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(54) Title: HYDROGEN SULFIDE PRODRUGS AND USES THEREOF

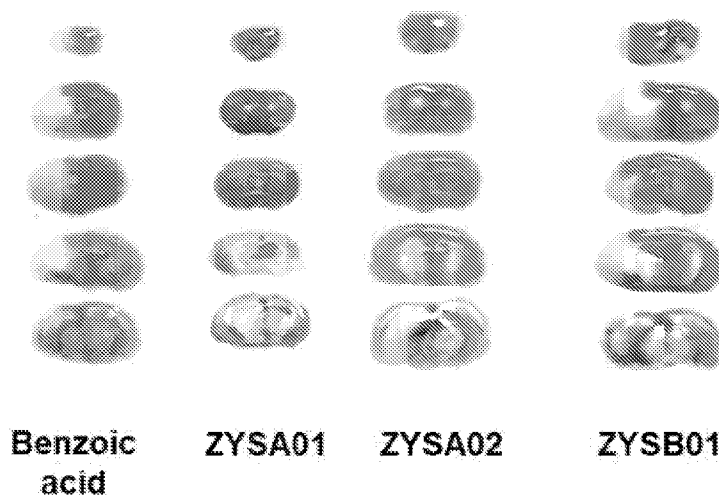


FIG. 1A

(57) **Abstract:** Provided herein are hydrogen sulfide compounds comprising a thiocarboxylic acid moiety, wherein the hydrogen sulfide compound releases hydrogen sulfide under enzyme-catalyzed conditions. Also provided herein are pharmaceutical compositions comprising the hydrogen sulfide compounds disclosed herein and a pharmaceutically acceptable carrier. Also provided herein are kits comprising the hydrogen sulfide compounds provided herein or a pharmaceutical composition provided herein. Further provided herein are methods of preventing or preventing a cerebrovascular disease, an anti-inflammatory condition, rheumatic or rheumatoid arthritis, gout, high blood pressure, a high blood lipids condition, or liver toxicity in a subject, comprising administering to the subject an effective amount of a hydrogen sulfide compound provided herein, or a pharmaceutical composition provided herein.



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(81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

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HYDROGEN SULFIDE PRODRUGS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

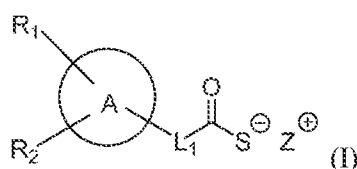
[0001] The present application claims priority to Chinese Appl. No. CN202311051861.8 filed August 21, 2023, which application is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Though hydrogen sulfide (H_2S) used to be considered only as a toxic gas with an unpleasant odor, recent studies have shown that H_2S is the third gaseous signaling molecule synthesized in mammalian cells after CO and NO, involved in a variety of physiological and pathological processes. Studies have shown that H_2S can dilate blood vessels to lower blood pressure, fight oxidative stress to reduce tissue damage, regulate intestinal flora, and protect mucous membranes. However, high concentrations of H_2S are toxic, and capitalizing on the properties of H_2S as a gas signaling molecule requires its controlled and slow release. Therefore, developing H_2S compounds to manage the controlled and slow release of H_2S has captured the interest of researchers. However, there are a number of problems that prevent the development of H_2S compounds for clinical use.

BRIEF SUMMARY

[0003] Provided herein are compounds of Formula I:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Z⁺ is Na⁺, K⁺, or H⁺;

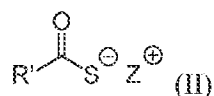
A is substituted or unsubstituted C₆-C₂₀ aryl or substituted or unsubstituted C₃-C₂₀ heteroaryl;

L₁ is a bond, -(CH₂)_n-, C₂-C₆ branched alkyl, -O-(CH₂)_n-C(CH₃)₂-, -R₅C(=O)NHR₆-, -O-(CH₂)_n-, or -O-(CH₂)_n-O-;

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

each R_1 and R_2 are independently hydrogen, halogen, -CN, -NO₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₂NR₃R₄-, C₆-C₁₀ aryl, or C₃-C₁₀ heteroaryl, wherein each R_3 , R_4 , R_5 , and R_6 are independently hydrogen or C₁-C₆ alkyl.

[0004] Also provided herein are compounds of Formula II:

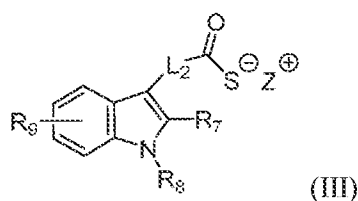


or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Z^+ is Na⁺, K⁺, or H⁺; and

R' is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted bridged cycloalkyl, or substituted or unsubstituted spirocycloalkyl.

[0005] Also provided herein are compounds of Formula III:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Z^+ is Na⁺, K⁺, or H⁺;

L_2 is a bond, -(CH₂)_n-, or C₂-C₆ branched alkyl;

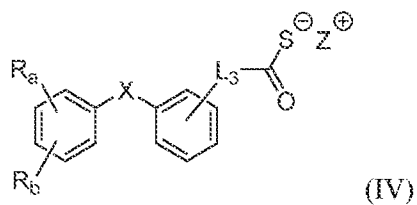
n is 0, 1, 2, 3, or 4;

R_7 is hydrogen or C₁-C₆ alkyl;

R_8 is hydrogen, -C(=O)-R₁₀, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, or C₁-C₆ haloalkoxy, wherein R_{10} is substituted or unsubstituted C₆-C₁₀ aryl or substituted or unsubstituted C₃-C₁₀ heteroaryl, wherein when substituted by a substituent, the substituent is selected from the group consisting of halogen, -OH, -CN, -NO₂, C₁-C₄ alkyl, C₁-C₄ alkoxy, and C₁-C₄ haloalkyl; and

R_9 is hydrogen, halogen, -CN, -NO₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, or C₁-C₆ haloalkoxy.

[0006] Further provided herein are compounds of Formula IV:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Z^+ is Na^+ , K^+ , or H^+ ;

L_3 is a bond, $-(CH_2)_n-$, or C_2 - C_6 branched alkyl;

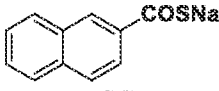
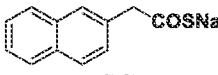
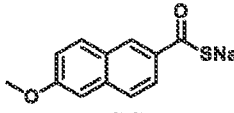
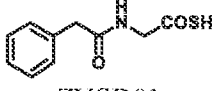
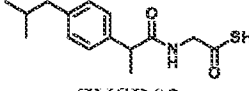
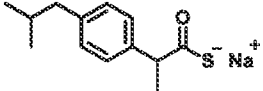
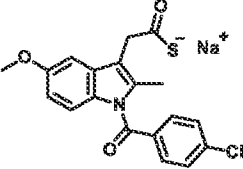
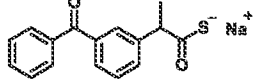
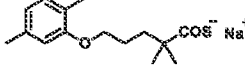
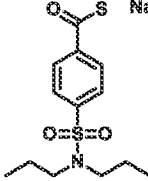
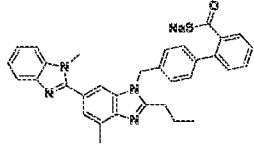
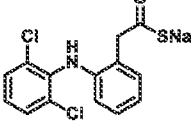
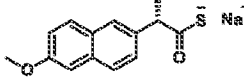
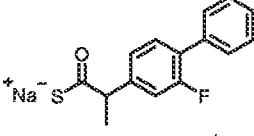
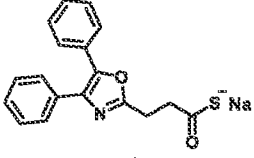
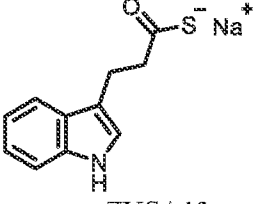
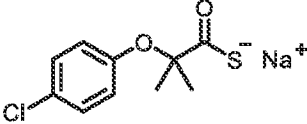
n is 0, 1, 2, 3, or 4;

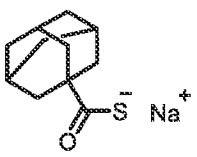
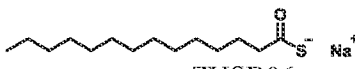
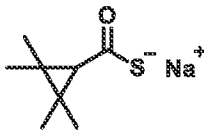
X is $-NH-$ or $-C(=O)-$;

each R_a and R_b are independently hydrogen, halogen, $-CN$, $-NO_2$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, or C_1 - C_6 haloalkoxy.

[0007] Provided herein are compounds selected from the group consisting of:

ZYSA01	ZYSA02	ZYSA03
ZYSA04	ZYSA05	ZYSA06
ZYSA07	ZYSA08	ZYSB01
ZYSB02	ZYSB03	

 ZYSC01	 ZYSC02	 ZYSC03
 ZYSD01	 ZYSD02	
 ZYSH01(S- bupropfen)	 ZYSH02(S- indomethacin)	 ZYSH03(S- Ketoprofen)
 ZYSH04(S- Gemfibrozil)	 ZYSH05(S- Probenecid)	 ZYSH06(S- telmisartan)
 ZYSH21(S- diclofenac)	 ZYSH31(S- naproxen)	 ZYSH07 (Flurbiprofen)
 ZYSH08 (Oxaprozin)	 ZYSA12 (3-indolepropionic acid)	 ZYSA13

 ZYSB04	 ZYSB08
 ZYSB07	 ZYSB06
 ZYSB05	 ZYSB09

and a pharmaceutically acceptable salt or prodrug thereof.

[0008] Provided herein is a pharmaceutical composition comprising a compound of Formula I, Formula II, Formula III, or Formula IV and a pharmaceutically acceptable carrier.

[0009] Also provided herein is a kit comprising a compound of Formula I, Formula II, Formula III, or Formula IV or a pharmaceutical composition comprising a compound of Formula I, Formula II, Formula III, or Formula IV and a pharmaceutically acceptable carrier.

[0010] Further provided herein are methods of treating or preventing a cerebrovascular disease, an anti-inflammatory condition, rheumatic or rheumatoid arthritis, gout, high blood pressure, a high blood lipids condition, or liver toxicity in a subject, comprising administering to the subject an effective amount of a compound of Formula I, Formula II, Formula III, or Formula IV or a pharmaceutical composition comprising a compound of Formula I, Formula II, Formula III, or Formula IV and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF DRAWINGS

[0011] The foregoing aspects and others will be readily appreciated by the skilled artisan from the following description of illustrative embodiments when read in conjunction with the accompanying drawings.

[0012] FIG. 1A shows images of mouse brain infarct area in the presence of benzoic acid, ZYSA01, ZYSA02, and ZYSB01.

[0013] FIG. 1B shows a graph of the quantitative analysis of infarct size in the presence of benzoic acid, ZYSA01, ZYSA02, and ZYSB01.

[0014] FIG. 1C shows a graph of the analysis of serum lactate dehydrogenase (LDH) levels in the presence of benzoic acid, ZYSA01, ZYSA02, and ZYSB01.

[0015] FIG. 1D shows a graph of the analysis of the tissue malondialdehyde (MDA) levels in the presence of benzoic acid, ZYSA01, ZYSA02, and ZYSB01.

[0016] FIG. 2A shows images of the mouse brain infarct area in the presence of telmisartan and ZYSH06.

[0017] FIG. 2B shows a graph of the quantitative analysis of infarct area in the presence of telmisartan and ZYSH06.

[0018] FIG. 2C shows a graph of the analysis of serum LDH levels in the presence of telmisartan and ZYSH06.

[0019] FIG. 2D shows a graph of the analysis of tissue MDA level in the presence of telmisartan and ZYSA06.

[0020] FIG. 3 shows the blood concentration-time curve of ZYSH21 interconversion with diclofenac (DCF) after ZYSH21 was administered orally (10 mg/kg).

[0021] FIG. 4 shows a graph depicting changes in paw swelling rates of rats in the DCF and ZYSH21 groups after 10 mg/kg gavage administration, n=8.

[0022] FIG. 5 shows a graph of the percentage of gastric ulcers in diclofenac (DCF) and ZYSH21 treated rats after 10 mg/kg gavage administration, n=8.

[0023] FIG. 6A shows a bar graph of the serum levels of aspartate aminotransferase (AST) in diclofenac (DCF) (150 mg/kg, i.p.) and ZYSH21 (157 mg/kg, i.p.) treated rats after 24 h of administration.

[0024] FIG. 6B shows a bar graph of the serum levels of alanine transaminase (ALT) in diclofenac (DCF) (150 mg/kg, i.p.) and ZYSH21 (157 mg/kg, i.p.) treated rats after 24 h of administration.

[0025] FIG. 7 shows the serum uric acid levels in both normal and collagen-induced arthritis (CIA) rats across three distinct treatment groups: 1) the CIA group, which did not receive any drug treatment; 2) the group treated with 10 mg/kg diclofenac (DCF), referred to as the DCF(H) group; and 3) the group treated with 10.5 mg/kg ZYSH21 by gavage, referred to as the ZYSH21(H) group, n=8, *P<0.05, **P<0.01, ***P<0.001.

[0026] FIG. 8 shows the blood concentration-time curve of the interconversion of ZYSH31 to naproxen (NPX) after ZYSH31 was administered by oral gavage (10 mg/kg).

[0027] FIG. 9 shows the change in paw swelling rate in both normal and collagen-induced arthritis (CIA) rats across three distinct treatment groups: 1) the CIA group, which did not receive any drug treatment; 2) the group treated with 10 mg/kg naproxen, referred to as NPX(H) group; and 3) the group treated with 10.5 mg/kg ZYSH31, referred to as the ZYSH31(H) group, n=6, *P<0.05, **P<0.01, ***P<0.001.

[0028] FIG. 10 shows the percentage of gastric ulcers in rats across different treatment groups following gavage administration: NPX(H) at 10 mg/kg, ZYSH31(H) at 10.5 mg/kg, NPX(L) at 5 mg/kg, and ZYSH31(L) at 5.2 mg/kg, n=6, *P<0.05, **P<0.01, ***P<0.001.

[0029] FIG. 11A shows a bar graph of AST levels in serum after 24 h administration of NPX (150 mg/kg, i.p.) and ZYSH31 (159 mg/kg, i.p.), n=6.

[0030] FIG. 11B shows a bar graph of ALT levels in serum after 24 h administration of NPX (150 mg/kg, i.p.) and ZYSH31 (159 mg/kg, i.p.), n=6.

[0031] FIG. 12 shows the serum albumin levels in both normal and collagen-induced arthritis (CIA) rats across three distinct treatment groups: 1) the CIA group, which did not receive any drug treatment; 2) the group treated with 10 mg/kg naproxen (NPX), referred to as the NPX(H) group; and 3) the group treated with 10.5 mg/kg ZYSH31 by gavage, referred to as the ZYSH31(H) group, n=6, *P<0.05, **P<0.01, ***P<0.001.

DETAILED DESCRIPTION

[0032] Before the present disclosure is described in detail, it is to be understood that the terminology used herein is for purposes of describing particular examples and embodiments only and is not intended to be limiting.

[0033] Described herein are novel hydrogen sulfide compounds developed to provide the slow and controlled release of hydrogen sulfide under biologically applicable conditions. The present disclosure demonstrates that compounds with a thiocarboxylic acid structure can be enzymatically hydrolyzed under enzyme-catalyzed conditions to release hydrogen sulfide. By using a thiocarboxylic acid as a new type of carrier of hydrogen sulfide, the rate of hydrolysis of thiocarboxylic acid can be controlled by, for example, esterase, thus slowly releasing hydrogen sulfide.

[0034] In contrast to some existing hydrolytic donors that can be hydrolyzed to generate hydrogen sulfide in an aqueous environment, the compounds described herein are stable in an aqueous environment in the absence of an enzyme and can only slowly release hydrogen sulfide through enzyme catalysis. Such a design allows for slow and controllable release of hydrogen sulfide in the treatment and avoids uncontrollable risk of rapid release of hydrogen sulfide donor locally in the process of use, which is an important consideration for biopharmaceuticals.

[0035] The hydrogen sulfide compounds described herein showcase the important characteristics of 1) simple synthesis, 2) reduced manufacturing costs, and 3) improved efficiency.

[0036] For simple synthesis, different functions of hydrogen sulfide compounds can be realized by changing the structure and chemical properties of the parent compound having a carboxylic acid moiety. For compounds of the present disclosure, there is no need to change the core structure of a parent compound when converting a carboxylic acid to a thiocarboxylic acid, thereby simplifying synthesis and immediate application of such compounds.

[0037] Importantly, as there is no need to develop new compounds having new core structures where the function of a new compounds needs to be tested, time and cost of synthesis of the new compounds and its application is greatly reduced.

[0038] Finally, in the hydrogen sulfide compounds described herein, the thiocarboxylic acid moiety can be hydrolyzed by an enzyme, releasing hydrogen sulfide. In certain embodiments, the enzyme may include any enzyme capable of breaking down the thiocarboxylic acid moiety into a carboxylic acid structure and releasing hydrogen sulfide. In a non-limiting example, the enzyme is porcine liver esterase (PLE). Not intending to be bound by theory, the anti-inflammatory, cardioprotective and gastrointestinal protective properties of hydrogen sulfide can serve to improve the toxic side-effects of the existing drugs, while at the same time exerting the pharmacological functions of hydrogen sulfide and realizing its clinical application. Therefore, the hydrogen sulfide compounds described herein exhibit improved therapeutic effect with reduced toxic side effects. As a non-limiting example, in the pharmaceutical treatment of cerebral infarction and inflammation, the therapeutic efficacy of the parent compound may be enhanced by using the thiocarboxylic acid compound synthesized as outlined in the present disclosure, while the adverse effects of

the compound on human health is mitigated. Further discussion is outlined in the Description below and the Examples.

DEFINITIONS

[0039] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0040] It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present disclosure will be limited only by the appended claims.

[0041] As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present disclosure.

[0042] Embodiments of the present disclosure employ, unless otherwise indicated, techniques of synthetic organic chemistry, biochemistry, biology, molecular biology, pharmacology, and the like, which are within the skill of the art. Such techniques are explained fully in the literature.

[0043] It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an, and “the” include plural referents unless the context clearly dictates otherwise. In this specification and in the claims that follow, reference will be made to a number of terms that shall be defined to have the following meanings unless a contrary intention is apparent.

[0044] As used herein a “hydrogen sulfide compound” may refer to a compound that can release hydrogen sulfide when enzymatically hydrolyzed under enzyme-catalyzed conditions or a compound having a carboxylic acid structure that is subsequently thiolated. In some embodiments, a “hydrogen sulfide compound” may be the same as a “thiolated compound” or a “thiocarboxylic acid compound” comprising a thiocarboxylic acid structure.

[0045] As used herein, “alkyl” means a noncyclic straight chain or branched, unsaturated or saturated hydrocarbon such as those containing from 1 to 30 carbon atoms, typically 1 to 20 carbon atoms. As used herein, alkyl may refer to an alkyl with 1 to 20 carbons (C₁₋₂₀alkyl), or with 1 to 19 carbons, (C₁₋₁₉alkyl), or with 1 to 18 carbons, (C₁₋₁₈alkyl), or with 1 to 17 carbons, (C₁₋₁₇alkyl), or with 1 to 16 carbons, (C₁₋₁₆alkyl), or with 1 to 15 carbons, (C₁₋₁₅alkyl), or with 1 to 14 carbons, (C₁₋₁₄alkyl), or with 1 to 13 carbons, (C₁₋₁₃alkyl), or with 1 to 12 carbons, (C₁₋₁₂alkyl), or with 1 to 11 carbons, (C₁₋₁₁alkyl), or with 1 to 10 carbons, (C₁₋₁₀alkyl), or with 1 to 9 carbons, (C₁₋₉alkyl), or with 1 to 8 carbons, (C₁₋₈alkyl), or with 1 to 7 carbons, (C₁₋₇alkyl), or with 1 to 6 carbons, (C₁₋₆alkyl), or with 1 to 5 carbons, (C₁₋₅alkyl), or with 1 to 4 carbons, (C₁₋₄alkyl), or with 1 to 3 carbons, (C₁₋₃alkyl), or with 1 to 2 carbons, (C₁₋₂alkyl). Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-septyl, n-octyl, n-nonyl, and the like; while saturated branched alkyls include isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl, and the like. Unsaturated alkyls contain at least one double or triple bond between adjacent carbon atoms (referred to as an “alkenyl” or “alkynyl”, respectively). Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like; while representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, 3-methyl-1-butyne, and the like.

