IMIDAZOLE-BASED COMPOUNDS, COMPOSITIONS COMPRISING THEM AND METHODS OF THEIR USE

This application claims priority to U.S. patent application 11/698,253, filed January 25, 2007, and U.S. provisional application nos. 60/776,473, filed February 24, 2006, and 60/815,221, filed June 20, 2006, all of which are incorporated herein by reference.

1. FIELD OF THE INVENTION

This invention relates to imidazole-based compounds, and methods of their use for the treatment, prevention and management of various diseases and disorders.

2. BACKGROUND

Sphingosine-1-phosphate (S1P) is a bioactive molecule with potent effects on multiple organ systems. Saba, J.D. and Hla, T. Circ. Res. 94:724-734 (2004). Although some believe the compound is an intracellular secondary messenger, its mode of action is still a subject of debate. *Id.* Indeed, even its metabolism is poorly understood. Hla, T., Science 309:1682-3 (2005). Researchers currently believe that S1P is formed by the phosphorylation of sphingosine, and degraded by dephosphorylation or cleavage. Its cleavage into ethanolamine phosphate and a long-chain aldehyde is reportedly catalyzed by S1P lyase. *Id.*; Pyne & Pyne, Biochem J. 349:385-402 (2000).

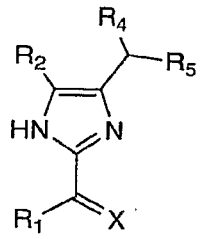
Sphingosine-1-phosphate lyase is a vitamin B_6-dependent enzyme localized in the membrane of the endoplasmic reticulum. Van Veldhoven and Mannaerts, J. Biol. Chem. 266:12502-12507 (1991); Van Veldhoven and Mannaerts, Adv. Lipid. Res. 26:69 (1993). The polynucleotide and amino acid sequences of human SP1 lyase and its gene products are described in PCT Patent Application No. WO 99/16888.

Recently, Schwab and coworkers concluded that a component of caramel color III, 2-acetyl-4-tetrahydroxybutylimidazole (THI), inhibits S1P lyase activity when administered to mice. Schwab, S. *et al.*, Science 309:1735-1739 (2005). While others have postulated that THI exerts its effects by a different mechanism (*see, e.g.*, Pyne, S.G., ACGC Chem. Res. Comm. 11:108-112 (2000)), it is clear that administration of the

compound to rats and mice induces lymphopenia and causes the accumulation of mature T cells in the thymus. *See, e.g.*, Schwab, *supra*; Pyne, S.G., ACGC Chem. Res. Comm. 11:108-112 (2000); Gugsyan, R., *et al.*, Immunology 93(3):398-404 (1998); Halweg, K.M. and Büchi, G., J.Org.Chem. 50:1134-1136 (1985); U.S. patent 4,567,194 to Kroeplien and Rosdorfer. Still, there are no known reports of THI having an immunological effect in animals other than mice and rats. Although U.S. patent 4,567,194 alleges that THI and some related compounds may be useful as immunosuppressive medicinal agents, studies of the compound in humans found no immunological effects. *See* Thuvander, A. and Oskarsson, A., Fd. Chem. Toxic. 32(1):7-13 (1994); Houben, G.F., *et al.*, Fd. Chem. Toxic. 30(9):749-757 (1992).

3. SUMMARY OF THE INVENTION

This invention is directed, in part, to compounds of formula **I**:



I

and pharmaceutically acceptable salts and solvates (*e.g.*, hydrates) thereof, wherein: X is O or NR_3; R_1 is OR_{1A}, NHOH, hydrogen, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; R_2 is OR_{2A}, $C(O)OR_{2A}$, hydrogen, halogen, nitrile, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; R_3 is OR_{3A}, $N(R_{3A})_2$, $NHC(O)R_{3A}$, $NHSO_2R_{3A}$, or hydrogen; R_4 is OR_{4A}, $OC(O)R_{4A}$, hydrogen, halogen, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; R_5 is $N(R_{5A})_2$, hydrogen, hydroxy, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; and each of R_{1A}, R_{2A}, R_{3A}, R_{4A}, and R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl.

This invention also encompasses pharmaceutical compositions comprising compounds of formula **I**, and methods of treating inflammatory diseases and disorders using compounds of formula **I**.

4. BRIEF DESCRIPTION OF THE FIGURES

Certain aspects of this invention can be understood with reference to the following figures:

Figure 1 provides a representative flow cytometry (FACS) dot plot showing the effect of vehicle control (VC), a compound of the invention (Compound 1), and THI on T cell composition (CD4+ and CD8+) of thymus, and the mean/Sd for all mice (n = 3).

Figure 2 provides a representative FACS dot plot showing the effect of vehicle control (VC), a compound of the invention (Compound 1), and THI on a subset of CD4+ cells (recent thymic emigrants) in mice.

Figure 3 provides a representative FACS dot plot showing the effect of vehicle control (VC), a compound of the invention (Compound 1), and THI on a subset of CD8+ cells (recent thymic emigrants) in mice.

Figure 4 shows the effects of vehicle control, THI, Compound 1, and 1-(4-methyl-5-((1S,2R,3R)-1,2,3,4-tetrahydroxybutyl)thiazol-2-yl)ethanone (Compound 2) on whole blood counts of mice.

Figure 5 shows the effect of single oral dosing of a compound of the invention on collage-induced arthritis in mice.

Figure 6 shows the effect of single oral dosing of a compound of the invention on white blood cell and lymphocyte counts of cynomolgus monkeys.

5. DETAILED DESCRIPTION

This invention results, in part, from studies of S1P lyase gene-disrupted mice, and largely relates to compounds believed to be useful in the treatment, prevention and/or management of autoimmune and inflammatory diseases and disorders.

5.1. Definitions

Unless otherwise indicated, the term "alkenyl" means a straight chain, branched and/or cyclic hydrocarbon having from 2 to 20 (*e.g.*, 2 to 10 or 2 to 6) carbon atoms, and

including at least one carbon-carbon double bond. Representative alkenyl moieties include vinyl, allyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 2-decenyl and 3-decenyl.

Unless otherwise indicated, the term "alkyl" means a straight chain, branched and/or cyclic ("cycloalkyl") hydrocarbon having from 1 to 20 (*e.g.*, 1 to 10 or 1 to 4) carbon atoms. Alkyl moieties having from 1 to 4 carbons are referred to as "lower alkyl." Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl and dodecyl. Cycloalkyl moieties may be monocyclic or multicyclic, and examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and adamantyl. Additional examples of alkyl moieties have linear, branched and/or cyclic portions (*e.g.*, 1-ethyl-4-methyl-cyclohexyl). The term "alkyl" includes saturated hydrocarbons as well as alkenyl and alkynyl moieties.

Unless otherwise indicated, the term "alkylaryl" or "alkyl-aryl" means an alkyl moiety bound to an aryl moiety.

Unless otherwise indicated, the term "alkylheteroaryl" or "alkyl-heteroaryl" means an alkyl moiety bound to a heteroaryl moiety.

Unless otherwise indicated, the term "alkylheterocycle" or "alkyl-heterocycle" means an alkyl moiety bound to a heterocycle moiety.

Unless otherwise indicated, the term "alkynyl" means a straight chain, branched or cyclic hydrocarbon having from 2 to 20 (*e.g.*, 2 to 20 or 2 to 6) carbon atoms, and including at least one carbon-carbon triple bond. Representative alkynyl moieties include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1-butynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 5-hexynyl, 1-heptynyl, 2-heptynyl, 6-heptynyl, 1-octynyl, 2-octynyl, 7-octynyl, 1-nonynyl, 2-nonynyl, 8-nonynyl, 1-decynyl, 2-decynyl and 9-decynyl.

Unless otherwise indicated, the term "alkoxy" means an –O–alkyl group. Examples of alkoxy groups include, but are not limited to, $-OCH_3$, $-OCH_2CH_3$, $-O(CH_2)_2CH_3$, $-O(CH_2)_3CH_3$, $-O(CH_2)_4CH_3$, and $-O(CH_2)_5CH_3$.

Unless otherwise indicated, the term "aryl" means an aromatic ring or an aromatic or partially aromatic ring system composed of carbon and hydrogen atoms. An aryl moiety may comprise multiple rings bound or fused together. Examples of aryl moieties include, but are not limited to, anthracenyl, azulenyl, biphenyl, fluorenyl, indan, indenyl, naphthyl, phenanthrenyl, phenyl, 1,2,3,4-tetrahydro-naphthalene, and tolyl.

Unless otherwise indicated, the term "arylalkyl" or "aryl-alkyl" means an aryl moiety bound to an alkyl moiety.

Unless otherwise indicated, the term "circulating lymphocyte reduction agent" means a compound that has a CLRF of greater than about 20 percent.

Unless otherwise indicated, the term "circulating lymphocyte reduction factor" or "CLRF" means the decrease in the number of circulating lymphocytes in mice caused by oral administration of a single dose of a compound at 100 mg/kg, as determined by the method described in the Examples, below.

Unless otherwise indicated, the terms "halogen" and "halo" encompass fluorine, chlorine, bromine, and iodine.

Unless otherwise indicated, the term "heteroalkyl" refers to an alkyl moiety (*e.g.*, linear, branched or cyclic) in which at least one of its carbon atoms has been replaced with a heteroatom (*e.g.*, N, O or S).

Unless otherwise indicated, the term "heteroaryl" means an aryl moiety wherein at least one of its carbon atoms has been replaced with a heteroatom (*e.g.*, N, O or S). Examples include, but are not limited to, acridinyl, benzimidazolyl, benzofuranyl, benzoisothiazolyl, benzoisoxazolyl, benzoquinazolinyl, benzothiazolyl, benzoxazolyl, furyl, imidazolyl, indolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, phthalazinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolinyl, tetrazolyl, thiazolyl, and triazinyl.

Unless otherwise indicated, the term "heteroarylalkyl" or "heteroaryl-alkyl" means a heteroaryl moiety bound to an alkyl moiety.

Unless otherwise indicated, the term "heterocycle" refers to an aromatic, partially aromatic or non-aromatic monocyclic or polycyclic ring or ring system comprised of carbon, hydrogen and at least one heteroatom (*e.g.*, N, O or S). A heterocycle may comprise multiple (*i.e.*, two or more) rings fused or bound together. Heterocycles include heteroaryls. Examples include, but are not limited to, benzo[1,3]dioxolyl, 2,3-dihydro-

benzo[1,4]dioxinyl, cinnolinyl, furanyl, hydantoinyl, morpholinyl, oxetanyl, oxiranyl, piperazinyl, piperidinyl, pyrrolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl and valerolactamyl.

Unless otherwise indicated, the term "heterocyclealkyl" or "heterocycle-alkyl" refers to a heterocycle moiety bound to an alkyl moiety.

Unless otherwise indicated, the term "heterocycloalkyl" refers to a non-aromatic heterocycle.

Unless otherwise indicated, the term "heterocycloalkylalkyl" or "heterocycloalkyl-alkyl" refers to a heterocycloalkyl moiety bound to an alkyl moiety.

Unless otherwise indicated, the terms "manage," "managing" and "management" encompass preventing the recurrence of the specified disease or disorder in a patient who has already suffered from the disease or disorder, and/or lengthening the time that a patient who has suffered from the disease or disorder remains in remission. The terms encompass modulating the threshold, development and/or duration of the disease or disorder, or changing the way that a patient responds to the disease or disorder.

Unless otherwise indicated, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids and bases and organic acids and bases. Suitable pharmaceutically acceptable base addition salts include, but are not limited to, metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Suitable non-toxic acids include, but are not limited to, inorganic and organic acids such as acetic, alginic, anthranilic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, furoic, galacturonic, gluconic, glucuronic, glutamic, glycolic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phenylacetic, phosphoric, propionic, salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, and p-toluenesulfonic acid. Specific non-toxic acids include hydrochloric, hydrobromic, phosphoric, sulfuric, and methanesulfonic acids. Examples of specific salts thus include hydrochloride and mesylate salts. Others are well-known in the art. *See, e.g., Remington' s Pharmaceutical*

Sciences (18th ed., Mack Publishing, Easton PA: 1990) and *Remington: The Science and Practice of Pharmacy* (19th ed., Mack Publishing, Easton PA: 1995).

Unless otherwise indicated, the terms "prevent," "preventing" and "prevention" contemplate an action that occurs before a patient begins to suffer from the specified disease or disorder, which inhibits or reduces the severity of the disease or disorder. In other words, the terms encompass prophylaxis.

Unless otherwise indicated, a "prophylactically effective amount" of a compound is an amount sufficient to prevent a disease or condition, or one or more symptoms associated with the disease or condition, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the disease. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

Unless otherwise indicated, the term "S1P level enhancing agent" means a compound that has a SLEF of at least about 10-fold.

Unless otherwise indicated, the term "S1P level enhancing factor" or "SLEF" means the increase in S1P in the spleens of mice caused by oral administration of a single dose of a compound at 100 mg/kg, as determined by the method described in the Examples, below.

Unless otherwise indicated, the term "stereoisomeric mixture" encompasses racemic mixtures as well as stereomerically enriched mixtures (*e.g.*, R/S = 30/70, 35/65, 40/60, 45/55, 55/45, 60/40, 65/35 and 70/30).

Unless otherwise indicated, the term "stereomerically pure" means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound. For example, a stereomerically pure composition of a compound having one stereocenter will be substantially free of the opposite stereoisomer of the compound. A stereomerically pure composition of a compound having two stereocenters will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound

and less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound, or greater than about 99% by weight of one stereoisomer of the compound and less than about 1% by weight of the other stereoisomers of the compound.

Unless otherwise indicated, the term "substituted," when used to describe a chemical structure or moiety; refers to a derivative of that structure or moiety wherein one or more of its hydrogen atoms is substituted with a chemical moiety or functional group such as, but not limited to, alcohol, aldehylde, alkoxy, alkanoyloxy, alkoxycarbonyl, alkenyl, alkyl (*e.g.*, methyl, ethyl, propyl, t-butyl), alkynyl, alkylcarbonyloxy (-OC(O)alkyl), amide (-C(O)NH-alkyl- or -alkylNHC(O)alkyl), amidinyl (-C(NH)NH-alkyl or -C(NR)NH_2), amine (primary, secondary and tertiary such as alkylamino, arylamino, arylalkylamino), aroyl, aryl, aryloxy, azo, carbamoyl (-NHC(O)O-alkyl- or –OC(O)NH-alkyl), carbamyl (*e.g.*, $CONH_2$, as well as CONH-alkyl, CONH-aryl, and CONH-arylalkyl), carbonyl, carboxyl, carboxylic acid, carboxylic acid anhydride, carboxylic acid chloride, cyano, ester, epoxide, ether (*e.g.*, methoxy, ethoxy), guanidino, halo, haloalkyl (*e.g.*, -CCl_3, -CF_3, -$C(CF_3)_3$), heteroalkyl, hemiacetal, imine (primary and secondary), isocyanate, isothiocyanate, ketone, nitrile, nitro, oxo, phosphodiester, sulfide, sulfonamido (*e.g.*, SO_2NH_2), sulfone, sulfonyl (including alkylsulfonyl, arylsulfonyl and arylalkylsulfonyl), sulfoxide, thiol (*e.g.*, sulfhydryl, thioether) and urea (-NHCONH-alkyl-).

