(54) Title: USE OF PRODRUGS OF 1,3-PROPANEDISULFONIC ACID OR PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF FOR THE TREATMENT OF SARCOIDOSIS

(55) Abstract: The present disclosure relates to methods for the treatment of sarcoidosis. In certain aspects and embodiments, the disclosure provides compositions containing a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof and/or the use of such compositions for the treatment of sarcoidosis. In another aspect, the disclosure relates to compositions containing a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof plus a second active agent. In yet another aspect, the disclosure relates to kits containing agents useful for the treatment of sarcoidosis.

Figure 1

Protocol

THP-1 5 x 10^3 cells/ml

PMA  SAA  KIACTA
200ng/ml → 10µg/ml + 0 ~ 10 mg/ml
48hr  24hr  24hr

PMA = phorbol 12-myri state 13-acetate (EMD Cat.# 524400)
SAA = serum amyloid A (PeroTech Cat.#300-13)
KIACTA C933 (NRA610-01-CF)

ELISA Kit
IL-1 α; MBL  Cat.#7620
IL-1 β; invitrogen Cat.#KHC0101
TNF, BD Cat.#550610
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USE OF PRODRUGS OF 1,3-PROPANEDISULFONIC ACID OR PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF FOR THE TREATMENT OF SARCOIDOSIS

FIELD OF THE INVENTION

[0001] The present disclosure relates to methods for the treatment of sarcoidosis.

BACKGROUND OF THE INVENTION


[0003] Sarcoidosis is a rare condition that causes small patches of red and swollen tissue, called granulomas that can develop in multiple organs in the body, but mostly the lungs and skin. Corticosteroids, the mainstay of therapy in sarcoidosis, nonspecifically suppress chronic granulomatous inflammation, often causing debilitating adverse effects but do not correct the underlying disease.

SUMMARY OF THE INVENTION

[0004] In various aspects and embodiments of the present disclosure, provided are methods for treating a subject with sarcoidosis, that include administering to said subject an effective amount of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof as well as relevant compositions for use in such methods. In certain embodiments, the prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof is a compound of any one of Formulae I - XV. In certain embodiments of the disclosure, the prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof is the disodium salt of a compound of any one of Formulae I - XV.
In some embodiments of the disclosure, the subject being treated has chronic sarcoidosis (as opposed to acute sarcoidosis). In certain embodiments of the disclosure the subject being treated has acute sarcoidosis.

In various embodiments of the disclosure, sarcoidosis may affect one or more of the lungs, liver, heart, nervous system (including the brain), skin, lymph glands, musculoskeletal system (e.g., bones, joints, muscles), spleen, eyes, sinuses, nasal mucosa, larynx, the gastrointestinal tract, reproductive organs, salivary glands and/or kidneys.

In certain embodiments of the disclosure, sarcoidosis specifically affects the lungs.

In some embodiments, the administration of a prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof results in the reduction in one or more inflammatory mediators selected from the group consisting of IL-18, IL-10 and TNF.

In some embodiments, the administration of a prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof results in the reduction and/or alleviation of sarcoidosis symptoms in the subject (e.g., granuloma formation, granulomatous inflammation, and the like).

In certain embodiments of the disclosure, the effective amount of a prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof comprises administration of at least 1mg/kg thereof to said subject per dose.

In certain embodiments of the disclosure, the effective amount of a prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof is administered more than once daily. Exemplary administration protocols contemplate administration of a prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof at least 2 times daily; at least 3 times daily; at least 4 times daily; at least 5 times daily; at least 6 times daily; or even more frequently, including continuous administration thereof. In certain embodiments the prodrug of 1,3-propanedisulfonic acid is administered to a subject (for example orally) in a dose of 400 mg, or 800 mg, or 1,200
mg per administration. In some embodiments the prodrug of 1,3-propanedisulfonic acid is administered to a subject in a dose of 400 mg QID, or 600 mg QID, or 800 mg QID, or 1000 mg QID, or 1,200 mg QID per administration.

[0012] In certain embodiments of the disclosure, no more than 20mg/kg of a prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof is administered to said subject per dose.

[0013] Prodrugs of 1,3-propanedisulfonic acid or pharmaceutically acceptable salts thereof can be administered in a variety of ways, e.g., by oral, parenteral, intraperitoneal, intraspinal, intracerebral, nasal, mucosal, transdermal, intravascular, intraarterial, intramuscular, or subcutaneous delivery, or the like.

[0014] In certain embodiments of the disclosure, prodrugs of 1,3-propanedisulfonic acid or pharmaceutically acceptable salts thereof are administered by oral delivery.

[0015] In certain embodiments of the disclosure, there are provided pharmaceutically acceptable compositions for the treatment of sarcoidosis, said compositions comprising a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor.

[0016] In certain embodiments of the disclosure, the above-described pharmaceutically acceptable compositions may further comprise a second agent traditionally employed for the treatment of sarcoidosis. An exemplary second agent is a corticosteroid.

BRIEF DESCRIPTION OF THE FIGURE

[0017] Figure 1 summarizes the protocol employed to evaluate the effect of prodrugs of 1,3-propanedisulfonic acid (or a pharmaceutically acceptable salts thereof) on SAA (serum amyloid A) stimulated inflammation in THP-1 cells.

DETAILED DESCRIPTION OF THE INVENTION

[0018] In accordance with the present disclosure, there are provided methods for treating a subject with sarcoidosis, said method comprising administering to said subject an effective amount of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof.
[0019] The term "subject" includes living organisms in which sarcoidosis or a related
disease can occur, or which are susceptible to sarcoidosis or related diseases. The term
"subject" includes animals (e.g., mammals, e.g., cats, dogs, horses, pigs, cows, goats,
sheep, rodents, e.g., mice or rats, rabbits, squirrels, bears, primates (e.g., chimpanzees,
monkeys, gorillas, and humans)), as well as chickens, ducks, peking ducks, geese, and
transgenic species thereof. The term "subject," includes to a subject, e.g., a human,
specifically chosen to receive a prodrug of 1,3-propanedisulfonic acid or a
pharmaceutically acceptable salt thereof, or a composition containing same.
Accordingly, in some embodiments, subjects include subjects who are at risk of or
have been diagnosed with sarcoidosis. Subjects at risk of developing sarcoidosis
include those with an underlying disease, such as an inflammatory disease, infection,
hereditary fever or neoplasm. In some embodiments, a preferred subject is a human.

[0020] The terms "treatment" or "treating" of a subject includes the application or
administration of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically
acceptable salt thereof, or a composition containing same to a subject (or application or
administration of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically
acceptable salt thereof to a cell or tissue from a subject) with the purpose of stabilizing,
curing, healing, alleviating, relieving, altering, remedying, less worsening,
ameliorating, improving, or affecting the disease or condition, the symptom of the
disease or condition, or the risk of (or susceptibility to) the disease or condition. The
term "treating" refers to any indicia of success in the treatment or amelioration of an
injury, pathology or condition, including any objective or subjective parameter such as
abatement; remission; lessening of the rate of worsening; stabilization, diminishing of
symptoms or making the injury, pathology or condition more tolerable to the subject;
slowing in the rate of degeneration or decline; making the final point of degeneration
less debilitating; or improving a subject's physical or mental well-being. In an
embodiment, the term "treating" can include increasing a subject's life expectancy.

[0021] The term "therapeutically effective amount" refers to the amount of a
compound which is effective to treat a subject, e.g., treat a subject for sarcoidosis or a
related disease or treat a subject having an underlying disease, such as, but not limited
to, an inflammatory disorder, a malignant neoplasm, or chronic microbial infection.
The therapeutically effective amount may vary based on the particular disorder(s) the
subject is suffering from, the age, weight, and lifestyle of a particular subject. In addition, the therapeutically effective amount may depend on the severity of the disease state, organ function, kidney function, or underlying disease (e.g., the subject may be suffering from an inflammatory disease, a malignant neoplasm, a chronic infection).

[0022] The dosage administered in the methods of the present disclosure may be selected such that desired pharmacokinetic parameters and/or biologically favorable parameters are obtained after administration of the compound of the disclosure to the subject. In one embodiment, the dosage is selected such that the subject receives at least 1mg/kg of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof per dose; in another embodiment, the dosage is selected such that the subject receives at least 2mg/kg of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof per dose; in still another embodiment, the dosage is selected such that the subject receives at least 3mg/kg of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof per dose; in yet another embodiment, the dosage is selected such that the subject receives at least 4mg/kg of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof per dose; in a still further embodiment, the dosage is selected such that the subject receives at least 5mg/kg of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof per dose; in some embodiments, the dosage is selected such that the subject receives at least 6mg/kg of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof per dose; in some embodiments, the dosage is selected such that the subject receives at least 7mg/kg of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof per dose; in some embodiments, the dosage is selected such that the subject receives at least 8mg/kg of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof per dose; in some embodiments, the dosage is selected such that the subject receives at least 9mg/kg of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof per dose; in some embodiments, the dosage is selected such that the subject receives at least 10mg/kg of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof per dose; in some embodiments, the dosage is selected such that the subject receives at least 15mg/kg of
a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof per dose. In some embodiments, no more than 20mg/kg of a prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof is administered to said subject per dose.

[0023] In a further embodiment, the disclosure also pertains, at least in part, to a pharmaceutical formulation. The formulation comprises an active agent which is a prodrug of 1,3-propane disulfonic acid or a pharmaceutically acceptable salt thereof in an amount effective to treat or prevent sarcoidosis, and a pharmaceutically acceptable carrier. In one embodiment, the formulation is orally administered to a subject having sarcoidosis in a dose of 400 mg of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof. In another embodiment, the formulation is orally administered to a subject having sarcoidosis in a dose of 800 mg of a prodrug of 1,3-propane disulfonic acid or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In yet another embodiment, the formulation is orally administered to a subject having sarcoidosis in a dose of 1200 mg of a prodrug of 1,3-propane disulfonic acid or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0024] In a further embodiment, the disclosure pertains to a pharmaceutical formulation comprising a prodrug of 1,3-propane disulfonic acid or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier for oral administration to a subject having sarcoidosis for twenty-four months in a dose of 400 mg of the active agent; or in a dose of 800 mg of the active agent; or in a dose of 1200 mg of the active agent.