[0046] As used herein, “haloalkyl” means a halogen-substituted alkyl group which is substituted with one or more of the same or different halogen atoms, e.g., -CH₂Cl, -CF₃, -CH₂CF₃, -CH₂CCl₃, and the like.

[0047] As used herein, “cycloalkyl” refers to a monocyclic or densely packed ring of all carbon, wherein one or more of the rings do not have a fully connected π -electronic systems, and wherein the ring or rings do not have fully connected π -electronic systems. As used herein, a “packed ring” refers to a structure where each ring in the system shares an adjacent pair of carbon atoms with the other rings in the system. In an embodiment, a cycloalkyl may refer to, but is not limited to, cyclopropane, cyclopentoxo, cyclohexyloxy, and the like. In other embodiments, a cycloalkyl may refer to, but is not limited to, cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, adamantane, cyclohexadiene, cycloheptane, and cycloheptatriene.

[0048] Non-aromatic mono or polycyclic alkyls are referred to herein as “carbocycles” or “carbocyclyl” groups. Representative saturated carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like; while unsaturated carbocycles include cyclopentenyl and cyclohexenyl, and the like.

[0049] “Heterocarbocycles” or heterocarbocyclyl” groups are carbocycles which contain from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur which may be saturated or unsaturated (but not aromatic), monocyclic or polycyclic, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized. Heterocarbocycles include morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranlyl, tetrahydropyranlyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranlyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranlyl, and the like.

[0050] As used herein, “aryl” means an aromatic carbocyclic monocyclic or polycyclic ring of 1 to 12 carbon atoms with a fully conjugated π -electron system. Non-limiting examples of aryl groups are phenyl, naphthyl and anthracenyl. Polycyclic ring systems may, but are not required to, contain one or more non-aromatic rings, as long as one of the rings is aromatic. In an embodiment, the aryl group may be substituted or unsubstituted. When substituted, the substituent is preferably one or more, more preferably one, two or three, and thus more preferably one or two.

[0051] As used herein, a “heteroaryl” refers to a stabilized monocyclic ring of up to 3-20 atoms in the ring or a bicyclic carbocyclic ring of up to 3-20 atoms in each ring. In certain embodiments, the stabilized monocyclic ring has 3-19 atoms in the ring, 3-18 carbons in the ring, 3-17 carbons in the ring, 3-16 carbons in the ring, 3-15 carbons in the ring, 3-14 carbons in the ring, 3-13 carbons in the ring, 3-12 carbons in the ring, 3-11 carbons in the ring, 3-10 carbons in the ring, 3-9 carbons in the ring, 3-8 carbons in the ring, 3-7 carbons in the ring, 3-6 carbons in the ring, 3-5 carbons in the ring, or 3-4 carbons in the ring. In certain embodiments, at least one of the rings is aromatic and contains 1 to 6 heteroatoms selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and polycyclic ring systems. Polycyclic ring systems may, but are not required to, contain one or more non-aromatic rings, as long as one of the rings is aromatic. Non-limiting examples of unsubstituted heteroaromatic bases are pyrrolyl, furanyl, thienyl, imidazolyl,

oxazolyl, thiazolyl, pyrazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, purinyl, acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, indolinyl, benzo-triazolyl, benzothiophenyl, benzofuranyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, tetrazolyl, triazinyl, and carbazolyl radicals, and the like. The heteroaryl group may be substituted or unsubstituted. When substituted, the substituent is preferably one or more, more preferably one, two or three, and thus more preferably one or two. Other representative heteroaryls are furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinolinyl, isoquinolinyl, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl. It is contemplated that the use of the term “heteroaryl” may include N-alkylated derivatives such as a 1-methylimidazol-5-yl substituent.

[0052] As used herein, “heterocycle” or “heterocyclyl” refers to mono- and polycyclic ring systems having 1 to 6 heteroatoms selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom. The mono- and polycyclic ring systems may be aromatic, non-aromatic or mixtures of aromatic and non-aromatic rings. Heterocycle includes heterocarbocycles, heteroaryls, and the like.

[0053] As used herein, “spirocycle” refers to a system where there are two rings in a molecule and these two rings share a carbon atom.

[0054] As used herein, a “bridge ring” refers to a polycyclic hydrocarbon that shares more than two carbon atoms (bridge carbons), and is classified as a bicyclic hydrocarbon, a tricyclic hydrocarbon, a tetracyclic hydrocarbon, etc., according to the number of constituent rings.

[0055] As used herein, the terms “halogen” or “halo” refer to fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

[0056] “Alkylthio” refers to an alkyl group as defined above with the indicated number of carbon atoms attached through a sulfur bridge. An example of an alkylthio is methylthio, (i.e., -S-CH₃).

[0057] “Alkoxy” refers to an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxo,

and s-pentoxy. Preferred alkoxy groups are methoxy, ethoxy, n-propoxy, i- propoxy, n-butoxy, s-butoxy, t-butoxy.

[0058] “Alkylsulfonyl” refers to an alkyl as defined above attached through a sulfonyl bridge (i.e., $-S(=O)_2\text{alkyl}$) such as mesyl and the like, and “Arylsulfonyl” refers to an aryl attached through a sulfonyl bridge (i.e., $-S(=O)_2\text{aryl}$).

[0059] “Alkylsulfonamide” refers to an alkyl as defined above attached through a sulfamoyl bridge (i.e., $-S(=O)_2\text{NHalkyl}$), and an “Arylsulfonamide” refers to an alkyl attached through a sulfamoyl bridge (i.e., (i.e., $-S(=O)_2\text{NHaryl}$).

[0060] “Alkylsulfinyl” refers to an alkyl as defined attached through a sulfinyl bridge (i.e. $-S(=O)\text{alkyl}$).

[0061] The term “substituted” refers to a molecule wherein at least one hydrogen atom is replaced with a substituent. When substituted, one or more of the groups are “substituents.” The molecule may be multiply substituted. In the case of an oxo substituent (“=O”), two hydrogen atoms are replaced. Example substituents within this context may include halogen, hydroxy, alkyl, alkoxy, nitro, cyano, oxo, carbocyclyl, carbocycloalkyl, heterocarbocyclyl, heterocarbocycloalkyl, alkyl, aryl, arylalkyl, heteroaryl, nitrogen dioxide, or heteroarylalkyl.

[0062] The term “optionally substituted,” as used herein, means that substitution is optional and therefore it is possible for the designated atom to be unsubstituted.

[0063] As used herein, “salts” refer to derivatives of the disclosed compounds where the parent compound is modified making acid or base salts thereof. Examples of salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkylamines, or dialkylamines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. In preferred embodiment, the salts are conventional nontoxic pharmaceutically acceptable salts including the quaternary ammonium salts of the parent compound formed, and non-toxic inorganic or organic acids. Preferred salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2- acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

[0064] “Subject” refers any animal, preferably a human patient, livestock, or domestic pet.

[0065] As used herein, “enzyme” refers to any enzyme capable of breaking down the thiocarboxylic acid moiety into a carboxylic acid and releasing hydrogen sulfide. In a non-limiting example, the enzyme is porcine liver esterase (PLE).

[0066] As used herein, the terms “prevent” and “preventing” include the prevention of the recurrence, spread or onset. It is not intended that the present disclosure be limited to complete prevention. In some embodiments, the onset is delayed, or the severity of the disease is reduced.

[0067] As used herein, the terms “treat” and “treating” are not limited to the case where the subject (e.g. patient) is cured and the disease is eradicated. Rather, embodiments of the present disclosure also contemplate treatment that merely reduces symptoms, and/or delays disease progression.

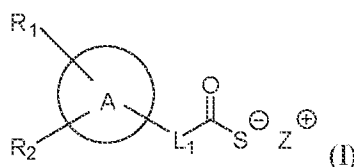
[0068] As used herein, the term “combination with” when used to describe administration with an additional treatment means that the agent may be administered prior to, together with, or after the additional treatment, or a combination thereof.

[0069] As used herein, the term “derivative” refers to a structurally similar compound that retains sufficient functional attributes of the identified analogue. The derivative may be structurally similar because it is lacking one or more atoms, substituted, a salt, in different hydration/oxidation states, or because one or more atoms within the molecule are switched, such as, but not limited to, replacing an oxygen atom with a sulphur atom or replacing an amino group with a hydroxyl group. The derivative may be a prodrug. Derivatives may be prepared by any variety of synthetic methods or appropriate adaptations presented in synthetic or organic chemistry textbooks, such as those provided in March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Wiley, 6th Edition (2007) Michael B. Smith or Domino Reactions in Organic Synthesis, Wiley (2006) Lutz F. Tietze hereby incorporated by reference.

[0070] An “excipient” refers to an inert substance added to a pharmaceutical composition facilitating administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

COMPOUNDS

[0071] In certain embodiments, the disclosure relates to compounds of Formula I:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Z^+ is Na^+ , K^+ , or H^+ ;

A is substituted or unsubstituted C_6 - C_{20} aryl or substituted or unsubstituted C_3 - C_{20} heteroaryl;

L_1 is a bond, $-(CH_2)_n-$, C_2 - C_6 branched alkyl, $-O-(CH_2)_n-C(CH_3)_2-$, $-R_5C(=O)NHR_6-$, $-O-(CH_2)_n-$, or $-O-(CH_2)_n-O-$;

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

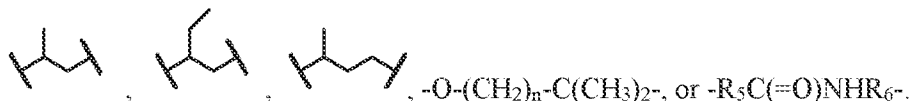
each R_1 and R_2 are independently hydrogen, halogen, $-CN$, $-NO_2$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-SO_2NR_3R_4-$, C_6 - C_{10} aryl, or C_3 - C_{10} heteroaryl, wherein each R_3 , R_4 , R_5 , and R_6 are independently hydrogen or C_1 - C_6 alkyl.

[0072] In certain embodiments, A is substituted or unsubstituted C_6 - C_{10} aryl or substituted or unsubstituted C_3 - C_{10} heteroaryl. In certain embodiments, A is substituted or unsubstituted C_6 - C_9 aryl, substituted or unsubstituted C_6 - C_8 aryl, or substituted or unsubstituted C_6 - C_7 aryl. In certain embodiments A is substituted or unsubstituted C_3 - C_9 heteroaryl, substituted or unsubstituted C_3 - C_8 heteroaryl, substituted or unsubstituted C_3 - C_7 heteroaryl, substituted or unsubstituted C_3 - C_6 heteroaryl, substituted or unsubstituted C_3 - C_5 heteroaryl, or substituted or unsubstituted C_3 - C_4 heteroaryl.

[0073] In certain embodiments, A is phenyl, naphthyl, anthracenyl, oxazolyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, thiazolyl, pyrazolyl, pyrimidyl, quinolyl, isoquinolyl, purinyl, acridyl, carbazolyl, cinnolyl, quinazolinyl, indolyl, benzyltriazolyl, benzothiophenyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, tetrazolyl, trizinyl, or carbazolyl.

[0074] In certain embodiments, L_1 is a bond, $-(CH_2)_n-$, C_2 - C_6 branched alkyl, $-O-(CH_2)_n-C(CH_3)_2-$, or $-R_5C(=O)NHR_6-$. In certain embodiments, L_1 is C_2 - C_5 branched alkyl, C_2 - C_4 branched alkyl, or C_2 - C_3 branched alkyl.

[0075] In certain embodiments, L_1 is a bond, $-(CH_2)_n-$, $-CH(CH_3)-$,



[0076] In certain embodiments, n is 0, 1, 2, 3, or 4. In certain embodiments, n is 0, 1, 2, or 3. In certain embodiments, n is 0, 1, or 2. In certain embodiments, n is 0 or 1.

[0077] In certain embodiments, R₁ is hydrogen, halogen, -CN, -NO₂, C₁-C₆ alkyl, C₆-C₁₀ aryl, or C₃-C₁₀ heteroaryl. In certain embodiments R₁ is C₁₋₅ alkyl, C₁₋₄ alkyl, C₁₋₃ alkyl or C₁₋₂ alkyl. In certain embodiments, R₁ is C₆-C₉ aryl, C₆-C₈ aryl, or C₆-C₇ aryl. In certain embodiments R₁ is C₃-C₉ heteroaryl, C₃-C₈ heteroaryl, C₃-C₇ heteroaryl, C₃-C₆ heteroaryl, C₃-C₅ heteroaryl, or C₃-C₄ heteroaryl.

[0078] In certain embodiments, R₁ is hydrogen, halogen, -CN, -NO₂, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, phenyl, naphthyl, anthracenyl, oxazolyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, or thiazolyl.

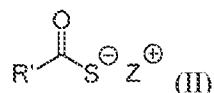
[0079] In certain embodiments, R₂ is hydrogen, halogen, -CN, -NO₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₂NR₃R₄-, C₆-C₁₀ aryl, or C₃-C₁₀ heteroaryl. In certain embodiments, R₂ is C₁₋₅ alkyl, C₁₋₄ alkyl, C₁₋₃ alkyl or C₁₋₂ alkyl. In certain embodiments, R₂ is C₁₋₅ alkoxy, C₁₋₄ alkoxy, C₁₋₃ alkoxy or C₁₋₂ alkoxy. In certain embodiments, R₂ is C₁₋₅ haloalkyl, C₁₋₄ haloalkyl, C₁₋₃ haloalkyl or C₁₋₂ haloalkyl. In certain embodiments, R₂ is C₁₋₅ haloalkoxy, C₁₋₄ haloalkoxy, C₁₋₃ haloalkoxy or C₁₋₂ haloalkoxy. In certain embodiments, R₂ is C₆-C₉ aryl, C₆-C₈ aryl, or C₆-C₇ aryl. In certain embodiments, R₂ is C₃-C₉ heteroaryl, C₃-C₈ heteroaryl, C₃-C₇ heteroaryl, C₃-C₆ heteroaryl, C₃-C₅ heteroaryl, or C₃-C₄ heteroaryl.

[0080] In certain embodiments, R₂ is hydrogen, halogen, -CN, -NO₂, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, ethoxy, ethoxy, propoxy, propoxyl, butoxy, cyclopropoxy, cyclobutoxy, -CH₂Cl, -CF₃, -CH₂CF₃, -CH₂CCl₃, -SO₂NR₃R₄-, phenyl, naphthyl, anthracenyl, oxazolyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, or thiazolyl.

[0081] In certain embodiments, each R₃, R₄, R₅, R₆ are each independently C₁-C₆ alkyl. In certain embodiments, each R₃, R₄, R₅, R₆ are each independently C₁₋₅ alkyl, C₁₋₄ alkyl, C₁₋₃ alkyl or C₁₋₂ alkyl.

[0082] In certain embodiments, each R₃, R₄, R₅, R₆ are each independently methyl, ethyl, propyl, isopropyl, butyl, or tert-butyl.

[0083] In certain embodiments, the disclosure relates to compounds of Formula II:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Z^+ is Na^+ , K^+ , or H^+ ; and

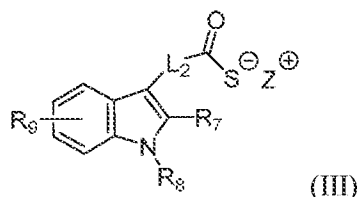
R' is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted bridged cycloalkyl, or substituted or unsubstituted spirocycloalkyl.

[0084] In certain embodiments, each R' has at least one substituent and wherein the at least one substituent is selected from the group consisting of halogen, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, and $\text{C}_1\text{-C}_6$ alkyl. In certain embodiments, each R' has at least one substituent and wherein the at least one substituent is selected from the group consisting of $\text{C}_1\text{-C}_5$ alkyl, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_3$ alkyl, and $\text{C}_1\text{-C}_2$ alkyl.

[0085] In certain embodiments, R' is substituted or unsubstituted $\text{C}_2\text{-C}_6$ branched alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{20}$ straight chain alkyl, substituted or unsubstituted $\text{C}_3\text{-C}_6$ cycloalkyl, or substituted or unsubstituted $\text{C}_8\text{-C}_{16}$ bridged cycloalkyl. In certain embodiments, R' is substituted or unsubstituted $\text{C}_2\text{-C}_5$ branched alkyl, substituted or unsubstituted $\text{C}_2\text{-C}_4$ branched alkyl, or substituted or unsubstituted $\text{C}_2\text{-C}_3$ branched alkyl. In certain embodiments, R' is substituted or unsubstituted $\text{C}_1\text{-C}_{19}$ straight chain alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{18}$ straight chain alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{17}$ straight chain alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{16}$ straight chain alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{15}$ straight chain alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{14}$ straight chain alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{13}$ straight chain alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{12}$ straight chain alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{11}$ straight chain alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ straight chain alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_9$ straight chain alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_8$ straight chain alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_7$ straight chain alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_6$ straight chain alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_5$ straight chain alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_4$ straight chain alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_3$ straight chain alkyl, or substituted or unsubstituted $\text{C}_1\text{-C}_2$ straight chain alkyl. In certain embodiments, R' is substituted or unsubstituted $\text{C}_3\text{-C}_6$ cycloalkyl, substituted or unsubstituted $\text{C}_3\text{-C}_5$ cycloalkyl, and substituted or unsubstituted $\text{C}_3\text{-C}_4$ cycloalkyl. In certain embodiments, R' is substituted or unsubstituted $\text{C}_8\text{-C}_{15}$ bridged cycloalkyl, substituted or unsubstituted $\text{C}_8\text{-C}_{14}$ bridged cycloalkyl, substituted or unsubstituted $\text{C}_8\text{-C}_{13}$ bridged cycloalkyl, substituted or unsubstituted $\text{C}_8\text{-C}_{12}$ bridged

cycloalkyl, substituted or unsubstituted C₈-C₁₁ bridged cycloalkyl, substituted or unsubstituted C₈-C₁₀ bridged cycloalkyl, or substituted or unsubstituted C₈-C₉ bridged cycloalkyl.

[0086] In certain embodiments, the disclosure relates to compounds of Formula III:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Z⁺ is Na⁺, K⁺, or H⁺;

L₂ is a bond, -(CH₂)_n-, or C₂-C₆ branched alkyl;

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

R₇ is hydrogen or C₁-C₆ alkyl;

R₈ is hydrogen, -C(=O)-R₁₀, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, or C₁-C₆ haloalkoxy, wherein R₁₀ is substituted or unsubstituted C₆-C₁₀ aryl or substituted or unsubstituted C₃-C₁₀ heteroaryl, wherein when substituted by a substituent, the substituent is selected from the group consisting of halogen, -OH, -CN, -NO₂, C₁-C₄ alkyl, C₁-C₄ alkoxy, and C₁-C₄ haloalkyl; and

R₉ is hydrogen, halogen, -CN, -NO₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, or C₁-C₆ haloalkoxy.

[0087] In certain embodiments, L₂ is -(CH₂)_n-; and n is 0, 1, 2 or 3. In certain embodiments, L₂ is -(CH₂)_n-; and n is 0, 1, or 2. In certain embodiments, L₂ is -(CH₂)_n-; and n is 0 or 1.

[0088] In certain embodiments, R₇ is hydrogen or C₁-C₄ alkyl. In certain embodiments, R₇ is hydrogen or C₁-C₃ alkyl or C₁-C₂ alkyl.

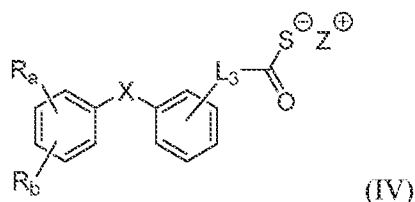
[0089] In certain embodiments, R₇ is methyl, ethyl, propyl, isopropyl, butyl, or tert-butyl.

[0090] In certain embodiments, R₈ is hydrogen or -C(=O)-R₁₀, wherein R₁₀ is substituted or unsubstituted phenyl, substituted or unsubstituted naphthalenyl, substituted or unsubstituted anthracenyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted furyl, substituted or unsubstituted thiophenyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted

pyrazolyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted quinolyl, and wherein when substituted by a substituent, the substituent is selected from the group consisting of halogen, -OH, -CN, -NO₂, methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[0091] In certain embodiments, R₉ is hydrogen, halogen, -CN, -NO₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, or C₁-C₆ haloalkyl. In certain embodiments, R₉ is C₁-C₅ alkyl, C₁-C₅ alkoxy, or C₁-C₅ haloalkyl. In certain embodiments, R₉ is C₁-C₄ alkyl, C₁-C₄ alkoxy, or C₁-C₄ haloalkyl. In certain embodiments, R₉ is C₁-C₃ alkyl, C₁-C₃ alkoxy, or C₁-C₃ haloalkyl. In certain embodiments, R₉ is C₁-C₂ alkyl, C₁-C₂ alkoxy, or C₁-C₂ haloalkyl.