Unless otherwise indicated, a "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment or management of a disease or condition, or to delay or minimize one or more symptoms associated with the disease or condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment or management of the disease or condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of a disease or condition, or enhances the therapeutic efficacy of another therapeutic agent.

Unless otherwise indicated, the terms "treat," "treating" and "treatment" contemplate an action that occurs while a patient is suffering from the specified disease or disorder, which reduces the severity of the disease or disorder, or retards or slows the progression of the disease or disorder.

Unless otherwise indicated, the term "include" has the same meaning as "include, but are not limited to," and the term "includes" has the same meaning as "includes, but is not limited to." Similarly, the term "such as" has the same meaning as the term "such as, but not limited to."

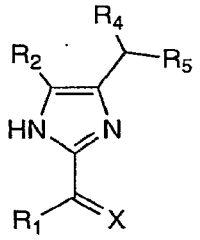
Unless otherwise indicated, one or more adjectives immediately preceding a series of nouns is to be construed as applying to each of the nouns. For example, the phrase "optionally substituted alky, aryl, or heteroaryl" has the same meaning as "optionally substituted alky, optionally substituted aryl, or optionally substituted heteroaryl."

It should be noted that a chemical moiety that forms part of a larger compound may be described herein using a name commonly accorded it when it exists as a single molecule or a name commonly accorded its radical. For example, the terms "pyridine" and "pyridyl" are accorded the same meaning when used to describe a moiety attached to other chemical moieties. Thus, the two phrases "XOH, wherein X is pyridyl" and "XOH, wherein X is pyridine" are accorded the same meaning, and encompass the compounds pyridin-2-ol, pyridin-3-ol and pyridin-4-ol.

It should also be noted that if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or the portion of the structure is to be interpreted as encompassing all stereoisomers of it. Moreover, any atom shown in a drawing with unsatisfied valences is assumed to be attached to enough hydrogen atoms to satisfy the valences. In addition, chemical bonds depicted with one solid line parallel to one dashed line encompass both single and double (*e.g.*, aromatic) bonds, if valences permit.

5.2. Compounds

This invention encompasses compounds of formula **I**:



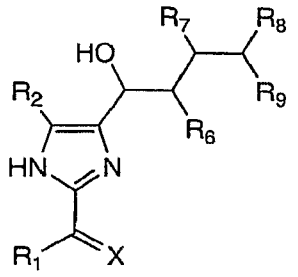
I

and pharmaceutically acceptable salts and solvates (*e.g.*, hydrates) thereof, wherein: X is O or NR_3; R_1 is OR_{1A}, NHOH, hydrogen, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; R_2 is OR_{2A}, $C(O)OR_{2A}$, hydrogen, halogen, nitrile, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; R_3 is OR_{3A}, $N(R_{3A})_2$, $NHC(O)R_{3A}$, $NHSO_2R_{3A}$, or hydrogen; R_4 is OR_{4A}, $OC(O)R_{4A}$, hydrogen, halogen, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; R_5 is $N(R_{5A})_2$, hydrogen, hydroxy, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; and each of R_{1A}, R_{2A}, R_{3A}, R_{4A}, and R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl.

Particular compounds of formula **I** are such that if X is O; R_1 is alkyl of 1 to 4 carbons, phenyl, benzyl or phenylethyl; R_2 is hydrogen; and one of R_4 and R_5 is hydroxyl; the other of R_4 and R_5 is not alkyl of 1 to 6 carbons, hydroxyalkyl of 1 to 6 carbons, polyhydroxyalkyl of 1 to 6 carbons having up to one hydroxyl per carbon, polyacetylalkyl of 1 to 6 carbons having up to one acetyl per carbon, phenyl, benzyl or phenylethyl.

In particular embodiments, the compound is not 2-acetyl-4-tetrahydroxybutylimidazole, 1-(4-(1,1,2,2,4-pentahydroxybutyl)-1H-imidazol-2-yl)ethanone, 1-(2-acetyl-1H-imidazol-4-yl)butane-1,1,2,2-tetrayl tetraacetate, or 1-(2-acetyl-1H-imidazol-4-yl)butane-1,1,2,2,4-pentayl pentaacetate.

A particular embodiment encompasses compounds of formula **II**:

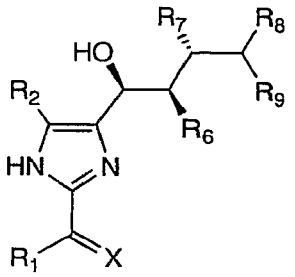


II

and pharmaceutically acceptable salts and solvates thereof, wherein: X is O or NR_3; R_1 is OR_{1A}, NHOH, hydrogen, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; R_2 is OR_{2A}, $C(O)OR_{2A}$, hydrogen, halogen, nitrile, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; R_3 is OR_{3A}, $N(R_{3A})_2$, $NHC(O)R_{3A}$, $NHSO_2R_{3A}$, or hydrogen; R_6 is OR_{6A}, $OC(O)R_{6A}$, $N(R_{6B})_2$, $NHC(O)R_{6B}$, hydrogen, or halogen; R_7 is OR_{7A}, $OC(O)R_{7A}$, $N(R_{7B})_2$, $NHC(O)R_{7B}$, hydrogen, or halogen; R_8 is OR_{8A}, $OC(O)R_{8A}$, $N(R_{8B})_2$, $NHC(O)R_{8B}$, hydrogen, or halogen; R_9 is CH_2OR_{9A}, $CH_2OC(O)R_{9A}$, $N(R_{9B})_2$, $NHC(O)R_{9B}$, hydrogen, or halogen; each of R_{1A}, R_{2A}, R_{3A}, R_{6A}, R_{7A}, R_{8A} and R_{9A} is independently hydrogen or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; and each of R_{6B}, R_{7B}, R_{8B} and R_{9B} is independently hydrogen or alkyl optionally substituted with one or more hydroxy or halogen groups;

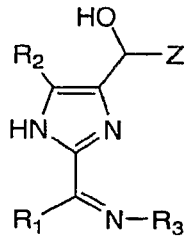
Particular compounds of formula **II** are such that: 1) if X is O, R_1 is alkyl of 1 to 4 carbons, phenyl, benzyl or phenylethyl, and R_2 is hydrogen, at least two of R_6, R_7, R_8 and R_9 are not hydroxyl or acetate; 2) if X is O, R_1 is methyl, R_2 is hydrogen, R_6 and R_7 are both hydroxyl, and one of R_8 and R_9 is hydrogen, the other is not $NHC(O)R_{9B}$; 3) if X is O, R_1 is OR_{1A}, R_{1A} is hydrogen or lower alkyl, and R_2 is hydrogen, at least one, but not all, of R_6, R_7, R_8 and R_9 is hydroxyl or acetate.

Particular compounds of the invention are of formula **II(a)**:



II(a)

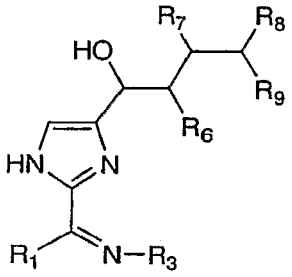
Others are of formula **III**:



III

wherein: Z is optionally substituted alkyl; R_1 is OR_{1A}, NHOH, hydrogen, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; R_2 is OR_{2A}, $C(O)OR_{2A}$, hydrogen, halogen, nitrile, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; R_3 is OR_{3A}, $N(R_{3A})_2$, $NHC(O)R_{3A}$, $NHSO_2R_{3A}$, or hydrogen; and each of R_{1A}, R_{2A}, and R_{3A} is independently hydrogen or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl.

Another embodiment of the invention encompasses compounds of formula **IV**:

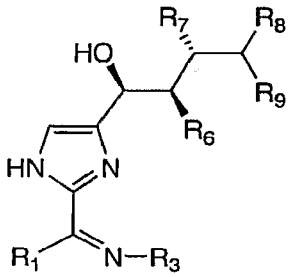


IV

and pharmaceutically acceptable salts and solvates thereof, wherein: R_1 is OR_{1A}, NHOH, hydrogen, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; R_3 is OR_{3A}, $N(R_{3A})_2$, $NHC(O)R_{3A}$,

$NHSO_2R_{3A}$, or hydrogen; R_6 is OR_{6A}, $OC(O)R_{6A}$, $N(R_{6B})_2$, $NHC(O)R_{6B}$, hydrogen, or halogen; R_7 is OR_{7A}, $OC(O)R_{7A}$, $N(R_{7B})_2$, $NHC(O)R_{7B}$, hydrogen, or halogen; R_8 is OR_{8A}, $OC(O)R_{8A}$, $N(R_{8B})_2$, $NHC(O)R_{8B}$, hydrogen, or halogen; R_9 is CH_2OR_{9A}, $CH_2OC(O)R_{9A}$, $N(R_{9B})_2$, $NHC(O)R_{9B}$, hydrogen, or halogen; and each of R_{1A}, R_{3A}, R_{6A}, R_{7A}, R_{8A} and R_{9A} is independently hydrogen or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl.

Particular compounds are of formula **IV(a)**:



IV(a)

With regard to each of the formulae shown above that contain the moieties described below, certain embodiments of the invention are such that:

In some, X is O. In others, X is NR_3.

In some, R_1 is hydrogen. In others, R_1 is optionally substituted lower alkyl. In others, R_1 is NHOH. In others, R_1 is OR_{1A} and R_{1A} is, for example, hydrogen or optionally substituted lower alkyl.

In some, R_2 is hydrogen. In others, R_2 is not hydrogen. In others, R_2 is nitrile. In others, R_2 is optionally substituted lower alkyl. In others, R_2 is OR_{2A}. In others, R_2 is $C(O)OR_{2A}$. In some, R_{2A} is hydrogen or optionally substituted lower alkyl.

In some, R_3 is OR_{3A}. In others, R_3 is $N(R_{3A})_2$ or $NHC(O)R_{3A}$. In others, R_3 is $NHSO_2R_{3A}$. In some, R_{3A} is hydrogen or optionally substituted lower alkyl. In others, R_{3A} is optionally substituted aryl or heterocycle.

In some, R_4 is OR_{4A}. In others, R_4 is halogen.

In some, R_5 is $N(R_{5A})_2$. In others, R_5 is hydrogen. In others, R_5 is hydroxyl. In others, R_5 is heteroalkyl (*e.g.*, alkoxy). In others, R_5 is optionally substituted alkyl. In others, R_5 is optionally substituted aryl.

In some, one or more of R_6, R_7, R_8, and R_9 is hydroxy or halogen. In some, all of R_6, R_7, R_8, and R_9 are hydroxyl or acetate.

In some, Z is alkyl optionally substituted with one or more hydroxyl, acetate or halogen moieties.

Compounds of the invention may contain one or more stereocenters, and can exist as racemic mixtures of enantiomers or mixtures of diastereomers. This invention encompasses stereomerically pure forms of such compounds, as well as mixtures of those forms. Stereoisomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. *See, e.g.*, Jacques, J., *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, S. H., *et al.*, *Tetrahedron 33*:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw Hill, NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions*, p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

This invention further encompasses stereoisomeric mixtures of compounds disclosed herein. It also encompasses configurational isomers of compounds disclosed herein, either in admixture or in pure or substantially pure form, such as cis (Z) and trans (E) alkene isomers and syn and anti oxime isomers.

Preferred compounds of the invention are circulating lymphocyte reduction agents. Certain compounds inhibit the amount of circulating lymphocytes, as determined using the method described in the Examples, by greater than about 20, 50, 75, 100, 150 or 200 percent. In this regard, it has been found that while THI is capable of reducing circulating lymphocytes in mice, many analogues and derivatives of THI, such as 1-(4-methyl-5-((1S,2R,3R)-1,2,3,4-tetrahydroxybutyl)thiazol-2-yl)ethanone, have little or no effect on circulating lymphocytes, despite reports to the contrary. *See* WO 97/46543.

Without being limited by theory, compounds of the invention are believed to affect the S1P metabolic pathway, and may inhibit S1P lyase directly or indirectly *in vivo*. Particular compounds are S1P level enhancing agents. Certain compounds increase the amount of S1P, as determined using the method described below in the Examples, by greater than about 10, 15, 20, 25, or 30-fold.

Compounds of the invention can be prepared by methods known in the art (*e.g.*, by varying and adding to the approaches described in Pyne, S.G., ACGC Chem. Res. Comm. 11:108-112 (2000); Halweg, K.M. and Büchi, G., J.Org.Chem. 50:1134-1136

(1985)). Compounds can also be made by the methods disclosed below and variants thereof, which will be apparent to those of ordinary skill in the art.

5.3. Methods of Use

This invention encompasses a method of modulating (*e.g.*, increasing) the amount of S1P in a patient (*e.g.*, a mouse, rat, dog, cat or human) in need thereof, which comprises administering to the patient an effective amount of a compound of the invention (*i.e.*, a compound disclosed herein).

Another embodiment encompasses a method of reducing the number of T-cells in the blood of a patient, which comprises administering to the patient an effective amount of a compound of the invention.

Another embodiment encompasses a method of treating, managing or preventing a disease affected by (or having symptoms affected by) S1P levels, which comprises administering to a patient in need thereof a therapeutically or prophylactically effective amount of a compound of the invention.

Another embodiment encompasses a method of suppressing immune response in a patient, which comprises administering to the patient an effective amount of a compound of the invention.

Another embodiment encompasses a method of treating, managing or preventing an autoimmune or inflammatory disease or disorder, which comprises administering to a patient in need thereof a therapeutically or prophylactically effective amount of a compound of the invention. Examples of diseases and disorders include ankylosing spondylitis, asthma (*e.g.*, bronchial asthma), atopic dermatitis, Behcet's disease, graft-vs-host disease, Kawasaki syndrome, lupus erythematosus, multiple sclerosis, myasthenia gravis, pollinosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleroderma, transplant rejection (*e.g.*, of organ, cell or bone marrow), type 1 diabetes, and uveitis.

Additional diseases and disorders include Addison's Disease, anti-phospholipid syndrome, autoimmune atrophic gastritis, achlorhydra autoimmune, Celiac Disease, Crohn's Disease, Cushing's Syndrome, dermatomyositis, Goodpasture's Syndrome, Grave's Disease, Hashimoto's thyroiditis, idiopathic adrenal atrophy, idiopathic thrombocytopenia, Lambert-Eaton Syndrome, pemphigoid, pemphigus vulgaris, pernicious anemia, polyarteritis nodosa, primary biliary cirrhosis, primary sclerosing

cholangitis, Raynauds, Reiter's Syndrome, relapsing polychondritis, Schmidt's Syndrome, Sjogren's Syndrome, sympathetic ophthalmia, Takayasu's Arteritis, temporal arteritis, thyrotoxicosis, ulcerative colitis, and Wegener's granulomatosis.