[0025] In another embodiment, the disclosure also pertains to a pharmaceutical formulation, comprising a prodrug of 1,3-propane disulfonic acid or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, wherein the formulation is orally administered for seven days in a dose of 400 mg QID of the active agent; or in a dose of 800 mg QID of the active agent; or in a dose of 1200 mg QID of the active agent; or in a dose of 1600 mg QID of the active agent; or in a dose of 2000 mg QID of the active agent.
In another further embodiment, the disclosure also pertains to a method of stabilizing or improving renal function or delaying progression of renal disease in a subject having sarcoidosis. The method includes orally administering an effective amount of a formulation comprising a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

In another embodiment, the disclosure pertains to a method of treating or preventing sarcoidosis in a subject. The method includes administering to a subject in need thereof, a therapeutically effective amount of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof, in combination with a second agent, such that AA amyloidosis is treated or prevented.

The term “in combination with” refers to the concurrent administration of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof and a second agent; the administration of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof can be carried out prior to administration of the second agent; or administration of the second agent can be carried out prior to administration of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof.

The compounds of the present disclosure contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of a prodrug of 1,3-propanedisulfonic acid.

These salts can likewise be prepared in situ during the final isolation and purification of the agents, or by separately reacting the purified agent in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of
base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

[0031] "Pharmaceutically acceptable salts" also includes, for example, derivatives of agents modified by making base salts thereof, as described further below and elsewhere in the present application. Examples of pharmaceutically acceptable salts include alkali or organic salts of acidic residues such as sulfonates. Pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent agent formed, for example, from non-toxic inorganic or organic acids. Such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric acid; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmoic, maleic, hydroxymaleic, phenylacetic, glutamic, mesylate, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic acid. Pharmaceutically acceptable salts may be synthesized from the parent agent which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts may be prepared by reacting the free acid or base forms of these agents with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two.

[0032] All acid, salt, base, and other ionic and non-ionic forms of the compounds described are included as compounds of the disclosure. For example, if a compound is shown as an acid herein, the salt forms of the compound are also included. Likewise, if a compound is shown as a salt, the acid and/or basic forms are also included.

[0033] Compounds of the present disclosure are employed in the form of a prodrug, i.e., agents which are converted in vivo to active forms (see, e.g., R.B. Silverman, 1992, "The Organic Chemistry of Drug Design and Drug Action," Academic Press, Chp. 8).

[0034] For example, prodrugs can be used to alter the biodistribution (e.g., to allow agents which would not typically enter the reactive site) or the pharmacokinetics for a particular agent. For example, a carboxylic acid group can be esterified, e.g., with a methyl group or an ethyl group to yield an ester. When the ester is administered to a
subject, the ester is cleaved, enzymatically or non-enzymatically, reductively, oxidatively, or hydrolytically, to reveal the anionic group. An anionic group can be esterified with moieties (e.g., acyloxyethyl esters) which are cleaved to reveal an intermediate agent which subsequently decomposes to yield the active agent. The prodrug moieties may be metabolized in vivo by esterases or by other mechanisms to carboxylic acids.

[0035] Examples of prodrugs and their uses are well known in the art (see, e.g., Berge, et al., "Pharmaceutical Salts", J Pharm. Sci. 66, 1-19 (1977)). Prodrugs can be prepared in situ during the final isolation and purification of the active agents, or by separately reacting the purified agent in its free acid form with a suitable derivatizing agent. Carboxylic acids can be converted into esters via treatment with an alcohol in the presence of a catalyst.

[0036] Examples of cleavable carboxylic acid prodrug moieties include substituted and unsubstituted, branched or unbranched lower alkyl ester moieties, (e.g., ethyl esters, propyl esters, butyl esters, pentyl esters, cyclopentyl esters, hexyl esters, cyclohexyl esters), lower alkenyl esters, dilower alkyl-amino lower-alkyl esters (e.g., dimethylaminoethyl ester), acylamino lower alkyl esters, acyloxy lower alkyl esters (e.g., pivaloyloxy methyl ester), aryl esters (phenyl ester), aryl-lower alkyl esters (e.g., benzyl ester), substituted (e.g., with methyl, halo, or methoxy substituents) aryl and aryl-lower alkyl esters, amides, lower-alkyl amides, dilower alkyl amides, and hydroxy amides.

[0037] Additional compounds contemplated for use herein include compounds of Formulae I - XV as follows:

Formula 1:

\[
\begin{array}{c}
    \text{R}^1 \\
    \text{L}^1 \\
    \text{N} \\
    \text{L}^2 \\
    \text{Y} \\
\end{array}
\]  

(1)

wherein:

\( \text{R}^1 \) is a substituted or unsubstituted cycloalkyl, heterocyclic, aryl, arylcycloalkyl, bicyclic or tricyclic ring, a bicyclic or tricyclic fused ring group, or a substituted or unsubstituted C2-C10 alkyl group;
R² is selected from the group consisting of hydrogen, alkyl, mercaptoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, thiazolyl, triazolyl, imidazolyl, benzothiazolyl, and benzoimidazolyl;

Y is S₈X⁺, OS₈X⁺, or SS₈X⁺;

X⁺ is hydrogen, a cationic group, or an ester-forming group (i.e., as in a prodrug, which are described elsewhere herein); and

each of L¹ and L² is independently a substituted or unsubstituted C₁-C₅ alkyl group or absent, or a pharmaceutically acceptable salt thereof, provided that when R¹ is alkyl, L¹ is absent.

[0038] Compounds of Formula II have the structure:

\[
\begin{array}{c}
\text{R}^2 \\
\text{O} \\
\text{R}^1 \quad \text{L} \\
\text{N} \quad \text{(CH}_2\text{)}^n \\
\text{Y}
\end{array}
\]  

(II)

wherein:

R¹ is a substituted or unsubstituted cyclic, bicyclic, tricyclic, or benzoheterocyclic group or a substituted or unsubstituted C₂-C₅ alkyl group;

R² is hydrogen, alkyl, mercaptoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, thiazolyl, triazolyl, imidazolyl, benzothiazolyl, benzoimidazolyl, or linked to R¹ to form a heterocycle;

Y is S₈X⁺, OS₈X⁺, or SS₈X⁺;

X⁺ is hydrogen, a cationic group, or an ester forming moiety;

m is 0 or 1;

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

L is substituted or unsubstituted C₁-C₃ alkyl group or absent, or a pharmaceutically acceptable salt thereof, provided that when R¹ is alkyl, L is absent.

[0039] Compounds of Formula III have the structure:
wherein:

A is nitrogen or oxygen;

R\(^{11}\) is hydrogen, a salt-forming cation, an ester forming group, -(CH\(_2\))\(_x\)Q, or when A is nitrogen, A and R\(^{11}\) taken together may be the residue of a natural or unnatural amino acid or a salt or ester thereof; 

Q is hydrogen, thiazolyl, triazolyl, imidazolyl, benzothiazolyl, or benzoimidazolyl;

\(x\) is 0, 1, 2, 3, or 4;

\(n\) is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

R\(^3\), R\(^{3a}\), R\(^4\), R\(^{4a}\), R\(^5\), R\(^{5a}\), R\(^6\), R\(^{6a}\), R\(^7\) and R\(^{7a}\) are each independently hydrogen, alkyl, mercaptoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, aroylcarbonyl, alkoxycarbonyl, cyano, halogen, amino, tetrazolyl, or two R groups on adjacent ring atoms taken together with the ring atoms form a double bond, provided that one of R\(^3\), R\(^{3a}\), R\(^4\), R\(^{4a}\), R\(^5\), R\(^{5a}\), R\(^6\), R\(^{6a}\), R\(^7\) and R\(^{7a}\) is a moiety of Formula IIia:

\[
\text{(IIIa)}
\]

wherein:

\(m\) is 0, 1, 2, 3, or 4;

R\(^A\), R\(^B\), R\(^C\), R\(^D\), and R\(^E\) are independently selected from the group of hydrogen, halogen, hydroxyl, alkyl, alkoxyl, halogenated alkyl, mercaptoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, cyano, thiazolyl, triazolyl, imidazolyl, tetrazolyl, benzothiazolyl, and benzoimidazolyl; and pharmaceutically acceptable salts and esters thereof, provided that said compound is not 3-(4-phenyl-1, 2, 3, 6-tetrahydro-l-pyridyl)-1-propanesulfonic acid.

[0040] Compounds of Formula IV have the structure:
wherein:

A is nitrogen or oxygen;

R\textsuperscript{11} is hydrogen, salt-forming cation, ester forming group, -(CH\textsubscript{2})\textsubscript{x}Q, or when A is nitrogen, A and R\textsuperscript{11} taken together may be the residue of a natural or unnatural amino acid or a salt or ester thereof;

Q is hydrogen, thiazolyl, triazolyl, imidazolyl, benzothiazolyl, or benzoimidazolyl;

x is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

R\textsuperscript{4}, R\textsuperscript{4a}, R\textsuperscript{5}, R\textsuperscript{5a}, R\textsuperscript{6}, R\textsuperscript{6a}, R\textsuperscript{7} and R\textsuperscript{7a} are each independently hydrogen, alkyl, mercaptoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, cyano, halogen, amino, tetrazolyl, R\textsuperscript{4} and R\textsuperscript{5} taken together, with the ring atoms they are attached to, form a double bond, or R\textsuperscript{6} and R\textsuperscript{7} taken together, with the ring atoms they are attached to, form a double bond;

m is 0, 1, 2, 3, or 4;

R\textsuperscript{8}, R\textsuperscript{9}, R\textsuperscript{10}, R\textsuperscript{11} and R\textsuperscript{12} are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkoxy, halogenated alkyl, mercaptoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, cyano, thiazolyl, triazolyl, imidazolyl, tetrazolyl, benzothiazolyl, and benzoimidazolyl, and pharmaceutically acceptable salts and esters thereof.

