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(54) Title: ALKOXYPYRIDINYL AND RELATED COMPOUNDS AND THEIR USE IN THERAPY

(57) Abstract: The invention provides alkoxypyridinyl and related compounds, pharmaceutical compositions, their use for agonizing G protein-coupled receptor 84 (GPR84), and their use in the treatment of a disease or condition, such as a cancer. The invention also provides combination therapy using a GPR84 agonist to treat a disease or condition, such as a cancer.

ALKOXYPYRIDINYL AND RELATED COMPOUNDS AND THEIR USE IN THERAPY

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 63/472,770, filed June 13, 2023, which is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The invention provides alkoxypyridinyl and related compounds, pharmaceutical compositions, their use for agonizing G protein-coupled receptor 84 (GPR84), and their use in the treatment of a disease or condition, such as a cancer. The invention also provides combination therapy using a GPR84 agonist to treat a disease or condition, such as a cancer.

BACKGROUND

[0003] Cancer continues to be a significant health problem despite the substantial research efforts and scientific advances reported in the literature for treating this disease. Solid tumors, such as prostate cancer, colon, rectum, skin cancer, breast cancer, and lung cancer remain highly prevalent among the world population. Existing therapies for treating cancer include localized therapies, such as surgery, radiation therapy, cryotherapy, and systemic therapies (e.g., chemotherapy, hormonal therapy, immune therapy, and targeted therapy) used alone or in combination. Support therapies are also used in some contexts, where supportive therapies are additional treatments that do not directly treat cancer but are used to reduce side effects and address patient quality of life. However, current treatment options for cancer are not effective for all patients and/or can have substantial adverse side effects. New therapies are needed to address this unmet need in cancer therapy.

[0004] G protein-coupled receptors are a class of membrane protein receptors and have over three-hundred human gene code-related proteins, which are involved in many cell physiological functions. GPR84 is a membrane protein receptor. Human GPR84 is expressed in bone marrow and peripheral blood leukocytes (including neutrophils, eosinophils and basophils). GPR84 has been reported to have important beneficial effects against cancer, including a role as an important metabolic sensing switch to orchestrate anti-tumorigenic macrophage polarization. See, for

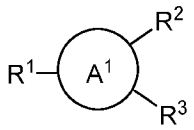
example, Xin *et al. In Journal for ImmunoTherapy of Cancer* (2022) vol. 10, Issue Suppl 2. GPR84 is also implicated in inflammatory diseases. GPR84 functions as an enhancer of inflammatory signaling in macrophages once inflammation is established. See, for example, Recio *et al. In Front Immunol.* (2018) vol. 9, 1419. Molecules having activity towards GPR84 are described in, for example, international patent application WO 2022/076446 and U.S. Patent Application Publication No 2018/0237399. New molecules having GPR84 agonist activity are needed to address diseases responsive to GPR84 agonism.

[0005] The present invention addresses the foregoing need and provides other related advantages.

SUMMARY

[0006] The invention provides alkoxypyridinyl and related compounds, pharmaceutical compositions, their use for agonizing G protein-coupled receptor 84 (GPR84), and their use in the treatment of a disease or condition, such as a cancer. The invention also provides combination therapy using a GPR84 agonist to treat a disease or condition, such as a cancer.

[0007] In particular, one aspect of the invention provides a collection of alkoxypyridinyl and related compounds, such as a compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description. Further description of additional collections of alkoxypyridinyl and related compounds are described in the detailed description. The compounds may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0008] Another aspect of the invention provides a method of treating a disease or condition responsive to GPR84 agonism. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound described herein, such as a compound of Formula I, to treat the disease or condition, as further described in the detailed description.

[0009] Another aspect of the invention provides a method of treating cancer. The method comprises administering to a subject in need thereof a therapeutically effective amount of a

compound described herein, such as a compound of Formula I, to treat the cancer, as further described in the detailed description

[0010] Another aspect of the invention provides a method of agonizing the activity of GPR84. The method comprises contacting a GPR84 with an effective amount of a compound described herein, such as a compound of Formula I, to agonize the activity of said GPR84, as further described in the detailed description.

[0011] Another aspect of the invention provides a method for treating a disease or condition responsive to GPR84 agonism. The method comprises administering to a subject in need thereof a therapeutically effective amount of (i) a GPR84 agonist and (ii) an additional therapeutic agent, such as an additional therapeutic agent that binds to a target selected from CCR4, CD19, CD20, CD22, CD30, CD33, CD38, CD47, CD52, CD79b, Claudin 18.2, CTLA-4, EGFR, FGFR2, GD2, HER2, LAG3, MET, Nectin-4, PDGFRa, PD-L1, RANKL, SLAMF7, TF, TROP2, VEGF, VEGFR, VEGFR2, or epidermal growth factor receptor with exon 20 insertion mutations, to treat the disease or condition, as further described in the detailed description.

[0012] Another aspect of the invention provides a method for treating a disease or condition responsive to GPR84 agonism. The method comprises administering to a subject in need thereof a therapeutically effective amount of (i) a GPR84 agonist and (ii) CAR-T therapy, to treat the disease or condition, as further described in the detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1A is a bar graph showing the extent of TTI-622-induced ADCP of A375 melanoma cells in a dose-response assay in the presence or absence of **I-4** at the indicated concentrations.

[0014] FIG. 1B is a bar graph showing selected data from **FIG. 1A**, including the condition producing the maximal ADCP response, with statistical significance indicated.

[0015] FIG. 2A is a bar graph showing the extent of TTI-622-induced ADCP of HCT116 colon adenocarcinoma tumor cells in a dose-response assay in the presence or absence of **I-4** at the indicated concentrations.

[0016] FIG. 2B is a bar graph showing selected data from **FIG. 2A**, including the condition producing the maximal ADCP response, with statistical significance indicated.

[0017] FIG. 3A is a bar graph showing the extent of magrolimab-induced ADCP of A375 melanoma cells in a dose-response assay in the presence or absence of **I-4** at the indicated concentrations.

[0018] FIG. 3B is a bar graph showing selected data from **FIG. 3A**, including the condition producing the maximal ADCP response, with statistical significance indicated.

[0019] FIG. 4A is a bar graph showing the extent of cetuximab-induced ADCP of HCT116 colon adenocarcinoma tumor cells in a dose-response assay in the presence or absence of **I-4** at the indicated concentrations.

[0020] FIG. 4B is a bar graph showing selected data from **FIG. 4A**, including the condition producing the maximal ADCP response, with statistical significance indicated.

[0021] FIG. 5A is a bar graph showing the extent of rituximab-induced ADCP of Ramos lymphoma cells in a dose-response assay in the presence or absence of **I-4** at the indicated concentrations.

[0022] FIG. 5B is a bar graph showing selected data from **FIG. 5A**, including the condition producing the maximal ADCP response, with statistical significance indicated.

[0023] FIG. 6A is a bar graph showing the extent of daratumumab-induced ADCP of MM.1S multiple myeloma cells in a dose-response assay in the presence or absence of **I-4** at the indicated concentrations.

[0024] FIG. 6B is a bar graph showing selected data from **FIG. 6A**, including the condition producing the maximal ADCP response, with statistical significance indicated.

[0025] FIG. 7 is a bar graph showing the extent of ADCP of Ramos lymphoma cells in the presence or absence of **I-4**, with ADCP induced by rituximab, magrolimab, or TTI-622 as indicated.

DETAILED DESCRIPTION

[0026] The invention provides alkoxypyridinyl and related compounds, pharmaceutical compositions, their use for agonizing G protein-coupled receptor 84 (GPR84), and their use in the treatment of a disease or condition, such as a cancer. The invention also provides combination therapy using a GPR84 agonist to treat a disease or condition, such as a cancer. The practice of

the present invention employs, unless otherwise indicated, conventional techniques of organic chemistry, pharmacology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology. Such techniques are explained in the literature, such as in *Comprehensive Organic Synthesis* (B.M. Trost & I. Fleming, eds., 1991-1992); *Handbook of Experimental Immunology* (D.M. Weir & C.C. Blackwell, eds.); *Current Protocols in Molecular Biology* (F.M. Ausubel *et al.*, eds., 1987, and periodic updates); and *Current Protocols in Immunology*" (J.E. Coligan *et al.*, eds., 1991), each of which is herein incorporated by reference in its entirety.

[0027] Various aspects of the invention are set forth below in sections; however, aspects of the invention described in one particular section are not to be limited to any particular section. Further, when a variable is not accompanied by a definition, the previous definition of the variable controls.

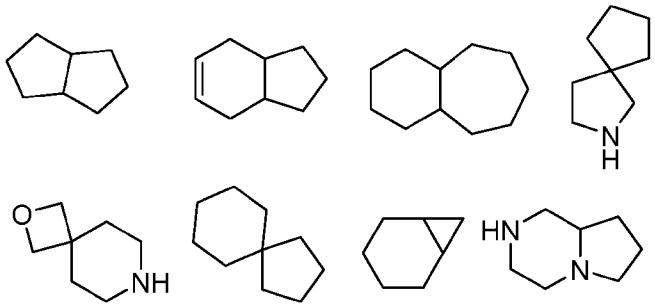
Definitions

[0028] Compounds of the present invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "-O-alkyl" etc. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics, 75th Ed.* Additionally, general principles of organic chemistry are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito: 1999, and *March's Advanced Organic Chemistry, 5th Ed.*, Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

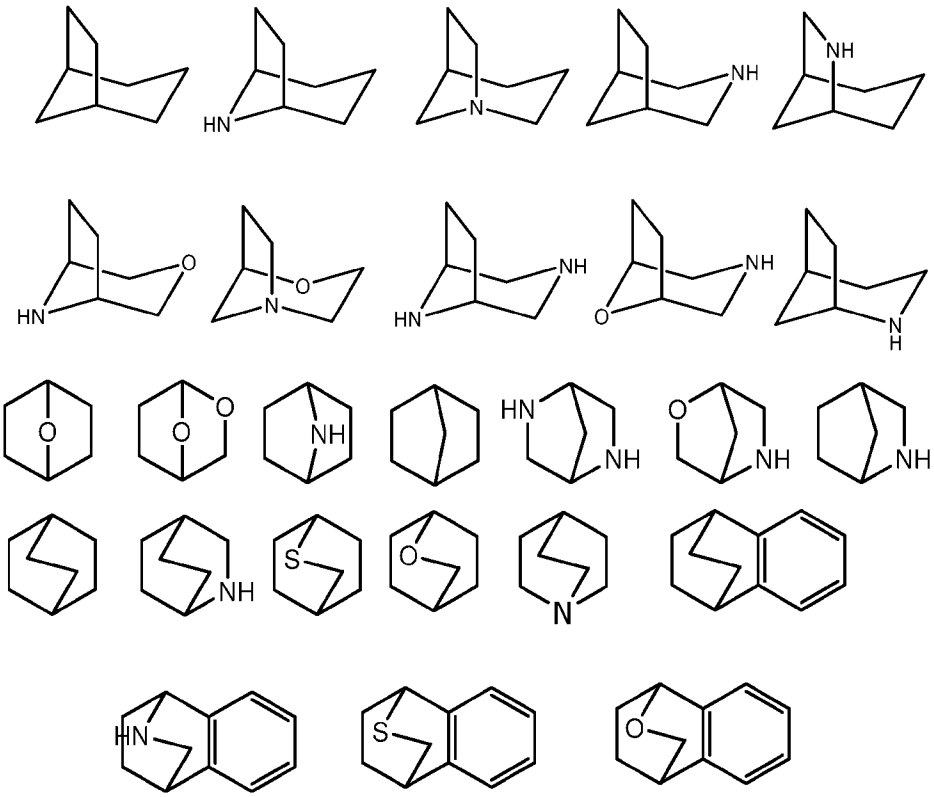
[0029] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (*i.e.*, unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "cycloaliphatic"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic

carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" refers to a monocyclic C_3-C_6 hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0030] As used herein, the term "bicyclic ring" or "bicyclic ring system" refers to any bicyclic ring system, *i.e.*, carbocyclic or heterocyclic, saturated or having one or more units of unsaturation, having one or more atoms in common between the two rings of the ring system. Thus, the term includes any permissible ring fusion, such as *ortho*-fused or spirocyclic. As used herein, the term "heterobicyclic" is a subset of "bicyclic" that requires that one or more heteroatoms are present in one or both rings of the bicycle. Such heteroatoms may be present at ring junctions and are optionally substituted, and may be selected from nitrogen (including N-oxides), oxygen, sulfur (including oxidized forms such as sulfones and sulfonates), phosphorus (including oxidized forms such as phosphates), boron, etc. In some embodiments, a bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. As used herein, the term "bridged bicyclic" refers to any bicyclic ring system, *i.e.*, carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one bridge. As defined by IUPAC, a "bridge" is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a "bridgehead" is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some embodiments, a bridged bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Such bridged bicyclic groups are well known in the art and include those groups set forth below where each group is attached to the rest of the molecule at any substitutable carbon or nitrogen atom. Unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. Exemplary bicyclic rings include:



[0031] Exemplary bridged bicyclics include:



[0032] The term "lower alkyl" refers to a C_{1-4} straight or branched alkyl group. Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and *tert*-butyl.

[0033] The term "lower haloalkyl" refers to a C_{1-4} straight or branched alkyl group that is substituted with one or more halogen atoms.

[0034] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen; or a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0035] The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

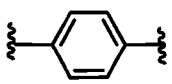
[0036] As used herein, the term "bivalent C_{1-8} (or C_{1-6}) saturated or unsaturated, straight or branched, hydrocarbon chain", refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

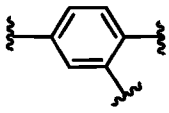
[0037] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, *i.e.*, $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0038] The term "-(C_0 alkylene)-" refers to a bond. Accordingly, the term "-(C_{0-3} alkylene)-" encompasses a bond (*i.e.*, C_0) and a -(C_{1-3} alkylene)- group.

[0039] The term "alkenylene" refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

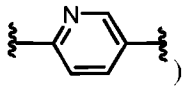
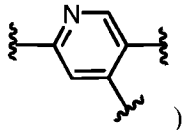
[0040] The term "halogen" or "halo" means F, Cl, Br, or I.

[0041] The term "aryl" used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic or bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring." In certain embodiments of the present invention, "aryl" refers to an aromatic ring system which includes, but is not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term "aryl," as it is used herein, is a group in which an aromatic ring is fused to one or more non–aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like. The term "phenylene" refers to a multivalent phenyl group having the appropriate number of open valences to account for groups attached to it. For example, "phenylene" is a bivalent phenyl group when it has two groups attached to it (*e.g.*, ); "phenylene" is a trivalent phenyl group

when it has three groups attached to it (*e.g.*, ). The term "arylene" refers to a bivalent aryl group.

[0042] The terms "heteroaryl" and "heteroar–," used alone or as part of a larger moiety, *e.g.*, "heteroaralkyl," or "heteroaralkoxy," refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms "heteroaryl" and "heteroar–", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where unless otherwise specified, the radical or point of attachment is on the heteroaromatic ring or on one of the rings to which the heteroaromatic ring is fused. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*–quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, and tetrahydroisoquinolinyl. A heteroaryl group may be mono– or bicyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring," "heteroaryl group," or "heteroaromatic," any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0043] The term "heteroarylene" refers to a multivalent heteroaryl group having the appropriate number of open valences to account for groups attached to it. For example, "heteroarylene" is a bivalent heteroaryl group when it has two groups attached to it; "heteroarylene" is a trivalent heteroaryl group when it has three groups attached to it. The term "pyridinylene" refers to a multivalent pyridine radical having the appropriate number of open valences to account for groups attached to it. For example, "pyridinylene" is a bivalent pyridine radical when it has two groups

attached to it (*e.g.*, ); "pyridinylene" is a trivalent pyridine radical when it has three groups attached to it (*e.g.*, ).

[0044] As used herein, the terms "heterocycle," "heterocyclyl," "heterocyclic radical," and "heterocyclic ring" are used interchangeably and refer to a stable 5– to 7–membered monocyclic or 7–10–membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4–dihydro–2*H*–pyrrolyl), NH (as in pyrrolidinyl), or $^{+}$NR (as in *N*–substituted pyrrolidinyl).

[0045] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, 2-oxa-6-azaspiro[3.3]heptane, and quinuclidinyl. The terms "heterocycle," "heterocyclyl," "heterocyclyl ring," "heterocyclic group," "heterocyclic moiety," and "heterocyclic radical," are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*–indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl. A heterocyclyl group may be mono– or bicyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted. The term "oxo-heterocyclyl" refers to a heterocyclyl substituted by an oxo group. The term "heterocyclylene" refers to a multivalent heterocyclyl group having the appropriate number of open valences to account for groups attached to it. For example, "heterocyclylene" is a bivalent heterocyclyl group when it has two groups attached to it; "heterocyclylene" is a trivalent heterocyclyl group when it has three groups attached to it.

[0046] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0047] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0048] Each optional substituent on a substitutable carbon is a monovalent substituent independently selected from halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; $-CH=CHPh$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR-$, $SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-S(O)(NR^\circ)R^\circ$; $-S(O)_2N=C(NR^\circ_2)_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-$

C(NH)NR°$_2$; –P(O)$_2$R°; -P(O)R°$_2$; -OP(O)R°$_2$; –OP(O)(OR°)$_2$; SiR°$_3$; –(C$_{1-4}$ straight or branched alkylene)O–N(R°)$_2$; or –(C$_{1-4}$ straight or branched alkylene)C(O)O–N(R°)$_2$.

[0049] Each R° is independently hydrogen, C$_{1-6}$ aliphatic, –CH$_2$Ph, –O(CH$_2$)$_{0-1}$Ph, -CH$_2$-(5-6 membered heteroaryl ring), or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted by a divalent substituent on a saturated carbon atom of R° selected from =O and =S; or each R° is optionally substituted with a monovalent substituent independently selected from halogen, –(CH$_2$)$_{0-2}$R$^\bullet$, –(haloR$^\bullet$), –(CH$_2$)$_{0-2}$OH, –(CH$_2$)$_{0-2}$OR$^\bullet$, –(CH$_2$)$_{0-2}$CH(OR$^\bullet$)$_2$; -O(haloR$^\bullet$), –CN, –N$_3$, –(CH$_2$)$_{0-2}$C(O)R$^\bullet$, –(CH$_2$)$_{0-2}$C(O)OH, –(CH$_2$)$_{0-2}$C(O)OR$^\bullet$, –(CH$_2$)$_{0-2}$SR$^\bullet$, –(CH$_2$)$_{0-2}$SH, –(CH$_2$)$_{0-2}$NH$_2$, –(CH$_2$)$_{0-2}$NHR$^\bullet$, –(CH$_2$)$_{0-2}$NR$^\bullet_2$, –NO$_2$, –SiR$^\bullet_3$, –OSiR$^\bullet_3$, -C(O)SR$^\bullet$, –(C$_{1-4}$ straight or branched alkylene)C(O)OR$^\bullet$, or –SSR$^\bullet$.

[0050] Each R$^\bullet$ is independently selected from C$_{1-4}$ aliphatic, –CH$_2$Ph, –O(CH$_2$)$_{0-1}$Ph, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each R$^\bullet$ is unsubstituted or where preceded by halo is substituted only with one or more halogens; or wherein an optional substituent on a saturated carbon is a divalent substituent independently selected from =O, =S, =NNR$^*_2$, =NNHC(O)R*, =NNHC(O)OR*, =NNHS(O)$_2$R*, =NR*, =NOR*, –O(C(R$^*_2$))$_{2-3}$O–, or –S(C(R$^*_2$))$_{2-3}$S–, or a divalent substituent bound to vicinal substitutable carbons of an "optionally substituted" group is –O(CR$^*_2$)$_{2-3}$O–, wherein each independent occurrence of R* is selected from hydrogen, C$_{1-6}$ aliphatic or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0051] When R* is C$_{1-6}$ aliphatic, R* is optionally substituted with halogen, –R$^\bullet$, -(haloR$^\bullet$), -OH, –OR$^\bullet$, –O(haloR$^\bullet$), –CN, –C(O)OH, –C(O)OR$^\bullet$, –NH$_2$, –NHR$^\bullet$, –NR$^\bullet_2$, or –NO$_2$, wherein each R$^\bullet$ is independently selected from C$_{1-4}$ aliphatic, –CH$_2$Ph, –O(CH$_2$)$_{0-1}$Ph, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each R$^\bullet$ is unsubstituted or where preceded by halo is substituted only with one or more halogens.

[0052] An optional substituent on a substitutable nitrogen is independently $-R^{\dagger}$, $-NR^{\dagger}_2$, $-C(O)R^{\dagger}$, $-C(O)OR^{\dagger}$, $-C(O)C(O)R^{\dagger}$, $-C(O)CH_2C(O)R^{\dagger}$, $-S(O)_2R^{\dagger}$, $-S(O)_2NR^{\dagger}_2$, $-C(S)NR^{\dagger}_2$, $-C(NH)NR^{\dagger}_2$, or $-N(R^{\dagger})S(O)_2R^{\dagger}$; wherein each $R^{\dagger}$ is independently hydrogen, C_{1-6} aliphatic, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, two independent occurrences of $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein when $R^{\dagger}$ is C_{1-6} aliphatic, $R^{\dagger}$ is optionally substituted with halogen, $-R^{\bullet}$, -(halo$R^{\bullet}$), -OH, $-OR^{\bullet}$, –O(halo$R^{\bullet}$), –CN, –C(O)OH, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each $R^{\bullet}$ is unsubstituted or where preceded by halo is substituted only with one or more halogens.

[0053] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, **1977**, *66*, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate,

pectinate, persulfate, 3–phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like.

[0054] Further, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al.*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al.*, *Journal of Pharmaceutical Sciences* **1977**, *66*(1), 1-19; P. Gould, *International J. of Pharmaceutics* **1986**, *33*, 201-217; Anderson *et al.*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference.

[0055] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0056] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (*e.g.*, enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the *R* and *S* configurations for each asymmetric center, *Z* and *E* double bond isomers, and *Z* and *E* conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. The invention includes compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention.

[0057] Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by

converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Alternatively, a particular enantiomer of a compound of the present invention may be prepared by asymmetric synthesis. Still further, where the molecule contains a basic functional group (such as amino) or an acidic functional group (such as carboxylic acid) diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means known in the art, and subsequent recovery of the pure enantiomers.

[0058] Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. Chiral center(s) in a compound of the present invention can have the *S* or *R* configuration as defined by the *IUPAC* 1974 Recommendations. Further, to the extent a compound described herein may exist as an atropisomer (*e.g.*, substituted biaryls), all forms of such atropisomer are considered part of this invention.

[0059] Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. If a chemical compound is referred to using both a chemical structure and a chemical name, and an ambiguity exists between the structure and the name, the structure predominates. It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

[0060] Unless specified otherwise, the term "about" refers to within ±10% of the stated value. The invention encompasses embodiments where the value is within ±9%, ±8%, ±7%, ±6%, ±5%, ±4%, ±3%, ±2%, or ±1% of the stated value.

[0061] The terms "a" and "an" as used herein mean "one or more" and include the plural unless the context is inappropriate.

[0062] The term "alkyl" refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-12, 1-10, or 1-6 carbon atoms, referred to herein as C_1-C_{12} alkyl, C_1-C_{10} alkyl, and C_1-C_6 alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-

methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

[0063] The term "cycloalkyl" refers to a monovalent saturated cyclic, bicyclic, or bridged cyclic (*e.g.*, adamantyl) hydrocarbon group of 3-12, 3-8, 4-8, or 4-6 carbons, referred to herein, *e.g.*, as "C_3-C_6 cycloalkyl," derived from a cycloalkane. Exemplary cycloalkyl groups include cyclohexyl, cyclopentyl, cyclobutyl, and cyclopropyl. The term "cycloalkylene" refers to a bivalent cycloalkyl group.

[0064] The term "haloalkyl" refers to an alkyl group that is substituted with at least one halogen. Exemplary haloalkyl groups include -CH_2F, -CHF_2, -CF_3, -CH_2CF_3, -CF_2CF_3, and the like. The term "haloalkylene" refers to a bivalent haloalkyl group.

[0065] The terms "alkenyl" and "alkynyl" are art-recognized and refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively.

[0066] The terms "alkoxyl" or "alkoxy" are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, *tert*-butoxy and the like. The term "haloalkoxyl" refers to an alkoxyl group that is substituted with at least one halogen. Exemplary haloalkoxyl groups include -OCH_2F, -$OCHF_2$, -OCF_3, -OCH_2CF_3, -OCF_2CF_3, and the like. The term "hydroxyalkoxyl" refers to an alkoxyl group that is substituted with at least one hydroxyl. Exemplary hydroxyalkoxyl groups include -OCH_2CH_2OH, -$OCH_2C(H)(OH)CH_2CH_2OH$, and the like. The term "alkoxylene" refers to a bivalent alkoxyl group.

[0067] The term "oxo" is art-recognized and refers to a "=O" substituent. For example, a cyclopentane substituted with an oxo group is cyclopentanone.

[0068] The symbol "$\sim\!\!\sim$" indicates a point of attachment.

[0069] When any substituent or variable occurs more than one time in any constituent or the compound of the invention, its definition on each occurrence is independent of its definition at every other occurrence, unless otherwise indicated.

[0070] One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

[0071] As used herein, the terms "subject" and "patient" are used interchangeably and refer to organisms to be treated by the methods of the present invention. Such organisms preferably include, but are not limited to, mammals (*e.g.*, murines, simians, equines, bovines, porcines, canines, felines, and the like), and, most preferably, include humans.

[0072] As used herein, the term "compound" refers to a quantity of molecules that is sufficient to be weighed, tested for its structural identity, and to have a demonstrable use (*e.g.*, a quantity that can be shown to be active in an assay, an *in vitro* test, or *in vivo* test, or a quantity that can be administered to a patient and provide a therapeutic benefit).

[0073] The term "IC_{50}" is art-recognized and refers to the concentration of a compound that is required to achieve 50% inhibition of the target.

[0074] As used herein, the term "effective amount" refers to the amount of a compound sufficient to effect beneficial or desired results (*e.g.*, a therapeutic, ameliorative, inhibitory, or preventative result). An effective amount can be administered in one or more administrations, applications, or dosages and is not intended to be limited to a particular formulation or administration route.

[0075] As used herein, the term "treating" includes any effect, *e.g.*, lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

[0076] As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

[0077] As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, such as a phosphate-buffered saline solution, water, emulsions (*e.g.*, such as oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, s*ee e.g.*, Martin, *Remington's Pharmaceutical Sciences, 15th Ed.*, Mack Publ. Co., Easton, PA [1975].

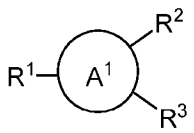
[0078] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present invention that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

[0079] As a general matter, compositions specifying a percentage are by weight unless otherwise specified.

I. Alkoxypyridinyl and Related Compounds

[0080] The invention provides alkoxypyridinyl and related compounds. The compounds may be used in the pharmaceutical compositions and therapeutic methods described herein. Exemplary compounds are described in the following sections, along with exemplary procedures for making the compounds.

[0081] One aspect of the invention provides a compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 is C_{2-12} alkoxyl, -[-O-(C_{1-2} alkylene)]$_n$-H, -(C_{1-6} alkylene)-[-O-(C_{1-2} alkylene)]$_n$-H, -C_{4-12} alkyl, -C(O)-(C_{4-12} alkyl), -(C_{1-10} alkylene)-R^6, -O-(C_{1-10} alkylene)-R^6, -N(R^4)([(C_{1-2} alkylene)-O-]$_n$-(C_{1-6} alkyl)), or -N(R^4)(R^5);

R^2 is hydroxyl, C_{1-4} alkoxyl, or hydrogen;

R^3 is hydroxyl, C_{1-4} haloalkyl, or hydrogen;

R^4 is C_{1-6} alkyl;

R^5 is C_{4-12} alkyl;

R^6 is a 5-6 membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the heteroaryl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-6} alkyl and halo;

A^1 is (i) a 6-membered heteroarylene containing 1 or 2 heteroatoms selected from nitrogen or (ii) a 5-membered heteroarylene containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

n is 1, 2, 3, 4, 5 or 6;

[0082] provided that R^1 is not C_{4-12} alkyl when $A^1(R^2)(R^3)$ taken together are a dihydroxy-pyrimidinyl or a dihydroxy-pyridinyl. The definitions of variables in Formula I above encompass multiple chemical groups. The application contemplates embodiments where, for example, (i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, (ii) the definition of a variable is a collection of two or more of the chemical groups selected from those set forth above, and (iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii).

[0083] In certain embodiments, the compound is a compound of Formula I.

[0084] As defined generally above, R^1 is C_{2-12} alkoxyl, -[-O-(C_{1-2} alkylene)]$_n$-H, -(C_{1-6} alkylene)-[-O-(C_{1-2} alkylene)]$_n$-H, -C_{4-12} alkyl, -C(O)-(C_{4-12} alkyl), -(C_{1-10} alkylene)-R^6, -O-(C_{1-10} alkylene)-R^6, -N(R^4)([(C_{1-2} alkylene)-O-]$_n$-(C_{1-6} alkyl)), or -N(R^4)(R^5). In certain embodiments, R^1 is C_{2-12} alkoxyl. In certain embodiments, R^1 is C_{6-10} alkoxyl. In certain embodiments, R^1 is C_8 alkoxyl. In certain embodiments, R^1 is -[-O-(C_{1-2} alkylene)]$_n$-H. In certain embodiments, R^1 is -(C_{1-6} alkylene)-[-O-(C_{1-2} alkylene)]$_n$-H. In certain embodiments, R^1 is -C_{4-12} alkyl. In certain embodiments, R^1 is -C_{7-10} alkyl. In certain embodiments, R^1 is -C_{10} alkyl. In certain embodiments, R^1 is -C(O)-(C_{4-12} alkyl). In certain embodiments, R^1 is -C(O)-(C_{8-12} alkyl). In certain embodiments, R^1 is -(C_{1-10} alkylene)-R^6. In certain embodiments, R^1 is -(C_{4-6} alkylene)-R^6. In

certain embodiments, R^1 is -O-(C_{1-10} alkylene)-R^6. In certain embodiments, R^1 is -N(R^4)([(C_{1-2} alkylene)-O-]$_n$-(C_{1-6} alkyl)). In certain embodiments, R^1 is -N(R^4)(R^5). In certain embodiments, R^1 is -C(O)-(C_{4-12} alkyl) or -O-(C_{1-10} alkylene)-R^6. In certain embodiments, R^1 is -N(R^4)([(C_{1-2} alkylene)-O-]$_n$-(C_{1-6} alkyl)) or -N(R^4)(R^5). In certain embodiments, R^1 is selected from the groups depicted in the compounds in Table 1 below.

[0085] As defined generally above, R^2 is hydroxyl, C_{1-4} alkoxyl, or hydrogen. In certain embodiments, R^2 is hydroxyl. In certain embodiments, R^2 is C_{1-4} alkoxyl. In certain embodiments, R^2 is hydrogen. In certain embodiments, R^2 is selected from the groups depicted in the compounds in Table 1 below.

[0086] As defined generally above, R^3 is hydroxyl, C_{1-4} haloalkyl, or hydrogen. In certain embodiments, R^3 is hydroxyl. In certain embodiments, R^3 is C_{1-4} haloalkyl. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is selected from the groups depicted in the compounds in Table 1 below.

[0087] As defined generally above, R^4 is C_{1-6} alkyl. In certain embodiments, R^4 is C_{1-4} alkyl. In certain embodiments, R^4 is C_{1-2} alkyl. In certain embodiments, R^4 is selected from the groups depicted in the compounds in Table 1 below.

[0088] As defined generally above, R^5 is C_{4-12} alkyl. In certain embodiments, R^5 is C_{6-10} alkyl. In certain embodiments, R^5 is C_{8-10} alkyl. In certain embodiments, R^5 is C_{6-8} alkyl. In certain embodiments, R^5 is selected from the groups depicted in the compounds in Table 1 below.

[0089] As defined generally above, R^6 is a 5-6 membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the heteroaryl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-6} alkyl and halo. In certain embodiments, R^6 is a 5-membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the heteroaryl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-6} alkyl and halo. In certain embodiments, R^6 is a 5-membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the heteroaryl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-6} alkyl. In certain embodiments, R^6 is a 5-membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the heteroaryl is substituted

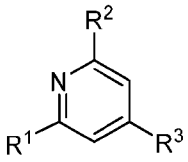
with 0, 1, or 2 substituents independently selected from the group consisting of halo. In certain embodiments, R^6 is a 6-membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the heteroaryl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-6} alkyl and halo. In certain embodiments, R^6 is a 6-membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the heteroaryl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-6} alkyl . In certain embodiments, R^6 is a 6-membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the heteroaryl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halo. In certain embodiments, R^6 is pyridinyl, pyrazolyl, or oxazolyl, each of which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-6} alkyl and halo. In certain embodiments, R^6 is selected from the groups depicted in the compounds in Table 1 below.

[0090] As defined generally above, A^1 is (i) a 6-membered heteroarylene containing 1 or 2 heteroatoms selected from nitrogen or (ii) a 5-membered heteroarylene containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, A^1 is (i) a 6-membered heteroarylene containing 1 or 2 heteroatoms selected from nitrogen. In certain embodiments, A^1 is (ii) a 5-membered heteroarylene containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, A^1 is pyridinylene. In certain embodiments, A^1 is pyrazolylene, oxazolylene, or 1,2,4-triazolylene. In certain embodiments, is A^1 selected from the groups depicted in the compounds in Table 1 below.

[0091] As defined generally above, n is 1, 2, 3, 4, 5 or 6. In certain embodiments, n is 1, 2, or 3. In certain embodiments, n is 4, 5 or 6. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is 3. In certain embodiments, n is 4. In certain embodiments, n is 5. In certain embodiments, n is 6. In certain embodiments, n is selected from the groups depicted in the compounds in Table 1 below.

[0092] The description above describes multiple embodiments relating to compounds of Formula I. The patent application specifically contemplates all combinations of the embodiments.

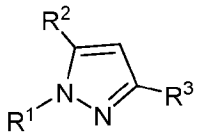
[0093] In certain embodiments, the compound of Formula I is further defined by Formula **Ia** or a pharmaceutically acceptable salt thereof:



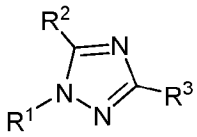
Ia.

[0094] In certain embodiments, the compound of Formula I is further defined by Formula **Ia.**

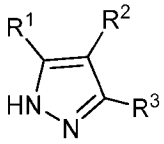
[0095] In certain embodiments, the compound of Formula I is further defined by Formula **Ib**, **Ic**, or **Id**, or a pharmaceutically acceptable salt thereof:



Ib



Ic

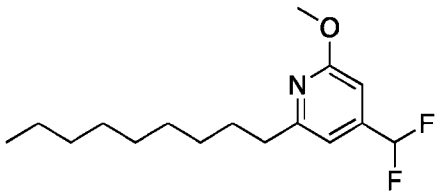
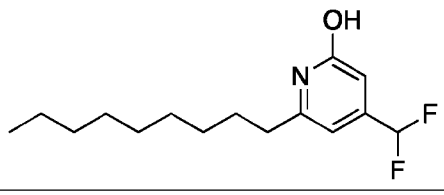
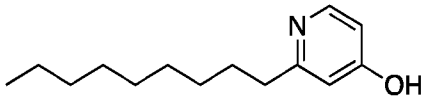


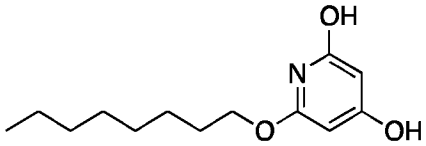
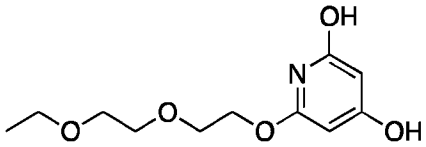
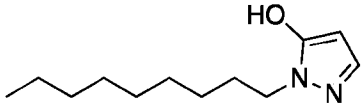
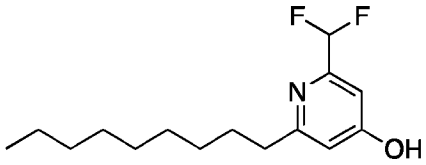
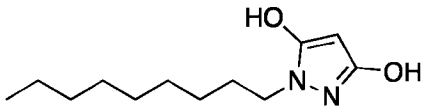
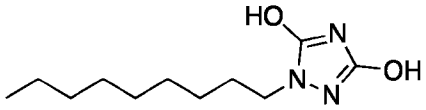
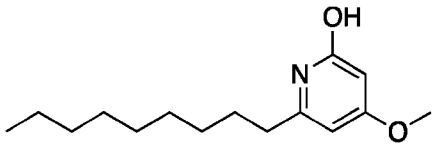
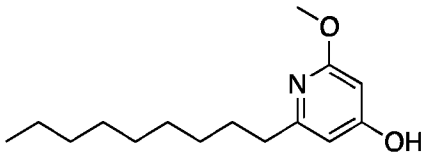
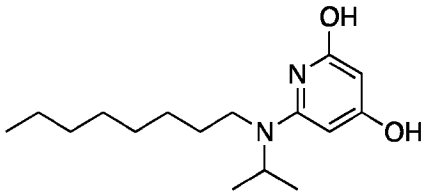
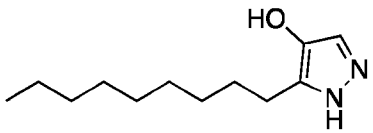
Id.

