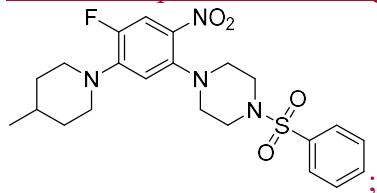


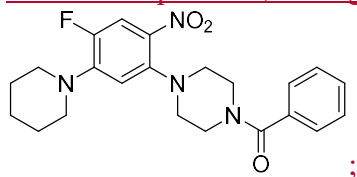
Example 17 provides experimental results demonstrating that apoptotic cells stimulate GPR174 Gs signaling pathway in cells expressing GPR174. As further described in Example 16 and shown in FIGURES 47A-47F, PS-mediated GPR174 Gs signaling is inhibited by representative GPR174 inhibitory compounds 6, 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:

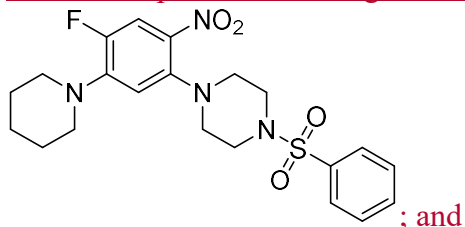
i. compound 10, having the structure:



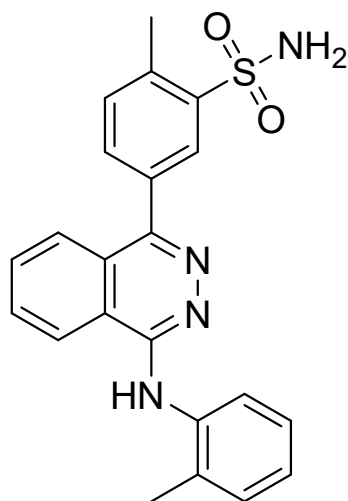
ii. compound 6, having the structure:



iii. compound 11, having the structure:



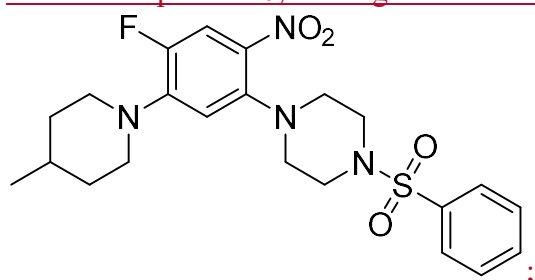
iv. compound 20, having the structure:



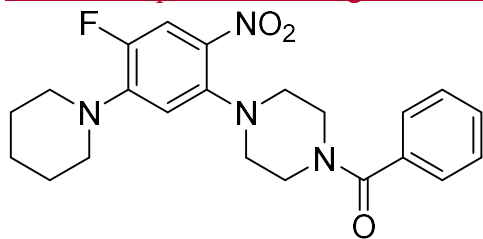
and at least one additional agent selected from the group consisting of: i. ~~ZM-241385~~ an adenosine-A2A (A2A)-receptor antagonist; ii. ~~SCH-58261~~ an adenosine-A2B (A2B)-receptor antagonist; iii. ~~PBF-509a~~ a CD73 inhibitor; iv. ~~MRS-1754a~~ a CD38 inhibitor; v. ~~and an anti-GITR antibody~~ 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.

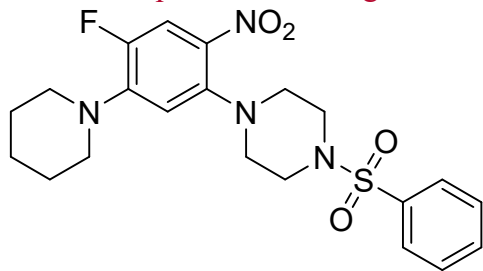
In another aspect, the present disclosure refers to use of a GPR174 inhibitor in the manufacture of a medicament for enhancing an anti-tumor immune response in a subject that is currently undergoing treatment with at least one of an A2aR antagonist, an A2bR antagonist, ~~a CD38 inhibitor, a CD39 inhibitor,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