[0041] Compounds of Formula V have the structure:

\[
\text{wherein:}
\]

A is nitrogen or oxygen;


\[ R^{11} \text{ is hydrogen, a salt-forming cation, an ester forming group, } -(\text{CH}_2)_xQ, \text{ or when } A \text{ is nitrogen, } A \text{ and } R^{11} \text{ taken together may be the residue of a natural or unnatural amino acid or a salt or ester thereof; } \\
Q \text{ is hydrogen, thiazolyl, triazolyl, imidazolyl, benzothiazolyl, or benzoimidaizolyl; } \\
x \text{ is } 0, 1, 2, 3, \text{ or } 4; \\
n \text{ is } 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 \text{ or } 10; \\
\text{aa is a natural or unnatural amino acid residue; } \\
m \text{ is } 0, 1, 2, \text{ or } 3; \\
R^{14} \text{ is hydrogen or a protecting group; and } \\
R^{15} \text{ is hydrogen, alkyl or aryl, and pharmaceutically acceptable salts and prodrugs thereof.} \]

[0042] Compounds of Formula VI have the structure:

\[ \text{wherein: } \\
n = 1, 2, 3, 4, 5, 6, 7, 8, 9, \text{ or } 10; \\
A = \text{oxygen or nitrogen; } \\
R^{11} = \text{hydrogen, a salt-forming cation, an ester forming group, } -(\text{CH}_2)_xQ, \text{ or when } A \text{ is nitrogen, } A \text{ and } R^{11} \text{ taken together may be the residue of a natural or unnatural amino acid or a salt or ester thereof; } \\
Q = \text{hydrogen, thiazolyl, triazolyl, imidazolyl, benzothiazolyl, or benzoimidaizolyl; } \\
x = 0, 1, 2, 3, \text{ or } 4; \\
R^{19} = \text{hydrogen, alkyl or aryl; } \\
Y^1 = \text{oxygen, sulfur, or nitrogen; } \\
Y^2 = \text{carbon, nitrogen, or oxygen; } \]
R\textsuperscript{20} is hydrogen, alkyl, amino, mercaptoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, thiazolyl, triazolyl, tetrazolyl, imidazolyl, benzothiazolyl, or benzoimidazolyl;

R\textsuperscript{21} is hydrogen, alkyl, mercaptoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, thiazolyl, triazolyl, tetrazolyl, imidazolyl, benzothiazolyl, benzoimidazolyl, or absent if \(Y\textsuperscript{2}\) is oxygen;

R\textsuperscript{22} is hydrogen, alkyl, mercaptoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, thiazolyl, triazolyl, tetrazolyl, imidazolyl, benzothiazolyl, benzoimidazolyl; or R\textsuperscript{22} is hydrogen, hydroxyl, alkoxy or aryloxy if \(Y\textsuperscript{1}\) is nitrogen; or R\textsuperscript{22} is absent if \(Y\textsuperscript{1}\) is oxygen or sulfur; or R\textsuperscript{22} and R\textsuperscript{21} may be linked to form a cyclic moiety if \(Y\textsuperscript{1}\) is nitrogen;

R\textsuperscript{23} is hydrogen, alkyl, amino, mercaptoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, thiazolyl, triazolyl, tetrazolyl, imidazolyl, benzothiazolyl, or benzoimidazolyl, or absent if \(Y\textsuperscript{2}\) is nitrogen or oxygen; or pharmaceutically acceptable salts thereof.

[0043] Compounds of Formula VII have the structure:

\[
\begin{align*}
\text{wherein:} \\
\text{n is } 2, 3, \text{ or } 4; \\
\text{A is oxygen or nitrogen;} \\
\text{R}\textsuperscript{11} \text{ is hydrogen, salt-forming cation, ester forming group, } -\text{(CH}_2\text{)}_x\text{Q, or when } \\
\text{A is nitrogen, A and R}\textsuperscript{11} \text{ taken together may be the residue of a natural or unnatural amino acid or a salt or ester thereof;} \\
\text{Q is hydrogen, thiazolyl, triazolyl, imidazolyl, benzothiazolyl, or} \\
\text{benzoimidazolyl;} \\
\text{x is } 0, 1, 2, 3, \text{ or } 4; \\
\text{G is a direct bond or oxygen, nitrogen, or sulfur;} \\
\text{z is } 0, 1, 2, 3, 4, \text{ or } 5; \\
\text{m is } 0 \text{ or } 1; \\
\end{align*}
\]
R\textsuperscript{24} is selected from the group consisting of hydrogen, alkyl, mercaptoalkyl, alkenyl, alkynyl, aroyl, alkylcarbonyl, aminoalkylcarbonyl, cycloalkyl, aryl, aroylalkyl, thiazolyl, triazolyl, imidazolyl, benzothiazolyl, and benzoimidazolyl;

each R\textsuperscript{25} is independently selected from hydrogen, halogen, cyano, hydroxyl, alkoxy, thiol, amino, nitro, alkyl, aryl, carbocyclic, or heterocyclic, and pharmaceutically acceptable salts thereof.

[0044] Compounds of Formula VIII have the structure:

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^1 \\
\text{L}^1 \\
\text{N} \\
\text{B} \\
\text{Y} \\
\text{M} \\
\text{W} \\
\text{v}
\end{array}
\]  
(VIII)

wherein:

R\textsuperscript{1} is hydrogen, a substituted or unsubstituted cycloalkyl, heterocyclic, aryl, arylcycloalkyl, bicyclic or tricyclic ring, a bicyclic or tricyclic fused ring group, or a substituted or unsubstituted C\textsubscript{2}-C\textsubscript{10} alkyl group;

R\textsuperscript{2} is selected from the group consisting of hydrogen, alkyl, mercaptoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, aroylalkyl, thiazolyl, triazolyl, imidazolyl, benzothiazolyl, and benzoimidazolyl;

Y is S\textsubscript{0}\textsubscript{3}X+, OS\textsubscript{0}\textsubscript{3}X+, or SS\textsubscript{0}\textsubscript{3}X+;

X\textsuperscript{+} is hydrogen, a cationic group, or an ester-forming group;

L\textsuperscript{1} is a substituted or unsubstituted C\textsubscript{1}-C\textsubscript{5} alkyl group or absent,

B is C\textsubscript{1}-C\textsubscript{5} alkyl, alkenyl, or alkynyl group, optionally fused with W when M is absent;

M is a covalent bond, amino, C\textsubscript{1}-C\textsubscript{6} alkyl, alkenyl, alkynyl, carboxyl, oxy, amide, ester, thioether, thioester or absent;

W is a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aroylalkyl, bicyclic or tricyclic ring, a bicyclic or tricyclic fused ring group, heterocyclic, thiazolyl, triazolyl, imidazolyl, benzothiazolyl, or benzoimidazolyl; and

v is 1, 2, 3, 4, 5, or 6; or a pharmaceutically acceptable salt, ester or prodrug thereof, provided that when Y is methyl, R\textsuperscript{1} and R\textsuperscript{2} are hydrogen, Y is S\textsubscript{0}\textsubscript{3}X+, M is a covalent bond, B is not CH\textsubscript{2}-CH(M-W)-CH\textsubscript{2}.
Compounds of Formula IX have the structure:

\[
\begin{align*}
R^3 & \quad \text{aa} & \quad \text{aa} & \quad \text{aa} & \quad \text{aa} & \quad \text{aa} \\
\end{align*}
\]

wherein:

- \(R^1\) is a substituted or unsubstituted cycloalkyl, heterocyclic, aryl, arylcycloalkyl, bicyclic or tricyclic ring, a bicyclic or tricyclic fused ring group, or a substituted or unsubstituted \(C_2-C_{10}\) alkyl group;
- \(R^2\) is selected from the group consisting of hydrogen, alkyl, mercaptoalkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, thiazoyl, triazolyl, imidazolyl, benzothiazolyl, and benzoimidazolyl;
- \(R^3\) is hydrogen or a protecting group;
- \(aa\) is a natural or unnatural amino acid residue;
- \(L^3\) is a covalent bond, amino, \(\text{Ci-C}_6\) alkyl, alkenyl, alkynyl, carboxyl, amide, aminooalkyl, ether, ester, thioether, thioester or absent;
- \(Y\) is \(\text{SO}_3^\text{X}^+\), \(\text{OSO}_3^\text{X}^+\), or \(\text{SSO}_3^\text{X}^+\);
- \(X^+\) is hydrogen, a cationic group, or ester-forming group; and
- each of \(L^1\) and \(L^2\) is independently a substituted or unsubstituted \(C_1-C_5\) alkyl group or absent, or a pharmaceutically acceptable salt, ester or prodrug thereof.

Compounds of Formula X have the structure:

\[
\begin{align*}
\end{align*}
\]

wherein:

- \(R^a\) is hydrogen, substituted or unsubstituted alkyl, aryl, heteroaryl, carboxyl, alkylxycarbonyl, or aminocarbonyl;
- \(R^b\) and \(R^c\) are each selected independently from hydrogen, substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, \(\text{CONH}_2\), or \(R^b, R^c\) and the carbon atom they are attached to can form a substituted or unsubstituted cyclic structure of 4 to 12-membered ring or a fused ring system; and
$X^+$ is hydrogen, a cationic group, or an ester-forming group, or a pharmaceutically acceptable salt, ester, or prodrug thereof.

[0047] Compounds of Formula XI have the structure:

wherein:

- $R^d$ is H or alkyl;
- $R^e$ and $R^f$ are each independently hydrogen, C1-C6 alkyl, or $R^e$ and $R^f$, taken together with the carbon they are attached to, form a 3 to 12-membered ring;
- $R^g$ is independently selected for each occurrence from the group consisting of hydrogen, alkyl, alkoxy, halogen, NO$_2$, and alkyl-SO$_2$;
- $q$ is 1, 2, 3, 4, or 5;
- $X^+$ is hydrogen, a cationic group, or an ester-forming group;
- $Ar$ is aryl or heteroaryl; and
- $Z$ is -($CH_2$)$_{0-3}$-, -(CHOH)-, (CH$_2$)$_{1-3}$, 0(CH$_2$)$_{1-3}$, or a carbonyl group, or a pharmaceutically acceptable salt, ester, or prodrug thereof.