The amount, route of administration and dosing schedule of a compound will depend upon factors such as the specific indication to be treated, prevented, or managed, and the age, sex and condition of the patient. The roles played by such factors are well known in the art, and may be accommodated by routine experimentation. In a particular embodiment, a compound of the invention is administered to a human patient in an amount of about 0.5, 1, 2.5 or 5 mpk.

5.4. Pharmaceutical Formulations

This invention encompasses pharmaceutical compositions comprising one or more compounds of the invention. Certain pharmaceutical compositions are single unit dosage forms suitable for oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal, or rectal), parenteral (*e.g.*, subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), or transdermal administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; aerosols (*e.g.*, nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; and sterile solids (*e.g.*, crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

The formulation should suit the mode of administration. For example, oral administration requires enteric coatings to protect the compounds of this invention from degradation within the gastrointestinal tract. Similarly, a formulation may contain ingredients that facilitate delivery of the active ingredient(s) to the site of action. For example, compounds may be administered in liposomal formulations, in order to protect them from degradative enzymes, facilitate transport in circulatory system, and effect delivery across cell membranes to intracellular sites.

Similarly, poorly soluble compounds may be incorporated into liquid dosage forms (and dosage forms suitable for reconstitution) with the aid of solubilizing agents, emulsifiers and surfactants such as, but not limited to, cyclodextrins (*e.g.*, α-cyclodextrin, β-cyclodextrin, Captisol®, and Encapsin™ (*see, e.g.*, Davis and Brewster, 2004, Nat. Rev. Drug Disc. 3:1023-1034), Labrasol®, Labrafil®, Labrafac®, cremafor, and non-aqueous solvents, such as, but not limited to, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, dimethyl sulfoxide (DMSO), biocompatible oils (*e.g.*, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols, fatty acid esters of sorbitan, and mixtures thereof (*e.g.*, DMSO:cornoil).

Poorly soluble compounds may also be incorporated into suspensions using other techniques known in the art. For example, nanoparticles of a compound may be suspended in a liquid to provide a nanosuspension (*see, e.g.*, Rabinow, 2004, Nature Rev. Drug Disc. 3:785-796). Nanoparticle forms of compounds described herein may be prepared by the methods described in U.S. Patent Publication Nos. 2004-0164194, 2004-0195413, 2004-0251332, 2005-0042177 A1, 2005-0031691 A1, and U.S. Patent Nos. 5,145,684, 5,510,118, 5,518,187, 5,534,270, 5,543,133, 5,662,883, 5,665,331, 5,718,388, 5,718,919, 5,834,025, 5,862,999, 6,431,478, 6,742,734, 6,745,962, the entireties of each of which are incorporated herein by reference. In one embodiment, the nanoparticle form comprises particles having an average particle size of less than about 2000 nm, less than about 1000 nm, or less than about 500 nm.

The composition, shape, and type of a dosage form will vary depending on its use. For example, a dosage form used in the acute treatment of a disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. *See, e.g.*, *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

5.4.1. Oral Dosage Forms

Pharmaceutical compositions of the invention suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules, and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. *See, e.g., Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

Typical oral dosage forms are prepared by combining the active ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by conventional methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary. Disintegrants may be incorporated in solid dosage forms to facility rapid dissolution. Lubricants may also be incorporated to facilitate the manufacture of dosage forms (*e.g.*, tablets).

5.4.2. Parenteral Dosage Forms

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are specifically sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited

to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

5.4.3. Transdermal, Topical and Mucosal Dosage Forms

Transdermal, topical, and mucosal dosage forms include, but are not limited to, ophthalmic solutions, sprays, aerosols, creams, lotions, ointments, gels, solutions, emulsions, suspensions, or other forms known to one of skill in the art. *See, e.g.*, *Remington's Pharmaceutical Sciences*, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990); and *Introduction to Pharmaceutical Dosage Forms*, 4th ed., Lea & Febiger, Philadelphia (1985). Transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide transdermal, topical, and mucosal dosage forms are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied.

Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients of the invention. For example, penetration enhancers may be used to assist in delivering active ingredients to the tissue.

The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates may also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or

penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

6. EXAMPLES

Aspects of this invention can be understood from the following examples, which do not limit its scope.

6.1. S1P Lysase Gene-Disrupted Mice

Gene trapping is a method of random insertional mutagenesis that uses a fragment of DNA coding for a reporter or selectable marker gene as a mutagen. Gene trap vectors have been designed to integrate into introns or exons in a manner that allows the cellular splicing machinery to splice vector encoded exons to cellular mRNAs. Gene trap vectors typically contain selectable marker sequences that are preceded by strong splice acceptor sequences and are not preceded by a promoter. Thus, when such vectors integrate into a gene, the cellular splicing machinery splices exons from the trapped gene onto the 5' end of the selectable marker sequence. Typically, such selectable marker genes can only be expressed if the vector encoding the gene has integrated into an intron. The resulting gene trap events are subsequently identified by selecting for cells that can survive selective culture.

Embryonic stem cells (derived murine strain A129) were mutated by a process involving the insertion of at least a portion of a genetically engineered vector sequence into the SP1 lyase gene. The mutated embryonic stem cells were then microinjected into blastocysts, which were subsequently introduced into pseudopregnant female hosts and carried to term using established methods. In this case, the virus inserted between exons 1 and 2, and disrupted the SP1 lyase gene. The resulting chimeric animals were subsequently bred to produce offspring capable of germline transmission of an allele containing the engineered mutation in the SP1 lyase gene.

Techniques useful to disrupt a gene in a cell, and especially an ES cell, that may already have a disrupted gene are disclosed in U.S. Patent Nos. 6,136,566; 6,139,833 and 6,207,371 and U.S. Patent Application No. 08/728,963, each of which are incorporated herein by reference in its entirety.

6.2. Hematological Effects of S1P Lyase Gene Disruption

Whole blood was collected by retrorbital bleed and placed in a capillary blood collection tube that contained EDTA. The blood was analyzed using the Cell-Dyn 3500R analyzer (Abbott Diagnostics). The analyzer employs dual technologies to provide the basis for a five-part white blood cell (WBC) differential identification. Multi-Angle Polarized Scatter Separation (M.A.P.S.S.) provides the primary white blood cell count and differential information, while impedance provides additional information in the presence of fragile lymphocytes and hypotonically resistant red blood cells.

Approximately 135 microliters of whole blood was aspirated into the analyzer using a peristaltic pump. Four independent measurement techniques were used by the Cell-Dyn 3500R System (Abbott, IL) to obtain the hematologic parameters. The WBC Optical Count (WOC) and the WBC differential data were measured in the optical flow channel, resulting in the identification of the WBC subpopulations (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) for the five part WBC differential. The WBC Impedance Count (WIC) was measured in one electrical impedance channel. The RBC and platelet data were measured in a second electrical impedance channel. The hemoglobin was measured in the spectrophotometric channel. The sample was aspirated, diluted, mixed, and the measurements for each parameter were obtained during each instrument cycle. The final hematological analysis parameters obtained were white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, red blood cells, hemoglobin, hematocrit, platlets, red cell distribution width, mean corpuscular volume and mean platelet volume.

Blood samples were obtained from a total of 16 mice. Analysis and comparison of the blood samples were obtained from seven wild-type mice, six heterozygous mice and three homozygous mice. There was no significant genotype associated differences between mice from different groups with regard to mean red blood cell (RBC) counts, hemoglobin levels, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet counts or mean platelet volume. There were differences in hematocrit and red cell distribution width. The mean hematocrit in homozygous (-/-) mice was 37 ± 2.56 percent, in heterozygous (+/-) mice, 40.9 ± 4 percent and in wild-type (+/+) mice it was 44.7 ± 2.7 percent. The red blood cell

distribution width in homozygous (-/-) mice was 25.2 ± 4.2 percent, in heterozygous (+/-) mice, 17.6 ± 1.9 percent and in wild-type (+/+) mice it was 17.2 ± 2 percent.

Similarly, SP1 lyase deficient mice had no significant differences in the total white blood cell counts as compared to heterozygous or wild-type mice. Homozygous (-/-) mice had a total white blood cell count of 7200 ± 700 cells/μl. Heterozygous (+/-) mice had total white blood cell count of 6200 ± 1800 cells/μl and wild-type (+/+) mice had a total white blood cell count of 7200 ± 2600 cells/μl.

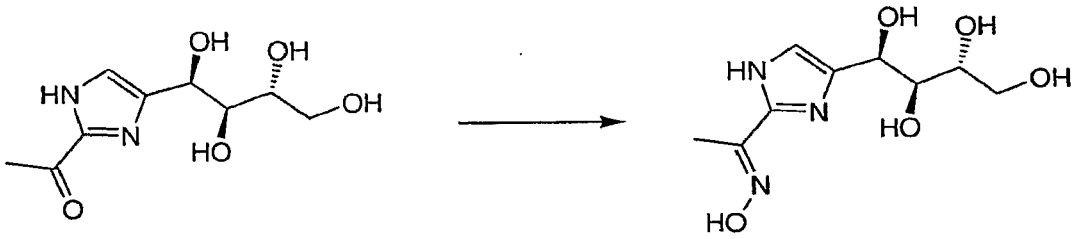
In the mice that were homozygous for disruption of SP1 lyase, lymphocyte counts was decreased, while the number of neutrophils, monocytes, eosinophils, and basophils were increased. The blood lymphocyte counts of mice homozygous(-/-) for disruption in the SP1 lyase gene was greatly reduced. The mean lymphocyte count in homozygous (-/-) mice was 847 ± 139 cells/μl, in heterozygous (+/-) mice the mean lymphocyte count was 4582 ± 2364 cells/μl, as opposed to the mean lymphocyte count in wild-type (+/+) mice which was 6126 ± 2151 cells/μl.

In contrast, mean neutrophil count in homozygous (-/-) mice was 5020 ± 612 cells/μl, while in heterozygous (+/-) mice the mean neutrophil count was 1380 ± 1140 cells/μl and wild-type (+/+) mice had a mean neutrophil count of only 886 ± 479 cells/μl. Similarly, the mean monocyte count in homozygous (-/-) mice was 950 ± 218 cells/μl, while in heterozygous (+/-) mice the mean monocyte count was 250 ± 108 cells/μl and in wild-type (+/+) mice the mean monocyte count was only 146 ± 92 cells/μl. Likewise with eosinophils, the mean eosinophil count in homozygous (-/-) mice was 247 ± 297 cells/μl, while in heterozygous (+/-) mice the mean eosinophil count was 8 ± 8 cells/μl and in wild-type (+/+) mice the mean eosinophil count was only 14 ± 21 cells/μl.

The same was true of basophils. The mean basophil count in homozygous (-/-) mice was 130 ± 90 cells/μl, in heterozygous (+/-) mice the mean basophil count was 7 ± 5 cells/μl and in wild-type (+/+) mice the mean basophil count was only 16 ± 11 cells/μl.

Similarly, the mean monocyte count in homozygous (-/-) mice was 950 ± 218 cells/μl, while in heterozygous (+/-) mice the mean monocyte count was 250 ± 108 cells/μl and in wild-type (+/+) mice the mean monocyte count was only 146 ± 92 cells/μl. Likewise with eosinophils, the mean eosinophil count in homozygous (-/-) mice was 247 ± 297 cells/μl, while in heterozygous (+/-) mice the mean eosinophil count was 8 ± 8 cells/μl and in wild-type (+/+) mice the mean eosinophil count was only 14 ± 21 cells/μl.

6.3. Synthesis of (Z)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime

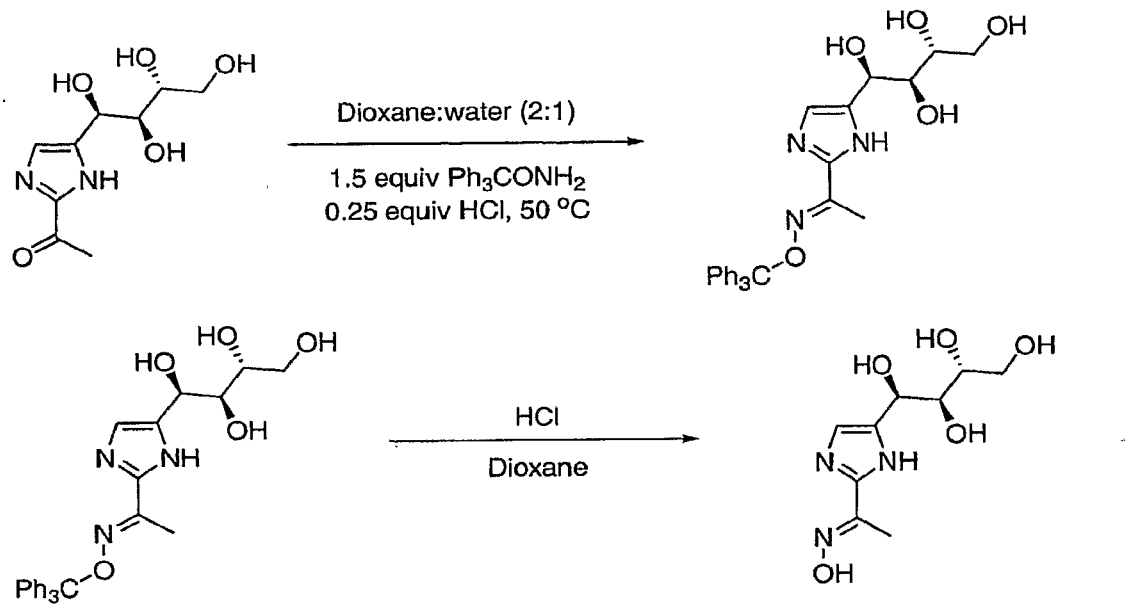


1-[4-((1R,2S,3R)-1,2,3,4-Tetrahydroxy-butyl)-1H-imidazol-2-yl]-ethanone (THI, prepared according to Halweg, K.M. and Büchi, G., J.Org.Chem. 50:1134-1136 (1985)) (350 mg, 1.52 mmol) was suspended in water (10 ml). Hydroxylamine hydrochloride (126.8 mg, 1.82 mmol, 1.2 eq.) and sodium acetate (247.3 mg, 3.04 mmol. 2 eq.) was added, and the suspension was stirred at 50°C. The reaction mixture turned clear after approximately 4 hours. Stirring was continued at 50°C for 16 hours. LCMS analysis indicated the formation of the product and the absence of starting material. The reaction mixture was allowed to attain room temperature and passed through a fine porosity filter. This solution was used directly to purify the product by using preparative HPLC: Atlantis HILIC silica column 30 x 100mm; 2% - 21% water in acetonitrile over 6 minutes; 45 ml/min; with detection at 254 nm. The product fractions were collected and the acetonitrile was evaporated under reduced pressure. The aqueous solution was lyophilized to yield the product, a mixture of approximately 3:1 anti:syn isomers, as a white solid: 284 mg (77%).

