling and a Treg attenuating agent and a pharmaceutically acceptable carrier.

In some examples, the GPR174 inhibitor is a small molecule inhibitor that is an inverse agonist of GPR174 signaling.

In some examples, the small molecule inhibitor is an antagonist of GPR174 signaling.

In some examples, the small molecule inhibitor inhibits phosphatidylserine (PS), or lysophosphatidylserine (LysoPS), or pepducin dependent activation of GPR174 signaling in a cell expressing GPR174 by at least 25%.

In another aspect, the present disclosure refers to use of a small-molecule inhibitor of GPR174 signaling and at least one of an adenosine-A2A (A2A) receptor antagonist, an adenosine-A2B (A2B) receptor antagonist, or a combination thereof, in the manufacture of a medicament for increasing the level of Th1 cytokines in human peripheral blood mononuclear cells (PBMCs).

In some examples, the stimulated immune response comprises a T-cell-mediated immune response.

In some examples, the T-cell mediated immune response comprises suppression of T-Reg activity, differentiation, growth and/or proliferation. In some examples, the T-cell mediated immune response comprises stimulation of Teffector activity, differentiation, growth and/or proliferation. In some examples, the T-cell mediated immune response comprises stimulation of Th1 cell activity, differentiation, growth and/or proliferation. In some examples, the T-cell mediated immune response comprises suppression of Th17 cell activity, differentiation, growth and/or proliferation. In one example, the T-cell mediated immune response comprises preferential growth and activation of Teffector cells over those of Tregulatory cells, resulting in a relative decrease in Tregulatory cell frequency, abundance and/or function.

In some examples, the stimulated immune response comprises a reduction

in immune-cell or cancer-cell associated programmed death-ligand 1 (PD-L1) expression or cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) expression or T cell immunoreceptor with Ig and ITIM domains (TIGIT) expression or amphiregulin (AREG) expression.

5 In some examples, the stimulated immune response comprises an NK-cell mediated immune response. In some examples, at least a portion of the T-cells or the NK-cells express GPR174. In some examples, the NK-cell mediated immune response comprises stimulation of NK-cell function, activity, differentiation, growth and/or proliferation.

In some examples, the stimulated immune response and/or amplified immune response comprises an increase in Th1 cytokine production in the presence of cancer cell-
10 derived exosomes.

In another aspect, the present disclosure refers to an *in vitro* method of increasing the level of Th1 cytokines in human peripheral blood mononuclear cells (PBMCs), the method comprising contacting human PBMCs with a small-molecule inhibitor of GPR174 signaling and at least one of an adenosine-A2A (A2A) receptor antagonist, an adenosine-A2B
15 (A2B) receptor antagonist, or a combination thereof.

In some examples, the patient is suffering from, or harboring a neoplasm not recognized by the body as self. In some examples, the neoplasm is a non-malignant neoplasm, such as a non-malignant tumor. In some examples, the neoplasm is a malignant tumor. In some examples, the neoplasm (either malignant or non-malignant tumor) comprises a T cell
20 infiltrate. In some examples, tumor cells are destroyed by the immune response stimulated by the GPR174 inhibitory compound either as a single agent, or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent.

In some examples, the patient is a cancer patient. In some examples, the
25 mammalian patient is a human. In some examples, the cancer is a solid tumor. In some examples, the cancer is a blood cancer. In some examples, the cancer is as disclosed herein. In some examples, at least a portion of the cancer cells express GPR174. In some examples, the GPR174 has 90% or greater sequence identity to SEQ ID NO:1.

In some examples, T-cell activity, differentiation, proliferation, and/or growth
30 is stimulated in a population of peripheral blood mononuclear cells (PBMCs) contacted with the GPR174 small molecule inhibitor either as a single agent, or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control population of PBMCs not contacted with the GPR174 small molecule inhibitor.

35 In some examples, the fraction of FoxP3⁺Helios⁺ T-cells (regulatory T-cells) is decreased by at least 20% in a population of PBMCs contacted with the GPR174 small

molecule inhibitor either as a single agent, or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor, and/or a Treg attenuating agent as compared to a control population of PBMCs not contacted with the small molecule GPR174 inhibitor.

5 In some examples, the cAMP level is decreased by at least 20%, at least 50%, or at least 75% in a cell expressing GPR174 contacted with the small molecule inhibitor of GPR174 signaling either as a single agent, or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell expressing GPR174 not contacted with
10 the GPR174 small molecule inhibitor.

 In some examples, the activity of protein kinase A (PKA) is decreased by at least 20% in cells expressing GPR174 contacted with the small molecule inhibitor of GPR174 either as a single agent, or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating
15 agent, as compared to a control cell not contacted with the GPR174 small molecule inhibitor.

 In some examples, the PKA activity is decreased by at least 20%, at least 50%, or at least 75% in a cell expressing GPR174 contacted with the small molecule inhibitor of GPR174 signaling either as a single agent, or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or
20 a Treg attenuating agent as compared to a control cell expressing GPR174 not contacted with the GPR174 small molecule inhibitor.

 In some examples, the production of one or more of IL-2, IFN- γ , TNF- α , IL-6, and IL-10 is increased by at least 20% in peripheral blood mononuclear cells (PBMCs) contacted with the small molecule inhibitor of GPR174 as compared to control cells not
25 contacted with the small molecule inhibitor.

 In some examples, the production of one or more of IL-2, IFN- γ , TNF- α , and GM-CSF is increased by at least 20% in peripheral blood mononuclear cells (PBMCs) contacted with the small molecule inhibitor of GPR174 in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor,
30 and/or a Treg attenuating agent as compared to control cells not contacted with the small molecule inhibitor of GPR174.

In some examples, the production of IL-17A is decreased by at least 20% in PBMCs contacted with the small molecule inhibitor as compared to control cells not contacted with the small molecule inhibitor.

5 In some examples, the production of one or more cytokines is decreased by at least 20%, at least 50%, or at least 80% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some examples, the production of IL-17A is decreased by at least 20%, at least 50%, or at least 80% in a population of PBMCs
10 exposed to a small molecule inhibitor of GPR174 signaling as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling.

 In some examples, the production of one or more cytokines is increased by at least 20%, at least 50%, or at least 80% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling as compared to a population of PBMCs not exposed to the small
15 molecule inhibitor of GPR174 signaling. In some examples, the cytokine is selected from IL-2, IFN- γ , TNF, IL-6, and IL-10.

 In some examples, the production of one or more cytokines is increased by at least 20%, at least 50%, or at least 80% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 in combination with at least one of an A2aR antagonist, an A2bR
20 antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to control cells not contacted with the small molecule inhibitor of GPR174. In some examples, the cytokine is a T helper type 1 cell (Th1) cytokine selected from IL-2, IFN- γ , TNF, and GM-CSF.

 In some examples, the production of one or more cytokines is increased by at
25 least 20%, at least 50%, at least 100%, at least 500%, or at least 1000% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some
30 examples, the cytokine is selected from IL-2, IFN- γ , TNF, and GM-CSF. In some examples, the production of one or more of IL-2, IFN- γ , TNF, or GM-CSF is increased by at least 20%, at least 50%, at least 100%, at least 500%, or at least 1000% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or

in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor, and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling.

In some examples, the production of IL-2 is increased by at least 100%, at least 500%, or at least 1000% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some examples, the production of IFN- γ is increased by at least 50%, at least 100%, or at least 500% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some examples, the production of TNF- α is increased by at least 50%, at least 100%, or at least 500% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling.

In some examples, the production of GM-CSF is increased by at least 50%, at least 100%, or at least 500% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling.

In some examples, the production of one or more cytokines are not modulated and do not increase or decrease by more than 20% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some examples, the cytokine or cytokines is selected from the group consisting of: IL-4, IL-5, IL-9, IL-13, IL-17F, IL-21, and IL-22.

In some examples, the production of one or more cytokines is decreased by at least 20%, at least 50%, or at least 80% in a cell expressing GPR174 contacted with the small molecule inhibitor as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor. In some examples, the production of IL-17A is decreased by at least 20%, at least 50%, or at least 80% in a cell expressing GPR174 contacted with the small molecule inhibitor as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor.

In some examples, the production of one or more cytokines is increased by at least 20%, at least 50%, at least 100%, at least 500%, or at least 1000% in a cell expressing GPR174 contacted with the small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174. In some examples, the production of one or more of IL-2, IFN- γ , TNF, or GM-CSF is increased by at least 20%, at least 50%, at least 100%, at least 500%, or at least 1000% in a cell expressing GPR174 contacted with the small molecule inhibitor of GPR174 as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174. In some examples, the production of IL-2 is increased by at least 100%, at least 500%, or at least 1000% in a cell expressing GPR174 contacted with a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174. In some examples, the production of IFN- γ is increased by at least 50%, at least 100%, or at least 500% in a cell expressing GPR174 contacted with a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174. In some examples, the production of TNF- α is increased by at least 50%, at least 100%, or at least 500% in a cell expressing GPR174 contacted with a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg

attenuating agent as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174.

5 In some examples, the production of one or more of IL-4, IL-5, IL-9, IL-13, IL-17F, IL-21, and IL-22 are not modulated and do not increase or decrease by more than 20% in a cell expressing GPR174 contacted with a small molecule inhibitor of GPR174 signaling as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor. In some examples, the patient has one or more tumor(s) which may or may not comprise infiltrating regulatory T-cells.

10 In some examples, provided herein is a method of inhibiting the level of cAMP in a cell that expresses GPR174, the method comprising contacting the cell with a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent.

15 In some examples, the cAMP level is decreased by at least 20%, at least 50%, or at least 75% in a cell expressing GPR174 contacted with the small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174.

20 In some examples, the contacting is *in vivo*. In some examples, the contacting is *in vitro*. In some examples, the contacting is *ex vivo*.

25 In some examples, the cell is an immune cell. In some examples, the cell is a T-cell or NK-cell. In some examples, the NK-cell or T-cell activity, differentiation, growth and/or proliferation is stimulated. In some examples, the cell is a mammalian cell. In some examples, the cell is a human cell. In some examples, the cell is a thymus, lymph node, spleen, bone marrow, or PMBC cell.

In some examples, the GPR174 has 90% or greater sequence identity, such as 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% to SEQ ID NO:1. In some examples, the GPR174 has a sequence set forth as SEQ ID NO:1.

30 In some examples, provided herein is a method of modulating the level of one or more cytokines in PBMCs, the method comprising contacting the PBMCs with a small-molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least

one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent.

In some examples, the contacting is *in vivo*. In some examples, the contacting is *in vitro*. In some examples, the contacting is *ex vivo*.

5 In some examples, the PBMCs comprise immune cells. In some examples, the immune cells comprise T-cells or NK-cells. In some examples, the activity, differentiation, growth and/or proliferation of the NK-cells or T-cells is stimulated. In some examples, the PBMCs comprise mammalian cells. In some examples, the PBMCs comprise human cells.

10 In some examples, the GPR174 has 90% or greater sequence identity to SEQ ID NO:1.

In some examples, the cytokine is selected from IL-2, IFN- γ , TNF, GM-CSF, IL-6, IL-17A, IL-10, IL-4, IL-5, IL-9, IL-12, IL-13, IL-17F, IL-21, and IL-22. In some examples, the level of one or more cytokines is increased. In some examples, the level of one or more of cytokines selected from the group consisting of IL-2, IFN- γ , TNF and GM-CSF is
15 increased. In some examples, the level of one or more cytokines is decreased. In some examples, the level of one or more cytokines is not modulated.

In some examples, the level of one or more cytokines is decreased by at least 20%, at least 50%, or at least 80% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some examples, the level of IL-17A is decreased
20 by at least 20%, at least 50%, or at least 80% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling.

In some examples, the level of one or more cytokines is increased by at least 20%, at least 50%, or at least 80% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some examples, the cytokine is selected from
25 IL-2, IFN- γ , TNF, and GM-CSF.
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In some examples, the level of one or more cytokines is increased by at least

20%, at least 50%, at least 100%, at least 500%, or at least 1000% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some examples, the cytokine is selected from IL-2, IFN- γ , TNF, and GM-CSF. In some examples, the level of one or more of IL-2, IFN- γ , TNF- α , or GM-CSF is increased by at least 20%, at least 50%, at least 100%, at least 500%, or at least 1000% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling.

In some examples, the level of IL-2 is increased by at least 100%, at least 500%, or at least 1000% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some examples, the level of IFN- γ is increased by at least 50%, at least 100%, or at least 500% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some examples, the level of TNF- α is increased by at least 50%, at least 100%, or at least 500% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling.

In some examples, the level of one or more cytokines are not modulated and do not increase or decrease by more than 20% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some examples, the cytokine or

cytokines is selected from the group consisting of: IL-4, IL-5, IL-9, IL-13, IL-17F, IL-21, and IL-22.

In some examples, the level of one or more cytokines is decreased by at least 20%, at least 50%, or at least 80% in a cell expressing GPR174 contacted with the small molecule inhibitor as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor. In some examples, the level of IL-17A is decreased by at least 20%, at least 50%, or at least 80% in a cell expressing GPR174 contacted with the small molecule inhibitor as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor.

In some examples, the level of one or more cytokines is increased by at least 20%, at least 50%, at least 100%, at least 500%, or at least 1000% in a cell expressing GPR174 contacted with the small molecule inhibitor of GPR174 either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174. In some examples, the level of one or more of IL-2, IFN- γ , TNF, or GM-CSF is increased by at least 20%, at least 50%, at least 100%, at least 500%, or at least 1000% in a cell expressing GPR174 contacted with the small molecule inhibitor of GPR174 either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174.

In some examples, the level of IL-2 is increased by at least 100%, at least 500%, or at least 1000% in a cell expressing GPR174 contacted with a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174.

In some examples, the level of IFN- γ is increased by at least 50%, at least 100%, or at least 500% in a cell expressing GPR174 contacted with a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell expressing GPR174 not contacted with

the small molecule inhibitor of GPR174.

In some examples, the level of TNF (also referred to as "TNF- α ") is increased by at least 50%, at least 100%, or at least 500% in a cell expressing GPR174 contacted with a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with
5 at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174.

In some examples, the level of one or more of IL-4, IL-5, IL-9, IL-13, IL-17F, IL-21, and IL-22 are not modulated and do not increase or decrease by more than 20% in a cell
10 expressing GPR174 contacted with a small molecule inhibitor of GPR174 signaling as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor.

In some examples, provided herein is a pharmaceutical composition comprising a small molecule inhibitor of GPR174 signaling and a pharmaceutically acceptable excipient.

In some examples, provided herein is a pharmaceutical composition comprising
15 a small molecule inhibitor of GPR174 signaling in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor and/or a CD73 inhibitor and a pharmaceutically acceptable excipient.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising a combination of an inhibitor of GPR174 signaling with at least one of an adenosine-A2A (A2A) receptor antagonist, an adenosine-A2B (A2B) receptor antagonist, a
20 CD73 inhibitor, a CD38 inhibitor, and a CD39 inhibitor and optionally a pharmaceutically acceptable excipient.

In some examples, provided herein is a pharmaceutical composition comprising a small molecule inhibitor of GPR174 signaling in combination with an A2aR antagonist and
25 a pharmaceutically acceptable excipient.

In some examples, provided herein is a pharmaceutical composition comprising a small molecule inhibitor of GPR174 signaling in combination with an A2bR antagonist and a pharmaceutically acceptable excipient.

In some examples, provided herein is a pharmaceutical composition comprising
30 a small molecule inhibitor of GPR174 signaling in combination with an A2aR antagonist and an A2bR antagonist and a pharmaceutically acceptable excipient.

In some examples, provided herein is a pharmaceutical composition comprising a small molecule inhibitor of GPR174 signaling in combination with a Treg attenuating agent and a pharmaceutically acceptable excipient.

35 In some examples, provided herein is a pharmaceutical composition comprising a small molecule inhibitor of GPR174 and at least one of (i) an A2aR antagonist

and/or an A2bR antagonist; and (ii) at least one of a CD73 inhibitor and/or a CD38 inhibitor and/or a CD39 inhibitor. In some examples, the pharmaceutical composition further comprises a Treg attenuating agent.

5 In some examples, the small molecule inhibitor of GPR174 does not comprise an alkyl chain comprising 10 or more C atoms. In some examples, the small molecule inhibitor of GPR174 is not pepducin, LysoPS, PS, or a compound disclosed in US Pub. No. 2015/0361119. In some examples, the small molecule inhibitor has a molecular weight from about 50 Da to about 2500 Da. In some examples, the small molecule inhibitor has a molecular weight from about 50 to 800 Da, such as from about 100 Da to about 800 Da.

10 In some examples, the small molecule inhibitor alters the cellular distribution of a recombinant GPR174 polypeptide modified to include a nuclear localization signal as compared to the cellular distribution of the recombinant GPR174 polypeptide in the absence of the inhibitor. In some examples, the small molecule inhibitor competitively binds to GPR174 as compared to any one of compounds 1-59. In some examples, the small molecule inhibitor
15 has an EC₅₀ for GPR174 of less than 15 μ M as determined by a cellular redistribution assay (CRA). CRA is described in detail herein under "Screening Methods." In some examples, the small molecule inhibitor binds competitively to GPR174 as compared to any one of compounds 1-59 and results in an altered apparent binding affinity of the compound for GPR174 when a cell expressing GPR174 is contacted with the compound and the small molecule inhibitor at
20 the same time as compared to the binding affinity of compound for GPR174 alone. In some examples, the small molecule inhibitor causes a difference in the inhibitory activity of any one of reference compounds 1-59 in a GPR174-mediated signaling assay when tested in the presence of said reference compound as compared to the inhibitory activity of the reference compound alone. In some examples, the small molecule inhibitor binds allosterically to
25 GPR174 as compared to any one of compounds 1-59. In some examples, the small molecule inhibitor is specific for GPR174 as compared to one or more GPCRs in a reference panel of GPCRs as disclosed herein. In some examples, the small molecule inhibitor is specific for GPR174 relative to P2Y10. In some examples, the small molecule inhibitor is specific for GPR174 relative to GPR34. In some examples, the small molecule inhibitor inhibits the Gs
30 signaling pathway.

In some examples, T-cell activity, differentiation, proliferation, and/or growth is stimulated in a population of peripheral blood mononuclear cells (PBMCs) contacted

with the small molecule inhibitor of GPR174 either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control population of PBMCs not contacted with the small molecule inhibitor of GPR174.

5 In some examples, the subpopulation of regulatory T-cells is decreased in a population of PBMCs contacted with the small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control population of PBMCs not contacted with the small molecule inhibitor
10 of GPR174.

 In some examples, the fraction of FoxP3⁺Helios⁺ T-cells (regulatory T-cells) is decreased by at least 20% in a population of PBMCs contacted with the small molecule inhibitor of GPR174 either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or
15 a Treg attenuating agent as compared to a control population of PBMCs not contacted with the small molecule inhibitor of GPR174.

 In some examples, the level of cAMP is decreased by at least 20% in a cell expressing GPR174 contacted with the small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist,
20 a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174.

 In some examples, the cAMP level is decreased by at least 20%, at least 50%, or at least 75% in a cell expressing GPR174 contacted with the small molecule inhibitor of
25 GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174.