[0048] Compounds of Formula XII have the structure:

wherein:

- $R^h$ is hydrogen, benzyl, aryl-alkyl, aryl, or alkyl;
- $R^l$, $R^k$, $R^m$, $R^n$, and $R^o$ are each independently hydrogen, substituted or unsubstituted aryl, substituted or unsubstituted benzyl, alkyl, alkenyl, carbocyclic, heterocyclic, absent or together may be linked to form a ring structure;
- $X^+$ is hydrogen, a cationic group, or an ester-forming group; and
t\(^1\) and t\(^2\) are each single or double bonds, provided that both t\(^1\) and t\(^2\) are not both double bonds, or a pharmaceutically acceptable salt, ester, or prodrug thereof.

**[0049]** Compounds of Formula XIII have the structure:

\[
\begin{align*}
\text{R}\overset{\text{P}}{\text{P}} \quad \text{(XIII)} \\
\text{wherein:} \\
\text{n}^1 \text{ is } 0, 1, 2, \text{ or } 3; \\
\text{P is a covalent bond, alkyl, alkyloxy, amino, alkylamino, sulfur, or alkylthio;} \\
\text{X}^+ \text{ is hydrogen, a cationic group, or an ester-forming group; and} \\
\text{R}^p \text{ is a natural or unnatural amino acid residue, or a pharmaceutically acceptable salt, ester, or prodrug thereof.}
\end{align*}
\]

**[0050]** Compounds of Formula XIV have the structure:

\[
\begin{align*}
\text{R}^2 \quad \text{R}^5 \\
\text{(XIV)} \\
\text{wherein:} \\
\text{n}^2 \text{ is } 0, 1, 2, \text{ or } 3, \text{ selected such that three carbons are between the } \text{SO}_3^+\text{X}^+ \text{ group and the nitrogen atom in the ring;} \\
\text{X}^+ \text{ is hydrogen, a cationic group, or an ester-forming group;} \\
\text{R}^5 \text{ is hydrogen or when n}^2 \text{ is } 3, \text{ R}^5 \text{ is } (\text{CH}_2)_3\text{SO}_3^+\text{X}^+; \\
\text{R}^q \text{ and Rr are each selected independently from hydrogen or alkyl, or a pharmaceutically acceptable salt, ester, or prodrug thereof.}
\end{align*}
\]

**[0051]** Compounds of Formula XV have the structure:

\[
\begin{align*}
\text{R}^l \quad \text{R}^u \\
\text{R}^l \quad \text{R}^v \\
\text{R}^u \quad \text{R}^v \quad \text{R}^n \quad \text{SO}_3^+\text{X}^+ \\
\text{(XV)} \\
\end{align*}
\]
wherein:

\( R^i \) is hydrogen, alkyl, or aryl;

\( R^u \) and \( R^v \) are each independently for each occurrence selected from hydrogen, alkyl, benzyl, alkyl, alkenyl, carbocyclic, heterocyclic, or two \( R^u \) or \( R^v \) groups on adjacent carbon atoms may form a double bond, or together with the carbon atoms they are attached to form a carbocyclic or heterocyclic ring;

\( n^3 \) is 4, 5, 6, or 7; and

\( X^+ \) is hydrogen, a cationic group, or an ester-forming group; or a pharmaceutically acceptable salt, ester, or prodrug thereof.

[0052] The chemical structures herein are drawn according to the conventional standards known in the art. Thus, where an atom, such as a carbon atom, as drawn appears to have an unsatisfied valency, then that valency is assumed to be satisfied by a hydrogen atom even though that hydrogen atom is not necessarily explicitly drawn. The structures of some of the compounds of this invention include stereo genic carbon atoms. It is to be understood that isomers arising from such asymmetry (e.g., all enantiomers and diastereomers) are included within the scope of this invention unless indicated otherwise. That is, unless otherwise stipulated, any chiral carbon center may be of either (R)- or (S)-stereochemistry. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically-controlled synthesis. Furthermore, alkenes can include either the E- or Z- geometry, where appropriate. In addition, the compounds of the present invention may exist in unsolvated as well as solvated forms with acceptable solvents such as water, THF, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0053] A "small molecule" refers to a compound that is not itself the product of gene transcription or translation (e.g., protein, RNA, or DNA) and preferably has a low molecular weight, e.g., less than about 2500 amu.

[0054] In general, the term "nucleophile" is art-recognized to mean a chemical group having a reactive pair of electrons that reacts with a compound by displacing a leaving group (commonly another nucleophile), such as commonly occur in aliphatic chemistry as unimolecular (known as "SN 1") or bimolecular ("SN2") reactions. Examples of nucleophiles include uncharged compounds such as amines, mercaptans,
and alcohols, and charged groups such as alkoxides, thiolates, carbanions, and a variety of organic and inorganic anions. Illustrative anionic nucleophiles include, inter alia, simple anions such as azide, cyanide, thiocyanate, acetate, formate, or chloroformate, and bisulfite. Organometallic reagents such as organocuprates, organozincs, organolithiums, Grignard reagents, enolates, and acetylides, will under appropriate reaction conditions, be suitable nucleophiles.

[0055] Similarly, an "electrophile" means an atom, molecule, or ion able to accept an electron pair, particularly a pair of electrons from a nucleophile, such as typically occurs during an electrophilic substitution reaction. In an electrophilic substitution reaction, an electrophile binds to a substrate with the expulsion of another electrophile, e.g., the substitution of a proton by another electrophile such as a nitronium ion on an aromatic substrate (e.g., benzene). Electrophiles include cyclic compounds such as epoxides, aziridines, episulfides, cyclic sulfates, carbonates, lactones, and lactams; and non-cyclic electrophiles include sulfates, sulfonates (e.g., tosylates), chlorides, bromides, and iodides. Generally, an electrophile may be a saturated carbon atom (e.g., a methylene group) bonded to a leaving group; however, an electrophile may also be an unsaturated group, such as an aldehyde, ketone, ester, or conjugated (α,β-unsaturated) analog thereof, which upon reaction with a nucleophile forms an adduct.

[0056] The term "leaving group" generally refers to a group that is readily displaced and substituted by a nucleophile (e.g., an amine, a thiol, an alcohol, or cyanide). Such leaving groups are well known and include carboxylates, N-hydroxysuccinimide ("NHS"), N-hydroxybenzotriazole, a halogen (fluorine, chlorine, bromine, or iodine), alkoxides, and thioalkoxides. A variety of sulfur-based leaving groups are routinely used in synthetic chemistry, including alkane sulfonyloxy groups (e.g., C₁⁻C₄ alkane such as methane sulfonyloxy, ethane sulfonyloxy, propane sulfonyloxy, and butane sulfonyloxy groups) and the halogenated analogs (e.g., halogeno(Ci-C4 alkane) sulfonyloxy groups, such as trifluoromethane sulfonyloxy (i.e., triflate), 2,2,2-trichloroethane sulfonyloxy, 3,3,3-tribromopropane sulfonyloxy, and 4,4,4-trifluorobutane sulfonyloxy groups), as well as arylsulfonyloxy groups (e.g., C₆-Cio aryl optionally substituted with 1 to 3 C₁⁻C₄ alkyl groups, such as benzene sulfonyloxy, a-naphthylsulfonyloxy, β-naphthylsulfonyloxy, p-toluenesulfonyloxy.
(i.e., tosylates), 4-tert-butylbenzene sulfonyloxy, mesitylene sulfonyloxy, and 6-ethyl-
a-naphthylsulfonyloxy groups).

[0057] "Activated esters" may be represented by the formula -COL, where L is a
leaving group, typical examples of which include N-hydroxysulfosuccinimidyl and N-
hydroxysuccinimidyl groups; aryloxy groups substituted with electron-withdrawing
groups (e.g., p-nitro, pentafluoro, pentachloro, p-cyano, or p-trifluoromethyl); and
carboxylic acids activated by a carbodiimide to form an anhydride or mixed anhydride,
e.g., -OCOR or -OCNR\textsuperscript{a}NHR\textsuperscript{b}, where R\textsuperscript{a} and R\textsuperscript{b} are independently C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{5}-C\textsubscript{8}
alkyl (e.g., cyclohexyl), C\textsubscript{6} perfluoroalkyl, or C\textsubscript{6} alkoxy groups. An activated
ester may be formed in situ or may be an isolable reagent. Sulfo succinimidyl esters,
pentafluorothiophenol esters, and sulfotetrafluorophenol are preferred activated esters.
However, the ester leaving group may be, for example, substituted or unsubstituted C\textsubscript{1}-
C\textsubscript{6} alkyl (such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl,
pentyl, or hexyl), or substituted or unsubstituted C\textsubscript{6}C\textsubscript{4} aryl or heterocyclic groups,
such as 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2,2,2-
trichloroethyl, 3-fluoropropyl, 4-chlorobutyl, methoxymethyl, 1,1-dimethyl-
1-methoxymethyl, ethoxymethyl, N-propoxymethyl, isopropoxymethyl, N-
butoxymethyl, tert-butoxymethyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, 1-
(isoproxy )ethyl, 3-methoxypropyl-4-methoxybutyl, fluoromethoxymethyl, 2,2,2-
trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 3-fluoropropoxymethyl, 4-
chlorobutoxyethyl, dibromomethoxyethyl, 2-chloroethoxypropyl, fluoromethoxybutyl,
2-methoxyethoxymethyl, ethoxymethoxyethyl, methoxyethoxypropyl,
methoxyethoxybutyl, benzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, a-
naphthylmethyl, [J-naphthylmethyl, diphenylmethyl, triphenylmethyl, a-
naphthydiphenylmethyl, 9-anthrylmethyl, 4-methylbenzyl, 2,4,6-trimethylbenzyl,
3,4,5-trimethylbenzyl, 4-methoxybenzyl, 4-methoxyphenylidiphenylmethyl, 2-
nitrobenzyl, 4-nitrobenzyl, 4-chlorobenzyl, 4-bromobenzyl, 4-cyanobenzyl, 4-
cyanobenzylidiphenylmethyl, or bis(2-nitrophenyl)methyl groups.