[0092] In certain embodiments, the disclosure relates to compounds of Formula IV:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

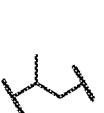
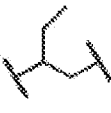
Z⁺ is Na⁺, K⁺, or H⁺;

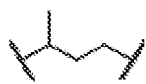
L₃ is a bond, -(CH₂)_n-, or C₂-C₆ branched alkyl;

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

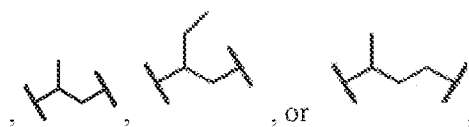
X is -NH- or -C(=O)-;

each R_a and R_b are independently hydrogen, halogen, -CN, -NO₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, or C₁-C₆ haloalkoxy.

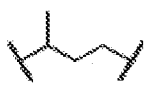
[0093] In certain embodiments, L₃ is a bond, -(CH₂)_n-, -CH(CH₃)-, , , or



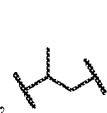
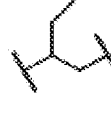
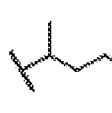
; and n is 0, 1, 2 or 3. In certain embodiments, L₃ is a bond, -(CH₂)_n-, -CH(CH₃)-



, or

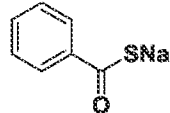
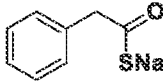
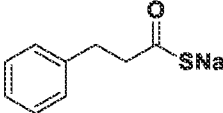
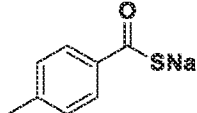
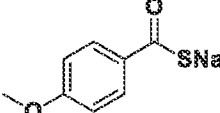
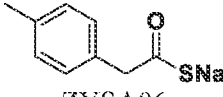
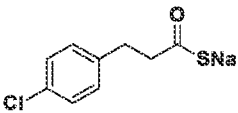
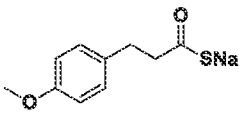
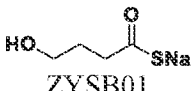
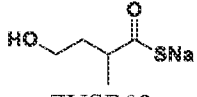
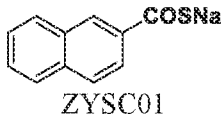
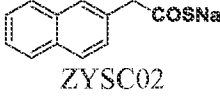
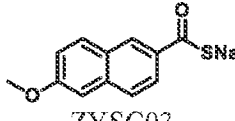


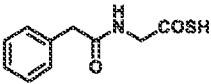
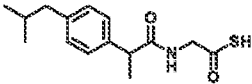
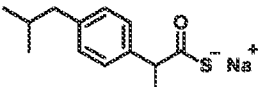
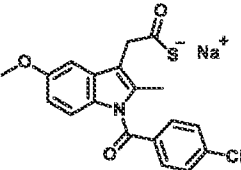
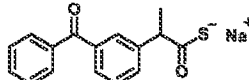
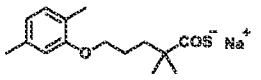
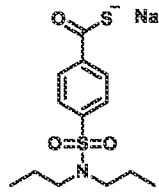
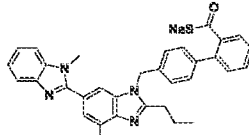
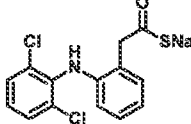
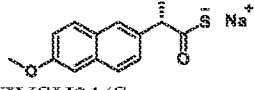
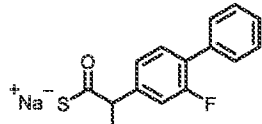
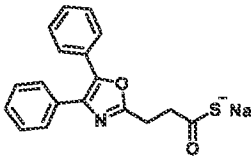
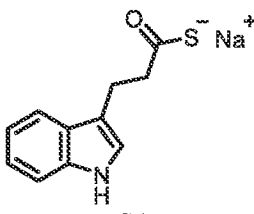
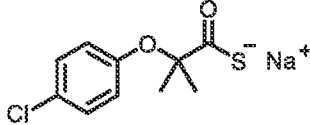
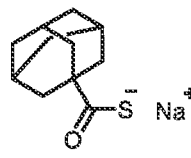
; and n is 0, 1, or 2. In certain embodiments, L₃ is a

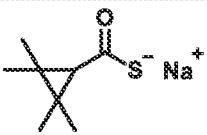
bond, -(CH₂)_n-, -CH(CH₃)-, , , or ; and n is 0 or 1.

[0094] In certain embodiments, each R_a and R_b are independently selected from hydrogen, halogen, -CN, -NO₂, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl, or C₁-C₄ haloalkoxy. In certain embodiments, each R_a and R_b are independently selected from C₁-C₃ alkyl or C₁-C₂ alkyl. In certain embodiments, each R_a and R_b are independently selected from C₁-C₃ alkoxy or C₁-C₂ alkoxy. In certain embodiments, each R_a and R_b are independently selected from C₁-C₃ haloalkyl or C₁-C₂ haloalkyl. In certain embodiments, each R_a and R_b are independently selected from C₁-C₃ haloalkoxy or C₁-C₂ haloalkoxy.

[0095] In certain embodiments, the disclosure relates to the following compounds:

 ZYSA01	 ZYSA02	 ZYSA03
 ZYSA04	 ZYSA05	 ZYSA06
 ZYSA07	 ZYSA08	 ZYSB01
 ZYSB02	 ZYSB03	
 ZYSC01	 ZYSC02	 ZYSC03

 ZYSD01	 ZYSD02	
 ZYSH01(S- buprofen)	 ZYSH02(S- indomethacin)	 ZYSH03(S- Ketoprofen)
 ZYSH04(S- Gemfibrozil)	 ZYSH05(S- Probenecid)	 ZYSH06(S- telmisartan)
 ZYSH21(S- diclofenac)	 ZYSH31(S- naproxen)	 ZYSH07 (Flurbiprofen)
 ZYSH08 (Oxaprozin)	 ZYSA12 (3-indolepropionic acid)	 ZYSA13
 ZYSB04		 ZYSB08

 ZYSB07	 ZYSB06
 ZYSB05	 ZYSB09

and a pharmaceutically acceptable salt or prodrug thereof.

[0096] In certain embodiments, the disclosure relates to a compound comprising a thiocarboxylic acid moiety, wherein the compound releases hydrogen sulfide under enzyme-catalyzed conditions.

[0097] In certain embodiments, the compound is a thiolated sartan compound. In an embodiment, the thiolated sartan compound is thiolated valsartan, thiolated eplosartan, or thiolated timosartan.

FORMULATIONS

[0098] Described herein are thiocarboxylic acid compounds for use in the preparation of hydrogen sulfide compounds that can be used as prodrugs. Ultimately, compounds having a carboxylic acid structure can be thiolated to form a compound having a thiocarboxylic acid structure which can, in turn, be enzymatically hydrolyzed under enzyme-catalyzed conditions to release hydrogen sulfide.

[0099] Not intending to be bound by theory, the mechanism of hydrogen sulfide release from the thiocarboxylic acid structure in the precursor described in the present disclosure is as follows:



[0100] In an embodiment, prior to thiolation, the precursor compounds may be drug. In certain embodiments, the drug may be used as a drug for treating a cardiovascular or cerebrovascular diseases, an anti-inflammatory drug, an antipyretic drug, a rheumatic or rheumatoid arthritis drug, an anti-gout drug, a drug for lowering blood pressure, a drug for lowering blood lipids, or a drug for reducing the hepatic toxicity of another drug in response to GSH depletion or mitochondrial damage, and the like. In another embodiment, the carboxylic acid precursor compounds are: clofibrate lipid-regulating drugs, sartans,

sulfonamides, indoles, non-steroidal anti-inflammatory drugs, and the like. In another preferred embodiment, these carboxylic acid precursor compounds include, but are not limited to, diclofenac, ketoprofen, indolepropionic acid, indomethacin, timosartan, gemfibrozil, naproxen, oxaprozin, ibuprofen, flurbiprofen, probenecid, and the like. Other compounds having a carboxylic acid structure can also be thiolated to form the hydrogen sulfide compound of the present disclosure for the slow and controlled release of hydrogen sulfide under enzyme catalyzed conditions.

[0101] In an embodiment, the hydrogen sulfide compounds are made from sartans having a carboxylic acid structure that is thiolated to form a thiocarboxylic acid structure, capable of releasing hydrogen sulfide under enzyme-catalyzed conditions. As used herein, “sartans” refers to any sartan having a carboxylic acid structure and for clinical use. In an embodiment, preferred sartans are valsartan, epsomartan, or telmisartan. In an embodiment, when multiple carboxylic acid structures are contained in a single compound, one or more of the carboxylic acids can be thiolated to form a hydrogen sulfide compound.

[0102] In certain embodiments, the hydrogen sulfide compounds described in the present disclosure, the thiolation of carboxylic acids of existing drugs can be carried out by means of chemical synthesis commonly used in the art.

[0103] The compounds of the present disclosure may be used alone as a single therapeutic agent or in combination with other active agents as described below.

[0104] Pharmaceutical compositions disclosed herein may be in the form of pharmaceutically acceptable salts, as generally described below. Some preferred, but non-limiting examples of suitable pharmaceutically acceptable organic and/or inorganic acids are hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, acetic acid and citric acid, as well as other pharmaceutically acceptable acids known per se (for which reference is made to the references referred to below).

[0105] When the compounds of the disclosure contain an acidic group as well as a basic group, the compounds of the disclosure may also form internal salts, and such compounds are within the scope of the disclosure. When a compound contains a hydrogen-donating heteroatom (e.g. NH), salts are contemplated to covers isomers formed by transfer of said hydrogen atom to a basic group or atom within the molecule.

[0106] Pharmaceutically acceptable salts of the compounds include the acid addition and base salts thereof. Suitable acid addition salts are formed from acids that form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/hchloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts. Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminum, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts. Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts. For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002), incorporated herein by reference.

[0107] As previously described, the compounds described herein may be administered in the form of prodrugs. A prodrug can include a covalently bonded carrier that releases the active parent drug when administered to a mammalian subject. Prodrugs can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Prodrugs include, for example, compounds wherein a carboxylic acid of the parent drug is thiolated and, when administered to a mammalian subject, is enzymatically hydrolyzed to release hydrogen sulfide. Methods of structuring a compound as prodrugs can be found in the book of Testa and Mayer, Hydrolysis in Drug and Prodrug Metabolism, Wiley (2006).

[0108] The hydrogen sulfide prodrug described herein can be administered to a subject. The hydrogen sulfide prodrug refers to compounds of the present disclosure, or a pharmaceutical composition including compounds of the present disclosure, in an environment sufficient for the formation of hydrogen sulfide.

[0109] Pharmaceutical compositions for use in the present disclosure typically include an effective amount of a compound and a suitable pharmaceutical acceptable carrier. The preparations may be prepared in a manner known *per se*, which usually involves mixing the

at least one compound according to the disclosure with the one or more pharmaceutically acceptable carriers, and, if desired, in combination with other pharmaceutical active compounds, when necessary under aseptic conditions. Reference is made to standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences: *Remington, J. P. (2021). Remington: the science and practice of pharmacy (A. Adejare, Ed.; 23rd edition). Academic Press is an imprint of Elsevier.*

[0110] Generally, for pharmaceutical use, the compounds may be formulated as a pharmaceutical preparation comprising at least one compound and at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant, and optionally one or more further pharmaceutically active compounds.

[0111] The pharmaceutical preparations of the disclosure are preferably in a unit dosage form, and may be suitably packaged, for example in a box, blister, vial, bottle, sachet, ampoule or in any other suitable single-dose or multi-dose holder or container (which may be properly labeled); optionally with one or more leaflets containing product information and/or instructions for use. Generally, such unit dosages will contain between 10 and 500 mg and preferably between 50 and 150 mg, of the at least one compound of the disclosure, e.g. about 25, 50, 75, 100, 200 or 300 mg per unit dosage.

[0112] The compounds can be administered by a variety of routes including the oral, ocular, rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes, depending mainly on the specific preparation used. The compound will generally be administered in an "effective amount", by which is meant any amount of a compound that, upon suitable administration, is sufficient to achieve the desired therapeutic or prophylactic effect in the subject to which it is administered. Usually, depending on the condition to be prevented or treated and the route of administration, such an effective amount will usually be between 0.01 to 1000 mg per kilogram body weight of the patient per day, more often between 0.1 and 500 mg, such as between 1 and 250 mg, for example about 5, 10, 20, 50, 100, 150, 200 or 250 mg, per kilogram body weight of the patient per day, which may be administered as a single daily dose, divided over one or more daily doses. The amount(s) to be administered, the route of administration and the further treatment regimen may be determined by the treating clinician, depending on factors such as the age, gender and general condition of the patient and the nature and severity of the disease/symptoms to be treated.

Reference is again made to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

[0113] Depending upon the manner of introduction, the compounds described herein may be formulated in a variety of ways. Formulations containing one or more inhibitors can be prepared in various pharmaceutical forms, such as granules, tablets, capsules, suppositories, powders, controlled release formulations, suspensions, emulsions, creams, gels, ointments, salves, lotions, or aerosols and the like. Preferably, these formulations are employed in solid dosage forms suitable for simple, and preferably oral, administration of precise dosages. Solid dosage forms for oral administration include, but are not limited to, tablets, soft or hard gelatin or non-gelatin capsules, and caplets. However, liquid dosage forms, such as solutions, syrups, suspension, shakes, and the like can also be utilized. In another embodiment, the formulation is administered topically. Suitable topical formulations include, but are not limited to, lotions, ointments, creams, and gels. In a preferred embodiment, the topical formulation is a gel. In another embodiment, the formulation is administered intranasally.

[0114] Formulations containing one or more of the compounds described herein may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, diluents, binders, lubricants, disintegrators, fillers, pH modifying agents, preservatives, antioxidants, solubility enhancers, and coating compositions.

[0115] A carrier may also include all components of the coating composition which may include plasticizers, pigments, colorants, stabilizing agents, surfactants, and glidants. Delayed release, extended release, and/or pulsatile release dosage formulations may be prepared as described in standard references such as "Pharmaceutical dosage form tablets", eds. Liberman et. al. (New York, Marcel Dekker, Inc., 1989), "Remington – The science and practice of pharmacy", 20th ed., Lippincott Williams & Wilkins, Baltimore, MD, 2000, and "Pharmaceutical dosage forms and drug delivery systems", 6th Edition, Ansel et al., (Media, PA: Williams and Wilkins, 1995). These references provide information on carriers, materials, equipment and process for preparing tablets and capsules and delayed release dosage forms of tablets, capsules, and granules.

[0116] Examples of suitable coating materials include, but are not limited to, cellulose polymers such as cellulose acetate phthalate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate; polyvinyl acetate phthalate, acrylic acid polymers and copolymers, and methacrylic resins that are commercially available, zein, shellac, and polysaccharides.

[0117] Optional pharmaceutically acceptable excipients present in the drug-containing tablets, beads, granules or particles include, but are not limited to, diluents, binders, lubricants, disintegrants, colorants, stabilizers, and surfactants. Diluents, also referred to as “fillers,” are typically necessary to increase the bulk of a solid dosage form so that a practical size is provided for compression of tablets or formation of beads and granules. Suitable diluents include, but are not limited to, dicalcium phosphate dihydrate, calcium sulfate, lactose, sucrose, mannitol, sorbitol, cellulose, microcrystalline cellulose, kaolin, sodium chloride, dry starch, hydrolyzed starches, pregelatinized starch, silicone dioxide, titanium oxide, magnesium aluminum silicate and powdered sugar.

[0118] Binders are used to impart cohesive qualities to a solid dosage formulation, and thus ensure that a tablet or bead or granule remains intact after the formation of the dosage forms. Suitable binder materials include, but are not limited to, starch, pregelatinized starch, gelatin, sugars (including sucrose, glucose, dextrose, lactose and sorbitol), polyethylene glycol, waxes, natural and synthetic gums such as acacia, tragacanth, sodium alginate, cellulose, including hydroxypropyl methylcellulose, hydroxypropyl cellulose, ethylcellulose, and magnesium aluminum silicate, and synthetic polymers such as acrylic acid and methacrylic acid copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, aminoalkyl methacrylate copolymers, polyacrylic acid/polymethacrylic acid and polyvinylpyrrolidone.

[0119] Lubricants are used to facilitate tablet manufacture. Examples of suitable lubricants include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, glycerol behenate, polyethylene glycol, talc, and mineral oil.

[0120] Disintegrants are used to facilitate dosage form disintegration or “breakup” after administration, and generally include, but are not limited to, starch, sodium starch glycolate, sodium carboxymethyl starch, sodium carboxymethylcellulose, hydroxypropyl cellulose, pregelatinized starch, clays, cellulose, arginine, gums or cross-linked polymers, such as cross-linked PVP.

[0121] Stabilizers are used to inhibit or retard drug decomposition reactions which include, by way of example, oxidative reactions.

[0122] Surfactants may be anionic, cationic, amphoteric or nonionic surface-active agents. Suitable anionic surfactants include, but are not limited to, those containing carboxylate, sulfonate and sulfate ions. Examples of anionic surfactants include sodium, potassium, ammonium of long chain alkyl sulfonates and alkyl aryl sulfonates such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium bis-(2-ethylthioxy)-sulfosuccinate; and alkyl sulfates such as sodium lauryl sulfate. Cationic surfactants include, but are not limited to, quaternary ammonium compounds such as benzalkonium chloride, benzethonium chloride, cetrimonium bromide, stearyl dimethylbenzyl ammonium chloride, polyoxyethylene and coconut amine. Examples of nonionic surfactants include ethylene glycol monostearate, propylene glycol myristate, glyceryl monostearate, glyceryl stearate, polyglyceryl-4-oleate, sorbitan acylate, sucrose acylate, PEG-150 laurate, PEG-400 monolaurate, polyoxyethylene monolaurate, polysorbates, polyoxyethylene octylphenylether, PEG-1000 cetyl ether, polyoxyethylene tridecyl ether, polypropylene glycol butyl ether, stearyl monoisopropanolamide, and polyoxyethylene hydrogenated tallow amide. Examples of amphoteric surfactants include sodium N-dodecyl-beta-alanine, sodium N-lauryl-beta-iminodipropionate, myristoamphoacetate, lauryl betaine, and lauryl sulfobetaine.

[0123] If desired, the tablets, beads, granules, or particles may also contain minor amount of nontoxic auxiliary substances such as wetting or emulsifying agents, dyes, pH buffering agents, or preservatives.

[0124] The concentration of the inhibitor(s) to carrier and/or other substances may vary from about 0.5 to about 70 wt % (weight percent). For oral use, the pharmaceutical formulation will generally contain from about 5 to about 70% by weight of the active material. For other uses, the pharmaceutical formulation will generally have from about 0.5 to about 60 wt % of the active material.

[0125] The compositions described herein can be formulation for modified or controlled release. Examples of controlled release dosage forms include extended-release dosage forms, delayed release dosage forms, pulsatile release dosage forms, and combinations thereof.

[0126] The extended-release formulations are generally prepared as diffusion or osmotic systems, for example, as described in "Remington -- The science and practice of pharmacy"

(20th ed., Lippincott Williams & Wilkins, Baltimore, MD, 2000). A diffusion system typically consists of two types of devices, a reservoir and a matrix, and is well known and described in the art. The matrix devices are generally prepared by compressing the drug with a slowly dissolving polymer carrier into a tablet form. The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers, and fatty compounds. Plastic matrices include, but are not limited to, methyl acrylate-methyl methacrylate, polyvinyl chloride, and polyethylene. Hydrophilic polymers include, but are not limited to, cellulosic polymers such as methyl and ethyl cellulose, hydroxyalkyl celluloses such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and Carbopol® 934, polyethylene oxides and mixtures thereof. Fatty compounds include, but are not limited to, various waxes such as carnauba wax and glyceryl tristearate and wax-type substances including hydrogenated castor oil or hydrogenated vegetable oil, or mixtures thereof.