 In some examples, the activity of PKA is decreased by at least 20% in cells
30 expressing GPR174 contacted with the small molecule inhibitor of GPR174 either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a

control cell not contacted with the small molecule inhibitor of GPR174.

In some examples, the PKA activity is decreased by at least 20%, at least 50%, or at least 75% in a cell expressing GPR174 contacted with the small molecule inhibitor of GPR174 either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174.

In some examples, the level of one or more cytokines is modulated in PBMCs contacted with the small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to control cells not contacted with the small molecule inhibitor of GPR174.

In some examples, the level of one or more of IL-2, IFN- γ , TNF, and GM-CSF is increased by at least 20% in PBMCs contacted with the small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to control cells not contacted with the small molecule inhibitor of GPR174.

In some examples, the level of IL-17A is decreased by at least 20% in PBMCs contacted with the small molecule inhibitor as compared to control cells not contacted with the small molecule inhibitor.

In some examples, the level of one or more cytokines is decreased by at least 20%, at least 50%, or at least 80% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some examples, the level of IL-17A is decreased by at least 20%, at least 50%, or at least 80% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling.

In some examples, the level of one or more cytokines is increased by at least 20%, at least 50%, or at least 80% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor

and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some examples, the cytokine is selected from IL-2, IFN- γ , TNF and GM-CSF.

5 In some examples, the level of one or more cytokines is increased by at least 20%, at least 50%, at least 100%, at least 500%, or at least 1000% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some examples, the cytokine is selected from IL-2, IFN- γ , TNF, and GM-CSF. In some examples, the level of one or more of IL-2, IFN- γ , TNF, or GM-CSF is increased by at least 20%, at least 50%, at least 100%, at least 500%, or at least 1000% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling.

In some examples, the level of IL-2 is increased by at least 100%, at least 500%, or at least 1000% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some examples, the level of IFN- γ is increased by at least 50%, at least 100%, or at least 500% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some examples, the level of TNF- α is increased by at least 50%, at least 100%, or at least 500% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling.

In some examples, the level of one or more cytokines are not modulated and do not increase or decrease by more than 20% in a population of PBMCs exposed to a small molecule inhibitor of GPR174 signaling as compared to a population of PBMCs not exposed to the small molecule inhibitor of GPR174 signaling. In some examples, the cytokine or
5 cytokines is selected from the group consisting of: IL-4, IL-5, IL-9, IL-13, IL-17F, IL-21, and IL-22.

In some examples, the level of one or more cytokines is decreased by at least 20%, at least 50%, or at least 80% in an immune cell contacted with the small molecule inhibitor as compared to a control cell expressing GPR174 not contacted with the small
10 molecule inhibitor. In some examples, the level of IL-17A is decreased by at least 20%, at least 50%, or at least 80% in an immune cell contacted with the small molecule inhibitor as compared to a control cell not contacted with the small molecule inhibitor

In some examples, the level of one or more cytokines is increased by at least 20%, at least 50%, at least 100%, at least 500%, or at least 1000% in an immune cell contacted
15 with the small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell not contacted with the small molecule inhibitor of GPR174. In some examples, the level of one or more of IL-2, IFN- γ , TNF, or GM-CSF is increased by at least 20%, at least 50%, at least
20 100%, at least 500%, or at least 1000% in an immune cell contacted with the small molecule inhibitor of GPR174 either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell not contacted with the small molecule inhibitor of GPR174.

In some examples, the level of IL-2 is increased by at least 100%, at least 500%,
25 or at least 1000% in an immune cell contacted with a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell not contacted with the small molecule inhibitor
30 of GPR174. In some examples, the level of IFN- γ is increased by at least 50%, at least 100%, or at least 500% in an immune cell contacted with a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR

antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell not contacted with the small molecule inhibitor of GPR174. In some examples, the level of TNF- α is increased by at least 50%, at least 100%, or at least 500% in an immune cell contacted with a small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell not contacted with the small molecule inhibitor of GPR174.

In some examples, the level of one or more of IL-4, IL-5, IL-9, IL-13, IL-17F, IL-21, and IL-22 are not modulated and do not increase or decrease by more than 20% in an immune cell contacted with a small molecule inhibitor of GPR174 signaling as compared to a control cell not contacted with the small molecule inhibitor.

In some examples, the small molecule inhibitor reduces ligand-induced receptor internalization of GPR174 in cells expressing GPR174 as compared to control cells not contacted with the small molecule inhibitor.

In some examples, the receptor internalization is reduced by at least 10%, at least 20%, at least 50%, or at least 80% in a cell expressing GPR174 contacted with a small molecule inhibitor of GPR174 signaling as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor. In some examples, the receptor internalization is reduced by 1-99% in a cell expressing GPR174 contacted with a small molecule inhibitor of GPR174 signaling as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor. In some examples, the receptor internalization is reduced by 1-20%, 20-40%, 40-60%, 60-80%, or 80-99% in a cell expressing GPR174 contacted with a small molecule inhibitor of GPR174 signaling as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor.

In some examples, the β -arrestin recruitment is reduced by at least 10%, at least 20%, at least 50%, or at least 80% in a cell expressing GPR174 contacted with a small molecule inhibitor of GPR174 signaling as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor. In some examples, the β -arrestin recruitment is reduced by 1-99% in a cell expressing GPR174 contacted with a small molecule inhibitor of GPR174 signaling as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor. In some examples, the β -arrestin recruitment is reduced by 1-

20%, by 20-40%, 40-60%, 60-80%, or by 80-99% in a cell expressing GPR174 contacted with a small molecule inhibitor of GPR174 signaling as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor.

In some examples, provided herein is a composition comprising a small
5 molecule inhibitor of GPR174 either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent and a cell expressing GPR174.

In some examples, the cell is a mammalian cell. In some examples, the cell is a human cell. In some example, the cell is an immune cell. In some examples, the cell is a T
10 cell. In some examples, the T cell is a naïve T cell. In some examples, the T cell is a regulatory T cell. In some examples, the T cell is an effector T cell. In some examples, the cell is a thymus, lymph node, spleen, bone marrow, or PBMC cell. In some examples, the level of cAMP is decreased by at least 20% in the composition as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174. In some examples, the activity of
15 PKA is decreased by at least 20% in the composition as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174. In some examples, the level of one or more cytokines is modulated in the composition as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174.

In some examples, the cAMP level is decreased by at least 20%, at least 50%,
20 or at least 75% in a cell expressing GPR174 contacted with the small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell expressing GPR174 not contacted with the small molecule inhibitor of GPR174.

In some examples, the PKA activity is decreased by at least 20%, at least 50%,
25 or at least 75% in a cell expressing GPR174 contacted with the small molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent as compared to a control cell expressing GPR174 not contacted with
30 the small molecule inhibitor of GPR174.

In some examples, provided herein is a composition comprising a small

molecule inhibitor of GPR174 signaling either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent and a population of cells, wherein at least a portion of the population of cells express GPR174, and wherein at least a portion of the population of cells expressing GPR174 comprises T-cells.

In some examples, wherein the population of cells comprise cancer cells. In some examples, the population of T-cells comprises regulatory T cells. In some examples, the population of T-cells comprises effector T cells.

In another example, the disclosure features a method of inhibiting a GPR174-mediated signaling pathway (*e.g.*, a Gs signaling pathway) in a cell. The method includes the step of contacting a cell with an isolated compound predetermined to functionally interact with GPR174 either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent, where the cell includes a GPR174-mediated signaling pathway and expresses GPR174 (*e.g.*, a GPR174 polypeptide) and the isolated compound inhibits the ability of the GPR174 to modulate the GPR174-mediated signaling pathway, thereby inhibiting the GPR174-mediated signaling pathway in the cell. In certain examples, the compound is capable of functionally interacting with human GPR174 having the sequence set forth as SEQ ID NO:1, or a naturally occurring variant of GPR174 having at least 90% identity to SEQ ID NO:1. In particular examples, the isolated compound is capable of altering the cellular distribution of a recombinant GPR174 polypeptide (*e.g.*, human GPR174 having the sequence of SEQ ID NO:1) modified to alter cellular distribution as compared to the cellular distribution of the recombinant GPR174 polypeptide in the absence of the compound. In some examples, the cell is contacted *in vivo* in a subject suffering from a disease such as cancer.

In a related example, the disclosure features a method of inhibiting a GPR174-mediated signaling pathway in a cell by (i) providing an isolated compound predetermined to functionally interact with human GPR174 and to inhibit a GPR174-mediated signaling pathway in cells expressing GPR174; and (ii) contacting a cell expressing GPR174 with said isolated compound either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent, thereby inhibiting a GPR174-mediated signaling pathway in the cell. In some examples, the cell expresses human GPR174 having the sequence set forth as SEQ

ID NO:1 or a naturally occurring variant of GPR174 having at least 90% identity to SEQ ID NO:1 (such as at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%) identity to SEQ ID NO:1 and to inhibit a GPR174-mediated signaling pathway in cells expressing GPR174. In some examples, the method comprises contacting a cell expressing human GPR174 with an isolated compound predetermined to functionally interact with human GPR174 having the sequence set forth as SEQ ID NO:1 or a naturally occurring variant of GPR174 having at least 90% (such as at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%) identity to SEQ ID NO:1 and to inhibit a GPR174-mediated signaling pathway in cells expressing GPR174. In some examples, step (i) comprises performing at least one assay to measure functional interaction of said compound with GPR174 prior to contacting a cell in accordance with step (ii).

In either example, the compound optionally competitively binds the same region of GPR174 as any one of compounds 1-59, provided below.

In another example, the disclosure features a method of using a small molecule chemical compound for inhibiting a GPR174-mediated signaling pathway in a cell, said method comprising the steps of

(a) providing a small molecule chemical compound that functionally interacts with GPR174 and inhibits a GPR174-mediated Gs signaling pathway in cells expressing GPR174, wherein the compound is characterized by at least one of the following criteria:

(i) said compound has a structure selected from the group consisting of Formula I, II, III, IV, V and VI (or (I), (II), (III), (IV), (V), (Va), or (VI)); or

(ii) said compound changes the binding affinity of any one of reference compounds 1-59 (as set forth in Table 1) to GPR174; or

(iii) said compound causes a difference in the inhibitory activity of any one of reference compounds 1-59 (as set forth in Table 1), in a GPR174-mediated signaling pathway assay when tested in the presence of the reference compound as compared to the inhibitory activity of the reference compound alone; and

(b) contacting a cell expressing GPR174 that includes a GPR174-mediated Gs signaling pathway with the compound according to step (a) either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent, thereby inhibiting a GPR174-mediated signaling pathway in the cell.

In another example, the disclosure features a method of using a small molecule chemical compound for inhibiting a GPR174-mediated signaling pathway in a cell, said method comprising the steps of

(a) providing a small molecule chemical compound that functionally interacts
5 with GPR174 and inhibits a GPR174-mediated Gs signaling pathway in cells expressing GPR174, wherein the compound is characterized by at least one of the following criteria:

(i) said compound has a structure selected from the group consisting of
Formula I, II, III, IV, V and VI (or (I), (II), (III), (IV), (V), (Va), or (VI)); or

(ii) said compound changes the apparent binding affinity of any one of
10 reference compounds 1-59 (as set forth in Table 1) for GPR174; or

(iii) said compound causes a difference in the inhibitory activity of any
one of reference compounds 1-59 (as set forth in Table 1), in a GPR174-mediated
signaling pathway assay when tested in the presence of said reference compound as
compared to the inhibitory activity of the reference compound alone; and

(b) contacting a cell expressing GPR174 that includes a GPR174-mediated Gs
15 signaling pathway with the compound according to step (a) either as a single agent or in
combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a
CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent, thereby inhibiting a
GPR174-mediated signaling pathway in the cell.

20 In some examples, the compound changes the binding affinity of any one of the
compounds described herein (*e.g.*, any one of reference compounds 1-59 of Table 1). In certain
examples, the compound decreases (*i.e.*, inhibits) the binding affinity of any one of reference
compounds 1-59 to GPR174. In particular examples, the compound competitively decreases
(*i.e.*, competitively inhibits) the binding affinity of any one of reference compounds 1-59 to
25 GPR174. In alternate examples, the compound increases the binding affinity of any one of
reference compounds 1-59 to GPR174. In one example, said compound has a structure selected
from the group consisting of Formula I-VI. In one example, said compound inhibits
lysophosphatidylserine (LysoPS)-dependent activation of the GPR174 receptor in said cell. In
one example, said compound inhibits lysophosphatidylserine (LysoPS)-dependent activation
30 of the GPR174 receptor in said cell.

In one example, said compound inhibits phosphatidylserine (PS)-dependent
activation of the GPR174 receptor in said cell. As described herein in Examples 16 and 17, the

inventors have discovered that phosphatidylserine (PS) is an agonist for GPR174-mediated Gs signaling. Example 17 provides experimental results demonstrating that apoptotic cells stimulate GPR174 Gs signaling pathway in cells expressing GPR174. As further described in Example 16 and shown in FIGURES 47A-47F, PS-mediated GPR174 Gs signaling is inhibited by representative GPR174 inhibitory compounds 6, 10, 11, 20, 23 and 30 which belong to different chemical classes (*i.e.*, Groups I, II and IV). This data demonstrates that compounds 6, 10, 11, 20, 23, and 30 act as GPR174 antagonists and inhibit PS liposome-mediated cAMP signaling. Thus, PS liposome signaling through GPR174 is inhibited by multiple GPR174 inhibitory small molecule compounds with diverse chemical structures.

As described herein, extracellular PS is highly enriched in the tumor microenvironment and is found on the surface of tumor cells as well as endothelial cells of blood vessels permeating solid tumors. Furthermore, apoptotic neutrophils and activated platelets, both of which expose PS, are also recruited to solid tumors (see A.K and Rao D.A., *Blood* 120:4667-4668, 2012; Schlesinger, M., *Journal of Hematology and Oncology* (11) 125, 2018; Treffers L.W. et al., *Immunological Reviews* vol 273: 312-328, 2016; and Gregory A. D. and Houghton A. M., *Cancer Research* Vol 71 (7): 2411-6, 2011). Thus, high concentrations of PS are considered a major source of tumor-mediated immunosuppression and may play a role in resistance to cancer immunotherapies such as checkpoint inhibitors.

Accordingly, the experimental results described in Examples 16 and 17 provide support for a method of stimulating T-cell mediated immunity in a subject suffering from cancer comprising administering a GPR174 inhibitor either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent to said subject in an amount effective to stimulate T-cell mediated immunity as described herein.

As further described herein, the inventors have determined that cancer cell-derived exosomes stimulate GPR174 and inhibition of GPR174 in the presence of cancer cell-derived exosomes enhances Th1 cytokine levels to a greater extent than in the presence of PS liposomes, as described in Example 26. Accordingly, in one example, a method is provided for stimulating and/or amplifying an immune response in a mammalian subject suffering from, or at risk of developing cancer or cancer metastasis, comprising:

(a) determining the presence of cancer cell-derived exosome(s) expressing phosphatidylserine (PS) in a sample obtained from said mammalian subject; and

(b) administering a therapeutically effective amount of a GPR174 inhibitor to said subject.

In some examples, the GPR174 inhibitor is a small molecule that inhibits PS-mediated immune suppression. In some examples, the sample is a tissue, cell or cell extract, or a fluid selected from the group consisting of blood, serum, plasma, sputum, urine, saliva and tears. In some examples, step (a) comprises contacting said sample or exosome extract obtained from said sample with a PS binding agent and thereby determining the presence of said cancer cell-derived exosome. As exosome surface membranes reflect the plasma membrane of their parent cells, exosomes from tumor cells are characterized by having phosphatidylserine (PS) on their surface, as opposed to exosomes from normal cells. Exemplary PS-binding agents include, for example an anti-PS antibody or any other PS-binding agent such as, for example, PKC, protein S, factor VII, factor III and other known PS-binding agents. The PS binding agent may be labeled with a detectable agent, such as a radioactive isotope, a colorimetric label, a fluorescent label, a magnetic resonance label, an enzyme, an affinity ligand or a luminescent label. Exosomes may be extracted from a sample obtained from a subject by various means such as, for example, selective precipitation, affinity purification or by differential centrifugation according to known methods (see, *e.g.*, Zhang Y. et al., Mol Cell 39:133-144, 2010). In some examples, the step (a) comprises determining a quantitative amount of cancer cell-derived exosomes in a sample obtained from a subject. In some examples, the method comprises determining whether or not the subject has an amount of cancer cell-derived exosomes above a threshold indicative of the presence of cancer (*i.e.* one or more tumors). In general, normal tumor-free individuals have undetectable levels of PS-exosomes in an unconcentrated sample. In contrast, patients with tumors will typically exhibit values above 100 pg/50 μ L of sample in an unconcentrated sample. Thus, values greater than 50 pg/50 μ L plasma (or serum) are indicative of a malignancy (*i.e.*, cancer or one or more tumors).

It is known that PS-expressing exosomes are released from tumor cells and circulating PS-positive tumor exosomes can be detected in biological fluids such as blood and urine. In some examples, said cancer cell-derived exosome(s) expressing PS is from a lung cancer cell, a pancreatic cancer cell, an ovarian cancer cell, a breast cancer cell, a colon cancer cell, a renal cancer cell, a liver cancer cell, a skin cancer cell, a brain cancer cell, a head and neck cancer cell or a thyroid cancer cell, or any other cancer cell type disclosed herein. In some

examples, the method further comprises administering to said subject at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent.

5 In some examples, the GPR174 inhibitory compound changes the apparent binding affinity of any one of the compounds described herein (*e.g.*, any one of reference compounds 1-59 of Table 1) for GPR174. In certain examples, the compound decreases the apparent binding affinity of any one of reference compounds 1-59 for GPR174. In particular examples, the compound competitively binds to GPR174 and decreases the apparent binding affinity of any one of reference compounds 1-59 for GPR174. In alternate examples, the compound allosterically binds to GPR174 and decreases the apparent binding affinity of any one of reference compounds 1-59 for GPR174. In alternate examples, the compound increases the apparent binding affinity of any one of reference compounds 1-59 for GPR174. In one example, said compound has a structure selected from the group consisting of Formula I-VI. In one example, said compound inhibits lysophosphatidylserine (LysoPS)-dependent activation of the GPR174 receptor in said cell. In one example, said compound inhibits PS-dependent activation of the GPR174 receptor in said cell.

The cell expressing GPR174 may be a eukaryotic cell, such as a mammalian cell (*e.g.*, a human cell). The cell may be in a mammal (*e.g.*, a human, non-human primate, rodent, canine, feline, equine, swine or bovine). In some examples, the cell is contacted *in vitro*. In some examples, the cell is in a mammal and is contacted *in vivo*. In some examples, the cell expressing GPR174 is an immune cell, such as a T cell. In particular examples, the mammal (*e.g.*, human) may be suffering from, or at risk for developing cancer.