[0058] The term "electron-withdrawing group" is art-recognized and describes the
ability of a substituent to attract valence electrons (e.g., pi-electrons) from neighboring
atoms, e.g., the substituent is more electronegative than neighboring atoms, or it draws
electrons to itself more than a hydrogen atom would at the same position. The
Hammett sigma value ($\sigma$) is an accepted measure of a group's electron-donating and withdrawing ability, especially the sigma para value ($\sigma_p$). See, e.g., "Advanced Organic Chemistry" by J. March, 5th Ed., John Wiley & Sons, Inc., New York, pp.368-75 (2001). The Hammett constant values are generally negative for electron-donating groups ($\sigma_p = -0.66$ for $\text{NH}_2$) and positive for electron-withdrawing groups ($\sigma_p = 0.78$ for a nitro group), $\sigma_p$ indicating para substitution. Exemplary electron-withdrawing groups include nitro, acyl (ketone), formyl (aldehyde), sulfonyl, trifluoromethyl, halogeno (e.g., chloro and fluoro), and cyano groups, among others. Conversely, an "electron-donating group" designates a substituent that contributes electrons more than hydrogen would if it occupied the same position in the molecule. Examples include amino (including 15 alkylamino and dialkylamino), aryI, alkoxy (including aralkoxy), aryloxy, mercapto and alkylthio, and hydroxyl groups, among others.

[0059] As used herein, "alkyl" groups include saturated hydrocarbons having one or more carbon atoms, including straight-chain alkyl groups (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.), cyclic alkyl groups (or "cycloalkyl" or "alicyclic" or "carbocyclic" groups) (e.g., cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc.), branched-chain alkyl groups (isopropyl, tert-butyl, sec-butyl, isobutyl, etc.), and alkyl-substituted alkyl groups (e.g., alkyl-substituted cycloalkyl groups and cycloalkyl-substituted alkyl groups). The term "aliphatic group" includes organic moieties characterized by straight or branched-chains, typically having between 1 and 22 carbon atoms. In complex structures, the chains may be branched, bridged, or cross-linked. Aliphatic groups include alkyl groups, alkenyl groups, and alkynyl groups.

[0060] In certain embodiments, a straight-chain or branched-chain alkyl group may have 30 or fewer carbon atoms in its backbone, e.g., C$_1$-C$_{30}$ for straight-chain or C$_3$-C$_{30}$ for branched-chain. In certain embodiments, a straight-chain or branched-chain alkyl group may have 20 or fewer carbon atoms in its backbone, e.g., C$_i$-C$_{20}$ for straight-chain or C$_3$-C$_{20}$ for branched-chain, and more preferably 18 or fewer. Likewise, preferred cycloalkyl groups have from 4-10 carbon atoms in their ring structure, and more preferably have 4-7 carbon atoms in the ring structure. The term "lower alkyl"
refers to alkyl groups having from 1 to 6 carbons in the chain, and to cycloalkyl groups having from 3 to 6 carbons in the ring structure.

[0061] Unless the number of carbons is otherwise specified, "lower" as in "lower aliphatic," "lower alkyl," "lower alkenyl," etc. as used herein means that the moiety has at least one and less than about 8 carbon atoms. In certain embodiments, a straight-chain or branched-chain lower alkyl group has 6 or fewer carbon atoms in its backbone (e.g., \( \text{Ci-C}_6 \) for straight-chain, \( \text{C}_3\text{-C}_6 \) for branched-chain), and more preferably 4 or fewer. Likewise, preferred cycloalkyl groups have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term "\( \text{Ci-C}_6 \) alkyl" as in "\( \text{Ci-C}_6 \) alkyl" means alkyl groups containing 1 to 6 carbon atoms.

[0062] Moreover, unless otherwise specified the term alkyl includes both "unsubstituted alkyls" and "substituted alkyls," the latter of which refers to alkyl groups having substituents replacing one or more hydrogens on one or more carbons of the hydrocarbon backbone. Such substituents may include, for example, alkenyl, alkynyl, halogeno, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy, arylcarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy, alkylcarbonylamino, dialkylamino, arylaminocarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino ), acylamino (including alky carbonylamino, arylcarbonylamino, carbamoyl and ureido ), imino, sulfhydryl, alkythio, arylthio, thiocarboxylate, sulfates, alkylsulfanyl, sulfonato, sulfamoyl- sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclic, alkylaryl, or aromatic (including heteroaromatic) groups.

[0063] An "arylalkyl" group is an alkyl group substituted with an aryl group (e.g., phenylmethyl (i.e., benzyl)). An "alkylaryl" moiety is an aryl group substituted with an alkyl group (e.g., p-methylphenyl (i.e., p-tolyl)). The term "\( n \)-alkyl" means a straight-chain (i.e., unbranched) unsubstituted alkyl group. An "alkylene" group is a divalent analog of the corresponding alkyl group. The terms "alkenyl" and "alkynyl" refer to unsaturated aliphatic groups analogous to alkyls, but which contain at least one double or triple carbon-carbon bond respectively. Suitable alkenyl and alkynyl groups include groups having 2 to about 12 carbon atoms, preferably from 2 to about 6 carbon atoms.
The term "aromatic group" or "aryl group" includes unsaturated and aromatic cyclic hydrocarbons as well as saturated and aromatic heterocycles containing one or more rings. Aryl groups may also be fused or bridged with alicyclic or heterocyclic rings that are not aromatic so as to form a polycycle (e.g., tetralin). An "arylene" group is a divalent analog of an aryl group. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (e.g., tetralin).

The term "heterocyclic group" includes closed ring structures analogous to carbocyclic groups in which one or more of the carbon atoms in the ring is an element other than carbon, for example, nitrogen, sulfur, or oxygen. Heterocyclic groups may be saturated or unsaturated. Additionally, heterocyclic groups (such as pyrrolyl, pyridyl, isoquinolyl, quinolyl, purinyl, and furyl) may have aromatic character, in which case they may be referred to as "heteroaryl" or "heteroaromatic" groups.

Unless otherwise stipulated, aryl and heterocyclic (including heteroaryl) groups may also be substituted at one or more constituent atoms. Examples of heteroaromatic and heteroalicyclic groups may have 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, 0, or S heteroatoms. In general, the term "heteroatom" includes atoms of any element other than carbon or hydrogen, preferred examples of which include nitrogen, oxygen, sulfur, and phosphorus. Heterocyclic groups may be saturated or unsaturated or aromatic.

Examples of heterocycles include, but are not limited to, acridinyl; azocinyl; benzimidazolyl; benzofuranyl; benzothiofuranlyl; benzothiophenyl; benzoazolyl; benzthiazolyl; benztriazolyl; benzotetrazolyl; benzisoxazolyl; benzisothiazolyl; benzimidazolinyl; carbazolyl; 4aH-carbazolyl; carboline; chroman; chromen; 15-cinnolinyl; decahydroquinolinyl; 2H,6H-1,5,2-dithiazinyl; dihydrofuro[2,3-b]tetrahydrofuran; fIrlanyl; furazanyl; imidazolidinyl; imidazolinyln; imidazolyl; 1H-indazolyl; indolenyln; indolinyln; indolizinlyln; indolyl; 3H-indolyl; isobenzofuranyln; isochromanyln; isoindazolinyln; isoindolinyln; isoquinolinyl; isothiazolyn; isoazolyn; methylenedioxyphenyn; morpholinyln; naphthyridinyln; octahydroisoquinolinyl; oxadiazolyl; 1,2,3-oxadiazolyl; 1,2,4-oxadiazolyl; 1,2,5-oxadiazolyl; 1,3,4-oxadiazolyl; oxazolidinyln; oxazolyl; oxazolidinyln; pyrimidinyln; phenanthridinyln; phenanthrolinyln; phenazinyl; phenothiazinyl; phenoxythiinyl;
phenoxazinyl; phthalazinyl; piperazinyl; piperidinyl; piperidonyl; piperonyl; pyridazinyl; pyridoazazole; pyridoimidazole; pyridothiazole; pyridyl; pyrimidinyl; pyrroldinyl; pyrrolinyl; quinazolinyl; quinolinyl; quinolizinyl; quinoxalinyl; quinolinonyl; 1H-indazolyl; oxazolidinyl; benzotriazolyl; benzisoxazolyl; oxindolyl; benzoxazolinyl; and isatinoyl groups. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

[0068] A common hydrocarbon aryl group is a phenyl group having one ring. Two-ring hydrocarbon aryl groups include naphthyl, indenyl, benzocyclooctenyl, benzocycloheptenyl, pentalenyl, and azulenyl groups, as well as the partially hydrogenated analogs thereof such as indanyl and tetrahydronaphthyl. Exemplary three ring hydrocarbon aryl groups include acephenthylenyl, fluorenyl, phenalenyl, phenanthrenyl, and anthracenyl groups.

[0069] Aryl groups also include heteromonocyclic aryl groups, i.e., single-ring heteroaryl groups, such as thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, and pyridazinyl groups; and oxidized analogs thereof such as pyridonyl, oxazolonyl, pyrazolonyl, isoxazolonyl, and thiazolonyl groups. The corresponding hydrogenated (i.e., non-aromatic) heteromonocyclic groups include pyrroldinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl and piperidino, piperazinyl, and morpholino and morpholinyl groups.