[0127] In certain embodiments, the plastic material is a pharmaceutically acceptable acrylic polymer, including but not limited to, acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

[0128] In certain embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

[0129] Alternatively, extended release formulations can be prepared using osmotic systems or by applying a semi-permeable coating to the dosage form. In the latter case, the desired drug release profile can be achieved by combining low permeable and high permeable coating materials in suitable proportion.

[0130] The devices with different drug release mechanisms described above can be combined in a final dosage form comprising single or multiple units. Examples of multiple units include, but are not limited to, multilayer tablets and capsules containing tablets, beads, or granules[0131] An immediate release portion can be added to the extended release

system by means of either applying an immediate release layer on top of the extended release core using a coating or compression process or in a multiple unit system such as a capsule containing extended and immediate release beads.

[0132] Extended release tablets containing hydrophilic polymers are prepared by techniques commonly known in the art such as direct compression, wet granulation, or dry granulation. Their formulations usually incorporate polymers, diluents, binders, and lubricants as well as the active pharmaceutical ingredient. The usual diluents include inert powdered substances such as starches, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders include substances such as starch, gelatin and sugars such as lactose, fructose, and glucose. Natural and synthetic gums, including acacia, alginates, methylcellulose, and polyvinylpyrrolidone can also be used. Polyethylene glycol, hydrophilic polymers, ethylcellulose and waxes can also serve as binders. A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. In certain embodiments, the lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

[0133] Extended release tablets containing wax materials are generally prepared using methods known in the art such as a direct blend method, a congealing method, and an aqueous dispersion method. In the congealing method, the drug is mixed with a wax material and either spray-congealed or congealed and screened and processed.

[0134] Delayed release formulations are created by coating a solid dosage form with a polymer film, which is insoluble in the acidic environment of the stomach, and soluble in the neutral environment of the small intestine.

[0135] The delayed release dosage units can be prepared, for example, by coating a drug or a drug-containing composition with a selected coating material. The drug-containing composition may be, e.g., a tablet for incorporation into a capsule, a tablet for use as an inner core in a "coated core" dosage form, or a plurality of drug-containing beads, particles or granules, for incorporation into a tablet or capsule. Preferred coating materials include biodegradable, gradually hydrolyzable, gradually water-soluble, and/or enzymatically

degradable polymers, and may be conventional “enteric” polymers. Enteric polymers, as will be appreciated by those skilled in the art, become soluble in the higher pH environment of the lower gastrointestinal tract or slowly erode as the dosage form passes through the gastrointestinal tract, while enzymatically degradable polymers are degraded by bacterial enzymes present in the lower gastrointestinal tract, particularly in the colon. Suitable coating materials for effecting delayed release include, but are not limited to, cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methylcellulose phthalate, methylcellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate vinyl polymers and copolymers such as polyvinyl pyrrolidone, vinyl acetate, vinyl acetate phthalate, vinyl acetate crotonic acid copolymer, and ethylene-vinyl acetate copolymer; enzymatically degradable polymers such as azo polymers, pectin, chitosan, amylose and guar gum; zein and shellac. Combinations of different coating materials may also be used. Multi-layer coatings using different polymers may also be applied.

[0136] The preferred coating weights for particular coating materials may be readily determined by those skilled in the art by evaluating individual release profiles for tablets, beads and granules prepared with different quantities of various coating materials. It is the combination of materials, method and form of application that produce the desired release characteristics, which one can determine only from the clinical studies.

[0137] The coating composition may include conventional additives, such as plasticizers, pigments, colorants, stabilizing agents, glidants, etc. A plasticizer is normally present to reduce the fragility of the coating and will generally represent about 10 wt % to 50 wt % relative to the dry weight of the polymer. Examples of typical plasticizers include polyethylene glycol, propylene glycol, triacetin, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl acetyl citrate, castor oil and acetylated monoglycerides. A stabilizing agent is preferably used to stabilize particles in the dispersion. Typical stabilizing agents are nonionic emulsifiers such as sorbitan esters, polysorbates and polyvinylpyrrolidone. Glidants are recommended to reduce sticking effects during film formation and drying and will generally represent approximately 25 wt % to 100 wt % of the polymer weight in the coating solution. One effective glidant is talc. Other

glidants such as magnesium stearate and glycerol monostearates may also be used. Pigments such as titanium dioxide may also be used. Small quantities of an anti-foaming agent, such as a silicone (e.g., simethicone), may also be added to the coating composition.

[0138] The formulation can provide pulsatile delivery of the one or more inhibitors. By “pulsatile” is meant that a plurality of drug doses are released at spaced apart intervals of time. Generally, upon ingestion of the dosage form, release of the initial dose is substantially immediate, i.e., the first drug release “pulse” occurs within about one hour of ingestion. This initial pulse is followed by a first-time interval (lag time) during which very little or no drug is released from the dosage form, after which a second dose is then released. Similarly, a second nearly drug release-free interval between the second and third drug release pulses may be designed. The duration of the nearly drug release-free time interval will vary depending upon the dosage form design e.g., a twice daily dosing profile, a three times daily dosing profile, etc. For dosage forms providing a twice daily dosage profile, the nearly drug release-free interval has a duration of approximately 3 hours to 14 hours between the first and second dose. For dosage forms providing a three times daily profile, the nearly drug release-free interval has a duration of approximately 2 hours to 8 hours between each of the three doses.

[0139] In one embodiment, the pulsatile release profile is achieved with dosage forms that are closed and preferably sealed capsules housing at least two drug-containing “dosage units” wherein each dosage unit within the capsule provides a different drug release profile. Control of the delayed release dosage unit(s) is accomplished by a controlled release polymer coating on the dosage unit, or by incorporation of the active agent in a controlled release polymer matrix. Each dosage unit may comprise a compressed or molded tablet, wherein each tablet within the capsule provides a different drug release profile. For dosage forms mimicking a twice a day dosing profile, a first tablet releases drug substantially immediately following ingestion of the dosage form, while a second tablet releases drug approximately 3 hours to less than 14 hours following ingestion of the dosage form. For dosage forms mimicking a three times daily dosing profile, a first tablet releases drug substantially immediately following ingestion of the dosage form, a second tablet releases drug approximately 3 hours to less than 10 hours following ingestion of the dosage form, and the third tablet releases drug at least 5 hours to approximately 18 hours following ingestion of the dosage form. It is possible that the dosage form includes more than three tablets. While the dosage form will not generally include more than a third tablet, dosage forms housing more than three tablets can be utilized.

[0140] Alternatively, each dosage unit in the capsule may comprise a plurality of drug-containing beads, granules or particles. As is known in the art, drug-containing “beads” refer to beads made with drug and one or more excipients or polymers. Drug-containing beads can be produced by applying drug to an inert support, e.g., inert sugar beads coated with drug or by creating a “core” comprising both drug and one or more excipients. As is also known, drug-containing “granules” and “particles” comprise drug particles that may or may not include one or more additional excipients or polymers. In contrast to drug-containing beads, granules and particles do not contain an inert support. Granules generally comprise drug particles and require further processing. Generally, particles are smaller than granules, and are not further processed. Although beads, granules and particles may be formulated to provide immediate release, beads and granules are generally employed to provide delayed release.

[0141] In one embodiment, the compound is formulated for topical administration. Suitable topical dosage forms include lotions, creams, ointments, and gels. A “gel” is a semisolid system containing a dispersion of the active agent, i.e., inhibitor, in a liquid vehicle that is rendered semisolid by the action of a thickening agent or polymeric material dissolved or suspended in the liquid vehicle. The liquid may include a lipophilic component, an aqueous component or both. Some emulsions may be gels or otherwise include a gel component. Some gels, however, are not emulsions because they do not contain a homogenized blend of immiscible components. Methods for preparing lotions, creams, ointments, and gels are well known in the art.

[0142] The compounds described herein can be administered in combination with other active compounds. These compounds include but are not limited to analgesics, anti-inflammatory drugs, antipyretics, antidepressants, antiepileptics, antihistamines, antimigraine drugs, antimuscarinics, anxiolytics, sedatives, hypnotics, antipsychotics, bronchodilators, anti-asthma drugs, cardiovascular drugs, corticosteroids, dopaminergics, electrolytes, gastrointestinal drugs, muscle relaxants, nutritional agents, vitamins, parasympathomimetics, stimulants, anorectics and anti-narcoleptics. The additional active agent(s) can be formulated for immediate release, controlled release, or combinations thereof.

[0143] In certain embodiments, the disclosure relates to a pharmaceutical composition comprising a compound as discussed in the previous section and a pharmaceutically acceptable carrier, as outlined above. In certain embodiments, the disclosure relates to a

pharmaceutical composition comprising a compound as discussed in the previous section and a pharmaceutically acceptable excipient, as outlined above.

KITS

[0144] Also provided herein are kits for the slow and controlled release of hydrogen sulfide under biologically applicable conditions. A kit can include any of the compound or compositions described herein. For example, a kit can include a compound of Formula I, Formula II, Formula III, Formula IV, or combinations thereof. In certain embodiments, a kit can include the pharmaceutical composition(s) described herein. A kit can further include one or more additional agents, such as an antibiotic agent (e.g., metronidazole, furazolidone, or paromomycin), an antiparasitic agent (e.g., tinidazole or mebendazole), and/or an antiprotozoal agent (e.g., nitazoxanide or quinacrine). A kit can include an oral formulation of any of the compounds or compositions described herein. A kit can additionally include directions for use of the kit (e.g., instructions for treating a subject), a container, a means for administering the compounds or compositions, and/or a carrier.

METHODS OF USE

[0145] In certain embodiments, the disclosure relates to methods of treating or preventing a cerebrovascular disease, an anti-inflammatory condition, rheumatic or rheumatoid arthritis, gout, high blood pressure, a high blood lipids condition, or liver toxicity in a subject, comprising administering to the subject an effective amount of a compound disclosed herein, or a pharmaceutical composition disclosed herein to a subject in need thereof. In some embodiments, the subject is diagnosed with, exhibiting symptoms of, or at risk of the disease or condition. In some embodiments, the disease or condition is cardiovascular and cerebrovascular diseases, neurodegenerative diseases, metabolic diseases, inflammatory disease, chronic pain, and other painful disorders.

[0146] In certain embodiments, the methods described herein include a method of treating or reducing the risk of disorders associated with cerebrovascular disease, an anti-inflammatory condition, rheumatic or rheumatoid arthritis, gout, high blood pressure, a high blood lipids condition, or liver toxicity in a subject, comprising administering to the subject an effective amount of a compound disclosed herein or a pharmaceutical composition disclosed herein to a subject in need thereof.

[0147] In certain embodiments, the methods described herein include an antipyretic or an analgesic compound. In certain embodiments, the method described herein include a compound that reduces liver toxicity on GSH depletion or mitochondrial damage.

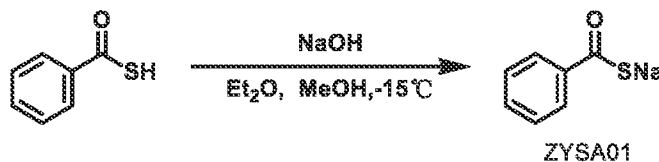
[0148] Aspects of the disclosure may be further understood by reference to the following non-limiting examples.

EXAMPLES

Example 1: Compound Synthesis

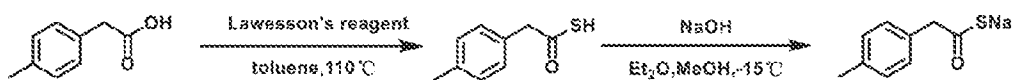
[0149] All compounds were purchased from Bide Pharmaceutical Company (Shanghai, China). All solvents and reagents were used as obtained without further purification. ^1H NMR and ^{13}C NMR spectra were obtained on a BRUKER® AV-300, BRUKER® AV-400, BRUKER® AV-500, BRUKER® AV-600 spectrometer (Bruker Corp., Billerica, MA). Chemical shifts (δ) are reported in ppm and coupling constants (J) are in Hertz (Hz). The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Flash chromatography was performed using silica gel 60 F₂₅₄ plates. ESI mass spectrometry was measured on AGILENT® Q-TOF 6520 (Agilent Technologies, Inc. Santa Clara, CA).

Scheme 1: Synthesis of ZYSA01



[0150] To a solution of thiobenzoic acid (1.00 g, 7.24 mmol) in methanol was added sodium hydroxide (NaOH; 0.23 g, 5.80 mmol), and the reaction mixture was stirred in ice-salt bath for 5 minutes. Methanol (MeOH) was removed under reduced pressure and the residue was washed with diethyl ether (Et₂O). ZYSA01 was obtained as a white solid (1.15 g, 70%). ZYSA01. ^1H NMR (300 MHz, CD₃OD) δ 8.15 – 7.70 (m, 2H), 7.47 – 6.94 (m, 3H). ^{13}C NMR (75 MHz, CD₃OD) δ 213.44, 144.40, 130.00, 128.90, 127.90, 127.40, 126.96.

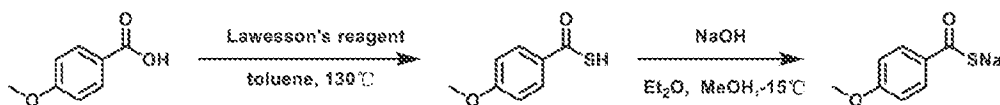
Scheme 2: Synthesis of ZYSA06



ZYSA06

[0151] To a solution of para-methylphenylacetic acid (100 mg, 0.66 mmol) in toluene was added Lawesson's reagent (148 mg, 0.33 mmol). The vessel was sealed with sealing film and purged with argon for 5 minutes. The reaction mixture was stirred at 110 °C for 1.5 hours until the reaction was completed as indicated by TLC analysis. Toluene was removed under reduced pressure. The organic phase was purified by column chromatography, eluting with dichloromethane (DCM), to give a crude product. To the dissolved crude product in methanol (MeOH) was added sodium hydroxide (NaOH; 19 mg, 0.462 mmol). The reaction mixture was stirred in an ice-salt bath for 5 minutes. MeOH was removed under reduced pressure and the residue was washed with diethyl ether (Et₂O) to yield **ZYSA06** as a white solid (87 mg, 70%). **ZYSA06**. ¹H NMR (500 MHz, DMSO-d₆) δ 7.98 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 7.9 Hz, 2H), 2.30 (s, 3H). ¹³C NMR (75 MHz, DMSO-d₆) δ 212.98, 136.06, 133.90, 128.99, 128.09, 58.04, 20.70. HRMS calculated for C₉H₉NaOS requires 211.0164 for [M+Na]⁺, found 211.01606.

Scheme 3: Synthesis of ZYSA05



ZYSA05

[0152] The synthesis of **ZYSA05** followed the same protocol of **ZYSA06** (except the reaction temperature was 130 °C). **ZYSA05** was obtained as a white solid (88 mg, 77%). **ZYSA05**. ¹H NMR (500 MHz, DMSO-d₆) δ 8.05 (dd, J = 9.2, 2.3 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 3.75 (s, 3H). ¹³C NMR (126 MHz, DMSO-d₆) δ 207.50, 160.76, 138.57, 130.16, 112.25, 55.57. HRMS calculated for C₈H₇NaO₂S requires 212.99567 for [M+Na]⁺, found 212.99475.

Scheme 4: Synthesis of ZYSA02

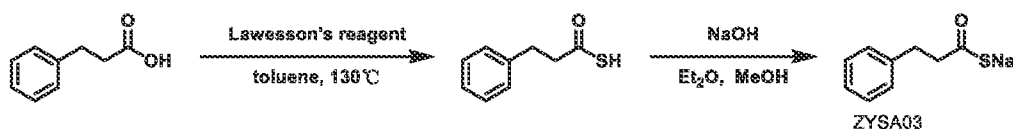


ZYSA02

[0153] The synthesis of **ZYSA02** followed the same protocol of **ZYSA06** (except the reaction temperature was 130 °C). **ZYSA02** was obtained as a white solid (88 mg, 77%). **ZYSA02**. ¹H NMR (300 MHz, DMSO-d₆) δ 7.19-7.08 (m, 5H), 3.68 (s, 2H). ¹³C NMR (101

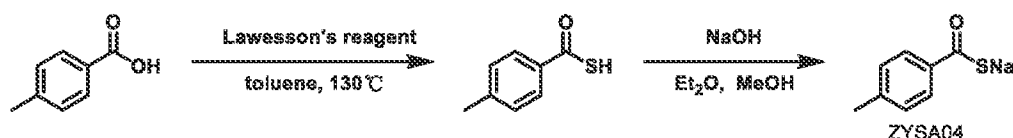
MHz, CD₃OD) δ 137.89, 128.85, 127.64, 125.64, 57.34. HRMS calculated for C₈H₇NaOS requires 197.00075 for [M+Na]⁺, found 197.00005.

Scheme 5: Synthesis of ZYSA03



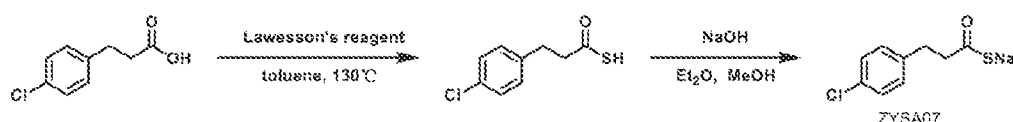
[0154] The synthesis of ZYSA03 followed the same protocol of ZYSA06 (except the reaction temperature was 130 °C). ZYSA03 was obtained as a white solid (68 mg, 74%). ZYSA03. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.22 (t, *J* = 10.0 Hz, 2H), 7.17-7.10 (m, 3H), 2.79 (t, *J* = 5.0 Hz, 2H), 2.63 (t, *J* = 10.0 Hz, 2H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 215.98, 143.31, 128.69, 128.55, 125.76, 53.24, 33.75. HRMS calculated for C₉H₉OS requires 165.03796 for [M-H]⁻, found 165.03782.

Scheme 5: Synthesis of ZYSA04



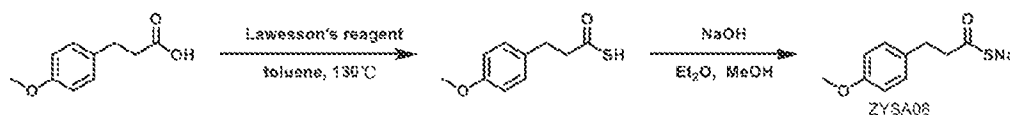
[0155] The synthesis of ZYSA04 followed the same protocol of ZYSA06 (except the reaction temperature was 130 °C). ZYSA04 was obtained as a white solid (770 mg, 60%). ZYSA04. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.98 (d, *J* = 8.1 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 2.30 (s, 3H). ¹³C NMR (126 MHz, DMSO-*d*₆) δ 207.96, 143.21, 138.62, 128.47, 127.74, 21.32. HRMS calculated for C₈H₇NaOS requires 151.02231 for [M-H]⁻ found: 151.02295.

Scheme 6: Synthesis of ZYSA07



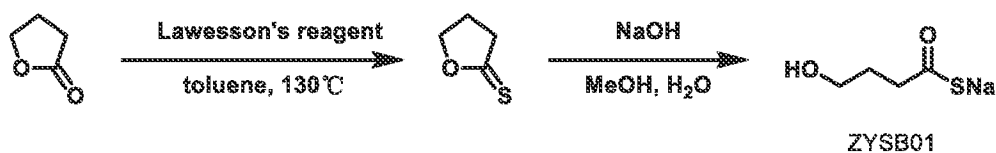
[0156] The synthesis of ZYSA07 followed the same protocol of ZYSA06 (except the reaction temperature was 130 °C). ZYSA07 was obtained as a white solid (73 mg, 67%). ZYSA07. ¹H NMR (300 MHz, CD₃OD) δ 7.23-7.17 (m, 4H), 2.95 (m, 4H). ¹³C NMR (101 MHz, CD₃OD) δ 140.75, 131.00, 129.63, 127.84, 52.23, 32.80. HRMS calculated for C₉H₈ClNaOS requires 244.97743 for [M+Na]⁺ found: 244.97661.