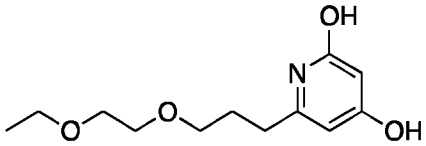
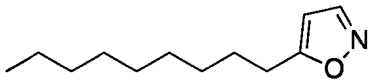
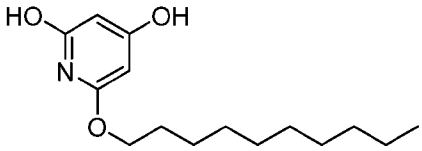
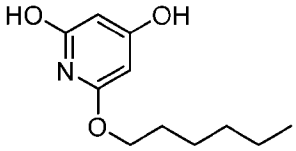
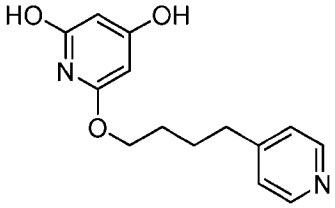
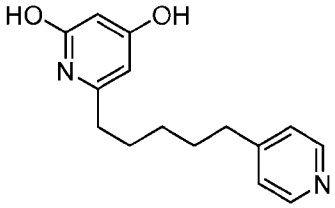
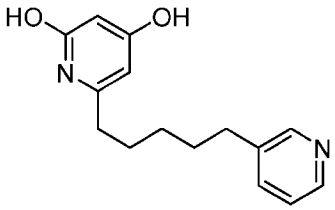
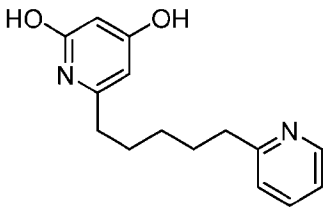
[0096] In certain embodiments, the compound of Formula I is further defined by Formula **Ib**, **Ic**, or **Id.**

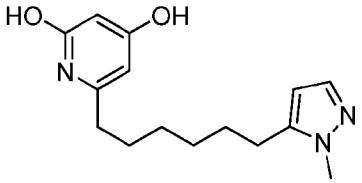
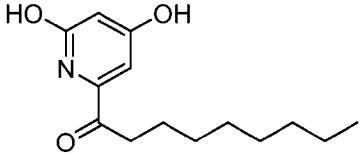
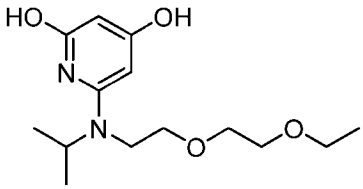
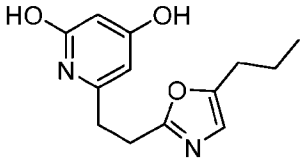
[0097] Another aspect of the invention provides a compound in Table 1 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1.

TABLE 1.

Compound No.	Chemical Structure
I-1	
I-2	
I-3	

Compound No.	Chemical Structure
I-4	
I-5	
I-6	
I-7	
I-8	
I-9	
I-10	
I-11	
I-12	
I-13	

Compound No.	Chemical Structure
I-14	
I-15	
I-16	
I-17	
I-18	
I-19	
I-20	
I-21	

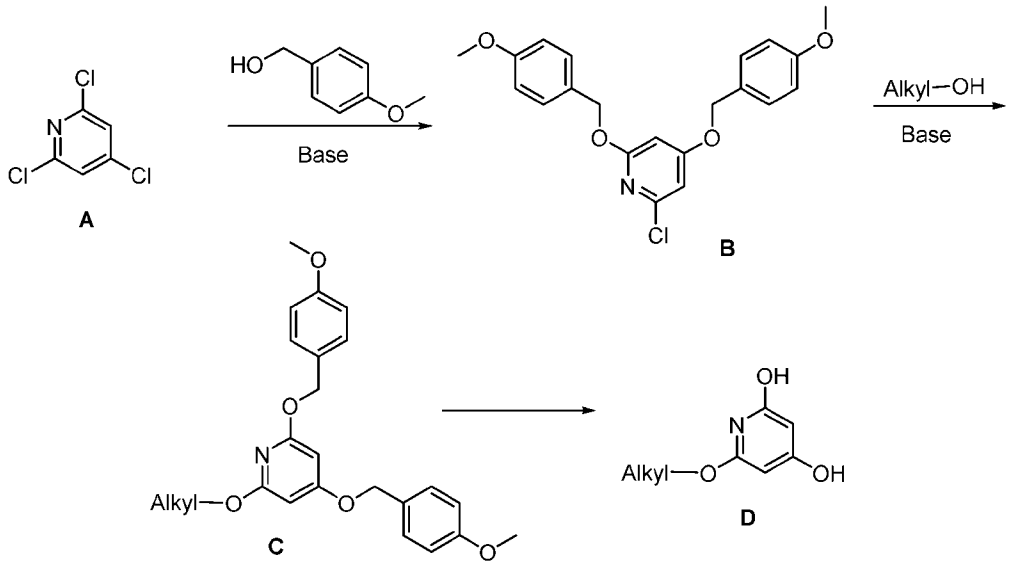
Compound No.	Chemical Structure
I-22	
I-23	
I-24	
I-25	

[0098] Methods for preparing compounds described herein are illustrated in the following synthetic scheme. The scheme is provided for the purpose of illustrating the invention, and is not intended to limit the scope or spirit of the invention. Starting materials shown in the scheme can be obtained from commercial sources or can be prepared based on procedures described in the literature.

[0099] In the schemes, it is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated (for example, use of protecting groups or alternative reactions). Protecting group chemistry and strategy is well known in the art, for example, as described in detail in *Protecting Groups in Organic Synthesis, 3rd Edition*, T. W. Greene and P. G. M. Wuts, John Wiley & Sons, 1999 and *Greene's Protective Groups in Organic Synthesis, 5th Ed.*, (Peter G. M. Wuts, John Wiley & Sons: 2014), the entire contents of both of which are hereby incorporated by reference.

[0100] The synthetic route illustrated in Scheme 1 is a general method for preparing compounds of Formula **D**. Reaction of chloropyridine **A** with (4-methoxyphenyl)methanol provides compound **B**. Reaction of compound **B** with a hydroxy-alkane compound under basic conditions provides compound **C**. Removal of the protecting groups (e.g., under acidic conditions, such as trifluoroacetic acid) provides the final compound of Formula **D**.

SCHEME 1.



[0101] The modular synthetic route illustrated in Scheme 1 can be adjusted to provide additional compounds by conducting functional group transformations on the intermediate and final compounds. Such functional group transformations are well known in the art, as described in, for example, *Comprehensive Organic Synthesis* (B.M. Trost & I. Fleming, eds., 1991-1992); *Organic Synthesis, 3rd Ed.* (Michael B. Smith, Wavefunction, Inc., Irvine: 2010); *Modern Methods of Organic Synthesis, 4th Ed.* (William Carruthers and Iain Coldham, Cambridge University Press, Cambridge: 2004); *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 8th Ed.*, (Michael B. Smith, John Wiley & Sons, New York: 2020); and *Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 3rd Ed.* (Richard C. Larock, ed., John Wiley & Sons, New York: 2018).

II. Therapeutic Applications of Alkoxypyridinyl and Related Compounds

[0102] The alkoxypyridinyl and related compounds described herein, such as a compound of Formula I, or other compounds in Section I, provide therapeutic benefits to subjects suffering from cancer and other diseases and conditions.

[0103] Accordingly, one aspect of the invention provides a method of treating a disease or condition responsive to GPR84 agonism. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound described herein, such as a compound of Formula I, to treat the disease or condition. In certain embodiments, the compound is a compound of Formula Ia, Ib, Ic or defined by one of the embodiments described above. Further description of exemplary diseases or conditions responsive to GPR84 agonism is provided herein below.

[0104] Another aspect of the invention provides a method of agonizing the activity of GPR84. The method comprises contacting a GPR84 with an effective amount of a compound described herein, such as a compound of Formula I, to agonize the activity of said GPR84. In certain embodiments, the compound is a compound of Formula Ia, Ib, Ic or defined by one of the embodiments described above.

Exemplary Diseases or Conditions Responsive to GPR84 Agonism

[0105] In certain embodiments, the disease or condition responsive to GPR84 agonism is an infectious disease or condition, a neurological or neurodegenerative disease or condition, or cancer.

[0106] In certain embodiments, the disease or condition responsive to GPR84 agonism is cancer.

[0107] In certain embodiments, the cancer is a solid tumor. In certain embodiments, the cancer is ovarian cancer, uterine cancer, endometrial cancer, cervical cancer, prostate cancer, testicular cancer, breast cancer, brain cancer, lung cancer, oral cancer, esophageal cancer, head and neck cancer, stomach cancer, colon cancer, rectal cancer, skin cancer, sebaceous gland carcinoma, bile duct and gallbladder cancers, liver cancer, pancreatic cancer, bladder cancer, urinary tract cancer, kidney cancer, eye cancer, thyroid cancer, or a neuroendocrine cancer.

[0108] In certain embodiments, the cancer is a solid tumor. In certain embodiments, the cancer is a sarcoma or carcinoma.

[0109] In certain embodiments, the cancer is prostate cancer, breast cancer, lung cancer, liver cancer, bladder cancer, urinary tract cancer, or eye cancer. In certain embodiments, the cancer is prostate cancer. In certain embodiments, the cancer is breast cancer. In certain embodiments, the cancer is lung cancer. In certain embodiments, the cancer is liver cancer. In certain embodiments, the cancer is bladder cancer. In certain embodiments, the cancer is urinary tract cancer. In certain embodiments, the cancer is eye cancer.

[0110] In certain embodiments, the cancer is a B-cell non-Hodgkin's Lymphoma, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL), mature B-cell acute leukemia (B-AL), chronic lymphocytic leukemia (CLL), follicular lymphoma, multiple myeloma, head and neck cancer, colorectal cancer, a squamous cell carcinoma, HER2 overexpressing breast cancer, gastric junction adenocarcinoma, gastro-esophageal junction adenocarcinoma, non-small cell lung cancer, hepatocellular carcinoma, gastric cancer, urothelial cancer, renal cancer, giant cell bone cancer, bone metastasis, neuroblastoma, mycosis fungoides, or Sézary syndrome.

[0111] In certain embodiments, the cancer is squamous-cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas (e.g., Burkitt's lymphoma and Non-Hodgkin's lymphoma); benign and malignant melanomas; myeloproliferative diseases; sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogliomas, ependymomas, gliobastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor and teratocarcinomas.

[0112] In certain embodiments, the cancer is a neuroblastoma, craniopharyngioma, glioma, glioblastoma, schwannoma, astrocytoma, oligodendroglioma, medulloblastoma, pinealoma, hemangioblastoma, retinoblastoma, ependymoma, chordoma, meningioma, medullary carcinoma,

small cell lung carcinoma, papillary adenocarcinoma, papillary carcinoma, mesothelioma, nasopharyngeal carcinoma, acoustic neuroma, oral cancer, esophageal cancer, head and neck cancer, stomach cancer, colon cancer, rectal cancer, skin cancer, melanoma, sweat gland carcinoma, sebaceous gland carcinoma, squamous cell carcinoma, basal cell carcinoma, bile duct and gallbladder cancers, liver cancer, hepatocellular carcinoma, pancreatic cancer, bladder carcinoma, renal cell carcinoma, kidney cancer, Wilms' tumor, thyroid cancer, parathyroid tumor, synovioma, soft tissue sarcoma (e.g., rhabdomyosarcoma (RMS)), Kaposi sarcoma, synovial sarcoma, osteosarcoma, Ewing's sarcoma, malignant rhabdoid tumor, leiomyosarcoma, liposarcoma, lymphangioendothelio-sarcoma, lymphangiosarcoma, myxosarcoma, osteogenic sarcoma, fibrosarcoma, chondrosarcoma, or endotheliosarcoma.

[0113] In certain embodiments, the cancer is a hematological cancer. In certain embodiments, the cancer is lymphoma, leukemia, or myeloma.

[0114] In certain embodiments, the cancer is a lymphoma. In certain embodiments, the cancer is Burkitt's lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, non-Hodgkin's lymphoma, lymphoid malignancies of T-cell or B-cell origin, peripheral T-cell lymphoma, adult T-cell leukemia-lymphoma, or Waldenström's macroglobulinemia.

[0115] In certain embodiments, the cancer is a leukemia. In certain embodiments, the cancer is acute leukemia, lymphoblastic leukemia, acute lymphoblastic leukemia, myelogenous leukemia, B-cell leukemia, T-cell leukemia, acute myelogenous leukemia, acute T-cell leukemia, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, chronic myelogenous leukemia, polycythemia vera, multiple myeloma, or erythroleukemia.

[0116] In certain embodiments, the cancer is a myelodysplastic and/or myeloproliferative syndrome. In certain embodiments, the cancer is a myelodysplastic syndrome. In certain embodiments, the cancer is a myeloproliferative syndrome.

[0117] In certain embodiments, the cancer is a cancer or related myeloproliferative disorder selected from histiocytosis, essential thrombocythemia, myelofibrosis, heavy chain disease, and other malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus.

[0118] In certain embodiments, the cancer is a malignant rhabdoid tumor, atypical teratoid rhabdoid tumor, epithelioid sarcoma, renal medullary carcinoma, pancreatic undifferentiated rhabdoid carcinoma, schwannoma, epithelioid malignant peripheral nerve sheath tumor, or diffuse intrinsic glioma.

[0119] In certain embodiments, the cancer is retinoblastoma multiforme, metastatic castration-resistant prostate cancer, prostate small cell neuroendocrine carcinoma, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, bladder cancer, or urinary tract cancer.

[0120] In certain embodiments, the cancer is fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, and hemangioblastoma. In certain embodiments, the cancer is a neuroblastoma, meningioma, hemangiopericytoma, multiple brain metastase, glioblastoma multiforms, glioblastoma, brain stem glioma, poor prognosis malignant brain tumor, malignant glioma, anaplastic astrocytoma, anaplastic oligodendroglioma, neuroendocrine tumor, rectal adeno carcinoma, Dukes C & D colorectal cancer, unresectable colorectal carcinoma, metastatic hepatocellular carcinoma, Kaposi's sarcoma, acute myeloblastic leukemia, acute myeloblastic leukemia with complex karyotype, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma, low grade follicular lymphoma, metastatic melanoma, localized melanoma, malignant mesothelioma, malignant pleural effusion mesothelioma syndrome, peritoneal carcinoma, papillary serous carcinoma, gynecologic sarcoma, soft tissue sarcoma, scelroderma, cutaneous vasculitis, Langerhans cell histiocytosis, leiomyosarcoma, fibrodysplasia ossificans progressive, hormone refractory prostate cancer, resected high-risk soft tissue sarcoma, unrescectable hepatocellular carcinoma, Waidenstrom's macroglobulinemia, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, hormone-insensitive prostate cancer,

chemotherapy-insensitive prostate cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, or leiomyoma.

[0121] In certain embodiments, the cancer an ADCP-resistant cancer. In certain embodiments, the cancer comprises U266 cells.

[0122] In certain embodiments, the cancer is a metastatic cancer. In certain embodiments, the cancer is a relapsed and/or refractory cancer.

[0123] In certain embodiments, the cancer is ovarian cancer, uterine cancer, gestational trophoblastic disease, endometrial cancer, cervical cancer, embryonal carcinoma, choriocarcinoma, prostate cancer (including hormone insensitive and castrate resistant prostate cancers), testicular tumors (including germ cell testicular cancer / seminoma), cystadenocarcinoma, breast cancer (including estrogen-receptor positive breast cancer), brain tumors (including neuroblastoma, craniopharyngioma, glioma, glioblastoma, schwannoma, astrocytoma, oligodendroglioma, medulloblastoma, and pinealoma), hemangioblastoma, retinoblastoma, ependymoma, chordoma, meningioma, medullary carcinoma, lung cancer (including small cell lung carcinoma, papillary adenocarcinomas, and papillary carcinoma), mesothelioma, nasopharyngeal carcinoma, acoustic neuroma, oral cancer, esophageal cancer, head and neck cancer, stomach cancer, colon cancer, rectal cancer, skin cancer, melanoma, sweat gland carcinoma, sebaceous gland carcinoma, squamous cell carcinoma, basal cell carcinoma, bile duct and gallbladder cancers, liver cancer, hepatocellular carcinoma, pancreatic cancer, bladder carcinoma, renal cell carcinoma, kidney cancer, Wilms' tumor, thyroid cancer, parathyroid tumor, synovioma, soft tissue sarcoma (e.g., rhabdomyosarcoma (RMS)), Kaposi sarcoma, synovial sarcoma, osteosarcoma, Ewing's sarcoma, malignant rhabdoid tumor, leiomyosarcoma, liposarcoma, lymphangioendothelio-sarcoma, lymphangiosarcoma, myxosarcoma, osteogenic sarcoma, fibrosarcoma, chondrosarcoma, or endotheliosarcoma.

[0124] In certain embodiments, the disease or condition responsive to GPR84 agonism is an infectious disease or condition.

[0125] In certain embodiments, the infectious disease or condition is Human granulocytic anaplasmosis; brucellosis; melioidosis; pneumonia; bronchitis; meningitis; Q fever; ehrlichiosis; tularemia; Legionnaire's disease; Listeriosis; tuberculosis; Rocky Mountain spotted fever; salmonellosis; HIV infection; or Helicobacter pylori infection.

[0126] In certain embodiments, the disease or condition responsive to GPR84 agonism is a neurodegenerative disease or condition.

[0127] In certain embodiments, the neurodegenerative disease or condition is a disease involving amyloid beta deposit formation or a disease of frontal neuronal degeneration. In certain embodiments, the disease involving amyloid beta deposit formation is Alzheimer disease; multiple sclerosis; Huntington's disease; or Parkinson's disease. In certain embodiments, the disease of frontal neuronal degeneration is frontotemporal dementia.

[0128] In certain embodiments, the disease or condition responsive to GPR84 agonism is selected from those listed in Table 2.

[0129] In certain embodiments, the disease or condition is septicemia. In certain embodiments, the disease or condition is obesity.

[0130] In certain embodiments, the subject is a human. In certain embodiments, the subject is an adult human. In certain embodiments, the subject is a pediatric human. In certain embodiments, the subject is a geriatric human.

[0131] Another aspect of the invention provides for the use of a compound described herein (such as a compound of Formula I or other compounds in Section I) in the manufacture of a medicament. In certain embodiments, the medicament is for treating a disease or condition described herein, such as cancer.

[0132] Another aspect of the invention provides for the use of a compound described herein (such as a compound of Formula I or other compounds in Section I) for treating a disease or condition, such as cancer.

III. Combination Therapy

[0133] Another aspect of the invention provides for combination therapy. In one embodiment, an alkoxypyridinyl or related compound described herein (*e.g.*, a compound of Formula I or other compounds in Section I) may be used in combination with an additional therapeutic agent to treat diseases or conditions, such as cancer. In another embodiment, a GPR84 agonist is used in combination with an additional therapeutic agent that binds to a target selected from CCR4, CD19, CD20, CD22, CD30, CD33, CD38, CD47, CD52, CD79b, Claudin 18.2, CTLA-4, EGFR, FGFR2, GD2, HER2, LAG3, MET, Nectin-4, PDGFRa, PD-L1, RANKL, SLAMF7, TF, TROP2, VEGF,

VEGFR, VEGFR2, or epidermal growth factor receptor with exon 20 insertion mutations, to treat a disease or condition, such as cancer. Such combination therapies are described in more detail below.

[0134] Accordingly, in certain embodiments, the present invention provides a method of treating a disease or condition comprising administering to a patient in need thereof an effective amount of a compound disclosed herein and co-administering simultaneously or sequentially an effective amount of one or more additional therapeutic agents, such as those described herein. In some embodiments, the method includes co-administering one additional therapeutic agent. In some embodiments, the method includes co-administering two additional therapeutic agents.

[0135] One or more additional therapeutic agents may be administered separately from a first compound or composition, as part of a multiple dosage regimen. Alternatively, one or more other therapeutic agents may be part of a single dosage form, mixed together with a first compound in a single composition. If administered as a multiple dosage regime, one or more other therapeutic agent and first compound may be administered simultaneously, sequentially or within a period of time from one another.

[0136] In certain embodiments, the compounds of the disclosure can be administered with one or more of a second therapeutic agent, sequentially or concurrently, either by the same route or by different routes of administration. When administered sequentially, the time between administrations is selected to benefit, among others, the therapeutic efficacy and/or safety of the combination treatment. In certain embodiments, the compound of the disclosure can be administered first followed by a second therapeutic agent, or alternatively, the second therapeutic agent administered first followed by the compound of the disclosure. In certain embodiments, the compound of the disclosure can be administered for the same duration as the second therapeutic agent, or alternatively, for a longer or shorter duration as the second therapeutic compound.

[0137] When administered concurrently, the compounds of the disclosure can be administered separately at the same time as the second therapeutic agent, by the same or different routes, or administered in a single composition by the same route. In certain embodiments, the compound of the disclosure is prepared as a first pharmaceutical composition, and the second therapeutic agent prepared as a second pharmaceutical composition, where the first pharmaceutical composition and the second pharmaceutical composition are administered simultaneously,

sequentially, or separately. In certain embodiments, the amount and frequency of administration of the second therapeutic agent can used standard dosages and standard administration frequencies used for the particular therapeutic agent. See, *e.g.*, *Physicians' Desk Reference, 70th Ed.*, PDR Network, 2015; incorporated herein by reference.

[0138] One aspect of the invention provides a method for treating a disease or condition responsive to GPR84 agonism, wherein the method comprises administering to a subject in need thereof a therapeutically effective amount of (i) a compound described herein (e.g., a compound of Formula I or other compound in Section 1) and (ii) an additional therapeutic agent, to treat the disease or condition.

[0139] Another aspect of the invention provides a method for treating a disease or condition responsive to GPR84 agonism, wherein the method comprises administering to a subject in need thereof a therapeutically effective amount of (i) a GPR84 agonist and (ii) an additional therapeutic agent that binds to a target selected from CCR4, CD19, CD20, CD22, CD30, CD33, CD38, CD47, CD52, CD79b, Claudin 18.2, CTLA-4, EGFR, FGFR2, GD2, HER2, LAG3, MET, Nectin-4, PDGFRa, PD-L1, RANKL, SLAMF7, TF, TROP2, VEGF, VEGFR, VEGFR2, or epidermal growth factor receptor with exon 20 insertion mutations, to treat the disease or condition. In certain embodiments, the target is CCR4, CD19, CD20, CD22, CD30, CD33, CD38, CD47, CD52, or CD79b. In certain embodiments, the target is Claudin 18.2 or CTLA-4. In certain embodiments, the target is EGFR, FGFR2, or epidermal growth factor receptor with exon 20 insertion mutations. In certain embodiments, the target is GD2, HER2, LAG3, MET, Nectin-4, PDGFRa, or PD-L1. In certain embodiments, the target is RANKL, SLAMF7, TF, or TROP2. In certain embodiments, the target is VEGF or VEGFR. In certain embodiments, the target is CCR4. In certain embodiments, the target is CD19. In certain embodiments, the target is CD20. In certain embodiments, the target is CD22. In certain embodiments, the target is CD30. In certain embodiments, the target is CD33. In certain embodiments, the target is CD38. In certain embodiments, the target is CD47. In certain embodiments, the target is CD52. In certain embodiments, the target is CD79b. In certain embodiments, the target is Claudin 18.2. In certain embodiments, the target is CTLA-4. In certain embodiments, the target is EGFR. In certain embodiments, the target is FGFR2. In certain embodiments, the target is GD2. In certain embodiments, the target is HER2. In certain embodiments, the target is LAG3. In certain embodiments, the target is MET. In certain embodiments, the target is Nectin-4. In certain

embodiments, the target is PDGFRa. In certain embodiments, the target is PD-L1. In certain embodiments, the target is RANKL. In certain embodiments, the target is SLAMF7. In certain embodiments, the target is TF. In certain embodiments, the target is TROP2. In certain embodiments, the target is VEGF. In certain embodiments, the target is VEGFR. In certain embodiments, the target is VEGFR2. In certain embodiments, the target is epidermal growth factor receptor with exon 20 insertion mutations.

[0140] In certain embodiments, the additional therapeutic agent is an inhibitor. In certain embodiments, the additional therapeutic agent is an agonist.

[0141] In certain embodiments, the additional therapeutic agent is an antibody. In certain embodiments, the additional therapeutic agent is Alemtuzumab, Amivantamab-vmjw (Amivantamab), Avelumab, Bemarituzumab, Bevacizumab, Cetuximab, Cosibelimab, Daratumumab, Denosumab, Dinutiximab, Elotuzumab, Ibritumomab tiuxetan, Isatuximab-irfc (Isatuximab), Magrolizumab, Margetuximab-cmkb (Margetuximab), Mogamulizumab-kpkc (Mogamulizumab), Naxitamab-gqgk (Naxitamab), Necitumumab, Obinutuzumab, Ofatumumab, Olaratumab, Panitumumab, Pertuzumab, Ramucirumab, Rituximab, Tafasitamab-cxix (Tafasitamab), Trastuzumab, TTI-622, evorpacept, a SIRPαFc fusion protein, or Zolbetuximab. In certain embodiments, the additional therapeutic agent is Alemtuzumab, Amivantamab-vmjw, Avelumab, Bemarituzumab, Bevacizumab, Cetuximab, Cosibelimab, Daratumumab, Denosumab, Dinutiximab, Elotuzumab, Ibritumomab tiuxetan, Isatuximab-irfc, Magrolizumab, Margetuximab-cmkb, Mogamulizumab-kpkc, Naxitamab-gqgk, Necitumumab, Obinutuzumab, Ofatumumab, Olaratumab, Panitumumab, Pertuzumab, Ramucirumab, Rituximab, Tafasitamab-cxix, Trastuzumab, TTI-622, evorpacept, a SIRPαFc fusion protein, or Zolbetuximab. In certain embodiments, the additional therapeutic agent is an antibody-drug-conjugate. In certain embodiments, the additional therapeutic agent is Brentuximab vedotin, Enfortumab vedotin, Gemtuzumab ozogamicin, Ibritumomab tiuxetan, Inotuzumab ozogamicin, Loncastuximab tesirine, Moxetumomab pasudotox, Polatuzumab vedotin, Sacituzumab govitecan, Tisotumab vedotin, Trastuzumab deruxtecan, or Trastuzumab emtansine. In certain embodiments, the additional therapeutic agent is a SIRPαFc fusion protein (such as described in U.S. Patent No. 10,906,954, which is herein incorporated by reference in its entirety). In certain embodiments, the additional agent is a fusion of a CD47-binding domain of human SIRPα linked to the Fc region of human IgG_4.

[0142] In certain embodiments, the additional therapeutic agent is Alemtuzumab. In certain embodiments, the additional therapeutic agent is Amivantamab-vmjw. In certain embodiments, the additional therapeutic agent is Avelumab. In certain embodiments, the additional therapeutic agent is Bemarituzumab. In certain embodiments, the additional therapeutic agent is Bevacizumab. In certain embodiments, the additional therapeutic agent is Cetuximab. In certain embodiments, the additional therapeutic agent is Cosibelimab. In certain embodiments, the additional therapeutic agent is Daratumumab. In certain embodiments, the additional therapeutic agent is Denosumab. In certain embodiments, the additional therapeutic agent is Dinutiximab. In certain embodiments, the additional therapeutic agent is Elotuzumab. In certain embodiments, the additional therapeutic agent is Ibritumomab tiuxetan. In certain embodiments, the additional therapeutic agent is Isatuximab-irfc. In certain embodiments, the additional therapeutic agent is Magrolizumab. In certain embodiments, the additional therapeutic agent is Margetuximab-cmkb. In certain embodiments, the additional therapeutic agent is Mogamulizumab-kpkc. In certain embodiments, the additional therapeutic agent is Naxitamab-gqgk. In certain embodiments, the additional therapeutic agent is Necitumumab. In certain embodiments, the additional therapeutic agent is Obinutuzumab. In certain embodiments, the additional therapeutic agent is Ofatumumab. In certain embodiments, the additional therapeutic agent is Olaratumab. In certain embodiments, the additional therapeutic agent is Panitumumab. In certain embodiments, the additional therapeutic agent is Pertuzumab. In certain embodiments, the additional therapeutic agent is Ramucirumab. In certain embodiments, the additional therapeutic agent is Rituximab. In certain embodiments, the additional therapeutic agent is Tafasitamab-cxix. In certain embodiments, the additional therapeutic agent is Trastuzumab. In certain embodiments, the additional therapeutic agent is TTI-622. In certain embodiments, the additional therapeutic agent is evorpacept. In certain embodiments, the additional therapeutic agent is a SIRPαFc fusion proteins. In certain embodiments, the additional therapeutic agent is Zolbetuximab. In certain embodiments, the additional therapeutic agent is an antibody-drug-conjugate. In certain embodiments, the additional therapeutic agent is Brentuximab vedotin, Enfortumab vedotin, Gemtuzumab ozogamicin, Ibritumomab tiuxetan, Inotuzumab ozogamicin, Loncastuximab tesirine, Moxetumomab pasudotox, Polatuzumab vedotin, Sacituzumab govitecan, Tisotumab vedotin, Trastuzumab deruxtecan, or Trastuzumab emtansine.

[0143] In certain embodiments, the additional therapeutic agent is Brentuximab vedotin. In certain embodiments, the additional therapeutic agent is Enfortumab vedotin. In certain embodiments, the additional therapeutic agent is Gemtuzumab ozogamicin. In certain embodiments, the additional therapeutic agent is Ibritumomab tiuxetan. In certain embodiments, the additional therapeutic agent is Inotuzumab ozogamicin. In certain embodiments, the additional therapeutic agent is Loncastuximab tesirine. In certain embodiments, the additional therapeutic agent is Moxetumomab pasudotox. In certain embodiments, the additional therapeutic agent is Polatuzumab vedotin. In certain embodiments, the additional therapeutic agent is Sacituzumab govitecan. In certain embodiments, the additional therapeutic agent is Tisotumab vedotin. In certain embodiments, the additional therapeutic agent is Trastuzumab deruxtecan. In certain embodiments, the additional therapeutic agent is Trastuzumab emtansine.

[0144] Another aspect of the invention provides a method for treating a disease or condition responsive to GPR84 agonism, wherein the method comprises administering to a subject in need thereof a therapeutically effective amount of (i) a GPR84 agonist and (ii) CAR-T therapy, to treat the disease or condition. In certain embodiments, the CAR-T therapy is idecabtagene vicleucel or lisocabtagene maraleucel. In certain embodiments, the CAR-T therapy is idecabtagene vicleucel, and the disease or condition is multiple myeloma, such as a relapsed or refractory multiple myeloma (RR-MM) after four or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. In certain embodiments, the CAR-T therapy is lisocabtagene maraleucel, and the disease or condition is a large B-cell lymphoma, such as a relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.

[0145] The methods may be further characterized according to the identity of the disease or condition to be treated. For example, in certain embodiments, the disease or condition is cancer. In certain embodiments, the cancer is a solid tumor. In certain embodiments, the cancer is ovarian cancer, uterine cancer, endometrial cancer, cervical cancer, prostate cancer, testicular cancer, breast cancer, brain cancer, lung cancer, oral cancer, esophageal cancer, head and neck cancer, stomach cancer, colon cancer, rectal cancer, skin cancer, sebaceous gland carcinoma, bile duct and gallbladder cancers, liver cancer, pancreatic cancer, bladder cancer, urinary tract cancer, kidney

cancer, eye cancer, thyroid cancer, lymphoma, or leukemia. In certain embodiments, the cancer is a B-cell non-Hodgkin's Lymphoma, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL), mature B-cell acute leukemia (B-AL), chronic lymphocytic leukemia (CLL), follicular lymphoma, multiple myeloma, head and neck cancer, colorectal cancer, a squamous cell carcinoma, HER2 overexpressing breast cancer, gastric junction adenocarcinoma, gastro-esophageal junction adenocarcinoma, non-small cell lung cancer, hepatocellular carcinoma, gastric cancer, urothelial cancer, renal cancer, giant cell bone cancer, bone metastasis, neuroblastoma, mycosis fungoides, or Sézary syndrome.

[0146] In certain embodiments, the disease or condition is an autoimmune and/or inflammatory disorder. In certain embodiments, the disease or condition is rheumatoid arthritis.

[0147] In certain embodiments, the method is further characterized according to the identity of both the additional therapeutic agent used (e.g., the inhibitor of a protein) and the disease or condition to be treated. Exemplary combinations of additional therapeutic agent used (e.g., the inhibitor of a protein) and the disease or condition to be treated are set forth in Table 2 below.

TABLE 2.

Name of Additional Therapeutic Agent	**Disease or Condition for Treatment**
Rituximab (Protein Target: CD20)	• B-Cell Non-Hodgkin Lymphoma. • Relapsed or refractory, low grade or follicular, B-Cell Non-Hodgkin Lymphoma (B-NHL) as a single agent. • First line (1L) B-NHL in combination with first line chemotherapy and, in patients achieving a complete response or partial response as single-agent maintenance therapy. • Diffuse large B-cell lymphoma • Non-progressing (including stable disease), low-grade, B-NHL as a single agent after 1L cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy. • 1L DLBCL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens. • 1L advanced stage, CD20-positive, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL) or mature B-cell acute leukemia (B-AL) in combination with chemotherapy.

Name of Additional Therapeutic Agent	Disease or Condition for Treatment
	• Chronic Lymphocytic Leukemia • Adult patients with Chronic Lymphocytic Leukemia • Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC). • Rheumatoid Arthritis. • Rheumatoid Arthritis in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies.
Ofatumumab (Protein Target: CD20)	• Chronic lymphocytic leukemia • Chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab.
Obinutuzumab (Protein Target: CD20)	• Chronic lymphocytic leukemia • In combination with chlorambucil, for the treatment of patients with previously untreated CLL (sp. if del(17p)/TP53 mutation) • Follicular lymphoma • In combination with bendamustine followed by GAZYVA monotherapy, for the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen. • In combination with chemotherapy followed by GAZYVA monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma.
Ibritumomab tiuxetan (Protein Target: CD20)	• Follicular lymphoma • Relapsed or refractory follicular lymphoma.
Tafasitamab-cxix (Protein Target: CD19)	• Diffuse large B-cell lymphoma • Relapsed or refractory DLBCL in combination with lenalidomide (pts not candidate for high dose chemo-autologous stem cell transplant (ASCT))
Alemtuzumab (Protein Target: CD52)	• Chronic lymphocytic leukemia

Name of Additional Therapeutic Agent	Disease or Condition for Treatment
Mogamulizumab-kpkc (Protein Target: CCR4)	• Mycosis fungoides • Sézary syndrome • Relapsed or refractory mycosis fungoides or Sézary syndrome
Daratumumab (Protein Target: CD38)	• Multiple myeloma • Multiple myeloma (MM) in combination with bortezomib, melphalan and prednisone (VMP) in newly diagnosed patients who are ineligible for ASCT. • MM in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for ASCT and in patients with RR-MM (second line (2L)). • MM in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for ASCT. • MM in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy. • MM in combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor. • MM in combination with carfilzomib and dexamethasone in patients with RR-MM who have received one to three prior lines of therapy. • MM as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent. • Light chain (AL) amyloidosis • Light chain (AL) amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone in newly diagnosed patients.
Isatuximab-irfc (Protein Target: CD38)	• Multiple myeloma • In combination with pomalidomide and dexamethasone, for the treatment of adult patients with MM who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor.