In another example, the disclosure features a compound for use in treating cancer, characterized in that the compound interacts with GPR174 to inhibit a GPR174-mediated signaling pathway (*e.g.*, a Gs signaling pathway) wherein the GPR174 inhibitory compound is used for treating cancer either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent. In certain examples, this GPR174 inhibitory compound is characterized in that it also exhibits the ability to alter the cellular distribution of a recombinant GPR174 polypeptide modified to include a nuclear localization signal as compared to the

cellular distribution of the recombinant GPR174 polypeptide in the absence of the compound. In some examples, the method comprises contacting a cancer cell expressing GPR174 and/or an immune cell expressing GPR174 with an isolated compound predetermined to functionally interact with GPR174 and inhibit a GPR174-mediated signaling pathway either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent. In some examples, the method comprises contacting an immune cell expressing GPR174, such as a T cell with a compound that inhibits a GPR174-mediated signaling pathway either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent. In some examples, the method comprises performing at least one assay to measure the functional interaction of said compound with GPR174 prior to administering said compound to the subject. In another example, the disclosure features a compound for use in treating a tumor in a patient suffering from cancer, characterized in that the compound interacts with GPR174 to inhibit a GPR174-mediated signaling pathway (*e.g.*, a Gs signaling pathway) either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent. In certain examples, this GPR174 inhibitory compound is characterized in that it also exhibits the ability to alter the cellular distribution of a recombinant GPR174 polypeptide modified to include a nuclear localization signal as compared to the cellular distribution of the recombinant GPR174 polypeptide in the absence of the compound. In some examples, the tumor comprises regulatory T cell (Treg) infiltration. In some examples, the tumor comprising Treg infiltration is a solid organ tumor. In some examples, the tumor is in a subject suffering from a cancer selected from the group consisting of breast, lung (such as small-cell lung cancer or non-small cell lung cancer), colorectal, cervical, renal, ovarian, melanoma, pancreatic, hepatocellular, gastric, glioblastoma, glioma, bladder, myeloma (such as multiple myeloma), prostate, thyroid, testicular, and esophageal cancer. In some examples, the method comprises performing at least one assay to measure the functional interaction of said compound with GPR174 prior to administering said compound to the subject

In another example, the disclosure features a method of treating or preventing cancer in a subject in need thereof. The method involves administering to the subject a compound that binds to and inhibits the GPR174 receptor, thereby inhibiting a GPR174-

mediated signaling pathway, wherein inhibition of the GPR174-mediated signaling pathway with a GPR174 inhibitory agent, optionally in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent, results in treatment or prevention of the cancer. In some examples, the method comprises administering to the subject an isolated compound predetermined to functionally interact with GPR174 and to inhibit a GPR174-mediated signaling pathway wherein inhibition of the signaling pathway results in the treatment of the cancer. In some examples, said GPR174 inhibitory compound is characterized by at least one of the following criteria:

(i) said compound has a structure selected from the group consisting of Formula I-VI;

(ii) said compound changes the binding affinity of any one of reference compounds 1-59 (as set forth in Table 1) to GPR174; and/or

(iii) said compound causes a difference in the inhibitory activity of any one of reference compounds 1-59 (as set forth in Table 1), in a GPR174-mediated signaling pathway assay when tested in the presence of said reference compound as compared to the inhibitory activity of the reference compound alone. In some examples, said compound inhibits LysoPS-dependent activation of the GPR174 receptor in said subject. In some examples, said compound inhibits PS-dependent activation of the GPR174 receptor in said subject. In some examples, said GPR174 inhibitory compound is characterized by at least one of the following criteria:

(i) said compound has a structure selected from the group consisting of Formula I-VI;

(ii) said compound changes the apparent binding affinity of any one of reference compounds 1-59 (as set forth in Table 1) for GPR174; and/or

(iii) said compound causes a difference in the inhibitory activity of any one of reference compounds 1-59 (as set forth in Table 1), in a GPR174-mediated signaling pathway assay when tested in the presence of said reference compound as compared to the inhibitory activity of the reference compound alone. In some examples, said compound inhibits LysoPS-dependent or PS-dependent activation of the GPR174 receptor in said subject. In another example, the disclosure features a method of stimulating T cell-mediated immunity in a subject suffering from cancer comprising administering to the subject a small molecule

compound predetermined to inhibit a GPR174-mediated signaling pathway either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor and/or a CD73 inhibitor. In some examples, the compound inhibits GPR174-mediated signaling in a regulatory T cell, thereby inhibiting the growth and/or proliferation and/or inhibiting the activity of the regulatory T cell. In some examples, the compound inhibits GPR174-mediated signaling in an effector T cell, thereby stimulating the growth and/or proliferation and/or cytotoxic activity of the effector T cell. In some examples, the subject is suffering from a tumor comprising regulatory T cells and inhibition of GPR174 inhibits and/or suppresses growth and/or proliferation of regulatory T cells. In some examples of any of the above examples, the cell is in a mammal, and said mammal is suffering from, or at risk for developing a cancer.

In some examples, the subject is suffering from or harboring a neoplasm not recognized by the body as self. In some examples, the neoplasm is a non-malignant neoplasm. In some examples, the neoplasm is a malignant neoplasm.

In some examples, the subject is suffering from, or is harboring, a malignant neoplasm (*i.e.*, cancer), selected from the group consisting of: acoustic neuroma, anal cancer (including carcinoma in situ), squamous cell carcinoma, adrenal tumor (including adenoma, hyperaldosteronism, adrenalcortical cancer), Cushing's syndrome, benign paraganglioma, appendix cancer (including pseudomyxoma peritonei, carcinoid tumors, non-carcinoid appendix tumors), bile duct cancer (including intrahepatic bile duct cancer, extrahepatic bile duct cancer, perihilar bile duct cancer, distal bile duct cancer), gallbladder cancer, bone cancer (including chondrosarcoma, osteosarcoma, malignant fibrous histiocytoma, fibrosarcoma, chordoma), brain tumor (including craniopharyngioma, dermoid cysts, epidermoid tumors, glioma, astrocytoma, low-grade astrocytoma, anaplastic astrocytoma, ependymoma, glioblastoma, oligodendrogliomas, hemangioblastoma, pineal gland tumors, pituitary tumors, sarcoma, chordoma), breast cancer (including lobular carcinoma, triple negative breast cancer, recurrent breast cancer, brain metastases), bladder cancer (including transitional cell bladder cancer, squamous cell carcinoma, adenocarcinoma), cancers of unknown urinary (CUP), (including adenocarcinoma, poorly differentiated carcinoma, squamous cell carcinoma, poorly differentiated malignant neoplasm, neuroendocrine carcinoma), cervical cancer (including squamous cell carcinoma, adenocarcinoma, mixed carcinoma), carcinoid tumors, childhood germ cell tumors (including yolk sac tumors, teratoma, embryonal carcinoma, polyembryoma,

spinal tumors, extradural spinal tumors, osteblastoma, enchondroma, aneurysmal bone cysts, giant cell tumors, hemangioma, eosinophilic granuloma, osteosarcoma, chordoma, chondrosarcoma, plasmacytoma); Stomach cancers (including lymphoma, gastrointestinal stromal tumors, carcinoid tumors); Testicular cancers (including germ cell tumors, 5 nonseminoma, seminoma, embryonal carcinoma, yolk sac tumors, teratoma, sertoli cell tumors, choriocarcinoma, stromal tumors, leydig cell tumors); Throat cancers (including squamous cell carcinoma); Thyroid cancers (including papillary thyroid cancer, follicular thyroid cancer, hurthle cell carcinoma, medullary thyroid cancer, anaplastic thyroid cancer); Uterine cancers (including endometrioid adenocarcinoma, uterine carcinosarcoma, uterine sarcoma); Vaginal 10 cancers (including squamous cell carcinoma, adenocarcinoma, melanoma, sarcoma); Vulvar cancers (including squamous cell carcinoma, adenocarcinoma, melanoma, sarcoma); von Hippel Lindau Diseases; Waldenström's Macroglobulinemias; and Wilms' Tumors.

In some examples, the subject is suffering from, or is harboring, a malignant or non-malignant neoplasm as set forth in paragraphs 1-10 below:

15 Connective tissue, (including adult fibrous tissue, embryonic (myxomatous) fibrous tissue, fat, cartilage, bone, notochord):

1a. benign neoplasms of the connective tissue include: fibroma, myxoma, lipoma, chondroma, osteoma and fibrous histiocytoma.

1b. malignant neoplasms of the connective tissue include: fibrosarcoma, 20 myxosarcoma, liposarcoma, chondrosarcoma, osteosarcoma, chordoma, malignant fibrosis histiocytoma,

Endothelium and Mesothelium (including blood vessels, lymph vessels and mesothelium):

2a. benign neoplasms of the endothelium and mesothelium include: 25 hemangioma, hemangiopericytoma and lymphangioma.

2b. malignant neoplasms of the endothelium and mesothelium include: hemangiosarcoma, angiosarcoma, lymphangiosarcoma and mesothelioma.

Blood and Lymphoid cells (including hematopoietic cells and lymphoid tissue,

3a. benign neoplasms of the blood and lymphoid cells include: preleukemias, 30 myeloproliferative disorders and plasmacytosis.

3b. malignant neoplasms of the blood and lymphoid cells include: plasmacytoma, multiple myeloma, Hodgkin lymphoma and Non-Hodgkin lymphoma.

Other Neural Crest-derived cells (including pigment-producing cells in skin, eyes, and occasional other sites, Schwann cells of peripheral nervous system and Merkel cells in squamous epithelium):

5 8a. benign neoplasms of neural crest-derived cells include: nevus, schwannoma and neurilemmoma.

8b. malignant neoplasms of neural crest-derived cells include: melanoma, malignant schwannoma and Merkel cell neoplasm.

Tumors (including breast tissue and renal anlage tissue)

9a. benign neoplasms of breast tissue include fibroadenoma.

10 9b. malignant neoplasms of breast tissue include cystosarcoma phylloids; malignant neoplasms of renal anlage include Wilms tumor.

Ovary and Testis (including multipotential cells, germ cells, connective tissue stroma and epithelial tissue)

15 10a. Malignant neoplasms of ovary and testis include: seminoma (dysgerminoma in women), choriocarcinoma, embryonal carcinoma, endodermal sinus tumor, and teratocarcinoma and Sertoli-Leydig cell tumors.

In some examples, the subject is suffering from, or is harboring a non-malignant tumor selected from the group consisting of adenoma (including liver, adrenal, pituitary, thyroid and colon and gastric polyps), astrocytoma, craniopharyngioma, desmoid tumor, 20 enchondroma, fibromas or fibroids of any organ, such as uterine fibroma, ganglioneuroma, hemangioma, lipoma, lipoblastoma, hibernoma, lymphangioma, meningioma, myoma (including leiomyomas and rhabdomyomas), nevi or moles, neuroma, neurofibroma, schwannoma, osteochondroma and papilloma (including skin, cervix, breast duct and conjunctiva).

25 In some examples, the subject is a cancer patient, wherein the cancer is selected from the group consisting of breast cancer, melanoma, colon cancer, urological cancer, lung cancer, small-cell and non-small-cell lung cancer, relapsed or refractory malignancies, non-Hodgkin and Hodgkin lymphomas, lymphoma, follicular lymphoma, lymphocytic lymphoma, CNS lymphoma, T-cell lymphoma, AIDS-related lymphoma, acute lymphoblastic leukemia, 30 gastrointestinal cancers, liver cancer, hepatocellular carcinoma, ovarian cancer, pancreatic cancer, bile duct cancer, prostate cancer, renal carcinoma, bladder cancer, colorectal cancer, multiple myeloma, mesothelioma, cervical cancer, vaginal cancer, anal cancer,

oropharyngeal cancer, myelogenous leukemia, chronic myeloid leukemia, gastric cancer, nasopharyngeal carcinoma, head and neck carcinoma, glioblastoma, gliosarcoma, squamous cell brain cancer, malignant glioma, diffuse pontine gliomas, esophageal cancer, thyroid cancer, astrocytoma, thoracic cancer, endometrial cancer, cutaneous cell carcinoma, leukemia, 5 acinar cell carcinoma, adenocarcinoma, bronchioloalveolar carcinoma, cholangiocarcinoma, chordoma, giant cell carcinoma, intestinal carcinoma, major salivary gland carcinoma, malignant odontogenic neoplasm, malignant peripheral nerve sheath tumor, skin cancer, testicular cancer, germ cell tumor, neuroendocrine carcinoma, parathyroid carcinoma, pituitary gland carcinoma, placental choriocarcinoma, scrotal cancer, tracheal carcinoma, transitional 10 cell carcinoma, cancer of the uterus, vulvar cancer, kidney cancer, rectum cancer, fallopian tube carcinoma, peritoneal carcinoma, epithelial cancer, pleural mesothelioma, sarcomatoid carcinoma, synovial sarcoma, nephroblastoma, neuroblastoma, adult acute myeloid leukemia, myelodysplastic/myeloproliferative neoplasm, embryonal carcinoma, Kaposi sarcoma, bone cancer, uterine cancer, stomach cancer, carcinoma of the endometrium, cancer of the small 15 intestine, cancer of the endocrine system, cancer of the paragland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, cancer of the ureter, carcinoma of the pelvis, neoplasm of the central nervous system, primary tumor angiogenesis, spinal axis tumor, epidermoid cancer, environmentally induced cancers including those induced by asbestos, adenosarcoma, adenosquamous carcinoma, adrenocortical carcinoma, astrocytic 20 tumors, basal cell carcinoma, chondrosarcoma, Ewing's sarcoma, gallbladder cancer, hypopharyngeal cancer, intraocular melanoma, laryngeal cancer, leiomyosarcoma, lip and oral cavity cancer, malignant mesothelial tumors, malignant thymoma, medulloblastoma, medulloepithelioma, Merkel cell carcinoma, mucoepidermoid carcinoma, myelodysplastic syndrome, nasal cavity and paranasal sinus cancer, osteosarcoma, pulmonary blastoma, pineal 25 and supratentorial primitive neuroectodermal tumors, plasma cell neoplasm, retinoblastoma, rhabdomyosarcoma, sarcoma, neuroectodermal tumors and Wilm's tumor.

In some examples, the subject is a cancer patient suffering from, or harboring a solid tumor. In some examples, the cancer patient has a solid tumor that is infiltrated with lymphocyte cells that express GPR174.

30 In some examples, the subject has one or more tumors infiltrated with regulatory T cells, such as, for example, breast, lung (such as small-cell lung cancer or non-small cell lung cancer), colorectal, cervical, renal, ovarian, melanoma, pancreatic,

hepatocellular, gastric, glioblastoma, glioma, bladder, myeloma (such as multiple myeloma), prostate, thyroid, testicular, and esophageal cancer.

In some examples, the method comprises administering a GPR174 inhibitory compound as a single agent. In some examples, the method comprises administering a GPR174 inhibitory compound in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent. In some examples, the method comprises administering a GPR174 inhibitory compound in combination with an A2aR antagonist. In some examples, the method comprises administering a GPR174 inhibitory compound in combination with an A2bR antagonist. In some examples, the method comprises administering a GPR174 inhibitory compound in combination with a Treg attenuating agent, such as, for example, an agent that binds to one or more of GITR, CTLA-4, CD25, LAG3, TIGIT, NRP1, TGF- β , CCR2, CCR4, CCR8, TNFR2, and/or EZH2 and attenuates, depletes or otherwise impairs the tumor suppressor function of Treg cells. In some examples, the Treg attenuating agent is a small molecule. In some examples, the Treg attenuating agent is selected from the group consisting of an anti-GITR, anti-CTLA-4, anti-CD25, anti-LAG3, anti-TIGIT, anti-NRP1, anti-TGF- β , anti-CCR2, anti-CCR4, anti-CCR8, anti-TNFR2, and/or anti-EZH2 antibody. Exemplary Treg attenuating agents for use in the compositions and methods of the disclosure are provided in Example 25.

In some examples, the method further includes administering one or more additional therapeutic agents. In certain examples, the cancer cell is further contacted with a chemotherapeutic agent.

In another example, the disclosure features a pharmaceutical composition including a combination of a GPR174 inhibitor selected from any of the compounds described below (*e.g.*, those of Formulas I-VI and the compounds 1-59 of Table 1) and an inhibitor of ATP-Adenosine-A2aR-A2bR-mediated signaling (such as an A2aR antagonist, an A2bR antagonist and/or a CD73 inhibitor and/or a CD38 inhibitor and/or a CD39 inhibitor and/or a Treg attenuating agent) and a pharmaceutically acceptable carrier. The pharmaceutical composition may be in unit dosage form. In particular examples, the compound may be formulated for oral, intravenous, intraperitoneal, intramuscular, topical, rectal, cutaneous, subcutaneous, nasal, skin (*e.g.*, as a transdermal patch), intracerebroventricular, intraparenchymal, intrathecal, inhalational, intracranial or ocular administration. The

pharmaceutical compositions may be used to carry out the methods disclosed herein.

In another example, the disclosure features compounds of Formula I that have activity as GPR174 inhibitors. In some examples, the compounds of Formula I have a structure in accordance with Formula IA or Formula IB or Formula IC as described herein. In some
5 examples, the disclosure features pharmaceutical compositions comprising a compound of Formula I, such as a compound in accordance with Formula IA or Formula IB or Formula IC as described herein. Compounds of Formula I are useful in the methods of inhibiting at least one GPR174-mediated signaling pathway either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a
10 CD73 inhibitor and/or a Treg attenuating agent for treating or preventing cancer as described herein.

In another example, the disclosure features compounds of Formula II that have activity as GPR174 inhibitors. In some examples, the compounds of Formula II have a structure in accordance with Formula IIA, Formula IIB, Formula IIC, Formula IID or Formula
15 IIE as described herein. In some examples, the disclosure features pharmaceutical compositions comprising a compound of Formula II, such as a compound in accordance with Formula IIA, Formula IIB, Formula IIC, Formula IID or Formula IIE as described herein. Compounds of Formula II are useful in the methods of inhibiting at least one GPR174-mediated signaling pathway either as a single agent or in combination with at least one of an A2aR
20 antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent for treating or preventing cancer as described herein.

In another example, the disclosure features compounds of Formula III that have activity as GPR174 inhibitors. In some examples, the compounds of Formula III have a structure in accordance with Formula IIIA, Formula IIIB, Formula IIIC, Formula IIID, Formula
25 IIIE, or Formula IIIF as described herein. In some examples, the disclosure features pharmaceutical compositions comprising a compound of Formula III, such as a compound in accordance with Formula IIIA, Formula IIIB, Formula IIIC, Formula IIID, Formula IIIE or Formula IIIF as described herein. Compounds of Formula III are useful in the methods of inhibiting at least one GPR174-mediated signaling pathway either as a single agent or in
30 combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent for treating or preventing cancer as described herein.

In another example, the disclosure features compounds of Formula IV that have activity as GPR174 inhibitors. In some examples, the compounds of Formula IV have a structure in accordance with Formula IVA, Formula IVB, Formula IVC, Formula IVD, or Formula IVE as described herein. In some examples, the disclosure features pharmaceutical compositions comprising a compound of Formula IV, such as a compound in accordance with Formula IVA, Formula IVB, Formula IVC, Formula IVD or Formula IVE as described herein. Compounds of Formula IV are useful in the methods of inhibiting at least one GPR174-mediated signaling pathway either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent for treating or preventing cancer as described herein.