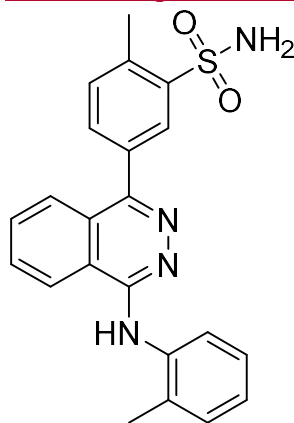
ii. compound 6, having the structure:



iii. compound 11, having the structure:



5 iv. compound 20, having the structure:



and wherein the A2A receptor antagonist, A2B receptor antagonist, and Treg attenuating agent are selected from the group consisting of:

- 10 i. ZM-241385;
ii. SCH-58261;
iii. PBF-509;
iv. MRS-1754; and
v. an anti-GITR antibody.

15 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

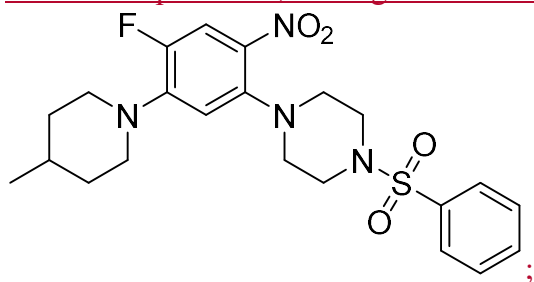
in immune-cell or cancer-cell associated programmed death-ligand 1 (PD-L1) expression or cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) expression or T cell immunoreceptor with Ig and ITIM domains (TIGIT) expression or amphiregulin (AREG) expression.

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.

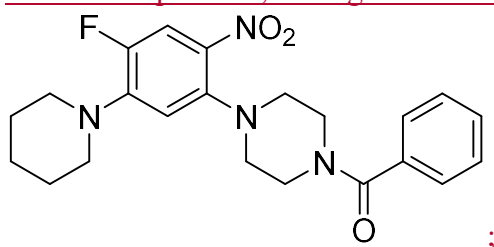
In some examples, the stimulated immune response and/or amplified immune response comprises an increase in Th1 cytokine production in the presence of cancer cell-
10 derived exosomes.

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 an ~~small-molecule~~ inhibitor of GPR174 signaling selected from the group consisting of:

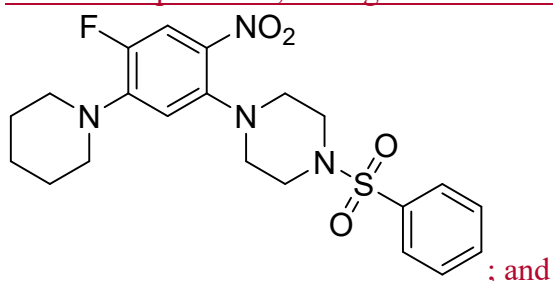
15 i. compound 10, having the structure:



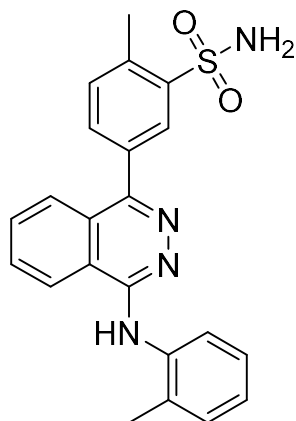
ii. compound 6, having the structure:



iii. compound 11, having the structure:



20 iv. compound 20, having the structure:



_____ and at least one of an adenosine-A2A (A2A) receptor antagonist, an adenosine-A2B (A2B) receptor antagonist, or a combination thereof, wherein the A2A receptor antagonist and A2B receptor antagonist are selected from the group consisting of:

- i. ZM-241385;
- ii. SCH-58261;
- iii. PBF-509; and
- iv. MRS-1754.

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 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 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 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.

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

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 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.