Name of Additional Therapeutic Agent	Disease or Condition for Treatment
	• In combination with carfilzomib and dexamethasone, for the treatment of adult patients with RR-MM who have received 1 to 3 prior lines of therapy.
Elotuzumab (Protein Target: SLAMF7)	• Multiple myeloma • In combination with lenalidomide and dexamethasone for the treatment of adult patients with RR-MM who have received one to three prior therapies. • Combination with pomalidomide and dexamethasone for the treatment of adult patients with RR-MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.
Cetuximab (Protein Target: EGFR)	• Head and Neck Cancer • Squamous cell carcinoma • Locally or regionally advanced squamous cell carcinoma of head and neck (SCCHN) in combination with radiation therapy. • Recurrent locoregional disease or metastatic SCCHN in combination with platinum-based therapy with fluorouracil. • Recurrent or metastatic SCCHN progressing after platinum-based therapy. • Colorectal cancer • K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by an FDA-approved test. • In combination with FOLFIRI for first-line treatment. • In combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy. • As a single-agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.
Panitumumab (Protein Target: EGFR)	• Colorectal cancer • RAS WT metastatic CRC • In combination with FOLFOX for first-line treatment.

Name of Additional Therapeutic Agent	Disease or Condition for Treatment
	• As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy.
Necitumumab (Protein Target: EGFR)	• Non-small cell lung cancer • In combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic squamous NSCLC.
Amivantamab-vmjw (Protein Target: EGFR Ex20 & MET)	• Non-small cell lung cancer • Adult patients with locally advanced or metastatic NSCLC with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.
Trastuzumab (Protein Target: Her2)	• Breast cancer • Adjuvant for the treatment of HER2 overexpressing breast cancer as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel, with docetaxel and carboplatin, or as a single agent following multi-modality anthracycline based therapy. • In mBrCa, In combination with paclitaxel for first-line treatment of HER2-overexpressing mBrCa or as a single agent for treatment of HER2-overexpressing BrCa in patients who have received one or more chemotherapy regimens for metastatic disease. • Gastric or gastroesophageal junction adenocarcinoma • HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma in combination with cisplatin and capecitabine or 5-fluorouracil.
Pertuzumab (Protein Target: Her2)	• Breast cancer • In combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy. • The neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive).

Name of Additional Therapeutic Agent	Disease or Condition for Treatment
	• The adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence, in combination with trastuzumab and chemotherapy.
Margetuximab-cmkb (Protein Target: Her2)	• Breast cancer • In combination with chemotherapy, for the treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.
Zolbetuximab (Protein Target: Claudin 18.2)	• Gastro-esophageal junction adenocarcinoma • Previously untreated, locally advanced unresectable or metastatic HER2-/Claudin 18.2+ gastric or gastro-esophageal junction adenocarcinoma.
Ramucirumab (Cyramza) (Protein Target: VEGFR2)	• Metastatic gastric or gastro-esophageal junction adenocarcinoma • As a single agent or in combination with paclitaxel, for treatment of advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy. • Non-small cell lung cancer • In combination with erlotinib, for first-line treatment of metastatic NSCLC with EGFR ex19 deletions or ex21 (L858R) mutations. • In combination with docetaxel, for treatment of metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA. • Colorectal cancer • In combination with FOLFIRI, for the treatment of metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. • Hepatocellular carcinoma • As a single agent, for the treatment of HCC in patients who have an alpha fetoprotein of ≥400 ng/mL and have been treated with sorafenib.

Name of Additional Therapeutic Agent	Disease or Condition for Treatment
Bemarituzumab (Protein Target: FGFR2)	• Gastric cancer • FGFR2 OE Gastric cancer1L with FOLFOX6 or chemo + nivolumab.
Olaratumab (Protein Target: PDGFRα)	• Soft tissue sarcoma in combination with doxorubicin therapy for patients who do not have a curative option with surgery or radiation.
Cosibelimab (Protein Target: PD-L1)	• Cutaneous squamous cell carcinoma (cSCC).
Avelumab (Protein Target: PD-L1)	• Urothelial cancer, Renal cancer
Magrolimab (Protein Target: CD47)	• Triple negative breast cancer (alone and in combination with standard of care) • Metastatic colorectal cancer, (alone and in combination with standard of care and bevacizumab) • Urothelial cancer (alone and in combination with standard of care) • Head and neck squamous cell carcinoma alone and in combination with standard of carc and /or cetuximab • Low and high Myelodysplastic syndrome with azacytidine • Acute myeloid leukemia alone and with standard of care and or venetoclax • Diffuse large B cell lymphoma, alone and with standard of care, including rituximab,or Obinutuzumab • Multiple myeloma, alone and with standard of care including daratumumab, elotuzumab and Isatuximab-irfc
TTI-622 (Protein Target: CD47)	• Multiple myeloma, alone and with standard of care including daratumumab, elotuzumab and Isatuximab-irfc • Diffuse large B cell lymphoma, alone and with standard of care, including rituximab,or Obinutuzumab or lenalidomide or Tafasitamab-cxix • Ovarian cancer aloen an in combination with Pegylated liposomal doxorubicin • Low and high Myelodysplastic syndrome with azacytidine

Name of Additional Therapeutic Agent	Disease or Condition for Treatment
	• Acute myeloid leukemia alone and with standard of care and or venetoclax
Bevacizumab (Protein Target: VEGF)	• Metastatic colorectal cancer, in combination with intravenous fluorouracilbased chemotherapy for first- or second-line treatment. • Metastatic colorectal cancer, in combination with fluoropyrimidineirinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab product-containing regimen. • Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment. • Recurrent glioblastoma in adults • Metastatic renal cell carcinoma in combination with interferon alfa. • Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan. • Epithelial ovarian, fallopian tube, or primary peritoneal cancer: a) in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, for stage III or IV disease following initial surgical resection; b) in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens; or c) in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Avastin as a single agent, for platinum-sensitive recurrent disease • Hepatocellular Carcinoma (HCC) in combination with atezolizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy
Denosumab (Protein Target: RANKL)	• Prevention of skeletal-related events in patients with bone metastases from solid tumors. • Treatment of adults and skeletally mature adolescents with giant cell

Name of Additional Therapeutic Agent	Disease or Condition for Treatment
	tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
Dinutiximab (Protein Target: GD2)	• Neuroblastoma • In combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA), for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy.
Naxitamab-gqgk (Protein Target: GD2)	• Neuroblastoma • In combination with granulocyte-macrophage colony-stimulating factor (GMCSF), for the treatment of pediatric patients 1 year of age and older and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease to prior therapy.

[0148] In certain embodiments, the additional therapeutic agent is a combination of two, three, or four therapeutic agents or treatments. In certain embodiments, the additional therapeutic agent is a combination of two therapeutic agents or treatments. In certain embodiments, the additional therapeutic agent is a combination of three therapeutic agents or treatments. In certain embodiments, the additional therapeutic agent is a combination of four therapeutic agents or treatments. In certain embodiments, the treatment is radiation therapy.

[0149] In certain embodiments, the additional therapeutic agent is Rituximabin in combination with CHOP. In certain embodiments, the additional therapeutic agent is Rituximab in combination with CVP. In certain embodiments, the additional therapeutic agent is Rituximab in combination with fludarabine and cyclophosphamide. In certain embodiments, the additional therapeutic agent is Rituximab in combination with BTKi. In certain embodiments, the additional therapeutic agent is Rituximab in combination with venetoclax.

[0150] In certain embodiments, the additional therapeutic agent is Rituximab in combination with CAR-T. In certain embodiments, the additional therapeutic agent is Rituximab in combination with venetoclast. In certain embodiments, the additional therapeutic agent is Rituximab in combination with Ibrutinib. In certain embodiments, the additional therapeutic agent is Rituximab in combination with acalabrutinib. In certain embodiments, the additional therapeutic agent is Rituximab in combination with zanubrutinib. In certain embodiments, the additional therapeutic agent is Rituximab in combination with tirabrutinib. In certain embodiments, the additional therapeutic agent is Rituximab in combination with orelabrutinib. In certain embodiments, the additional therapeutic agent is Rituximab in combination with idelalisib. In certain embodiments, the additional therapeutic agent is Rituximab in combination with autologous stem cell transplantation (ASCT). In certain embodiments, the additional therapeutic agent is Rituximab in combination with Copanlisib. In certain embodiments, the additional therapeutic agent is Rituximab in combination with Tazemetostat. In certain embodiments, the additional therapeutic agent is Rituximab in combination with Axicabtagene ciloleucel. In certain embodiments, the additional therapeutic agent is Rituximab in combination with Tisagenlecleucel. In certain embodiments, the additional therapeutic agent is Rituximab in combination with Mosunetuzumab-axgb. In certain embodiments, the additional therapeutic agent is Rituximab in combination with Lisocabtagene maraleucel. In certain embodiments, the additional therapeutic agent is Rituximab in combination with Polatuzumab vedotin-piiq.

[0151] In certain embodiments, the additional therapeutic agent is Obinutuzumab in combination with chlorambucil. In certain embodiments, the additional therapeutic agent is Obinutuzumab in combination with acalabrutinib. In certain embodiments, the additional therapeutic agent is Obinutuzumab in combination with Venetoclax. In certain embodiments, the additional therapeutic agent is Obinutuzumab in combination with ibrutinib. In certain embodiments, the additional therapeutic agent is Obinutuzumab in combination with bendamustine.

[0152] In certain embodiments, the additional therapeutic agent is Tafasitamab-cxix in combination with Lenalidomide.

[0153] In certain embodiments, the additional therapeutic agent is Daratumumab in combination with bortezomib, melphalan and prednisone (VMP). In certain embodiments, the additional therapeutic agent is Daratumumab in combination with lenalidomide and dexamethasone. In

certain embodiments, the additional therapeutic agent is Daratumumab in combination with bortezomib, thalidomide, and dexamethasone. In certain embodiments, the additional therapeutic agent is Daratumumab in combination with bortezomib and dexamethasone. In certain embodiments, the additional therapeutic agent is Daratumumab in combination with pomalidomide and dexamethasone. In certain embodiments, the additional therapeutic agent is Daratumumab in combination with carfilzomib and dexamethasone. In certain embodiments, the additional therapeutic agent is Daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone.

[0154] In certain embodiments, the additional therapeutic agent is Daratumumab in combination with Elotuzumab, lenalidomide, dexamethasone, and Bortezomib. In certain embodiments, the additional therapeutic agent is Daratumumab in combination with bendamustine, dexamethasone, and either carfilzomib or bortezomib. In certain embodiments, the additional therapeutic agent is Daratumumab in combination with Idecabtagene autoleucel. In certain embodiments, the additional therapeutic agent is Daratumumab in combination with Ciltacabtagene autoleucel. In certain embodiments, the additional therapeutic agent is Daratumumab in combination with Teclistamab-cqyv.

[0155] In certain embodiments, the additional therapeutic agent is Isatuximab-irfc in combination with carfilzomib and dexamethasone. In certain embodiments, the additional therapeutic agent is Isatuximab-irfc in combination with pomalidomide and dexamethasone.

[0156] In certain embodiments, the additional therapeutic agent is Isatuximab-irfc in combination with bendamustine, dexamethasone, and either carfilzomib or bortezomib. In certain embodiments, the additional therapeutic agent is Isatuximab-irfc in combination with Idecabtagene autoleucel. In certain embodiments, the additional therapeutic agent is Isatuximab-irfc in combination with Ciltacabtagene autoleucel. In certain embodiments, the additional therapeutic agent is Isatuximab-irfc in combination with Teclistamab-cqyv.

[0157] In certain embodiments, the additional therapeutic agent is Elotuzumab in combination with lenalidomide and dexamethasone. In certain embodiments, the additional therapeutic agent is Elotuzumab in combination with pomalidomide and dexamethasone.

[0158] In certain embodiments, the additional therapeutic agent is Elotuzumab in combination with bendamustine, dexamethasone, and either carfilzomib or bortezomib. In certain

embodiments, the additional therapeutic agent is Elotuzumab in combination with Idecabtagene autoleucel. In certain embodiments, the additional therapeutic agent is Elotuzumab in combination with Ciltacabtagene autoleucel. In certain embodiments, the additional therapeutic agent is Elotuzumab in combination with Teclistamab-cqyv.

[0159] In certain embodiments, the additional therapeutic agent is Cetuximab in combination with radiation therapy. In certain embodiments, the additional therapeutic agent is Cetuximab in combination with platinum-based therapy with fluorouracil. In certain embodiments, the additional therapeutic agent is Cetuximab in combination with FOLFIRI. In certain embodiments, the additional therapeutic agent is Cetuximab in combination with irinotecan.

[0160] In certain embodiments, the additional therapeutic agent is Cetuximab in combination with Regorafenib. In certain embodiments, the additional therapeutic agent is Cetuximab in combination with trifluridine and tipiracil. In certain embodiments, the additional therapeutic agent is Cetuximab in combination with trifluridine, tipiracil, and bevacizumab. In certain embodiments, the additional therapeutic agent is Cetuximab in combination with a Her2 inhibitor. In certain embodiments, the additional therapeutic agent is Cetuximab in combination with a BrafV600E inhibitor.

[0161] In certain embodiments, the additional therapeutic agent is Panitumumab in combination with FOLFOX.

[0162] In certain embodiments, the additional therapeutic agent is Panitumumab in combination with Regorafenib. In certain embodiments, the additional therapeutic agent is Panitumumab in combination with trifluridine and tipiracil. In certain embodiments, the additional therapeutic agent is Panitumumab in combination with trifluridine, tipiracil, and bevacizumab. In certain embodiments, the additional therapeutic agent is Panitumumab in combination with a Her2 inhibitor. In certain embodiments, the additional therapeutic agent is Panitumumab in combination with a BrafV600E inhibitor.

[0163] In certain embodiments, the additional therapeutic agent is Necitumumab in combination with gemcitabine and cisplatin.

[0164] In certain embodiments, the additional therapeutic agent is Amivantamab-vmjw in combination with Nivo. In certain embodiments, the additional therapeutic agent is Amivantamab-

vmjw in combination with Pembro. In certain embodiments, the additional therapeutic agent is Amivantamab-vmjw in combination with Atezo. In certain embodiments, the additional therapeutic agent is Amivantamab-vmjw in combination with Docetaxel. In certain embodiments, the additional therapeutic agent is Amivantamab-vmjw in combination with Gemcitabine.

[0165] In certain embodiments, the additional therapeutic agent is Trastuzumab in combination with doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel. In certain embodiments, the additional therapeutic agent is Trastuzumab in combination with docetaxel and carboplatin. In certain embodiments, the additional therapeutic agent is Trastuzumab in combination with paclitaxel. In certain embodiments, the additional therapeutic agent is Trastuzumab in combination with cisplatin and capecitabine. In certain embodiments, the additional therapeutic agent is Trastuzumab in combination with 5-fluorouracil.

[0166] In certain embodiments, the additional therapeutic agent is Trastuzumab in combination with Fam-trastuzumab deruxtecan-nxki. In certain embodiments, the additional therapeutic agent is Trastuzumab in combination with Sacituzumab govitecan. In certain embodiments, the additional therapeutic agent is Trastuzumab in combination with systemic chemotherapy. In certain embodiments, the additional therapeutic agent is Trastuzumab in combination with a biomarker guided Rx. In certain embodiments, the additional therapeutic agent is Trastuzumab in combination with a Her2 inhibitor. In certain embodiments, the additional therapeutic agent is Trastuzumab in combination with a BrafV600E inhibitor.

[0167] In certain embodiments, the additional therapeutic agent is Pertuzumab in combination with trastuzumab and docetaxel. In certain embodiments, the additional therapeutic agent is Pertuzumab in combination with trastuzumab and chemotherapy.

[0168] In certain embodiments, the additional therapeutic agent is Margetuximab-cmkb in combination with chemotherapy. In certain embodiments, the additional therapeutic agent is Margetuximab-cmkb in combination with capecitabine. In certain embodiments, the additional therapeutic agent is Margetuximab-cmkb in combination with capecitabine. In certain embodiments, the additional therapeutic agent is Margetuximab-cmkb in combination with eribulin. In certain embodiments, the additional therapeutic agent is Margetuximab-cmkb in combination with gemcitabine. In certain embodiments, the additional therapeutic agent is Margetuximab-cmkb in combination with vinorelbine.

[0169] In certain embodiments, the additional therapeutic agent is Margetuximab-cmkb in combination with lapatinib. In certain embodiments, the additional therapeutic agent is Margetuximab-cmkb in combination with tucatinib. In certain embodiments, the additional therapeutic agent is Margetuximab-cmkb in combination with neratinib.

[0170] In certain embodiments, the additional therapeutic agent is Zolbetuximab in combination with mFOLFOX6.

[0171] In certain embodiments, the additional therapeutic agent is Zolbetuximab in combination with Regorafenib and trifluridine. In certain embodiments, the additional therapeutic agent is Zolbetuximab in combination with Regorafenib and tipiracil. In certain embodiments, the additional therapeutic agent is Zolbetuximab in combination with Regorafenib, Bevacizumab, and trifluridine. In certain embodiments, the additional therapeutic agent is Zolbetuximab in combination with Regorafenib, Bevacizumab and tipiracil.

[0172] In certain embodiments, the additional therapeutic agent is Ramucirumab in combination with paclitaxel. In certain embodiments, the additional therapeutic agent is Ramucirumab in combination with erlotinib. In certain embodiments, the additional therapeutic agent is Ramucirumab in combination with docetaxel. In certain embodiments, the additional therapeutic agent is Ramucirumab in combination with FOLFIRI.

[0173] In certain embodiments, the additional therapeutic agent is Ramucirumab in combination with Osimertinob.

[0174] In certain embodiments, the additional therapeutic agent is Olaratumab in combination with doxorubicine.

[0175] In certain embodiments, the additional therapeutic agent is Avelumab. In certain embodiments, the additional therapeutic agent is Magrolizumab. In certain embodiments, the additional therapeutic agent is TTI-622. In certain embodiments, the additional therapeutic agent is Bevacizumab. In certain embodiments, the additional therapeutic agent is Denosumab.

[0176] In certain embodiments, the additional therapeutic agent is Dinutiximab in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA).

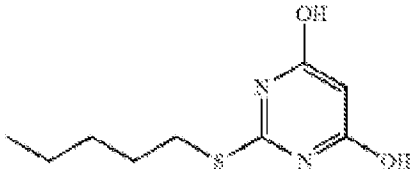
[0177] In certain embodiments, the additional therapeutic agent is Naxitamab-gqgk in combination with granulocyte-macrophage colony-stimulating factor (GMCSF).

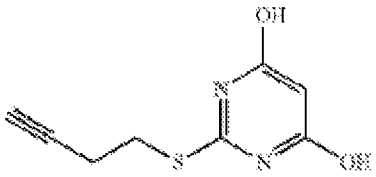
GPR84 Agonist

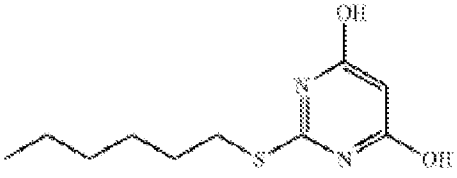
[0178] The methods may be further characterized according to the identity of the GPR84 agonist. In certain embodiments, the GPR84 agonist is a compound described in Section 1 herein.

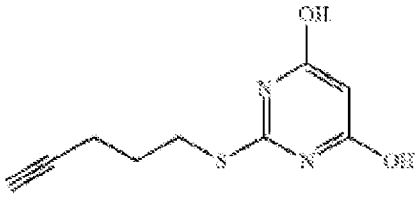
[0179] In certain embodiments, the GPR84 agonist may comprise: medium chain fatty acid capric acid, ZQ-16, (octylamino) pyrimidine-2,4(lH,3H)- dione (6-n-octylaminouracil), 6-OAU), DL-175 (ACS Chem. Biol. 2019, 14, 9, 2055-2064), a diindolemethane derivative (J. Med. Chem. 2017, 60, 9, 3636—3655), 2-alkylpyrimidine-4,6- diol, 6-Alkylpyridine-2,4-diol (ACS Med. Chem. Lett. 2016, 7, 6, 579-583), embelin (patent WO 2007/027661A2), or other known GPR84 agonist (see, e.g., J. Med. Chem. 2020, 63, 5, 2391-2410; ACS Omega 2018, 3, 3, 3365-3383; PCT Publication No. WO 2022/076446; and U.S. Patent Application Publication No. 2018/0237399, each incorporated herein by reference in their entirety). In some embodiments the GPR84 agonist comprises medium chain fatty acid capric acid. In some embodiments the GPR84 agonist is selected from the group consisting of ZQ-16, (octylamino) pyrimidine-2,4(lH,3H)-dione (6-n-octylaminouracil, 6-OAU), or a combination thereof.

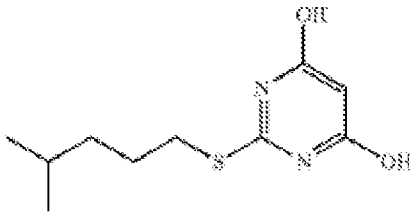
[0180] In certain embodiments, the GPR84 agonist is one of the following:

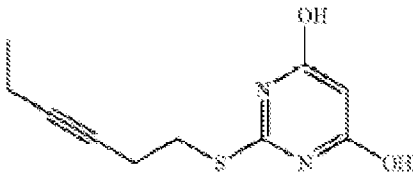


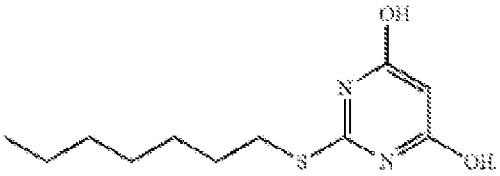


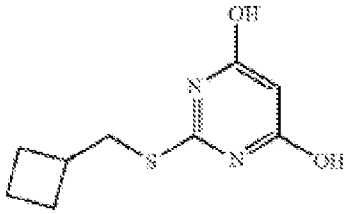


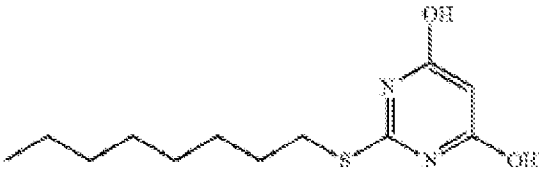


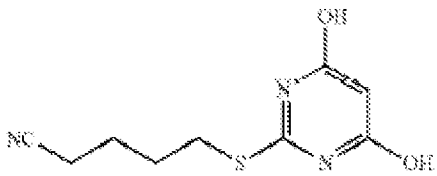


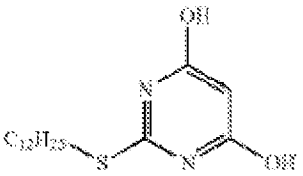


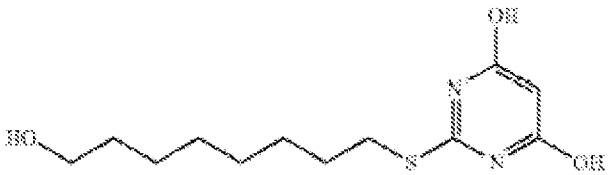


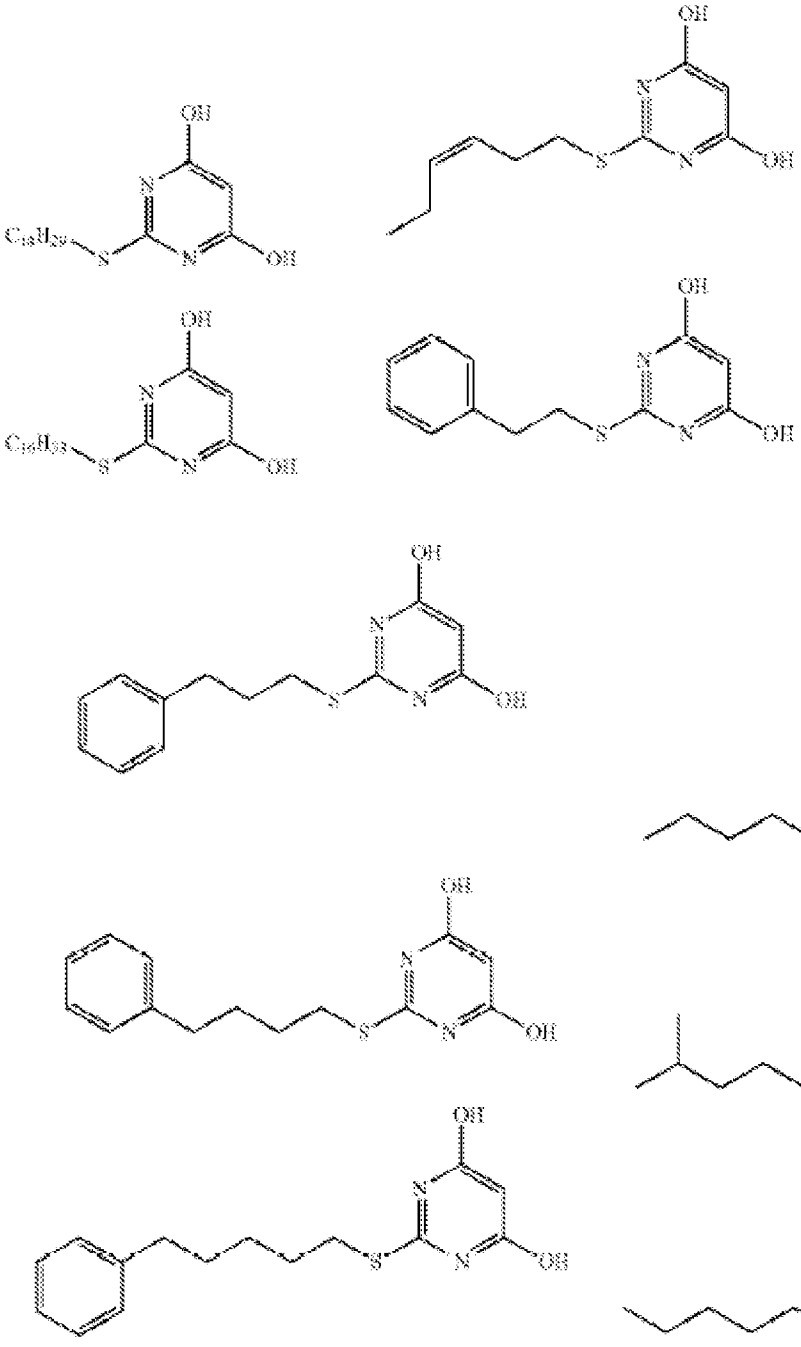


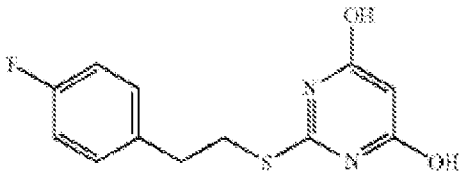


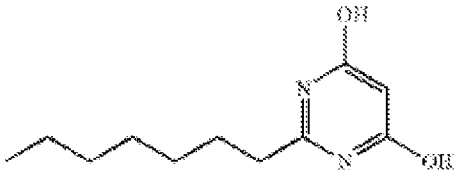


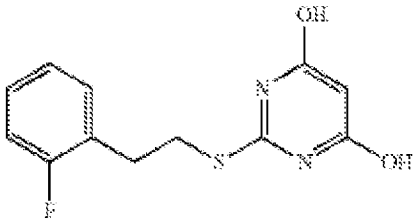


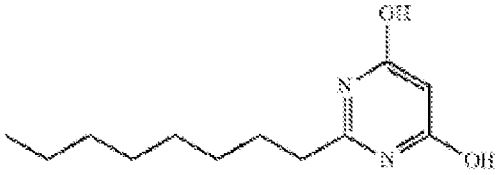


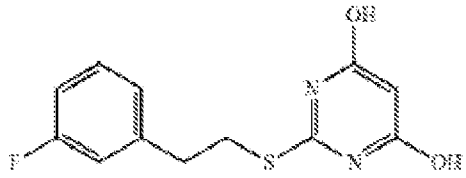


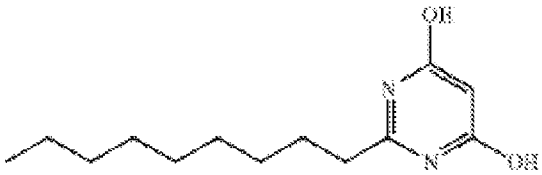


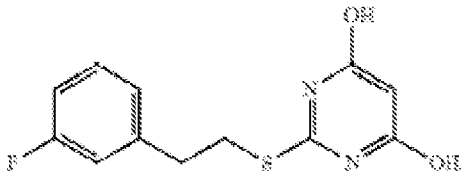


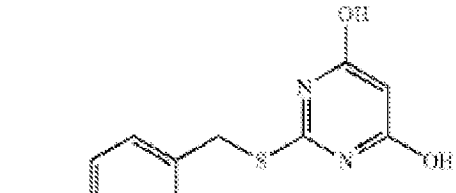


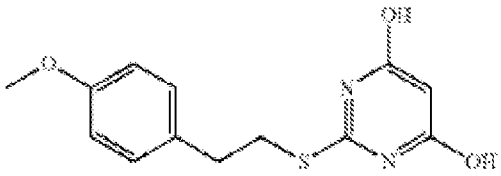


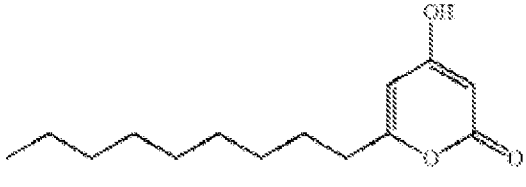


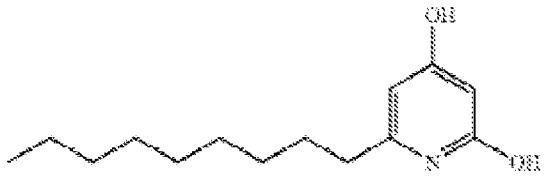


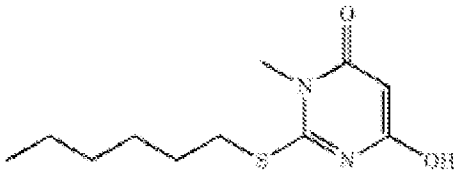


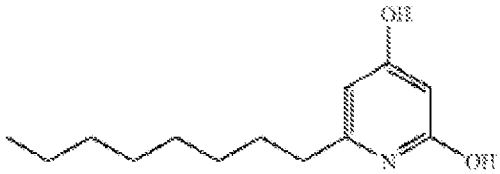


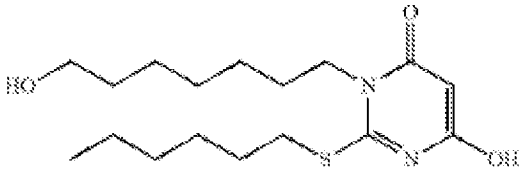


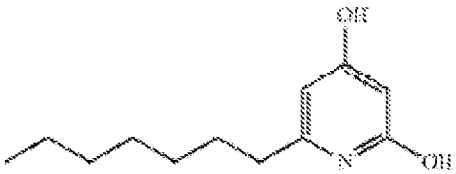


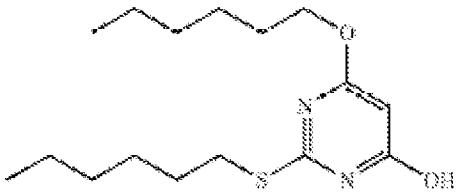


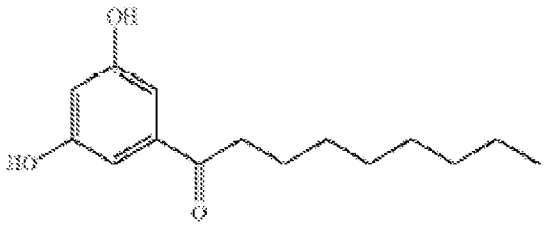


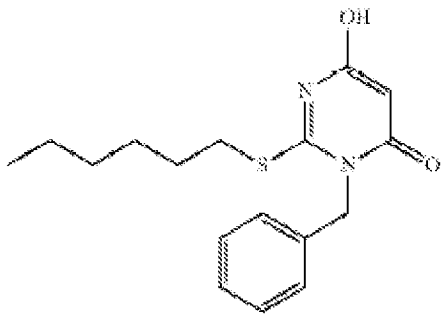


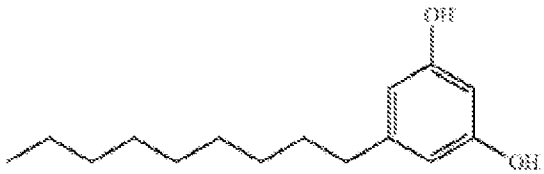


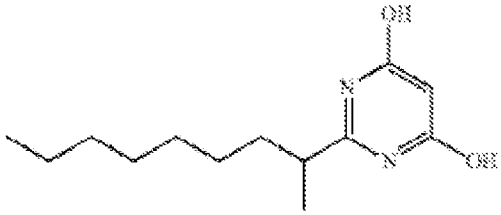


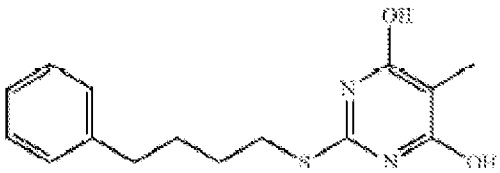


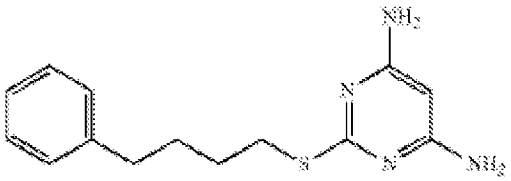


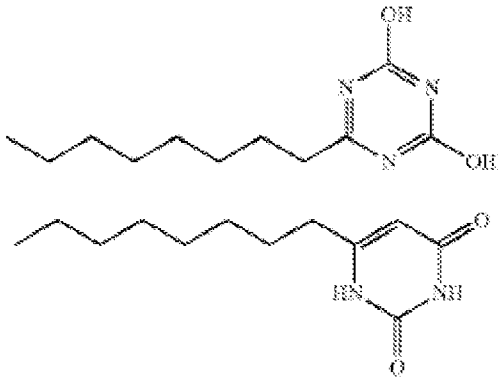


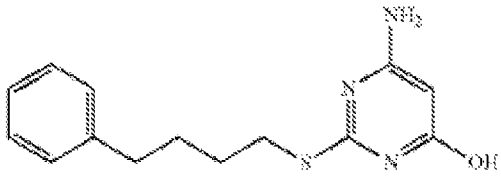


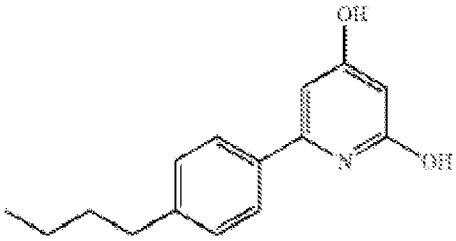


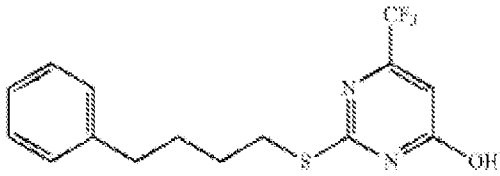


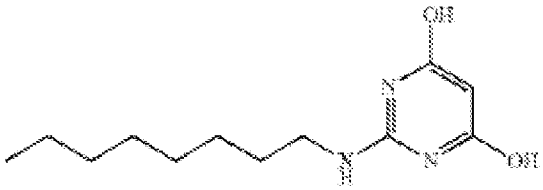


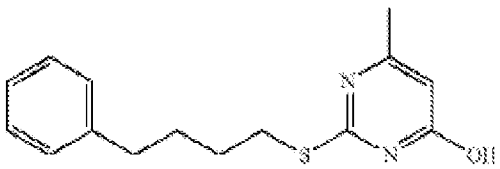


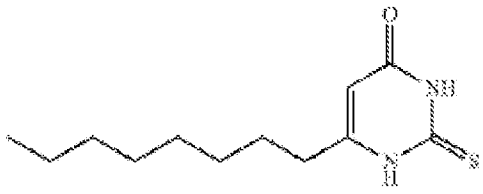


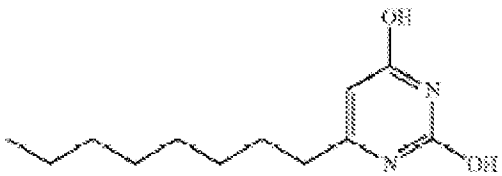


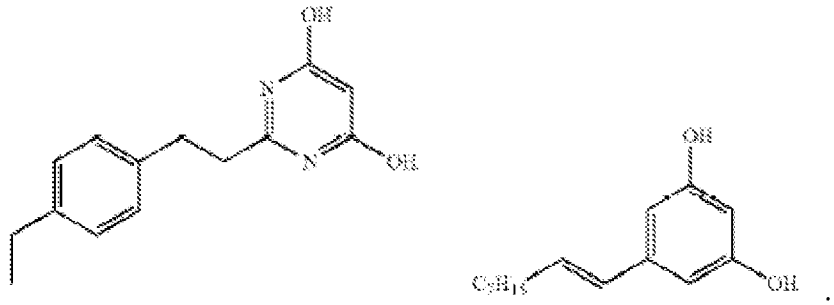












Further Exemplary Additional Therapeutic Agents

[0181] In certain embodiments, the additional therapeutic agent is a leukotriene inhibitor, non-steroidal anti-inflammatory drug (NSAID), steroid, tyrosine kinase inhibitor, receptor kinase inhibitor, modulator of nuclear receptor family of transcription factor, HSP90 inhibitor, adenosine receptor (A_2A) agonist, disease modifying antirheumatic drugs (DMARDS), phosphodiesterase (PDE) inhibitor, neutrophil elastase inhibitor, modulator of Axl kinase, an anti-cancer agent, anti-allergic agent, anti-nausea agent (or anti-emetic), pain reliever, cytoprotective agent, or a combination thereof. In certain embodiments, the additional therapeutic agent is an anti-cancer agent, an analgesic, an anti-inflammatory agent, or a combination thereof.