LCMS: Sunfire C-18 column, 4.6 x 50mm; 0 – 17% MeOH (0.1% TFA) in water (0.1% TFA) over 5 min; flow rate = 3 ml/min; Detection 220nm; Retention times : 0.56 min (syn isomer, 246.0 (M+1)) and 0.69 min (anti isomer, 246.0 (M+1)). ^{1}H NMR (D_2O and DCl) δ 2.15 and 2.22 (singlets, 3H), 3.5 – 3.72 (m, 4H), 4.76 (br, OH protons and H-$_2O$), 4.95 and 4.97 (singlets, 1H), 7.17 and 7.25 (singlets, 1H). ^{13}C NMR (D_2O and DCl) δ 10.80, 16.76, 63.06, 64.59, 64.75, 70.86, 72.75, 72.85, 117.22, 117.64, 135.32, 138.39, 141.35, 144.12.

6.4. Synthesis of (E)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime

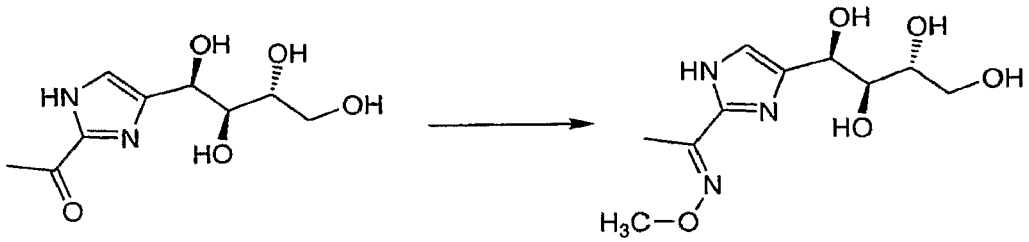
This compound was prepared in two steps, as shown below



First, to a flask charged with THI (21.20 mmol, 4.88g) is added water (25 ml) and 1N aqueous HCl (21.2 ml, 21.2 mmol). After all solids dissolved, a solution of trityl hydroxylamine (25.44 mmol, 7.00 g) in dioxane (55 ml) was added and the reaction was maintained at 50°C for 4h. At completion, the reaction was cooled room temperature and the solution was adjusted to pH=7 by addition of 1N aqueous NaOH. The neutralized solution was then concentrated to a plastic mass, which was purified by flash chromatography on silica gel [10% MeOH/1% NH_4OH (5% wt. solution in water) in DCM] to provide the trityl-ether as clear plastic. Treatment of the plastic mass with hexane and concentration provided a white foam, which could be dried under vacuum to a flakey solid (10.00 g, 97% yield).

Second, to a vigorously stirred, room temperature solution of the trityl oxime-ether (4.8 g, 10 mmol) in dioxane (90 ml) is added a solution of HCl in dioxane (4M, 60 ml). After a few minutes, a white precipitant was observed, and stirring was continued for a total of 30 minutes, before filtering over a fritted glass filter and rinsing the cake with dioxane and ether. The cake was redissolved in water (200 ml), sonicated for 5 min, then cooled to 0°C, treated with celite (5 g), and filtered over a fritted glass filter. The aqueous solution was concentrated to dryness, then isolated from methanol (30 ml) / diethyl ether (60 ml) to provide the *E*-oxime as an analytically pure white powder (3.8 g, 80% yield).

6.5. Synthesis of (Z)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone O-methyl oxime

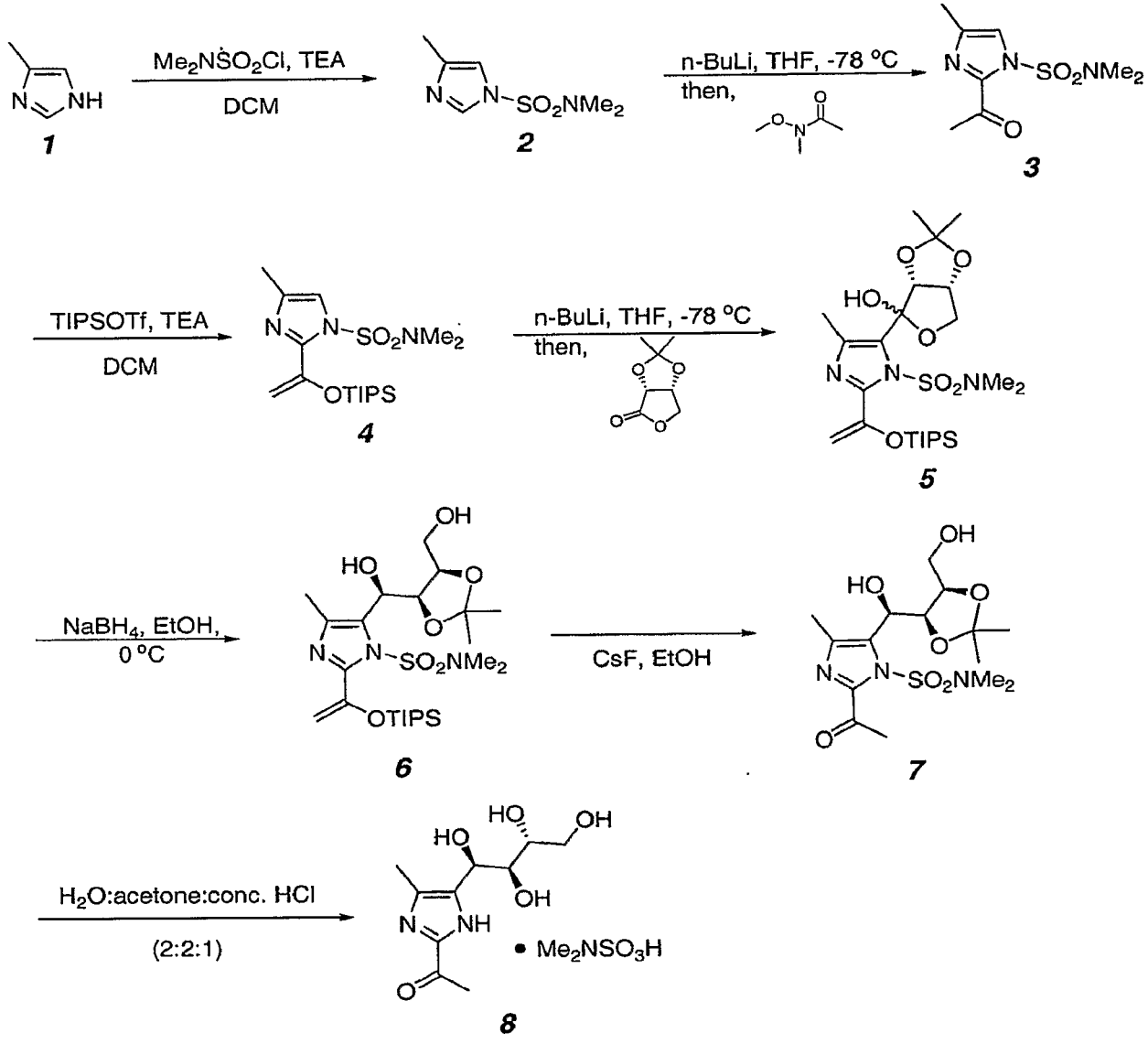


The captioned compound was prepared as described above in Example 6.3, by using methoxylamine hydrochloride in place of hydroxylamine hydrochloride, in 74% yield. The product was a white fluffy solid.

LCMS: Sunfire C-18 column, 4.6 x 50mm; 0 – 17% MeOH (0.1% TFA) in water (0.1% TFA) over 5 min; flow rate = 3 ml/min; Detection 220 nm; Retention times : 1.59 minutes (syn isomer, 260.1 (M+1)) and 1.73 min (anti isomer, 260.1 (M+1)). ^{1}H NMR (D_2O) δ 2.18 and 2.22 (singlets, 3H), 3.54 – 3.60 (m, 1H), 3.66 – 3.79 (m, 3H), 3.94 and 3.95 (singlets, 3H), 4.76 (br, OH protons and H_2O), 4.93 and 4.97 (singlets, 1H), 7.17 and 7.25 (singlets, 1H). ^{13}C NMR (D_2O) δ 11.55, 17.56, 62.32, 62.38, 62.99, 63.07, 67.09, 71.54, 73.86, 119.09, 138.64, 139.79, 142.95, 144.98, 148.97.

6.6. Synthesis of 1-(5-methyl-4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone

The captioned compound was prepared in seven steps, using the process outlined below.



4-Methylimidazole-1-dimethylaminosulfonamide (2): To a room temperature solution of 4-methyl imidazole *1* (3.00 g, 36.54 mmol) in toluene (200 ml) was consecutively added triethylamine 5.6 ml, 40.20 mmol) and *N,N*-dimethylaminosulfamoyl chloride (3.9 ml, 36.54 mmol). The vessel was stored in a 5°C refrigerator for 48 hours, then the solids were filtered off from the reaction and the liquor was concentrated to

obtain a 2.5:1 mixture of regioisomers *2* and *2a*. The crude product was purified by flash chromatography over silica gel (80-100% ethyl acetate:hexane eluent) to obtain a *2:2a* in a 5.5:1 mixture of regioisomers (4.31 g, 62% yield): M+1=190.1

4-Methy-2-acetylimidazole-1-dimethylaminosulfonamide (3): To a -78°C solution of the imidazole *2* (1.99 g, 10.54 mmol) in tetrahydrofuran (70 ml) was added slowly a solution of *n*-BuLi in hexane (2.5M, 11.60 ml). After 40 minutes, *N*-methoxy-*N*-methylacetamide (1.30 g, 12.65 mmol) was added dropwise to the cooled solution. The reaction was allowed to warm to room temperature and maintained for 2 hours. At completion, the reaction was quenched by addition of saturated aqueous NH_4Cl (20 ml), then diluted with water (20 ml). The layers were separated, and the organic layer was washed with ethyl acetate (2 x 30 ml). The combined organics were washed with brine (20 ml), then dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography over silica (60-80% ethyl acetate:hexane eluent) to provide *3* as an oil (1.85 g, 76% yield): M+1 = 232.1.

4-Methyl-2-(1-(triisopropylsilyloxy)vinyl)-1-dimethylaminosulfonamide (4): To a solution of imidazole **3** (1.65 g, 7.14 mmol) in dichloromethane (45 ml) was consecutively added triethylamine (1.00 ml, 14.28 mmol) and triisopropylsilyl trifluoromethanesulfonate (2.12 ml, 7.86 mmol). The reaction was maintained at room temperature for 20 hours, then quenched by the addition of saturated aqueous $NaHCO_3$ (20 ml). The mixture was diluted with water (20 ml) and the layers were separated. The aqueous layer was washed with dichloromethane (2 x 20 ml) and the combined organics were washed with brine solution (20 ml), then dried over $MgSO_4$ and concentrated. The resulting oil was purified by flash chromatography over silica gel (1-2% methanol:dichloromethane eluent) to provide silyl enol ether *4* as an orange oil (2.26 g, 83% yield): M+1= 388.2.

Lactol (5): To a -78°C solution of imidazole *4* (2.26 g, 5.84 mmol) in tetrahydrofuran (40 ml) was slowly added a hexane solution of *n*-BuLi (2.5M, 3.27 ml). After 30 minutes, a solution of (-)-2,3-*O*-isopropylidine-*D*-erythronolactone (1.66 g, 10.51 mmol) in tetrahydrofuran (10 ml) was added slowly to the -78°C solution. The reaction was maintained at -78°C for 2 hours, then allowed to warm to 0°C before quenching the reaction by addition of saturated aqueous NH_4Cl (20 ml). The mixture was diluted with water (10 ml) and the layers were separated. The organics were washed with

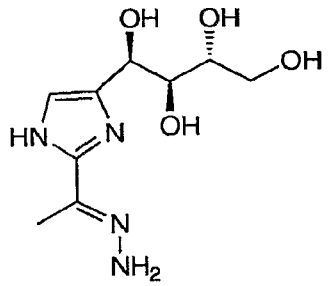
ethyl acetate (2 x 20 ml) and the combined organics were washed with brine (20 ml), then dried over $MgSO_4$ and concentrated. The crude product was purified on silica gel (30-50% ethyl acetate:hexane eluent) to provide the lactol *5* (2.69 g, 85% yield) as a white foam: M+1 =546.4. .

Diol (6): To a 0°C solution of the lactol *5* (2.09 g, 3.83 mmol) in ethanol (70 ml) was added granular $NaBH_4$ (1.4 g, 38.32 mmol) in a few portions. After 2 hours, the reaction was warmed to room temperature for 30 minutes, then concentrated. The residue was redissolved in water (40 ml) and ethyl acetate (40 ml). The biphasic mixture was stirred vigorously for 10 minutes, then the layers were separated. The aqueous layer was washed with ethyl acetate (2 x 40 ml) and the combined organics were washed with brine (30 ml), then dried over $MgSO_4$ and concentrated. The crude foam was purified by flash chromatography over silica (5% methanol:dichloromethane eluent) to provide diol *6* (1.88g, 90% yield) as a 3:1 mixture of inseparable diasteromers at the benzylic position: M+1= 547.4.

Imidazole (7): Cesium fluoride (315 mg, 2.08 mmol) was added to a solution of the imidazole *6* (567 mg, 1.04 mmol) in ethanol (10 ml) and warmed to 65°C. After 1 hour, the reaction was cooled to room temperature and treated with saturated aqueous NH_4Cl (1 ml), then concentrated. The crude product was purified by flash chromatography over silica gel (5% methanol:dichloromethane eluent) to provide imidazole *7* (380 mg, 94% yield) as a white foam: M+1=392.1.

Final Product (8): The protected imidazole *7* (380 mg, 0.97 mmol) was dissolved in acetone (6 ml) and consecutively treated with water (6 ml) and concentrated aqueous HCl (3 ml). The vessel was warmed to 40°C for 45 minutes, then cooled to room temperature and concentrated. The crude material was purified by reverse phase preparative chromatography using a 150mm x 30 mm Zorbax C-6 column using unbuffered solvents by the following method: 1% acetonitrile:water isocratic run for 5 minutes (T_R=1.52 minutes). Following lyophylization, compound *8* was obtained as the dimethylaminosulfamic acid salt an amorphous solid: M+1= 245.1; ^{1}H NMR (400 MHz, $CDCl_3$) *major* δ 5.04 (d, 1H), 3.62 (comp. m, 2H), 3.42 (comp. m, 2H), 2.62 (s, 6H), 2.43 (s, 3H), 2.21 (s, 3H); *minor* δ 5.01 (d, 1H), 3.79 (comp. m, 2H), 3.55 (comp. m, 2H), 2.62 (s, 6H), 2.43 (s, 3H), 2.21 (s, 3H).