Scheme 7: Synthesis of ZYSA08



[0157] The synthesis of **ZYSA08** followed the same protocol of **ZYSA06** (except the reaction temperature was 130 °C). **ZYSA08** was obtained as a white solid (88 mg, 77%). **ZYSA08**. ¹H NMR (300 MHz, CD₃OD) δ 7.07 (d, J = 8.7 Hz, 2H), 6.84 – 6.71 (m, 2H), 3.70 (s, 3H), 2.76 – 2.66 (m, 2H), 2.64 – 2.54 (m, 2H). ¹³C NMR (101 MHz, CD₃OD) δ 157.84, 133.94, 128.83, 128.77, 113.28, 54.24, 52.99, 32.76. HRMS calculated for C₁₀H₁₁NaO₂S requires 241.02697 for [M+Na]⁺ found: 241.02629.

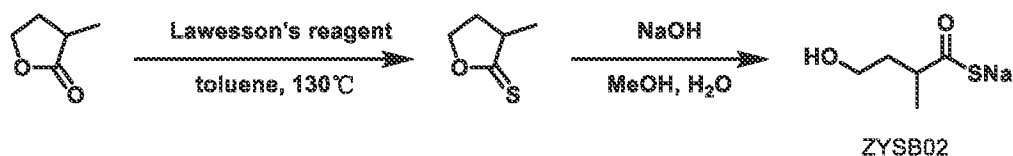
Scheme 8: Synthesis of ZYSB01



[0158] To a solution of γ -butyrolactone (2 g, 23.2 mmol) in toluene (30 mL) was added Lawesson's reagent (5.6 g, 13.9 mmol). The vessel was sealed with sealing film and purged with argon for 5 mins. The resulting mixture was stirred at 130 °C for 5 hours until the reaction was completed indicated by TLC analysis. Toluene was removed under reduced pressure. The crude product was purified by column chromatography (eluent: petroleum ether/ethyl acetate = 5/1) to remove impurities and thio- γ -butyrolactone was obtained as a yellow oily liquid (647 mg, 30%).

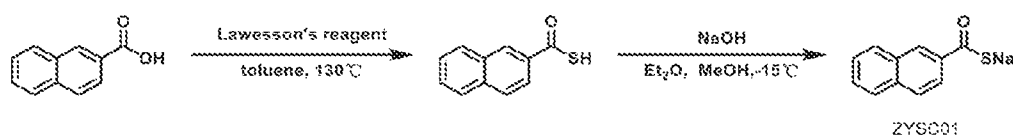
[0159] To a solution of thio- γ -butyrolactone (193 mg, 1.9 mmol) in methanol (MeOH) was added sodium hydroxide (91 mg, 2.3 mmol). The reaction was stirred at room temperature for 3 hours, and thin layer chromatography (TLC) monitoring indicated the reaction was complete. The solvent was removed under reduced pressure. **ZYSB01** was obtained as a white solid (183 mg, 70%). **ZYSB01**. ¹H NMR (300 MHz, CD₃OD) δ 3.57 (t, J = 6.0 Hz, 2H), 2.71 (t, J = 6.0 Hz, 2H), 1.91-1.82 (m, 2H). ¹³C NMR (75 MHz, CD₃OD) δ 221.88, 61.32, 34.48, 30.28. HRMS calculated for C₄H₇NaO₂S requires 164.99567 for [M+Na]⁺ found: 164.99546.

Scheme 9: Synthesis of ZYSB02



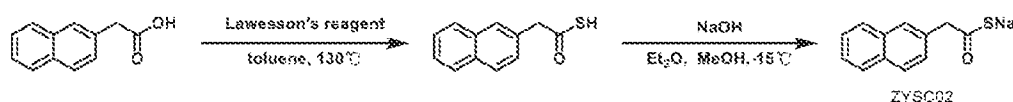
[0160] The synthesis of ZYSB02 followed the same protocol of ZYSB01. ZYSB02 was obtained as a white solid (750 mg, 40%). ZYSB02. ^1H NMR (300 MHz, CD_3OD) δ 3.60-3.54 (m, 2H), 2.96-2.85 (m, 1H), 1.98-1.85 (m, 1H), 1.58-1.49 (m, 1H), 1.11 (d, $J = 6.0$ Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD) δ 226.19, 60.17, 50.79, 37.99, 18.63. HRMS calculated for $\text{C}_5\text{H}_9\text{NaO}_2\text{S}$ requires 179.01132 for $[\text{M}+\text{Na}]^+$ found: 179.01092.

Scheme 10: Synthesis of ZYSC01



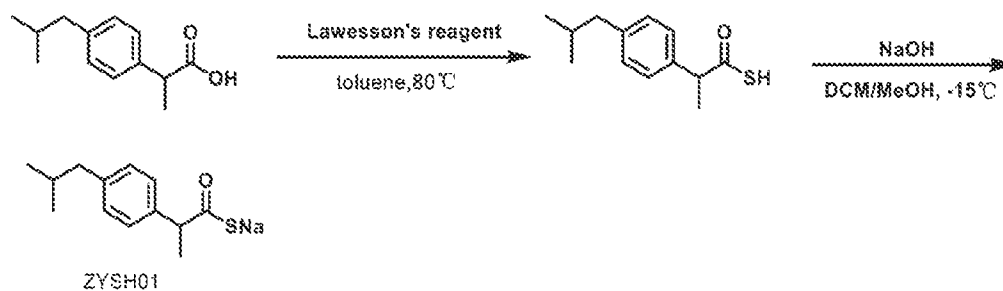
[0161] The synthesis of ZYSC01 followed the same protocol of ZYSA06 (except the reaction temperature was 130 °C). ZYSC01 was obtained as a white solid (78 mg, 67%). ZYSC01. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.56 (s, 1H), 8.26 (d, $J = 9.0$ Hz, 1H), 7.96-7.84 (m, 2H), 7.74 (d, $J = 9.0$ Hz, 1H), 7.48-7.46 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 213.07, 141.61, 134.56, 132.63, 128.91, 128.00, 127.11, 126.56, 126.27, 125.67, 125.37. HRMS calculated for $\text{C}_{11}\text{H}_7\text{NaOS}$ requires 233.00075 for $[\text{M}+\text{Na}]^+$ found: 233.00008.

Scheme 11: Synthesis of ZYSC02



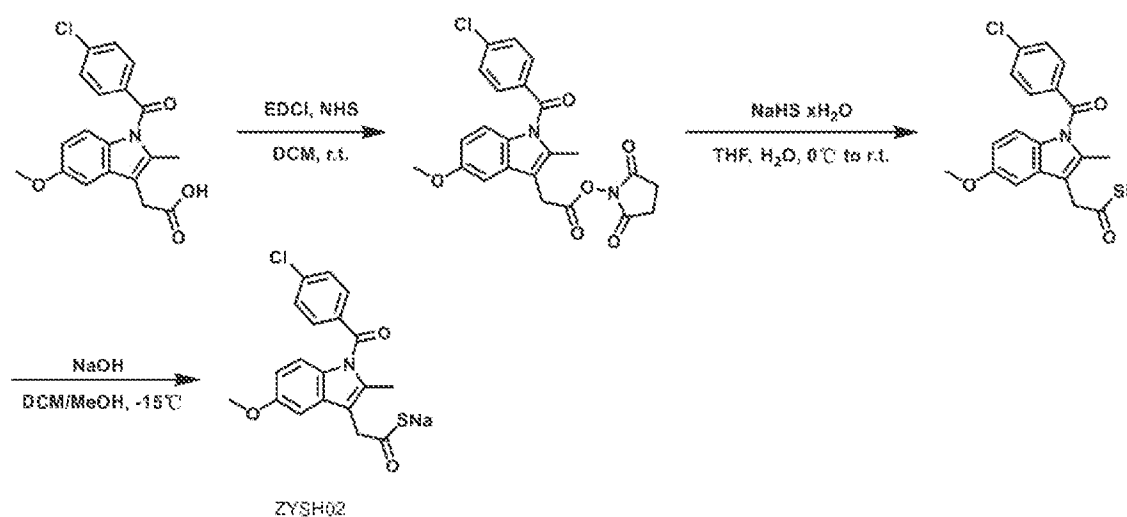
[0162] The synthesis of ZYSC02 followed the same protocol of ZYSA06 (except the reaction temperature was 130 °C). ZYSC02 was obtained as a white solid (608 mg, 77%). ZYSC02. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.83-7.78 (m, 2H), 7.73 (d, $J = 9.0$ Hz, 1H), 7.62 (s, 1H), 7.46-7.36 (m, 3H), 3.86 (s, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 135.52, 133.67, 132.26, 127.60, 127.20, 127.11, 127.08, 127.02, 125.30, 124.76, 57.46. HRMS calculated for $\text{C}_{12}\text{H}_9\text{OS}$ requires 201.03796 for $[\text{M}-\text{H}]^-$ found: 201.03773.

Scheme 12: Synthesis of ZYSH01



[0163] The synthesis of **ZYSH01** followed the same protocol of **ZYSA06** (except the reaction temperature was 80°C). **ZYSH01** was obtained as a white solid (658 mg, 67%). **ZYSH01**. ^1H NMR (400 MHz, CD_3OD) δ 7.30 – 7.25 (m, 2H), 7.07 – 6.97 (m, 2H), 4.16 (q, $J = 7.1$ Hz, 1H), 2.41 (d, $J = 7.1$ Hz, 2H), 1.81 (dp, $J = 13.5, 6.8$ Hz, 1H), 1.40 (d, $J = 7.1$ Hz, 3H), 0.88 (d, $J = 6.6$ Hz, 6H). ^{13}C NMR (101 MHz, CD_3OD) δ 142.27, 140.36, 129.66, 128.36, 60.80, 46.11, 31.50, 22.73, 20.42. HRMS calculated for $\text{C}_{13}\text{H}_{17}\text{O}_2\text{S}$ requires 221.10056 for $[\text{M}-\text{H}]^-$, found 221.009995.

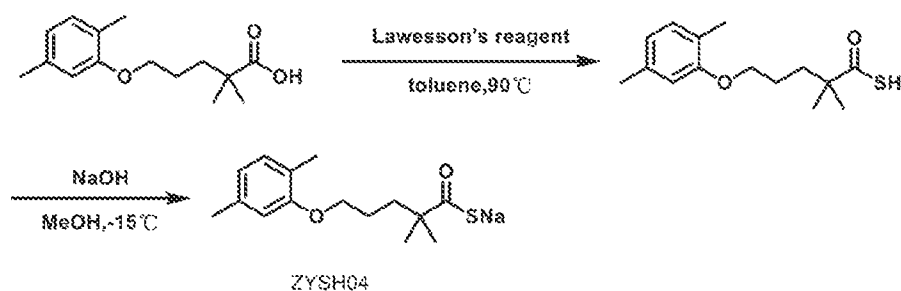
Scheme 13: Synthesis of ZYSH02



[0164] To a solution of indomethacin (893 mg, 3 mmol) in dichloromethane (DCM; 15 mL) was added 1-ethyl-3-(dimethylammonopropyl)carbodiimide hydrochloride (EDCI HCl; 690 mg, 3.6 mmol) and N-hydroxysuccinimide (NHS; 518 mg, 4.5 mmol). The reaction mixture was stirred at room temperature (r.t) for 24 hours. DCM was removed under reduced pressure. The crude product was purified by column chromatography (white solid, 1.24 g, yield = 91%).

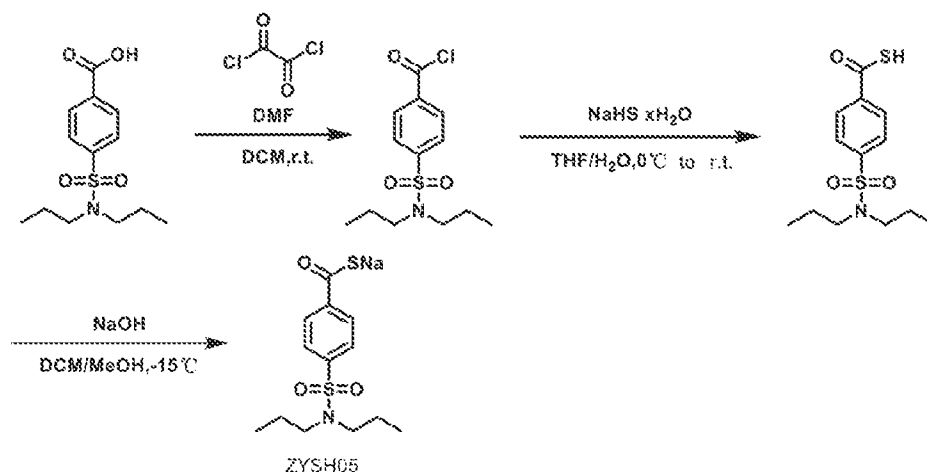
[0165] To a solution of crude product in tetrahydrofuran (THF) solution was added sodium hydrosulfide hydrate (136 mg, 2 mmol). The mixture was stirred in an ice bath for 1 hour. The reaction was completed as indicated by TLC analysis. The solvent was removed under reduced pressure. The organic phase was purified by column chromatography, eluting with DCM, to give a crude product. The crude product was dissolved in an appropriate amount of methanol (MeOH) and cooled in an ice-salt bath. After cooling, a MeOH solution of sodium hydroxide (NaOH) was added (18.48 mg, 0.462 mmol) and stirred for 5 minutes in the ice-salt bath. MeOH was removed under reduced pressure and the residue was washed with diethyl ether (Et₂O). The reaction yielded sodium thioindomethacinate (white solid, 854 mg, yield = 72%). **ZYSH02**. ¹H NMR (300 MHz, CD₃OD) δ 7.74 – 7.67 (m, 2H), 7.58 – 7.51 (m, 2H), 7.13 (d, J = 2.5 Hz, 1H), 6.95 (d, J = 8.9 Hz, 1H), 6.62 (dd, J = 9.0, 2.6 Hz, 1H), 4.04 (s, 2H), 3.80 (s, 3H), 2.26 (s, 3H), 1.90 (s, 1H). ¹³C NMR (101 MHz, CD₃OD) δ 180.47, 167.57, 154.63, 140.44, 134.56, 132.15, 132.08, 130.72, 129.98, 129.83, 111.51, 110.80, 108.50, 101.90, 56.29, 47.65, 24.23, 11.85, -15.68. HRMS calculated for C₁₉H₁₅ClNO₃ S requires 372.04667 for [M-H]⁺, found 372.04594.

Scheme 14: Synthesis of ZYSH04



[0166] The synthesis of **ZYSH04** followed the same protocol of **ZYSA06** (except the reaction temperature was 90 °C). **ZYSH04** was obtained as a white solid (790 mg, 57%). **ZYSH04**. ¹H NMR (400 MHz, CD₃OD) δ 6.92 (d, J = 7.5 Hz, 1H), 6.65 (d, J = 1.5 Hz, 1H), 6.59 (d, J = 7.4 Hz, 1H), 3.95 – 3.82 (m, 2H), 2.26 (s, 3H), 2.12 (s, 3H), 1.77 (d, J = 3.4 Hz, 3H), 1.21 (s, 6H). ¹³C NMR (101 MHz, CD₃OD) δ 157.06, 136.12, 129.69, 122.99, 120.14, 111.61, 68.41, 50.92, 38.81, 26.75, 25.15, 20.10, 14.64. HRMS calculated for C₁₅H₂₁O₂S requires 265.12677 for [M-Na]⁺, found 265.12605.

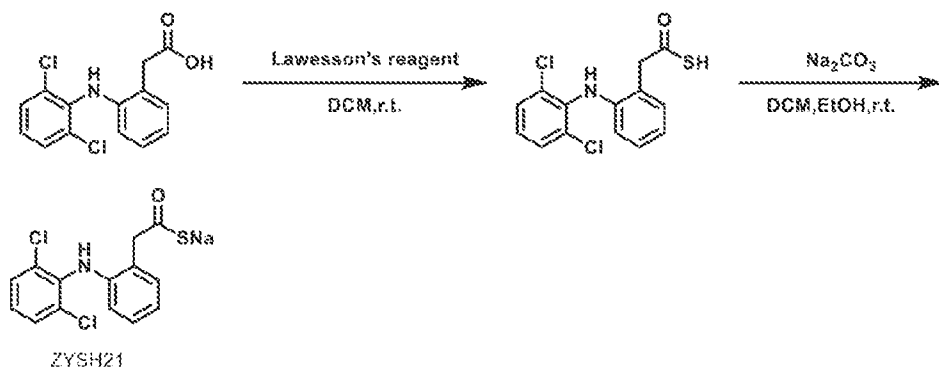
Scheme 15: Synthesis of ZYSH05



[0167] A solution of propofol (285 mg, 1 mmol) in dichloromethane (DCM) was purged with argon for 5 minutes and then oxalyl chloride (170 μ L, 4 mmol, 2 eq) and dimethylformamide (DMF; 2 drops) were added using a syringe. The mixture was stirred at room temperature for 1 hour. DCM was removed under reduced pressure and the obtained residue was dissolved in tetrahydrofuran (THF; 3 mL), which was directly used in the next reaction.

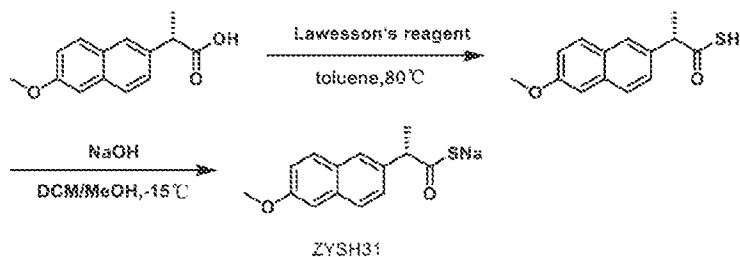
[0168] To a solution of residue in THF solution was added sodium hydrosulfide hydrate (136 mg, 2 mmol). The mixture was stirred in an ice bath for 1 hour. The reaction was completed as indicated by TLC analysis. The solvent was removed under reduced pressure. The organic phase was purified by column chromatography, eluting with DCM, to give a crude product. The obtained residue was suspended in methanol (MeOH). The mixture was stirred at 0 °C for 5 min, and then NaOH (64mg, 1.6 mmol) was added into the reaction mixture. The MeOH was removed under vacuum and the residue was washed with DCM and diethyl ether (Et_2O) 3 times. A bright yellow solid was obtained (119 mg, 36%). **ZYSH05**. ^1H NMR (300 MHz, CD_3OD) δ 8.26 – 8.18 (m, 2H), 7.77 – 7.70 (m, 2H), 3.10 (d, J = 7.6 Hz, 4H), 1.55 (h, J = 7.4 Hz, 4H), 0.88 (t, J = 7.4 Hz, 6H). ^{13}C NMR (101 MHz, CD_3OD) δ 212.67, 149.16, 141.93, 129.60, 127.23, 51.31, 23.11, 11.43. HRMS calculated for $\text{C}_{16}\text{H}_{14}\text{NO}_3\text{S}$ requires 300.06999 for $[\text{M}-\text{H}]^-$, found 300.07259.

Scheme 16: Synthesis of ZYSH21



[0169] To a solution of 2- [(2,6-dichlorophenyl) amino] - benzene sodium acetate (504 mg, 1.58 mmol) in dichloromethane (DCM) was added Lawesson's reagent (351 mg, 0.869 mmol). The mixture was stirred at room temperature for 1 hour. DCM was removed under reduced pressure. The crude product was purified by column chromatography, and the pure product was dissolved in 1.5 mL of dichloromethane (DCM) and 0.4 mL of 0.1 M of sodium bicarbonate (NaHCO₃) ethanol solution. The resulting mixture was stirred at room temperature for 30 minutes. The ethanol was removed under vacuum and the residue was washed with DCM and diethyl ether (Et₂O) for 3 times. A white solid was obtained (301 mg, 60%). **ZYSH21**. ¹H NMR (300MHz, DMSO-d₆): δ 9.17 (s, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.25-7.04 (m, 2H), 6.95 (d, J = 7.5 Hz, 1H), 6.79 (d, J = 7.3Hz, 1H), 6.26 (d, J = 7.8 Hz, 1H), 3.87 (s, 2H), ¹³C NMR(DMSO-d₆): 214.3, 143.4, 138.4, 130.9, 129.6, 129.5, 128.9, 126.4, 124.7, 120.8, 116.6, 56.8. HRMS calculated for C₁₄H₁₂Cl₂NOS requires 312.00112 for [M+H]⁺, found 312.0012.