[0182] In certain embodiments, the additional therapeutic agent is a leukotriene inhibitor. Examples of leukotriene inhibitors considered for use in combination therapies of the invention include but are not limited to montelukast, zafirlukast, pranlukast, zileuton, or combinations thereof.

[0183] In certain embodiments, the additional therapeutic agent is a an NSAID. Examples of NSAIDs considered for use in combination therapies of the invention include but are not limited to acetylsalicylic acid, diflunisal, salsalate, ibuprofen, dexibuprofen, naioxen, fenoprofen, ketoprofen, dexketoprofen, flurbiprofen, oxaprozin, loxoprofen, indomethacin, tolmetin, sulindac, etodolac, ketorolac, diclofenac, aceclofenac, nabumetone, piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, phenylbutazone, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, celecoxib, or combinations thereof.

[0184] In certain embodiments, the additional therapeutic agent is a steroid. Examples of steroids considered for use in combination therapies of the invention include but are not limited to

prednisone, prednisolone, methylprednisone, triacmcinolone, betamethasone, dexamethasone, and prodrugs thereof.

[0185] In certain embodiments, the additional therapeutic agent is a tyrosine kinase inhibitor. Examples of tyrosine kinase inhibitors considered for use in combination therapies of the invention include but are not limited to inhibitors of the following kinases, including, among others: JAK, Syk, JNK/SAPK, MAPK, PI-3K, and/or Ripk2. In certain embodiments, the tyrosine kinase inhibitor is ruxolitinib, tofacitinib, oclactinib, filgotinib, ganotinib, lestaurtinib, momelotinib, pacritinib, upadacitinib, peficitinib, fedratinib, bentamapimod, D-JNKI-1 (XG-102, AM-111), ponatinib, WEHI-345, OD36, GSK583, idelalisib, copanlisib, taselisib, duvelisib, alpelisib, umbralisib, dactolisib, CUDC-907, entospletinib, fostamatinib, or combinations thereof.

[0186] In certain embodiments, the additional therapeutic agent is a receptor kinase inhibitor, including among others, an inhibitor of EGFR or HER2. Examples of receptor kinase inhibitors considered for use in combination therapies of the invention include but are not limited to gefitinib, erlotinib, neratinib, lapatinib, cetuximab, panitumumab, vandetanib, necitumumab, osimertinib, trastuzumab, neratinib, lapatinib, pertuzumab, or combinations thereof.

[0187] In certain embodiments, the additional therapeutic agent is a modulator of nuclear receptor family of transcription factors, including, among others, an inhibitor of PPAR, RXR, FXR, or LXR. In certain embodiments, the inhibitor is pioglitazone, bexarotene, obeticholic acid, ursodeoxycholic acid, fexaramine, hypocholamide, or combinations thereof.

[0188] In certain embodiments, the additional therapeutic agent is an HSP90 inhibitor. Examples of HSP90 inhibitors considered for use in combination therapies of the invention include but are not limited to ganetespib, 17-AAG (17-allylaminogeldanamycin, NSC330507), 17-DMAG (17-dimethylaminoethylamino-17-demethoxy-geldanamycin, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010, or combinations thereof.

[0189] In certain embodiments, the additional therapeutic agent is an adenosine receptor 2A (A_2A) agonist. Examples of adenosine receptor agonists considered for use in combination therapies of the invention include but are not limited to those disclosed in U.S. Pat. No. 9,067,963, which is incorporated herein by reference. In certain embodiments, the adenosine receptor agonist is LNC-3050, LNC-3015, LNC-3047, LNC-3052, or combinations thereof.

[0190] In certain embodiments, the additional therapeutic agent is selected from disease modifying antirheumatic drugs (DMARDS). Examples of DMARDS considered for use in combination therapies of the invention include but are not limited to tocilizumab, certolizumab, etanercept, adalimumab, anakinra, abatacept, infliximab, rituximab, golimumab, uteskinumab, or combinations thereof.

[0191] In certain embodiments, the additional therapeutic agent is a phosphodiesterase (PDE) inhibitor. Examples of phosphodiesterase inhibitor considered for use in combination therapies of the invention include but are not limited to apremilast, crisaborole, piclimilast, drotaverine, ibudulast, roflumilast, sildenafil, tadalafil, vardenafil, or combinations thereof.

[0192] In certain embodiments, the additional therapeutic agent is a neutrophil elastase inhibitor. Examples of neutrophil elastase inhibitors considered for use in combination therapies of the invention include but are not limited to sivelestat.

[0193] In certain embodiments, the additional therapeutic agent is a modulator of Axl kinase. Examples of modulators of Axl kinase considered for use in combination therapies of the invention include but are not limited to bemcentinib (BGB324 or R428), TP-0903, LY2801653, amuvatinib (MP-470), bosutinib (SKI-606), MGCD 265, ASP2215, cabozantinib (XL184), foretinib (GSK1363089/XL880), and SGI-7079. In certain embodiments, the modulator of Axl kinase is a monoclonal antibody targeting AXL (*e.g.*, YW327.6S2) or an AXL decoy receptor (*e.g.*, GL2I.T), or glesatinib, merestinib, or a dual Flt3-Axl inhibitor such as gilteritinib.

[0194] In certain embodiments, the additional therapeutic agent is an anti-cancer agent or chemo-therapeutic agent. Examples of anti-cancer agents considered for use in combination therapies of the invention include but are not limited erlotinib, bortezomib, fulvestrant, sunitib, imatinib mesylate, letrozole, finasunate, platins such as oxaliplatin, carboplatin, and cisplatin, finasunate, fluorouracil, rapamycin, leucovorin, lapatinib, lonafamib, sorafenib, gefitinib, camptothecin, topotecan, bryostatin, adezelesin, anthracyclin, carzelesin, bizelesin, dolastatin, auristatins, duocarmycin, eleutherobin, taxols such as paclitaxel or docetaxel, cyclophosphamide, doxorubicin, vincristine, prednisone or prednisolone, other alkylating agents such as mechlorethamine, chlorambucil, and ifosfamide, antimetabolites such as azathioprine or mercaptopurine, other microtubule inhibitors (vinca alkaloids like vincristine, vinblastine, vinorelbine, and vindesine, as well as taxanes), podophyllotoxins (etoposide, teniposide, etoposide

phosphate, and epipodophyllotoxins), topoisomerase inhibitors, other cytotoxins such as actinomycin, daunorubicin, valrubicin, idarubicin, edrecolomab, epirubicin, bleomycin, plicamycin, mitomycin, as well as other anticancer antibodies (cetuximab, bevacizumab, ibritumomab, abagovomab, adecatumumab, afutuzumab, alacizumab, alemtuzumab, anatumomab, apolizumab, bavituximab, belimumab, bivatuzumab mertansine, blinatumomab, brentuximab vedotin, cantuzumab mertansine, catumazomab, cetuximab, citatuzumab bogatox, cixutumumab, clivatuzumab tetraxetan, conatumumab, dacetuzumab, daclizumab, detumomab, ecromeximab, edrecolomab, elotuzumab, epratuzumab, ertumaxomab, etaracizumab, farletuzumab, figitumumab, fresolimumab, galiximab, gembatumumab vedotin, gemtuzumab, ibritumomab tiuxetan, inotuzumab ozogamicin, intetumumab, ipilimumab, iratumumab, labetuzumab, lexatumumab, lintuzumab, lucatumumab, lumilisimab, mapatumumab, matuzumab, milatuzumab, mitumomab, nacolomab tafenatox, naptumomab estafenatox, necitumumab, nimotuzumab, ofatumumab, olaratumab, oportuzumab monatox, oregovomab, panitumumab, pemtumomab, pertuzumab, pintumomab, pritumumab, ramucirumab, rilotumumab, robatumumab, rituximab, sibrotuzumab, tacatuzumab tetraxetan, taplitumomab paptox, tenatumomab, ticilimumab, tigatuzumab, tositumomab or ^{131}I-tositumomab, trastuzumab, tremelimumab, tuocotuzumab celmoleukin, veltuzumab, visilizumab, volocixumab, votumumab, zalutumumab, zanolimumab, IGN-101, MDX-010, ABX-EGR, EMD72000, ior-t1, MDX-220, MRA, H-11 scFv, huJ591, TriGem, TriAb, R3, MT-201, G-250, ACA-125, Onyvax-105, CD:-960,Cea-Vac, BrevaRex AR54, IMC-1C11, GlioMab-H, ING-1, anti-LCG MAbs, MT-103, KSB-303, Therex, KW2871, anti-HMI.24, Anti-PTHrP, 2C4 antibody, SGN-30, TRAIL-RI MAb, Prostate Cancer antibody, H22xKi-r, ABX-Mai, Imuteran, Monopharm-C), and antibody-drug conjugates comprising any of the above agents (especially auristatins MMAE and MMAF, maytansinoids like DM-1, calicheamycins, or various cytotoxins).

[0195] In certain embodiments, the additional therapeutic agent is selected from anastrozole (ARIMIDEX®), bicalutamide (CASODEX®), bleomycin sulfate (BLENOXANE®), busulfan (MYLERAN®), busulfan injection (BUSULFEX®), capecitabine (XELODA®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (PARAPLATIN®), carmustine (BiCNU®), chlorambucil (LEUKERAN®), cisplatin (PLATINOL®), cladribine (LEUSTATIN®), cyclophosphamide (CYTOXAN® or NEOSAR®), cytarabine, cytosine arabinoside (CYTOSAR-U®), cytarabine liposome injection (DEPOCYT®), dacarbazine (DTIC-

Dome®), dactinomycin (actinomycin D, COSMEGAN®), daunorubicin hydrochloride (CERUBIDINE®), daunorubicin citrate liposome injection (DAUNOXOME®), dexamethasone, docetaxel (TAXOTERE®), doxorubicin hydrochloride (ADRIAMYCIN®, RUBEX®), etoposide (VEPESID®), fludarabine phosphate (FLUDARA®), 5-fluorouracil (ADRUCIL®, EFUDEX®), flutamide (EULEXIN®), tezacitibine, gemcitabine (difluorodeoxycitidine), hydroxyurea (HYDREA®), idarubicin (IDAMYCIN®), ifosfamide (IFEX®), irinotecan (CAMPTOSAR®), L-asparaginase (ELSPAR®), leucovorin calcium, melphalan (ALKERAN®), 6-mercaptopurine (PURINETHOL®), methotrexate (FOLEX®), mitoxantrone (NOVANTRONE®), gemtuzumab ozogamicin (MYLOTARGTM), paclitaxel (TAXOL®), nab-paclitaxel (ABRAXANE®), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (GLIADEL®), tamoxifen citrate (NOLVADEX®), teniposide (VUMON®), 6-thioguanine, thiotepa, tirapazamine (TIRAZONE®), topotecan hydrochloride for injection (HYCAMPTIN®), vinblastine (VELBAN®), vincristine (ONCOVIN®), and vinorelbine (NAVELBINE®).

[0196] In certain embodiments, the additional therapeutic agent is capable of inhibiting BRAF, MEK, CDK4/6, SHP-2, HDAC, EGFR, MET, mTOR, PI3K or AKT, or a combination thereof. In a particular embodiment, the compounds of the present invention are combined with another therapeutic agent selected from vemurafinib, debrafinib, LGX818, trametinib, MEK162, LEE011, PD-0332991, panobinostat, verinostat, romidepsin, cetuximab, gefitinib, erlotinib, lapatinib, panitumumab, vandetanib, INC280, everolimus, simolimus, BMK120, BYL719 or CLR457, or a combination thereof.

[0197] In certain embodiments, the additional therapeutic agent is selected based on the disease or condition that is being treated. For example, in the treatment of melanoma, the additional therapeutic agent is selected from aldesleukin (e.g., PROLEUKIN®), dabrafenib (e.g., TAFINLAR®), dacarbazine, recombinant interferon alfa-2b (e.g., INTRON® A), ipilimumab, trametinib (e.g., MEKINIST®), peginterferon alfa-2b (e.g., PEGINTRON®, SYLATRONTM), vemurafenib (e.g., ZELBORAF®)), and ipilimumab (e.g., YERVOY®).

[0198] For the treatment of ovarian cancer, the additional therapeutic agent is selected from doxorubicin hydrochloride (Adriamycin®), carboplatin (PARAPLATIN®), cyclophosphamide (CYTOXAN®, NEOSAR®), cisplatin (PLATINOL®, PLATINOL-AQ®), doxorubicin hydrochloride liposome (DOXIL®, DOX-SL®, EVACET®, LIPODOX®), gemcitabine

hydrochloride (GEMZAR®), topotecan hydrochloride (HYCAMTIN®), and paclitaxel (TAXOL®).

[0199] For the treatment of thyroid cancer, the additional therapeutic agent is selected from doxorubicin hydrochloride (Adriamycin®), cabozantinib-S-malate (COMETRIQ®), and vandetanib (CAPRELSA®).

[0200] For the treatment of colon cancer, the additional therapeutic agent is selected from fluorouracil (e.g., ADRUCIL®, EFUDEX®, FLUOROPLEX®), bevacizumab (AVASTIN®), irinotecan hydrochloride (CAMPTOSTAR®), capecitabine (XELODA®), cetuximab (ERBITUX®), oxaliplatin (ELOXATIN®), leucovorin calcium (WELLCOVORIN®), regorafenib (STIVARGA®), panitumumab (VECTIBIX®), and ziv-aflibercept (ZALTRAP®).

[0201] For the treatment of lung cancer, the additional therapeutic agent is selected from methotrexate, methotrexate LPF (e.g., FOLEX®, FOLEX PFS®, Abitrexate®, MEXATE®, MEXATE-AQ®), paclitaxel (TAXOL®), paclitaxel albumin-stabilized nanoparticle formulation (ABRAXANE®), afatinib dimaleate (GILOTRIF®), pemetrexed disodium (ALIMTA®), bevacizumab (AVASTIN®), carboplatin (PARAPLATIN®), cisplatin (PLATINOL®, PLATINOL-AQ®), crizotinib (XALKORI®), erlotinib hydrochloride (TARCEVA®), gefitinib (IRESSA®), and gemcitabine hydrochloride (GEMZAR®).

[0202] For the treatment of pancreatic cancer, the other therapeutic agent may be selected from fluorouracil (ADRUCIL®), EFUDEX®, FLUOROPLEX®), erlotinib hydrochloride (TARCEVA®), gemcitabine hydrochloride (GEMZAR®), and mitomycin or mitomycin C (MITOZYTREXTM, MUTAMYCIN®).

[0203] For the treatment of cervical cancer, the additional therapeutic agent is selected from bleomycin (BLENOXANE®), cisplatin (PLATINOL®, PLATINOL-AQ®) and topotecan hydrochloride (HYCAMTIN®).

[0204] For the treatment of head and neck cancer, the additional therapeutic agent is selected from methotrexate, methotrexate LPF (e.g., FOLEX®, FOLEX PFS®, Abitrexate®, MEXATE®, MEXATE-AQ®), fluorouracil (ADRUCIL®, EFUDEX®, FLUOROPLEX®), bleomycin (BLENOXANE®), cetuximab (ERBITUX®), cisplatin (PLATINOL®, PLATINOL-AQ®) and docetaxel (TAXOTERE®).

[0205] For the treatment of leukemia, including chronic myelomonocytic leukemia (CMML), the additional therapeutic agent is selected from bosutinib (BOSULIF®), cyclophosphamide (CYTOXAN®, NEOSAR®), cytarabine (CYTOSAR-U®, TARABINE PFS®), dasatinib (SPRYCEL®), imatinib mesylate (GLEEVEC®), ponatinib (ICLUSIG®), nilotinib (TASIGNA®) and omacetaxine mepesuccinate (SYNRIBO®).

[0206] In some instances, patients may experience allergic reactions to the compounds of the present invention and/or other anti-cancer agent(s) during or after administration. Therefore, anti-allergic agents may be administered to minimize the risk of an allergic reaction. Suitable anti-allergic agents include corticosteroids, such as dexamethasone (e.g., DECADRON®), beclomethasone (e.g., BECLOVENT®), hydrocortisone (also known as cortisone, hydrocortisone sodium succinate, hydrocortisone sodium phosphate; e.g., ALA-CORT®, hydrocortisone phosphate, Solu-CORTEF®, HYDROCORT Acetate® and LANACORT®), prednisolone (e.g., DELTA-Cortel®, ORAPRED®, PEDIAPRED® and PRELONE®), prednisone (e.g., DELTASONE®, LIQUID RED®, METICORTEN® and ORASONE®), methylprednisolone (also known as 6-methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate; e.g., DURALONE®, MEDRALONE®, MEDROL®, M-PREDNISOL® and SOLU-MEDROL®); antihistamines, such as diphenhydramine (e.g., BENADRYL®), hydroxyzine, and cyproheptadine; and bronchodilators, such as the beta-adrenergic receptor agonists, albuterol (e.g., PROVENTIL®), and terbutaline (BRETHINE®).

[0207] In other instances, patients may experience nausea during and after administration of the compound of the present invention and/or other anti-cancer agent(s). Therefore, anti-emetics may be administered in preventing nausea (upper stomach) and vomiting. Suitable anti-emetics include aprepitant (EMEND®), ondansetron (ZOFRAN®), granisetron HCl (KYTRIL®), lorazepam (ATIVAN®. dexamethasone (DECADRON®), prochlorperazine (COMPAZINE®), casopitant (REZONIC® and Zunrisa®), and combinations thereof.

[0208] In yet other instances, medication to alleviate the pain experienced during the treatment period is prescribed to make the patient more comfortable. Common over-the-counter analgesics, such TYLENOL®, are often used. Opioid analgesic drugs such as hydrocodone/paracetamol or hydrocodone/acetaminophen (e.g., VICODIN®), morphine (e.g., ASTRAMORPH® or

AVINZA®), oxycodone (e.g., OXYCONTIN® or PERCOCET®), oxymorphone hydrochloride (OPANA®), and fentanyl (e.g., DURAGESIC®) are also useful for moderate or severe pain.

[0209] Furthermore, cytoprotective agents (such as neuroprotectants, free-radical scavengers, cardioprotectors, anthracycline extravasation neutralizers, nutrients and the like) may be used as an adjunct therapy to protect normal cells from treatment toxicity and to limit organ toxicities. Suitable cytoprotective agents include amifostine (ETHYOL®), glutamine, dimesna (TAVOCEPT®), mesna (MESNEX®), dexrazoxane (ZINECARD® or TOTECT®), xaliproden (XAPRILA®), and leucovorin (also known as calcium leucovorin, citrovorum factor and folinic acid).

[0210] In yet another aspect, a compound of the present invention may be used in combination with known therapeutic processes, for example, with the administration of hormones or in radiation therapy. In certain instances, a compound of the present invention may be used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.

[0211] The doses and dosage regimen of the active ingredients used in the combination therapy may be determined by an attending clinician. In certain embodiments, the compound described herein (*e.g.*, a compound of Formula I or other compounds in Section I) and the additional therapeutic agent(s) are administered in doses commonly employed when such agents are used as monotherapy for treating the disease or condition. In other embodiments, the compound described herein (*e.g.*, a compound of Formula I or other compounds in Section I) and the additional therapeutic agent(s) are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating the disease or condition. In certain embodiments, the compound described herein (*e.g.*, a compound of Formula I or other compounds in Section I) and the additional therapeutic agent(s) are present in the same composition, which is suitable for oral administration.

[0212] In certain embodiments, the compound described herein (*e.g.*, a compound of Formula I or other compounds in Section I) and the additional therapeutic agent(s) may act additively or synergistically. A synergistic combination may allow the use of lower dosages of one or more agents and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration of one or more agents may lower toxicity of the therapy without reducing the efficacy of the therapy.

[0213] Another aspect of this invention is a kit comprising a therapeutically effective amount of a compound described herein (*e.g.*, a compound of Formula I or other compounds in Section I), a pharmaceutically acceptable carrier, vehicle or diluent, and optionally at least one additional therapeutic agent listed above. In certain embodiments, the kit further comprises instructions, such as instructions for treating a disease described herein.

IV. Pharmaceutical Compositions and Dosing Considerations

[0214] As indicated above, the invention provides pharmaceutical compositions, which comprise a therapeutically-effective amount of one or more of the compounds described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. The pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, *e.g.*, those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally. In certain embodiments, the invention provides a pharmaceutical composition comprising a compound described herein (*e.g.*, a compound of Formula I) and a pharmaceutically acceptable carrier.

[0215] The phrase "therapeutically effective amount" as used herein means that amount of a compound, material, or composition comprising a compound of the present invention which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment.

[0216] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0217] Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions. Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[0218] Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 0.1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

[0219] In certain embodiments, a formulation of the present invention comprises an excipient selected from the group consisting of cyclodextrins, celluloses, liposomes, micelle forming agents, *e.g.*, bile acids, and polymeric carriers, *e.g.*, polyesters and polyanhydrides; and a compound of the present invention. In certain embodiments, an aforementioned formulation renders orally bioavailable a compound of the present invention.

[0220] Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0221] Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

[0222] In solid dosage forms of the invention for oral administration (*e.g.*, capsules, tablets, pills, dragees, powders, granules, trouches and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds and surfactants, such as poloxamer and sodium lauryl sulfate; (7) wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and non-ionic surfactants; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, zinc stearate, sodium stearate, stearic acid, and mixtures thereof; (10) coloring agents; and (11) controlled release agents such as crospovidone or ethyl cellulose. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0223] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or

dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0224] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be formulated for rapid release, *e.g.*, freeze-dried. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0225] Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[0226] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[0227] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters,

microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0228] Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

[0229] Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

[0230] Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[0231] The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0232] Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[0233] Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[0234] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

[0235] Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0236] Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0237] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0238] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0239] Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio

of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

[0240] When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given *per se* or as a pharmaceutical composition containing, for example, 0.1 to 99% (more preferably, 10 to 30%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[0241] The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given in forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administrations are preferred.

[0242] The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[0243] The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[0244] These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

[0245] Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

[0246] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[0247] The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[0248] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[0249] In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Preferably, the compounds are administered at about 0.01 mg/kg to about 200 mg/kg, more preferably at about 0.1 mg/kg to about 100 mg/kg, even more preferably at about 0.5 mg/kg to about 50 mg/kg. When the compounds described herein are co-administered with another agent (*e.g.*, as sensitizing agents), the effective amount may be less than when the agent is used alone.

[0250] If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. Preferred dosing is one administration per day.

[0251] The invention further provides a unit dosage form (such as a tablet or capsule) comprising a imidazopyrimidine compound or related compound described herein in a therapeutically effective amount for the treatment of a disease or condition described herein.

IV. Medical Kits

[0252] Another aspect of the invention provides a medical kit comprising, for example, (i) a compound described herein, and (ii) instructions for use according to a method described herein.

EXAMPLES

[0253] The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustrating certain aspects and embodiments of the present invention, and are not intended to limit the invention.

[0254] The following abbreviations are used herein:

ACN	Acetonitrile
aq.	aqueous
DCM	dichloromethane
DMA	N,N-Dimethylacetamide
DMSO	Dimethylsulfoxide
DMF	Dimethylformamide
equiv	Equivalent
EtOAc or EA	Ethyl acetate
FA	Formic acid
h	Hour or hours
HPLC	High pressure liquid chromatography
HBSS	Hank's Balanced Salt solution buffer
LCMS	Liquid chromatography mass spectrometry
NMR	Nuclear Magnetic Resonance
PE	Petroleum ether
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

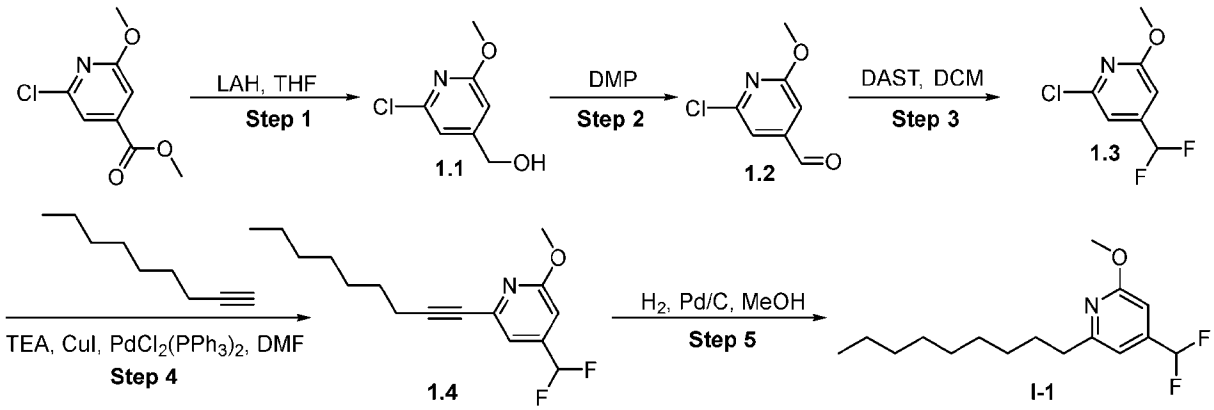
Analytical Instrumentation and Purification

[0255] NMR Instrument Details: Bruker Avance III HD 300MHz or 400MHz.

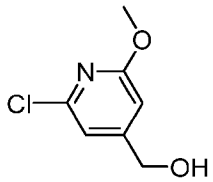
[0256] LCMS Instrument Details: Shimadzu LCMS-2010EV system coupled to SPD-M20A PDA and ELS detectors. Softa model 400.

Column	Specifications	Mobile Phase	Flow Rate
HALO AQ-C18	30mm*3.0mm 2μm	A:H_2O+0.05%TFA; B:CAN+0.05%TFA	1.5 mL/min
EVO-C18	50mm*3.0mm 2.6μm	A:H_2O+0.05% $NH_3.H_2O$; B:ACN	1.2 mL/min
Agilent SB-Aq	50mm*4.6mm 1.8μm	A:H_2O+0.1%FA; B:ACN+0.07%FA	1.5 mL/min
SB-Aq	50mm*3.0mm 2.5μm	A:H_2O+0.05%TFA; B:ACN	1.5 mL/min
L-column3 C18	30mm*3.0mm 3μm	A: 5 mM NH4HCO3 ; B:ACN	1.2 mL/min
Kinetex 2.6u XB-C18	50mm*3.0mm 2.6μm	A:H_2O+0.05%TFA; B:ACN	1.5 mL/min

EXAMPLE 1. Synthesis of 6-(octyloxy)pyridine-2,4-diol (I-1)



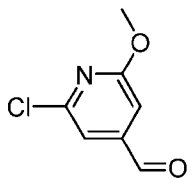
*Step 1. Synthesis of (2-chloro-6-methoxypyridin-4-yl)methanol (**1.1**)*



[0257] Into a 250 mL 3-necked round-bottom flask were added methyl 2-chloro-6-methoxypyridine-4-carboxylate (10.0 g, 49.6 mmol, 1.00 equiv) and THF (100 mL) at room

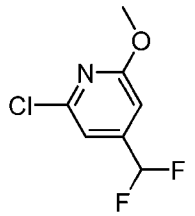
temperature. To the above mixture was added $LiAlH_4$ (1.41 g, 37.2 mmol, 0.75 equiv) in portions over 10 min at 0 °C. The resulting mixture was stirred for an additional 5 h at room temperature. The reaction was quenched with $Na_2SO_4 \cdot 10\ H_2O$ at 0 °C. The resulting mixture was filtered and the filter cake was washed with EtOAc (2x100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, and eluted with PE / EA (1:1) to afford (2-chloro-6-methoxypyridin-4-yl)methanol (**1.1**; 7.00 g, 81%) as a white solid. LCMS: calculated: $C_7H_8ClNO_2$: 173.02; observed: 174.02 $[M+H]^+$.

*Step 2. Synthesis of 2-chloro-6-methoxypyridine-4-carbaldehyde (**1.2**)*



[0258] Into a 40 mL vial were added (2-chloro-6-methoxypyridin-4-yl)methanol (**1.1**; 2.00 g, 11.5 mmol, 1.00 equiv) and DCM (20.0 mL) at room temperature. To the above mixture was added Dess-Martin periodinane (5.86 g, 13.8 mmol, 1.20 equiv) in portions over 10 min at room temperature. The resulting mixture was stirred for an additional 6 h at room temperature. The resulting mixture was filtered and the filter cake was washed with DCM (2x20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, and eluted with PE / EA (5:1) to afford 2-chloro-6-methoxypyridine-4-carbaldehyde (**1.2**; 1.5 g, 75.8%) as a white solid. LCMS: calculated: $C_7H_6ClNO_2$: 171.01; observed: 172.01 $[M+H]^+$.

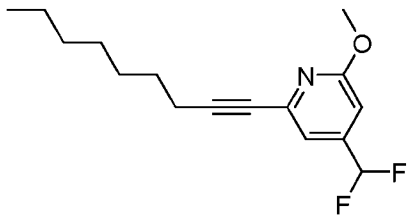
*Step 3. Synthesis of 2-chloro-4-(difluoromethyl)-6-methoxypyridine (**1.3**)*



[0259] Into a 40 mL vial were added 2-chloro-6-methoxypyridine-4-carbaldehyde (**1.2**; 1.50 g, 8.74 mmol, 1.00 equiv) and DCM (20.0 mL) at room temperature. To the above mixture was added DAST (4.23 g, 26.2 mmol, 3.00equiv) dropwise over 10 min at 0 °C. The resulting mixture was

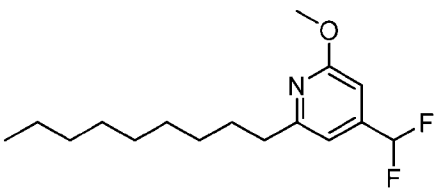
stirred overnight at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$ (aq.) (20 mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (2x20 mL). The combined organic layers were washed with brine (2x20 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 2-chloro-4-(difluoromethyl)-6-methoxypyridine (**1.3**; 1.2 g, 70%) as a white solid. LCMS: calculated: $C_7H_6ClF_2NO$: 193.01; observed: 194.01 $[M+H]^+$.

*Step 4. Synthesis of 4-(difluoromethyl)-2-methoxy-6-(non-1-yn-1-yl)pyridine (**1.4**)*



[0260] Into a 40 mL vial containing 2-chloro-4-(difluoromethyl)-6-methoxypyridine (**1.3**; 1.2 g, 6.19 mmol) were added 1-nonyne (0.77 g, 6.19 mmol, 1.00 equiv), Et_3N (10.0 mL), DMF (10.0 mL), CuI (0.59 g, 3.09 mmol, 0.500 equiv), and $Pd(PPh_3)_2Cl_2$ (0.87 g, 1.24 mmol, 0.200equiv) at room temperature. The solution was stirred overnight at 70 °C under a nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was extracted with EtOAc (2x20 mL). The combined organic layers were washed with brine (2x20 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (5:1) to afford 4-(difluoromethyl)-2-methoxy-6-(non-1-yn-1-yl)pyridine (**1.4**; 200 mg, 11.4%) as a brown solid. LCMS: calculated: $C_{16}H_{21}F_2NO$: 281.16; observed: 282.16 $[M+H]^+$.

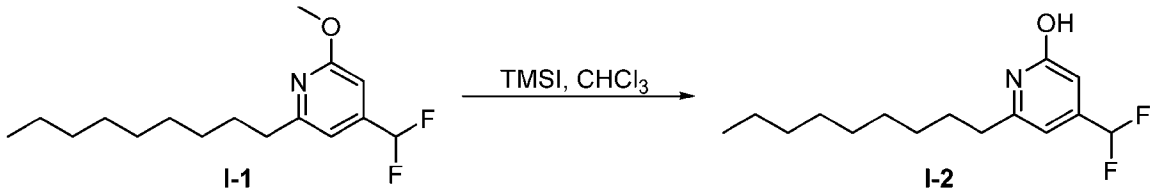
Step 5. Synthesis of 4-(difluoromethyl)-2-methoxy-6-nonylpyridine (**I-1**)



[0261] Into a 100 mL round-bottom flask were added 4-(difluoromethyl)-2-methoxy-6-(non-1-yn-1-yl)pyridine (**1.4**; 100 mg, 0.355 mmol, 1.00 equiv), MeOH (5.00 mL) and Pd/C (20.0 mg, 10%)

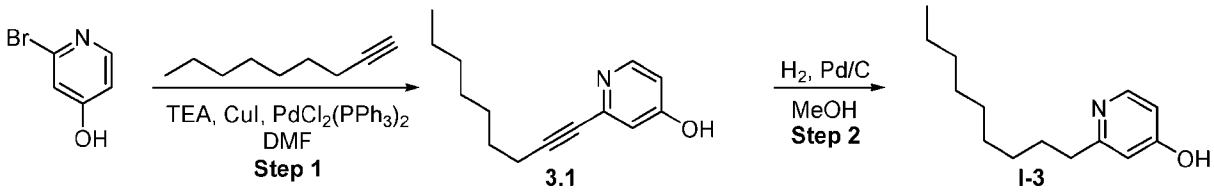
at room temperature. The solution was stirred overnight at room temperature under a hydrogen atmosphere. The resulting mixture was filtered, and the filter cake was washed with MeOH (2x20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column: C18 silica gel; mobile phase: MeCN in water (0.1% FA), 10% to 50% gradient in 10 min; detector: UV 254 nm. This resulted in 4-(difluoromethyl)-2-methoxy-6-nonylpyridine (**I-1**; 20.0 mg, 19%) as a white solid. ^{1}H NMR(400 MHz, DMSO-d_6) δ 7.15 – 6.83 (m, 2H), 6.77 (s, 1H), 3.87 (s, 3H), 2.70 (t, J = 7.6 Hz, 2H), 1.67 (p, J = 7.0 Hz, 2H), 1.27 (d, J = 21.7 Hz, 12H), 0.86 (t, J = 6.8 Hz, 3H). HPLC purity: 100%; LCMS: calculated: $C_{16}H_{25}F_2NO$: 285.19; observed: 286.2 $[M+H]^+$.