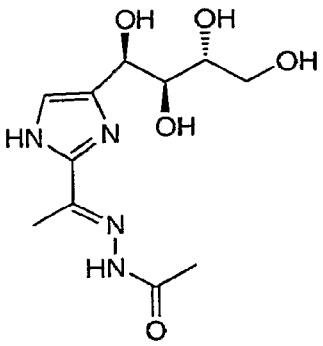
6.7. Synthesis of (1R,2S,3R)-1-(2-(1-hydrazonoethyl)-1H-imidazol-4-yl)butane-1,2,3,4-tetraol



1-[4-((1R,2S,3R)-1,2,3,4-Tetrahydroxy-butyl)-1H-imidazol-2-yl]-ethanone (THI, prepared according to Halweg, K.M. and Büchi, G., J. Org. Chem. 50:1134-1136 (1985)) (148 mg, 0.64 mmol) was suspended in methanol (3 ml) and water (1 ml). Hydrazine hydrate (35 mg, 0.7 mmol, 1.2 eq.) and acetic acid (one drop) were added, and the suspension was stirred at 50°C for 6 hours. LCMS analysis indicated the formation of the product and the absence of starting material. The reaction mixture was cooled to room temperature and diluted with tetrahydrofuran. The resulting white precipitate was collected and washed with tetrahydrofuran to yield the product, a mixture of approximately 3:1 E:Z isomers, as a white solid: 90mg (58%).

LCMS: Zorbax C-8 column, 4.6 x 150mm; 10 – 90% in water (10 mM ammonium acetate) over 6 min; flow rate = 2 ml/min; Detection 220nm; Retention times : 0.576 min (syn isomer, 245.0 (M+1)) and 1.08 min (anti isomer, 245.0 (M+1)). ^{1}H NMR (DMSO-d6) δ 2.5 (singlet, 3H under DMSO), 3.4 – 3.7 (m, 4H), 4.3 (m, 2H), 4.6 (m, 2H), 4.8 (m, 1H), 4.9 and 5.0 (doublets, 1H), 7.04 and 7.21 (singlets, 1H).

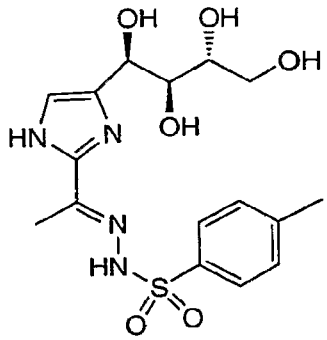
6.8. Synthesis of N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)acetohydrazide



1-[4-((1R,2S,3R)-1,2,3,4-Tetrahydroxy-butyl)-1H-imidazol-2-yl]-ethanone (160 mg, 0.70 mmol) was suspended in methanol (3 ml) and water (1 ml). Acetic hydrazide (56 mg, 0.75 mmol, 1.2 eq.) and hydrochloric acid (one drop, 12 N) were added, and the suspension was stirred at 50°C for 48 hours. LCMS analysis indicated the formation of the product and the absence of starting material. The reaction mixture was cooled to room temperature and diluted with tetrahydrofuran. The resulting white precipitate was collected and washed with tetrahydrofuran to yield the product, a mixture of approximately 3:1 E:Z isomers, as a white solid: 129 mg (65%).

LCMS: Sunfire C-18 column, 4.6 x 50mm; 2 – 20% in water (10 mM ammonium acetate) over 2.5 min; flow rate = 3.5 ml/min; Detection 220 nm; Retention time: 0.53 min (287.1 (M+1)). ^{1}H NMR (DMSO-d6) δ 2.2 (singlets, 3H), 2.5 (singlets, 3H under DMSO), 3.4 – 3.7 (m, 4H), 4.3 (br, 2H), 4.6-5.0 (br, 4H), 7.0 (br, 1H), 10.30 and 10.37 (singlets, 1H).

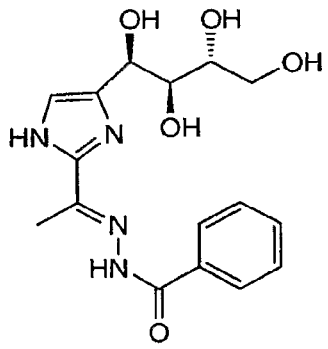
6.9. Synthesis of (E)-4-methyl-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)benzenesulfonohydrazide



1-[4-((1R,2S,3R)-1,2,3,4-Tetrahydroxy-butyl)-1H-imidazol-2-yl]-ethanone (153 mg, 0.67 mmol) was suspended in methanol (3 ml) and water (1 ml). P-toluenesulfonyl hydrazide (140 mg, 0.75 mmol, 1.2 eq.) and hydrochloric acid (one drop, 12 N) were added, and the suspension was stirred at 50°C for 24 hours. LCMS analysis indicated the formation of the product and the absence of starting material. The reaction mixture was cooled to room temperature and dry-loaded on silica gel. Flash chromatography on silica gel (10g SiO_2, 4:1 ethyl acetate:methanol) to yield the product, a mixture of approximately 85:15 E:Z isomers, as a white solid: 142 mg (53%).

LCMS: Sunfire C-18 column, 4.6 x 50mm; 10-90% in water (10 mM ammonium acetate) over 2.5 min; flow rate = 3.5 ml/min; Detection 220nm; Retention times : 0.50 min (399.2 (M+1)) and 0.66 min (399.3 (M+1)). ^{1}H NMR (Methanol-d4) δ 2.2 (singlets, 3H), 2.41 and 2.45 (singlets, 3H), 3.6 – 3.85 (m, 4H), 4.99 and 5.05 (singlets, 1H), 7.09 (br s, 1H), 7.39 (d, 2H, j =8 Hz), 7.77 and 7.87 (d, 2H, j =8 Hz).

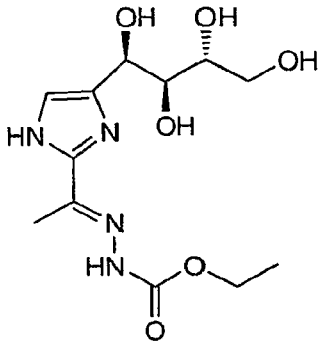
6.10. Synthesis of N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)benzohydrazide



1-[4-((1R,2S,3R)-1,2,3,4-Tetrahydroxy-butyl)-1H-imidazol-2-yl]-ethanone (150 mg, 0.65 mmol) was suspended in methanol (3 ml) and water (1 ml). Benzoic acid hydrazide (102 mg, 0.75 mmol, 1.2 eq.) and hydrochloric acid (one drop, 12 N) were added, and the suspension was stirred at 50°C for 18 hours. LCMS analysis indicated the formation of the product and the absence of starting material. The homogeneous reaction mixture was cooled to room temperature and concentrated in vacuo. C-18 Reverse-Phase SPE (10g Alltech Hi-load C18, gradient from water to 20% methanol/water) to yield the product, a mixture of approximately 1:1 E:Z isomers, as a colorless solid: 193 mg (85%).

LCMS: Sunfire C-18 column, 4.6 x 50mm; 10-90% in water (10 mM ammonium acetate) over 2.5 min; flow rate = 3.5 ml/min; Detection 220 nm; Retention time: 0.49 min (349.2 (M+1)). ^{1}H NMR (Methanol-d4) δ 2.2 (singlets, 3H), 2.42 and 2.45 (singlets, 3H), 3.6 – 3.85 (m, 4H), 5.11 and 5.14 (singlets, 1H), 7.30 (br s, 1H), 7.40-7.7 (m, 4H), 7.80 and 7.95 (m, 2H), 8.1 (br s, 1H).

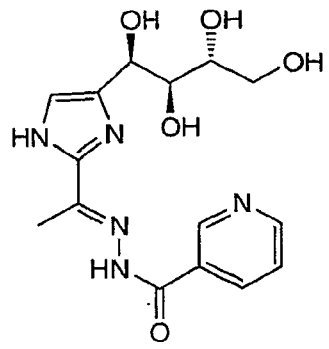
6.11. Synthesis of (E)-ethyl 2-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)hydrazinecarboxylate



1-[4-((1R,2S,3R)-1,2,3,4-Tetrahydroxy-butyl)-1H-imidazol-2-yl]-ethanone (150 mg, 0.65 mmol) was suspended in methanol (3 ml) and water (1 ml). Ethyl carbazate (78 mg, 0.75 mmol, 1.2 eq.) and hydrochloric acid (one drop, 12 N) were added, and the suspension was stirred at 50°C for 18 hours. LCMS analysis indicated the formation of the product and the absence of starting material. The reaction mixture was cooled to room temperature, concentrated in vacuo, and diluted with acetone. The resulting white precipitate was collected and washed with acetone to yield the product, one apparent isomer, as a white solid: 96mg (47%).

LCMS: Sunfire C-18 column, 4.6 x 50mm; 2 – 20% in water (10 mM ammonium acetate) over 2.5 min; flow rate = 3.5 ml/min; Detection 220 nm; Retention time: 0.25 min (317.35 (M+1)). ^{1}H NMR (Methanol-d4) δ 1.36 (t, 3H, j =8 Hz), 2.28 (s, 3H), 2.42 and 2.45 (singlets, 3H), 3.60 – 3.85 (m, 4H), 4.34 (dd, 2H, j =8 Hz), 5.08 (s, 1H), 7.27 (s, 1H).

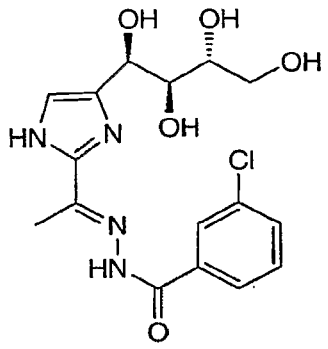
6.12. Synthesis of (E)-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)nicotinohydrazide



1-[4-((1R,2S,3R)-1,2,3,4-Tetrahydroxy-butyl)-1H-imidazol-2-yl]-ethanone (215 mg, 0.93 mmol) was suspended in methanol (3 ml) and water (1 ml). Nicotinic acid hydrazide (137 mg, 1.0 mmol, 1.1 eq.) and hydrochloric acid (one drop, 12 N) were added, and the suspension was stirred at 50°C for 48 hours. LCMS analysis indicated the formation of the product and the absence of starting material. The reaction mixture was cooled to room temperature, and partially concentrated in vacuo. The resulting white precipitate was collected and washed with water to yield the product, one apparent isomer, as a white solid: 311 mg (95%).

LCMS: Sunfire C-18 column, 4.6 x 50mm; 10 – 90% in water (10 mM ammonium acetate) over 2.5 min; flow rate = 3.5 ml/min; Detection 220nm; Retention time: 0.22 min (350.27 (M+1)). ^{1}H NMR (DMSO-d_6) δ 2.37 (s, 3H), 3.60 – 3.85 (m, 4H), 4.40 (m, 2H), 4.71 (m, 1H), 5.01 (m, 2H), 5.16 (m, 1H), 7.25 (br, 1H), 7.64 (br, 1H). 8.35 (br, 1H). 8.80 (br, 1H). 9.14 (br, 1H).

6.13. Synthesis of 3-chloro-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)benzohydrazide

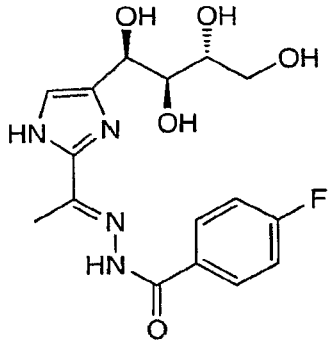


1-[4-((1R,2S,3R)-1,2,3,4-Tetrahydroxy-butyl)-1H-imidazol-2-yl]-ethanone (194 mg, 0.84 mmol) was suspended in ethanol (4 ml) and water (1 ml). 3-chlorobenzoic acid hydrazide (170 mg, 1.0 mmol, 1.2 eq.) and hydrochloric acid (one drop, 12 N) were added, and the suspension was stirred at 50°C for 48 hours. LCMS analysis indicated the formation of the product and the absence of starting material. The reaction mixture was cooled to room temperature, and partially concentrated in vacuo. The resulting white precipitate was collected and washed with ethanol to yield the product, as a ~3:1 E:Z mixture, as a white solid: 108mg (33%).

LCMS: Sunfire C-18 column, 4.6.x 50mm; 10– 90% in water (10 mM ammonium acetate) over 2.5 min; flow rate = 3.5 ml/min; Detection 220nm; Retention time: 0.63 min

(383.23 (M+1)). ^{1}H NMR (Methanol-d4) δ 2.44 (s, 3H), 3.60 – 3.90 (m, 4H), 5.12 (s, 1H), 7.29 (s, 1H), 7.65 (m, 2H), 8.04 (m, 2H).

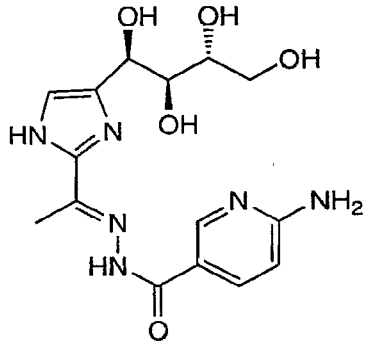
6.14. Synthesis of (E)-4-fluoro-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)benzohydrazide



1-[4-((1R,2S,3R)-1,2,3,4-Tetrahydroxy-butyl)-1H-imidazol-2-yl]-ethanone (172 mg, 0.74 mmol) was suspended in ethanol (4 ml) and water (1 ml). 4-fluorobenzoic acid hydrazide (131 mg, 0.85 mmol, 1.1 eq.) and hydrochloric acid (one drop, 12 N) were added, and the suspension was stirred at 55°C for 48 hours. LCMS analysis indicated the formation of the product and the absence of starting material. The reaction mixture was cooled to room temperature, and partially concentrated in vacuo. The resulting white precipitate was collected and washed with ethanol to yield the product, as one apparent isomer, as a white solid: 97 mg (35%).

LCMS: Sunfire C-18 column, 4.6 x 50mm; 10– 90% in water (10 mM ammonium acetate) over 2.5 min; flow rate = 3.5 ml/min; Detection 220nm; Retention time: 0.55 min (367.24 (M+1)). ^{1}H NMR (Methanol-d4, one drop DCl) δ 2.55 (s, 3H), 3.60 – 3.90 (m, 4H), 5.22 (s, 1H), 7.30 (m, 2H), 7.54 (s, 1H), 8.08 (m, 2H).