In another example, the disclosure features compounds of Formula V that have activity as GPR174 inhibitors. In some examples, the disclosure features pharmaceutical compositions comprising a compound of Formula V as described herein. Compounds of Formula V are useful in the methods of inhibiting at least one GPR174-mediated signaling pathway either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent for treating or preventing cancer as described herein.

In another example, the disclosure features compounds of Formula Va that have activity as GPR174 inhibitors. In some examples, the disclosure features pharmaceutical compositions comprising a compound of Formula Va as described herein. Compounds of Formula Va are useful in the methods of inhibiting at least one GPR174-mediated signaling pathway either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor, and/or a Treg attenuating agent for treating or preventing cancer as described herein.

In another example, the disclosure features compounds of Formula VI that have activity as GPR174 inhibitors. In some examples, the disclosure features pharmaceutical compositions comprising a compound of Formula VI as described herein. Compounds of Formula VI are useful in the methods of inhibiting at least one GPR174-mediated signaling pathway either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent for treating or preventing cancer as described herein.

In another example, the disclosure features a method of preparing a pharmaceutical composition including a compound that is an inhibitor of a GPR174-mediated signaling pathway, the compound having been contacted *in vitro* with a mammalian cell expressing GPR174 and determined to inhibit a GPR174-mediated signaling pathway, wherein
5 the ability of the compound to inhibit said GPR174-mediated signaling pathway is indicative of being a GPR174 inhibitor, the method comprising formulating the GPR174 inhibitory compound with a pharmaceutically acceptable carrier either as a single agent or in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent, wherein said GPR174 inhibitory
10 compound is characterized by at least one of the following criteria:

(i) said compound has a structure selected from the group consisting of Formula I-VI;

(ii) said compound changes the binding affinity of any one of reference compounds 1-59 (as set forth in Table 1) to GPR174; and/or

15 (iii) said compound causes a difference in the inhibitory activity of any one of reference compounds 1-59 (as set forth in Table 1), in a GPR174-mediated signaling pathway assay when tested in the presence of said reference compound as compared to the inhibitory activity of the reference compound alone.

In another example, the disclosure features a method of preparing a pharmaceutical composition including a compound that is an inhibitor of a GPR174-mediated signaling pathway, the compound having been contacted *in vitro* with a mammalian cell expressing GPR174 and determined to inhibit a GPR174-mediated signaling pathway, wherein
20 the ability of the compound to inhibit said GPR174-mediated signaling pathway is indicative of being a GPR174 inhibitor, the method comprising formulating the GPR174 inhibitory compound with a pharmaceutically acceptable carrier, either as a single agent or in combination
25 with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and/or a Treg attenuating agent wherein said GPR174 inhibitory compound is characterized by at least one of the following criteria:

(i) said compound has a structure selected from the group consisting of Formula
30 I-VI;

(ii) said compound changes the apparent binding affinity of any one of reference compounds 1-59 (as set forth in Table 1) to GPR174; and/or

(iii) said compound causes a difference in the inhibitory activity of any one of reference compounds 1-59 (as set forth in Table 1), in a GPR174-mediated signaling pathway assay when tested in the presence of said reference compound as compared to the inhibitory activity of the reference compound alone.

5 In another example, the disclosure features a GPR174-interacting compound comprising a structure according to any of Formulas I-VI disclosed herein and a detectable moiety. In some examples, the GPR174-interacting compound is characterized by at least one of the following criteria:

10 (i) said compound has a structure selected from the group consisting of Formula I-VI;

 (ii) said compound changes the binding affinity of any one of reference compounds 1-59 (as set forth in Table 1) to GPR174; and/or

 (iii) said compound causes a difference in the inhibitory activity of any one of reference compounds 1-59 (as set forth in Table 1), in a GPR174-mediated signaling pathway
15 assay when tested in the presence of said reference compound as compared to the inhibitory activity of the reference compound alone. In one example, the GPR174-interacting compound comprising a detectable moiety comprises a structure according to any of compounds 1-59 disclosed in Table 1. In particular examples, the detectable moiety is at least one of a radioisotope, a bioluminescent tag, a chemiluminescent tag, or a photo-affinity label. In one
20 example, the detectable moiety is a radioisotope.

 In another example, the disclosure features a GPR174-interacting compound comprising a structure according to any of Formulas I-VI disclosed herein and a detectable moiety. In some examples, the GPR174-interacting compound is characterized by at least one of the following criteria:

25 (i) said compound has a structure selected from the group consisting of Formula I-VI;

 (ii) said compound changes the apparent binding affinity of any one of reference compounds 1-59 (as set forth in Table 1) to GPR174; and/or

30 (iii) said compound causes a difference in the inhibitory activity of any one of reference compounds 1-59 (as set forth in Table 1), in a GPR174-mediated signaling pathway assay when tested in the presence of said reference compound as compared to the inhibitory activity of the reference compound alone. In one example, the GPR174-interacting

compound comprising a detectable moiety comprises a structure according to any of compounds 1-59 disclosed in Table 1. In particular examples, the detectable moiety is at least one of a radioisotope, a bioluminescent tag, a chemiluminescent tag, or a photo-affinity label. In one example, the detectable moiety is a radioisotope.

5 In any of the above examples, the GPR174 inhibitory compound may be a synthetic compound, a semi-synthetic compound (*e.g.*, a chemically modified steroid derived from a natural source), or a natural product. In certain examples, the compound is not an endogenous ligand of GPR174 (*e.g.*, is a surrogate ligand). In various examples, the compound is a functional inhibitor of a GPR174-mediated signaling pathway (*e.g.*, an antagonist, partial
10 agonist, inverse agonist, partial inverse agonist, or negative allosteric modulator). In some examples, the compound is an antagonist of GPR174 and inhibits at least one GPR174-mediated signaling pathway in the presence of an agonist or partial agonist. In some examples, the compound is an inverse agonist. In specific examples, the compound decreases GPR174-mediated signaling pathway activation at least 2/3, 1/2, 1/5, 1/10, 1/50, or 1/100 of the basal
15 activity at a concentration less than 40, 25, 10, 5, 1, 0.5, 0.25, 0.1, or 0.5 μM (*e.g.*, from 0.01 μM to 0.5 μM , from 0.01 μM to 0.5 μM , from 0.01 μM to 5 μM , from 0.01 μM to 10 μM , from 0.01 μM to 25 μM , or from 0.01 μM to 40 μM). In some examples, the compound is an inverse agonist and decreases at least one GPR174-mediated signaling pathway by at least 1/2 in comparison to basal activity at a concentration of less than 10 μM (*e.g.*, from 0.01 μM to 10
20 μM).

 The GPR174 inhibitory compound may be a polypeptide, an antibody, a non-peptide compound, an expression inhibitor (*e.g.*, GPR174 antisense nucleic acid molecules such as antisense RNA, antisense DNA or antisense oligonucleotides, GPR174 ribozymes or GPR174 RNAi molecules) that inhibits GPR174 expression, or a small molecule (*e.g.*, a small
25 organic or organometallic molecule).

 In some examples, the compound was not in development by any entity prior to January 11, 2019. In some examples, the compound is not a regulatory agency-approved compound. In some examples, the compound is a compound that was not approved prior to January 11, 2019 by the United States Food and Drug Administration or other regulatory
30 authority for use in a disease associated with GPR174. In some examples, the compound was not in development by any entity prior to January 11, 2019 for use in a disease associated with GPR174. In some examples, the compound was not approved prior to

January 11, 2019 by the United States Food and Drug Administration or equivalent regulatory authority as targeting GPR174. In particular examples, the compound is not an antibody or a receptor-binding fragment thereof. In particular examples, the compound is not a pepducin, a cell-penetrating membrane-tethered peptide (see, *e.g.*, Covic L. et al., *PNAS* 99(2):643-8 (2002)).

In particular examples of any example, the GPR174 inhibitory isolated compound is not LysoPS or PS.

In certain examples, the GPR174 inhibitory compound is capable of functionally interacting with human GPR174 having the sequence of SEQ ID NO: 1 and/or altering the cellular distribution of a recombinant GPR174 polypeptide (*e.g.*, human GPR174 having the sequence of SEQ ID NO: 1) modified to include a nuclear localization signal as compared to the cellular distribution of the recombinant GPR174 polypeptide in the absence of the compound.

The compound may be specific for GPR174, *e.g.*, as compared to a reference panel of GPCRs.

In particular examples of any example, the isolated compound selectively binds to GPR174 and does not bind to P2Y10.

In particular examples of any example, the isolated compound selectively binds to GPR174 and does not bind to GPR34.

In particular examples of any example, the isolated compound functionally interacts with GPR174 and does not bind to P2Y10.

In particular examples of any example, the isolated compound functionally interacts with GPR174 and does not bind to GPR34.

In particular examples of any example, the isolated compound is not disclosed in US2015/0361119.

In addition, the methods and compositions of any of the examples of the disclosure may employ any compound having a structure according to the formulas described below, such as the exemplary compounds in Table 1, or a pharmaceutically acceptable salt thereof.

In some examples, the GPR174 inhibitory compound has a structure according to the following formula (I):

optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkynyl; or

one of:

(i) R¹² and R¹³, together with the atoms to which each is attached, combine to form an optionally substituted 5-, 6-, or 7-member ring;

5 (ii) R¹³ and R¹⁴, together with the atoms to which each is attached, combine to form an optionally substituted 5-, 6-, or 7-member ring;

(iii) R¹⁴ and R¹⁵, together with the atoms to which each is attached, combine to form an optionally substituted 5-, 6-, or 7-member ring; and

(iv) R¹⁵ and R¹⁶, together with the atoms to which each is attached, combine to
10 form an optionally substituted 5-, 6-, or 7-member ring;

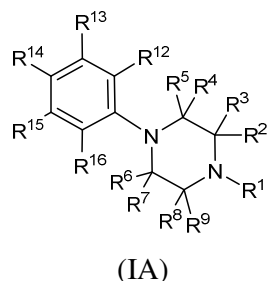
and

R¹⁷ is H, hydroxyl, cyano, optionally substituted amino, optionally substituted amido, optionally substituted carboxamide, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heterocyclyloyl,
15 optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₁-C₆ alkylsulfinyl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylsulfinyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfinyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₆ heteroalkyl,
20 optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₂-C₆ heteroalkynyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₄-C₁₀ cycloalkenyl, optionally substituted C₈-C₁₀ cycloalkynyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkenyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkenyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heterocyclyl, optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkenyl, or optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkynyl;
25 wherein three or fewer of X³, X⁴, X⁵, X⁶, and X⁷ are N; and
30 at least one of X¹ and X² is N.

In some examples of formula (I), X¹ is N. In certain examples of formula (I), X² is N. In particular examples of formula (I), X³ is CR¹². In other

examples of formula (I), X^4 is CR^{13} . In yet other examples of formula (I), X^5 is CR^{14} . In still other examples of formula (I), X^6 is CR^{15} . In certain other examples of formula (I), X^7 is CR^{16} .

In particular examples of formula (I), the isolated compound has the structure according to formula (IA):



In certain examples of formula (I) or (IA), R^2 is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_6 - C_{10} aryl C_1 - C_6 alkyl, optionally substituted C_1 - C_9 heteroaryl, optionally substituted C_1 - C_9 heteroaryl C_1 - C_6 alkyl, optionally substituted C_1 - C_9 heterocyclyl, or optionally substituted C_1 - C_9 heterocyclyl C_1 - C_6 alkyl. In some examples of formula (I) or (IA), R^2 is H or optionally substituted C_1 - C_6 alkyl. In other examples of formula (I) or (IA), R^2 is H.

In yet other examples of formula (I) or (IA), R^3 is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_6 - C_{10} aryl C_1 - C_6 alkyl, optionally substituted C_1 - C_9 heteroaryl, optionally substituted C_1 - C_9 heteroaryl C_1 - C_6 alkyl, optionally substituted C_1 - C_9 heterocyclyl, or optionally substituted C_1 - C_9 heterocyclyl C_1 - C_6 alkyl. In still other examples of formula (I) or (IA), R^3 is H or optionally substituted C_1 - C_6 alkyl. In particular examples of formula (I) or (IA), R^3 is H.

In some examples of formula (I) or (IA), R^4 is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_6 - C_{10} aryl C_1 - C_6 alkyl, optionally substituted C_1 - C_9 heteroaryl, optionally substituted C_1 - C_9 heteroaryl C_1 - C_6 alkyl, optionally substituted C_1 - C_9 heterocyclyl, or optionally substituted C_1 - C_9 heterocyclyl C_1 - C_6 alkyl. In certain examples of formula (I) or (IA), R^4 is H or optionally substituted C_1 - C_6 alkyl. In particular examples of formula (I) or (IA), R^4 is H.

In other examples of formula (I) or (IA), R⁵ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or
5 optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In yet other examples of formula (I) or (IA), R⁵ is H or optionally substituted C₁-C₆ alkyl. In still other examples of formula (I) or (IA), R⁵ is H.

In particular examples of formula (I) or (IA), R⁶ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or
10 optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In certain examples of formula (I) or (IA), R⁶ is H or optionally substituted C₁-C₆ alkyl. In some examples of formula (I) or (IA), R⁶ is H.

In certain examples of formula (I) or (IA), R⁷ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or
15 optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In other examples of formula (I) or (IA), R⁷ is H or optionally substituted C₁-C₆ alkyl. In still other examples of formula (I) or (IA), R⁷ is H.
20

In some examples of formula (I) or (IA), R⁸ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or
25 optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In certain examples of formula (I) or (IA), R⁸ is H or optionally substituted C₁-C₆ alkyl. In particular examples of formula (I) or (IA), R⁸ is H.

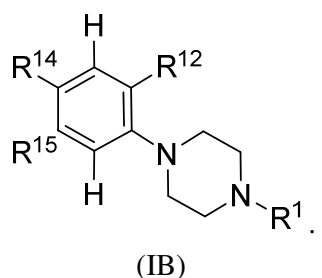
In other examples of formula (I) or (IA), R⁹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or
30

optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In yet other examples of formula (I) or (IA), R⁹ is H or optionally substituted C₁-C₆ alkyl. In still other examples of formula (I) or (IA), R⁹ is H.

In particular examples of formula (I) or (IA), R¹³ is H, hydroxy, optionally substituted amino, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₉ heteroaryl, or optionally substituted C₁-C₉ heterocyclyl. In certain examples of formula (I) or (IA), R¹³ is H or optionally substituted C₁-C₆ alkyl. In other examples of formula (I) or (IA), R¹³ is H.

In certain examples of formula (I) or (IA), R¹⁶ is H, halogen, cyano, nitro, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocyclyloyl, hydroxycarbonyl, optionally substituted ester, or optionally substituted C₁-C₉ heterocyclyl. In other examples of formula (I) or (IA), R¹⁶ is H or optionally substituted C₁-C₆ alkyl. In yet other examples of formula (I) or (IA), R¹⁶ is H.

In some examples of formula (I), the compound has the structure according to formula (IB):



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In certain examples of formula (I), (IA), or (IB), R¹² is H, halogen, cyano, nitro, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heterocyclyloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfonyl, hydroxycarbonyl, optionally substituted ester, optionally substituted carboxamide, optionally substituted C₁-C₆ alkanoyloxy, optionally substituted C₇-C₁₁

25

aryloxy, optionally substituted C₂-C₁₀ heteroaryloxy, optionally substituted C₂-C₁₀ heterocycloxy, optionally substituted C₁-C₉ heteroaryl, or optionally substituted C₁-C₉ heterocyclyl. In particular examples of formula (I), (IA), or (IB), R¹² is H, halogen, cyano, nitro, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkanoyl, optionally substituted C₁-C₆ alkylsulfonyl, hydroxycarbonyl, optionally substituted ester, optionally substituted carboxamide, optionally substituted C₁-C₆ alkanoyloxy, optionally substituted C₁-C₉ heteroaryl, or optionally substituted C₁-C₉ heterocyclyl. In other examples of formula (I), (IA), or (IB), R¹² is H, halogen, cyano, nitro, optionally substituted C₁-C₆ alkyl, optionally substituted ester, optionally substituted carboxamide, optionally substituted C₁-C₆ alkanoyloxy, or optionally substituted C₁-C₉ heteroaryl. In yet other examples of formula (I), (IA), or (IB), R¹² is H, halogen, nitro, optionally substituted ester, or optionally substituted C₁-C₆ alkanoyloxy. In still other examples of formula (I), (IA), or (IB), R¹² is halogen (*e.g.*, R¹² is fluorine). In certain examples of formula (I), (IA), or (IB), R¹² is nitro.

In particular examples of formula (I), (IA), or (IB), R¹⁴ is H, halogen, cyano, nitro, optionally substituted C₁-C₆ alkyl, hydroxycarbonyl, optionally substituted ester, optionally substituted carboxamide, optionally substituted C₁-C₆ alkanoyloxy, optionally substituted C₇-C₁₁ aryloxy, optionally substituted C₂-C₁₀ heteroaryloxy, optionally substituted C₂-C₁₀ heterocycloxy, optionally substituted C₁-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryl, optionally substituted C₂-C₁₀ heterocycloyl, optionally substituted C₂-C₁₀ heteroaryl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfinyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₉ heteroaryl, or optionally substituted C₁-C₉ heterocyclyl. In some examples of formula (I), (IA), or (IB), R¹⁴ is H, halogen, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted ester, optionally substituted carboxamide, optionally substituted C₁-C₆ alkanoyloxy, optionally substituted C₁-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryl, optionally substituted C₂-C₁₀ heterocycloyl, optionally substituted C₂-C₁₀ heteroaryl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylsulfonyl, or optionally substituted C₁-C₉ heteroaryl. In other examples of formula (I), (IA), or (IB), R¹⁴ is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted ester, optionally substituted carboxamide, optionally substituted C₁-C₆ alkanoyloxy, optionally substituted C₁-C₆ alkanoyl. In yet other examples of formula (I), (IA), or (IB), R¹⁴ is

halogen, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ alkanoyl. In still other examples of formula (I), (IA), or (IB), R¹⁴ is halogen (*e.g.*, R¹⁴ is fluorine). In some examples of formula (I), (IA), or (IB), R¹⁴ is optionally substituted C₁-C₆ alkanoyl. In particular examples of formula (I), (IA), or (IB), R¹⁴ is optionally substituted C₂-C₄ alkanoyl.

5 In certain examples of formula (I), (IA), or (IB), R¹⁴ is unsubstituted C₂-C₄ alkanoyl.

In some examples of formula (I), (IA), or (IB), R¹⁵ is H, optionally substituted amino, optionally substituted amido, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In certain examples of formula (I), (IA), or (IB), R¹⁵ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₉ heteroaryl, or optionally substituted C₁-C₉ heterocyclyl. In particular examples of formula (I), (IA), or (IB), R¹⁵ is H or optionally substituted C₁-C₉ heterocyclyl. In other examples of formula (I), (IA), or (IB), R¹⁵ is H. In yet other examples of formula (I), (IA), or (IB), R¹⁵ is optionally substituted C₁-C₉ heterocyclyl (*e.g.*, R¹⁵ is piperidinyl, methyl-substituted piperidinyl or benzpiperidinyl).