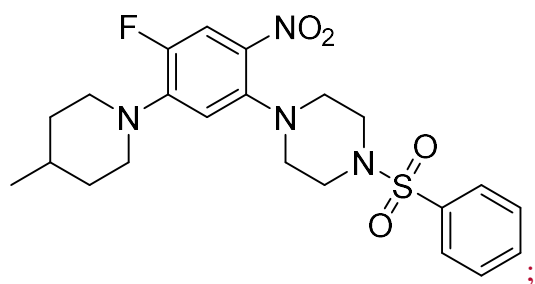
In some examples, the level of one or more of IL-4, IL-5, IL-9, IL-13, IL-17F, IL-21, and IL-22 are not modulated and do not increase or decrease by more than 20% in a cell expressing GPR174 contacted with a small molecule inhibitor of GPR174 signaling as compared to a control cell expressing GPR174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

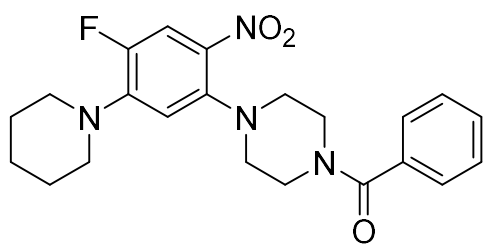
In some examples, provided herein is a pharmaceutical composition comprising a small molecule inhibitor of GPR174 signaling in combination with at least one of an A2aR antagonist, an A2bR antagonist, a CD38 inhibitor, a CD39 inhibitor and/or a CD73 inhibitor and a pharmaceutically acceptable excipient.

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 and, an adenosine-A2B (A2B) receptor antagonist, ~~a CD73 inhibitor, a CD38 inhibitor, and a CD39 inhibitor~~ and optionally a pharmaceutically acceptable excipient, wherein the GPR174 inhibitor is selected from the group consisting of:

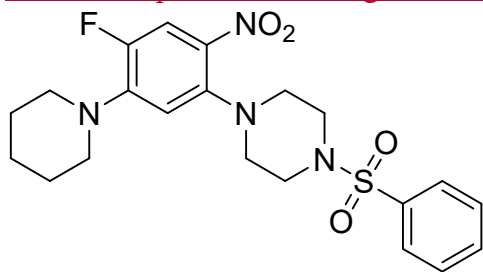
i. compound 10, having the structure:



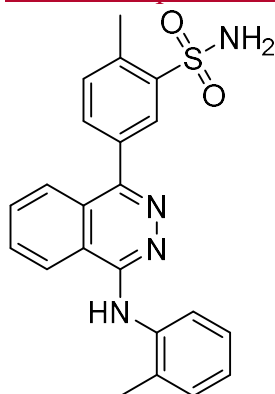
ii. compound 6, having the structure:



iii. compound 11, having the structure:



iv. compound 20, having the structure:



and wherein the adenosine-A2A (A2A) receptor antagonist and the adenosine-A2B (A2B) receptor antagonist are selected from the group consisting of:

- i. ZM-241385;
- ii. SCH-58261;
- iii. PBF-509; and
- iv. MRS-1754.

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

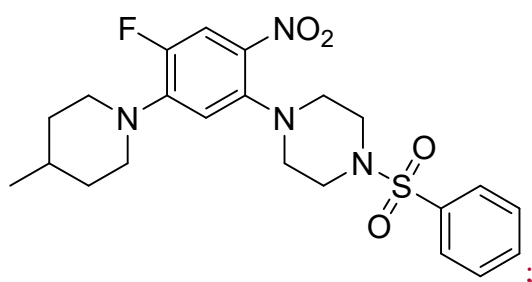
In some examples, provided herein is a pharmaceutical composition comprising a small molecule inhibitor of GPR174 signaling in combination with a Treg attenuating agent and a pharmaceutically acceptable excipient.

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

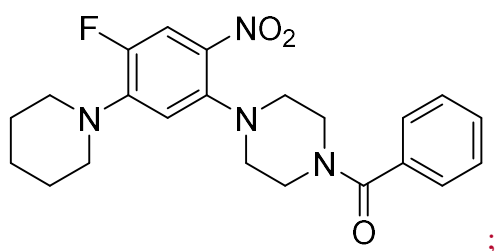
CLAIMS

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

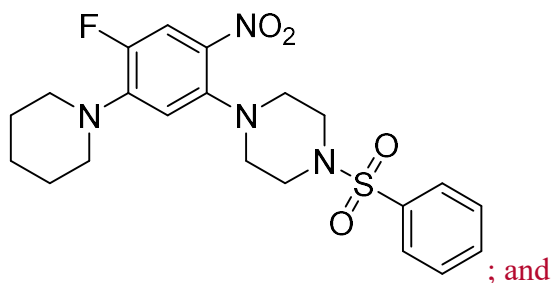
i. compound 10, having the structure:



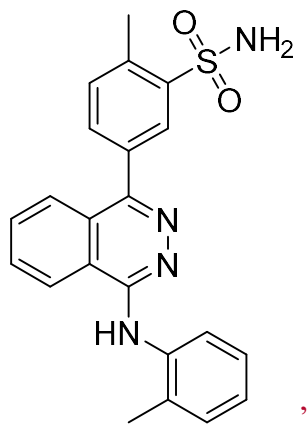
ii. compound 6, having the structure:



iii. compound 11, having the structure:



10 iv. compound 20, having the structure:



and at least one additional agent selected from the group consisting of:

- i. ZM-241385an adenosine-A₂A (A₂A) receptor antagonist;
- ii. SCH-58261an adenosine-A₂B (A₂B) receptor antagonist;
- iii. PBF-509aa CD73 inhibitor;
- iv. MRS-1754aa CD38 inhibitor; and
- v. an anti-GITR antibodya 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.

~~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.~~

~~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.~~

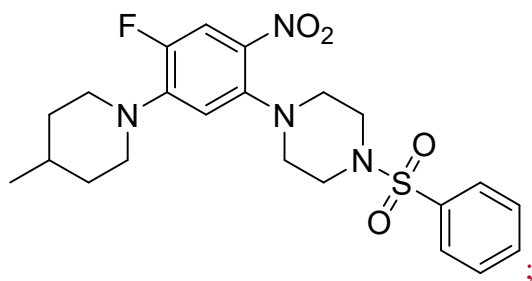
26. The use of claim 15, wherein ~~the small molecule~~ GPR174 inhibitor inhibits PS-dependent or LysoPS-dependent activation of GPR174 signaling in a cell expressing GPR174 by at least 25%.

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

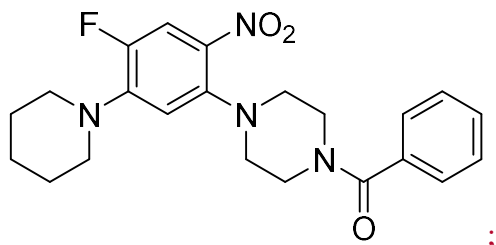
48. The use of claim 37, wherein the stimulated immune response comprises an NK-cell mediated immune response or an anti-tumor cytotoxic T-cell mediated immune response.

59. 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 an ~~small-~~
10 ~~molecule~~ inhibitor of GPR174 signaling selected from the group consisting of:

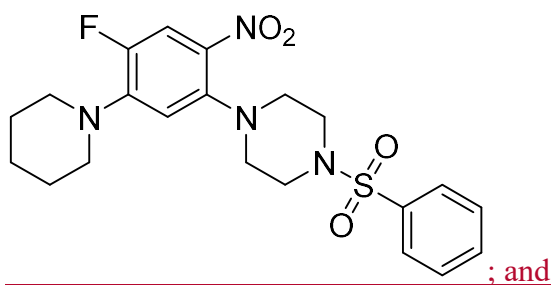
i. compound 10, having the structure:



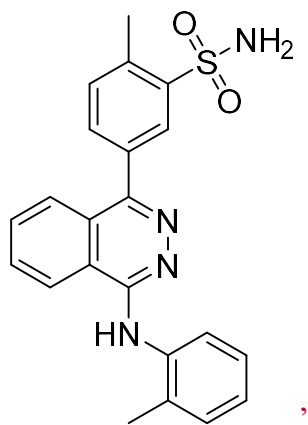
ii. compound 6, having the structure:



15 iii. compound 11, having the structure:



iv. compound 20, having the structure:



and at least one of an adenosine-A2A (A2A) receptor antagonist, an adenosine-A2B (A2B) receptor antagonist, or a combination thereof, wherein the A2A receptor antagonist and A2B receptor antagonist are selected from the group consisting of:

i. ZM-241385;

ii. SCH-58261;

iii. PBF-509; and

10 iv. MRS-1754.