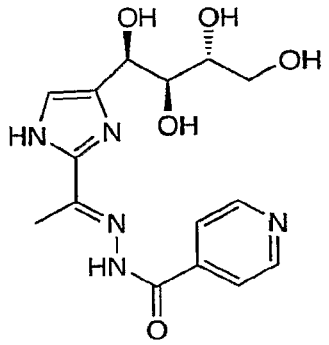
6.15. Synthesis of (E)-6-amino-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)nicotinohydrazide



1-[4-((1R,2S,3R)-1,2,3,4-Tetrahydroxy-butyl)-1H-imidazol-2-yl]-ethanone (115 mg, 0.50 mmol) was suspended in ethanol (4 ml) and water (1 ml). Substituted hydrazide (91 mg, 0.6 mmol, 1.2eq.) and hydrochloric acid (one drop, 12 N) were added, and the suspension was stirred at 55°C for 48 hours. LCMS analysis indicated the formation of the product and the absence of starting material. The reaction mixture was cooled to room temperature, and partially concentrated in vacuo. The resulting white precipitate was collected and washed with ethanol to yield the product, as one apparent isomer, as a white solid: 136mg (75%).

LCMS: Sunfire C-18 column, 4.6 x 50mm; 10– 90% in water (10 mM ammonium acetate) over 2.5 min; flow rate = 3.5 ml/min; Detection 220nm; Retention time: 0.15 min (365.32 (M+1)). ^{1}H NMR (Methanol-d4, one drop DCl) δ 2.58 (s, 3H), 3.60 – 3.90 (m, 4H), 5.22 (s, 1H), 7.17 (m, 1H), 7.54 (m, 1H), 8.44 (m, 1H), 8.68 (m, 1H).

6.16. Synthesis of (E)-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)isonicotinohydrazide

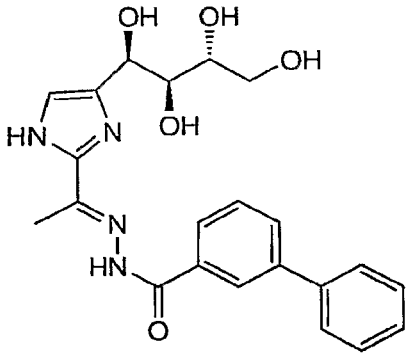


1-[4-((1R,2S,3R)-1,2,3,4-Tetrahydroxy-butyl)-1H-imidazol-2-yl]-ethanone (168 mg, 0.73 mmol) was suspended in ethanol (4 ml) and water (1 ml). Isonicotinic

hydrazide (110 mg, 0.80 mmol, 1.1eq.) and hydrochloric acid (one drop, 12 N) were added, and the suspension was stirred at 55°C for 24 hours. LCMS analysis indicated the formation of the product and the absence of starting material. The reaction mixture was cooled to room temperature, and partially concentrated in vacuo. The resulting white precipitate was collected and washed with ethanol to yield the product, as one apparent isomer, as a white solid: 136 mg (75%).

LCMS: Sunfire C-18 column, 4.6 x 50mm; 10– 90% in water (10 mM Ammonium Acetate) over 2.5 min; flow rate = 3.5 ml/min; Detection 220nm; Retention time: 0.15 min (365.32 (M+1)). ^{1}H NMR (Methanol-d4, one drop DCl) δ 2.63 (s, 3H), 3.60 – 3.90 (m, 4H), 5.12 (s, 1H), 7.58 (s, 1H), 8.63 (d, 2H, j = 8 Hz), 9.14 (d, 2H, j = 8 Hz).

6.17. Synthesis of (E)-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)biphenyl-3-carbohydrazide



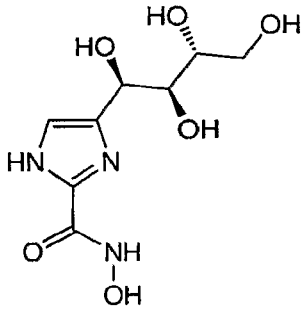
1-[4-((1R,2S,3R)-1,2,3,4-Tetrahydroxy-butyl)-1H-imidazol-2-yl]-ethanone (315 mg, 1.36 mmol) and biphenyl-3-carbohydrazide (360 mg, 1.81 mmol) were suspended in DMSO (2 ml). Concentrated hydrochloric acid (two drops) was added, and the suspension was stirred at 40°C for 5 hours. LCMS analysis indicated the formation of the product and the absence of starting material. The reaction mixture was cooled to room temperature, diluted with methanol and purified by reverse phase HPLC (10 mM NH_4OAc / acetonitrile). Two fractions (E and Z isomers) of the desired mass were collected separately and lyophized. Fraction one afforded a white solid, 95 mg (16%). Fraction two was a white solid, 82 mg (14%).

Fraction one: Analytical HPLC Zorbax C-8 column, 4.6 x 150mm; Solvent A = 10 mM ammonium acetate; Solvent B = MeCN; 5% B at 0 min, 5% B at 1 min, 90% B at 3

min, 4 min stop; flow rate = 3 ml/min; Detection 220 nm; Retention time : 2.9 min (note: contains ~5% of the other isomer). M+H = 425.28. ^{1}H NMR (DMSO-d6 with 2 drops D_2O) δ 2.3 (singlet, 3H) , 3.3 – 3.7 (m, 4H), 4.9 (m, 1H), 7.19 (s, 1H), 7.37 (m, 1H) 7.47 (m, 2H), 7.67 (m, 3H), 7.85-7.92 (m, 2H) and 8.15 (s, 1H). HSQC of the same sample correlated the proton signal at 2.3 (CH_3) with a carbon signal at 20 ppm.

Fraction two: Analytical HPLC Zorbax C-8 column, 4.6 x 150mm; Solvent A = 10 mM ammonium acetate; Solvent B = MeCN; 5% B at 0 min, 5% B at 1 min, 90% B at 3 min, 4 min stop; flow rate = 3 ml/min; Detection 220 nm; Retention time : 2.963 min (note: contains ~6% of the other isomer). M+H = 425.28. ^{1}H NMR (DMSO-d_6 with 2 drops D_2O) δ 2.4 (singlet, 3H), 3.4 – 3.6 (m, 4H), 4.77 and 4.86 (broad singlets, combined = 1H), 6.9 and 7.1 (broad singlets, combined = 1H), 7.40 (m, 1H) 7.50 (m, 2H), 7.61 (m, 1H), 7.73 (m, 2H), 7.87 (m, 2H) and 8.10 (s, 1H). HSQC of the same sample correlated the proton signal at 2.4 (CH_3) with a carbon signal at 13 ppm.

6.18. Synthesis of N-hydroxy-4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazole-2-carboxamide



1-[4-((1R,2S,3R)-1,2,3,4-Tetrahydroxy-butyl)-1H-imidazol-2-yl]-ethanone (18 g, 78.3 mmol) was suspended in dichloroethane (160 ml) and 2,2-dimethoxy propane (160 ml). 4-toluenesulfonic acid (3 g) was added and the mixture stirred at 70°C for 18 hours. The reaction was diluted with dichloromethane and washed with water, 5% bicarbonate, brine and then dry loaded onto SiO_2. Purification by flash chromatography (hexane / ethyl acetate) afforded 1-(4-((4S,4'R,5R)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-1H-imidazol-2-yl)ethanone as a colorless oil (18.8 g, 60.6 mmol, 77%; M+H calc: 311.4, obs: 311.3).

The product obtained above (20 g, 64.5 mmol) was dissolved in DMF. K_2CO_3 was added (12.5 g, 90.3 mmol) followed by benzyl bromide (10.7 ml, 90.3 mmol). The

reaction was heated at 50°C for 18 h. LC/MS analysis indicated starting material remained. An additional portion of benzyl bromide (5 ml, 42 mmol) was added and the temperature increased to 60°C. After 3 hours the reaction was quenched with cold water and extracted with ethyl acetate. The organic extracts were washed with water, then brine, dried over sodium sulfate, and loaded onto silica gel. Flash chromatography (20 to 40% ethyl acetate in hexane) afforded 1-(1-benzyl-4-((4S,4'R,5R)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-1H-imidazol-2-yl)ethanone (16.1 g, 62%).

The intermediate obtained (13g, 32.5 mmol) was dissolved in dioxane (120 ml) and treated with NaOH (13.2 g) dissolved in commercial bleach (200 ml, 6% NaOCl). After 2 h of vigorous stirring, the reaction was extracted with ethyl acetate. Organic extracts were washed with brine then dried over celite. Filtration and evaporation afforded a solid that was further dried in vacuo to afford 1-benzyl-4-((4S,4'R,5R)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-1H-imidazole-2-carboxylic acid (13 g, quantitative yield, M+H calc: 403.2, obs: 403.2).

The product obtained above (600 mg, 1.49 mmol), O-tritylhydroxylamine (820 mg, 2.98 mmol), EDAC (430 mg, 2.24 mmol) and HOBt (305 mg, 2.24 mmol) were combined with DMF (8 ml) and triethylamine (622 µl, 4.47 mmol). The reaction was stirred at ambient temperature for 22 h, concentrated and then loaded onto silica using DCM / MeOH. Flash chromatography (MeOH / DCM) afforded 1-benzyl-4-((4S,4'R,5R)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-N-(trityloxy)-1H-imidazole-2-carboxamide (480 mg, 0.73 mmol, 49%, M+H calc: 660.3, obs: 660.4).

The product obtained above (480 mg, 0.73 mmol) was dissolved in ethanol (50 ml). $Pd(OH)_2$ (500 mg, 20% on carbon, wet) was added and the reaction stirred under H_2 (65 psi) for 18 h and filtered. Ethanol was removed in vacuo. The residue was dissolved in DCM and purified by flash chromatography (MeOH / DCM) to afford N-hydroxy-4-((4S,4'R,5R)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-1H-imidazole-2-carboxamide (150 mg, 0.46 mmol, 63%, M+H calc: 328.1, obs: 328.3).

The product obtained above (150 mg, 0.46 mmol) was dissolved in acetone (8 ml) and water (8 ml). The reaction was cooled to an internal temperature -15°C using a dry ice / acetone bath. Concentrated HCl (3 ml) was added at a rate such that the internal temperature remained below -10°C. The cold bath was removed and the reaction stirred at ambient temperature for 3 hours, at 4°C for 18 h and again at ambient temperature for 7

hours. After removal of the acetone and some water in vacuo, a precipitate formed. Dioxane (20 ml) was added followed by THF (10 ml). The solid was isolated by filtration, washed with THF / dioxane and dried in vacuo to afford N-hydroxy-4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazole-2-carboxamide as the hydrochloride salt (98 mg, 0.40 mmol, 87%).

Mass spec.: M+H calc: 248.1, obs: 248.2. Analytical HPLC: Luna Pheny-Hexyl, 5um, 4.6x50 mm, isocratic 10 mM ammonium acetate with 1% acetonitrile, flow rate = 3 ml/min, 220 nm detection, retention time = 0.245 min. ^{1}H NMR (DMSO-d6) δ 3.37-3.64 (m, 4H), 4.96 (broad singlet, 1H), 7.47 (s, 1H), 11.9 (broad singlet, 1H).

6.19. Measuring Effects on Lymphocytes in Mice

Compounds were administered by oral gavage or in drinking water. For oral dosing experiments, compounds were resuspended from crystals at 10 mg/ml in vehicle (*e.g.*, water). Mice (F1 hybrids of 129/B6 strain) were gavaged with a single 100 mg/kg dose of compound (equivalent to 100 mpk of the free base for each compound) or a vehicle-only control, and returned to their cages. Mice were anesthetized using isofluorane eighteen hours after dosing and tissues were collected for analysis as described below. For drinking water studies, compounds were dissolved at 50 mg/L in acidified water (pH = 2.8) containing 10 g/L glucose. The mice were allowed free access to compound-containing water (or glucose solution as a control) for 72 hours. At the end of 72 hours, tissues were collected for analysis.

CBC measurements were obtained as follows. Mice were anesthetized with isofluorane and blood was collected from the retroorbital plexus into EDTA blood collection tubes (Capiject-MQK, Terumo Medical Corp., Elkton, MD). Automated CBC analysis was performed using a Cell-Dyn 3500 (Abbott Diagnostics, Abbott Park, IL) or a HemaVet 850 (Drew Scientific, Inc., Oxford, CT) instrument.

Flow cytometry (FACS) measurements were obtained as follows. Twenty five μl whole blood was lysed by hyoptonic shock, washed once in 2 ml FACS wash buffer (FWB: PBS/0.1% BSA/0.1% NaN_3/2mM EDTA) and stained for 30 minutes at 4°C in the dark with a combination of fluorochrome-conjugated antibodies diluted in 50 μl FWB. After staining, the cells were washed once with 2 ml FWB and resuspended in 300 μl FWB for acquisition.

Standard procedures for non-sterile removal of spleen and thymus were followed. Organs were dispersed into single-cell suspensions by forcing the tissue through a 70 μm cell strainer (Falcon, Becton Dickinson Labware, Bedford, MA). For FACS analysis, RBCs were lysed by hypotonic lysis, washed, and $1x10^6$ cells were incubated with 10 μl anti-CD16/CD32 (Fc Block™, BD-PharMingen, San Diego, CA) (1/10 dilution in FWB) for 15 minutes at 4°C. The cells were stained with a combination of fluorochrome-conjugated antibodies diluted in 50-100 μl FWB, added directly to the cells in Fc Block, for 30 minutes at 4°C in the dark. After staining the cells were washed once with 1 ml FWB, and resuspended in 300 μl FWB for acquisition. All antibodies were purchased from BD-PharMingen, San Diego, CA unless otherwise specified. Samples were analyzed using a FACSCalibur flow cytometer and CellQuest Pro software (Becton Dickinson Immunocytometry Systems, San Jose, CA).

Antibody mixes used for the thymus were: TCRb APC Cy7; CD4 APC; CD8 PerCP; CD69 FITC; and CD62L PEl. Antibody mixes used for spleen and blood were: B220 PerCP; TCRb APC; CD4 APC Cy7; CD8 PE Cy7; CD69 FITC; and CD62L PE.

6.20. Measuring Effects on S1P Levels in Mice

Levels of S1P in mouse (F1 hybrids of 129/B6 strain) spleen were measured using an adaptation of the radio-receptor binding assay described in Murata, N., *et al.*, Anal. Biochem. 282:115-120 (2000). This method utilized HEK293F cells overexpressing Edg-1, one of the S1P receptor subtypes, and was based on the competition of labeled S1P with unlabeled S1P in a given sample.

HEK293F cells were transfected with a pEFneo S1P receptor (Edg-1)-expression vector and a G418-resistant cell clone was selected. The Edg-1-expressing HEK293F cells were cultured on 12 multiplates in DMEM containing 5 % (v/v) FBS in a humidified air:CO_2 (19:1) atmosphere. Twenty four hours before the experiment, the medium was changed to fresh DMEM (without serum) containing 0.1% (w/v) BSA.