[0070] Aryl groups also include fused two-ring heteroaryls such as indolyl, isoindolyl, indolizinyl, indazolyl, quinolyl, isquinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl, chromenyl, isochromenyl, benzothienyl, benzimidazolyl, benzothiazolyl, purinyl, quinolizinyl, isoquinolyl, quinolonyl, naphthyridinyl, and pteridinyl groups, as well as the partially hydrogenated analogs such as chromanyl,
isochromanyl, indolinyl, isoindolinyl, and tetrahydroindolyl groups. Aryl groups also include fused three-ring groups such as phenoxathiinyl, carbazolyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, and dibenzofuranyl groups.

[0071] Some typical aryl groups include substituted or unsubstituted 5- and 6-membered single-ring groups. In another aspect, each Ar group may be selected from the group consisting of substituted or unsubstituted phenyl, pyrrolyl, furyl, thiényl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isooxazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl groups. Further examples include substituted or unsubstituted phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxaliny, 5-quinoxalanyl, 3-quinolyl, and 6-quinolyl groups.

[0072] The term "amine" or "amino," as used herein, refers to an unsubstituted or substituted moiety of the formula \(-NR^aR^b\), in which \(R^a\) and \(R^b\) are each independently hydrogen, alkyl, aryl, or heterocyclyl, or \(R^a\) and \(R^b\), taken together with the nitrogen atom to which they are attached, form a cyclic moiety having from 3 to 8 atoms in the ring. Thus, the term amino includes cyclic amino moieties such as piperidinyl or pyrroldinyl groups, unless otherwise stated. Thus, the term "alkylamino" as used herein means an alkyl group having an amino group attached thereto. Suitable alkyamine groups include groups having 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms. The term amino includes compounds or moieties in which a nitrogen atom is covalently bonded to at least one carbon or heteroatom. The term "dialkylamino" includes groups wherein the nitrogen atom is bound to at least two alkyl groups. The term "arylamino" and "diarylamino" include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively. The term "alkylarylamino" refers to an amino group which is bound to at least one alkyl group and at least one aryl group. The term "alkaminoalkyl" refers to an alkyl, alkenyl, or alkynyl group substituted with an alkyamine group. The term "amide" or
"aminocarbonyl" includes compounds or moieties which contain a nitrogen atom which is bound to the carbon of a carbonyl or a thiocarbonyl group.

[0073] The term "alkylthio" refers to an alkyl group, having a sulhydryl group attached thereto. Suitable alkylthio groups include groups having 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms.

[0074] The term "alkylcarboxyl" as used herein means an alkyl group having a carboxyl group attached thereto.

[0075] The term "alkoxy" as used herein means a n alkyl group having an oxygen atom attached thereto. Representative alkoxy groups include groups having 1 to about 12 carbon atoms, preferably 1 to about 6 carbon atoms, e.g., methoxy, ethoxy, propoxy, tert-butoxy and the like. Examples of alkoxy groups include methoxy, ethoxy, isopropyloxy, propoxy, butoxy, and pentoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxycarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino ), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido ), imino, sulhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfanyl, sulfonate, sulfamoyl, sulfonamide, nitro, trifluoromethyl, cyano, azide, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, etc., as well as perhalogenated alkoxy groups.

[0076] The term "acylamino" includes moieties wherein an amino moiety is bonded to an acyl group. For example, the acylamino group includes alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

[0077] The terms "alkoxycarbonyl", "alkylaminoalkyl" and "thioalkoxycarbonyl" include alkyl groups, as described above, which further include oxygen, nitrogen or sulfur atoms replacing one or more carbons of the hydrocarbon backbone.
The term "carbonyl" or "carboxy" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom. Examples of moieties which contain a carbonyl include aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc.

The term "ether" or "ethereal" includes compounds or moieties which contain an oxygen bonded to two carbon atoms. For example, an ether or ethereal group includes "alkoxyalkyl" which refers to an alkyl, alkenyl, or alkynyl group substituted with an alkoxy group.

A "sulfonate" group is a -SO\textsubscript{2}H or -SO\textsubscript{3}X\textsuperscript{+} group bonded to a carbon atom, where X\textsuperscript{+} is a cationic counter ion group. Similarly, a "sulfonic acid" compound has a -SO\textsubscript{3}H or -SO\textsubscript{3}X\textsuperscript{+} group bonded to a carbon atom, where X\textsuperscript{+} is a cationic group. A "sulfate" as used herein is a -OSO\textsubscript{3}H or -OSO\textsubscript{3}X\textsuperscript{+} group bonded to a carbon atom, and a "sulfuric acid" compound has a -SO\textsubscript{3}H or -OSO\textsubscript{3}X\textsuperscript{+} group bonded to a carbon atom, where X\textsuperscript{+} is a cationic group. According to the present disclosure, a suitable cationic group may be a hydrogen atom. In certain cases, the cationic group may actually be another group on the therapeutic compound that is positively charged at physiological pH, for example an amino group.

A "counter ion" is required to maintain electroneutrality. Examples of anionic counter ions include halide, triflate, sulfate, nitrate, hydroxide, carbonate, bicarbonate, acetate, phosphate, oxalate, cyanide, alkylcarboxylate, N-hydroxysuccinimide, N-hydroxybenzotriazole, alkoxide, thioalkoxide, alkane sulfonloxy, halogenated alkane sulfonloxy, arylsulfonloxy, bisulfate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, or lactobionate. Compounds containing a cationic group covalently bonded to an anionic group may be referred to as an "internal salt."

The term "nitro" means -NO\textsubscript{2}; the term "halogen" or "halogeno" or "halo" designates -F, -Cl, -Br or -I; the term "thiol," "thio," or "mercapto" means SH; and the term "hydroxyl" or "hydroxy" means -OH.

The term "acyl" refers to a carbonyl group that is attached through its carbon atom to a hydrogen (i.e., a formyl), an aliphatic group (e.g., acetyl), an aromatic group
(e.g., benzoyl), and the like. The term "substituted acyl" includes acyl groups where one or more of the hydrogen atoms on one or more carbon atoms are replaced by, for example, an alkyl group, alkynyl group, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diaryl am in o, and alkylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfanyl, sulfonate, sulfamoyl, sulfonamide, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0084] Unless otherwise specified, the chemical moieties of the compounds of the invention, including those groups discussed above, may be "substituted or unsubstituted." In some embodiments, the term "substituted" means that the moiety has substituents placed on the moiety other than hydrogen (i.e., in most cases, replacing a hydrogen), which allow the molecule to perform its intended function. Examples of substituents include moieties selected from straight or branched alkyl (preferably C₃-C₅), cycloalkyl (preferably C₅-C₈), alkoxy (preferably C₁-C₆), thioalkyl (preferably C₁-C₆), alkenyl (preferably C₂-C₆), alkynyl (preferably C₂-C₆), heterocyclic, carbocyclic, aryl (e.g., phenyl), aryloxy (e.g., phenoxy), aralkyl (e.g., benzyl), aryloxalkyl (e.g., phenox yalkyl), arylacetamidoyl, alkylaryl, heteroarylalkyl, alkylcarbonyl and arylcarbonyl or other such acyl group, heteroarylcarbonyl, and heteroaryl groups, as well as (CR’R")₀.₃NR'R" (e.g., -NH₂), (CR’R")₀.₃CN (e.g., -CN), -NO₂, halogen (e.g., -F, -Cl, -Br, or -I), (CRR")₀.₃C(halogen)₃ (e.g., -CF₃), (CRR")₀.₃CH(halogen)₂, (CRR")₀.₃CH₂(halogen), (CRR")₀.₃CONR'R". (CRR")₀.₃(CNH)NR'R", (CRR")₀.₃S(0)i₂NR'R", (CRR")₀.₃CHO, (CRR")₀.₃O(CRR")₀.₃H, (CRR")₀.₃S(O)₀.₃R (e.g., -SO₂H), (CRR")₀.₃O(CRR")₀.₃H (e.g., -CH₂OCH₃ and -OCH₃), (CRR")₀.₃S(CRR")₀.₃H (e.g., -SH and -SCH₃), (CRR")₀.₃OH (e.g., -OH), (CRR")₀.₃COR, (CRR")₀.₃OCOR (substituted or unsubstituted phenyl), (CRR")₀.₃C₅-C₈, cycloalkyl), (CRR")₀.₃CO₂R (e.g., -CO₂H), and (CRR")₀.₃OR groups, wherein R and
R" are each independently hydrogen, a C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, or aryl group; or the side chain of any naturally occurring amino acid.

[0085] In another embodiment, a substituent may be selected from straight or branched alkyl (preferably C_1-C_5), cycloalkyl (preferably C_3-C_6), alkoxy (preferably Ci-C_6), thioalkyl (preferably Ci-C_6), alkenyl (preferably C_2-C_6), alkynyl (preferably C_2-C_6), heterocyclic, carbocyclic, aryl (e.g., phenyl), aryloxy (e.g., phenoxy), aralkyl (e.g., benzyl), arloxyalkyl (e.g., phenoxyalkyl), alylacetamidoyl, alylaryl, heteroarylcarbonyl, or arylcarbonyl or other such acyl group, heteroarylacarbonyl, or heteroaryl group, (CRR")_0-o-ioNR"_0 (e.g., -NH_2), (CRR")_0-o-ioCN (e.g., -CN), N0_2, halogen (e.g., F, Cl, Br, or I), (CRR")_0-o-ioC(halogen)_(3) (e.g., -CF_3), (CRR")_0-o-ioCH(halogen)_(2), (CRR")_0-o-ioCH_(2)(halogen), (CRR")_0-o-ioCONR'R", (CRR")_0-o-io(CNH)NR'R", (CRR")_0-o-ioS(0)_1,2,3NR"_0, (CRR")_0-o-ioCHO, (CRR")_0-o-ioO(CRR")_0-o-ioH, (CRR")_0-o-ioS(0)_0,R"_0 (e.g., -SO_2H), (CRR")_0-o-ioO(CRR")_0-o-ioH (e.g., -CH_2OCH_3 and -OCH_3), (CRR")_0-o-ioS(CRR")_0=H (e.g., -SH and -SCH_3), (CRR")_0-o-ioOH (e.g., -OH), (CRR")_0-o-ioCOR, (CRR")_0-o-io (substituted or unsubstituted phenyl), (CRR")_0-o-io (C_3-C_8 cycloalkyl), (CRR")_0-o-ioC_0=O(R"_0 (e.g., -CO_2H), or (CRR")_0-o-ioOR group, or the side chain of any naturally occurring amino acid; wherein R and R" are each independently hydrogen, a C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, or aryl group, or R and R" taken together are a benzylidene group or a -(CH_2)_20(CH_2)_2- group.