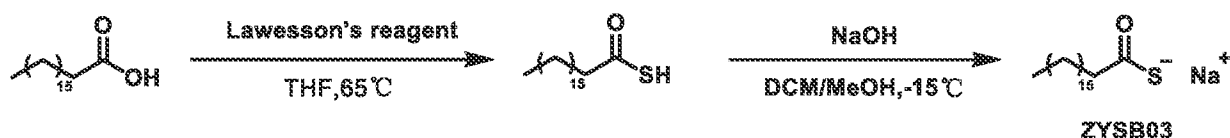
Scheme 17: Synthesis of ZYSH31



[0170] The synthesis of **ZYSH31** followed the same protocol of **ZYSA06** (except the reaction temperature was 80 °C). **ZYSH31** was obtained as a white solid (800 mg, 74%). **ZYSA31**. ¹H NMR (500 MHz, CD₃OD) δ 7.73 – 7.61 (m, 3H), 7.52 (dd, J = 8.6, 1.7 Hz, 1H), 7.15 (d, J = 2.5 Hz, 1H), 7.06 (dd, J = 8.9, 2.5 Hz, 1H), 4.32 (q, J = 7.1 Hz, 1H), 3.88 (s, 3H), 1.50 (d, J = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CD₃OD) δ 223.91, 158.64, 140.29, 134.84,

130.49, 130.16, 128.06, 127.35, 126.64, 119.28, 106.57, 61.10, 55.70, 20.41. HRMS calculated for $C_{14}H_{13}NaO_2S$ requires 291.04262 for $[M+Na]^+$, found 291.04247.

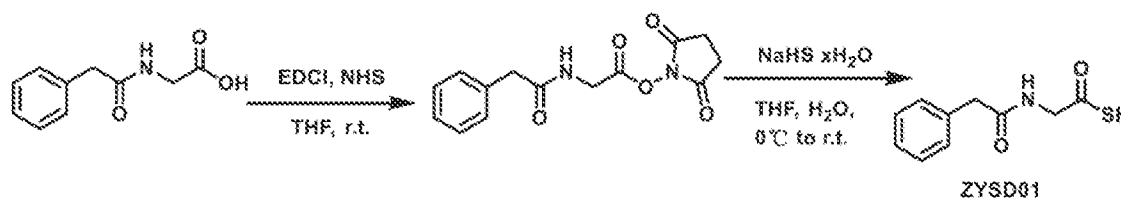
Scheme 18: Synthesis of ZYSB03



[0171] The synthesis of **ZYSB03** followed the same protocol as **ZYSA06** (except the reaction temperature was 65 °C). **ZYSB03** was obtained as a white solid (298mg, 74%).

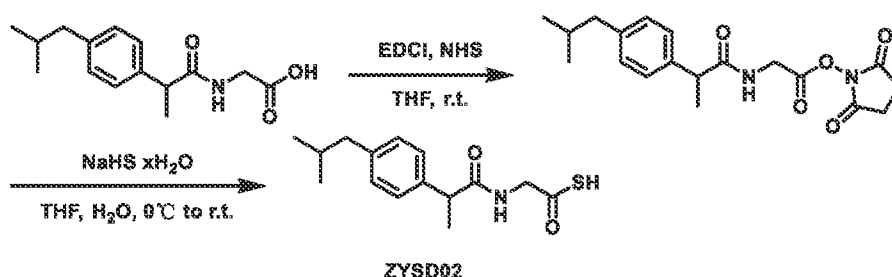
ZYSB03. 1H NMR (300 MHz, $DMSO-d_6$) δ 2.30 (t, $J = 7.5$ Hz, 2H), 1.43 (t, $J = 7.2$ Hz, 2H), 1.23 (s, 28H), 0.91 – 0.79 (m, 3H).

Scheme 19: Synthesis of ZYSD01



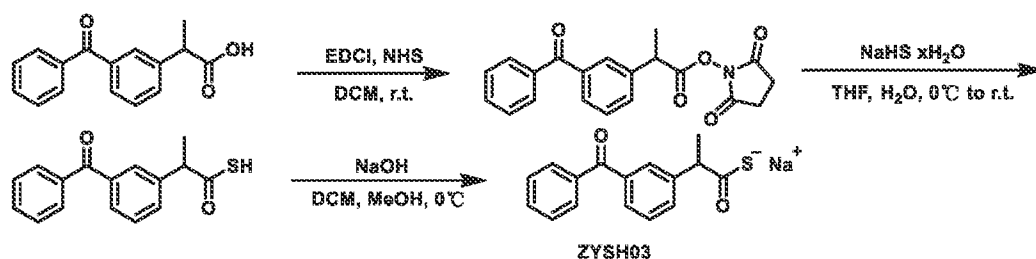
[0172] The synthesis of **ZYSD01** followed the same protocol of **ZYSH01**. **ZYSD01** was obtained as a white solid (42 mg, 20%). **ZYSD01**. 1H NMR (300 MHz, Methanol- d_4) δ 7.36 – 7.21 (m, 5H), 4.10 (s, 2H), 3.59 (s, 2H). ^{13}C NMR (75 MHz, MeOD) δ 175.56, 168.55, 140.18, 138.77, 128.96, 126.98, 45.64, 44.73, 40.58, 30.20, 21.41, 17.61.

Scheme 20: Synthesis of ZYSD02



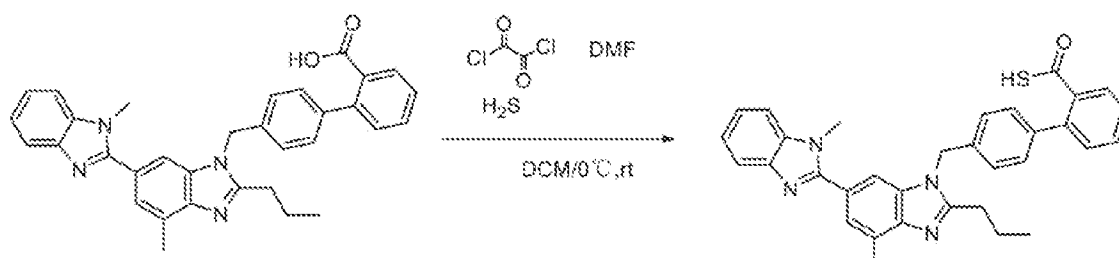
[0173] The synthesis of **ZYSD02** followed the same protocol as **ZYSH01**. **ZYSD02** was obtained as a white solid (35mg, 45%). **ZYSD02**. 1H NMR (300 MHz, Methanol- d_4) δ 7.26 (d, $J = 8.03$ Hz, 2H), 7.10 (d, $J = 8.10$ Hz, 2H), 4.04 (d, $J = 2.74$ Hz, 2H), 3.69 (q, $J = 7.08$ Hz, 1H), 2.44 (d, $J = 7.18$ Hz, 2H), 1.83 (hept, $J = 13.54, 6.76$ Hz, 1H), 1.46 (d, $J = 7.14$ Hz, 3H), 0.89 (d, $J = 6.61$ Hz, 6H). ^{13}C NMR (75 MHz, Methanol- d_4) δ 175.56, 168.55, 140.18, 138.77, 128.96, 126.98, 45.64, 44.73, 40.58, 30.20, 21.41, 17.61.

Scheme 21: Synthesis of ZYSH03



[0174] The synthesis of **ZYSH03** followed the same protocol of **ZYSH01**. **ZYSH03** was obtained as a white solid (800 mg, 74%). ¹H NMR (300 MHz, Chloroform-*d*) δ 7.83 – 7.70 (m, 4H), 7.65 – 7.43 (m, 5H), 4.25 – 3.89 (m, 1H), 1.58 (dd, *J* = 19.6, 7.1 Hz, 3H).

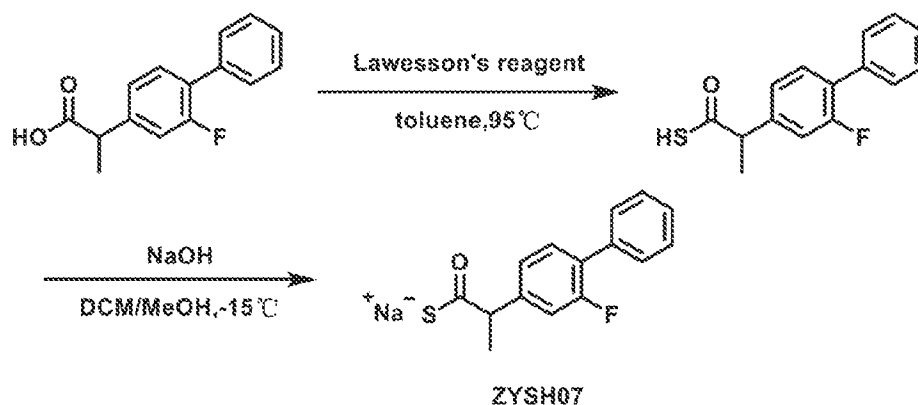
Scheme 22: Synthesis of ZYSH06



[0175] Telmisartan (500 mg, 0.99 mmol) was placed in a three-necked flask, vacuumed to replace N₂, and the compound was dissolved in dichloromethane (DCM). Oxalyl chloride (137 mg, 125 μL) was added dropwise under the condition of an ice bath, and a catalytic amount of dimethylformamide (DMF) was added dropwise. The mixture was stirred at room temperature for 1 hour, and then passed into the dry hydrogen sulfide gas. The crude product was purified by column chromatography and a yellow solid was obtained (300 mg, 57%).

ZYSH06. ¹H NMR (300 MHz, Methanol-*d*₄) δ 8.09 (s, 1H), 7.98 (d, *J* = 5.2 Hz, 1H), 7.89 (d, *J* = 9.4 Hz, 2H), 7.83 – 7.65 (m, 3H), 7.57 (d, *J* = 6.4 Hz, 1H), 7.46 (d, *J* = 6.8 Hz, 3H), 7.39 (d, *J* = 7.3 Hz, 3H), 5.92 (s, 2H), 4.04 (s, 3H), 2.86 (s, 3H), 1.95 (q, *J* = 7.6 Hz, 2H), 1.15 (t, *J* = 7.4 Hz, 3H).

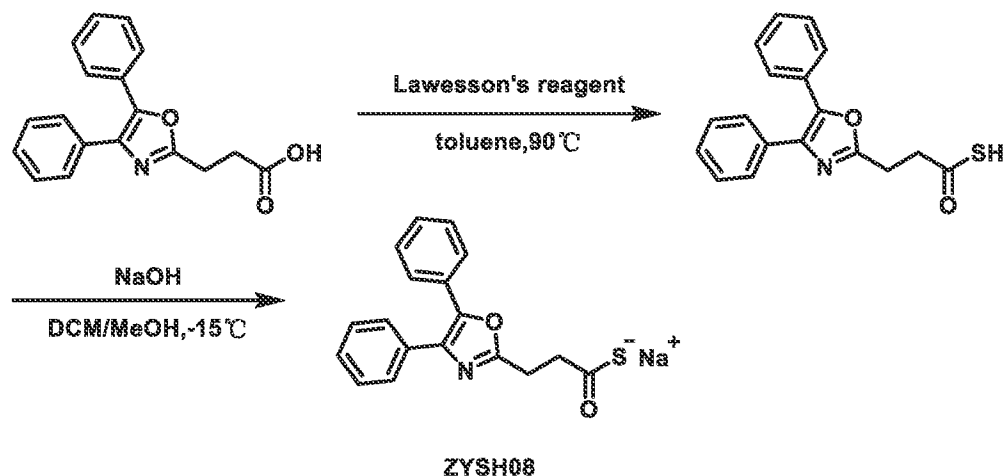
Scheme 23: Synthesis of ZYSH07



[0176] The synthesis of **ZYSH07** followed the same protocol of **ZYSA06** (except the reaction temperature was 95 °C). **ZYSH07** was obtained as a white solid (555mg, 49%).

ZYSH07. ^1H NMR (300 MHz, Methanol- d_4) δ 7.52 (dt, J = 8.2, 1.5 Hz, 2H), 7.46 – 7.31 (m, 4H), 7.29 – 7.19 (m, 2H), 4.24 (q, J = 7.1 Hz, 1H), 1.47 (d, J = 7.1 Hz, 3H). ^{13}C NMR (75MHz, Methanol- d_4) δ 222.80, 162.37, 159.12, 146.94, 137.30, 131.12, 129.90, 129.36, 128.39, 127.87, 127.69, 125.01, 115.80, 60.61, 20.26.

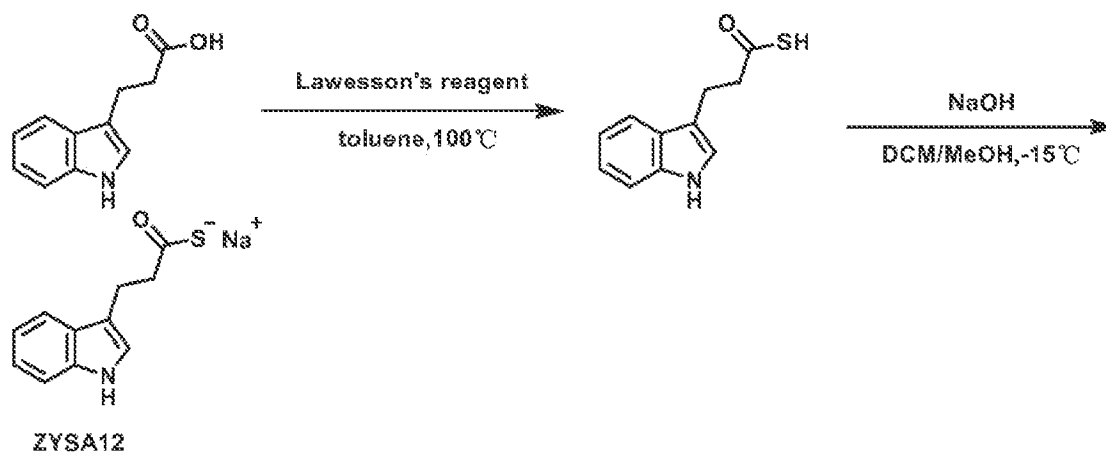
Scheme 24: Synthesis of ZYSH08



[0177] The synthesis of **ZYSH08** followed the same protocol of **ZYSA06** (except the reaction temperature was 90 °C). **ZYSH08** was obtained as a white solid (324mg, 34%).

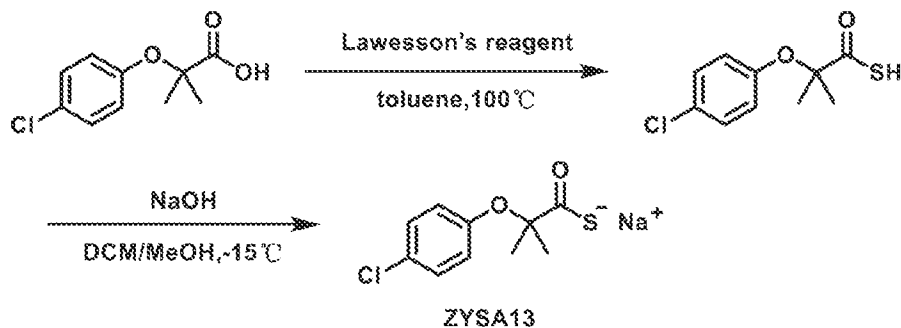
ZYSH08. ^1H NMR (300 MHz, Methanol- d_4) δ 7.45 (dddd, J = 56.6, 7.8, 4.8, 2.1 Hz, 10H), 3.18 (s, 4H). ^{13}C NMR (75MHz, Methanol- d_4) δ 218.16, 163.98, 145.30, 134.48, 132.18, 128.67, 128.39, 128.31, 128.01, 127.83, 126.12, 46.65, 25.42.

Scheme 25: Synthesis of ZYSA12



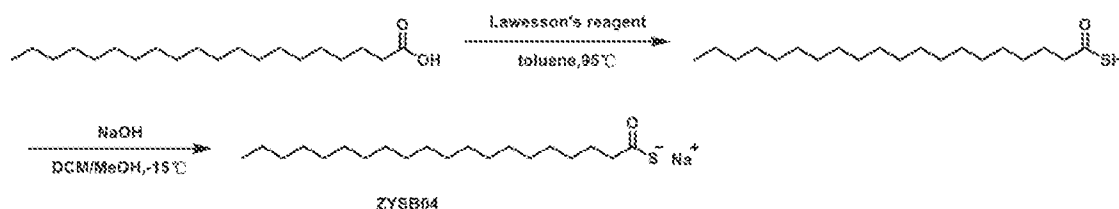
[0178] The synthesis of **ZYSA12** followed the same protocol of **ZYSA06** (except the reaction temperature was 100 °C). **ZYSA12** was obtained as a white solid (413mg, 45%). **ZYSA12**. ¹H NMR (300 MHz, Methanol-d₄) δ 7.57 (dt, J = 7.7, 1.0 Hz, 1H), 7.29 (dt, J = 8.1, 1.0 Hz, 1H), 7.08 – 6.93 (m, 3H), 3.11 – 2.96 (m, 4H). ¹³C NMR (75 MHz, Methanol-d₄) δ 223.45, 138.06, 128.74, 122.55, 122.03, 119.37, 119.23, 116.05, 111.99, 53.02, 24.54.

Scheme 26: Synthesis of ZYSA13



[0179] The synthesis of **ZYSA13** followed the same protocol of **ZYSA06** (except the reaction temperature was 100 °C). **ZYSA13** was obtained as a white solid (342mg, 65%). **ZYSA13**. ¹H NMR (300 MHz, Methanol-d₄) δ 7.12 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 1.61 (s, 6H). ¹³C NMR (75 MHz, Methanol-d₄) δ 223.38, 156.36, 129.37, 126.33, 121.40, 88.18, 27.92.

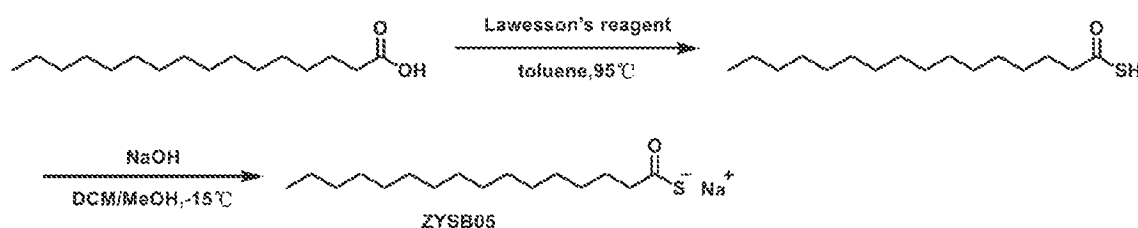
Scheme 27: Synthesis of ZYSB04



[0180] The synthesis of **ZYSB04** followed the same protocol of **ZYSA06** (except the reaction temperature was 95 °C). **ZYSB04** was obtained as a white solid (435mg, 76%).

ZYSB04. ^1H NMR (300 MHz, DMSO- d_6) δ 2.29 (t, J = 7.6 Hz, 2H), 1.43 (s, 2H), 1.23 (s, 32H), 0.85 (s, 3H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 217.09, 51.30, 31.41, 29.18, 28.85, 27.30, 22.19, 13.95.

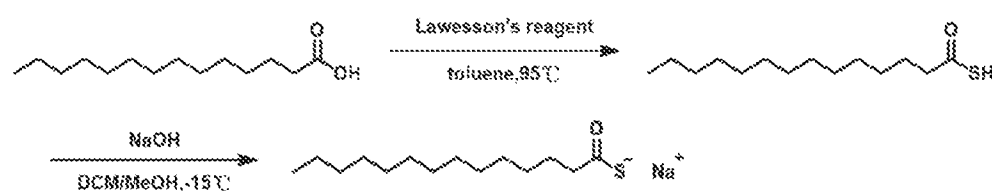
Scheme 28: Synthesis of ZYSB05



[0181] The synthesis of **ZYSB05** followed the same protocol of **ZYSA06** (except the reaction temperature was 95 °C). **ZYSB05** was obtained as a white solid (643mg, 54%).

ZYSB05. ^1H NMR (300 MHz, DMSO- d_6) δ 2.30 (t, J = 7.5 Hz, 2H), 1.48 – 1.39 (m, 2H), 1.23 (s, 24H), 0.89 – 0.81 (m, 3H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 216.68, 51.34, 31.35, 29.13, 28.97, 28.77, 27.26, 22.15, 13.98.