In some examples of Formula (IB), R¹ is selected from the group consisting of C₁-C₆ alkanoyl, C₆-C₁₀ aryl, C₇-C₁₁ aryloyl, C₂-C₁₀ heteroaryloyl, C₂-C₇ alkoxycarbonyl, and C₆-C₁₀ arylsulfonyl, wherein R¹ is optionally substituted;

25 R¹² is H, nitro, or halogen;

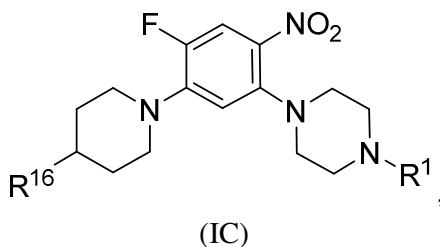
R¹⁴ is C₁-C₆ alkanoyl or halogen; and

R¹⁵ is H or optionally substituted C₁-C₉ heterocyclyl.

In some examples of Formula (IB), R¹ is selected from an optionally substituted group consisting of C₁-C₆-alkanoyl, C₇-C₁₁ aryloyl, C₂-C₁₀ heteroaryloyl, C₂-C₇ alkoxycarbonyl, and C₆-C₁₀ arylsulfonyl.

In some examples of formula (IB), R¹² is nitro, and R¹⁴ is fluoro.

In some examples of formula (IB), R¹⁵ is optionally substituted piperidin-1-yl or optionally substituted azepan-1-yl. In some examples of formula (I), (IA), or (IB), the compound has the structure according to formula (IC):



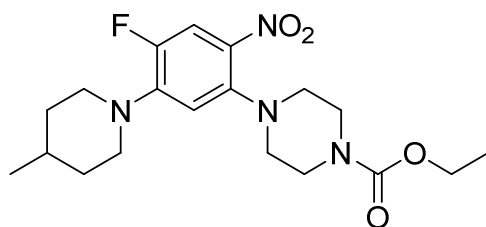
wherein R¹⁶ is H or C₁-C₆ alkyl.

In some examples of formula (IC), R¹⁶ is H or methyl.

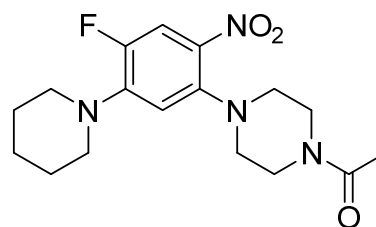
In particular examples of formula (I), (IA), (IB), or (IC), R¹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocyclyloyl, optionally substituted ester, optionally substituted carboxamide, optionally substituted C₁-C₆ alkylsulfonyl, substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₉ heterocyclylsulfonyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In certain examples of formula (I), (IA), (IB), or (IC), R¹ is optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocyclyloyl, optionally substituted ester, optionally substituted carboxamide, optionally substituted C₁-C₆ alkylsulfonyl, substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₉ heterocyclylsulfonyl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, or optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In particular examples of formula (I), (IA), (IB), or (IC), R¹ is optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted ester, optionally substituted carboxamide, optionally substituted C₁-C₆ alkylsulfonyl, substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl,

or optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl. In some examples of formula (I), (IA), (IB), or (IC), R¹ is optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted ester, optionally substituted C₆-C₁₀ arylsulfonyl, or optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl. In other examples of formula (I), (IA), (IB), or (IC), R¹ is optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₆-C₁₀ arylsulfonyl, or optionally substituted ester. In yet other examples of formula (I), (IA), (IB), or (IC), R¹ is optionally substituted C₂-C₇ alkoxycarbonyl (*e.g.*, methyloxycarbonyl or ethyloxycarbonyl). In still other examples of formula (I), (IA), (IB), or (IC), R¹ is optionally substituted C₂-C₆ alkanoyl (*e.g.*, R¹ is acetyl, propanoyl, n-butanoyl, isobutanoyl, or t-pentanoyl). In some examples of formula (I), (IA), (IB), or (IC), R¹ is optionally substituted C₇-C₁₁ aryloyl (*e.g.*, R¹ is 4-fluorobenzoyl or benzoyl). In other examples of formula (I), (IA), (IB), or (IC), R¹ is optionally substituted C₂-C₁₀ heteroaryloyl (*e.g.*, R¹ is 2-thiophenecarbonyl). In certain examples of formula (I), (IA), (IB), or (IC), R¹ is optionally substituted C₆-C₁₀ arylsulfonyl (*e.g.*, R¹ is *p*-tolylsulfonyl or phenylsulfonyl). In other examples of formula (I), (IA), (IB), or (IC), R¹ is optionally substituted C₁-C₆ alkyl, (*e.g.*, R¹ is ethyl or methyl).

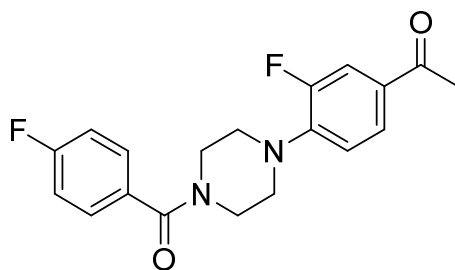
In particular examples of formula (I), (IA), (IB), or (IC), the isolated compound is compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 53:



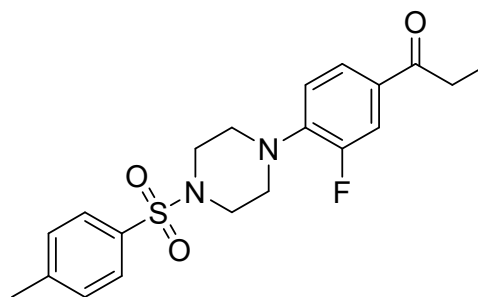
1



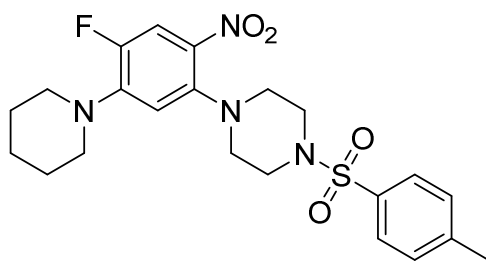
2



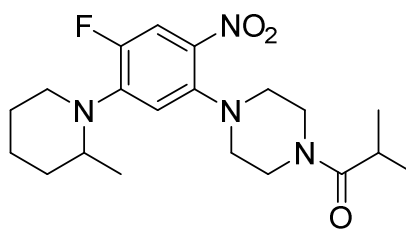
3



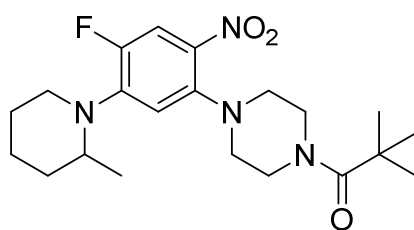
4



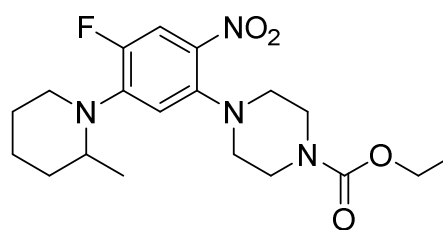
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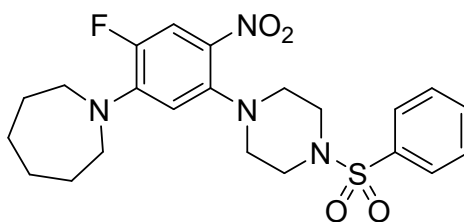
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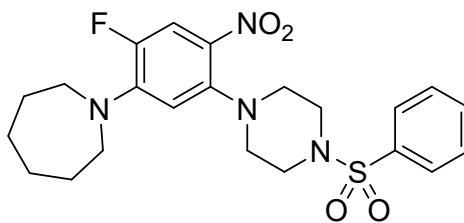


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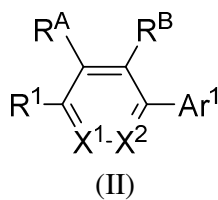
53

In a particular example of formula (IB), the isolated compound is compound 53:



53

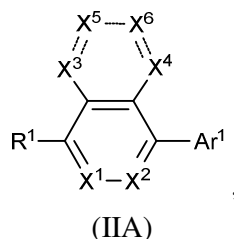
5 In some examples, the GPR174 inhibitory compound has a structure according to formula (II):



or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,

In some examples of formula (II), R^A and R^B , together with the atoms to which each is attached, combine to form an optionally substituted carbocyclic ring. In certain examples of formula (II), R^A and R^B , together with the atoms to which each is attached, combine to form an optionally substituted heterocyclic ring. In particular examples of formula (II), R^A and R^B , together with the atoms to which each is attached, combine to form an optionally substituted 6-membered ring. In other examples of formula (II), R^A and R^B , together with the atoms to which each is attached, combine to form an optionally substituted non-aromatic ring. In yet other examples of formula (II), R^A and R^B , together with the atoms to which each is attached, combine to form an optionally substituted aromatic ring.

In still other examples of formula (II), the isolated compound has a structure according to formula (IIA):



wherein

X^3 is N, CR^4 ;

X^4 is N, CR^5 ;

X^5 is N, CR^6 ;

X^6 is N, CR^7 , or absent; and

each of R^4 , R^5 , R^6 , and R^7 is, independently, H, halo, hydroxy, optionally

substituted amino, optionally substituted amido, thiol, cyano, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 alkoxy, optionally substituted C_6 - C_{10} aryloxy, optionally substituted C_1 - C_9 heteroaryloxy, optionally substituted C_2 - C_6 alkanoyl, optionally substituted C_7 - C_{11} aryloyl, optionally substituted C_2 - C_{10} heteroaryloyl, optionally substituted C_2 - C_{10} heterocyclyloyl, hydroxycarbonyl, optionally substituted C_2 - C_7 alkoxy carbonyl, optionally substituted carboxamide, optionally substituted C_1 - C_6 alkanoyloxy, optionally substituted C_7 - C_{11} aryloyloxy, optionally substituted C_2 - C_{10} heteroaryloyloxy, optionally substituted C_2 - C_{10} heterocyclyloyloxy, optionally substituted C_1 - C_6 thioalkyl, optionally substituted C_1 - C_6 alkylsulfinyl, optionally substituted C_1 - C_6 alkylsulfonyl, optionally substituted C_6 - C_{10} arylthio,

optionally substituted C₆-C₁₀ arylsulfinyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylthio, optionally substituted C₁-C₉ heteroarylsulfinyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₉ heterocyclylsulfinyl, optionally substituted C₁-C₉ heterocyclylsulfonyl, optionally substituted sulfamoyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₂-C₆ heteroalkynyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₄-C₁₀ cycloalkenyl, optionally substituted C₈-C₁₀ cycloalkynyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkenyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkenyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heterocyclyl, optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkenyl, or optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkynyl;

wherein

three or fewer of X¹, X², X³, X⁴, X⁵, and X⁶ are N.

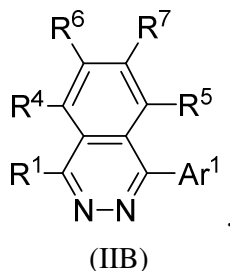
In particular examples of formula (IIA), X³ is CR⁴.

In still other examples of formula (IIA), X⁴ is CR⁵.

In other examples of formula (IIA), X⁵ is CR⁶. In yet other examples of formula (IIA), X⁶ is CR⁷.

In some examples of formula (II) or (IIA), X¹ is N. In certain examples of formula (II) or (IIA), X² is N.

In still other examples of formula (II), the isolated compound has a structure of formula (IIB):



In some examples of formula (IIA) or (IIB), R⁴ is H, optionally substituted amino, halo, optionally substituted amido, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉

heteroaryloxy, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocyclyloyl, hydroxycarbonyl, optionally substituted C₂-C₇ alkoxycarbonyl, optionally substituted carboxamide, optionally substituted C₁-C₆ alkanoyloxy, optionally substituted C₇-C₁₁ aryloxyloxy, optionally substituted C₂-C₁₀ heteroaryloxyloxy, optionally substituted C₂-C₁₀ heterocyclyloxyloxy, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₉ heterocyclylsulfonyl, optionally substituted sulfamoyl, optionally substituted C₁-C₆ thioalkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In certain examples of formula (IIA) or (IIB), R⁴ is H, optionally substituted amino, halo, optionally substituted amido, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₇ alkoxycarbonyl, optionally substituted C₂-C₇ alkoxycarbonyl, optionally substituted carboxamide, optionally substituted C₁-C₆ alkanoyloxy, optionally substituted C₇-C₁₁ aryloxyloxy, optionally substituted C₂-C₁₀ heteroaryloxyloxy, optionally substituted C₂-C₁₀ heterocyclyloxyloxy, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted sulfamoyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₉ heteroaryl, or optionally substituted C₁-C₉ heterocyclyl. In particular examples of formula (IIA) or (IIB), R⁴ is H, halo, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted carboxamide, or optionally substituted sulfamoyl. In other examples of formula (IIA) or (IIB), R⁴ is H.

In yet other examples of formula (IIA) or (IIB), R⁵ is H, optionally substituted amino, halo, optionally substituted amido, optionally substituted carboxamide, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocyclyloyl, hydroxycarbonyl, optionally substituted C₂-C₇ alkoxycarbonyl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally

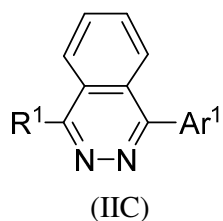
substituted C₁-C₉ heterocyclysulfonyl, optionally substituted C₁-C₆ thioalkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In still other examples of formula (IIA) or (IIB), R⁵ is H, optionally substituted amino, halo, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₉ heteroaryl, or optionally substituted C₁-C₉ heterocyclyl. In some examples of formula (IIA) or (IIB), R⁵ is H, optionally substituted amino, halo, optionally substituted C₁-C₆ alkyl, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, or optionally substituted C₆-C₁₀ aryl. In particular examples of formula (IIA) or (IIB), R⁵ is H.

In certain examples of formula (IIA) or (IIB), R⁶ is H, optionally substituted amino, halo, optionally substituted amido, optionally substituted carboxamide, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocyclyl, hydroxycarbonyl, optionally substituted C₂-C₇ alkoxycarbonyl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₉ heterocyclysulfonyl, optionally substituted C₁-C₆ thioalkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In other examples of formula (IIA) or (IIB), R⁶ is H, optionally substituted amino, halo, optionally substituted amido, optionally substituted carboxamide, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₇ alkoxycarbonyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₉ heteroaryl, or optionally substituted C₁-C₉ heterocyclyl. In yet other examples of formula (IIA) or (IIB), R⁶ is H,

optionally substituted amino, optionally substituted amido, halo, or optionally substituted C₁-C₆ alkyl. In still other examples of formula (IIA) or (IIB), R⁶ is H.

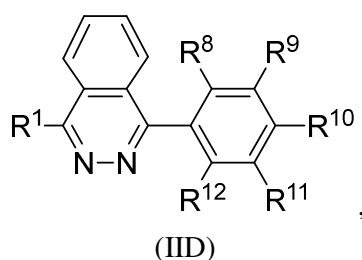
In some examples of formula (IIA) or (IIB), R⁷ is H, optionally substituted amino, halo, optionally substituted amido, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocyclyloyl, hydroxycarbonyl, optionally substituted C₂-C₇ alkoxycarbonyl, optionally substituted carboxamide, optionally substituted C₁-C₆ alkanoyloxy, optionally substituted C₇-C₁₁ aryloyloxy, optionally substituted C₂-C₁₀ heteroaryloyloxy, optionally substituted C₂-C₁₀ heterocyclyloyloxy, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₉ heterocyclylsulfonyl, optionally substituted sulfamoyl, optionally substituted C₁-C₆ thioalkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In certain examples of formula (IIA) or (IIB), R⁷ is H, optionally substituted amino, halo, optionally substituted amido, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₇ alkoxycarbonyl, optionally substituted carboxamide, optionally substituted C₁-C₆ alkanoyloxy, optionally substituted C₇-C₁₁ aryloyloxy, optionally substituted C₂-C₁₀ heteroaryloyloxy, optionally substituted C₂-C₁₀ heterocyclyloyloxy, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted sulfamoyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₉ heteroaryl, or optionally substituted C₁-C₉ heterocyclyl. In particular examples of formula (IIA) or (IIB), R⁷ is H, halo, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted carboxamide, or optionally substituted sulfamoyl. In other examples of formula (IIA) or (IIB), R⁷ is H.

In yet other examples of formula (II), the isolated compound has the structure according to formula (IIC):



In some examples of formula (II), (IIA), (IIB), or (IIC), Ar¹ is optionally substituted C₆-C₁₀ aryl. In other examples of formula (II), (IIA), (IIB), or (IIC), Ar¹ is optionally substituted C₆ aryl.

In yet other examples of formula (II), the isolated compound has the structure according to formula (IID):



wherein

each of R⁸, R⁹, R¹⁰, R¹¹, and R¹² is, independently, H, halo, hydroxy, optionally substituted amino, optionally substituted amido, thiol, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocycloyl, hydroxycarbonyl, optionally substituted C₂-C₇ alkoxy carbonyl, optionally substituted carboxamide, optionally substituted C₁-C₆ alkanoyloxy, optionally substituted C₇-C₁₁ aryloxyloxy, optionally substituted C₂-C₁₀ heteroaryloxyloxy, optionally substituted C₂-C₁₀ heterocycloxyloxy, optionally substituted C₁-C₆ thioalkyl, optionally substituted C₁-C₆ alkylsulfinyl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylthio, optionally substituted C₆-C₁₀ arylsulfinyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylthio, optionally substituted C₁-C₉ heteroarylsulfinyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₉ heterocyclylsulfinyl, optionally substituted C₁-C₉ heterocyclylsulfonyl, optionally substituted sulfamoyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₂-C₆ heteroalkynyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally

substituted C₄-C₁₀ cycloalkenyl, optionally substituted C₈-C₁₀ cycloalkynyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkenyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkenyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heterocyclyl, optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkenyl, or optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkynyl;

or any two of adjacent R⁸, R⁹, R¹⁰, R¹¹, and R¹², together with the two adjacent carbon atoms to which they are attached, form a 5, 6, or 7-membered optionally substituted carbocyclic or heterocyclic ring.

In certain examples of formula (IID), R⁸ is H, halo, or optionally substituted C₁-C₆ alkyl. In other examples of formula (IID), R⁸ is H.

In particular examples of formula (IID), R¹¹ is H, halo, or optionally substituted C₁-C₆ alkyl. In other examples of formula (IID), R¹¹ is H.

In some examples of formula (IID), R¹² is H, halo, or optionally substituted C₁-C₆ alkyl. In other examples of formula (IID), R¹² is H.