[0086] It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with the permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is meant to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. The permissible substituents can be one or more.

[0087] In some embodiments, a "substituent" may be selected from the group consisting of, for example, halogeno, trifluoromethyl, nitro, cyano, C_6-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_6 alkylcarboonyloxy, arylcarboonyloxy, C_6-C_6 alkoxycarboonyloxy, aryloxyarboonyloxy, C_6-C_6 alkylcarboonyl, C_6-C_6 alkoxycarboonyl,
Ci-C₆ alkoxy, Ci-C₆ alkylthio, arylthio, heterocyclyl, aralkyl, and aryl (including heteroaryl) groups.

[0088] Compounds contemplated for use in accordance with the present disclosure may be readily prepared employing synthetic methods known in the art. See, for example, WO2006/085149, the entire contents of which are hereby incorporated by reference herein.

[0089] In another embodiment, the disclosure pertains to a pharmaceutical formulation for treating sarcoidosis, comprising a therapeutically effective amount of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof in a formulation such that the formulation has at least one favorable biological property (FBP) upon administration to a subject. Formulations contemplated for use herein can be readily prepared employing methods known in the art. See, for example, WO2006/085149, the entire contents of which are hereby incorporated by reference herein.

[0090] The term "pharmaceutical formulation" includes pharmaceutical compositions as described below. In a further embodiment, the pharmaceutical formulations are designed to have favorable biological properties which enhance the ability of the compounds of the disclosure to treat sarcoidosis and/or related diseases. The favorable biological properties of the formulation were discovered by administering the compounds of the disclosure to subjects during clinical trials.

[0091] The disclosure also pertains, at least in part, to a pharmaceutical composition comprising a therapeutically effective amount of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof and second agent. In a further embodiment, the therapeutically effective amount is effective to treat sarcoidosis.

[0092] In a further embodiment, the disclosure pertains to a packaged pharmaceutical composition. The packaged pharmaceutical composition includes a therapeutically effective amount of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof packaged in combination with a label or insert advising that the composition be administered in combination with a second agent. In a further embodiment, the therapeutically effective amount is effective to treat sarcoidosis.
In yet another further embodiment, the disclosure pertains to a packaged pharmaceutical composition, which includes a therapeutically effective amount of a second agent packaged in combination with a label or insert advising that the composition be administered in combination with a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof.

The term "label or insert" includes, but is not limited to all written, electronic, or spoken communication with the subject, or with any person substantially responsible for the care of the subject, regarding the administration of the compositions of the present disclosure. An insert may further include information regarding coadministration of the compositions of the present disclosure with other compounds or compositions, e.g., second agents. Additionally, an insert may include instructions regarding administration of the compositions of the present disclosure without food.

In yet another embodiment, the disclosure pertains to a packaged pharmaceutical composition, which includes a container holding a pharmaceutical composition comprising a therapeutically effective amount of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof in combination with a label or insert advising that the composition be administered without food.

Prodrugs of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof may be supplied in a solution with an appropriate solvent or in a solvent-free form (e.g., lyophilized). In another aspect of the disclosure, the agents and buffers necessary for carrying out the methods of the disclosure may be packaged as a kit. The kit may be commercially used according to the methods described herein and may include instructions for use in a method of the disclosure. Additional kit components may include acids, bases, buffering agents, inorganic salts, solvents, antioxidants, preservatives, or metal chelators. The additional kit components are present as pure compositions, or as aqueous or organic solutions that incorporate one or more additional kit components. Any or all of the kit components optionally further comprise buffers.

Prodrugs of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof may also be administered in a variety of ways, e.g., parenterally, intraperitoneally, intraspinaly, intracerebrally, and the like. See, for example,
WO2006/085149, the entire contents of which are hereby incorporated by reference herein. Dispersions can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

[0098] To administer a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof by other than parenteral administration, it may be necessary to coat the active agent with, or co-administer the active agent with, a material to prevent its inactivation. For example, a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof may be administered to a subject in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan et al., J. Neuroimmunol. 7, 27 (1984)). It should be noted that the term "pharmaceutical composition" includes the "pharmaceutical formulations" described above.

[0099] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases, the composition must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi.

[0100] Suitable pharmaceutically acceptable vehicles include, without limitation, any non-immunogenic pharmaceutical adjuvants suitable for oral, parenteral, nasal, mucosal, transdermal, intravascular (IV), intraarterial (IA), intramuscular (IM), and subcutaneous (SC) administration routes, such as phosphate buffer saline (PBS).

[0101] The vehicle can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various
antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, isotonic agents are included, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

[0102] Sterile injectable solutions can be prepared by incorporating the therapeutic agent in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the therapeutic agent into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient (i.e., the compound of the disclosure) plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0103] Prodrugs of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof can be orally administered, for example, with an inert diluent or an assimilable edible carrier. Prodrugs of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof in the compositions and preparations may, of course, be varied. The amount of prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof in such therapeutically useful compositions is such that a suitable dosage will be obtained.

[0104] The present disclosure therefore includes pharmaceutical formulations comprising a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof, in pharmaceutically acceptable vehicles for aerosol, oral and parenteral
administration. Also, the present disclosure includes such compounds, or salts thereof, which have been lyophilized and which may be reconstituted to form pharmaceutically acceptable formulations for administration, as by intravenous, intramuscular, or subcutaneous injection. Administration may also be intradermal or transdermal.

[0105] In accordance with the present disclosure, a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof may be administered orally or through inhalation as a solid, or may be administered intramuscularly or intravenously as a solution, suspension or emulsion. Alternatively, the agents or salts may also be administered by inhalation, intravenously or intramuscularly as a liposomal suspension.

[0106] Pharmaceutical compositions or formulations are also provided which are suitable for administration as an aerosol, by inhalation. These formulations comprise a solution or suspension of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof, or a plurality of solid particles of the agent or salt. The desired formulation may be placed in a small chamber and nebulized. Nebulization may be accomplished by compressed air or by ultrasonic energy to form a plurality of liquid droplets or solid particles comprising the agents or salts. The liquid droplets or solid particles should have a particle size in the range of about 0.5 to about 5 microns. The solid particles can be obtained by processing the solid agent of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof, in any appropriate manner known in the art, such as by micronization. The size of the solid particles or droplets will be, for example, from about 1 to about 2 microns. In this respect, commercial nebulizers are available to achieve this purpose.

[0107] A pharmaceutical formulation suitable for administration as an aerosol may be in the form of a liquid, the formulation will comprise a water-soluble form of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof, in a carrier which comprises water. A surfactant may be present which lowers the surface tension of the formulation sufficiently to result in the formation of droplets within the desired size range when subjected to nebulization.

[0108] Peroral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically acceptable vehicles suitable for preparation of such
compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, tragacanth, and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

[0109] Pharmaceutical compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject agent is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, waxes, and shellac.

[0110] Other compositions useful for attaining systemic delivery of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

[0111] Prodrugs of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof can also be administered topically to a subject, e.g., by the direct laying on or spreading of a composition containing same on the epidermal or epithelial tissue of the subject, or transdermally via a "patch". Such compositions include, for example, lotions, creams, solutions, gels and solids. These topical compositions may comprise an effective amount, usually at least about 0.1 wt %, or even from about 1 wt % to about 5 wt %, of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof. Suitable carriers for topical administration typically remain in place on the skin as a continuous film, and resist being removed by perspiration or immersion in water. Generally, the carrier is organic in nature and capable of having dispersed or dissolved therein the therapeutic agent. The carrier may include
pharmaceutically acceptable emollients, emulsifiers, thickening agents, solvents and
the like.

[0112] Toxicity and therapeutic efficacy of such agents can be determined by standard
pharmaceutical procedures in cell cultures or experimental animals, e.g., for
determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the
dose therapeutically effective in 50% of the population). The dose ratio between toxic
and therapeutic effects is the therapeutic index and can be expressed as the ratio
LD50/ED50, and usually a larger therapeutic index is more efficacious. While
compounds that exhibit toxic side effects may be used, care should be taken to design a
delivery system that targets such agents to the site of affected tissue in order to
minimize potential damage to unaffected cells and, thereby, reduce side effects.

[0113] It is understood that appropriate doses depend upon a number of factors within
the ken of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of a
prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof
will vary, for example, depending upon the identity, size, and condition of the subject
or sample being treated, further depending upon the route by which the composition is
to be administered, if applicable, and the effect which the practitioner desires the
prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof to
have upon the subject. Exemplary doses include milligram or microgram amounts of a
prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof per
kilogram of subject or sample weight (e.g., about 1 microgram per kilogram to about
500 milligrams per kilogram, about 100 micrograms per kilogram to about 5
milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms
per kilogram). It is furthermore understood that appropriate doses depend upon the
potency. Such appropriate doses may be determined using the assays known in the art.
When a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt
thereof is to be administered to an animal (e.g., a human), a physician, veterinarian, or
researcher may, for example, prescribe a relatively low dose at first, subsequently
increasing the dose until an appropriate response is obtained. In addition, it is
understood that the specific dose level for any particular animal subject will depend
upon a variety of factors including the activity of the specific compound employed, the
age, body weight, general health, gender, and diet of the subject, the time of
administration, the route of administration, the rate of excretion, and any drug combination. See, for example, WO2007/004072, the entire contents of which are hereby incorporated by reference herein.