EXAMPLE 2. Synthesis of 4-(difluoromethyl)-6-nonylpyridin-2-ol (I-2)

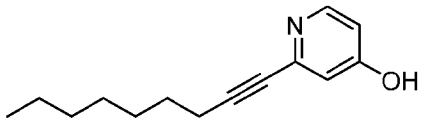


[0262] Into a 40 mL vial were added 4-(difluoromethyl)-2-methoxy-6-nonylpyridine (**I-1**; 100 mg, 0.350 mmol, 1.00equiv), $CHCl_3$ (5.00 mL) and TMSI (280 mg, 1.40 mmol, 4.00equiv) at room temperature. The resulting mixture was stirred overnight at 70 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column: C18 silica gel; mobile phase: MeCN in water (10mmol/L NH_4HCO_3), 10% to 50% gradient in 10 min; detector: UV 254 nm. This resulted in 4-(difluoromethyl)-6-nonylpyridin-2-ol (**I-2**; 20.0 mg, 21%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (s, 1H), 6.81 (t, J = 55.1 Hz, 1H), 6.32 (s, 1H), 6.10 (s, 1H), 2.47 (d, J = 7.5 Hz, 2H), 1.57 (t, J = 7.5 Hz, 2H), 1.37 – 1.18 (d, J = 6.1 Hz, 12H), 0.86 (t, J = 6.6 Hz, 3H); HPLC purity: 99.0%; LCMS: calculated: $C_{15}H_{23}F_2NO$: 271.17; observed: 272.17 $[M+H]^+$.

EXAMPLE 3. Synthesis of 2-(difluoromethyl)-6-nonylpyridin-4-ol (I-3)

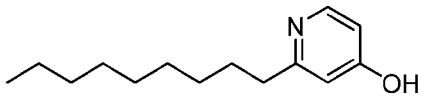


*Step 1. Synthesis of 2-(non-1-yn-1-yl)pyridin-4-ol (**3.1**)*



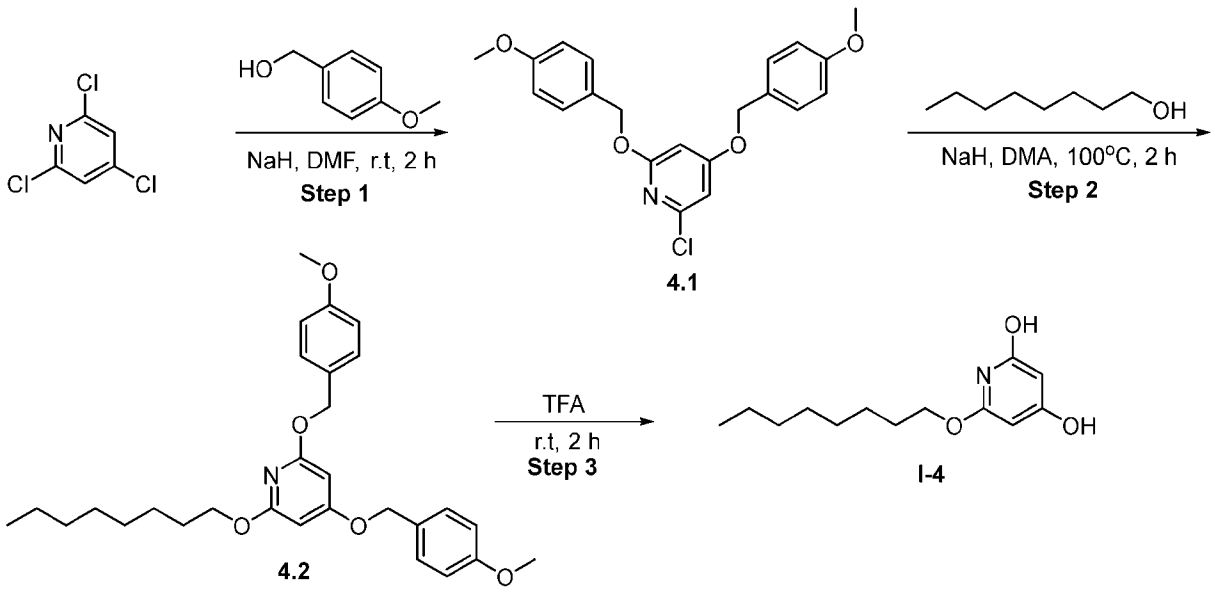
[0263] Into a 40 mL vial were added 2-bromopyridin-4-ol (0.600 g, 3.44 mmol, 1.00 equiv), 1-nonyne (0.51 g, 4.13 mmol, 1.20 equiv), DMF (10.0 mL), Et_3N (1.74 g, 17.2 mmol, 5.00 equiv), CuI (0.330 g, 1.72 mmol, 0.500 equiv) and $Pd(PPh_3)_2Cl_2$ (0.240 g, 0.345 mmol, 0.100 equiv) at room temperature. The resulting mixture was stirred overnight at 110 °C under a nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (2x20 mL). The combined organic layers were washed with brine (2x20 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (1:1) to afford 2-(non-1-yn-1-yl)pyridin-4-ol (**3.1**; 400 mg, 53.3%) as a white solid. LCMS: calculated: $C_{14}H_{19}NO$: 217.15; observed: 218.15 $[M+H]^+$.

*Step 2. Synthesis of 2-nonylpyridin-4-ol (**I-3**)*



[0264] Into a 50 mL round-bottom flask were added 2-(non-1-yn-1-yl)pyridin-4-ol (**3.1**; 200 mg, 0.920 mmol, 1.00 equiv), MeOH (20 mL) and Pd/C (48.9 mg, 20%) at room temperature. The resulting mixture was stirred overnight at room temperature under a hydrogen (1 atm) atmosphere. The resulting mixture was filtered, and the filter cake was washed with MeOH (2x20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column: C18 silica gel; mobile phase: MeCN in water (0.1% FA), 10% to 50% gradient in 10 min; detector: UV 254 nm. This resulted in 2-nonylpyridin-4-ol (**I-3**; 30.0 mg, 14.7%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 10.90 (s, 1H), 7.465(s, 1H) 5.94 (s, 2H), 1.74 – 1.49 (m, 2H), 1.40 – 1.17 (m, 12H), 0.88 (q, J = 4.5, 2.8 Hz, 3H); HPLC purity: 95.6%; LCMS: calculated: $C_{14}H_{23}NO$: 221.18; observed: 222.3 $[M+H]^+$.

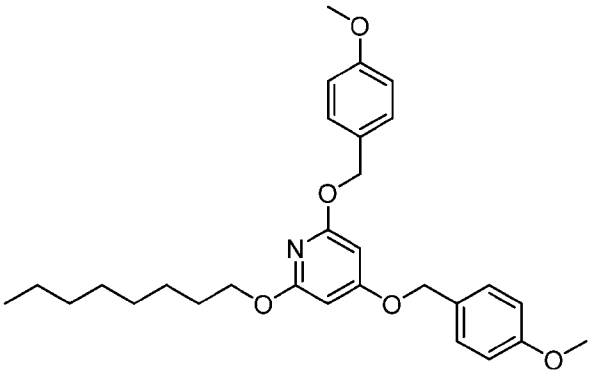
EXAMPLE 4. Synthesis of 6-(octyloxy)pyridine-2,4-diol (I-4)



*Step 1. Synthesis of 2-chloro-4,6-bis((4-methoxybenzyl)oxy)pyridine (**4.1**)*

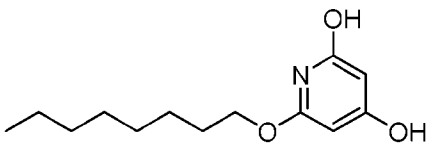
[0265] To a solution of anise alcohol (1.51 g, 11.0 mmol, 2.00 equiv) in DMF (10.0 mL) was added sodium hydride (0.260 g, 11.0 mmol, 2.00 equiv, 60% in oil) at 0 °C. The mixture was stirred for 15 min. 2,4,6-trichloropyridine (1.00 g, 5.48 mmol, 1.00 equiv) was added and the mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EtOAc (3x10mL). The combined organic layers were washed with brine (1x10 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 2-chloro-4,6-bis((4-methoxybenzyl)oxy)pyridine (**4.1**; 700 mg, 33%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42 – 7.33 (m, 4H), 7.01 – 6.90 (m, 4H), 6.79 (d, J = 1.8 Hz, 1H), 6.47 (d, J = 1.8 Hz, 1H), 5.21 (s, 2H), 5.10 (s, 2H), 3.76 (s, 6H).

*Step 2. Synthesis of 2,4-bis((4-methoxybenzyl)oxy)-6-(octyloxy)pyridine (**4.2**)*



[0266] To a solution of octanol (203 mg, 1.56 mmol, 2.00 equiv) in DMA (3 mL) was added sodium hydride (28.0 mg, 1.17 mmol, 1.50 equiv, 60% in oil) at 0 °C. The mixture was stirred for 15 min. To the above solution was added 2-chloro-4,6-bis((4-methoxybenzyl)oxy)pyridine (**4.1**; 300 mg, 0.778 mmol, 1.00 equiv), and the mixture was warmed to 100 °C and stirred for 2 h. The reaction was allowed to cool down to room temperature and quenched by the addition of water (5 mL) at room temperature. The resulting mixture was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (3 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (1:1) to afford 2,4-bis((4-methoxybenzyl)oxy)-6-(octyloxy)pyridine (**4.2**; 110 mg, 29%) as a white solid. LCMS: calculated: $C_{29}H_{37}NO_5$: 479.27; observed: 480.30 $[M+H]^+$.

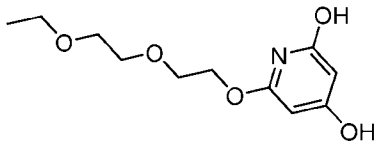
*Step 3. Synthesis of 6-(octyloxy)pyridine-2,4-diol (**I-4**)*



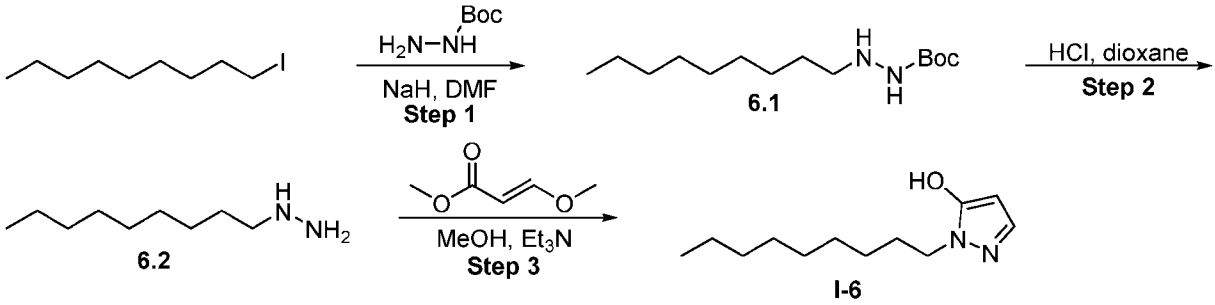
[0267] The solution of 2,4-bis((4-methoxybenzyl)oxy)-6-(octyloxy)pyridine (**4.2**; 100 mg, 0.208 mmol, 1.00 equiv) in trifluoroacetic acid (1 mL) was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions: column: Sunfire Prep C18 OBD, 19*150mm, 5 μm; mobile phase A: water (0.1% FA), mobile phase B: ACN; flow rate: 30 mL/min; gradient: 30% to 65 % B in 8 min; wavelength: 254nm/220nm. This resulted in 6-(octyloxy)pyridine-2,4-diol (**I-4**;

4 mg, 8%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.26 (m, 2H), 5.46 (m, 2H), 4.04 (t, J = 6.6 Hz, 2H), 1.64 (t, J = 7.0 Hz, 2H), 1.32 – 1.24 (m, 10H), 0.92 – 0.81 (m, 3H). HPLC purity: 95.6%; LCMS: calculated: $C_{13}H_{21}NO_3$: 239.15; observed: 240.20 $[M+H]^+$.

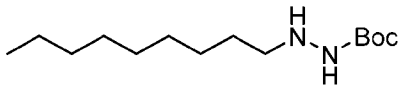
[0268] The following compounds were prepared using similar procedures to those described for the preparation of **I-4**:

Compound No	Structure	Analytical Data
I-5		Yield: 20 mg, 26.50%; Appearance: White solid; ^{1}HNMR (300 MHz, DMSO-d_6): δ 10.34 (s, 1H), 10.25 (s, 1H), 5.53 (d, J = 6.0 Hz, 2H), 4.19 (t, J = 4.8 Hz, 2H), 3.71 – 3.63 (m, 2H), 3.58 – 3.52 (m, 2H), 3.51 – 3.46 (m, 2H), 3.43 (d, J = 7.0 Hz, 2H), 1.10 (t, J = 7.0 Hz, 3H); HPLC purity: 99.2%; LCMS Calculated for: $C_{11}H_{17}NO_5$: 243.11; Observed: 244.10 $[M+H]^+$

EXAMPLE 5. Synthesis of 2-nonylpyrazol-3-ol (I-6)



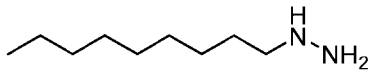
*Step 1. Synthesis of N'-nonyltert-butoxycarbohydrazide (**6.1**)*



[0269] Into a 250mL 3-necked round-bottom flask were added tert-butoxycarbohydrazide (6.86 g, 51.9 mmol, 1.20 equiv) and DMF (110 mL) at room temperature. To the above mixture was added NaH (1.56 g, 64.9 mmol, 1.50 equiv) in portions over 0.5 h at 0 °C. The resulting mixture was

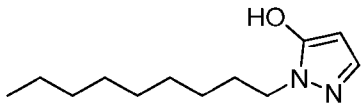
stirred for 1 h at 0 °C. To the above mixture was added iodononane (11.0 g, 43.3 mmol, 1.00 equiv) dropwise over 10 min at 0 °C. The resulting mixture was stirred for an additional 2 h at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (2x100 mL). The combined organic layers were washed with brine (2x100 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (1:1) to afford N'-nonyltert-butoxycarbohydrazide (**6.1**; 5.00 g, 44%) as a colorless oil. LCMS: calculated: $C_{14}H_{30}N_2O_2$: 258.23; observed: 259.23 $[M+H]^+$.

*Step 2. Synthesis of nonylhydrazine dihydrochloride (**6.2**)*



[0270] Into a 100 mL round-bottom flask were added N'-nonyltert-butoxycarbohydrazide (**6.1**; 5.00 g, 19.3 mmol, 1.00 equiv), DCM (50.0 mL) and HCl (gas) in 1,4-dioxane (19.3 mL) at room temperature. The resulting mixture was stirred overnight at room temperature. The mixture basified to pH 9 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with EtOAc (2x30 mL). The combined organic layers were washed with brine (2x20mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in nonylhydrazine dihydrochloride (**6.2**; 2.50 g, 55.9%) as a white solid. LCMS: calculated: $C_9H_{22}N_2$: 158.18; observed: 159.18 $[M+H]^+$.

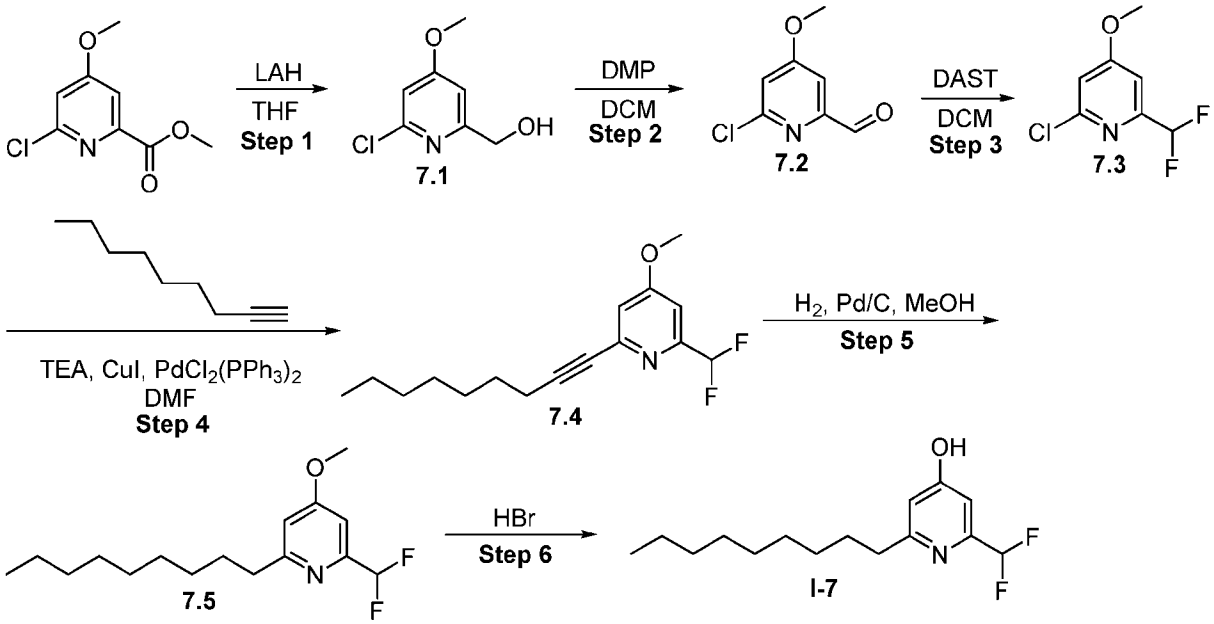
*Step 3. Synthesis of 2-nonylpyrazol-3-ol (**I-6**)*



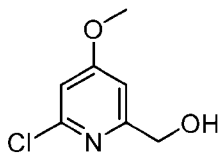
[0271] Into a 8 mL vial were added nonylhydrazine (**6.2**; 200 mg, 1.26 mmol, 1.00 equiv), methyl (*E*)-3-methoxyacrylate (220 mg, 1.90 mmol, 1.50 equiv), Et_3N (384 mg, 3.79 mmol, 3.00 equiv) and MeOH (5.00 ml) at room temperature. The resulting mixture was stirred overnight at 70 °C. The mixture was allowed to cool down to room temperature. The residue was purified by Prep-HPLC with the following conditions: column: C18 silica gel; mobile phase: MeCN in water (0.1% FA), 10% to 50% gradient in 10 min; detector: UV 254 nm. This resulted in 2-nonylpyrazol-3-ol (**I-6**; 20.0 mg, 7%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6): δ 10.69 (s, 1H), 7.08 (d, J =

1.8 Hz, 1H), 5.29 (d, J = 1.8 Hz, 1H), 3.80 (t, J = 7.0 Hz, 2H), 1.64 (t, J = 6.9 Hz, 2H), 1.31 – 1.12 (m, 12H), 0.91 – 0.81 (m, 3H); HPLC purity: 98.3%; LCMS: calculated: $C_{12}H_{22}N_2O$: 210.17; observed: 211.2 $[M+H]^+$.

EXAMPLE 6. Synthesis of 2-(difluoromethyl)-6-nonylpyridin-4-ol (I-7)

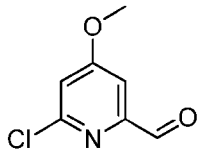


*Step 1. Synthesis of (6-chloro-4-methoxypyridin-2-yl)methanol (**7.1**)*



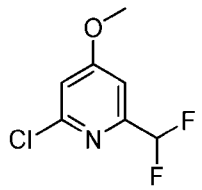
[0272] To a stirred solution of methyl 6-chloro-4-methoxypyridine-2-carboxylate (4.00 g, 19.8 mmol, 1.00 equiv) in THF (40 mL) was added $LiAlH_4$ (0.450 g, 11.9 mmol, 0.600 equiv) in portions at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched with sodium sulfate decahydrate at 0 °C. The resulting mixture was filtered and the filter cake was washed with EA (3x20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (1:2) to afford (6-chloro-4-methoxypyridin-2-yl)methanol (**7.1**; 2.50 g, 65%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6): δ 7.01 – 6.99 (m, 1H), 6.98-6.96 (m, 1H), 5.61 – 5.46 (m, 1H), 4.46 (s, 2H), 3.87 (s, 3H); LCMS: calculated: $C_7H_8ClNO_2$: 173.02; observed: 174.02 $[M+H]^+$.

*Step 2. Synthesis of 6-chloro-4-methoxypicolinaldehyde (**7.2**)*



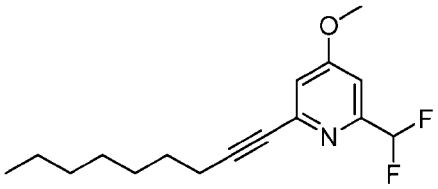
[0273] To a stirred solution of (6-chloro-4-methoxypyridin-2-yl)methanol (**7.1**; 2.50 g, 14.4 mmol, 1.00 equiv) in DCM (25.0 mL) was added Dess-Martin periodinane (7.33 g, 17.3 mmol, 1.20 equiv) in portions at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (200 mL), and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (2:1) to afford 6-chloro-4-methoxypicolinaldehyde (**7.2**; 2.30 g, 83%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.85 (s, 1H), 7.46 (d, J = 2.3 Hz, 1H), 7.44 (d, J = 2.2 Hz, 1H), 3.96 (s, 3H). LCMS: calculated: $C_7H_6ClNO_2$: 171.01; observed: 172.20 $[M+H]^+$.

*Step 3. Synthesis of 2-chloro-6-(difluoromethyl)-4-methoxypyridine (**7.3**)*



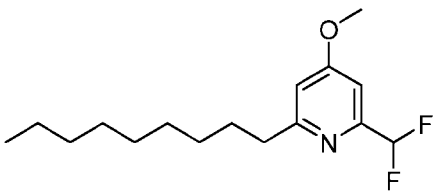
[0274] To a stirred solution of 6-chloro-4-methoxypicolinaldehyde (**7.2**; 2.40 g, 13.9 mmol, 1.00 equiv) in DCM (24.0 mL) was added DAST (7.89 g, 48.9 mmol, 3.50 equiv) dropwise at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched with water at 0 °C. The resulting mixture was extracted with DCM (3x50 mL). The combined organic layers were washed with brine (150 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (3:1) to afford 2-chloro-6-(difluoromethyl)-4-methoxypyridine (**7.3**; 2.20 g, 73%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.31 – 7.25 (m, 2H), 6.89 (d, J = 54.6 Hz, 1H), 3.94 (s, 3H). LCMS: calculated: $C_7H_6ClF_2NO$: 193.01; observed: 194.20 $[M+H]^+$.

*Step 4. Synthesis of 2-(difluoromethyl)-4-methoxy-6-(non-1-yn-1-yl)pyridine (**7.4**)*



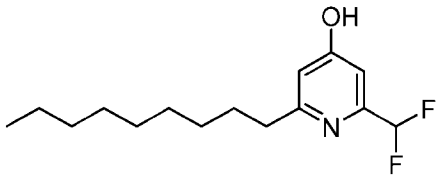
[0275] A solution of 2-chloro-6-(difluoromethyl)-4-methoxypyridine (**7.3**; 200 mg, 1.03 mmol, 1.00 equiv), 1-nonyne (141 mg, 1.13 mmol, 1.10 equiv), $PdCl_2(PPh_3)_2$ (72.5 mg, 0.103 mmol, 0.100 equiv) and CuI (98.3 mg, 0.516 mmol, 0.500 equiv) in TEA (2.50 mL) and DMF (2.50 mL) was stirred for 16 h at 110 °C under a nitrogen atmosphere. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EA (3x30 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (1:1) to afford 2-(difluoromethyl)-4-methoxy-6-(non-1-yn-1-yl)pyridine (**7.4**; 120 mg, 39%) as a yellow solid. LCMS: calculated: $C_{16}H_{21}F_2NO$: 281.16; observed: 281.90 $[M+H]^+$.

*Step 5. Synthesis of 2-(difluoromethyl)-4-methoxy-6-nonylpyridine (**7.5**)*



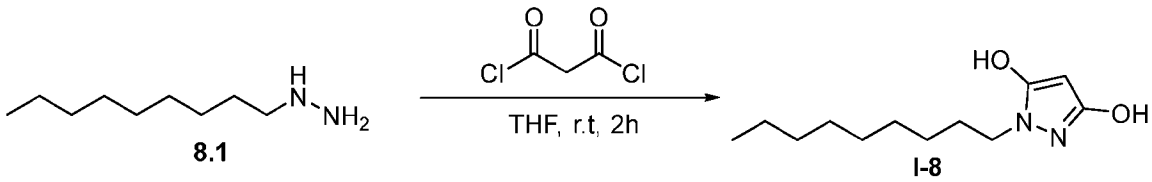
[0276] A solution of 2-(difluoromethyl)-4-methoxy-6-(non-1-yn-1-yl)pyridine (**7.4**; 120 mg, 0.427 mmol, 1.00 equiv) and Pd/C (120 mg, 20%) in MeOH (2.00 mL) was stirred for 3 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered and the filter cake was washed with MeOH (3x5 mL). The filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. LCMS calculated: $C_{16}H_{25}F_2NO$: 285.19; observed: 286.19 $[M+H]^+$.

*Step 6. Synthesis of 2-(difluoromethyl)-6-nonylpyridin-4-ol (**I-7**)*



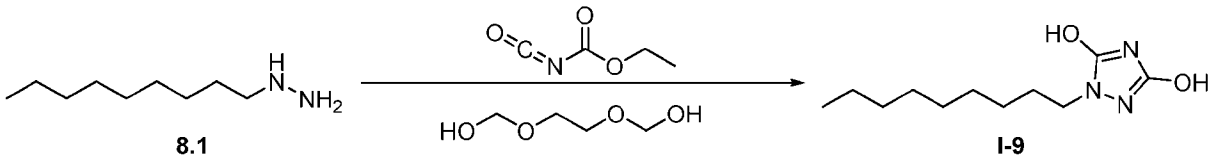
[0277] A solution of 2-(difluoromethyl)-4-methoxy-6-nonylpyridine (**7.4**; 60.0 mg, 0.210 mmol, 1.00 equiv) in HBr in water (0.500 mL, 48.0%) was stirred for 24 h at 110 °C. The resulting mixture was concentrated under vacuum. The crude product was purified by Chiral-Prep-HPLC with the following conditions: column, SunFire Prep C18 OBD, 19*150 mm, 5um; mobile phase: water (10 mmol/L NH_4HCO_3+0.1%$NH_3 \cdot H_2O$) and ACN (12% ACN up to 24% in 7 min); detector: UV 220 nm, to afford 2-(difluoromethyl)-6-nonylpyridin-4-ol (**I-7**; 15 mg, 26%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.95 – 6.53 (m, 3H), 2.61 (d, J = 7.7 Hz, 2H), 1.38-1.19 (m, 12H), 0.91 – 0.80 (m, 3H). LCMS: calculated: $C_{15}H_{23}F_2NO$: 271.17; observed: 272.20 $[M+H]^+$.

EXAMPLE 7. Synthesis of 1-nonylpyrazole-3,5-diol (I-8)



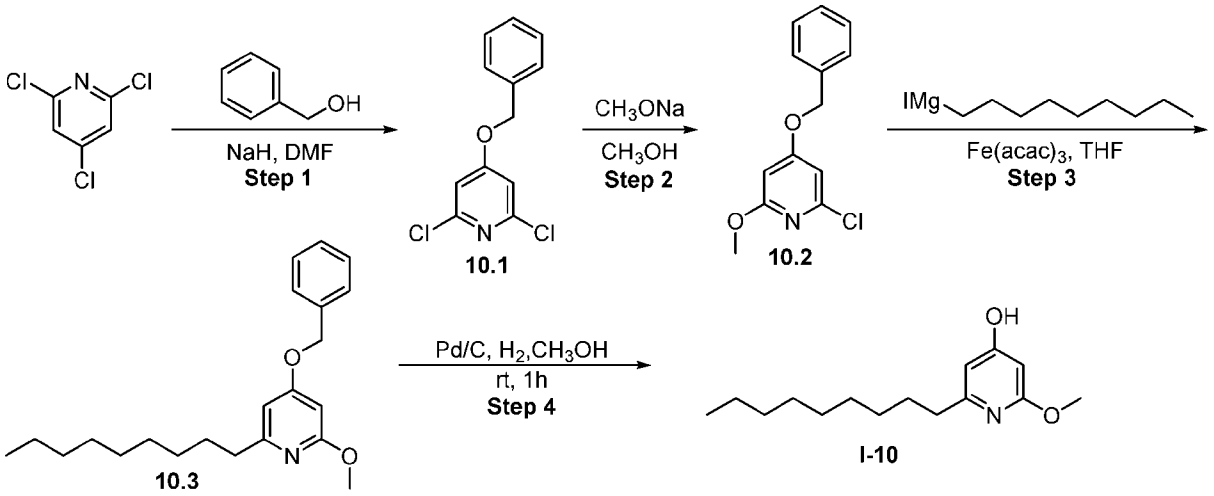
[0278] Into a 8 mL vial were added nonylhydrazine (200 mg, 1.26 mmol, 1.00 equiv), THF (5.00 mL), and propanedioyl dichloride (178 mg, 1.26 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature under a nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column: C18 silica gel; mobile phase: MeCN in water (0.1% FA), 10% to 50% gradient in 10 min; detector: UV 254 nm. This resulted in 1-nonylpyrazole-3,5-diol (**I-8**; 10.0 mg, 3.5%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.63 (s, 1H), 3.41 (t, J = 7.0 Hz, 2H), 3.24 (s, 2H), 1.53 (p, J = 6.9 Hz, 2H), 1.34 – 1.16 (m, 12H), 0.86 (t, J = 6.6 Hz, 3H); HPLC purity: 99.7%; LCMS: calculated: $C_{12}H_{22}N_2O_2$: 226.17; observed: 227.2 $[M+H]^+$.

EXAMPLE 8. Synthesis of 1-nonyl-1,2,4-triazole-3,5-diol (I-9)

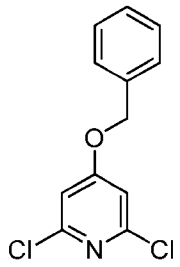


[0279] Into a 8 mL vial were added ethyl N-carbonylcarbamate (200 mg, 1.74 mmol, 1.00 equiv), nonylhydrazine (313 mg, 1.98 mmol, 1.00 equiv), and dimethylol glycol (5.00 mL) at room temperature. The resulting mixture was stirred for 4 h at 160 °C. The mixture was allowed to cool down to room temperature. The residue was purified by reversed-phase flash chromatography with the following conditions: column: C18 silica gel; mobile phase: MeCN in water (0.1% FA), 10% to 50% gradient in 10 min; detector: UV 254 nm. This resulted in 1-nonyl-1,2,4-triazole-3,5-diol (**I-9**; 30.0 mg, 6.67%) as a white solid ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 2H), 3.33 (d, J = 7.2 Hz, 2H), 1.53 (q, J = 7.1 Hz, 2H), 1.25 (s, 12H), 0.86 (t, J = 6.6 Hz, 3H); HPLC purity: 99.8%; LCMS: calculated: $C_{11}H_{21}N_3O_2$: 227.16; observed: 228.16 $[M+H]^+$.

EXAMPLE 9. Synthesis of 2-methoxy-6-nonylpyridin-4-ol (I-10)

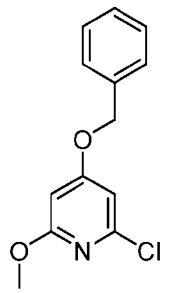


*Step 1. Synthesis of 4-(benzyloxy)-2,6-dichloropyridine (**10.1**)*



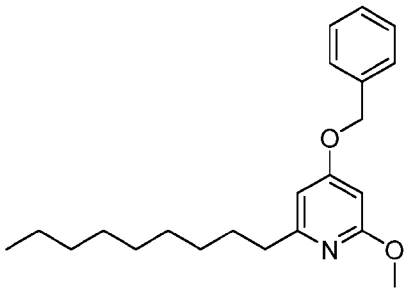
[0280] A solution of 2,4,6-trichloropyridine (500 mg, 2.74 mmol, 1.00 equiv) and NaH (60%, 132 mg, 5.48 mmol, 2.00 equiv) in DMF was stirred for 4 h at room temperature. The resulting mixture was diluted with H_2O (30 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with a NaCl solution (3x10 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (5:1) to afford 4-(benzyloxy)-2,6-dichloropyridine (**10.1**; 780 mg, 52%) as a yellow oil.

*Step 2. Synthesis of 4-(benzyloxy)-2-chloro-6-methoxypyridine (**10.2**)*



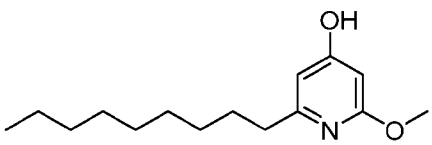
[0281] A solution of 4-(benzyloxy)-2,6-dichloropyridine (**10.1**; 780 mg, 3.07 mmol, 1.00 equiv) and sodium methylate solution (30%, 166 mg, 3.07 mmol, 1.00 equiv) in CH_3OH (10.0 mL) was stirred for 5 h at room temperature. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with H_2O (40 mL). The resulting mixture was extracted with EtOAc (3x15 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (1:1) to afford 4-(benzyloxy)-2-chloro-6-methoxypyridine (**10.2**; 154 mg, 16%) as a yellow oil.

*Step 3. Synthesis of 4-(benzyloxy)-2-methoxy-6-nonylpyridine (**10.3**)*



[0282] To a stirred solution of 4-(benzyloxy)-2-chloro-6-methoxypyridine (**10.2**; 144 mg, 0.577 mmol, 1.00 equiv) and $Fe(acac)_3$ (40.7 mg, 0.115 mmol, 0.2.00 equiv) in THF (2.00 mL) was added iodo(nonyl)magnesium (0.870 mL, 0.865 mmol, 1 M, 1.50 equiv) dropwise at room temperature under an N_2 atmosphere. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched by adding an ammonium chloride aqueous solution (10.0 mL) at room temperature. The resulting mixture was extracted with EA (3x5 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with EA:PE (1:15) to afford 4-(benzyloxy)-2-methoxy-6-nonylpyridine (**10.3**; 40 mg, 20%) as a light-yellow oil.