In certain examples of formula (IID), R⁹ is H, optionally substituted amino, halo, optionally substituted amido, optionally substituted carboxamide, cyano, nitro, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocyclyloyl, hydroxycarbonyl, optionally substituted C₂-C₇ alkoxycarbonyl, optionally substituted C₁-C₆ alkylsulfinyl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylsulfinyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfinyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₉ heterocyclylsulfonyl, optionally substituted sulfamoyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In other examples of formula (IID), R⁹ is H, optionally substituted amido, halo, cyano,

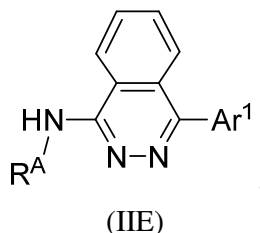
optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₇ alkoxy carbonyl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₉ heterocyclylsulfonyl, optionally substituted sulfamoyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₉ heteroaryl, or optionally substituted C₁-C₉ heterocyclyl. In yet other examples of formula (IID), R⁹ is H, optionally substituted carboxamide, halo, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₁-C₉ heterocyclylsulfonyl, or optionally substituted sulfamoyl. In still other examples of formula of formula (IID), R⁹ is optionally substituted sulfamoyl (*e.g.*, unsubstituted sulfamoyl).

In certain examples of formula (IID), R¹⁰ is H, halo, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₂-C₆ alkanoyl, hydroxycarbonyl, optionally substituted C₂-C₇ alkoxy carbonyl, optionally substituted carboxamide, optionally substituted C₁-C₆ thioalkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In yet other examples of formula (IID), R¹⁰ is H, halo, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In still other examples of formula (IID), R¹⁰ is optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ cycloalkyl. In some examples of formula of formula (IID), R¹⁰ is optionally substituted C¹-C⁶ alkyl (*e.g.*, methyl).

In particular examples of formula (II), (IIA), (IIB), (IIC), or (IID), R¹ is H, hydroxy, optionally substituted amino, halo, thiol, optionally substituted amido, optionally substituted carboxamide, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, optionally substituted C₁-C₆ alkanoyloxy, optionally substituted C₇-C₁₁ aryloxy, optionally substituted C₂-C₁₀ heteroaryloxy, optionally substituted C₂-C₁₀ heterocyclyloxy, optionally substituted C₁-C₆ thioalkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀

aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In certain examples of formula (IID), R¹⁰ is H, optionally substituted amino, optionally substituted amido, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In some examples of formula (II), (IIA), (IIB), (IIC), or (IID), R¹ is H, optionally substituted amino, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₉ heteroaryl, or optionally substituted C₁-C₉ heterocyclyl. In other examples of formula (II), (IIA), (IIB), (IIC), or (IID), R¹ is optionally substituted amino. In yet other examples of formula (IID), R¹⁰ is substituted amino, wherein at least one substituent is phenyl. In still other examples of formula (II), (IIA), (IIB), (IIC), or (IID), R¹ is substituted amino, wherein at least one substituent is *o*-tolyl.

In some examples of formula (II), the compound of formula (II) has a structure of formula (IIE):



wherein

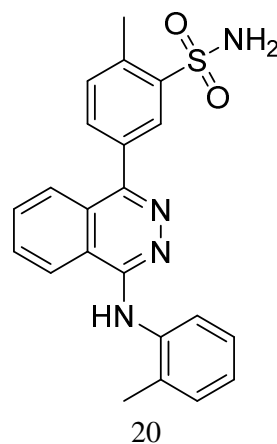
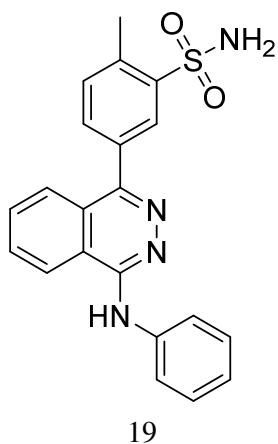
R^A is an optionally substituted phenyl, and

Ar¹ is an optionally substituted phenyl.

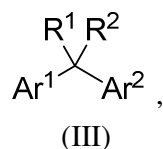
In some examples of formula (IIE), R^A is phenyl or 2-methylphenyl.

In some examples of formula (IIE), Ar¹ is 3-aminosulfonyl-4-methylphenyl.

In some examples of formula (II), (IIA), (IIB), or (IIC), the isolated compound is compound 19 or 20:



In some examples, the GPR174 inhibitory compound has a structure according to formula (III):



5 or a stereoisomer thereof, or a tautomer, or a pharmaceutically acceptable salt thereof, wherein

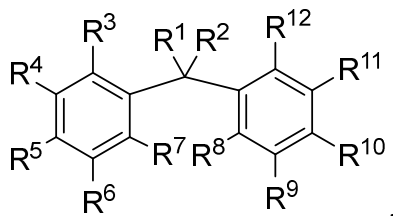
each of R^1 and R^2 is, independently, H, halo, cyano, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl; and

10 each of Ar^1 and Ar^2 is, independently, optionally substituted C_6 - C_{10} aryl or optionally substituted C_1 - C_9 heteroaryl.

In certain examples of formula (III), Ar^1 is optionally substituted C_6 - C_{10} aryl. In other examples of formula (III), Ar^1 is optionally substituted C_6 aryl, *e.g.*, optionally substituted phenyl.

In certain examples of formula (III), Ar^2 is optionally substituted C_6 - C_{10} aryl. 15 In other examples of formula (III), Ar^2 is optionally substituted C_6 aryl, *e.g.*, optionally substituted phenyl.

In yet other examples of formula (III), the isolated compound has the structure according to formula (IIIA):



(IIIA)

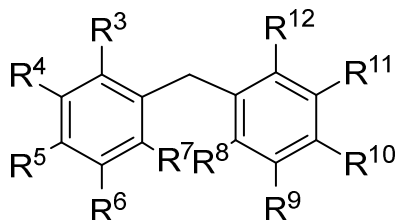
wherein

each of R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, and R¹² is, independently, H, halo, hydroxy, optionally substituted amino, optionally substituted amido, thiol, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocyclyloyl, hydroxycarbonyl, optionally substituted C₂-C₇ alkoxycarbonyl, optionally substituted carboxamide, optionally substituted C₂-C₆ alkanoyloxy, optionally substituted C₇-C₁₁ aryloxyloxy, optionally substituted C₂-C₁₀ heteroaryloxyloxy, optionally substituted C₂-C₁₀ heterocyclyloxyloxy, optionally substituted C₂-C₆ alkanoylamino, optionally substituted C₇-C₁₁ aryloylamino, optionally substituted C₂-C₁₀ heteroaryloylamino, optionally substituted C₂-C₁₀ heterocyclyloylamino, optionally substituted C₁-C₆ thioalkyl, optionally substituted C₁-C₆ alkylsulfinyl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylthio, optionally substituted C₆-C₁₀ arylsulfinyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylthio, optionally substituted C₁-C₉ heteroarylsulfinyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₉ heterocyclylsulfinyl, optionally substituted C₁-C₉ heterocyclylsulfonyl, optionally substituted sulfamoyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₂-C₆ heteroalkynyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₄-C₁₀ cycloalkenyl, optionally substituted C₈-C₁₀ cycloalkynyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkenyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkenyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heterocyclyl, optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkenyl, or optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkynyl.

In particular examples of formula (III) or (IIIA), R¹ is H, halo, or optionally substituted C₁-C₆ alkyl. In other examples of formula (III) or (IIIA), R¹ is H, halo, or methyl. In yet other examples of formula (III) or (IIIA), R¹ is H.

In certain examples of formula (III) or (IIIA), R^2 is H, halo, or optionally substituted C_1 - C_6 alkyl. In other examples of formula (III) or (IIIA), R^2 is H, halo, or methyl. In yet other examples of formula (III) or (IIIA), R^2 is H.

In some examples of formula (III) or (IIIA), the isolated compound has the
5 structure according to formula (IIIB):



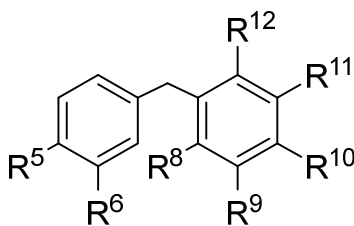
(IIIB)

In particular examples of formula (III), (IIIA), or (IIIB), R^3 is H, halo, or optionally substituted C_1 - C_6 alkyl. In other examples of formula (III), (IIIA), or (IIIB), R^3 is H.

10 In certain examples of formula (III), (IIIA), or (IIIB), R^4 is H, halo, or optionally substituted C_1 - C_6 alkyl. In other examples of formula (III), (IIIA), or (IIIB), R^4 is H.

In some examples of formula (III), (IIIA), or (IIIB), R^7 is H, halo, or optionally substituted C_1 - C_6 alkyl. In other examples of formula (III), (IIIA), or (IIIB), R^7 is H.

In other examples of formula (III), (IIIA), or (IIIB), the isolated compound has
15 the structure according to formula (IIIC):



(IIIC)

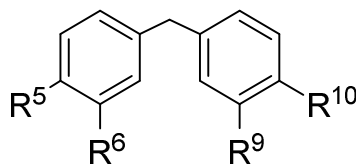
In particular examples of formula (III), (IIIA), (IIIB), or (IIIC), R^{11} is H, halo, or optionally substituted C_1 - C_6 alkyl. In other examples of formula (III), (IIIA), (IIIB), or
20 (IIIC), R^{11} is H.

In certain examples of formula (III), (IIIA), (IIIB), or (IIIC), R^{12} is H, halo, or optionally substituted C_1 - C_6 alkyl. In other examples of formula (III), (IIIA), (IIIB), or

(IIIC), R^{12} is H.

In some examples of formula (III), (IIIA), (IIIB), or (IIIC), R⁸ is H, halo, or optionally substituted C₁-C₆ alkyl. In other examples of formula (III), (IIIA), (IIIB), or (IIIC), R⁸ is H.

5 In other examples of formula (III), (IIIA), (IIIB), or (IIIC), the isolated compound has the structure according to formula (IIID):



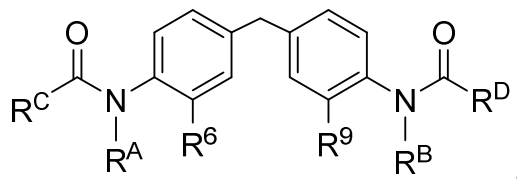
(IIID)

In some examples of formula (III), (IIIA), (IIIB), (IIIC), or (IIID), R⁵ is H, halo, cyano, optionally substituted amino, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocycloyl, optionally substituted C₂-C₆ alkanoyloxy, optionally substituted C₇-C₁₁ aryloxy, optionally substituted C₂-C₁₀ heteroaryloxy, optionally substituted C₂-C₁₀ heterocycloxy, optionally substituted C₂-C₆ alkanoylamino, optionally substituted C₇-C₁₁ aryloylamino, optionally substituted C₂-C₁₀ heteroaryloylamino, optionally substituted C₂-C₁₀ heterocycloylamino, hydroxycarbonyl, optionally substituted carboxamide, optionally substituted C₁-C₆ alkylsulfonyl, substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₉ heterocyclylsulfonyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In other examples of formula (III), (IIIA), (IIIB), (IIIC), or (IIID), R⁵ is optionally substituted amino, optionally substituted C₂-C₆ alkanoyloxy, optionally substituted C₇-C₁₁ aryloxy, optionally substituted C₂-C₁₀ heteroaryloxy, optionally substituted C₂-C₁₀ heterocycloxy, optionally substituted C₂-C₆ alkanoylamino, optionally substituted C₇-C₁₁ aryloylamino, optionally substituted C₂-C₁₀ heteroaryloylamino, optionally substituted C₂-C₁₀ heterocycloylamino, hydroxycarbonyl, or optionally substituted carboxamide. In yet other examples of formula (III), (IIIA), (IIIB), (IIIC), or (IIID), R⁵ is optionally substituted amino, optionally substituted C₂-C₆ alkanoylamino, optionally substituted C₇-C₁₁

aryloylamino, optionally substituted C₂-C₁₀ heteroaryloylamino, or optionally substituted C₂-C₁₀ heterocyclyloylamino.

In particular examples of formula (III), (IIIA), (IIIB), (IIIC), or (IIID), R¹⁰ is H, halo, cyano, optionally substituted amino, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocyclyloyl, optionally substituted C₂-C₆ alkanoyloxy, optionally substituted C₇-C₁₁ aryloxy, optionally substituted C₂-C₁₀ heteroaryloxy, optionally substituted C₂-C₁₀ heterocyclyloxy, optionally substituted C₂-C₆ alkanoylamino, optionally substituted C₇-C₁₁ aryloylamino, optionally substituted C₂-C₁₀ heteroaryloylamino, optionally substituted C₂-C₁₀ heterocyclyloylamino, hydroxycarbonyl, optionally substituted carboxamide, optionally substituted C₁-C₆ alkylsulfonyl, substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₉ heterocyclylsulfonyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In other examples of formula (III), (IIIA), (IIIB), (IIIC), or (IIID), R¹⁰ is optionally substituted amino, optionally substituted C₂-C₆ alkanoyloxy, optionally substituted C₇-C₁₁ aryloxy, optionally substituted C₂-C₁₀ heteroaryloxy, optionally substituted C₂-C₁₀ heterocyclyloxy, optionally substituted C₂-C₆ alkanoylamino, optionally substituted C₇-C₁₁ aryloylamino, optionally substituted C₂-C₁₀ heteroaryloylamino, optionally substituted C₂-C₁₀ heterocyclyloylamino, hydroxycarbonyl, or optionally substituted carboxamide. In yet other examples of formula (III), (IIIA), (IIIB), (IIIC), or (IIID), R¹⁰ is optionally substituted amino, optionally substituted C₂-C₆ alkanoylamino, optionally substituted C₇-C₁₁ aryloylamino, optionally substituted C₂-C₁₀ heteroaryloylamino, or optionally substituted C₂-C₁₀ heterocyclyloylamino.

In certain examples of formula (III), (IIIA), (IIIB), (IIIC), or (IIID), the isolated compound has the structure according to formula (IIIE):



(IIIE)

30

wherein

each of R^A and R^B is, independently, H or optionally substituted C₁-C₆ alkyl;

and

each of R^C and R^D is, independently, H, optionally substituted C₁-C₆ alkyl,

5 optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₉ heteroaryl, or optionally substituted C₁-C₉ heterocyclyl.

In some examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R^A is H. In other examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R^B is H.

10 In certain examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R^C is optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₉ heteroaryl. In other examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R^C is optionally substituted C₄ heteroaryl, *e.g.*, thiophen-2-yl.

15 In other examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R^D is optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₉ heteroaryl. In still other examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R^D is optionally substituted C₄ heteroaryl, *e.g.*, thiophen-2-yl.

In particular examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R⁶ is H, halo, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In other examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R⁶ is H, halo, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ cycloalkyl. In other examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R⁶ is H, halo, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ cycloalkyl. In still other examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R⁶ is H or optionally substituted C₁-C₆ alkyl. In some examples of formula (III), (IIIA), (IIIB), (IIIC), or (IIID), R⁶ is H. In other examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R⁶ is C₁-C₆ alkyl, *e.g.*, methyl.

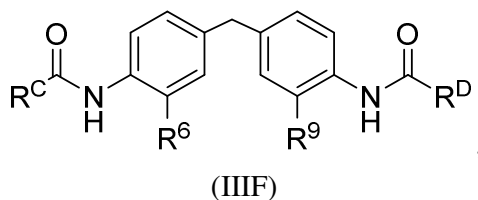
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In certain examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R⁹ is H, halo, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl, or optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl. In other examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R⁹ is H, halo, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ cycloalkyl. In other examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R⁹ is H, halo, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ cycloalkyl. In still other examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R⁹ is H or optionally substituted C₁-C₆ alkyl. In some examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R⁹ is H. In other examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE), R⁹ is C₁-C₆ alkyl, *e.g.*, methyl.

In some examples, the compound of formula (III) has a structure of formula (IIIF):



20

wherein

each of R^C and R^D is independently optionally substituted C₁-C₉ heteroaryl; and

each of R⁶ and R⁹ is independently optionally substituted C₁-C₆ alkyl.

In some examples of formula (IIIF), each of R^C and R^D is independently unsubstituted C₁-C₉ heteroaryl; and each of R⁶ and R⁹ is independently unsubstituted C₁-C₆ alkyl.

25

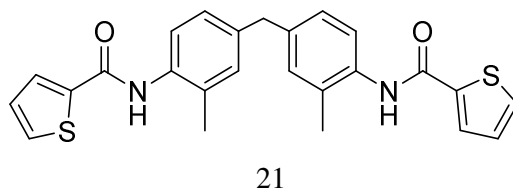
In some examples of formula (IIIF), each of R^C and R^D is thien-2-yl.

In some examples of formula (IIIF), each of R⁶ and R⁹ is methyl.

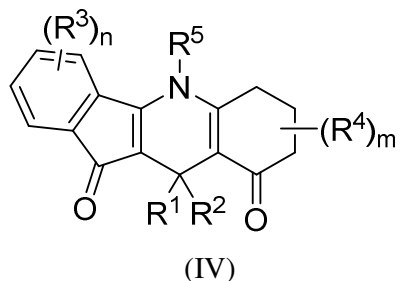
In some examples of formula (III), (IIIA), (IIIB), (IIIC), (IIID), or (IIIE),

30

the isolated compound is compound 21:



In some examples, the GPR174 inhibitory compound has a structure according
5 to formula (IV):



or a stereoisomer thereof, or a tautomer thereof, or a pharmaceutically
acceptable salt thereof, wherein

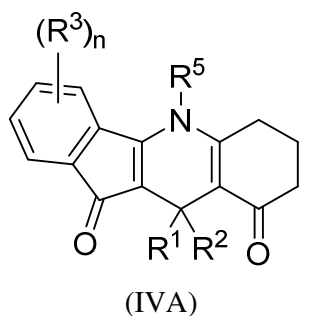
10 each of R^1 and R^2 is, independently, H, hydroxy, halo, optionally substituted
amino, optionally substituted amido, thiol, cyano, optionally substituted C_1 - C_6 alkyl, optionally
substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6
alkoxy, optionally substituted C_6 - C_{10} aryloxy, optionally substituted C_1 - C_9 heteroaryloxy,
optionally substituted C_2 - C_6 alkanoyl, optionally substituted C_7 - C_{11} aryloyl, optionally
15 substituted C_2 - C_{10} heteroaryloyl, optionally substituted C_2 - C_{10} heterocycloyl,
hydroxycarbonyl, optionally substituted C_2 - C_7 alkoxy carbonyl optionally substituted
carboxamide, optionally substituted C_1 - C_6 alkanoyloxy, optionally substituted C_7 - C_{11}
aryloyloxy, optionally substituted C_2 - C_{10} heteroaryloyloxy, optionally substituted C_2 - C_{10}
heterocycloyloxy, optionally substituted C_1 - C_6 thioalkyl, optionally substituted C_1 - C_6
20 alkylsulfinyl, optionally substituted C_1 - C_6 alkylsulfonyl, optionally substituted C_6 - C_{10} arylthio,
optionally substituted C_6 - C_{10} arylsulfinyl, optionally substituted C_6 - C_{10} arylsulfonyl, optionally
substituted C_1 - C_9 heteroarylthio, optionally substituted C_1 - C_9 heteroarylsulfinyl, optionally
substituted C_1 - C_9 heteroarylsulfonyl, optionally substituted C_1 - C_9 heterocyclylsulfinyl,
optionally substituted C_1 - C_9 heterocyclylsulfonyl, optionally substituted C_1 - C_6 heteroalkyl,
25 optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted C_2 - C_6 heteroalkynyl,
optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted C_4 - C_{10} cycloalkenyl, optionally
substituted C_8 - C_{10} cycloalkynyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_6 -

alkyloxycarbonyl, optionally substituted C₁-C₆ alkylsulfinyl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylsulfinyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfinyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₉ heterocyclisulfinyl, optionally substituted C₁-C₉ heterocyclisulfonyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₂-C₆ heteroalkynyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₄-C₁₀ cycloalkenyl, optionally substituted C₈-C₁₀ cycloalkynyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkenyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkenyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heterocyclyl, optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkenyl, or optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkynyl.

n is 0, 1, 2, 3, or 4; and
m is 0, 1, 2, 3, 4, 5, or 6.