610. The method of claim 59, wherein the PBMCs comprise T-cells or NK-cells.

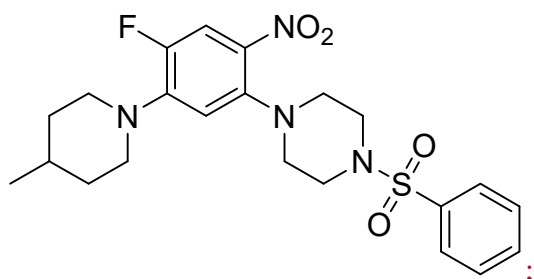
711. The method of any one of claims 59-610, wherein the level of at least one of Th1 cytokines IFN- γ , IL-2, TNF, or GM-CSF is increased by at least 20%.

812. A pharmaceutical composition comprising a combination of an inhibitor of GPR174 signaling with at least one of an adenosine-A2A (A2A) receptor antagonist, and an adenosine-

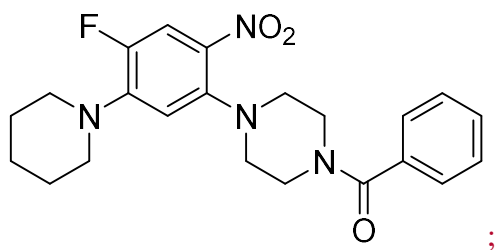
15

A2B (A2B) receptor antagonist, ~~a CD73 inhibitor, a CD38 inhibitor, and a CD39 inhibitor~~ and optionally a pharmaceutically acceptable excipient, wherein the GPR174 inhibitor is selected from the group consisting of:

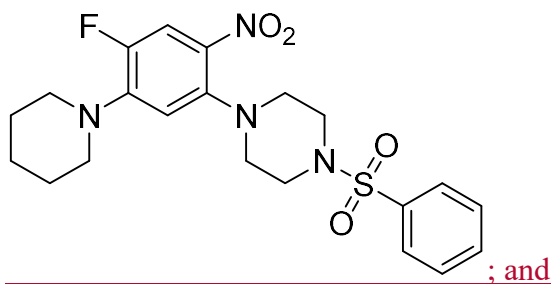
i. compound 10, having the structure:



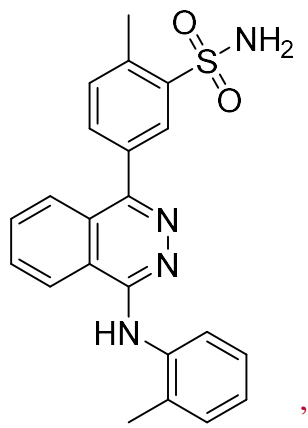
ii. compound 6, having the structure:



iii. compound 11, having the structure:



10 iv. compound 20, having the structure:



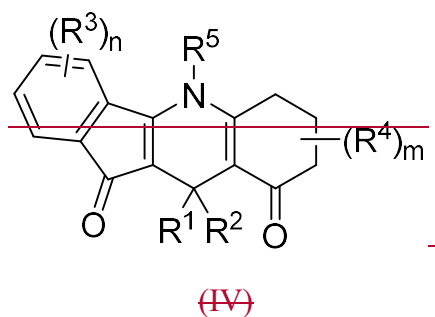
and wherein the adenosine-A2A (A2A) receptor antagonist and the adenosine-A2B (A2B) receptor antagonist are selected from the group consisting of:

- 5 i. ZM-241385;
 ii. SCH-58261;
 iii. PBF-509; and
 iv. MRS-1754.