Eighteen hours after the test compound was administered, mice were sacrificed and their spleens were removed and frozen. S1P was obtained from the frozen tissue using known methods. *See, e.g.*, Yatomi, Y., *et al.*, FEBS Lett. 404:173-174 (1997). In particular, 10 mouse spleens in 1 ml ice cold 50 mM phosphate buffer (pH 7.5) containing 1 mM EGTA, 1mM DTT and Roche complete protease inhibitors were

homogenized three times at one minute intervals on ice. The result is centrifuged at 2500 rpm and 4°C for 10 minutes to remove cell debris. The supernatant was then ultracentrifuged at 45000 rpm and 4°C in a 70Ti rotor for 1 hour to pull down the membrane-associated proteins. The supernatant was discarded, and the pellet was resuspended in minimal volume (~1 ml) of ice cold 50 mM phosphate buffer (pH 7.5) containing 1 mM EGTA, 1 mM DTT and 33% glycerol with Roche complete protease inhibitors present. The total protein concentration was measured using the Bradford assay.

S1P was extracted into chloroform/KCl/NH_4OH (pH ~ 12), and the upper aqueous phase is kept. It was then extracted in chloroform/methanol/HCl (pH < 1), and the lower organic phase was kept and evaporated to provide S1P, which was stored in a freezer until used. Just before the assay, the dried sample was dissolved by sonication in a binder buffer consisting of 20 mM Tris-HCl (pH 7.5), 100 mM NaCl, 15 mM NaF, and 0.4 % (w/v) BSA.

The S1P content of a sample was measured by a radioreceptor-binding assay based on a competitive binding of [^{33}P]S1P with S1P in the sample on Edg-1-expressing cells. Edg-1-expressing HEK293F cells in confluent 12 multiplates were washed twice with the ice-cold binding buffer and then incubated with the same buffer containing 1 nM [^{33}P]S1P (about 18,00 dpm per well) and increasing doses of authentic S1P or test sample in a final volume of 0.4 ml. The plates were kept on ice for 30 minutes, and the cells were washed twice with the same ice-cold binding buffer to remove unbound ligand. The cells were solubilized with a solution composed of 0.1 % SDS, 0.4 % NaOH, and 2 % Na_2CO_3, and the radioactivity was counted by a liquid scintillation counter. The S1P content in the assay well was estimated by extrapolation from the standard displacement curve. The content of S1P in the initial test sample(s) was calculated by multiplying the value obtained from the standard curve by the recovery efficiency of S1P extraction and the dilution factor.

6.21. Compounds' Effects on Lymphocytes in Mice

Using the methods described above, the *in vivo* effects of various compounds were determined. As shown in Figures 1-3, when administered to mice (F1 hybrids of

129/B6 strain) in drinking water, both THI and a representative compound of the invention (Compound 1) diminished lymphocyte egress from the thymus.

Figure 4 shows the effects of vehicle control (drinking water), THI, compound 1, and 1-(4-methyl-5-((1S,2R,3R)-1,2,3,4-tetrahydroxybutyl)thiazol-2-yl)ethanone (Compound 2) on whole blood counts. Interestingly, the *in vivo* effects reported by Pyne (WO 97/46543) for Compound 2 were not observed.

6.22. Collagen-Induced Arthritis Model

Collagen-induced arthritis (CIA) is a widely used model of rheumatoid arthritis (RA), a disease of the joint caused by autoimmune and inflammatory processes. *See generally*, Wooley P.H. *et al.*, J. Immunol. 135(4):2443-2451; A. Persidis, Nature Biotechnology 17:726-728; Current Protocols in Immunology (John Wiley & Son, Inc. 1996). Early studies established a hierarchy of responsiveness to CIA linked to certain H-2 haplotypes. More recently, Campbell and coworkers re-evaluated CIA in C57BL/129sv (H-2b) mice and found that mice derived from C57B6 background can develop CIA. Campbell I. K, *et al.* Eur. J. Immunol. 30: 1568-1575 (2000).

Here, collagen for injection, 2mg/ml chicken collagen type II (CII) (Sigma) was dissolved in 10 mM acetic acid by stirring overnight at 4°C. Complete Freund's adjuvant (CFA) was purchased ready-made (Sigma). Using a glass syringe, CII was emulsified in an equal volume of CFA just prior to immunization. To immunize mice, a glass syringe and 26G needle were used, and mice were injected with CII/CFA emulsion intradermally at the base of the tail. CFA and 100 μg of chicken CII in a total volume of 50 μl CFA were used for each injection. A booster immunization of 100 μg of CII emulsified in CFA was given via the same route 3 weeks after the primary immunization.

Injection of the collagen led to footpad and joint swelling of mice. Mice were inspected every two to three days for the onset of arthritis, which was assessed by combination of caliper measurements of the thickness of hind footpad and visual evaluation of the affected joints of hind legs. The progression of CIA was followed for 10 weeks after the initial onset of the disease, after which time the disease was assessed by histology of the joints. Mice were considered negative for arthritis if they did not develop CIA within 150 days of type II collagen immunization.

The presence or absence of arthritis in mice was determined by an established visual scoring system. In mouse CIA, any or four paws can be affected. The inflammation at its peak extends from ankle all the way through the digit, and is characterized by extreme swelling and erythema. Once arthritis appeared, each paw was examined 2 to 3 times a week. To evaluate the severity of the inflammation, the widely used visual scoring of 0 to 4 was used, wherein: 0 = normal, no evidence of erythema and swelling; 1 = erythema and mild swelling confined to the mid-foot or ankle joint or individual digits; 2 = erythema and mild swelling extending to the ankle and the mid-foot or swelling in more than one digit; 3 = erythema and moderate swelling extending from the ankle to the metatarsal joints; and 4 = erythema and severe swelling encompassing the ankle, foot and digits.

6.23. Effect in Collagen-Induced Arthritis Model

The effect of a compound of the invention in the CIA model was determined using 30 mice (F1 hybrids of 129/B6 strain) in the model described above. The mice were randomly divided into two blinded groups, which received 0 mpk (vehicle control) or 100 mpk of the compound. The vehicle was sterile, distilled water. The vehicle control was dosed at 10 µl/g body weight.

Dosing was carried out once a day by oral gavage. It began three days prior to initiation of the CIA experiment, and continued throughout the duration of the experiment. Figure 5 shows the effect of the compound on CIA over time, wherein the cumulative score is the sum of the fore-limb and ankle scores.

6.24. The Effect of a Compound in Monkeys

The effect of a compound of the invention in twenty non-naïve, male, cynomolgus monkeys was investigated by Covance Research Products Inc. (Alice, TX). Each animal was identified with an individually numbered tattoo. The animals were acclimated for approximately 11 days prior to dose administration. At the time of dose administration, animals were considered to be young adult/adult in age.

During acclimation and the test period, animals were housed in individual cages. Animals were not commingled for at least 48 hours after dose administration to allow monitoring of any vehicle- or test article-related effects. Animals had access to

non-certified primate diet *ad libitum,* except as specified for dose administration. Fruits and other treats were also provided, as appropriate, during non-fasted periods. Water was provided *ad libitum.*

The tested compound was stored protected from light in a sealed container on desiccant under ambient conditions (approximate room temperature). Distilled water was supplied by Covance for oral administration to animals in the vehicle control group. The test article dose formulations for the test were prepared on the day of administration. For each group, an appropriate quantity of the test article was weighed and an appropriate volume of either distilled water.

All animals were fasted overnight prior to dosing through approximately 4 hours postdose. Individual doses were calculated based on body weights taken on the day of dose administration.

The oral dose was administered via nasogastric intubation. Prior to withdrawing the gavage tube, the tube was flushed with approximately 5 ml of water. For hematology analysis, blood (approximately 0.5 ml) was collected from each animal predose (Day -7), predose (Day -3), and at 8, 16, 24, 32, and 48 hours postdose. The whole blood hematology tests were performed using the fresh samples obtained on the day of collection.

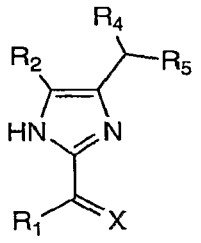
As shown in Figure 6, a single oral dose of the compound had a significant effect on the monkeys' white blood cell and lymphocyte counts, when measured 32 hours after dosing.

All cited publications, patents, and patent applications are herein incorporated by reference in their entireties.

CLAIMS

What is claimed is:

1. A circulating lymphocyte reduction agent of formula **I**:



I

or a pharmaceutically acceptable salt or solvate (*e.g.*, hydrate) thereof, wherein:

X is O or NR_3;

R_1 is OR_{1A}, NHOH, hydrogen, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl;

R_2 is OR_{2A}, $C(O)OR_{2A}$, hydrogen, halogen, nitrile, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl;

R_3 is OR_{3A}, $N(R_{3A})_2$, $NHC(O)R_{3A}$, $NHSO_2R_{3A}$, or hydrogen;

R_4 is OR_{4A}, $OC(O)R_{4A}$, hydrogen, halogen, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl;

R_5 is $N(R_{5A})_2$, hydrogen, hydroxy, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; and

each of R_{1A}, R_{2A}, R_{3A}, R_{4A}, and R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl;

with the proviso that: if X is O; R_1 is alkyl of 1 to 4 carbons, phenyl, benzyl or phenylethyl; R_2 is hydrogen; and one of R_4 and R_5 is hydroxyl; the other of R_4 and R_5 is not alkyl of 1 to 6 carbons, hydroxyalkyl of 1 to 6 carbons, polyhydroxyalkyl of 1 to 6 carbons having up to one hydroxyl per carbon, polyacetylalkyl of 1 to 6 carbons having up to one acetyl per carbon, phenyl, benzyl or phenylethyl.

2. The circulating lymphocyte reduction agent of claim 1, which has a CLRF of greater than about 50 percent.

3. The circulating lymphocyte reduction agent of claim 1, wherein X is O.

4. The circulating lymphocyte reduction agent of claim 1, wherein X is NR_3.

5. The circulating lymphocyte reduction agent of claim 1, wherein R_1 is hydrogen.

6. The circulating lymphocyte reduction agent of claim 1, wherein R_1 is optionally substituted lower alkyl.

7. The circulating lymphocyte reduction agent of claim 1, wherein R_1 is NHOH.

8. The circulating lymphocyte reduction agent of claim 1, wherein R_1 is OR_{1A}.

9. The circulating lymphocyte reduction agent of claim 7, wherein R_{1A} is hydrogen or optionally substituted lower alkyl.

10. The circulating lymphocyte reduction agent of claim 1, wherein R_2 is hydrogen.

11. The circulating lymphocyte reduction agent of claim 1, wherein R_2 is not hydrogen.

12. The circulating lymphocyte reduction agent of claim 1, wherein R_2 is nitrile.

13. The circulating lymphocyte reduction agent of claim 1, wherein R_2 is optionally substituted lower alkyl.

14. The circulating lymphocyte reduction agent of claim 1, wherein R_2 is OR_{2A}.

15. The circulating lymphocyte reduction agent of claim 1, wherein R_2 is $C(O)OR_{2A}$.

16. The circulating lymphocyte reduction agent of claim 14 or 15, wherein R_{2A} is hydrogen or optionally substituted lower alkyl.

17. The circulating lymphocyte reduction agent of claim 1, wherein R_3 is OR_{3A}.

18. The circulating lymphocyte reduction agent of claim 1, wherein R_3 is $N(R_{3A})_2$ or $NHC(O)R_{3A}$.

19. The circulating lymphocyte reduction agent of claim 1, wherein R_3 is $NHSO_2R_{3A}$.

20. The circulating lymphocyte reduction agent of claim 17, 18 or 19, wherein R_{3A} is hydrogen or optionally substituted lower alkyl.

21. The circulating lymphocyte reduction agent of claim 17, 18 or 19, wherein R_{3A} is optionally substituted aryl or heterocycle.

22. The circulating lymphocyte reduction agent of claim 1, wherein R_4 is OR_{4A}.

23. The circulating lymphocyte reduction agent of claim 1, wherein R_4 is halogen.

24. The circulating lymphocyte reduction agent of claim 1, wherein R_5 is $N(R_{5A})_2$.

25. The circulating lymphocyte reduction agent of claim 1, wherein R_5 is hydrogen.

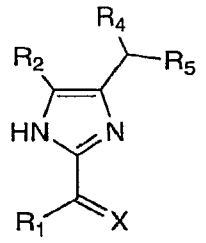
26. The circulating lymphocyte reduction agent of claim 1, wherein R_5 is hydroxyl.

27. The circulating lymphocyte reduction agent of claim 1, wherein R_5 is heteroalkyl (*e.g.*, alkoxy).

28. The circulating lymphocyte reduction agent of claim 1, wherein R_5 is optionally substituted alkyl.

29. The circulating lymphocyte reduction agent of claim 1, wherein R_5 is optionally substituted aryl.

30. A S1P level enhancing agent of formula **I**:



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

X is O or NR_3;

R_1 is OR_{1A}, NHOH, hydrogen, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl;

R_2 is OR_{2A}, $C(O)OR_{2A}$, hydrogen, halogen, nitrile, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl;

R_3 is OR_{3A}, $N(R_{3A})_2$, $NHC(O)R_{3A}$, $NHSO_2R_{3A}$, or hydrogen;

R_4 is OR_{4A}, $OC(O)R_{4A}$, hydrogen, halogen, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl;

R_5 is $N(R_{5A})_2$, hydrogen, hydroxy, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; and

each of R_{1A}, R_{2A}, R_{3A}, R_{4A}, and R_{5A} is independently hydrogen or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl;

with the proviso that the agent is not 2-acetyl-4-tetrahydroxybutylimidazole, 1-(4-(1,1,2,2,4-pentahydroxybutyl)-1H-imidazol-2-yl)ethanone, 1-(2-acetyl-1H-imidazol-4-yl)butane-1,1,2,2-tetrayl tetraacetate, or 1-(2-acetyl-1H-imidazol-4-yl)butane-1,1,2,2,4-pentayl pentaacetate.

31. The S1P level enhancing agent of claim 30, which has a SLEF of greater than about 20 fold.

32. The S1P level enhancing agent of claim 30, wherein X is O.

33. The S1P level enhancing agent of claim 30, wherein X is NR_3.

34. The S1P level enhancing agent of claim 30, wherein R_1 is hydrogen.

35. The S1P level enhancing agent of claim 30, wherein R_1 is optionally substituted lower alkyl.

36. The S1P level enhancing agent of claim 30, wherein R_1 is NHOH.

37. The S1P level enhancing agent of claim 30, wherein R_1 is OR_{1A}.

38. The S1P level enhancing agent of claim 30, wherein R_{1A} is hydrogen or optionally substituted lower alkyl.

39. The S1P level enhancing agent of claim 30, wherein R_2 is hydrogen.

40. The S1P level enhancing agent of claim 30, wherein R_2 is not hydrogen.

41. The S1P level enhancing agent of claim 30, wherein R_2 is nitrile.

42. The S1P level enhancing agent of claim 30, wherein R_2 is optionally substituted lower alkyl.

43. The S1P level enhancing agent of claim 30, wherein R_2 is OR_{2A}.

44. The S1P level enhancing agent of claim 30, wherein R_2 is $C(O)OR_{2A}$.

45. The S1P level enhancing agent of claim 43 or 44, wherein R_{2A} is hydrogen or optionally substituted lower alkyl.

46. The S1P level enhancing agent of claim 30, wherein R_3 is OR_{3A}.

47. The S1P level enhancing agent of claim 30, wherein R_3 is $N(R_{3A})_2$ or $NHC(O)R_{3A}$.

48. The S1P level enhancing agent of claim 30, wherein R_3 is $NHSO_2R_{3A}$.

49. The S1P level enhancing agent of claim 46, 47 or 48, wherein R_{3A} is hydrogen or optionally substituted lower alkyl.