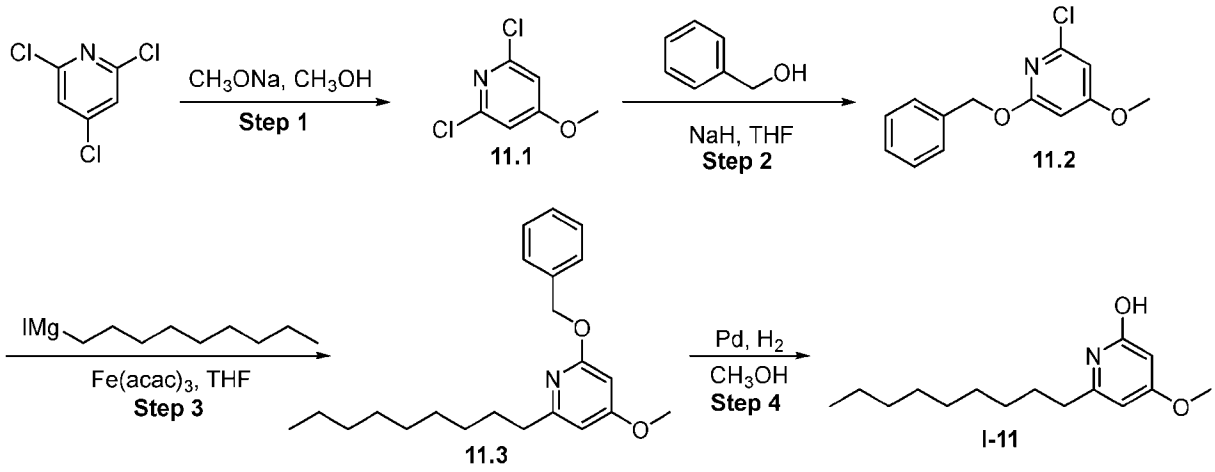
*Step 4. Synthesis of 2-methoxy-6-nonylpyridin-4-ol (**I-10**)*



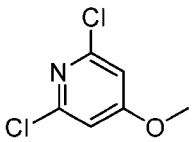
[0283] To a solution of 4-(benzyloxy)-2-methoxy-6-nonylpyridine (40.0 mg, 0.117 mmol, 1.00 equiv) in MeOH (5.0 mL) and EtOAc (5.0 mL) was added Pd/C (10%, 10.0 mg) under a nitrogen atmosphere. The mixture was hydrogenated at room temperature for 1 h under a hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column: XBridge Prep OBD C18, 30*150 mm, 5 μm; mobile phase A: water (10 mmol/L NH_4HCO_3+0.05%$NH_3.H_2O$), mobile phase B: ACN; flow rate: 60 mL/min; gradient: 48% B to 62% B in 10 min; wavelength: 254 nm/220 nm. This resulted in 2-methoxy-6-nonylpyridin-4-ol (**I-10**; 6 mg, 20%) as a grey semi-solid. ^1H NMR (300 MHz, DMSO-d_6): δ 10.27 (s, 1H), 6.25

(s, 1H), 5.91 (s, 1H), 3.76 (s, 3H), 2.52 – 2.45 (m, 2H), 1.60 (t, J = 7.3 Hz, 2H), 1.30 – 1.22 (m, 12H), 0.86 (t, J = 6.5 Hz, 3H); LCMS: calculated: $C_{15}H_{25}NO_2$: 251.19; observed: 252.2 $[M+H]^+$.

EXAMPLE 10. Synthesis of 4-methoxy-6-nonylpyridin-2-ol (I-11)

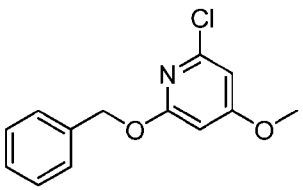


*Step 1. Synthesis of 2,6-dichloro-4-methoxypyridine (**11.1**)*



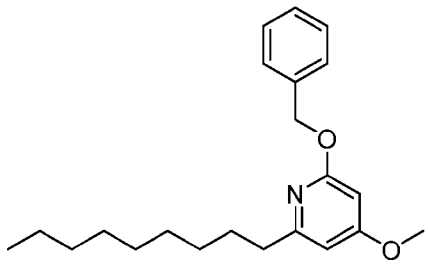
[0284] A solution of 2,4,6-trichloropyridine (310 mg, 1.70 mmol, 1.00 equiv) and sodium methylate solution (91.8 mg, 1.70 mmol, 1.00 equiv, 30%) in methanol (4.0 mL) was stirred for 5 h at 30 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with H_2O (20 mL). The resulting mixture was extracted with EtOAc (3x10 mL). The combined organic layers were washed with a NaCl solution (3x10 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (1:1) to afford 2,6-dichloro-4-methoxypyridine (**11.1**; 153 mg, 40%) as a yellow oil.

*Step 2. Synthesis of 2-(benzyloxy)-6-chloro-4-methoxypyridine (**11.2**)*



[0285] To a stirred solution of benzyl alcohol (146 mg, 1.35 mmol, 1.20 equiv) in THF (2.00 mL) was added NaH (67.4 mg, 1.69 mmol, 1.50 equiv, 60%) in portions at room temperature under an N_2 atmosphere. The resulting mixture was stirred for 30 min at room temperature. To the above mixture was added 2,6-dichloro-4-methoxypyridine (**11.1**; 200 mg, 1.12 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred for an additional 5 h at 60 °C. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of an ammonium chloride aqueous solution (20.0 mL) at room temperature. The resulting mixture was extracted with EA (2x10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with EA:PE (1:15) to afford 2-(benzyloxy)-6-chloro-4-methoxypyridine (**11.2**; 240 mg, 85%) as a light-yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 – 7.43 (m, 2H), 7.42 – 7.31 (m, 3H), 6.76 (d, J = 1.8 Hz, 1H), 6.45 (d, J = 1.9 Hz, 1H), 5.30 (s, 2H), 3.83 (s, 3H).

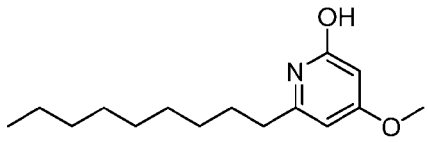
*Step 3. Synthesis of 2-(benzyloxy)-6-chloro-4-methoxypyridine (**11.3**)*



[0286] To a stirred solution of 2-(benzyloxy)-6-chloro-4-methoxypyridine (240 mg, 0.961 mmol, 1.00 equiv) and $Fe(acac)_3$ (67.9 mg, 0.192 mmol, 0.200 equiv) in THF (3.00 mL) was added iodo(nonyl)magnesium (1.44 mL, 1.44 mmol, 1 M, 1.5 equiv) dropwise at room temperature under an N_2 atmosphere. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of an ammonium chloride aqueous solution (10 mL) at room temperature. The resulting mixture was extracted with EA (3x5 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with EA:PE (1:15) to afford 2-(benzyloxy)-4-methoxy-6-nonylpyridine (**11.3**; 240 mg, 73%) as a light-yellow oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.53 – 7.45 (m, 2H), 7.44 – 7.31 (m, 3H),

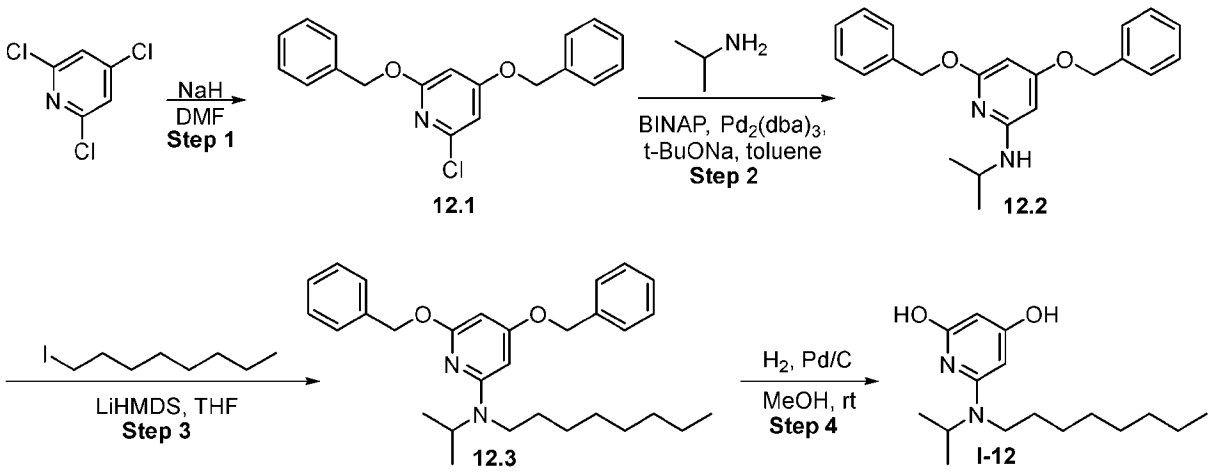
6.34 (d, J = 2.0 Hz, 1H), 6.11 (d, J = 2.0 Hz, 1H), 5.39 (s, 2H), 3.80 (s, 3H), 2.64 (t, J = 7.7 Hz, 2H), 1.80 – 1.63 (m, 2H), 1.43 – 1.15 (m, 12H), 0.98 – 0.81 (m, 3H).

*Step 4. Synthesis of 4-methoxy-6-nonylpyridin-2-ol (**I-11**)*

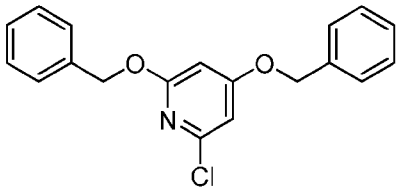


[0287] To a solution of 2-(benzyloxy)-4-methoxy-6-nonylpyridine (**11.3**; 240 mg, 0.703 mmol, 1.00 equiv) in MeOH (5.0 mL) and EtOAc (5.0 mL) was added Pd/C (10%, 20 mg) under a nitrogen atmosphere. The mixture was hydrogenated at room temperature for 1 h under a hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: Column: XBridge Prep OBD C18, 30*150 mm, 5 μm; mobile phase A: water (10mmol/L NH_4HCO_3+0.05%$NH_3.H_2O$), mobile phase B: ACN; flow rate: 60mL/min; gradient: 50% B to 68% B in 10 min; wavelength: 254nm/220nm. This resulted in 4-methoxy-6-nonylpyridin-2-ol (**I-11**; 90 mg, 50%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.02 (s, 1H), 5.67 (d, J = 2.4 Hz, 1H), 5.52 (d, J = 2.4 Hz, 1H), 3.69 (s, 3H), 2.36 (t, J = 7.6 Hz, 2H), 1.54 (q, J = 7.3 Hz, 2H), 1.30 – 1.19 (m, 12H), 0.86 (t, J = 6.5 Hz, 3H). LCMS: calculated: $C_{15}H_{25}NO_2$: 251.19; observed: 252.2 $[M+H]^+$.

EXAMPLE 11. Synthesis of 6-(isopropyl(octyl)amino)pyridine-2,4-diol (I-12)

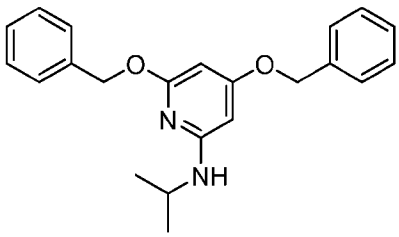


*Step 1. Synthesis of 2,4-bis(benzyloxy)-6-chloropyridine (**12.1**)*



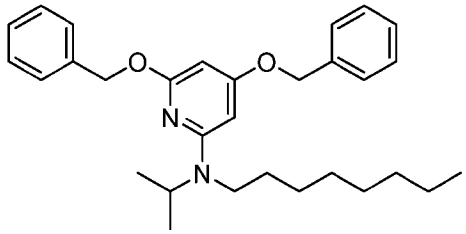
[0288] To a stirred solution of benzyl alcohol (356 mg, 3.28 mmol, 3.00 equiv) in DMF (2.00 mL) was added NaH (79.0 mg, 3.28 mmol, 3.00 equiv, 60% purity) at 0 °C. The mixture was stirred for 30 min. 2,4,6-trichloropyridine (200 mg, 1.10 mmol, 1.00 equiv) was added and the mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by the addition of water (10 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (5:1) to afford 2,4-bis(benzyloxy)-6-chloropyridine (**12.1**; 280 mg, 78%) as a colorless oil.

*Step 2. Synthesis of 4,6-bis(benzyloxy)-N-isopropylpyridin-2-amine (**12.2**)*



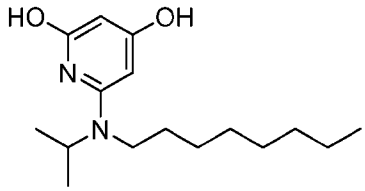
[0289] To a solution of 2,4-bis(benzyloxy)-6-chloropyridine (**12.1**; 210 mg, 0.645 mmol, 1.00 equiv) and isopropylamine (228 mg, 3.87 mmol, 6.00 equiv) in toluene (3 mL) were added t-BuONa (185 mg, 1.94 mmol, 3.00 equiv), BINAP (80.3 mg, 0.129 mmol, 0.200 equiv) and $Pd_2(dba)_3$ (59.0 mg, 0.065 mmol, 0.100 equiv). After stirring for 3 h at 100 °C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with EA:PE (5:95) to afford 4,6-bis(benzyloxy)-N-isopropylpyridin-2-amine (**12.2**; 190 mg, 84%) as a light-yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.47 – 7.23 (m, 10H), 6.15 (d, J = 7.7 Hz, 1H), 5.63 (q, J = 1.9 Hz, 2H), 5.25 (s, 2H), 5.04 (s, 2H), 3.97 – 3.82 (m, 1H), 1.10 (d, J = 6.4 Hz, 6H).

*Step 3. Synthesis of 4,6-bis(benzyloxy)-N-isopropyl-N-octylpyridin-2-amine (**12.3**)*



[0290] To a stirred solution of 4,6-bis(benzyloxy)-N-isopropylpyridin-2-amine (**12.2**; 190 mg, 0.545 mmol, 1.00 equiv) and 1-iodooctane (655 mg, 2.73 mmol, 5.00 equiv) in THF (2 mL) was added LiHMDS (2.73 mL, 2.73 mmol, 5.00 equiv) dropwise at room temperature under an N_2 atmosphere. The resulting mixture was stirred for 3 h at room temperature. The reaction was quenched with an ammonium chloride aqueous solution (10 mL). The resulting mixture was extracted with EA (2x10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with EA:PE (5:95) to afford 4,6-bis(benzyloxy)-N-isopropyl-N-octylpyridin-2-amine (**12.3**; 140 mg, 55%) as a light-yellow oil. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.49 – 7.29 (m, 10H), 5.76 (s, 1H), 5.64 (s, 1H), 5.34 (s, 2H), 5.06 (s, 2H), 3.38 (dt, *J* = 27.5, 6.7 Hz, 1H), 3.24 – 3.07 (m, 2H), 1.68 – 1.49 (m, 2H), 1.42 – 1.23 (m, 12H), 1.17 (d, *J* = 6.7 Hz, 6H), 0.90 (td, *J* = 6.9, 2.8 Hz, 3H).

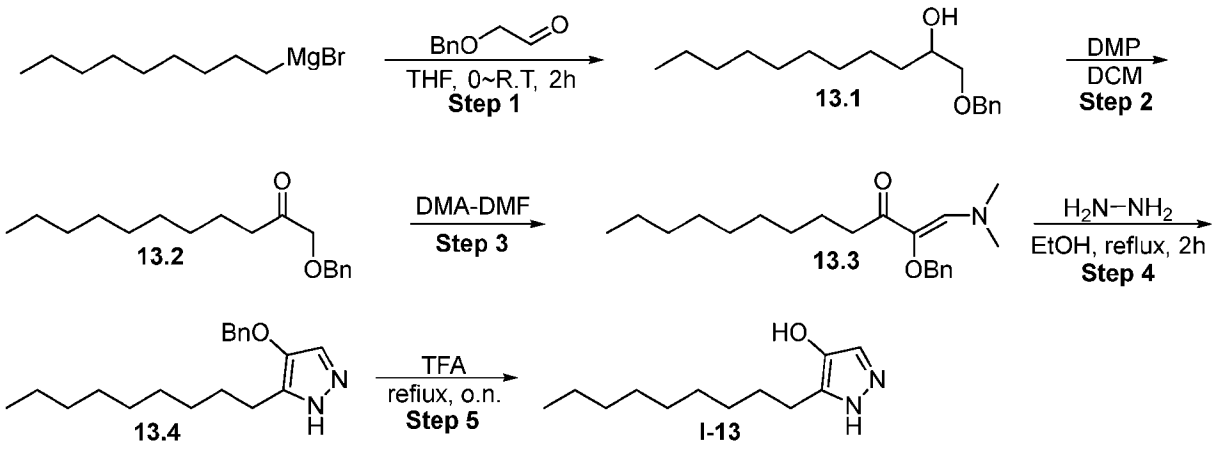
*Step 4. Synthesis of 6-(isopropyl(octyl)amino)pyridine-2,4-diol (**I-12**)*



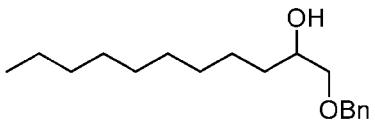
[0291] To a solution of 4,6-bis(benzyloxy)-N-isopropyl-N-octylpyridin-2-amine (**12.3**; 140 mg, 0.304 mmol, 1.00 equiv) in a mixture of MeOH (5 mL) and EA (5 mL) was added Pd/C (10%, 15 mg) under a nitrogen atmosphere. The mixture was hydrogenated at room temperature for 1 h under a hydrogen atmosphere using a hydrogen balloon. The mixture was filtered through a celite pad and concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions: column: XBridge Prep OBD C18, 30*150 mm, 5μm; mobile phase A: water (0.05%$NH_3.H_2O$), mobile phase B: ACN; flow rate: 60 mL/min; gradient: 15% B to 45% B in 10 min; wavelength: 254nm/220nm. This resulted in 6-(isopropyl(octyl) amino)pyridine-2,4-

diol (**I-12**; 6.5 mg, 6.8%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.67 (s, 2H), 5.19 (s, 1H), 5.11 (s, 1H), 4.50 (s, 1H), 3.05 (t, J = 7.9 Hz, 2H), 1.51 – 1.39 (m, 2H), 1.35 – 1.20 (m, 10H), 1.07 (d, J = 6.6 Hz, 6H), 0.87 (t, J = 6.5 Hz, 3H). HPLC purity: 89.4%; LCMS: calculated: $C_{16}H_{28}N_2O_2$: 280.22; observed: 281.20 $[M+H]^+$.

EXAMPLE 12. Synthesis of 3-nonyl-2H-pyrazol-4-ol (I-13)

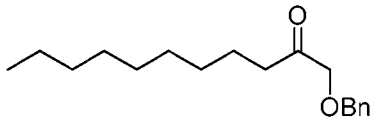


*Step 1. Synthesis of 1-(benzyloxy)undecan-2-ol (**13.1**)*



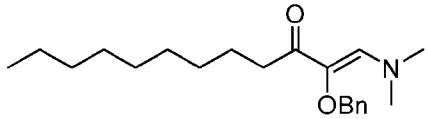
[0292] Into a 40 mL vial were added 2-(benzyloxy)acetaldehyde (1.40 g, 9.32 mmol, 1.00 equiv) and THF (20.0 mL) at room temperature. To the above mixture was added bromo(nonyl) magnesium (9.32 mL, 9.32 mmol, 1.00 equiv) dropwise at room temperature. The resulting mixture was stirred for an additional 2 h at room temperature. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (10.0 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (2x20 mL), and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, and eluted with PE / EA (1:1) to afford 1-(benzyloxy)undecan-2-ol (**13.1**; 2.00 g, 77%) as a white solid. LCMS: calculated: $C_{18}H_{28}O_2$: 278.22; observed: 279.22 $[M+H]^+$.

*Step 2. Synthesis of 1-(benzyloxy)undecan-2-one (**13.2**)*



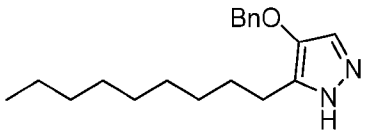
[0293] Into a 40 mL vial were added 1-(benzyloxy)undecan-2-ol (**13.1**; 2.00 g, 7.18 mmol, 1.00 equiv), DCM (20 mL) and Dess-Martin periodinane (4.57 g, 10.8 mmol, 1.50 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature under a nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (1:1) to afford 1-(benzyloxy)undecan-2-one (**13.2**; 1.50 g, 75%) as a white solid. LCMS: calculated: $C_{18}H_{28}O_2$: 276.21; observed: 277.21 $[M+H]^+$.

*Step 3. Synthesis of (1Z)-2-(benzyloxy)-1-(dimethylamino)dodec-1-en-3-one (**13.3**)*



[0294] Into a 40 mL vial were added 1-(benzyloxy)undecan-2-one (**13.3**; 1.40 g, 5.06 mmol, 1.00 equiv), DMF (10.0 mL) and DMF-DMA (0.72 g, 6.08 mmol, 1.20 equiv) at room temperature. The resulting mixture was stirred overnight at 90 °C under a nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (1:1) to afford (1Z)-2-(benzyloxy)-1-(dimethylamino)dodec-1-en-3-one (**13.3**; 0.400 g, 23%) as a white solid. LCMS calculated: $C_{21}H_{33}NO_2$: 331.25; observed: 332.15 $[M+H]^+$.

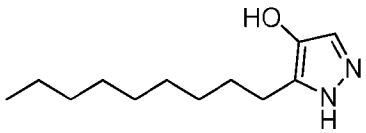
*Step 4. Synthesis of 4-(benzyloxy)-3-nonyl-2H-pyrazole (**13.4**)*



[0295] Into a 8 mL vial were added (1Z)-2-(benzyloxy)-1-(dimethylamino)dodec-1-en-3-one (**13.3**; 150 mg, 0.452 mmol, 1.00 equiv), EtOH (5.00 mL) and hydrazine monohydrochloride (37.2 mg, 0.542 mmol, 1.20 equiv) at room temperature. The resulting mixture was stirred for 2 h at 80 °C under a nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel

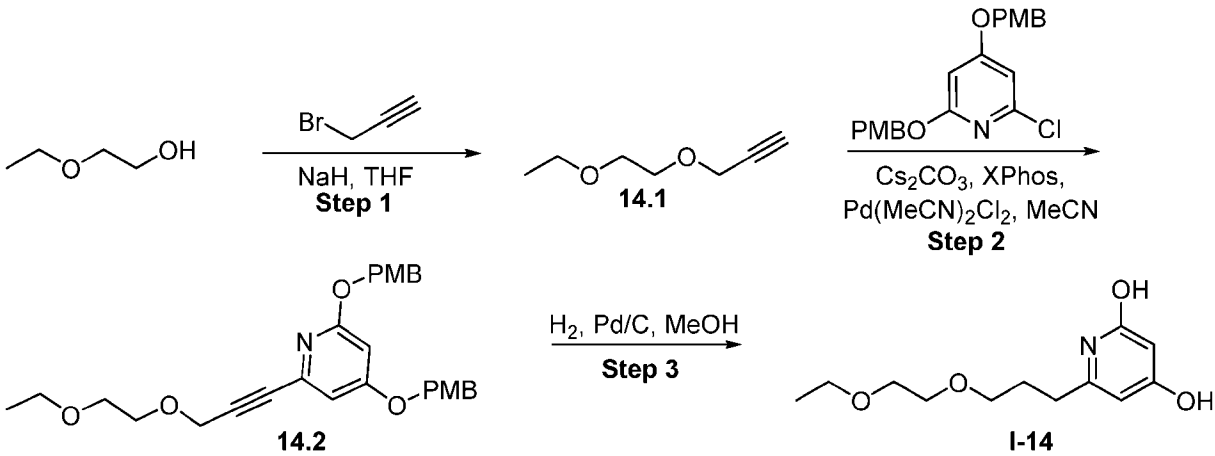
column chromatography and eluted with PE / EA (1:1) to afford 4-(benzyloxy)-3-nonyl-2H-pyrazole (**13.4**; 80.0 mg, 58%) as a grey solid. LCMS: calculated: $C_{19}H_{28}N_2O$: 300.22; observed: 301.22 $[M+H]^+$.

*Step 5. Synthesis of 3-nonyl-2H-pyrazol-4-ol (**I-13**)*

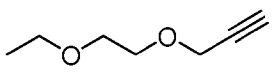


[0296] Into an 8 mL vial were added 4-(benzyloxy)-3-nonyl-2H-pyrazole (80.0 mg, 0.266 mmol, 1.00 equiv) and TFA (2.00 ml) at room temperature. The resulting mixture was stirred overnight at 80 °C. The mixture was allowed to cool down to room temperature. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.1% FA), 10% to 50% gradient in 10 min; detector: UV 254 nm. This resulted in 3-nonyl-2H-pyrazol-4-ol (**I-13**; 20.0 mg, 35%) as a grey solid. ^{1}H NMR (400 MHz, methanol-d_4): δ 7.19 (s, 1H), 2.61 (t, J = 7.6 Hz, 2H), 1.65 (t, J = 7.4 Hz, 2H), 1.38 – 1.29 (m, 12H), 0.95 – 0.88 (m, 3H); HPLC purity: 99.7%; LCMS: calculated: $C_{12}H_{22}N_2O$: 210.17; observed: 211.1 $[M+H]^+$.

EXAMPLE 13. Synthesis of 6-(3-(2-ethoxyethoxy)propyl)pyridine-2,4-diol (I-14)

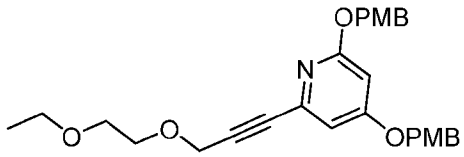


*Step 1. Synthesis of 3-(2-ethoxyethoxy)prop-1-yne (**14.1**)*



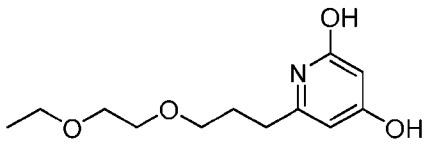
[0297] To a stirred solution of 2-ethoxyethanol (1.00 g, 11.1 mmol, 1.00 equiv) in THF (10.0 mL) was added NaH (0.400 g, 16.6 mmol, 1.50 equiv, 60% purity) in portions at 0 °C. The resulting mixture was stirred for 30 min at room temperature. To the above mixture was added propargyl bromide (1.32 g, 11.0 mmol, 1.00 equiv) dropwise at room temperature. The resulting mixture was stirred for an additional 2 h at room temperature. The reaction was quenched with ice water at 0 °C. The resulting mixture was extracted with EA (3x30 mL). The combined organic layers were washed with brine (100mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (1:1) to afford 1-ethoxy-2-(prop-2-yn-1-yloxy)ethane (**14.1**; 200 mg, 11.2%) as a white oil. LCMS: calculated: $C_7H_{12}O_2$: 128.08; observed: 129.08 $[M+H]^+$.

*Step 2. Synthesis of 2-(3-(2-ethoxyethoxy)prop-1-yn-1-yl)-4,6-bis((4-methoxybenzyl)oxy)pyridine (**14.2**)*



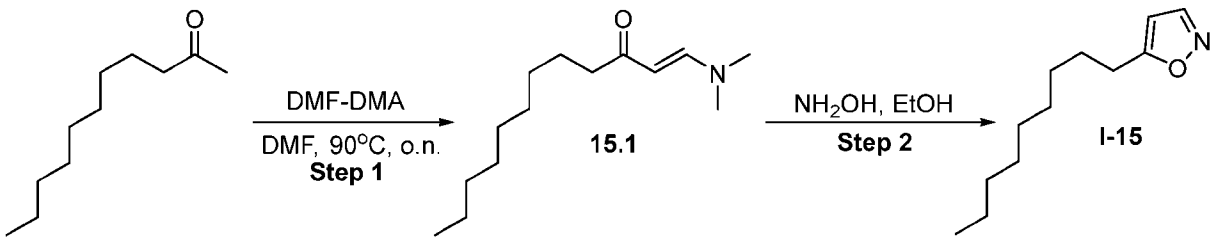
[0298] A solution of Cs_2CO_3 (763 mg, 2.34 mmol, 2.50 equiv), $Pd(CH_3CN)_2Cl_2$ (4.86 mg, 0.019 mmol, 0.0200 equiv), and XPhos (26.7 mg, 0.056 mmol, 0.060 equiv) in CH_3CN (2.00 mL) was treated with 1-ethoxy-2-(prop-2-yn-1-yloxy)ethane (**14.1**; 120 mg, 0.936 mmol, 1.00 equiv) for 15 min at room temperature under a nitrogen atmosphere followed by the addition of 2-chloro-4,6-bis[(4-methoxyphenyl)methoxy]pyridine (361 mg, 0.936 mmol, 1.00 equiv) dropwise at room temperature. The resulting mixture was stirred for an additional 16 h at 90 °C. The mixture was allowed to cool down to room temperature. The reaction was quenched with water at room temperature. The resulting mixture was extracted with EA (3x20 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (1:8) to afford 2-(3-(2-ethoxyethoxy)prop-1-yn-1-yl)-4,6-bis((4-methoxybenzyl)oxy)pyridine (**14.2**; 60.0 mg, 9%) as a yellow solid. LCMS: calculated: $C_{28}H_{31}NO_6$: 477.22; observed: 478.22 $[M+H]^+$.

*Step 3. Synthesis of 6-(3-(2-ethoxyethoxy)propyl)pyridine-2,4-diol (**I-14**)*

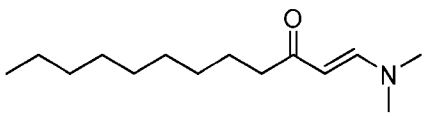


[0299] A solution of 2-(3-(2-ethoxyethoxy)prop-1-yn-1-yl)-4,6-bis((4-methoxybenzyl)oxy) pyridine (60.0 mg, 0.126 mmol, 1.00 equiv) and Pd/C (60.0 mg, 20%) in MeOH (5.00 mL) was stirred for 5 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered and the filter cake was washed with MeOH (3x3 mL). The filtrate was concentrated under reduced pressure. The crude product (50.0 mg) was purified by Prep-HPLC with the following conditions: column, SunFire Prep C18 OBD, 19*150 mm, 5 um; mobile phase, water (10 mmol/L NH_4HCO_3+0.1%$NH_3{\cdot}H_2O$) and ACN (12% ACN up to 24% in 6 min); detector: UV 220 nm) to afford 6-(3-(2-ethoxyethoxy)propyl)pyridine-2,4-diol (**I-14**; 4.00 mg, 12.5%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.84 (s, 1H), 5.59 (d, J = 2.3 Hz, 1H), 5.33 (d, J = 2.2 Hz, 1H), 3.47 (s, 4H), 3.46-3.40 (M, 2H), 3.41-3035 (m, 2H), 2.43 – 2.33 (m, 3H), 1.80-1.71 (m, 2H), 1.10 (d, J = 7.0 Hz, 3H). LCMS: calculated: $C_{12}H_{19}NO_4$: 241.13; observed: 242.13 $[M+H]^+$.

EXAMPLE 14. Synthesis of 5-nonyl-1,2-oxazole (I-15)



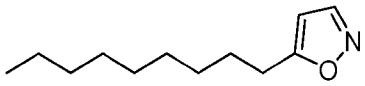
*Step 1. Synthesis of (1E)-1-(dimethylamino)dodec-1-en-3-one (**15.1**)*



[0300] Into a 250mL round-bottom flask were added undecan-2-one (10.0 g, 58.7 mmol, 1.00 equiv), DMF (100 mL) and DMF-DMA (10.5 g, 88.1 mmol, 1.50 equiv) at room temperature. The resulting mixture was stirred overnight at 90°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1)

to afford (1*E*)-1-(dimethylamino)dodec-1-en-3-one (**15.1**; 2.50 g, 18.9%) as a colorless oil. LCMS: calculated: $C_{14}H_{27}NO$: 225.21; observed: 226.21 $[M+H]^+$.

*Step 2. Synthesis of 5-nonyl-1,2-oxazole (**I-15**)*



[0301] Into a 40 mL vial were added (1*E*)-1-(dimethylamino)dodec-1-en-3-one (2.50 g, 11.1 mmol, 1.00 equiv), EtOH (25.0 mL) and hydroxylamine hydrochloride (0.92 g, 13.3 mmol, 1.20 equiv) at room temperature. The resulting mixture was stirred overnight at 80 °C under a nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (5:1) to afford 5-nonyl-1,2-oxazole (**I-15**; 2.0 g, 92%) as a colorless oil. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.16 (d, *J* = 1.7 Hz, 1H), 5.99 (d, *J* = 1.7 Hz, 1H), 2.79 (t, *J* = 7.6 Hz, 2H), 1.73 (q, *J* = 7.5 Hz, 2H), 1.47 – 1.19 (m, 12H), 0.99 – 0.85 (m, 3H); HPLC purity: 98.5%; LCMS: calculated: $C_{12}H_{21}NO$: 195.16; observed: 196.2 $[M+H]^+$.

EXAMPLE 15. cAMP reporter assay

[0302] Exemplary compounds were evaluated for activity in an cAMP assay. Experimental procedures and results are provided below.

Part I - Experimental Procedure

[0303] *Protocol 1:* Intracellular cAMP levels were measured using the DiscoverX HitHunter® Assay at Eurofins DiscoverX Corp. in Fremont, CA. Briefly, CHO-K1 cells stably expressing the human GPR84 cells were incubated with sample in the presence of EC80 forskolin [25 μM] to induce a response. Media was aspirated from cells and replaced with 15 μL 2:1 HBSS/10mM Hepes: cAMP XS+ Ab reagent. Intermediate dilution of sample stocks was performed to generate 4X sample in assay buffer containing 4x EC_{80} forskolin. 5 μL of 4X sample was added to cells and incubated at 37°C for 30 minutes. Final assay vehicle concentration was 1%. After appropriate compound incubation, the assay signal was generated through incubation with 20 μL cAMP XS+ ED/CL lysis cocktail for one hour, followed by incubation with 20 μL cAMP XS+ EA reagent for three hours at room temperature. Microplates were read following signal generation with a PerkinElmer EnvisionTM instrument for chemiluminescent signal

detection. For Gi agonist mode assays, percentage activity is calculated using the following formula % Activity = 100% x (1 - (mean RLU of test sample - mean RLU of MAX control) / (mean RLU of vehicle control - mean RLU of MAX control)).

[0304] *Protocol 2:* Culture Flp-In-293-human GPR84 cells in Dulbecco's Modified Eagle's Medium (DMEM) high glucose containing 10% fetal bovine serum, 2mM GlutaMAX, 1% penicillin-streptomycin and 200μg/ml hygromycin B at 37°C, 5% CO2 incubator. On the day of experiment, perform a 3-fold serial dilution of compounds in DMSO to obtain 10 concentration gradients. Then transfer 20 nL to 384-well assay plate using Echo and seal for use at room temperature. Digest and rinse the cells with TrypLE and PBS respectively, then resuspend the cells in assay buffer (1X HBSS + 20mM HEPES + 0.1%BSA + 500μM IBMX). Subsequently, seed 2,000 cells in 15μl per well into the 384-well assay plate, incubate at 37°C for 10 min. Meanwhile, prepare 8μM 4x forskolin working solution in assay buffer. Add 5μl 4x forskolin working solution to each well of the 384-well plate, incubate at 37°C for additional 30 min. After reaction, add 10 μl Eu-cAMP tracer and 10 μl Ulight-anti-cAMP detection reagent working solution to each well of the 384-well plate, incubate at 25°C for 1 h. Finally, collect data using Envision 2105 microplate reader with HTRF module.

Part II - Results

[0305] Table 3 shows the activity observed for exemplary compounds in the cAMP assays using either Protocol 1 or Protocol 2 from above. Compounds having an activity designated as "A" provided an EC_{50} of ≤ 0.05 μM; compounds having an activity designated as "B" provided an EC_{50} of 0.0501-0.5 μM; compounds having an activity designated as "C" provided an EC_{50} of 0.501-5.00 μM; and compounds having an activity designated as "D" provided an EC_{50} of ≥ 5.01 μM.

Table 3.

Compound No.	EC_{50}
I-1	D
I-2	D
I-3	C
I-4	A
I-5	B
I-6	C
I-7	C

I-8	A
I-9	B
I-10	C
I-11	B
I-12	D
I-13	D
I-14	B
I-15	D

EXAMPLE 16. GPR84 Agonist Enhancement of TTI-622-Induced ADCP of A375 Melanoma Cells

[0306] This Example describes coculture assays using J774A.1 mouse macrophages and A375 melanoma cells to measure antibody-dependent cellular phagocytosis (ADCP) induced by TTI-622. Experimental procedures and results are provided below.