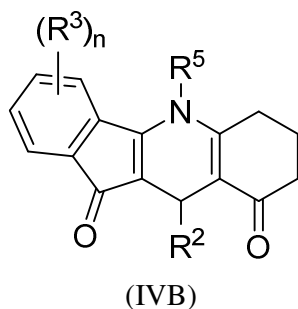
In some examples of formula (IV), m is 0.

In other examples of formula (IV), the isolated compound has a structure according to formula (IVA):



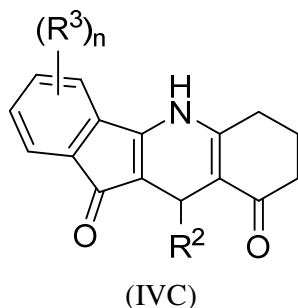
In particular examples of formula (IV) or (IVA), R¹ is H, halo, optionally substituted amino, optionally substituted amido, thiol, cyano, or optionally substituted C₁-C₆ alkyl. In other examples of formula (IV) or (IVA), R¹ is H, halo, or optionally substituted C₁-C₆ alkyl. In yet other examples of formula (IV) or (IVA), R¹ is H.

In certain examples of formula (IV) or (IVA), the isolated compound has a structure according to formula (IVB):



In some examples of formula (IV), (IVA), or (IVB), R^5 is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_2 - C_6 alkanoyl, optionally substituted C_7 - C_{11} aryloyl, optionally substituted C_2 - C_{10} heteroaryloyl, optionally substituted C_2 - C_{10} heterocyclyloyl, optionally substituted C_1 - C_6 alkyloxycarbonyl, optionally substituted C_1 - C_6 alkylsulfonyl, or optionally substituted C_6 - C_{10} arylsulfonyl. In other examples of formula (IV), (IVA), or (IVB), R^5 is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkanoyl, optionally substituted C_7 - C_{11} aryloyl, or optionally substituted C_1 - C_6 alkyloxycarbonyl. In yet other examples of formula (IV), (IVA), or (IVB), R^5 is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_2 - C_6 alkanoyl. In still other examples of formula (IV), (IVA), or (IVB), R^5 is H.

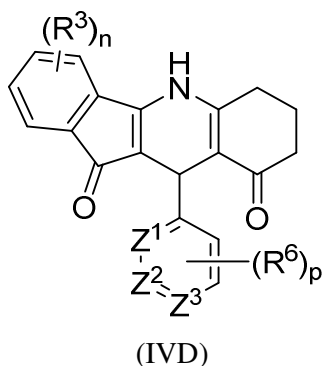
In certain examples of formula (IV), (IVA), or (IVB), the isolated compound has a structure according to formula (IVC):



In particular examples of formula (IV), (IVA), (IVB), or (IVC), R^2 is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted C_2 - C_6 heteroalkynyl, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted C_4 - C_{10} cycloalkenyl, optionally substituted C_8 - C_{10} cycloalkynyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_6 - C_{10} aryl C_1 - C_6 alkyl, optionally substituted C_6 - C_{10} aryl C_2 - C_6 alkenyl, optionally substituted C_6 - C_{10} aryl C_2 - C_6

alkynyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkenyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heterocyclyl, optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkenyl, or
 5 optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkynyl. In other examples of formula (IV), (IVA), (IVB), or (IVC), R² is optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₄-C₁₀ cycloalkenyl, optionally substituted C₈-C₁₀ cycloalkynyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₁-C₉ heteroaryl, or optionally substituted C₁-C₉ heterocyclyl. In yet other examples of formula (IV), (IVA), (IVB), or (IVC), R² is optionally substituted C₆-C₁₀
 10 aryl, optionally substituted C₁-C₉ heteroaryl, or optionally substituted C₁-C₉ heterocyclyl. In still other examples of formula (IV), (IVA), (IVB), or (IVC), R² is optionally substituted C₆-C₁₀ aryl or optionally substituted C₁-C₉ heteroaryl. In other examples of formula (IV), (IVA), (IVB), or (IVC), R² is optionally substituted pyridyl (*e.g.*, 2-pyridyl, 3-pyridyl, or 4-pyridyl). In certain examples of formula (IV), (IVA), (IVB), or (IVC), R² is optionally substituted
 15 phenyl.

In some examples of formula (IV), (IVA), (IVB), or (IVC), the isolated compound has a structure according to formula (IVD):



20 wherein R⁶ at each occurrence is independently, halo, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₆ heteroaryl, optionally substituted C₂-C₆ heterocyclyl, optionally substituted C₂-C₆ alkynyl, optionally substituted amino, optionally substituted amido, thiol, cyano, nitro, C₁-C₆ alkylsulfonyl, hydroxycarbonyl, optionally substituted C₂-C₇ alkoxy carbonyl, optionally
 25 substituted C₆-C₁₀ aryloxy, or optionally substituted C₂-C₆ heteroaryloxy;

Z¹ is C or N;

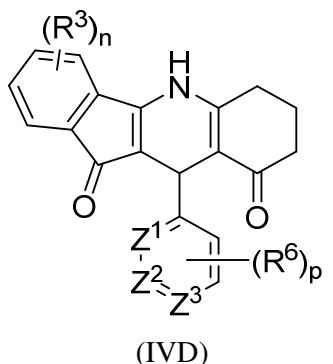
Z² is C or N;

Z^3 is N or C; and

p is 0, 1, 2, 3, 4, or 5.

In some examples of formula (IVD), Z^1 is C, Z^2 is C, and Z^3 is N. In other examples of formula (IVD), Z^1 is C, Z^2 is N, and Z^3 is C. In certain examples of formula (IVD),
5 Z^1 is N, Z^2 is C, and Z^3 is C. In certain other examples of formula (IVD), Z^1 is C, Z^2 is C, and Z^3 is C.

In some examples of formula (IV), (IVA), (IVB), or (IVC), the isolated compound has a structure according to formula (IVD):



10

wherein R^6 at each occurrence is independently, halo, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_6 heteroaryl, optionally substituted C_2 - C_6 heterocyclyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted amino, optionally substituted amido, thiol, cyano, nitro,
15 C_1 - C_6 alkylsulfonyl, hydroxycarbonyl, optionally substituted C_2 - C_7 alkoxycarbonyl, optionally substituted C_2 - C_6 alkoxy, optionally substituted C_2 - C_6 alkenoxy, optionally substituted C_6 - C_{10} aryloxy, or optionally substituted C_2 - C_6 heteroaryloxy;

Z^1 is CH or N;

Z^2 is CH or N;

20 Z^3 is N or CH; and

p is 0, 1, 2, 3, 4, or 5.

In some examples of formula (IVD), Z^1 is C, Z^2 is C, and Z^3 is N. In other examples of formula (IVD), Z^1 is C, Z^2 is N, and Z^3 is CH. In certain examples of formula (IVD), Z^1 is N, Z^2 is CH, and Z^3 is CH. In certain other examples of formula (IVD), Z^1 is CH,
25 Z^2 is CH, and Z^3 is CH.

In some examples of formula (IVD), p is 0. In other examples of formula (IVD), p is 1. In certain examples of formula (IVD), p is 2. In some examples

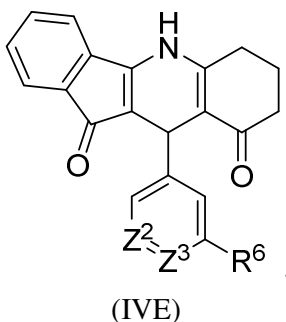
of formula (IVD), p is 1, and R⁶ is in the p- or m-position.

In certain examples of formula (IVD), R⁶ is methoxy, methyl, hydroxyl, ethoxy, ethyl, optionally substituted phenoxy, optionally substituted cyclopentyloxy, t-butoxy, allyoxy, isopropoxy, n-pentyloxy, trifluoromethoxy, difluoromethoxy, fluoro, chloro, nitro, 2-
5 hydroxyethoxy, optionally substituted 1,3,4-oxadiazolyl, or optionally substituted pyrrolidyl.

In particular examples of formula (IV), (IVA), (IVB), (IVC), or (IVD), R³ is H, halo, optionally substituted amino, optionally substituted amido, thiol, cyano, hydroxycarbonyl, optionally substituted C₂-C₇ alkoxy carbonyl, or optionally substituted C₁-C₆ alkyl.

10 In other examples of formula (IV), (IVA), (IVB), (IVC), or (IVD), n is 0.

In some examples of formula (IV), the compound has a structure of formula (IVE):



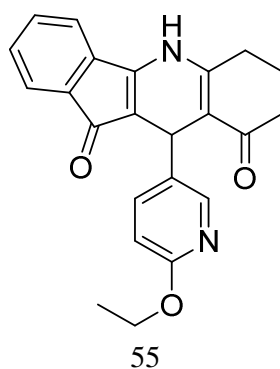
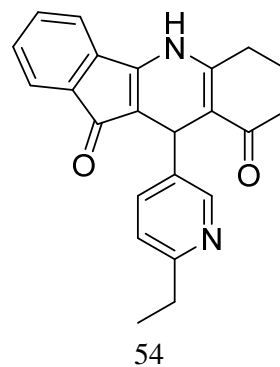
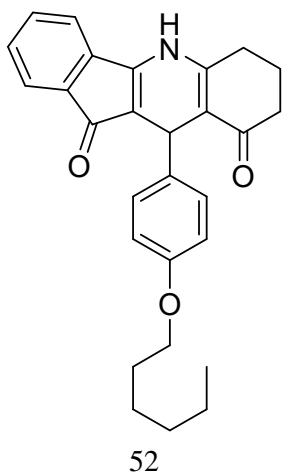
15 wherein

each of Z² and Z³ is independently CR⁶ or N; and

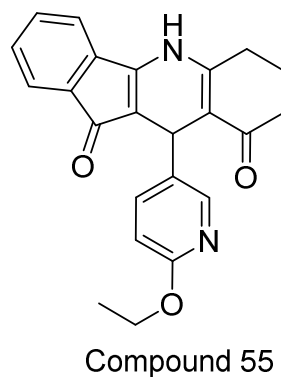
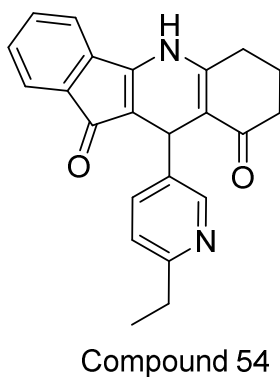
each of R⁶ is independently H, halogen, hydroxy, nitro, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₄-C₁₁ cycloalkoxy, optionally substituted C₁-C₆ haloalkoxy, optionally
20 substituted C₂-C₆-alkenoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, or optionally substituted C₁-C₉ heteroaryl;

or two adjacent R⁶ groups, taken together with the carbon atoms to which they are attached, form a C₁-C₉ heterocyclyl.

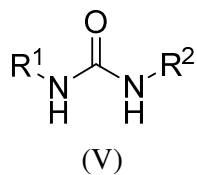
In some examples of formula IV, (IVA), (IVB), or (IVC), the isolated
25 compound is compound 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 54 or 55:



In some examples, the compound of formula (IVE) is compound 54 or 55.



In some examples, the GPR174 inhibitory compound has a structure according to the following formula (V):



or a stereoisomer thereof, or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein

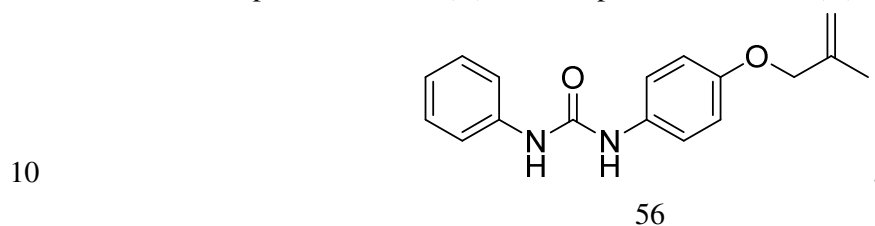
R¹ is phenyl, and
R² is optionally substituted C₆-C₁₀ aryl or optionally substituted C₁-C₉ heteroaryl.

In some examples of formula (V), R² is optionally substituted phenyl.

5 In some examples of formula (V), R² is phenyl substituted with *para*-C₂-C₆ alkenoxy.

In some examples of formula (V), R² is phenyl substituted with *para*-(2-methylallyl)oxy.

In some examples of formula (V), the compound of formula (V) is compound 56:



In some examples, the GPR174 inhibitory compound has a structure according to the following formula (Va):



or a stereoisomer thereof, or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein

X is O or S;

R^{1a} is an optionally substituted phenyl; and

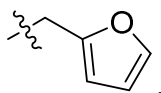
20 R^{2a} is an optionally substituted C₆-C₁₀ aryl, an optionally substituted C₃-C₉ heteroaryl or an optionally substituted C₃-C₁₀ heteroarylalkyl.

In some examples, R^{1a} is a substituted phenyl. In some more specific examples, R^{1a} is optionally substituted with halo (*e.g.*, F, Br, Cl, or I). In some examples, R^{1a} has the following structure:



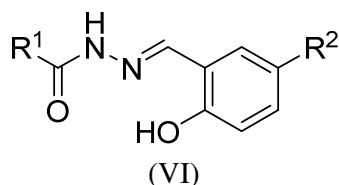
In some examples, R^{2a} is an optionally substituted C₃-C₁₀ heteroarylalkyl. In some examples, R^{2a} is unsubstituted. In some more specific examples, R^{2a} has the

following structure:



In some examples, X is O. In certain examples, X is S.

In some examples, provided herein is a GPR174 inhibitory compound according
5 to formula (VI):



or a stereoisomer thereof, or a tautomer thereof, or a pharmaceutically
acceptable salt thereof, wherein

10 R^1 is an optionally substituted C_1 - C_9 heteroaryl, and
 R^2 is halogen.

In some examples of formula (VI), the $N=C$ bond has the (E) configuration.

In some examples of formula (VI), the $N=C$ bond has the (Z) configuration.

In some examples of formula (VI), R^1 is an optionally substituted pyridinyl or
15 an optionally substituted furanyl.

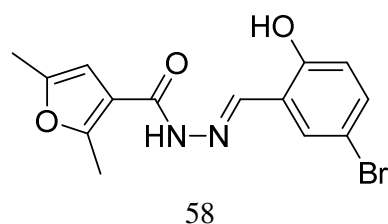
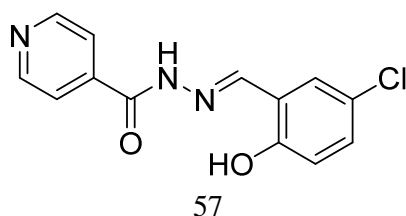
In some examples of formula (VI), R^1 is pyridin-4-yl.

In some examples of formula (VI), R^1 is 2,5-dimethyl-fur-3-yl.

In some examples of formula (VI), R^2 is halo.

In some examples of formula (VI), R^2 is chloro or bromo.

20 In some examples of formula (VI), the compound of formula (VI) is compound
57 or 58:



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

In any of the examples described herein, the compound may be a compound
25 described in Table 1 (*e.g.*, any of compounds 1-59).

In another example, the disclosure features a method of identifying a modulatory agent capable of modulating a GPR174-mediated Gs signaling pathway comprising:

5 (a) contacting a cell with a candidate modulatory agent, wherein said cell expresses GPR174 and includes the GPR174-mediated signaling pathway, and

(b) determining whether the candidate modulatory agent modulates a GPR174-mediated Gs signaling pathway in comparison to a cell contacted with a control or in comparison to a reference standard. In some examples, said candidate modulatory agent is a chemical compound comprising a structure according to any of Formulas I-VI disclosed herein. In certain examples, step (b) further involves performing an assay to detect at least one of the following: transcriptional reporter gene expression, GTPase activity, cAMP level, intracellular messenger level, calcium level, downstream kinase activity, transcriptional activation of downstream genes, change in cell morphology, change in cell growth rate, arachidonic acid release, or extracellular acidification rate.

10
15

In some examples, the candidate modulatory agent is selected from the group consisting of a compound, a nucleic acid, a natural extract, and a gas. In certain examples, the compound is a small molecule compound. In particular examples, the chemical compound includes a structure according to any of Formulas I-VI disclosed herein.

20 In another example, the disclosure features a method of identifying a modulatory agent capable of modulating GPR174-mediated Gs signaling pathway activity, comprising:

(a) contacting a cell expressing GPR174 with:
(i) at least one candidate modulatory agent; and
25 (ii) a reference chemical compound known to modulate GPR174-mediated Gs signaling pathway activity;
(b) determining the GPR174-mediated signaling pathway activity level in the cell contacted in accordance with step (a); and
(c) comparing the GPR174-mediated signaling pathway activity level in a cell
30 contacted with the reference chemical compound only with the GPR174-mediated signaling pathway activity determined in step (b); wherein a difference in GPR174-mediated signaling activity between the cell containing the candidate modulatory agent in the presence of the reference compound and the cell contacted with only the reference compound indicates that the candidate modulatory agent is capable of modulating GPR174 activity.

35 In some examples, said reference chemical compound known to modulate

GPR174-mediated Gs signaling pathway activity comprises a structure according to any of Formulas I-VI disclosed herein. In certain examples, step (b) further involves performing an assay to detect at least one of the following: transcriptional reporter gene expression, GTPase activity, cAMP level, intracellular messenger level, calcium level, downstream kinase activity, transcriptional activation of downstream genes, change in cell morphology, change in cell growth rate, arachidonic acid release, or extracellular acidification rate. In some examples, the candidate modulatory agent is selected from the group consisting of a compound, a nucleic acid, a natural extract, and a gas. In certain examples, the compound is a chemical compound. In particular examples, the small molecule compound includes a structure according to any of Formulas I-VI.

In another example, the disclosure features a method of identifying a modulatory agent capable of modulating GPR174-mediated signaling pathway activity. The method involves: (a) contacting a cell expressing GPR174 with (i) at least one candidate modulatory agent and (ii) a reference chemical compound known to modulate GPR174-mediated signaling pathway activity; (b) determining the GPR174-mediated signaling pathway activity level in the cell contacted in accordance with step (a); and (c) comparing the GPR174-mediated signaling pathway activity level in a cell contacted with the reference chemical compound only with the GPR174-mediated signaling pathway activity determined in step (b); in which a difference in GPR174-mediated signaling activity between the cell containing the candidate modulatory agent in the presence of the reference compound and the cell contacted with only the reference compound indicates that the candidate modulatory agent is capable of modulating GPR174 activity. In some examples, the reference chemical compound includes a structure according to any one of Formulas I-VI (*e.g.*, any of compounds 1-59).