50. The S1P level enhancing agent of claim 46, 47 or 48, wherein R_{3A} is optionally substituted aryl or heterocycle.

51. The S1P level enhancing agent of claim 30, wherein R_4 is OR_{4A}.

52. The S1P level enhancing agent of claim 30, wherein R_4 is halogen.

53. The S1P level enhancing agent of claim 30, wherein R_5 is $N(R_{5A})_2$.

54. The S1P level enhancing agent of claim 30, wherein R_5 is hydrogen.

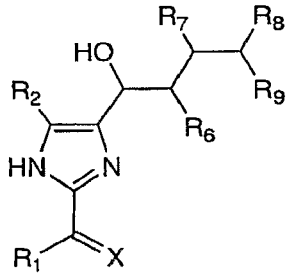
55. The S1P level enhancing agent of claim 30, wherein R_5 is hydroxyl.

56. The S1P level enhancing agent of claim 30, wherein R_5 is heteroalkyl (*e.g.*, alkoxy).

57. The S1P level enhancing agent of claim 30, wherein R_5 is optionally substituted alkyl.

58. The S1P level enhancing agent of claim 30, wherein R_5 is optionally substituted aryl.

59. A compound of formula **II**:



II

or a pharmaceutically acceptable salt or solvate thereof, wherein:

X is O or NR_3;

R_1 is OR_{1A}, NHOH, hydrogen, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl;

R_2 is OR_{2A}, $C(O)OR_{2A}$, hydrogen, halogen, nitrile, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl;

R_3 is OR_{3A}, $N(R_{3A})_2$, $NHC(O)R_{3A}$, $NHSO_2R_{3A}$, or hydrogen;

R_6 is OR_{6A}, $OC(O)R_{6A}$, $N(R_{6B})_2$, $NHC(O)R_{6B}$, hydrogen, or halogen;

R_7 is OR_{7A}, $OC(O)R_{7A}$, $N(R_{7B})_2$, $NHC(O)R_{7B}$, hydrogen, or halogen;

R_8 is OR_{8A}, $OC(O)R_{8A}$, $N(R_{8B})_2$, $NHC(O)R_{8B}$, hydrogen, or halogen;

R_9 is CH_2OR_{9A}, $CH_2OC(O)R_{9A}$, $N(R_{9B})_2$, $NHC(O)R_{9B}$, hydrogen, or halogen;

each of R_{1A}, R_{2A}, R_{3A}, R_{6A}, R_{7A}, R_{8A} and R_{9A} is independently hydrogen or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl; and

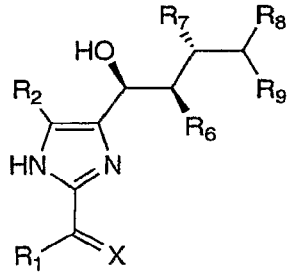
each of R_{6B}, R_{7B}, R_{8B} and R_{9B} is independently hydrogen or alkyl optionally substituted with one or more hydroxy or halogen groups;

with the provisos that: 1) if X is O, R_1 is alkyl of 1 to 4 carbons, phenyl, benzyl or phenylethyl, and R_2 is hydrogen, at least two of R_6, R_7, R_8 and R_9 are not hydroxyl or acetate; 2) if X is O, R_1 is methyl, R_2 is hydrogen, R_6 and R_7 are both hydroxyl, and one of R_8 and R_9 is hydrogen, the other is not $NHC(O)R_{9B}$; 3) if X is O, R_1 is OR_{1A}, R_{1A} is hydrogen or lower alkyl, and R_2 is hydrogen, at least one, but not all, of R_6, R_7, R_8 and R_9 is hydroxyl or acetate.

60. The compound of claim 59, which is a circulating lymphocyte reduction agent.

61. The compound of claim 59, which is a S1P level enhancing agent.

62. The compound of claim 59, which is of formula **II(a)**:



II(a)

63. The compound of claim 62, wherein X is O.

64. The compound of claim 62, wherein X is NR_3.

65. The compound of claim 62, wherein R_1 is hydrogen.

66. The compound of claim 62, wherein R_1 is optionally substituted lower alkyl.

67. The compound of claim 62, wherein R_1 is NHOH.

68. The compound of claim 62, wherein R_1 is OR_{1A}.

69. The compound of claim 67, wherein R_{1A} is hydrogen or optionally substituted lower alkyl.

70. The compound of claim 62, wherein R_2 is hydrogen.

71. The compound of claim 62, wherein R_2 is not hydrogen.

72. The compound of claim 62, wherein R_2 is nitrile.

73. The compound of claim 62, wherein R_2 is optionally substituted lower alkyl.

74. The compound of claim 62, wherein R_2 is OR_{2A}.

75. The compound of claim 62, wherein R_2 is $C(O)OR_{2A}$.

76. The compound of claim 74 or 75, wherein R_{2A} is hydrogen or optionally substituted lower alkyl.

77. The compound of claim 62, wherein R_3 is OR_{3A}.

78. The compound of claim 62, wherein R_3 is $N(R_{3A})_2$ or $NHC(O)R_{3A}$.

79. The compound of claim 62, wherein R_3 is $NHSO_2R_{3A}$.

80. The compound of claim 77, 78 or 79, wherein R_{3A} is hydrogen or optionally substituted lower alkyl.

81. The compound of claim 77, 78 or 79, wherein R_{3A} is optionally substituted aryl or heterocycle.

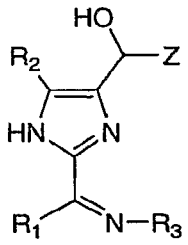
82. The compound of claim 62, wherein X is O and R_2 is not hydrogen.

83. The compound of claim 82, wherein R_2 is optionally substituted lower alkyl.

84. The compound of claim 62, wherein one or more of R_6, R_7, R_8, and R_9 is hydroxy or halogen.

85. The compound of claim 62, wherein all of R_6, R_7, R_8, and R_9 are hydroxyl or acetate.

86. A compound of formula **III**:



III

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z is optionally substituted alkyl;

R_1 is OR_{1A}, NHOH, hydrogen, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl;

R_2 is OR_{2A}, $C(O)OR_{2A}$, hydrogen, halogen, nitrile, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl;

R_3 is OR_{3A}, $N(R_{3A})_2$, $NHC(O)R_{3A}$, $NHSO_2R_{3A}$, or hydrogen;

each of R_{1A}, R_{2A}, and R_{3A} is independently hydrogen or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl.

87. The compound of claim 86, wherein Z is alkyl optionally substituted with one or more hydroxyl, acetate or halogen moieties.

88. The compound of claim 86, wherein R_1 is optionally substituted lower alkyl.

89. The compound of claim 86, wherein R_1 is NHOH.

90. The compound of claim 86, wherein R_2 is hydrogen or halogen.

91. The compound of claim 86, wherein R_3 is OR_{3A}.

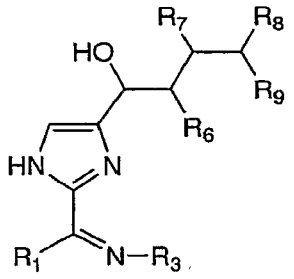
92. The compound of claim 86, wherein R_3 is $N(R_{3A})_2$ or $NHC(O)R_{3A}$.

93. The compound of claim 86, wherein R_3 is $NHSO_2R_{3A}$.

94. The compound of claim 91, 92 or 93, wherein R_{3A} is hydrogen or optionally substituted lower alkyl.

95. The compound of claim 91, 92 or 93, wherein R_{3A} is optionally substituted aryl or heterocycle.

96. A compound of formula **IV**:



IV

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R_1 is OR_{1A}, NHOH, hydrogen, or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl;

R_3 is OR_{3A}, $N(R_{3A})_2$, $NHC(O)R_{3A}$, $NHSO_2R_{3A}$, or hydrogen;

R_6 is OR_{6A}, $OC(O)R_{6A}$, $N(R_{6B})_2$, $NHC(O)R_{6B}$, hydrogen, or halogen;

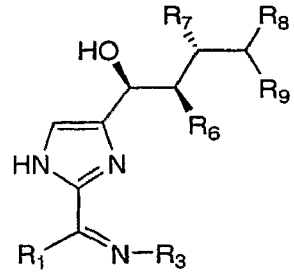
R_7 is OR_{7A}, $OC(O)R_{7A}$, $N(R_{7B})_2$, $NHC(O)R_{7B}$, hydrogen, or halogen;

R_8 is OR_{8A}, $OC(O)R_{8A}$, $N(R_{8B})_2$, $NHC(O)R_{8B}$, hydrogen, or halogen;

R_9 is CH_2OR_{9A}, $CH_2OC(O)R_{9A}$, $N(R_{9B})_2$, $NHC(O)R_{9B}$, hydrogen, or halogen; and

each of R_{1A}, R_{3A}, R_{6A}, R_{7A}, R_{8A} and R_{9A} is independently hydrogen or optionally substituted alkyl, aryl, alkylaryl, arylalkyl, heteroalkyl, heterocycle, alkylheterocycle, or heterocyclealkyl.

97. The compound of claim 96, which is of formula **IV(a)**:



IV(a)

98. The compound of claim 96, wherein one or more of R_6, R_7, R_8, and R_9 is hydroxy or halogen.

99. The compound of claim 96, wherein all of R_6, R_7, R_8, and R_9 are hydroxyl or acetate.

100. The compound of claim 97, wherein all of R_6, R_7, R_8, and R_9 are hydroxyl or acetate.

101. The compound of claim 97, wherein R_1 is optionally substituted lower alkyl.

102. The compound of claim 97, wherein R_1 is NHOH.

103. The compound of claim 97, wherein R_3 is OR_{3A}.

104. The compound of claim 97, wherein R_3 is $N(R_{3A})_2$ or $NHC(O)R_{3A}$.

105. The compound of claim 97, wherein R_3 is $NHSO_2R_{3A}$.

106. The compound of claim 103, 104 or 105, wherein R_{3A} is hydrogen or optionally substituted lower alkyl.

107. The compound of claim 103, 104 or 105, wherein R_{3A} is optionally substituted aryl or heterocycle.

108. A compound, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is:

1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime;

(E)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime;

(Z)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)-ethanone oxime;

1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone O-methyl oxime;

(E)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone O-methyl oxime;

(Z)-1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone O-methyl oxime;

1-(5-methyl-4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethanone;

(1R,2S,3R)-1-(2-(1-hydrazonoethyl)-1H-imidazol-4-yl)butane-1,2,3,4-tetraol;

N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)acetohydrazide;

4-methyl-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)benzenesulfonohydrazide;

(E)-4-methyl-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)benzenesulfonohydrazide;

(Z)-4-methyl-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)benzenesulfonohydrazide;

N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)benzohydrazide;

ethyl 2-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)hydrazinecarboxylate;

(E)-ethyl 2-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)hydrazinecarboxylate;

(Z)-ethyl 2-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)hydrazinecarboxylate;

N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)nicotinohydrazide;

(E)-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)nicotinohydrazide;

(Z)-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)nicotinohydrazide;

3-chloro-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)benzohydrazide;

4-fluoro-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)benzohydrazide;

(E)-4-fluoro-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)benzohydrazide;

(Z)-4-fluoro-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)benzohydrazide;

6-amino-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)nicotinohydrazide;

(E)-6-amino-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)nicotinohydrazide;

(Z)-6-amino-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)nicotinohydrazide;

N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)isonicotinohydrazide;

(E)-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)isonicotinohydrazide;

(Z)-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)isonicotinohydrazide;

N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)biphenyl-3-carbohydrazide;

(E)-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)biphenyl-3-carbohydrazide;

(Z)-N'-(1-(4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazol-2-yl)ethylidene)biphenyl-3-carbohydrazide; or

N-hydroxy-4-((1R,2S,3R)-1,2,3,4-tetrahydroxybutyl)-1H-imidazole-2-carboxamide.

109. A pharmaceutical composition comprising a circulating lymphocyte reduction agent of claim 1 and a pharmaceutically acceptable excipient or diluent.

110. A pharmaceutical composition comprising a S1P level enhancing agent of claim 30 and a pharmaceutically acceptable excipient or diluent.

111. A pharmaceutical composition comprising a compound of claim 59, 84, 96 or 108 and a pharmaceutically acceptable excipient or diluent.

112. A method of reducing the number of circulating lymphocytes in a patient, which comprises administering to the patient an effective amount of a circulating lymphocyte reduction agent of claim 1.

113. A method of modulating the amount of S1P in a patient, which comprises administering to the patient an effective amount of a S1P level enhancing agent of claim 30.

114. A method of suppressing immune response in a patient, which comprises administering to the patient an effective amount of a circulating lymphocyte reduction agent of claim 1.

115. A method of suppressing immune response in a patient, which comprises administering to the patient an effective amount of a S1P level enhancing agent of claim 30.

116. A method of suppressing immune response in a patient, which comprises administering to the patient an effective amount of a compound of claim 59, 84, 96 or 108.

117. A method of treating, managing or preventing a disease or disorder, which comprises administering to a patient in need thereof a therapeutically or prophylactically effective amount of a circulating lymphocyte reduction agent of claim 1, wherein the disease or disorder is rheumatoid arthritis, asthma, atopic dermatitis, Behcet's disease, graft-vs-host disease, lupus erythematosus, multiple sclerosis, pollinosis, psoriasis, transplant rejection or uveitis.

118. A method of treating, managing or preventing a disease or disorder, which comprises administering to a patient in need thereof a therapeutically or prophylactically effective amount of a S1P level enhancing agent of claim 30, wherein the disease or disorder is rheumatoid arthritis, asthma, atopic dermatitis, Behcet's disease, graft-vs-host disease, lupus erythematosus, multiple sclerosis, pollinosis, psoriasis, transplant rejection or uveitis.

119. A method of treating, managing or preventing a disease or disorder, which comprises administering to a patient in need thereof a therapeutically or prophylactically effective amount of a compound of claim 59, 84, 96 or 108, wherein the disease or disorder is rheumatoid arthritis, asthma, atopic dermatitis, Behcet's disease, graft-vs-host disease, lupus erythematosus, multiple sclerosis, pollinosis, psoriasis, transplant rejection or uveitis.