Part I – Experimental Procedure

[0307] The day prior to the coculture assay, J774A.1 mouse macrophages (ATCC TIB-67) cultured in complete HI-DMEM media (containing 10% heat-inactivated (HI) FBS, GlutaMAX, 100 units/ml penicillin, 100 µg/ml streptomycin) were plated in assay plates at 10,000 cells/well in 40µl HI-DMEM + 100ng/ml LPS media. The next day, A375 melanoma cells (ATCC CRL-1619) cultured in complete RPMI media (containing 10% HI FBS, GlutaMAX, 100 units/ml penicillin, 100 µg/ml streptomycin) were harvested, counted, and stained with pHrodo-Red-SE dye for 20 minutes. After labeling, the tumor cells were washed and resuspended in 1 ml PBS per 10^6 cells in 0.4% DMSO. Tumor cells were then opsonized with 5 µg/ml TTI-622 fusion protein (human SIRPα CD47-binding domain fused to IgG4 Fc, produced in-house) without and with **I-4** at 50 nM, 16.5 nM, 5.5 nM, 1.85 nM, 0.6 nM, or 0.2 nM or with 5 µg/ml human IgG4 isotype control (IchorBio #ICH2257) alone in each experiment, for 30 minutes at 37°C. These samples were then placed in coculture with the J774A.1 mouse macrophages at a 1:1 E:T ratio, resulting in final coculture concentrations of 1 µg/ml TTI-622 fusion protein or hIgG4 control; 10 nM, 3.3 nM, 1.1 nM, 0.37 nM, 0.12 nM, or 0.04 nM **I-4**; and 0.08% DMSO. The coculture assay was imaged over multiple timepoints using an Incucyte S3 imager. Data from the 6-hour timepoint were processed.

Part II – Results

[0308] Experimental results are shown in **FIG. 1A** and **FIG. 1B**. Selected data from **FIG. 1A** (hIgG4 control, TTI-622 fusion protein alone, and the highest-activity condition, TTI-622 fusion protein with 1.1 nM **I-4**) are shown in **FIG. 1B**, with statistical significance indicated (using unpaired t-test, $p < 0.01$ (**)).

[0309] Results of this experiment show that GPR84 agonism by **I-4** significantly enhances the ADCP-inducing effect of TTI-622 in A375 melanoma cells.

EXAMPLE 17. GPR84 Agonist Enhancement of TTI-622-Induced ADCP of HCT116 Colon Adenocarcinoma Tumor Cells

[0310] Coculture assays were conducted as described in Example 16, except that HCT116 colon adenocarcinoma tumor cells (ATCC CCL-247) were used instead of A375 melanoma cells. Data from the 6-hour timepoint were processed and represented in **FIG. 2A**. Selected data from **FIG. 2A** (hIgG4 control, TTI-622 fusion protein alone, and the highest-activity condition, TTI-622 fusion protein with 0.37 nM **I-4**) are shown in **FIG. 2B**, with statistical significance indicated (using unpaired t-test, $p < 0.05$ (*)).

[0311] Results of this experiment show that GPR84 agonism by **I-4** significantly enhances the ADCP-inducing effect of TTI-622 in HCT116 colon adenocarcinoma tumor cells.

EXAMPLE 18. GPR84 Agonist Enhancement of Magrolimab-Induced ADCP of A375 Melanoma Cells

[0312] Coculture assays were conducted as described in Example 16, except that human anti-CD47 magrolimab (IchorBio, ICH5036) at a final coculture concentration of 0.2 μg/ml was used instead of TTI-622. Data from the 6-hour timepoint were processed and represented in **FIG. 3A**. Selected data from **FIG. 3A** (hIgG4 control, magrolimab alone, and the highest-activity condition, magrolimab with 1.1 nM **I-4**) are shown in **FIG. 3B**, with statistical significance indicated (using unpaired t-test, $p < 0.001$ (***)).

[0313] Results of this experiment show that GPR84 agonism by **I-4** significantly enhances the ADCP-inducing effect of magrolimab in A375 melanoma cells.

EXAMPLE 19. GPR84 Agonist Enhancement of Cetuximab-Induced ADCP of HCT116 Colon Adenocarcinoma Tumor Cells

[0314] Coculture assays were conducted as described in Example 17, except that human anti-EGFR cetuximab (SelleckChem, A2000) at a final coculture concentration of 1 μg/ml was used instead of TTI-622, and human IgG1 isotype control (BioXCell, BE0297) was used instead of human IgG4 isotype control. Data from the 6-hour timepoint were processed and represented in **FIG. 4A**. Selected data from **FIG. 4A** (hIgG4 control, cetuximab alone, and the highest-activity condition, cetuximab with 0.37 nM **I-4**) are shown in **FIG. 4B**, with statistical significance indicated (using unpaired t-test, $p < 0.01$ (**)).

[0315] Results of this experiment show that GPR84 agonism by **I-4** significantly enhances the ADCP-inducing effect of cetuximab in HCT116 colon adenocarcinoma tumor cells.

EXAMPLE 20. GPR84 Agonist Enhancement of Rituximab-Induced ADCP of Ramos Lymphoma Cells

[0316] Coculture assays were conducted as described in Example 19, except that human anti-CD20 rituximab (BioXCell, SIM0008) at a final coculture concentration of 0.1 μg/ml was used instead of cetuximab; Ramos cells (ATCC CRL-1596) were used instead of HCT116 colon adenocarcinoma tumor cells; and coculture was performed at a 1:2 E:T ratio. Data from the 6-hour timepoint were processed and represented in **FIG. 5A**. Selected data from **FIG. 5A** (hIgG4 control, rituximab alone, and the highest-activity condition, rituximab with 1.1 nM **I-4**) are shown in **FIG. 5B**, with statistical significance indicated (using unpaired t-test, $p < 0.001$ (***)).

[0317] Results of this experiment show that GPR84 agonism by **I-4** significantly enhances the ADCP-inducing effect of rituximab in Ramos cells.

EXAMPLE 21. GPR84 Agonist Enhancement of Daratumumab-Induced ADCP of MM.1S Multiple Myeloma Cells

[0318] Coculture assays were conducted as described in Example 19, except that human anti-CD38 daratumumab (SelleckChem #A2027) at a final coculture concentration of 1 μg/ml was used instead of cetuximab; MM.1S multiple myeloma cells (Pharmaron Cell Bank) were used instead of A375 melanoma cells; and two additional concentrations of **I-4** were tested (0.013 nM and 0.004 nM final coculture concentrations). Data from the 6-hour timepoint were processed and represented in **FIG. 6A**. Selected data from **FIG. 6A** (hIgG4 control, daratumumab alone, and the

highest-activity condition, daratumumab with 1.1 nM **I-4**) are shown in **FIG. 6B**, with statistical significance indicated (using unpaired t-test, $p < 0.01$ (**)).

[0319] Results of this experiment show that GPR84 agonism by **I-4** significantly enhances the ADCP-inducing effect of daratumumab in MM.1S cells.

EXAMPLE 22. GPR84 Agonist Enhancement of ADCP of Ramos Lymphoma Cells Induced by Various Agents

[0320] Coculture assays were conducted as described in Example 20, except that human anti-CD47 magrolimab (IchorBio, ICH5036) was used at a final coculture concentration of 0.2 μg/ml, and TTI-622 was used at a final coculture concentration of 1 ug/ml as additional treatment conditions. In addition, **I-4** was assayed in the absence of opsonizing agent. Data from the 6-hour timepoint, using concentrations of 0.37 nM for each **I-4** condition shown, were processed and represented in **FIG. 7**, with statistical significance indicated (using unpaired t-test, $p < 0.05$ (*), $p < 0.01$ (**)).

[0321] Results of this experiment show that GPR84 agonism by **I-4** alone does not enhance ADCP, but that GPR84 agonism by **I-4** in the presence of various opsonizing agents significantly enhances ADCP.

EXAMPLE 23. GPR84 Agonist Enhancement of ADCP of Various Cancer Cells Induced by Various Agents (Mouse Macrophage System)

[0322] The GPR84 agonist enhancement of ADCP of various cancer cells induced by an agent may be evaluated using an assay based on that described in Example 16, except that the ADCP-inducing agent, the cancer cell line, the IgG isotype control, and the coculture E:T ratio may be, for example, as set forth in Table 4, and the final coculture concentration of the ADCP-inducing agent may be, for example, 0.1, 1, or 10 μg/ml..

TABLE 4.

ADCP-Inducing Agent (Target)	**Cancer Cell Line(s)**	**IgG Isotype Control**	**Coculture E:T Ratio**
Rituximab (CD20)	Ramos lymphoma cells	IgG_1	1:2
Ofatumumab (CD20)	Ramos lymphoma cells	IgG_1	1:2
Obinutuzumab (CD20)	Ramos lymphoma cells	IgG_1	1:2
Ibritumomab tiuxetan (CD20)	Ramos lymphoma cells	IgG_1	1:2

ADCP-Inducing Agent (Target)	Cancer Cell Line(s)	IgG Isotype Control	Coculture E:T Ratio
Tafasitamab-cxix (CD19)	Daudi lymphoma cells	IgG_1	1:2
Alemtuzumab (CD52)	Kasumi-3 AML cells	IgG_1	1:2
Mogamulizumab-kpkc (CCR4)	HH t-cell lymphoma cells	afucosylated IgG_1	1:2
Daratumumab (CD38)	MM.1S multiple myeloma cells	IgG_1 (plus hyaluronidase)	1:2
Isatuximab-irfc (CD38)	MM.1S multiple myeloma cells	IgG_1	1:2
Elotuzumab (SLAMF7)	U266 multiple myeloma cells, MM.1S multiple myeloma cells	IgG_1	1:2
Cetuximab (EGFR)	HCT116 colon adenocarcinoma tumor cells	IgG_1	1:1
Panitumumab (EGFR)	HCT116 colon adenocarcinoma tumor cells	IgG_4	1:1
Necitumumab (EGFR)	HCT116 colon adenocarcinoma tumor cells	IgG_1	1:1
Amivantamab-vmjw (EGFR Ex20 and MET)	HCC827 or H1975 lung cancer cells	IgG_1	1:1
Trastuzumab (HER2)	SKBR-3 breast cancer cells	IgG_1	1:1
Pertuzumab (HER2)	SKBR-3 breast cancer cells	IgG_1	1:1
Margetuximab-cmkb (HER2)	SKBR-3 breast cancer cells	$IgG_{1\text{-kappa}}$	1:1
Zolbetuximab (CLDN18.2)	KATO-III human gastric carcinoma cells, NUGC-4 signet ring cell carcinoma cells	IgG_1	1:1
Ramucirumab(VEGFR2)	Ba/F3-VEGFR2 cells	IgG_1	1:1
Bemarituzumab (FGFR2)	Ba/F3-FGFR2 cells	IgG_1	1:1
Olaratumab (PDGFRα)	Ba/F3-PDGFRα cells	IgG_1	1:1
Cosibelimab (PD-L1)	RKO colon carcinoma cells	IgG_1	1:1
Avelumab (PD-L1)	RKO colon carcinoma cells	IgG_1	1:1
Magrolimab (CD47)	A375 melanoma cells, HCT116 colon adenocarcinoma cells, Ramos cells	IgG_4	1:1
B6H12 (CD47)	A375 melanoma cells, HCT116 colon adenocarcinoma cells, Ramos cells	IgG_1	1:1

ADCP-Inducing Agent (Target)	Cancer Cell Line(s)	IgG Isotype Control	Coculture E:T Ratio
TTI-622 (CD47)	A375 melanoma cells, HCT116 colon adenocarcinoma cells, Ramos cells, U266 multiple myeloma cells, SKBR-3 breast cancer cells, RKO colon carcinoma cells, DU4475 breast cancer cells, MDA-MB-231 breast cancer cells, MDA-MB-468 breast cancer cells, BT474 breast cancer cells, MCF7 breast cancer cells, T47D breast cancer cells	IgG_4	1:1
Bevacizumab (VEGF)	N/A	IgG_1	N/A
Denosumab (RANKL)	N/A	IgG_4	N/A
Dinutiximab (GD2)	IMR-32 neuroblastoma cells	IgG_1	1:1
Naxitamab-gqgk (GD2)	IMR-32 neuroblastoma cells	IgG_1	1:1

[0323] Exemplary agents that may be evaluated for GPR84 agonist enhancement of ADCP of various cancer cells include any of compounds **I-1** through **I-25**, a medium chain fatty acid capric acid, ZQ-16; (octylamino) pyrimidine-2,4(lH,3H)-dione (6-n-octylaminouracil) (6-OAU); DL-175; a diindolemethane derivative; a 2-alkylpyrimidine-4,6-diol; a 6-alkylpyridine-2,4-diol; embelin; or another GPR84 agonist , *e.g.*, another GPR84 agonist recited herein. Each row of Table 3 corresponds to a separate set of coculture experiments.

EXAMPLE 24. GPR84 Agonist Enhancement of ADCP of Various Cancer Cells Induced by Various Agents (Human Macrophage System)

[0324] The GPR84 agonist enhancement of ADCP of various cancer cells induced by an agent may be evaluated using an assay based on that described in Example 16, except that human monocyte-derived macrophages may be used in place of J774A mouse macrophages. To differentiate monocyte derived macrophages, CD14+ monocyctes from human donor samples may be cultured in complete HI-RPMI media (containing 10% heat-inactivated (HI) FBS, GlutaMAX, 100 units/ml penicillin, 100 µg/ml streptomycin) supplemented with 40ng/ml M-CSF for a period of 7 days. Data from the 4-hour timepoints may be processed and analyzed.

EXAMPLE 25. GPR84 Agonist Enhancement of Tumor Cell Depletion by ADCP induced by Various Agents (Human or Mouse Macrophage Coculture System)

[0325] The GPR84 agonist enhancement of ADCP of various cancer cells induced by an agent may be evaluated using an assay based on that described in Example 16, except that macrophages may be plated at 30,000 cells/well in complete growth media the day prior to the coculture assay. Human macrophages may be derived as described in Example 24, and mouse macrophages may be treated as described in Example 16. Tumor cell lines chosen from Table 3 may be additionally stained with CFSE (ThermoFisher #C34554, final concentration of 1uM) for 20 minutes at the time of labeling with pHrodo-Red-SE. After 24 hours of coculture, the contents of each well may be harvested and counterstained with anti-CD11b-APC antibody (BioLegend, clone #IRF44 for human macrophages and clone #M1/70 for mouse macrophages). Samples may then be analyzed using a flow cytometer to quantify the number of CFSE-positive, CD11b-negative cells that are remaining in the population.

EXAMPLE 26. GPR84 Agonist Enhancement of ADCP of Various Cancer Cells Induced by Various Agents readout by Flow Cytometry (Human or Mouse Macrophage Coculture System)

The GPR84 agonist enhancement of ADCP of various cancer cells induced by an agent may be evaluated using an assay based on that described in Example 25. At the end of the assay, phagocytosis may be quantified as the %pHrodo-Red-SE positive of the CD11b-positive population.

INCORPORATION BY REFERENCE

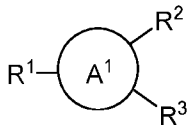
[0326] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[0327] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

Claims:

1. A compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 is C_{2-12} alkoxyl, -[-O-(C_{1-2} alkylene)]$_n$-H, -(C_{1-6} alkylene)-[-O-(C_{1-2} alkylene)]$_n$-H, -C_{4-12} alkyl, -C(O)-(C_{4-12} alkyl), -(C_{1-10} alkylene)-R^6, -O-(C_{1-10} alkylene)-R^6, -N(R^4)([(C_{1-2} alkylene)-O-]$_n$-(C_{1-6} alkyl)), or -N(R^4)(R^5);

R^2 is hydroxyl, C_{1-4} alkoxyl, or hydrogen;

R^3 is hydroxyl, C_{1-4} haloalkyl, or hydrogen;

R^4 is C_{1-6} alkyl;

R^5 is C_{4-12} alkyl;

R^6 is a 5-6 membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the heteroaryl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-6} alkyl and halo;

A^1 is (i) a 6-membered heteroarylene containing 1 or 2 heteroatoms selected from nitrogen or (ii) a 5-membered heteroarylene containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

n is 1, 2, 3, 4, 5 or 6;

provided that R^1 is not C_{4-12} alkyl when A^1(R^2)(R^3) taken together are a dihydroxy-pyrimidinyl or a dihydroxy-pyridinyl.

2. The compound of claim 1, wherein the compound is a compound of Formula I.

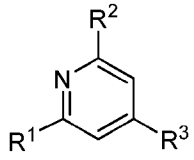
3. The compound of claim 1 or 2, wherein A^1 is a 6-membered heteroarylene containing 1 or 2 heteroatoms selected from nitrogen.

4. The compound of claim 1 or 2, wherein A^1 is pyridinylene.

5. The compound of claim 1 or 2, wherein A^1 is a 5-membered heteroarylene containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

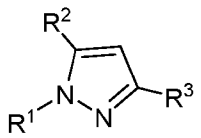
6. The compound of claim 1 or 2, wherein A^1 is pyrazolylene, oxazolylene, or 1,2,4-triazolylene.

7. The compound of claim 1, wherein the compound is represented by Formula **Ia** or a pharmaceutically acceptable salt thereof:

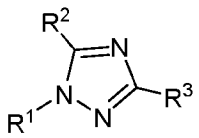


Ia.

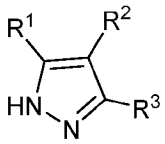
8. The compound of claim 1, wherein the compound is represented by Formula **Ib**, **Ic**, or **Id**, or a pharmaceutically acceptable salt thereof:



Ib



Ic



Id.

9. The compound of any one of claims 1-8, wherein R^1 is C_{2-12} alkoxyl.

10. The compound of any one of claims 1-8, wherein R^1 is C_{6-10} alkoxyl.

11. The compound of any one of claims 1-8, wherein R^1 is C_8 alkoxyl.

12. The compound of any one of claims 1-8, wherein R^1 is -[-O-(C_{1-2} alkylene)]$_n$-H or -(C_{1-6} alkylene)-[-O-(C_{1-2} alkylene)]$_n$-H.

13. The compound of any one of claims 1-8, wherein R^1 is -C_{4-12} alkyl.

14. The compound of any one of claims 1-8, wherein R^1 is -C_{7-10} alkyl.

15. The compound of any one of claims 1-8, wherein R^1 is -(C_{1-10} alkylene)-R^6.

16. The compound of any one of claims 1-8, wherein R^1 is -(C_{4-6} alkylene)-R^6.

17. The compound of any one of claims 1-8, wherein R^1 is -C(O)-(C_{4-12} alkyl) or -O-(C_{1-10} alkylene)-R^6.

18. The compound of any one of claims 1-8, wherein R^1 is -N(R^4)([(C_{1-2} alkylene)-O-]$_n$-(C_{1-6} alkyl)) or -N(R^4)(R^5).

19. The compound of any one of claims 1-18, wherein R^2 is hydroxyl.

20. The compound of any one of claims 1-18, wherein R^2 is C_{1-4} alkoxyl.

21. The compound of any one of claims 1-18, wherein R^2 is hydrogen.

22. The compound of any one of claims 1-21, wherein R^3 is hydroxyl.

23. The compound of any one of claims 1-21, wherein R^3 is C_{1-4} haloalkyl.

24. The compound of any one of claims 1-21, wherein R^3 is hydrogen.

25. The compound of any one of claims 1-8 or 18, wherein R^4 is C_{1-2} alkyl.

26. The compound of any one of claims 1-8 or 18, wherein R^5 is C_{6-10} alkyl.

27. The compound of any one of claims 1-8 or 15-17, wherein R^6 is pyridinyl, pyrazolyl, or oxazolyl, each of which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_{1-6} alkyl and halo.

28. The compound of any one of claims 1-8, 12 or 18, wherein n is 2, 3, or 4.

29. A compound in Table 1, or a pharmaceutically acceptable salt thereof.

30. A pharmaceutical composition comprising a compound of any one of claims 1-29 and a pharmaceutically acceptable carrier.

31. A method for treating a disease or condition responsive to GPR84 agonism, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-29 to treat the disease or condition.

32. The method of claim 31, where the disease or condition responsive to GPR84 agonism is an infectious disease or condition, a neurological or neurodegenerative disease or condition, or cancer.

33. A method for treating cancer, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-29 to treat the cancer.

34. The method of claim 33, wherein the cancer is a solid tumor.

35. The method of claim 32, wherein the cancer is ovarian cancer, uterine cancer, endometrial cancer, cervical cancer, prostate cancer, testicular cancer, breast cancer, brain cancer, lung cancer, oral cancer, esophageal cancer, head and neck cancer, stomach cancer, colon cancer,

rectal cancer, skin cancer, sebaceous gland carcinoma, bile duct and gallbladder cancers, liver cancer, pancreatic cancer, bladder cancer, urinary tract cancer, kidney cancer, eye cancer, thyroid cancer, lymphoma, or leukemia.

36. The method of any one of claims 32-35, wherein the subject is a human.

37. A method of agonizing the activity of GPR84, comprising contacting a GPR84 with an effective amount of a compound of any one of claims 1-29 to agonize the activity of said GPR84.

38. A method for treating a disease or condition responsive to GPR84 agonism, comprising administering to a subject in need thereof a therapeutically effective amount of (i) a GPR84 agonist and (ii) an additional therapeutic agent that binds to a target selected from CCR4, CD19, CD20, CD22, CD30, CD33, CD38, CD47, CD52, CD79b, Claudin 18.2, CTLA-4, EGFR, FGFR2, GD2, HER2, LAG3, MET, Nectin-4, PDGFRa, PD-L1, RANKL, SLAMF7, TF, TROP2, VEGF, VEGFR, VEGFR2, or epidermal growth factor receptor with exon 20 insertion mutations, to treat the disease or condition.

39. The method of claim 38, wherein the additional therapeutic agent is an inhibitor.

40. The method of claim 38, wherein the additional therapeutic agent is an agonist.

41. The method of claim 38, wherein the target is CCR4, CD19, CD20, CD22, CD30, CD33, CD38, CD47, CD52, or CD79b.

42. The method of claim 38, wherein the target is Claudin 18.2 or CTLA-4.

43. The method of claim 38, wherein the target is EGFR, FGFR2, or epidermal growth factor receptor with exon 20 insertion mutations.

44. The method of claim 38, wherein the target is GD2, HER2, LAG3, MET, Nectin-4, PDGFRa, or PD-L1.

45. The method of claim 38, wherein the target is RANKL, SLAMF7, TF, or TROP2.

46. The method of claim 38, wherein the target is VEGF or VEGFR.

47. The method of any one of claims 38-46, wherein the additional therapeutic agent is an antibody.

48. The method of any one of claims 38-46, wherein the additional therapeutic agent is Alemtuzumab, Amivantamab-vmjw, Avelumab, Bemarituzumab, Bevacizumab, Cetuximab, Cosibelimab, Daratumumab, Denosumab, Dinutiximab, Elotuzumab, Ibritumomab tiuxetan, Isatuximab-irfc, Magrolizumab, Margetuximab-cmkb, Mogamulizumab-kpkc, Naxitamab-gqgk, Necitumumab, Obinutuzumab, Ofatumumab, Olaratumab, Panitumumab, Pertuzumab, Ramucirumab, Rituximab, Tafasitamab-cxix, Trastuzumab, TTI-622, a SIRPαFc fusion protein, or Zolbetuximab.

49. The method of any one of claims 38-46, wherein the additional therapeutic agent is an antibody-drug-conjugate.

50. The method of any one of claims 38-46, wherein the additional therapeutic agent is Brentuximab vedotin, Enfortumab vedotin, Gemtuzumab ozogamicin, Ibritumomab tiuxetan, Inotuzumab ozogamicin, Loncastuximab tesirine, Moxetumomab pasudotox, Polatuzumab vedotin, Sacituzumab govitecan, Tisotumab vedotin, Trastuzumab deruxtecan, or Trastuzumab emtansine.

51. A method for treating a disease or condition responsive to GPR84 agonism, comprising administering to a subject in need thereof a therapeutically effective amount of (i) a GPR84 agonist and (ii) CAR-T therapy, to treat the disease or condition.

52. The method of claim 51, wherein the CAR-T therapy is idecabtagene vicleucel or lisocabtagene maraleucel.

53. The method of any one of claims 38-52, wherein the disease or condition is cancer.

54. The method of claim 53, wherein the cancer is a solid tumor.

55. The method of claim 53, wherein the cancer is ovarian cancer, uterine cancer, endometrial cancer, cervical cancer, prostate cancer, testicular cancer, breast cancer, brain cancer, lung cancer, oral cancer, esophageal cancer, head and neck cancer, stomach cancer, colon cancer, rectal cancer, skin cancer, sebaceous gland carcinoma, bile duct and gallbladder cancers, liver cancer, pancreatic cancer, bladder cancer, urinary tract cancer, kidney cancer, eye cancer, thyroid cancer, or a neuroendocrine cancer.

56. The method of claim 53, wherein the cancer is a B-cell non-Hodgkin's Lymphoma, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL),

mature B-cell acute leukemia (B-AL), chronic lymphocytic leukemia (CLL), follicular lymphoma, multiple mycloma, head and neck cancer, colorectal cancer, a squamous cell carcinoma, HER2 overexpressing breast cancer, gastric junction adenocarcinoma, gastro-esophageal junction adenocarcinoma, non-small cell lung cancer, hepatocellular carcinoma, gastric cancer, urothelial cancer, renal cancer, giant cell bone cancer, bone metastasis, neuroblastoma, mycosis fungoides, or Sézary syndrome.

57. The method of claim 53, wherein the cancer is a hematological cancer.

58. The method of claim 57, wherein the cancer is lymphoma, leukemia, or myeloma.

59. The method of any one of claims 38-52, wherein the disease or condition is an autoimmune and/or inflammatory disorder.

60. The method of claim 59, wherein the disease or condition is rheumatoid arthritis.

61. The method of claim 38, wherein the method is further characterized by:

a) the additional therapeutic agent is Rituximab, and the disease or condition is:

- B-Cell Non-Hodgkin Lymphoma;
- Relapsed or refractory, low grade or follicular, B-Cell Non-Hodgkin Lymphoma (B-NHL) as a single agent;
- First line (1L) B-NHL in patients achieving a complete response or partial response as single-agent maintenance therapy, and wherein the Rituximab is administered in combination with a first line chemotherapy;
- Diffuse large B-cell lymphoma;
- Non-progressing (including stable disease), low-grade, B-NHL as a single agent after 1L cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy;
- 1L DLBCL, where the the Rituximab is administered in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimen;
- 1L advanced stage, CD20-positive, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL) or mature B-cell acute leukemia (B-AL), wherein the Rituximab is administered in combination with chemotherapy;
- Chronic Lymphocytic Leukemia;

- Chronic Lymphocytic Leukemia; or
- Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC);

b) the additional therapeutic agent is Ofatumumab, and the disease or condition is:

- Chronic lymphocytic leukemia; or
- Chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab;

c) the additional therapeutic agent is Obinutuzumab, and the disease or condition is:

- Chronic lymphocytic leukemia;
- previously untreated CLL (sp. if del(17p)/TP53 mutation), wherein the Obinutuzumab is administered in combination with chlorambucil;
- Follicular lymphoma;
- follicular lymphoma, wherein the Obinutuzumab is administered in combination with bendamustine followed by GAZYVA monotherapy, for the treatment of patients who relapsed after, or are refractory to, a rituximab-containing regimen; or
- previously untreated stage II bulky, III or IV follicular lymphoma, wherein the Obinutuzumab is administered in combination with chemotherapy followed by GAZYVA monotherapy in patients achieving at least a partial remission;

d) the additional therapeutic agent is Ibritumomab tiuxetan, and the disease or condition is:

- Follicular lymphoma; or
- Relapsed or refractory follicular lymphoma;

e) the additional therapeutic agent is Tafasitamab-cxix, and the disease or condition is:

- Diffuse large B-cell lymphoma; or
- Relapsed or refractory DLBCL, wherein the Tafasitamab-cxix is administered in combination with lenalidomide;

f) the additional therapeutic agent is Alemtuzumab, and the disease or condition is Chronic lymphocytic leukemia;

g) the additional therapeutic agent is Mogamulizumab-kpkc, and the disease or condition is:

- Mycosis fungoides;
- Sézary syndrome; or
- Relapsed or refractory mycosis fungoides or Sézary syndrome;

h) the additional therapeutic agent is Daratumumab, and the disease or condition is:

- Multiple myeloma;
- Multiple myeloma (MM), wherein the Daratumumab is administered in combination with bortezomib, melphalan and prednisone (VMP) in newly diagnosed patients who are ineligible for ASCT;
- Multiple myeloma, wherein the Daratumumab is administered in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for ASCT and in patients with RR-MM (second line (2L));
- Multiple myeloma, wherein the Daratumumab is administered in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for ASCT;
- Multiple myeloma, wherein the Daratumumab is administered in combination with bortezomib and dexamethasone in a patient who has received at least one prior therapy;
- Multiple myeloma, wherein the Daratumumab is administered in combination with pomalidomide and dexamethasone in a patient who has received at least one prior line of therapy including lenalidomide and a proteasome inhibitor;
- Multiple myeloma, wherein the Daratumumab is administered in combination with carfilzomib and dexamethasone in a patient with RR-MM who has received one to three prior lines of therapy;
- Multiple myeloma, wherein the patient has received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who is double-refractory to a PI and an immunomodulatory agent;
- Light chain amyloidosis; or
- Light chain amyloidosis, wherein the Daratumumab is administered in combination with bortezomib, cyclophosphamide and dexamethasone in a patient newly diagnosed with Light chain amyloidosis;

i) the additional therapeutic agent is Isatuximab-irfc, and the disease or condition is:

- Multiple myeloma;
- Multiple myeloma for the treatment of adult patients, wherein the Isatuximab-irfc is administered in combination with pomalidomide and dexamethasone, wherein patient has received at least 2 prior therapies including lenalidomide and a proteasome inhibitor; or
- RR-Multiple myeloma in an adult patient who has received 1 to 3 prior lines of therapy, wherein the Isatuximab-irfc is administered in combination with carfilzomib and dexamethasone;

j) the additional therapeutic agent is Elotuzumab, and the disease or condition is:

- Multiple myeloma;
- RR-Multiple myeloma is an adult patient who has received one to three prior therapies, wherein the Elotuzumab is administered in combination with lenalidomide and dexamethasone; or
- RR-Multiple myeloma in a patient who has received at least two prior therapies including lenalidomide and a proteasome inhibitor, wherein the Elotuzumab is administered in combination with pomalidomide and dexamethasone;

k) the additional therapeutic agent is Cetuximab, and the disease or condition is:

- Head and Neck Cancer;
- Squamous cell carcinoma;
- Locally or regionally advanced squamous cell carcinoma of head and neck (SCCHN), wherein the Cetuximab is administered in combination with radiation therapy;
- Recurrent locoregional disease or metastatic SCCHN, wherein the Cetuximab is administered in combination with platinum-based therapy with fluorouracil;
- Recurrent or metastatic SCCHN progressing after platinum-based therapy;
- Colorectal cancer;
- K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by an FDA-approved test;
- Cancer, wherein the Cetuximab is administered in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy; or

- Cancer, wherein wherein the Cetuximab is administered as a single-agent in a patient who has failed oxaliplatin- and irinotecan-based chemotherapy or who is intolerant to irinotecan;

l) the additional therapeutic agent is Panitumumab, and the disease or condition is:

- Colorectal cancer;
- RAS WT metastatic CRC;
- Cancer characterized by disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy;

m) the additional therapeutic agent is Necitumumab, and the disease or condition is:

- Non-small cell lung cancer; or
- Metastatic squamous NSCLC, wherein the Necitumumab is administered in combination with gemcitabine and cisplatin, for first-line treatment of patients;

n) wherein the additional therapeutic agent is Amivantamab-vmjw, and the disease or condition is:

- Non-small cell lung cancer; or
- Locally advanced or metastatic NSCLC with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, where the disease has progressed on or after platinum-based chemotherapy;

o) wherein the additional therapeutic agent is Trastuzumab, and the disease or condition is:

- Breast cancer;
- HER2 overexpressing breast cancer, wherein the Trastuzumab is administered as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel, with docetaxel and carboplatin, or as a single agent following multi-modality anthracycline based therapy;
- mBrCa, wherein the Trastuzumab is administered in combination with paclitaxel for first-line treatment of HER2-overexpressing mBrCa or as a single agent for treatment of HER2-overexpressing BrCa in patients who have received one or more chemotherapy regimens for metastatic disease.
- Gastric or gastroesophageal junction adenocarcinoma; or

- HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, wherein the Trastuzumab is administered in combination with cisplatin and capecitabine or 5-fluorouracil;

p) wherein the additional therapeutic agent is Pertuzumab, and the disease or condition is:

- Breast cancer;
- HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy, wherein the Pertuzumab is administered in combination with trastuzumab and docetaxel;
- HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (either greater than 2 cm in diameter or node positive); or
- HER2-positive early breast cancer at high risk of recurrence, wherein the Pertuzumab is administered in combination with trastuzumab and chemotherapy;

q) wherein the additional therapeutic agent is Margetuximab-cmkb, and the disease or condition is:

- Breast cancer; or
- metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease, wherein the Margetuximab-cmkb is administered in combination with chemotherapy;

r) wherein the additional therapeutic agent is Zolbetuximab, and the disease or condition is:

- Gastro-esophageal junction adenocarcinoma; or
- Previously untreated, locally advanced unresectable or metastatic HER2-/Claudin 18.2+ gastric or gastro-esophageal junction adenocarcinoma;

s) wherein the additional therapeutic agent is Ramucirumab, and the disease or condition is:

- Metastatic gastric or gastro-esophageal junction adenocarcinoma;
- Advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy, wherein the Ramucirumab is administered as a single agent or in combination with paclitaxel;
- Non-small cell lung cancer;

- first-line treatment of metastatic NSCLC with EGFR ex19 deletions or ex21 (L858R) mutations, wherein the Ramucirumab is administered in combination with erlotinib;
- metastatic NSCLC with disease progression on or after platinum-based chemotherapy, wherein the Ramucirumab is administered in combination with docetaxel;
- EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA;
- Colorectal cancer;
- Metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine, wherein the Ramucirumab is administered in combination with FOLFIRI;
- Hepatocellular carcinoma; or
- HCC in patients who have an alpha fetoprotein of ≥400 ng/mL and have been treated with sorafenib;

t) wherein the additional therapeutic agent is Bemarituzumab, and the disease or condition is:

- Gastric cancer; or
- FGFR2 OE Gastric cancer1L with FOLFOX6 or chemotherapy + nivolumab; or

u) wherein the additional therapeutic agent is Olaratumab, and the disease or condition is soft tissue sarcoma, wherein the is Olaratumab is administered in combination with doxorubicin therapy for patients who do not have a curative option with surgery or radiation;

v) wherein the additional therapeutic agent is Cosibelimab, and the disease or condition is Cutaneous squamous cell carcinoma (cSCC);

w) wherein the additional therapeutic agent is Avelumab, and the disease or condition is:

- Urothelial cancer; or
- Renal cancer;

x) wherein the additional therapeutic agent is Magrolimab, and the disease or condition is:

- Triple negative breast cancer, wherein the Magrolimab is administered alone and in combination with standard of care;

- Metastatic colorectal cancer, wherein the Magrolimab is administered alone and in combination with standard of care and bevacizumab;
- Urothelial cancer, wherein the Magrolimab is administered alone and in combination with standard of care;
- Head and neck squamous cell carcinoma, wherein the Magrolimab is administered alone and in combination with standard of care and/or cetuximab;
- Low and high Myelodysplastic syndrome with azacytidine;
- Acute myeloid leukemia, wherein the Magrolimab is administered alone and with standard of care and or venetoclax;
- Diffuse large B cell lymphoma, wherein the Magrolimab is administered alone and with standard of care, including rituximab,or Obinutuzumab; or
- Multiple myeloma, wherein the Magrolimab is administered alone and with standard of care including daratumumab, elotuzumab and Isatuximab-irfc;

y) wherein the additional therapeutic agent is TTI-622, and the disease or condition is:

- Multiple myeloma, wherein the TTI-622 is administered alone and with standard of care including daratumumab, elotuzumab and Isatuximab-irfc;
- Diffuse large B cell lymphoma, wherein the TTI-622 is administered alone and with standard of care, including rituximab,or Obinutuzumab or lenalidomide or Tafasitamab-cxix;
- Ovarian cancer, wherein the TTI-622 is administered alone an in combination with Pegylated liposomal doxorubicin;
- Low and high Myelodysplastic syndrome, wherein the TTI-622 is administered with azacytidine; or
- Acute myeloid leukemia, wherein the TTI-622 is administered alone or with standard of care and/or venetoclax;

z) wherein the additional therapeutic agent is Bevacizumab, and the disease or condition is:

- Metastatic colorectal cancer, wherein the Bevacizumab is administered in combination with intravenous fluorouracilbased chemotherapy for first- or second-line treatment
- Metastatic colorectal cancer, wherein the Bevacizumab is administered in combination with fluoropyrimidineirinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for

second-line treatment in patients who have progressed on a first-line bevacizumab product-containing regimen;

- Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, wherein the Bevacizumab is administered in combination with carboplatin and paclitaxel for first-line treatment;
- Recurrent glioblastoma in adults;
- Metastatic renal cell carcinoma, wherein the Bevacizumab is administered in combination with interferon alfa;
- Persistent, recurrent, or metastatic cervical cancer, wherein the Bevacizumab is administered in combination with paclitaxel and cisplatin, or paclitaxel and topotecan;
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer, wherein the Bevacizumab is administered: a) in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, for stage III or IV disease following initial surgical resection; b) in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens; or c) in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Avastin as a single agent, for platinum-sensitive recurrent disease; or
- Hepatocellular Carcinoma (HCC), wherein the Bevacizumab is administered in combination with atezolizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy;

aa) wherein the additional therapeutic agent is Denosumab, and the disease or condition is:

- bone metastases from solid tumors for prevention of skeletal-related events in patients; or
- giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity;

ab) wherein the additional therapeutic agent is Dinutiximab, and the disease or condition is:

- Neuroblastoma; or
- high-risk neuroblastoma in pediatric patients who achieve at least a partial response to prior first-line multiagent, multimodality therapy, wherein the Dinutiximab is administered in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid (RA); or

ac) wherein the additional therapeutic agent is Naxitamab-gqgk, and the disease or condition is:

- Neuroblastoma; or
- relapsed or refractory high-risk neuroblastoma in the bone or bone marrow in pediatric patients 1 year of age and older and adult patients who have demonstrated a partial response, minor response, or stable disease to prior therapy, wherein the Naxitamab-gqgk is administered in combination with granulocyte-macrophage colony-stimulating factor (GMCSF).