10 ~~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 ~~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 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 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 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, 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 aryloxy, optionally substituted C₂-C₁₀ heteroaryloxy, optionally substituted C₂-C₁₀ heterocyclyloxy, optionally substituted C₁-C₆ thioalkyl, optionally substituted C₁-C₆ alkylsulfonyl, optionally substituted 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-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 C₂-C₆ alkanoyl, optionally substituted C₇-C₁₁ aryloyl, optionally substituted C₂-C₁₀ heteroaryloyl, optionally substituted C₂-C₁₀ heterocyclyloyl, optionally substituted C₁-C₆ alkylloxycarbonyl, 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-

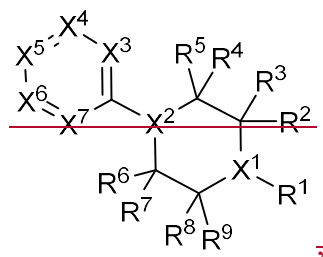
~~C₉-heterocyclyl-C₁-C₆-alkyl, optionally substituted C₁-C₉-heterocyclyl-C₂-C₆-alkenyl, or optionally substituted C₁-C₉-heterocyclyl-C₂-C₆-alkynyl.~~

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

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

5

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



~~(I)~~

10

~~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;~~

15

~~X⁴ is N or CR¹³;~~

~~X⁵ is N or CR¹⁴;~~

~~X⁶ is N or CR¹⁵;~~

~~X⁷ is N or CR¹⁶;~~

~~each of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ is, independently, H, hydroxy,~~

20

~~thiol, optionally substituted amino, optionally substituted amido, 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 C₁-C₆-alkanoyloxy, optionally substituted C₇-C₁₁-aryloyloxy, optionally substituted C₂-C₁₀-heteroaryloyloxy, optionally substituted C₂-C₁₀-heterocyclyloyloxy, optionally substituted C₁-C₆-alkylsulfinyl, optionally substituted C₁-C₆~~

25

alkylsulfonyl, optionally substituted C₆-C₁₀⁻arylsulfinyl, optionally substituted C₆-C₁₀
 arylsulfonyl, optionally substituted C₁-C₉heteroarylsulfinyl, optionally substituted C₁-C₉
 heteroarylsulfonyl, optionally substituted C₁-C₉heterocyclylsulfinyl, optionally substituted C₁-
 C₉heterocyclylsulfonyl, optionally substituted C₁-C₆heteroalkyl, optionally substituted C₂-C₆
 5 heteroalkenyl, optionally substituted C₂-C₆heteroalkynyl, optionally substituted C₃-C₁₀
 cycloalkyl, optionally substituted C₄-C₁₀cycloalkenyl, optionally substituted C₈-C₁₀
 cycloalkynyl, optionally substituted C₆-C₁₀aryl, optionally substituted C₆-C₁₀aryl C₁-C₆alkyl,
 optionally substituted C₆-C₁₀aryl C₂-C₆alkenyl, optionally substituted C₆-C₁₀aryl C₂-C₆
 alkynyl, optionally substituted C₁-C₉heteroaryl, optionally substituted C₁-C₉heteroaryl C₁-C₆
 10 alkyl, optionally substituted C₁-C₉heteroaryl C₂-C₆alkenyl, optionally substituted C₁-C₉
 heteroaryl C₂-C₆alkynyl, optionally substituted C₁-C₉heterocyclyl, optionally substituted C₁-
 C₉heterocyclyl C₁-C₆alkyl, optionally substituted C₁-C₉heterocyclyl C₂-C₆alkenyl, or
 optionally substituted C₁-C₉heterocyclyl C₂-C₆alkynyl; or

R² and R³ combine to form =O, =S, or =NR¹⁷; or

R⁴ and R⁵ combine to form =O, =S, or =NR¹⁷; or

R⁶ and R⁷ combine to form =O, =S, or =NR¹⁷; or

R⁸ and R⁹ combine to form =O, =S, or =NR¹⁷;

each of R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, and R¹⁶ is, independently, H, hydroxy,