In certain examples, step (b) further involves performing an assay to detect at least one of the following: transcriptional reporter gene expression, GTPase activity, cAMP level, intracellular messenger level, calcium level, downstream kinase activity, transcriptional activation of downstream genes, change in cell morphology, change in cell growth rate, arachidonic acid release, or extracellular acidification rate.

In some examples, the candidate modulatory agent is selected from the group consisting of a compound, a nucleic acid, a natural extract, and a gas. In certain examples, the compound is a small molecule chemical compound.

In another example, the disclosure features a method of using a small molecule

chemical compound for inhibiting a GPR174-mediated signaling pathway in a cell. The method involves the following steps:

- (a) providing a small molecule chemical compound that functionally interacts with GPR174 and inhibits a GPR174-mediated Gs signaling pathway in cells expressing GPR174, wherein the compound is characterized by at least one of the following criteria:
- (i) the compound has a structure selected from the group consisting of Formula I, II, III, IV, V and VI (or (I), (II), (III), (IV), (V), (Va), or (VI)); or
 - (ii) the compound changes the binding affinity of any one of reference compounds 1-59 (as set forth in Table 1) to GPR174; or
 - (iii) the compound causes a difference in the inhibitory activity of any one of reference compounds 1-59 (as set forth in Table 1) in a GPR174-mediated signaling pathway assay when tested in the presence of the reference compound as compared to the inhibitory activity of the reference compound alone; and
- (b) contacting a cell expressing GPR174 that includes a GPR174-mediated signaling pathway with the compound according to step (a), thereby inhibiting a GPR174-mediated signaling pathway in the cell.

In another example, the disclosure features a method of using a small molecule chemical compound for inhibiting a GPR174-mediated signaling pathway in a cell. The method involves the following steps:

- (a) providing a small molecule chemical compound that functionally interacts with GPR174 and inhibits a GPR174-mediated Gs signaling pathway in cells expressing GPR174, wherein the compound is characterized by at least one of the following criteria:
- (i) the compound has a structure selected from the group consisting of Formula I, II, III, IV, V and VI (or (I), (II), (III), (IV), (V), (Va), or (VI)); or
 - (ii) the compound changes the apparent binding affinity of any one of reference compounds 1-59 (as set forth in Table 1) to GPR174; or
 - (iii) said compound causes a difference in the inhibitory activity of any one of reference compounds 1-59 (as set forth in Table 1), in a GPR174-mediated signaling pathway assay when tested in the presence of said reference compound as compared to the inhibitory activity of the reference compound alone; and
- (b) contacting a cell expressing GPR174 that includes a GPR174-mediated signaling pathway with the compound according to step (a), thereby inhibiting a GPR174-

mediated signaling pathway in the cell.

In some examples, the compound changes the binding affinity of any one of reference compounds 1-59 (as set forth in Table 1) to GPR174. In certain examples, the compound decreases (*i.e.*, inhibits) the binding affinity of any one of reference compounds 1-59 to GPR174. In particular examples, the compound competitively decreases (*i.e.*, competitively inhibits) the binding affinity of any one of reference compounds 1-59 to GPR174. In other examples, the compound increases the binding affinity of any one of reference compounds 1-59 (as set forth in Table 1) to GPR174.

In some examples, the compound changes the apparent binding affinity of any one of reference compounds 1-59 (as set forth in Table 1) for GPR174. In certain examples, the compound decreases the apparent binding affinity of any one of reference compounds 1-59 for GPR174. In particular examples, the compound competitively binds to GPR174 and decreases the apparent binding affinity of any one of reference compounds 1-59 for GPR174. In alternate examples, the compound allosterically binds to GPR174 and decreases the apparent binding affinity of any one of reference compounds 1-59 for GPR174. In other examples, the compound increases the binding affinity of any one of reference compounds 1-59 (as set forth in Table 1) for GPR174.

In certain examples of any of the above examples of the disclosure, the GPR174-mediated signaling pathway is a Gs pathway.

In some examples of any of the above examples, the cell is in a mammalian subject in need of treatment for any condition, disease or disorder described herein.

Inhibition of ATP-Adenosine-A2aR- and/or A2bR-mediated signaling (such as an A2aR antagonist, and/or an A2bR antagonist and/or a CD73 inhibitor and/or a CD38 inhibitor and/or a CD39 inhibitor)

Adenosine signaling, via the A2A receptor and/or the A2B receptor pathway in particular, has been identified as a promising approach to cancer immunotherapy. Leone *et al.*, "Targeting adenosine for cancer immunotherapy", *J. ImmunoTher. Cancer.*, 2018, 6:57. Allard *et al.*, "The ectonucleotidases CD39 and CD73: novel checkpoint inhibitor targets", *Immunol. Rev.*, 2017, 276(1), 121-144 (see also Table 15 below). Adenosine is an immunosuppressive metabolite produced at high levels within the tumor microenvironment. Adenosine signaling has emerged as a key metabolic pathway that regulates tumor immunity. In particular, adenosine signaling through the A2A receptor expressed on immune cells potently dampens

CLAIMS

1. Use of a GPR174 inhibitor and at least one additional agent selected from the group consisting of:

- i. an adenosine-A2A (A2A) receptor antagonist;
- 5 ii. an adenosine-A2B (A2B) receptor antagonist;
- iii. a CD73 inhibitor;
- iv. a CD38 inhibitor;
- v. a CD39 inhibitor; and
- vi. a Treg attenuating agent,

10 in the manufacture of a medicament for treating cancer, wherein the GPR174 inhibitor and the at least one additional agent are to be administered simultaneously, or sequentially in any order, provided that the effects of the first administered inhibitor or antagonist remain present at the time of the second administered inhibitor or antagonist.

15 2. The use of claim 1, wherein the additional agent is a Treg attenuating agent.

3. The use of claim 2, wherein the Treg attenuating agent binds to one or more of GITR, CTLA-4, CD25, LAG3, TIGIT, NRP1, TGF- β , CCR2, CCR4, CCR8, TNFR2, or EZH2.

20 4. The use of any one of claims 1-3, wherein the Treg attenuating agent is an anti-GITR, anti-CTLA-4, anti-CD25, anti-LAG3, anti-TIGIT, anti-NRP1, anti-TGF- β , anti-CCR2, anti-CCR4, anti-CCR8, or anti-TNFR2 antibody, or an EZH2 inhibitor.

5. The use of any one of claims 1-4, wherein the GPR174 inhibitor is a small molecule GPR174 inhibitor or an antibody that specifically binds to GPR174.

25 6. The use of claim 5, wherein the small molecule GPR174 inhibitor inhibits PS-dependent or LysoPS-dependent activation of GPR174 signaling in a cell

expressing GPR174 by at least 25%.

7. The use of any one of claims 1-6, wherein the GPR174 inhibitor stimulates immune response in the patient by inhibiting a GPR174 G-alpha-s signaling.

8. The use of claim 7, wherein the stimulated immune response comprises
5 an NK-cell mediated immune response or an anti-tumor cytotoxic T-cell mediated immune response.

9. An *in vitro* method of increasing the level of Th1 cytokines in human peripheral blood mononuclear cells (PBMCs), the method comprising contacting human PBMCs with a small-molecule inhibitor of GPR174 signaling and at least one of an
10 adenosine-A2A (A2A) receptor antagonist, an adenosine-A2B (A2B) receptor antagonist, or a combination thereof.

10. The method of claim 9, wherein the PBMCs comprise T-cells or NK-cells.

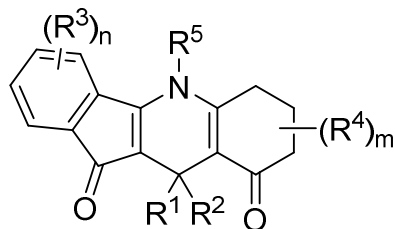
11. The method of any one of claims 9-10, wherein the level of at least one
15 of Th1 cytokines IFN- γ , IL-2, TNF, or GM-CSF is increased by at least 20%.

12. A pharmaceutical composition comprising a combination of an inhibitor of GPR174 signaling with at least one of an adenosine-A2A (A2A) receptor antagonist, an adenosine-A2B (A2B) receptor antagonist, a CD73 inhibitor, a CD38 inhibitor, and a CD39 inhibitor and optionally a pharmaceutically acceptable excipient.

20 13. The composition of claim 12, wherein the inhibitor of GPR174 is a small molecule, wherein the small molecule does not comprise an alkyl chain comprising 10 or more C atoms; or wherein the small molecule is not lysophosphatidylserine (LysoPS) or a compound disclosed in US20150361119A1.

14. The pharmaceutical composition of claim 12 or claim 13, wherein the GPR174 inhibitor competitively binds to GPR174 as compared to any one of compounds 1-59.

15. The pharmaceutical composition of claim 12, wherein the GPR174 inhibitor has a structure according to formula (IV):



or a stereoisomer thereof, or a tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein

each of R¹ and R² is, independently, H, hydroxy, halo, optionally substituted amino, optionally substituted amido, thiol, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocycloyl, hydroxycarbonyl, optionally substituted ester, optionally substituted carboxamide, optionally substituted C₁-C₆ alkanoyloxy, optionally substituted C₇-C₁₁ aryloyloxy, optionally substituted C₂-C₁₀ heteroaryloyloxy, optionally substituted C₂-C₁₀ heterocycloyloxy, optionally substituted C₁-C₆ thioalkyl, optionally substituted C₁-C₆ alkylsulfinyl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylthio, optionally substituted C₆-C₁₀ arylsulfinyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylthio, optionally substituted C₁-C₉ heteroarylsulfinyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₉ heterocyclylsulfinyl, optionally substituted C₁-C₉ heterocyclylsulfonyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₂-C₆ heteroalkynyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₄-C₁₀ cycloalkenyl, optionally substituted C₈-C₁₀ cycloalkynyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkenyl, optionally substituted C₆-C₁₀ aryl C₂-C₆

alkynyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkenyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heterocyclyl, optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkenyl, or
5 optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkynyl;

each of R³ and R⁴ is, independently, H, hydroxy, halo, optionally substituted amino, optionally substituted amido, thiol, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy,
10 optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocyclyloyl, hydroxycarbonyl, optionally substituted ester, optionally substituted carboxamide, optionally substituted C₁-C₆ alkanoyloxy, optionally substituted C₇-C₁₁ aryloyloxy, optionally substituted C₂-C₁₀ heteroaryloyloxy, optionally substituted C₂-C₁₀ heterocyclyloyloxy, optionally substituted C₁-C₆ thioalkyl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted
15 C₆-C₁₀ arylthio, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylthio, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₂-C₆ heteroalkynyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₄-C₁₀ cycloalkenyl, optionally substituted C₈-C₁₀ cycloalkynyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkenyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkenyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heterocyclyl, optionally substituted C₁-
20 C₉ heterocyclyl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkenyl, or optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkynyl;

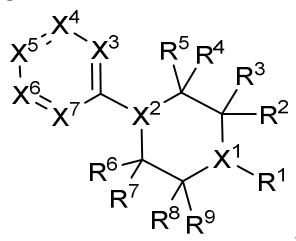
R⁵ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₆-C₁₀ aryloxy, optionally substituted C₁-C₉ heteroaryloxy, optionally substituted
30 C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocyclyloyl, optionally substituted C₁-C₆ alkyloxycarbonyl, optionally substituted C₁-C₆ alkylsulfinyl, optionally substituted C₁-C₆

alkylsulfonyl, optionally substituted C₆-C₁₀ arylsulfinyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfinyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₉ heterocyclylsulfinyl, optionally substituted C₁-C₉ heterocyclylsulfonyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₂-C₆ heteroalkynyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₄-C₁₀ cycloalkenyl, optionally substituted C₈-C₁₀ cycloalkynyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkenyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkenyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heterocyclyl, optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkenyl, or optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkynyl.

n is 0, 1, 2, 3, or 4; and

m is 0, 1, 2, 3, 4, 5, or 6.

16. The composition of claim 12, wherein the GPR174 inhibitor has a structure according to the following formula (I),



(I)

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, wherein,

X¹ is N or CR¹⁰;

X² is N or CR¹¹;

X³ is N or CR¹²;

X⁴ is N or CR¹³;

X⁵ is N or CR¹⁴;

X⁶ is N or CR¹⁵;

X^7 is N or CR^{16} ;

each of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is, independently, H, hydroxy, thiol, optionally substituted amino, optionally substituted amido, cyano, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 alkoxy, optionally substituted C_6 - C_{10} aryloxy, optionally substituted C_1 - C_9 heteroaryloxy, optionally substituted C_2 - C_6 alkanoyl, optionally substituted C_7 - C_{11} aryloyl, optionally substituted C_2 - C_{10} heteroaryloyl, optionally substituted C_2 - C_{10} heterocyclyloyl, hydroxycarbonyl, optionally substituted C_2 - C_7 alkoxycarbonyl, optionally substituted carboxamide, optionally substituted C_1 - C_6 alkanoyloxy, optionally substituted C_7 - C_{11} aryloyloxy, optionally substituted C_2 - C_{10} heteroaryloyloxy, optionally substituted C_2 - C_{10} heterocyclyloyloxy, optionally substituted C_1 - C_6 alkylsulfinyl, optionally substituted C_1 - C_6 alkylsulfonyl, optionally substituted C_6 - C_{10} arylsulfinyl, optionally substituted C_6 - C_{10} arylsulfonyl, optionally substituted C_1 - C_9 heteroarylsulfinyl, optionally substituted C_1 - C_9 heteroarylsulfonyl, optionally substituted C_1 - C_9 heterocyclylsulfinyl, optionally substituted C_1 - C_9 heterocyclylsulfonyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted C_2 - C_6 heteroalkynyl, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted C_4 - C_{10} cycloalkenyl, optionally substituted C_8 - C_{10} cycloalkynyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_6 - C_{10} aryl C_1 - C_6 alkyl, optionally substituted C_6 - C_{10} aryl C_2 - C_6 alkenyl, optionally substituted C_6 - C_{10} aryl C_2 - C_6 alkynyl, optionally substituted C_1 - C_9 heteroaryl, optionally substituted C_1 - C_9 heteroaryl C_1 - C_6 alkyl, optionally substituted C_1 - C_9 heteroaryl C_2 - C_6 alkenyl, optionally substituted C_1 - C_9 heteroaryl C_2 - C_6 alkynyl, optionally substituted C_1 - C_9 heterocyclyl, optionally substituted C_1 - C_9 heterocyclyl C_1 - C_6 alkyl, optionally substituted C_1 - C_9 heterocyclyl C_2 - C_6 alkenyl, or optionally substituted C_1 - C_9 heterocyclyl C_2 - C_6 alkynyl; or

R^2 and R^3 combine to form $=O$, $=S$, or $=NR^{17}$; or

R^4 and R^5 combine to form $=O$, $=S$, or $=NR^{17}$; or

R^6 and R^7 combine to form $=O$, $=S$, or $=NR^{17}$; or

R^8 and R^9 combine to form $=O$, $=S$, or $=NR^{17}$;

each of R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , and R^{16} is, independently, H, hydroxy, halogen, thiol, optionally substituted amino, optionally substituted amido, cyano, nitro, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_1 - C_6 alkoxy, optionally substituted C_6 - C_{10} aryloxy,

optionally substituted C₁-C₉ heteroaryloxy, optionally substituted C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocyclyloyl, hydroxycarbonyl, optionally substituted C₂-C₇ alkoxycarbonyl, optionally substituted carboxamide, optionally substituted C₁-C₆ alkanoyloxy, optionally substituted C₇-C₁₁ aryloxyloxy, optionally substituted C₂-C₁₀ heteroaryloxyloxy, optionally substituted C₂-C₁₀ heterocyclyloxyloxy, optionally substituted C₁-C₆ alkylsulfinyl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylsulfinyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfinyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₂-C₆ heteroalkynyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₄-C₁₀ cycloalkenyl, optionally substituted C₈-C₁₀ cycloalkynyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkenyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkenyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heterocyclyl, optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkenyl, or optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkynyl; or

one of:

(i) R¹² and R¹³, together with the atoms to which each is attached, combine to form an optionally substituted 5-, 6-, or 7-member ring;

(ii) R¹³ and R¹⁴, together with the atoms to which each is attached, combine to form an optionally substituted 5-, 6-, or 7-member ring;

(iii) R¹⁴ and R¹⁵, together with the atoms to which each is attached, combine to form an optionally substituted 5-, 6-, or 7-member ring; and

(iv) R¹⁵ and R¹⁶, together with the atoms to which each is attached, combine to form an optionally substituted 5-, 6-, or 7-member ring;

and

R¹⁷ is H, hydroxyl, cyano, optionally substituted amino, optionally substituted amido, optionally substituted carboxamide, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₁-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀

heterocyclyloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₁-C₆ alkylsulfinyl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted C₆-C₁₀ arylsulfinyl, optionally substituted C₆-C₁₀ arylsulfonyl, optionally substituted C₁-C₉ heteroarylsulfinyl, optionally substituted C₁-C₉ heteroarylsulfonyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₂-C₆ heteroalkynyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₄-C₁₀ cycloalkenyl, optionally substituted C₈-C₁₀ cycloalkynyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₆-C₁₀ aryl C₁-C₆ alkyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkenyl, optionally substituted C₆-C₁₀ aryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heteroaryl, optionally substituted C₁-C₉ heteroaryl C₁-C₆ alkyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkenyl, optionally substituted C₁-C₉ heteroaryl C₂-C₆ alkynyl, optionally substituted C₁-C₉ heterocyclyl, optionally substituted C₁-C₉ heterocyclyl C₁-C₆ alkyl, optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkenyl, or optionally substituted C₁-C₉ heterocyclyl C₂-C₆ alkynyl;
wherein three or fewer of X³, X⁴, X⁵, X⁶, and X⁷ are N; and
at least one of X¹ and X² is N.

17. The composition of claim 15, wherein the composition further comprises a small molecule Treg attenuating agent.

18. Use of a GPR174 inhibitor in the manufacture of a medicament for enhancing an anti-tumor immune response in a subject that is currently undergoing treatment with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor, a CD73 inhibitor and a Treg attenuating agent.

19. The use of claim 18, wherein the Treg attenuating agent binds to one or more of GITR, CTLA-4, CD25, LAG3, TIGIT, NRP1, TGF- β , CCR2, CCR4, CCR8, TNFR2, and/or EZH2.

20. The use of claim 18, wherein GPR174 inhibitor is a small molecule that inhibits PS-dependent or LysoPS-dependent activation of GPR174 signaling in a cell expressing GPR174 by at least 25%.

21. Use of a small-molecule inhibitor of GPR174 signaling and at least one of an adenosine-A2A (A2A) receptor antagonist, an adenosine-A2B (A2B) receptor antagonist, or a combination thereof, in the manufacture of a medicament for increasing the level of Th1 cytokines in human peripheral blood mononuclear cells (PBMCs).

5 22. The use of claim 21, wherein the PBMCs comprise T-cells or NK-cells.

23. The use of any one of claims 21-22, wherein the level of at least one of Th1 cytokines IFN- γ , IL-2, TNF, or GM-CSF is increased by at least 20%.