62. The method of any one of claims 38-61, wherein the GPR84 agonist is a compound of any one of claims 1-29.

GPR84 Agonism Enhances the Effect of TTI-622

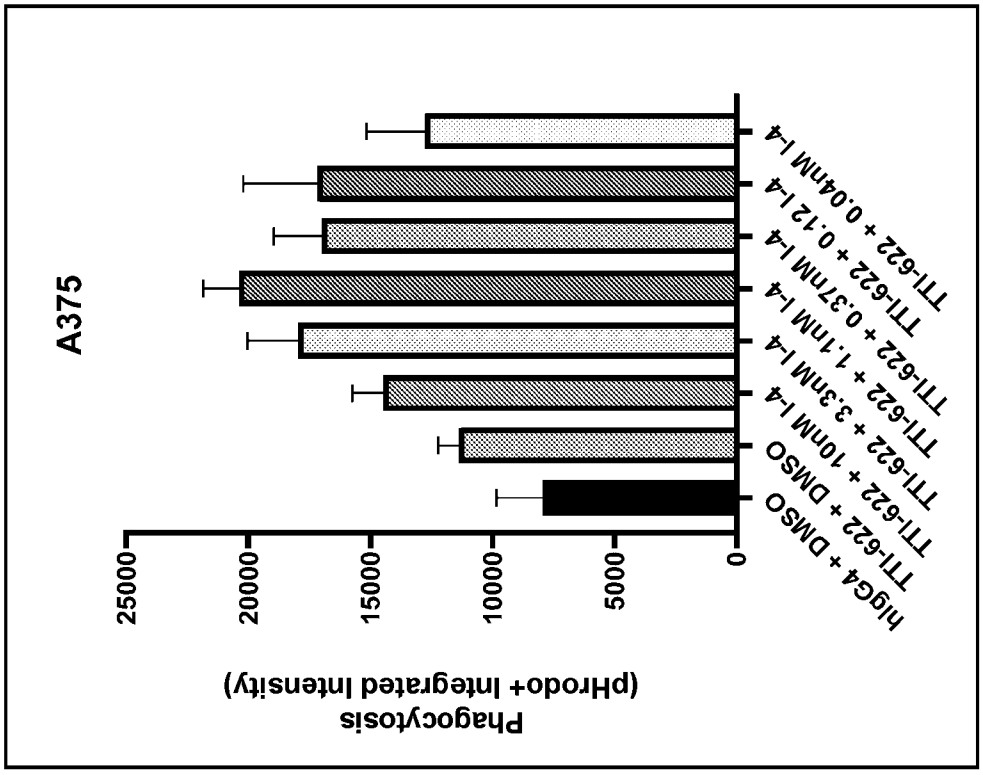


FIG. 1A

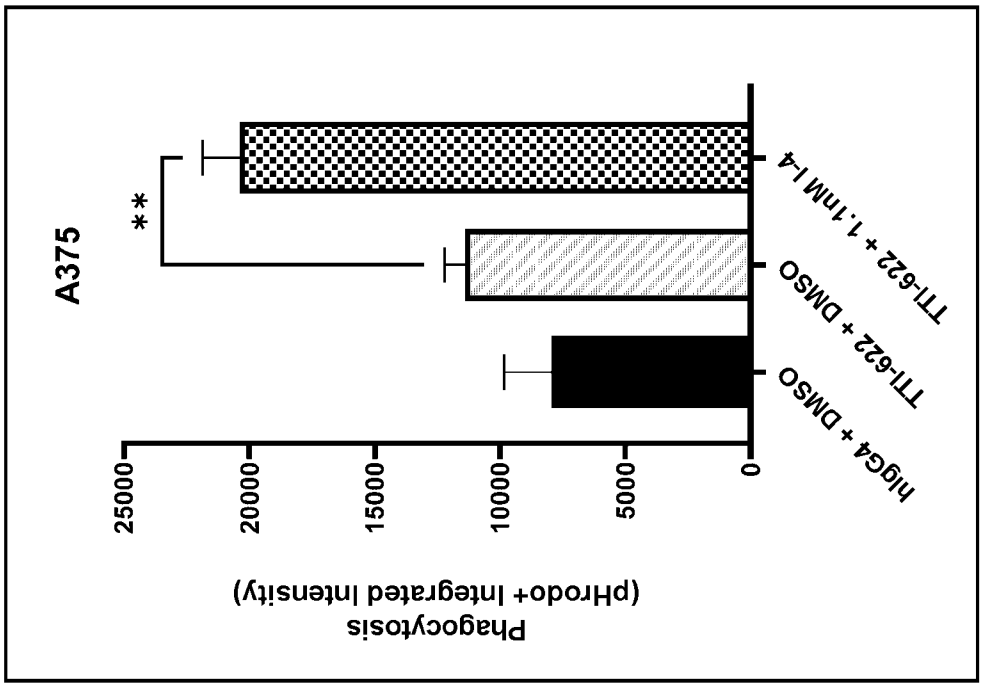


FIG. 1B

GPR84 Agonism Enhances the Effect of TTI-622

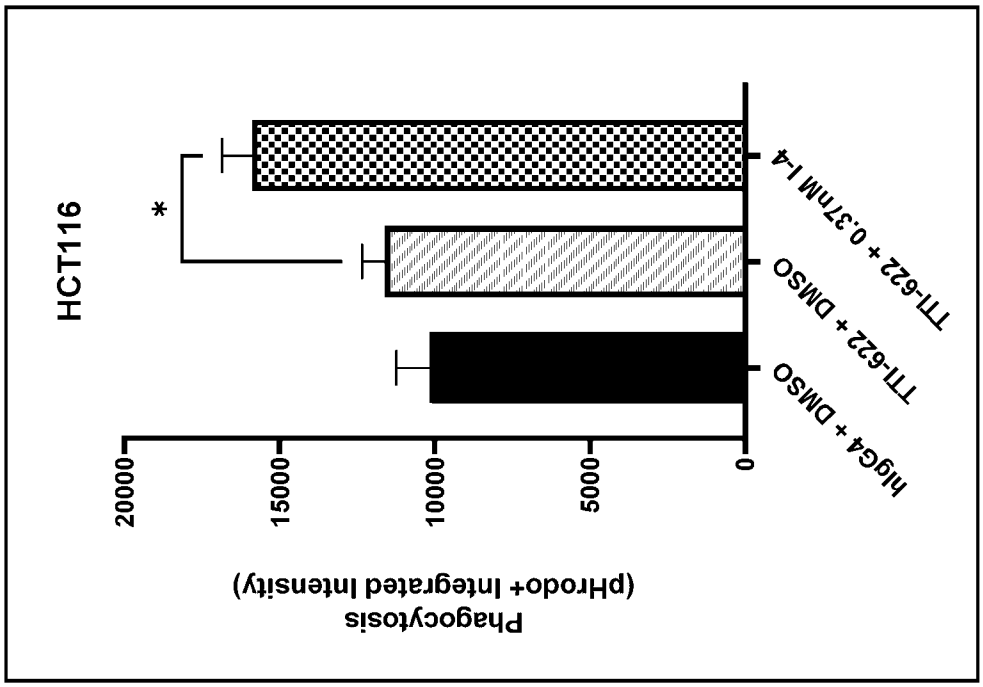


FIG. 2B

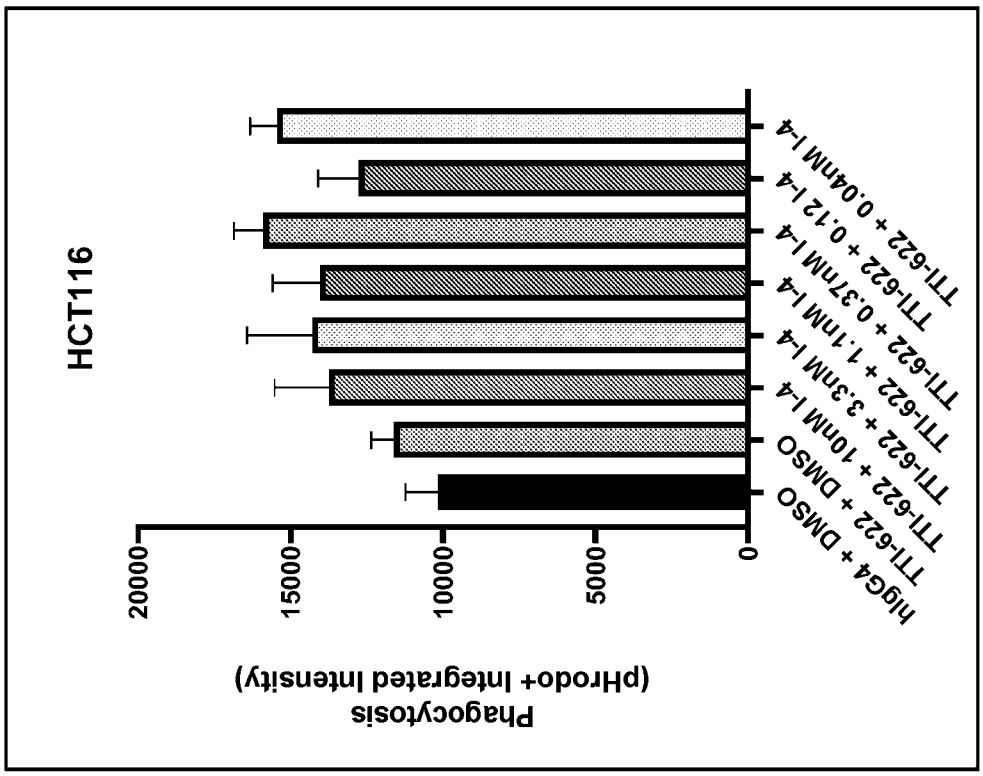


FIG. 2A

GPR84 Agonism Enhances the Effect of Magrolimab

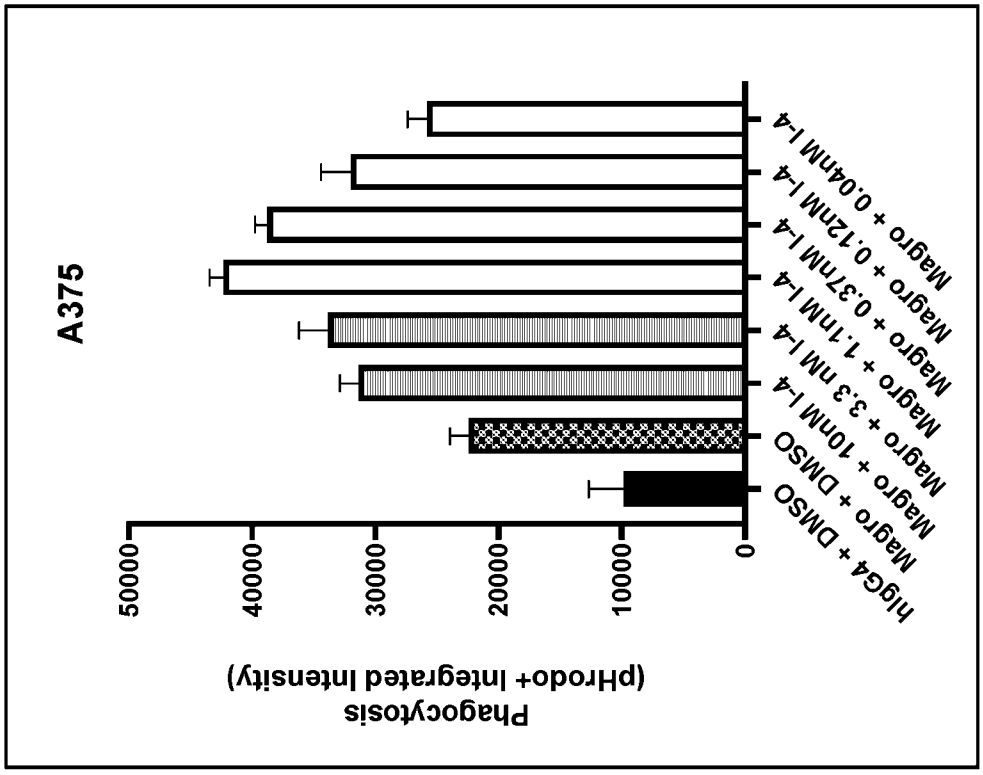


FIG. 3A

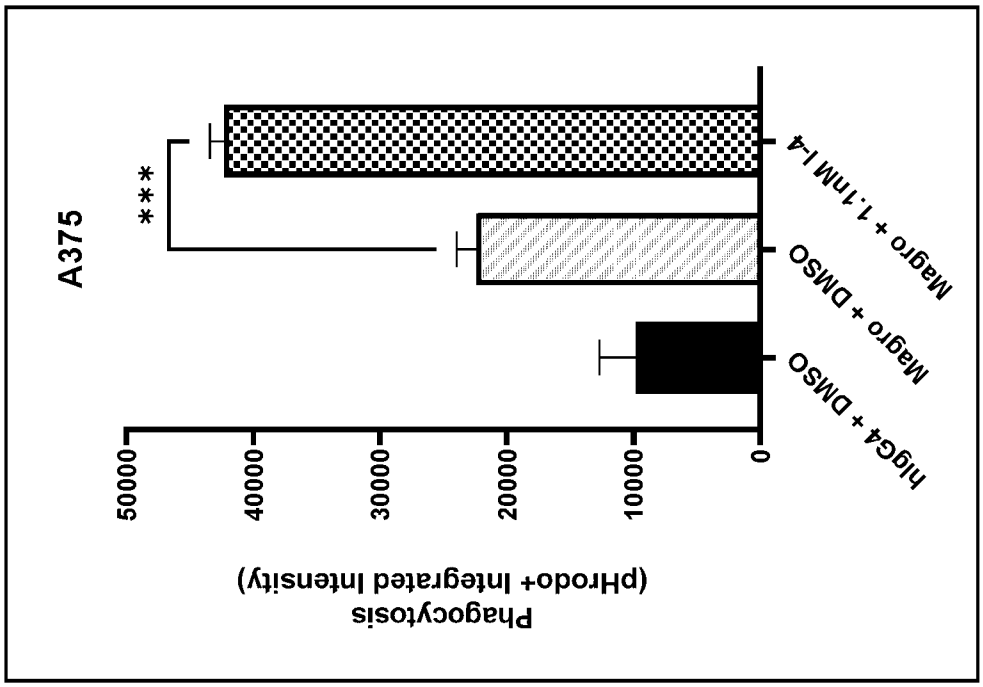


FIG. 3B

GPR84 Agonism Enhances the Effect of Cetuximab

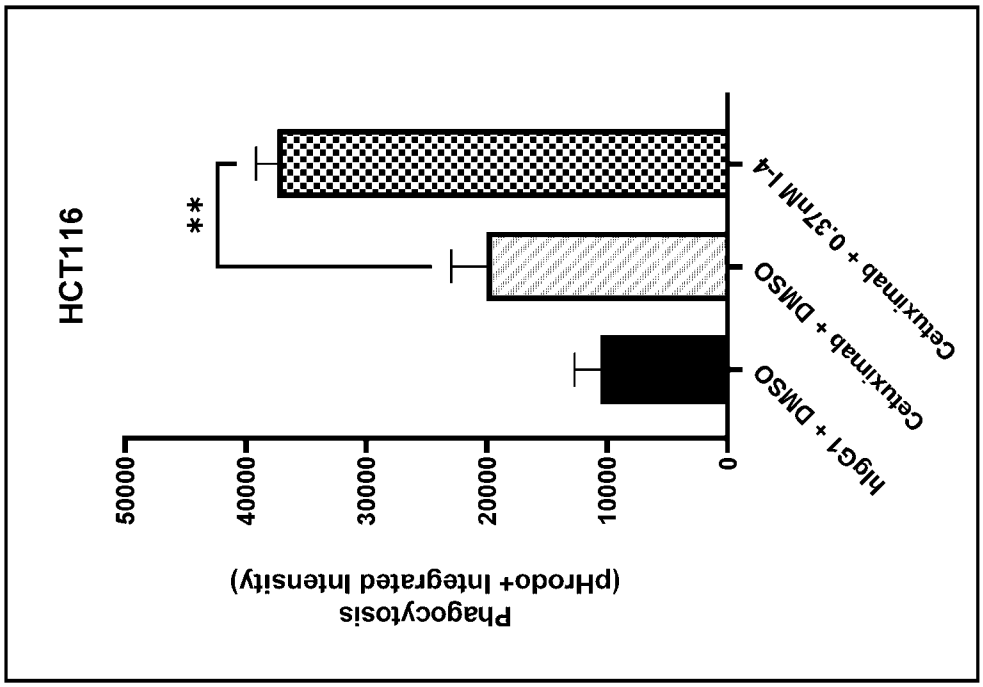


FIG. 4B

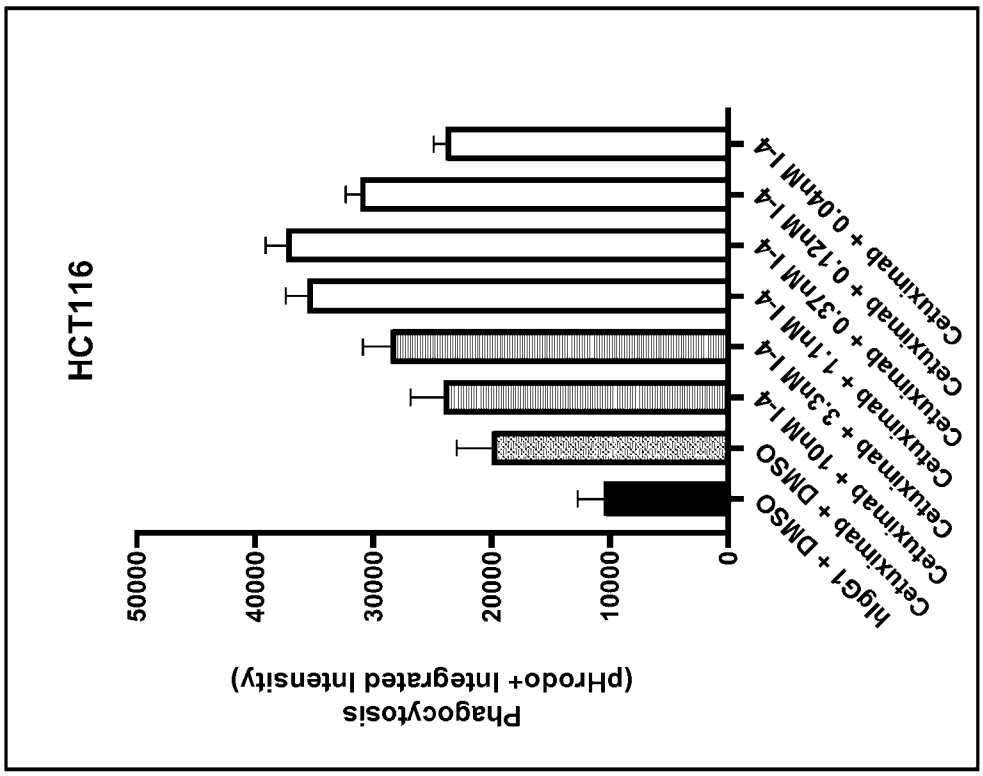


FIG. 4A

GPR84 Agonism Enhances the Effect of Rituximab

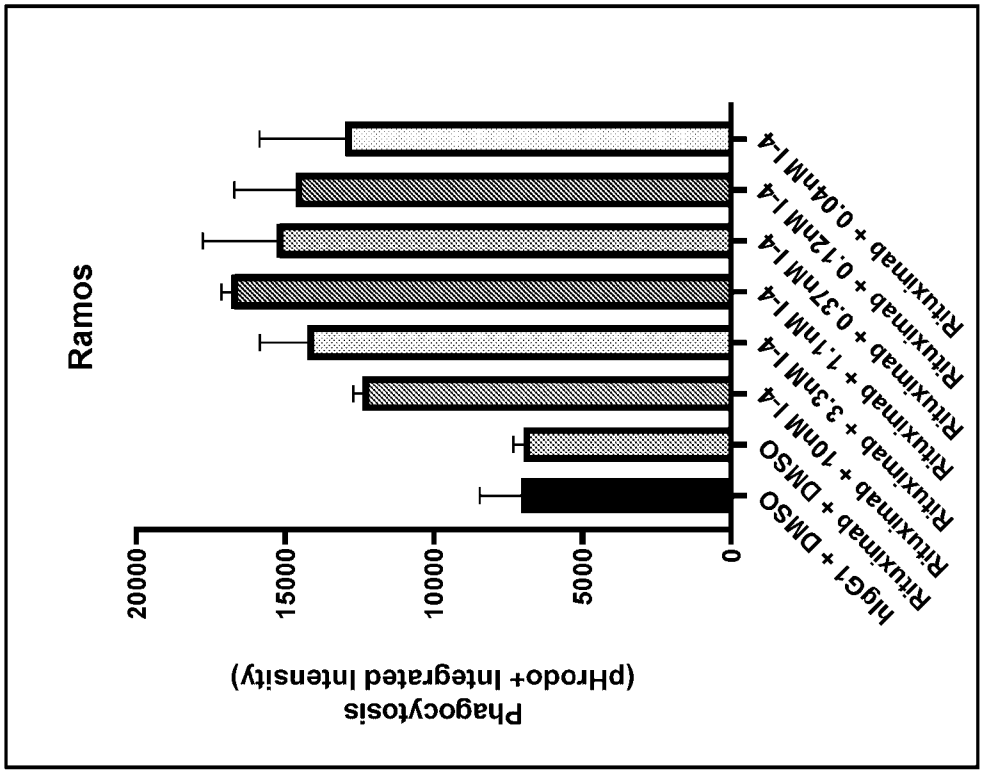


FIG. 5A

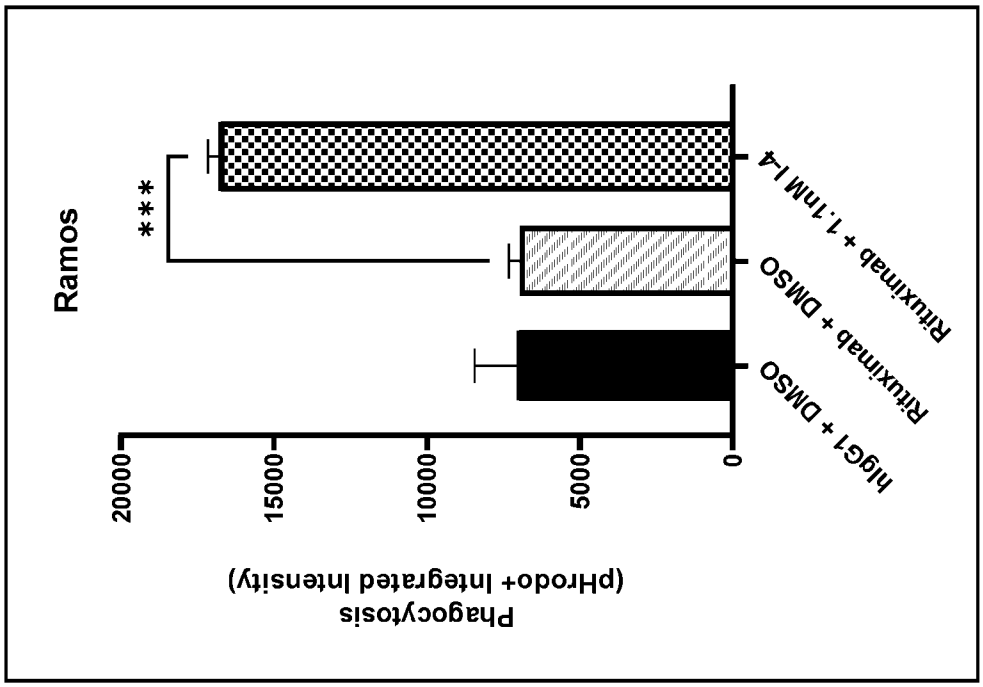


FIG. 5B

GPR84 Agonism Enhances the Effect of Daratumumab

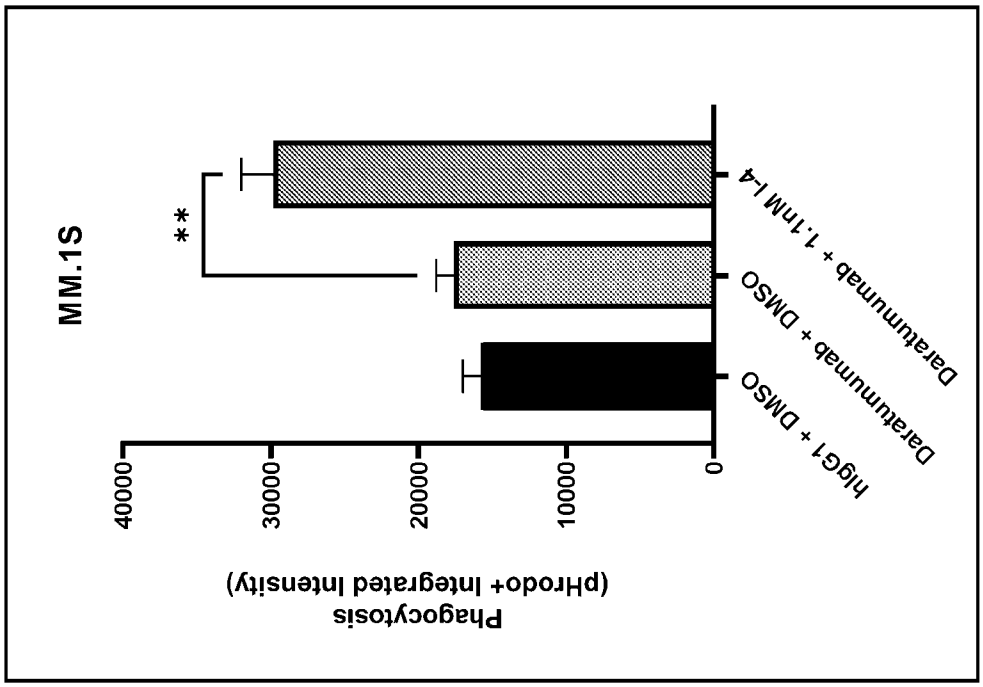


FIG. 6B

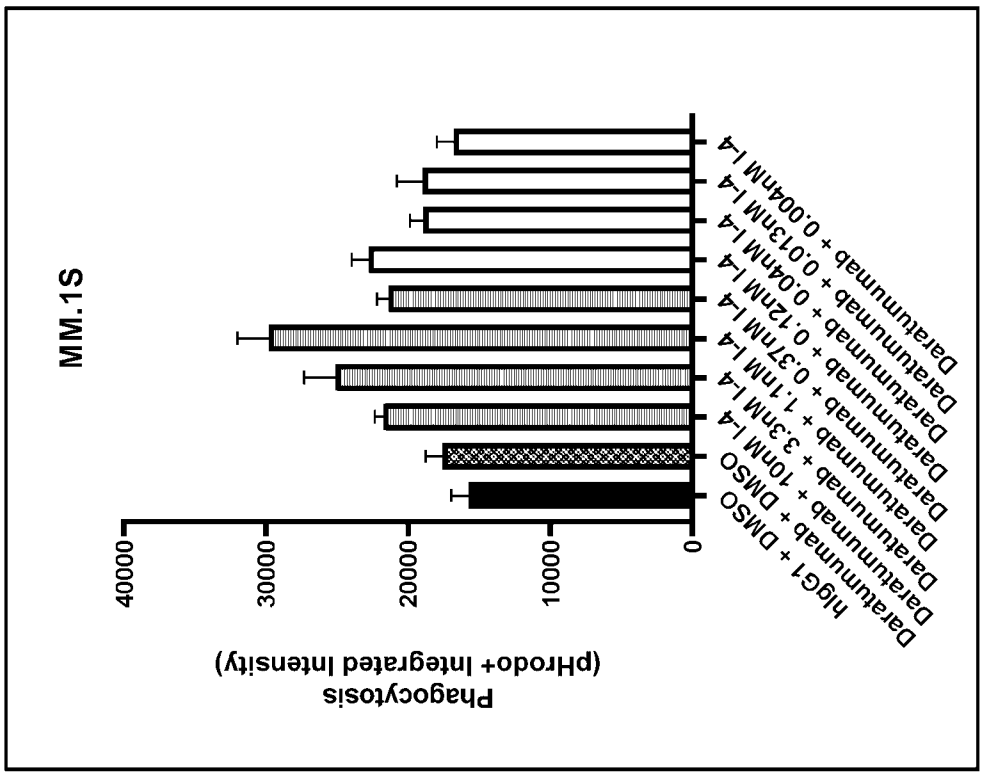


FIG. 6A

GPR84 Agonism Enhances the Effect of Various Tumor-Targeting Agents

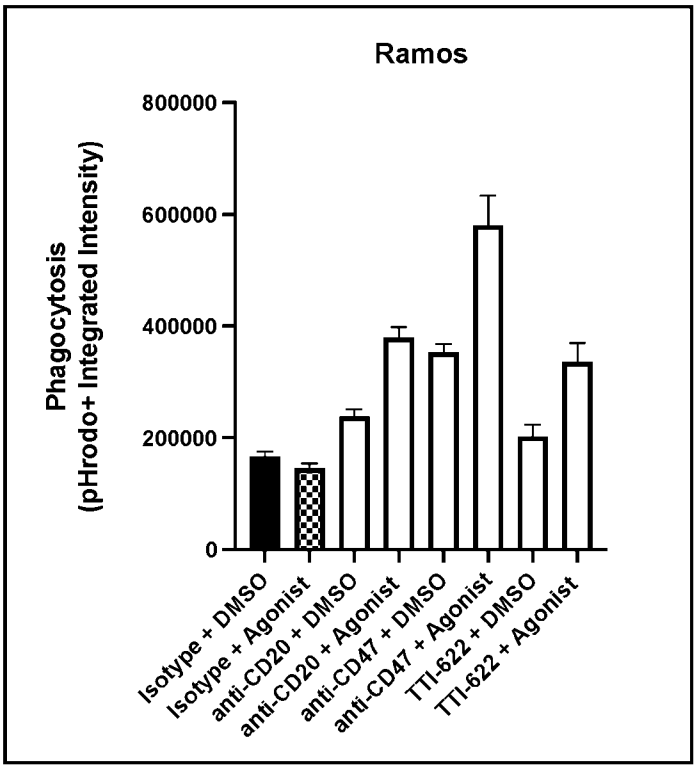


FIG. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/033492

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D213/69 A61K31/42 A61K31/44 A61K31/4402 A61K31/4409
A61P35/00 C07D213/64 C07D213/68 C07D231/18 C07D231/34
C07D249/12 C07D261/08 C07D401/06 C07D401/12 C07D413/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/140163 A1 (MERCK & CO INC [US]; BRNARDIC EDWARD J [US] ET AL.) 19 November 2009 (2009-11-19) page 37; examples P3-4, P3-8	1-4,7, 13,21,24
X	WO 2012/019299 A1 (BOEHRINGER INGELHEIM INT [DE]; EDWARDS PAUL J [CA] ET AL.) 16 February 2012 (2012-02-16) page 37; example K	1-4,7,9, 19,22,24

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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 September 2024	27/09/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fazzi, Raffaella

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YVES P AUBERSON ET AL: "Ligand Specific Efficiency (LSE) Index for PET Tracer Optimization", CHEMMEDCHEM COMMUNICATIONS, WILEY-VCH, DE, vol. 11, no. 13, 19 May 2016 (2016-05-19), pages 1415-1427, XP072416811, ISSN: 1860-7179, DOI: 10.1002/CMDC.201600112 page 1418; example 14	1-4,9, 19,22,24
X	WO 00/27821 A1 (BASF AG [DE]; GOETZ NORBERT [DE]; GOETZ ROLAND [DE]; RACK MICHAEL [DE]) 18 May 2000 (2000-05-18) page 15; examples 3.4, 3.9, 3.10	1,2,5,6, 8-13, 19-25
X	KARDILE RAHUL DADABHAU ET AL: "Gold-Catalyzed [4 + 1]-Annulation Reactions between 1,4-Diyn-3-ols and Isoxazoles To Construct a Pyrrole Core", ORGANIC LETTERS, vol. 20, no. 13, 19 June 2018 (2018-06-19) , pages 3806-3809, XP093201979, US ISSN: 1523-7060, DOI: 10.1021/acs.orglett.8b01398 page 3807; figure 2; example 2c	1,2,5,6, 8-13, 19-25
X	CHURYKAU DZMITRY ET AL: "A Convenient Procedure for Transformation of Tertiary Cyclopropanols into 5-Substituted Isoxazoles", SYNLETT, vol. 2006, no. 20, December 2006 (2006-12) , pages 3427-3430, XP093202144, DE ISSN: 0936-5214, DOI: 10.1055/s-2006-956475 Retrieved from the Internet: URL:https://www.thieme-connect.de/products /ejournals/pdf/10.1055/s-2006-956475.pdf> table 1	1,2,5,6, 8-13, 19-25
X	GAGNON PAUL E. ET AL: "SYNTHESES AND ABSORPTION SPECTRA OF 2-SUBSTITUTED-3-HYDROXY-5-PYRAZOLONES: 4-n -HEXYL-5-PYRAZOLONES-4-C 14", CANADIAN JOURNAL OF CHEMISTRY, vol. 32, no. 9, September 1954 (1954-09), pages 823-838, XP093202200, Ottawa, Canada ISSN: 0008-4042, DOI: 10.1139/v54-105 table IV	1,2,5,6, 8-13, 19-25

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/033492

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	LIU YANG ET AL: "Design and Synthesis of 2-Alkylpyrimidine-4,6-diol and 6-Alkylpyridine-2,4-diol as Potent GPR84 Agonists", ACS MEDICINAL CHEMISTRY LETTERS, vol. 7, no. 6, 9 June 2016 (2016-06-09), pages 579-583, XP055861093, US ISSN: 1948-5875, DOI: 10.1021/acsmedchemlett.6b00025 example 51	1-62

X	EP 3 372 590 A1 (SHANGHAI INST MATERIA MEDICA CAS [CN]) 12 September 2018 (2018-09-12) page 6; example LY237	1-62

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2024/033492

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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