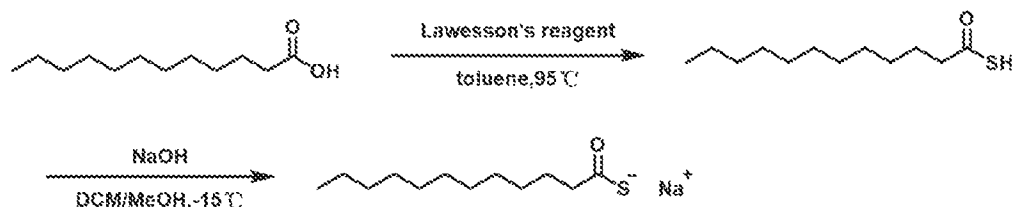
Scheme 29: Synthesis of ZYSB06



[0182] The synthesis of **ZYSB06** followed the same protocol of **ZYSA06** (except the reaction temperature was 95 °C). **ZYSB06** was obtained as a white solid (467mg, 62%).

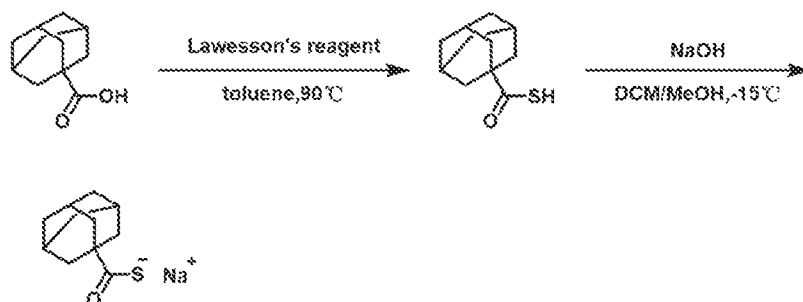
ZYSB06. ^1H NMR (300 MHz, Methanol- d_4) δ 2.64 – 2.58 (m, 2H), 1.63 (t, J = 7.4 Hz, 2H), 1.28 (s, 20H), 0.95 – 0.84 (m, 3H). ^{13}C NMR (75 MHz, Methanol- d_4) δ 224.09, 52.32, 33.09, 30.79, 30.50, 30.42, 29.00, 23.75, 14.48.

Scheme 30: Synthesis of ZYSB07



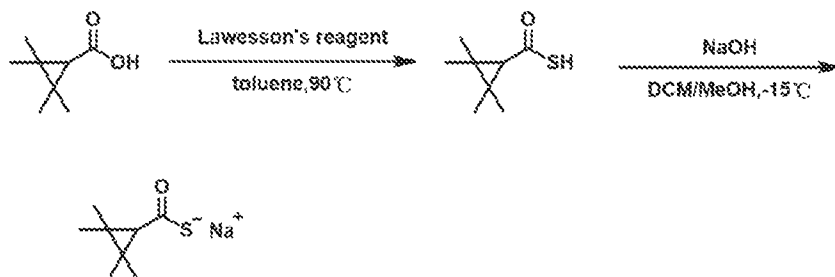
[0183] The synthesis of ZYSB07 followed the same protocol of ZYSA06 (except the reaction temperature was 95 °C). ZYSB07 was obtained as a white solid (342mg, 45%). ZYSB07. ^1H NMR (400 MHz, DMSO- d_6) δ 2.33 – 2.27 (m, 2H), 1.44 (p, J = 7.3 Hz, 2H), 1.23 (s, 16H), 0.87 – 0.83 (m, 3H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 51.26, 31.36, 29.15, 28.95, 28.78, 27.25, 22.15, 13.99.

Scheme 31: Synthesis of ZYSB08



[0184] The synthesis of ZYSB08 followed the same protocol of ZYSA06 (except the reaction temperature was 90 °C). ZYSB08 was obtained as a white solid (273mg, 31%). ZYSB08. ^1H NMR (300 MHz, Methanol- d_4) δ 1.99 – 1.92 (m, 9H), 1.71 (t, J = 2.9 Hz, 6H). ^{13}C NMR (75 MHz, Methanol- d_4) δ 229.92, 51.23, 42.43, 38.05, 30.40.

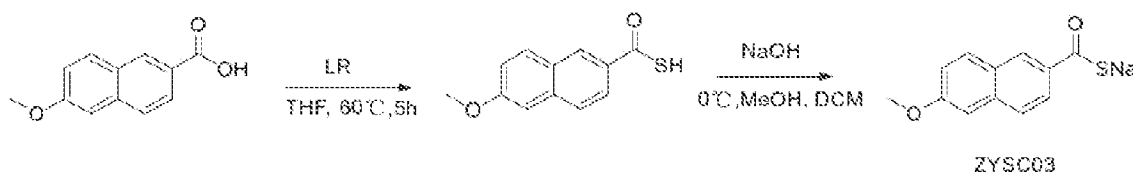
Scheme 31: Synthesis of ZYSB09



[0185] The synthesis of ZYSB09 followed the same protocol of ZYSA06 (except the reaction temperature was 90 °C). ZYSB09 was obtained as a white solid (144mg, 34%).

ZYSB09. ^1H NMR (300 MHz, Methanol- d_4) δ 2.17 (s, 1H), 1.17 (d, J = 14.5 Hz, 12H). ^{13}C NMR (75 MHz, Methanol- d_4) δ 218.04, 52.65, 32.03, 24.27, 17.13.

Scheme 32: Synthesis of ZYSC03



[0186] The synthesis of **ZYSC03** followed the same protocol of **ZYSA06** (except the reaction temperature was 60°C). **ZYSC03** was obtained as a white solid (76 mg, 65%).

ZYSC03. ^1H NMR (300 MHz, Methanol- d_4) δ 8.61 (s, 1H), 8.19 (dd, J = 8.6, 1.8 Hz, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.23 (d, J = 2.5 Hz, 1H), 7.12 (dd, J = 9.0, 2.5 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, Methanol- d_4) δ 214.25, 160.13, 140.92, 137.48, 131.78, 129.52, 129.24, 127.30, 126.54, 119.87, 106.47, 55.78.

Example 2: Biological Assay Data and Procedures

Determination of the half-life of released hydrogen sulfide

[0187] Detection of pig liver esterase (PLE) hydrolysis of ZYSA series thiocarboxylic acids and generation of corresponding carboxylic acids:

[0188] First, 4.5 mL of PBS buffer of pig liver esterase (PLE) (3 U/mL) was added to a 20 mL reaction vial. Then, 0.5 mL of PBS buffer (5 mM) of ZYSA was added and the mixture was co-incubated in a water bath at 37 °C. An equal amount of 200 μL of the solution was pipetted at each time point and transferred to a 1.5 mL centrifuge tube containing 200 μL of chromatography acetonitrile. The solution was transferred to a -20 °C refrigerator for rapid freezing and centrifuged for 10 minutes (13.0 x 1000 r/c). After quick freezing in a refrigerator at -20 °C, the solution was centrifuged for 10 minutes (13.0 x 1000 r/min) and the supernatant was aspirated for HPLC detection.

Determination of hydrogen sulfide release from ZYSA series thiocarboxylic acids by methylene blue method

[0189] Compounds of the ZYSA series, as described above, were dissolved in 5 mL of PBS buffer solution (reaching a final concentration 500 μM) at pH=7.4 and then co-incubated with 3 U/mL PLE. An equal amount of 200 μL of the solution was aspirated at each time point and transferred to a 1.5 mL centrifuge tube containing 200 μL of zinc acetate (1%, w/v). The tube

was then centrifuged for 10 minutes (13.0 x 1000 r/min). The supernatant was removed, and the precipitate was washed with PBS (100 μ L x 2). Following, 600 μ L of N,N-dimethyl-1,4-phenylenediamine sulfate (0.2% w/v dissolved in 20% H₂SO₄ solution) and 50 μ L of ferric chloride (10% w/v dissolved in 0.2% H₂SO₄ solution) were added to the centrifuge tube. After transferring to a metal bath at 37 °C for 30 minutes of incubation, an absorbance at 740 nm was detected by UV absorption spectrophotometer. The concentration of hydrogen sulfide was calculated from the standard curve of sodium hydrosulfide.

[0190] With the methylene blue method, the compounds showed a release hydrogen sulfide at a certain rate under esterase conditions, with the release $t_{1/2}$ shown in **Table 1**.

Table 1. Structure and nomenclature of thiocarboxylic acids and their half-lives for the release of hydrogen sulfide.

Compound Number	ZYSA01	ZYSA02	ZYSA03
$t_{1/2}$	150 $\pm$ 15 min	32.7 $\pm$ 1.7 min	7.1 $\pm$ 0.1 min
Peak time of H ₂ S (min)	60 min	38 $\pm$ 6 min	20 $\pm$ 9 min
Peak concentration of H ₂ S (μ M)	67 $\pm$ 4 μ M	113 $\pm$ 2 μ M	124 $\pm$ 2 μ M
Compound Number	ZYSA04	ZYSA05	ZYSA06
$t_{1/2}$	27.5 $\pm$ 0.7 min	22.5 $\pm$ 3.5 min	26.5 $\pm$ 0.3 min
Peak time of H ₂ S (min)	60 min	60 min	65 $\pm$ 23 min
Peak concentration of H ₂ S (μ M)	105 $\pm$ 2 μ M	100 $\pm$ 1 μ M	103 $\pm$ 2 μ M
Compound Number	ZYSA07	ZYSA08	ZYSB01
$t_{1/2}$	5.8 $\pm$ 0.6 min	16.2 $\pm$ 3.2 min	1525 $\pm$ 61 min
Peak time of H ₂ S (min)	40 $\pm$ 17 min	45 $\pm$ 15min	330 min

Peak concentration of H ₂ S (μM)	129±2 μM	120±3 μM	32±1 μM
Compound Number	ZYSB02	ZYSB03	ZYSC01
t _{1/2}	1619±21 min		29.6±1.1 min
Peak time of H ₂ S (min)	110±191 min	70±46 min	45 min
Peak concentration of H ₂ S (μM)	21±2 μM	142±3 μM	104±8 μM
Compound Number	ZYSC02	ZYSH21	ZYSH31
t _{1/2}	26.6±0.3 min	47.9±5.8 min	208.4±2.1 min
Peak time of H ₂ S (min)	38±6 min	90 min	180 min
Peak concentration of H ₂ S (μM)	92±6 μM	62±9 μM	34±5 μM
Compound Number	ZYSH01	ZYSH02	ZYSH03
t _{1/2}	112 min	242 min	468 min
Peak time of H ₂ S (min)	110 min	90 min	120 min
Peak concentration of H ₂ S (μM)	90±0 μM	29 μM	25 μM
Compound Number	ZYSH04	ZYSH05	ZYSH06
t _{1/2}	238±9 min	2518±62 min	67.9±0.2 min
Peak time of H ₂ S (min)	155±35 min	120 min	40±23 min
Peak concentration of H ₂ S (μM)	43±1 μM	11±1 μM	9±0 μM

Example 3: Efficacy data of compound ZYSA01 as prepared in Example 1*Determination of infarct area*

[0191] Mouse brains were frozen at -20 °C for 20 minutes and cut into 5 pieces, each 1 mm thick. Each section was immediately stained with 1% 2,3,5-triphenyltetrazolium chloride (TTC) solution for 30 minutes at 37 °C and fixed in 4% paraformaldehyde (PFA) solution. Infarcted areas were unstained and normal areas were stained red (FIG. 1A). Each pair of sections was photographed and the infarct area was calculated by ImageJ. The formula was as follows:

$$\text{Infarct volume} = \text{Sum of Infarct Area/Total Area}$$

See FIG. 1B. Not intending to be bound by theory, ZYSA01 was significantly better than benzoic acid. The experimental results show that ZYSA01 can significantly reduce the infarct size compared with benzoic acid in cerebral ischemia and other diseases, showing a good therapeutic effect.

Determination of serum LDH level and brain tissue LDA level

[0192] After blood collection, serum was collected by centrifugation at 3000 g for 10 minutes at 4 °C. The method of lactate dehydrogenase (LDH) determination was described in the instruction manual of Lactate Dehydrogenase (LDH) Activity Assay Kit (Solarbio, Beijing, China, NO. BC0685). Brain tissues were taken to determine the malondialdehyde (MDA) level, and the method of measurement was described in the instruction manual of Malondialdehyde (MDA) Content Assay Kit used (Solarbio, Beijing, NO. BC0025) Not intending to be bound by theory, the LDH level reflects the damage of cell membranes caused by ischemia-reperfusion injury, and the MDA level reflects the peroxidation of membrane lipids caused by ischemia-reperfusion injury. It was found that ZYSB21 showed a greater potential in the middle cerebral artery occlusion (MCAO) model, **p<0.01 as shown in FIG. 1C, FIG. 1D.

Example 4: Activity data for Compound ZYSH06 (Telmisartan)*Verification of cerebral infarct activity*

[0193] Mouse model of middle cerebral artery occlusion 25-30 g C57/6J mice were randomly divided. Telmisartan was used as the control group. For the drug administration group, the drug was administered at a dose of 0.5×10^{-4} mol/kg. The rest of the groups were administered the middle cerebral artery occlusion model. Anesthesia was induced with 3%

isoflurane and maintained with 0.6% isoflurane after anesthesia. After sterilization, a median incision was made in the neck. Blunt dissection was performed to expose the left common carotid artery (CCA), internal carotid artery (ICA), and external carotid artery (ECA). The proximal end of the CCA was separated from the distal end of the ECA and ligated. The CCA was ligated distally, and a suture (Beijing Sinon Biotechnology Co., Ltd., Beijing, China) was inserted and passed through the ICA until the cerebral artery (MCA) was occluded in the middle. Drugs were administered by gavage at the time of infarction, and 1 hour and 20 minutes after infarction, the suture was removed and was reperfed. Other treatments were applied as described above. After 24 hours, blood was collected, mice were executed by cervical dislocation, craniotomy was performed, and brain tissue was collected for subsequent experiments.

Infarct area

[0194] Mouse brains were frozen at -20 °C for 20 minutes and sliced into 5 pieces, each 1 mm thick. Each section was immediately stained with 1% 2,3,5-triphenyltetrazolium chloride (TTC) solution for 30 minutes at 37 °C and fixed in 4% paraformaldehyde (PFA) solution. Infarcted areas were unstained and normal areas were stained red. Each pair of sections was then photographed, and the infarct area was calculated by ImageJ. The formula was as follows:

$$\text{Infarct Volume} = \text{Sum of Infarct Area/Total Area.}$$

Not intending to be bound by theory, results of the study showed that both the positive drug and the prodrug could significantly reduce the infarct area and showed a dose-dependent effect where ZYSA06 was significantly more potent than the positive drug, in which ZYSA06 showed greater superiority in reducing the infarct area compared to Telmisartan, as shown in FIG. 2A and FIG 2B.

Serum lactate dehydrogenase (LDH) level and brain tissue MDA level

[0195] After blood collection, serum was centrifuged at 3000 g for 10 minutes at 4 °C. The method of LDH determination was described in the instruction manual of Lacate Dehydrogenase(LDH) Activity Assay Kit (Solarbio, Beijing, China, NO. BC0685). Brain tissue was taken to determine the malondialdehyde (MDA) level in the tissue, and the method of measurement was described in the instruction manual of Malondialdehyde(MDA) Content Assay Kit used (Solarbio, Beijing, NO. BC0025). Not intending to be bound by theory, the

LDH level reflects the damage of cell membrane caused by ischemia-reperfusion injury, and the MDA level reflects the peroxidation of membrane lipids caused by ischemia-reperfusion injury. It was found that the ZYSA06 MCAO model (or the middle cerebral artery occlusion model) showed a greater potential for 0.5×10^{-4} mol/kg. ZYSA09 was able to significantly reduce MDA levels compared to the telmisartan group showing a significant difference $*p < 0.05$ as shown in FIG. 2C and FIG. 2D.

Example 4: Activity Data for Compound ZYSH21

ZYSH21 in vivo release of prodrug diclofecan (DCF) in rats

[0196] Five rats were fasted and watered freely for 10 hours (h) prior to drug administration by giving 10.50 mg/kg of ZYSH21 solution. Blood samples were collected at 0 h and 0.033, 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 6 and 8 h after administration, respectively. A 5 μ L aliquot of IS solution (1000 ng/ml naproxen) was added to a 50 μ L plasma sample in a centrifuge tube, vortexed and mixed for 10 seconds, and then 200 μ L of methanol (MeOH) was added to the mixture to precipitate proteins. The samples were vortex mixed for 1 minute and centrifuged at 12000 rpm for 5 minutes at 4 °C. Finally, the supernatant was characterized by triple quadrupole liquid mass spectrometer (FIG. 3).

Anti-inflammatory effect of ZYSH21

[0197] Wistar rats were divided into two groups of 8 rats each: 1) ZYSH21 (10 mg/kg/day) and 2) 2'-deoxycoformycin (DCF; 10 mg/kg/day). Separately, immune-grade natural type II collagen (CII) was dissolved in 0.05 mol/L acetic acid to prepare a 2 mg/mL solution. Emulsions were then prepared by homogenizing the type II collagen with Fuchs' incomplete adjuvant (1:1) at 4 °C, resulting in a final CII concentration of 1 mg/mL. The emulsion was fully emulsified in an ice bath with a homogenizer to the extent that it did not spread when added to a drop of water. Then the emulsified mixture was injected subcutaneously into the caudal root at a rate of 200 μ g of CII per animal per 0.2 mL per animal for 7 days, and then the emulsified mixture was injected subcutaneously into the dorsal region at a rate of 100 μ g of CII per animal per 0.1 mL for 7 days. Starting from the 16th day, the respective drugs were administered via gavage for 28 consecutive days. The changes in paw swelling rates were recorded throughout this time period. Compared with the normal group: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$. (FIG. 4).

ZYSH21 gastric safety

[0198] Wistar rats were divided into ZYSH21 (10 mg/kg/day, 5 mg/kg/day) and DCF (10 mg/kg/day, 5 mg/kg/day) groups with 8 rats in each. The drug/prodrug was administered for 28 consecutive days, and the percentage of ulcerated area was examined. It was found that the ulcerated area was extremely low in ZYSH21 (10 mg/kg/day, 5 mg/kg/day) treated group, while DCF (10 mg/kg/day, 5 mg/kg/day) had significant ulcerated spots (FIG. 5).

ZYSH21 acute liver injury

[0199] C57BL/6JNifdc mice were fasted for 10 h before drug administration, and water was freely available. The mice were randomly divided into three groups: saline control group, DCF group, and ZYSH21 group, with DCF administered at a dose of 150 mg/kg and ZYSH21 administered isomorphically, 6 mice in each group. ZYSH21 was administered by intraperitoneal injection for 24 h. Blood was collected from the eyeballs at 24 hours and the mice were sacrificed by spinal dislocation method. Serum levels of aspartate transaminase (AST) and alanine transaminase (ALT) were determined (FIG. 6A and FIG. 6B, respectively).

ZYSH21 renal injury

[0200] Wistar rats were divided into two groups of 8 rats each: 1) ZYSH21 (10 mg/kg/day) and 2) DCF (10 mg/kg/day). The drug/prodrug were administered for 28 consecutive days. The level of uric acid (UA), an indicator of renal impairment, was significantly decreased, and maintained within the normal level (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$) (FIG. 7).

Example 5: Activity Data for Compound ZYSH31*Release of prodrug NPX from ZYSH31 in rats*

[0201] Five rats were fasted for 10 hours before drug administration by giving 10.60 mg/kg ZYSH31 solution. Blood samples were collected at 0 h, 0.033, 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 6, and 8 h after drug administration, respectively. A 5 μ L aliquot of IS solution (1000 ng/ml diclofenac) was added to a 50 μ L plasma sample in a centrifuge tube, vortexed and mixed for 10 seconds, and then 200 μ L of methanol (MeOH) was added to the mixture to precipitate proteins. The samples were vortex mixed for 1 minute and centrifuged at 12000 r-min⁻¹ for 5 minutes at 4 °C, and finally the supernatant was analyzed using a triple quadrupole quadrupole liquid mass spectrometer (FIG. 8).

Anti-inflammatory effect of ZYSH31

[0202] Wistar rats were divided into two groups of 6 rats each: ZYSH31 (10 mg/kg/day), NPX (10 mg/kg/day). Separately, immune-grade natural type II collagen (CII) was dissolved in 0.05 mol/l acetic acid to make a 2 mg/ml solution, and emulsions were prepared by homogenizing the type II collagen with Fuchs' incomplete adjuvant (1:1) at 4 °C. The final concentration of CII was 1 mg/ml. The emulsion was fully emulsified with a homogenizer in an ice bath to the extent that it did not diffuse when added to a drop of water. Then the emulsified mixture was injected subcutaneously into the caudal root at a rate of 200 µg of CII per animal per 0.2 ml per animal for 7 days. Changes in the degree of paw swelling were recorded. Paw swelling rate was assessed from day 0 to day 36. Compared with the normal group: *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. (FIG. 9).