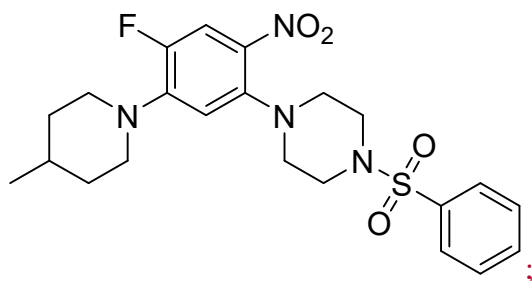
halogen, thiol, optionally substituted amino, optionally substituted amido, cyano, nitro,
 20 optionally substituted C₁-C₆alkyl, optionally substituted C₂-C₆alkenyl, optionally substituted
 C₂-C₆alkynyl, optionally substituted C₁-C₆alkoxy, optionally substituted C₆-C₁₀aryloxy,
 optionally substituted C₁-C₉heteroaryloxy, optionally substituted C₂-C₆alkanoyl, optionally
 substituted C₇-C₁₁aryloyl, optionally substituted C₂-C₁₀heteroaryloyl, optionally substituted
 C₂-C₁₀heterocyclyloyl, hydroxycarbonyl, optionally substituted C₂-C₇alkoxycarbonyl,
 25 optionally substituted carboxamide, optionally substituted C₁-C₆alkanoyloxy, optionally
 substituted C₇-C₁₁aryloyloxy, optionally substituted C₂-C₁₀heteroaryloyloxy, optionally
 substituted C₂-C₁₀heterocyclyloyloxy, optionally substituted C₁-C₆alkylsulfinyl, optionally
 substituted C₁-C₆alkylsulfonyl, optionally substituted C₆-C₁₀⁻arylsulfinyl, optionally
 substituted C₆-C₁₀⁻arylsulfonyl, optionally substituted C₁-C₉heteroarylsulfinyl, optionally
 30 substituted C₁-C₉heteroarylsulfonyl, optionally substituted C₁-C₆heteroalkyl, optionally
 substituted C₂-C₆heteroalkenyl, optionally substituted C₂-C₆heteroalkynyl, optionally
 substituted C₃-C₁₀cycloalkyl, optionally substituted C₄-C₁₀cycloalkenyl, optionally

~~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.~~

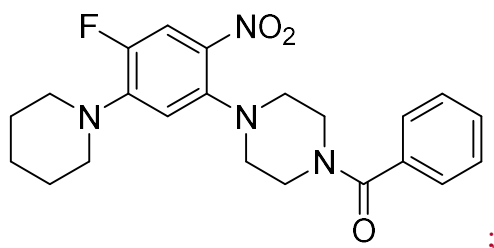
- 5 17. ~~The composition of claim 15, wherein the composition further comprises a small molecule Treg attenuating agent.~~

918. 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~~
 10 and a Treg attenuating agent, wherein the GPR174 inhibitor is selected from the group consisting of:

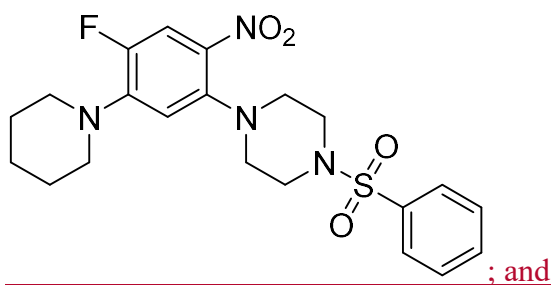
- i. compound 10, having the structure:



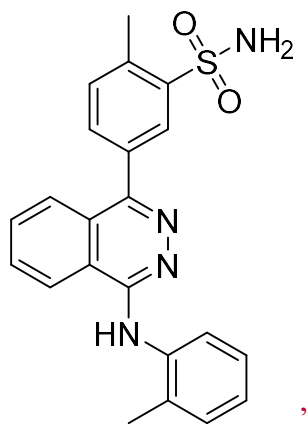
- ii. compound 6, having the structure:



- iii. compound 11, having the structure:



iv. _____ compound 20, having the structure:



_____ and wherein the A2A receptor antagonist, A2B receptor antagonist, and Treg attenuating agent
5 _____ are selected from the group consisting of:

i. _____ ZM-241385;

ii. _____ SCH-58261;

iii. _____ PBF-509;

iv. _____ MRS-1754; and

10 v. _____ an anti-GITR antibody.

~~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.~~

~~1020.~~ The use of claim ~~918~~, wherein the GPR174 inhibitor ~~is a small molecule that~~ inhibits PS-dependent or LysoPS-dependent activation of GPR174 signaling in a cell expressing
15 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%.