[0114] For subjects having sarcoidosis, doses may depend on the state of renal function in the subject, as measured, for example, by the rate of creatinine clearance, which may affect the rate of clearance of the compound from the subject. In this case, subjects with a lower rate of creatinine clearance would be expected to achieve a particular plasma concentration at a lower dose than those with a higher rate of creatinine clearance. For example, the dosage of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof may be selected to be about 1200 mg twice daily for a creatinine clearance rate of >80 mL/min. For a creatinine clearance rate of between about 30 and 80 mL/min, the dosage of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof may be selected to be about 800 mg twice daily. For a creatinine clearance rate of between about 20 and 30 mL/min, the dosage of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof may be selected to be about 400 mg twice daily. In addition, the dosage also may be adjusted based on the changing creatinine clearance rates in the subject.

[0115] The term "creatinine clearance" is art recognized and refers to the rate at which the kidneys clear creatinine from the blood. Creatinine is a substance that is easily excreted by the kidney in healthy subjects. Creatinine clearance generally compares the level of creatinine in urine with the creatinine level in the blood. Clearance is often measured as milliliters/minute (ml/min).

[0116] In certain embodiments of the present disclosure, a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers can be orally administered in an amount determined in accordance with the subject's rate of creatinine clearance. For example, when the formulation is administered in a dose of 400 mg, a mean plasma concentration profile of a prodrug of 1,3propanedisulfonic acid having a mean AUC of about 10,000-12,000 ng-h/mL- 20%, and a mean Cmax of about 800-900 ng/mL ±
20% is achieved; or when the formulation is administered in a dose of 800 mg, a mean plasma concentration profile of the active agent having a mean AUC of about 9,000-10,500 ng-h/mL 20%, and a mean Cmax of about 750-875 ng/mL ± 20% is achieved; or when the formulation is administered in a dose of 1200 mg, a mean plasma concentration profile of the active agent having a mean AUC of about 5,000-6,000 ng-h/mL ± 20%, and a mean Cmax of about 800-925 ng/mL 10 20% is achieved.

[0117] Parenteral compositions may be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit containing a predetermined quantity of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof calculated to produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The specifications for the dosage unit forms of the disclosure are dictated by and directly dependent on (a) the unique characteristics of the therapeutic agent and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof for the treatment of sarcoidosis or related disease.

[0118] Various aspects of the present disclosure are illustrated by the following non-limiting examples. The examples are for illustrative purposes and are not a limitation on any practice of the present disclosure. It will be understood that variations and modifications can be made without departing from the spirit and scope of the disclosure. One of ordinary skill in the art readily knows how to synthesize or commercially obtain the reagents and components described herein.

[0119] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures, embodiments, claims, and examples described herein. Such equivalents are considered to be within the scope of this disclosure and covered by the claims appended hereto. The contents of all references, issued patents, and published patent applications cited throughout this application are hereby incorporated by reference. The disclosure is further illustrated by the following example, which should not be construed as further limiting.
EXAMPLE 1

[0120] THP-1 cells are subjected to PMA (phorbol 12-myristate 13-acetate (EMD Cat.# 524400)), SAA (serum amyloid A (PeroTech Cat.#300-13)), and a prodrug of 1,3-propanedisulfonic acid (e.g., a compound of any one of Formulae I - XV)). The protocol is summarized in Figure 1. The SAA treated cells are used as a positive control, with the SAA increasing the inflammatory mediators, TNF, IL-18 and IL-10. A prodrug of 1,3-propanedisulfonic acid is added to the cell cultures and the effect on TNF, IL-18 and IL-10 levels is measured.

EXAMPLE 2

[0121] In the protocol described in Example 1, a prodrug of 1,3-propanedisulfonic acid at a concentration of 5 mg/ml and above inhibits SAA-induced production of the inflammatory mediator, IL-18 by the THP-1 cells.

[0122] In the protocol described in Example 1, a prodrug of 1,3-propanedisulfonic acid at a concentration of 2.5 mg/ml and above inhibits SAA-induced production of the inflammatory mediator, IL-10 by the THP-1 cells.

[0123] In the protocol described in Example 1, a prodrug of 1,3-propanedisulfonic acid at a concentration of 1.25 mg/ml and above inhibits SAA-induced production of the inflammatory mediator, IL-TNF by the THP-1 cells.

EXAMPLE 3

[0124] A patient is diagnosed with sarcoidosis, and a prodrug of 1,3-propane disulfonic acid is administered to the patient. The treatment results in the reduction and/or alleviation of sarcoidosis symptoms in the patient.

[0125] Various modifications of the present disclosure, in addition to those shown and described herein, will be apparent to those skilled in the art of the above description. Such modifications are also intended to fall within the scope of the appended claims.
[0126] Patents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the disclosure pertains. These patents and publications are incorporated herein by reference to the same extent as if each individual application or publication was specifically and individually incorporated herein by reference.

[0127] The foregoing description is illustrative of particular embodiments of the disclosure, but is not meant to be a limitation upon the practice thereof. The following claims, including all equivalents thereof, are intended to define the scope of any the invention described herein.
That which is claimed is:

1. A method for treating a subject with sarcoidosis, said method comprising administering to said subject an effective amount of a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof.

2. The method of claim 1 wherein said subject has chronic sarcoidosis.

3. The method of claim 1 wherein said sarcoidosis affects the lungs, liver, heart, nervous system, skin, lymph glands, musculoskeletal system, spleen, eyes, sinuses, nasal mucosa, larynx, the gastrointestinal tract, reproductive organs, salivary glands and/or kidneys.

4. The method of claim 3 wherein said sarcoidosis affects the lungs.

5. The method of claim 1 wherein at least 1mg/kg of a prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof is administered to said subject per dose.

6. The method of claim 5 wherein said prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof is administered more than once daily.

7. The method of claim 5 wherein said prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof is administered 2, 3, 4, 5 or 6 times daily.

8. The method of claim 5 wherein no more than 20mg/kg of a prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof is administered to said subject per dose.

9. The method of claim 1 wherein said prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof is administered by oral, parenteral,
intraperitoneal, intraspinal, intracerebral, nasal, mucosal, transdermal, intravascular, intraarterial, intramuscular, or subcutaneous delivery.

10. The method of claim 1 wherein said prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof is administered by oral delivery.

11. The method of any one of the preceding claims wherein said prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof is a compound of any one of Formulae I - XV.

12. The method of any one of claims 1 - 10 wherein said prodrug of 1,3-propanedisulfonic acid or pharmaceutically acceptable salt thereof is the disodium salt of a compound of any one of Formulae I - XV.

13. A pharmaceutically acceptable composition for the treatment of sarcoidosis, said composition comprising a prodrug of 1,3-propanedisulfonic acid or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor.

14. The composition of claim 13 further comprising a second agent traditionally employed for the treatment of sarcoidosis.

15. The composition of claim 14 wherein said second agent is a corticosteroid.
Figure 1

Protocol

THP-1 5 x 10^5 cells/ml

<table>
<thead>
<tr>
<th></th>
<th>PMA</th>
<th>SAA</th>
<th>KIACCTA</th>
</tr>
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<tbody>
<tr>
<td>200ng/ml →</td>
<td>10μg/ml</td>
<td>+ 0 ~ 10 mg/ml</td>
<td></td>
</tr>
<tr>
<td>48hr</td>
<td>24hr</td>
<td>24hr</td>
<td></td>
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PMA = phorbol 12-myristate 13-acetate (EMD Cat.# 524400)
SAA = serum amyloid A (PeroTech Cat.#300-13)
KIACCTA C933 (NRA610-01-CF)

ELISA Kit

IL-18; MBL Cat.#7620
IL-10; invitrogen Cat.#KHC0101
TNF; BD Cat.#550610
# INTERNATIONAL SEARCH REPORT

**International application No.**  
PCT/US 16/56899  
**A. CLASSIFICATION OF SUBJECT MATTER**  
**IPC(8):** A61K 31/573, 31/4035 (2016.01)  
**CPC:** A61K 31/573, 31/4035  
According to International Patent Classification (IPC) or to both national classification and IPC.

**B. FIELDS SEARCHED**  
Minimum documentation searched (classification system followed by classification symbols)  
**IPC(8):** A61K 31/573, 31/4035 (2016.01)  
**CPC:** A61K 31/573, 31/4035  
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); EBSCO; PubMed; Google Scholar; sarcoidosis, pulmonary, lung, propanedisulfonic, sulfonyl, sodium, oral, chronic, corticosteroid, prednisone

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Y</strong></td>
<td>US 2014/0329746 A1 (KONG, X et al.) 06 November 2014; paragraphs [0024]-[0145], [0147], [0157], [0330], [0431], [0508], [0512], [0517], [0539]</td>
<td>1-10, 1/1-10, 12/1-10, 13-15</td>
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<td><strong>Y</strong></td>
<td>US 2014/0004182 A1 (ZELDIS, JB) 02 January 2014; abstract; paragraphs [0010], [0016MO018], [0024]-[0025], [0033]</td>
<td>1-10, 1/1-10, 12/1-10, 13-15</td>
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<tr>
<td><strong>A</strong></td>
<td>US 2015/0031702 A1 (GLAXOSMITHKLINE INTELLECTUAL PROPERTY (NO.2) LIMITED) 29 January 2015; entire document</td>
<td>1-10, 1/1-10, 12/1-10, 13-15</td>
</tr>
<tr>
<td><strong>P, X</strong></td>
<td>WO 2015/168315 A1 (IACHN SCHOOL OF MEDICINE AT MOUNT SINAI) 05 November 2015; entire document</td>
<td>1-10, 1/1-10, 12/1-10, 13-15</td>
</tr>
</tbody>
</table>

*Further documents are listed in the continuation of Box C.*

*Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance  
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"O" document referring to an oral disclosure, use, exhibition or other means  
"P" document published prior to the international filing date but later than the priority date claimed

*"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Date of the actual completion of the international search  
20 November 2016 (20.11.2016)

Date of mailing of the international search report  
13 JAN 2017

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