Stomach safety of ZYSH31

[0203] Wistar rats were divided into ZYSH31 (10 mg/kg/day, 5 mg/kg/day) and NPX (10 mg/kg/day, 5 mg/kg/day) groups with 6 rats in each. Drug administration was conducted for 28 consecutive days, in which the percentage of ulcerated area was extremely low in ZYSH31 (10 mg/kg/day, 5 mg/kg/day), whereas NPX (10 mg/kg/day, 5 mg/kg/day) had significant ulcerated spots (FIG. 10).

ZYSH31 Acute Liver Injury

[0204] C57BL/6JNifdc mice were fasted for 10 hours before administration of ZYSH31. Water was freely available. The mice were randomly divided into 3 groups, saline control group, NPX group, and ZYSH31 group. NPX was administered at a dose of 150 mg/kg, and ZYSH31 was administered isomorphically with 6 mice in each group. Twenty-four hours after intraperitoneal injection of giving ZYSH31, the serum and related samples were collected. The serum levels of alanine aminotransferase (AST) and alanine aminotransferase (ALT) were determined (FIG. 11A and 11B, respectively).

ZYSH31 renal injury

[0205] Wistar rats were divided into two groups of 6 rats each (ZYSH31 (10 mg/kg/day) and NPX (10 mg/kg/day)) for continuous drug administration for 28 days. Not intending to be bound by theory, results suggest that NPX albumin levels were significantly reduced as compared to the control group after treatment, and the pointer kidney function was damaged.

However, for ZYSH31 administration, there was no obvious difference compared with control group. (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$) (FIG. 12).

Example 6: Stabilization of compounds

[0206] ZYSA01-06, ZYSA12-ZYSA13, ZYSB01-03, ZYSC01-02, ZYSH01-ZYSH05, ZYSH31, and ZYSH21 were dissolved into a PBS solution to a final concentration of 500 μM . These samples were kept at room temperature under ambient conditions to observe their stability. ZYSA01-6 was monitored by HPLC, ZYSA12-ZYSA13, ZYSB02-03, ZYSC01-02, ZYSH01-ZYSH05, ZYSH31, ZYSH21, ZYSB01 by HPLC, and ZYSB01 by UV. Not intending to be bound by theory, the results suggest that ZYSA01-06, ZYSA12-ZYSA13, ZYSB01-03, ZYSC01-02, ZYSH01-ZYSH05, ZYSH31, ZYSH21 all have good stability with no significant decomposition was observed at the 144-h point.

Compound Number	ZYSA01	ZYSA02	ZYSA03
t _{1/2}	150 $\pm$ 15 min	32.7 $\pm$ 1.7 min	7.1 $\pm$ 0.1 min
Peak time of H ₂ S (min)	60 min	38 $\pm$ 6 min	20 $\pm$ 9 min
Peak concentration of H ₂ S (μM)	67 $\pm$ 4 μM	113 $\pm$ 2 μM	124 $\pm$ 2 μM
Compound Number	ZYSA04	ZYSA05	ZYSA06
t _{1/2}	27.5 $\pm$ 0.7 min	22.5 $\pm$ 3.5 min	26.5 $\pm$ 0.3 min
Peak time of H ₂ S (min)	60 min	60 min	65 $\pm$ 23 min
Peak concentration of H ₂ S (μM)	105 $\pm$ 2 μM	100 $\pm$ 1 μM	103 $\pm$ 2 μM
Compound Number	ZYSA07	ZYSA08	ZYSB01
t _{1/2}	5.8 $\pm$ 0.6 min	16.2 $\pm$ 3.2 min	1525 $\pm$ 61 min
Peak time of H ₂ S (min)	40 $\pm$ 17 min	45 $\pm$ 15min	330 min

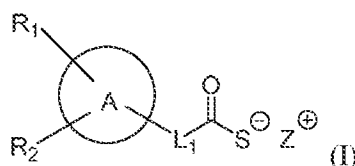
Peak concentration of H ₂ S (μM)	129±2 μM	120±3 μM	32±1 μM
Compound Number	ZYSB02	ZYSB03	ZYSC01
t _{1/2}	1619±21 min		29.6±1.1 min
Peak time of H ₂ S (min)	110±191 min	70±46 min	45 min
Peak concentration of H ₂ S (μM)	21±2 μM	142±3 μM	104±8 μM
Compound Number	ZYSC02	ZYSH21	ZYSH31
t _{1/2}	26.6±0.3 min	47.9±5.8 min	208.4±2.1 min
Peak time of H ₂ S (min)	38±6 min	90 min	180 min
Peak concentration of H ₂ S (μM)	92±6 μM	62±9 μM	34±5 μM
Compound Number	ZYSH01	ZYSH02	ZYSH03
t _{1/2}	112 min	242 min	468 min
Peak time of H ₂ S (min)	110 min	90 min	120 min
Peak concentration of H ₂ S (μM)	90±0 μM	29 μM	25 μM
Compound Number	ZYSH04	ZYSH05	ZYSH06
t _{1/2}	238±9 min	2518±62 min	67.9±0.2 min
Peak time of H ₂ S (min)	155±35 min	120 min	40±23 min
(min)			

Peak concentration of H ₂ S (μM)	43±1 μM	11±1 μM	9±0 μM
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EXEMPLARY EMBODIMENTS

[0207] Exemplary embodiments provided in accordance with the presently disclosed subject matter include, but are not limited to, the claims and the following embodiments:

[0208] Embodiment 1: A compound of Formula I:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Z⁺ is Na⁺, K⁺, or H⁺;

A is substituted or unsubstituted C₆-C₂₀ aryl or substituted or unsubstituted C₃-C₂₀ heteroaryl;

L₁ is a bond, -(CH₂)_n-, C₂-C₆ branched alkyl, -O-(CH₂)_n-C(CH₃)₂-, -R₅C(=O)NHR₆-, -O-(CH₂)_n-, or -O-(CH₂)_n-O-;

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

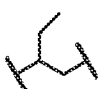
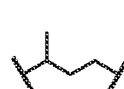
each R₁ and R₂ are independently hydrogen, halogen, -CN, -NO₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₂NR₃R₄-, C₆-C₁₀ aryl, or C₃-C₁₀ heteroaryl, wherein each R₃, R₄, R₅, and R₆ are independently hydrogen or C₁-C₆ alkyl.

[0209] Embodiment 2: The compound of embodiment 1, wherein A is substituted or unsubstituted C₆-C₁₀ aryl or substituted or unsubstituted C₃-C₁₀ heteroaryl.

[0210] Embodiment 3: The compound of embodiment 1 or embodiment 2, wherein A is phenyl, naphthyl, anthracenyl, oxazolyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, thiazolyl, pyrazolyl, pyrimidyl, quinolyl, isoquinolyl, purinyl, acridyl, carbazolyl, cinnolyl, quinazolinyl, indolyl, benzyltriazolyl, benzothiophenyl, benzo(f)uranyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, tetrazolyl, trizinyl, or carbazolyl.

[0211] Embodiment 4: The compound of any one of embodiments 1 to 3, wherein L₁ is a bond, -(CH₂)_n-, C₂-C₆ branched alkyl, -O-(CH₂)_n-C(CH₃)₂-, or -R₅C(=O)NHR₆-,

[0212] Embodiment 5: The compound of any one of embodiments 1 to 4, wherein:

L_1 is a bond, $-(CH_2)_n-$, $-\text{CH}(\text{CH}_3)-$, , , , $-\text{O}-(CH_2)_n-\text{C}(\text{CH}_3)_2-$, or $-\text{R}_5\text{C}(=\text{O})\text{NHR}_6-$.

[0213] Embodiment 6: The compound of any one of embodiments 1 to 4, wherein n is 0, 1, 2, 3, or 4.

[0214] Embodiment 7: The compound of any one of embodiments 1 to 6, wherein R_1 is hydrogen, halogen, $-\text{CN}$, $-\text{NO}_2$, C_1 - C_6 alkyl, C_6 - C_{10} aryl, or C_3 - C_{10} heteroaryl.

[0215] Embodiment 8: The compound of any one of embodiments 1 to 7, wherein R_1 is hydrogen, halogen, $-\text{CN}$, $-\text{NO}_2$, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, phenyl, naphthyl, anthracenyl, oxazolyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, or thiazolyl.

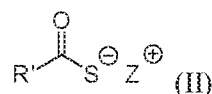
[0216] Embodiment 9: The compound of any one of embodiments 1 to 8, wherein R_2 is hydrogen, halogen, $-\text{CN}$, $-\text{NO}_2$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-\text{SO}_2\text{NR}_3\text{R}_4-$, C_6 - C_{10} aryl, or C_3 - C_{10} heteroaryl.

[0217] Embodiment 10: The compound of any one of embodiments 1 to 9, wherein R_2 is hydrogen, halogen, $-\text{CN}$, $-\text{NO}_2$, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, methoxy, ethoxy, propoxy, propoxyl, butoxy, cyclopropoxy, cyclobutoxy, $-\text{CH}_2\text{Cl}$, $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CCl}_3$, $-\text{SO}_2\text{NR}_3\text{R}_4-$, phenyl, naphthyl, anthracenyl, oxazolyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, or thiazolyl.

[0218] Embodiment 11: The compound of any one of embodiments 1 to 10, wherein each R_3 , R_4 , R_5 , R_6 are each independently C_1 - C_6 alkyl.

[0219] Embodiment 12: The compound of any one of embodiments 1 to 11, wherein each R_3 , R_4 , R_5 , R_6 are each independently methyl, ethyl, propyl, isopropyl, butyl, or tert-butyl.

[0220] Embodiment 13: A compound of Formula II:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

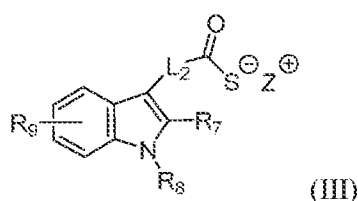
Z^+ is Na^+ , K^+ , or H^+ ; and

R' is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted bridged cycloalkyl, or substituted or unsubstituted spirocycloalkyl.

[0221] Embodiment 14: The compound of embodiment 13, wherein each R' has at least one substituent and wherein the at least one substituent is selected from the group consisting of halogen, -OH, -CN, -NO₂, and C₁-C₆ alkyl.

[0222] Embodiment 15: The compound of embodiment 13 or embodiment 14, wherein R' is substituted or unsubstituted C₂-C₆ branched alkyl, substituted or unsubstituted C₁-C₂₀ straight chain alkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, or substituted or unsubstituted C₈-C₁₆ bridged cycloalkyl.

[0223] Embodiment 16: A compound of Formula III:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Z⁺ is Na⁺, K⁺, or H⁺;

L₂ is a bond, -(CH₂)_n-, or C₂-C₆ branched alkyl;

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

R₇ is hydrogen or C₁-C₆ alkyl;

R₈ is hydrogen, -C(=O)-R₁₀, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, or C₁-C₆ haloalkoxy, wherein R₁₀ is substituted or unsubstituted C₆-C₁₀ aryl or substituted or unsubstituted C₃-C₁₀ heteroaryl, wherein when substituted by a substituent, the substituent is selected from the group consisting of halogen, -OH, -CN, -NO₂, C₁-C₄ alkyl, C₁-C₄ alkoxy, and C₁-C₄ haloalkyl; and

R₉ is hydrogen, halogen, -CN, -NO₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, or C₁-C₆ haloalkoxy.

[0224] Embodiment 17: The compound of embodiment 16, wherein:

L₂ is -(CH₂)_n-; and

n is 0, 1, 2 or 3.

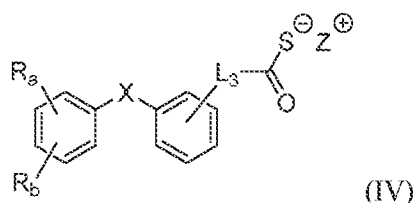
[0225] Embodiment 18: The compound of embodiment 16 or embodiment 17, wherein R₇ is hydrogen or C₁-C₄ alkyl.

[0226] Embodiment 19: The compound of any one of embodiments 16 to 18, wherein R₇ is methyl, ethyl, propyl, isopropyl, butyl, or tert-butyl.

[0227] Embodiment 20: The compound of any one of embodiments 16 to 19, wherein R_8 is hydrogen or $-C(=O)-R_{10}$, wherein R_{10} is substituted or unsubstituted phenyl, substituted or unsubstituted naphthalenyl, substituted or unsubstituted anthracenyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted furyl, substituted or unsubstituted thiophenyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted quinolyl, and wherein when substituted by a substituent, the substituent is selected from the group consisting of halogen, $-OH$, $-CN$, $-NO_2$, methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[0228] Embodiment 21: The compound of any one of embodiments 16 to 20, wherein R_9 is hydrogen, halogen, $-CN$, $-NO_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkyl.

[0229] Embodiment 22: A compound of Formula IV:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Z^+ is Na^+ , K^+ , or H^+ ;

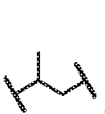
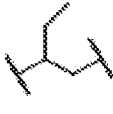
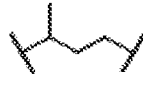
L_3 is a bond, $-(CH_2)_n-$, or C_2-C_6 branched alkyl;

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

X is $-NH-$ or $-C(=O)-$;

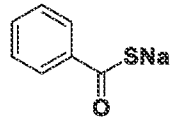
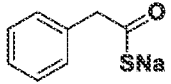
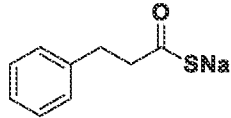
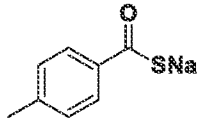
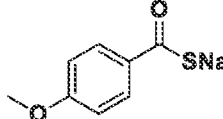
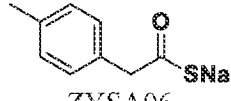
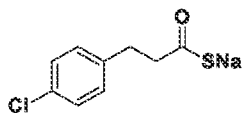
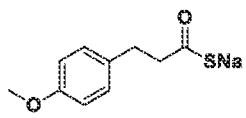
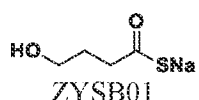
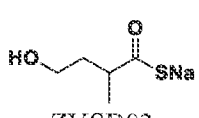
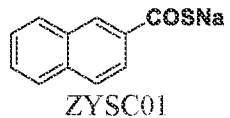
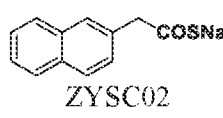
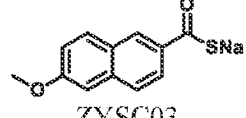
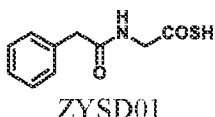
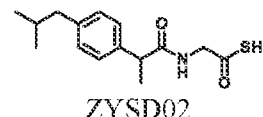
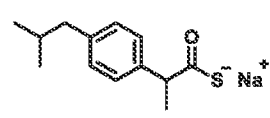
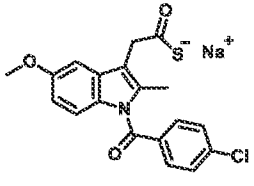
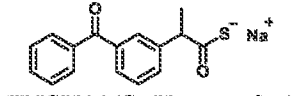
each R_a and R_b are independently hydrogen, halogen, $-CN$, $-NO_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, or C_1-C_6 haloalkoxy.

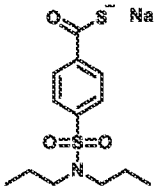
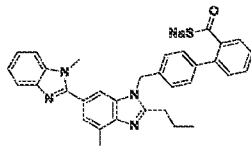
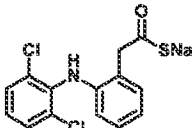
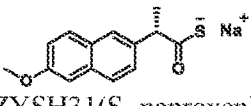
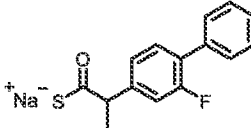
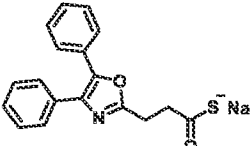
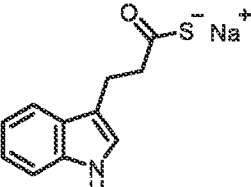
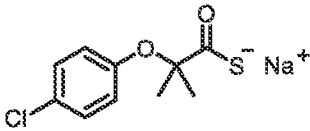
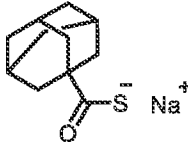
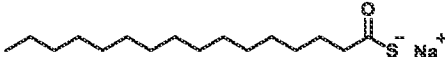
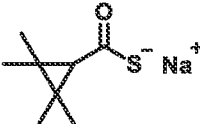
[0230] Embodiment 23: The compound of claim 22, wherein:

L_3 is a bond, $-(CH_2)_n-$, $-CH(CH_3)-$, , , or ; and n is 0, 1, 2 or 3.

[0231] Embodiment 24: The compound of embodiment 22 or embodiment 23, wherein each R_a and R_b are each independently hydrogen, halogen, $-CN$, $-NO_2$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy.

[0232] Embodiment 25: A compound selected from the group consisting of:

 ZYSA01	 ZYSA02	 ZYSA03
 ZYSA04	 ZYSA05	 ZYSA06
 ZYSA07	 ZYSA08	 ZYSB01
 ZYSB02	ZYSB03	
 ZYSC01	 ZYSC02	 ZYSC03
 ZYSD01	 ZYSD02	
 ZYSH01(S- bupropfen)	 ZYSH02(S- indomethacin)	 ZYSH03(S- Ketoprofen)

 ZYSH04(S- Gemfibrozil)	 ZYSH05(S- Probenecid)	 ZYSH06(S- telmisartan)
 ZYSH21(S- diclofenac)	 ZYSH31(S- naproxen)	 ZYSH07 (Flurbiprofen)
 ZYSH08 (Oxaprozin)	 ZYSA12 (3-indolepropionic acid)	 ZYSA13
 ZYSB04		 ZYSB08
 ZYSB07	 ZYSB06	
 ZYSB05	 ZYSB09	

and a pharmaceutically acceptable salt or prodrug thereof.

[0233] Embodiment 26: A pharmaceutical composition comprising a compound of any one of claims 1 to 25 and a pharmaceutically acceptable carrier.

[0234] Embodiment 27: A kit comprising a compound of any one of embodiments 1 to 25 or a pharmaceutical composition of embodiment 26.

[0235] Embodiment 28: A method of treating or preventing a cerebrovascular disease, an anti-inflammatory condition, rheumatic or rheumatoid arthritis, gout, high blood pressure, a high blood lipids condition, or liver toxicity in a subject, comprising administering to the subject an effective amount of a compound of any one of embodiments 1 to 25, or a pharmaceutical composition of embodiment 26.

[0236] Embodiment 29: The method of embodiment 28, wherein the compound is an antipyretic or an analgesic compound.

[0237] Embodiment 30: The method of embodiment 28 or embodiment 29, wherein the compound reduces liver toxicity on GSH depletion or mitochondrial damage

[0238] Embodiment 31: A compound comprising a thiocarboxylic acid moiety, wherein the compound releases hydrogen sulfide under enzyme-catalyzed conditions.

[0239] Embodiment 32: The compound of embodiment 31, wherein the compound is a thiolated sartan compound.

[0240] Embodiment 33: The compound of embodiment 32, wherein the thiolated sartan compound is thiolated valsartan, thiolated eplosartan, or thiolated timosartan.

[0241] All references throughout this application, for example patent documents, including issued or granted patents or equivalents and patent application publications, and non-patent literature documents or other source material are hereby incorporated by reference herein in their entireties, as though individually incorporated by reference.

[0242] All patents and publications mentioned in the specification are indicative of the levels of skill of those skilled in the art to which the invention pertains. References cited herein are incorporated by reference herein in their entirety to indicate the state of the art, in some cases as of their filing date, and it is intended that this information can be employed herein, if needed, to exclude (for example, to disclaim) specific embodiments that are in the prior art.

[0243] When a group of substituents is disclosed herein, it is understood that all individual members of those groups and all subgroups and classes that can be formed using the substituents are disclosed separately. When a Markush group or other grouping is used

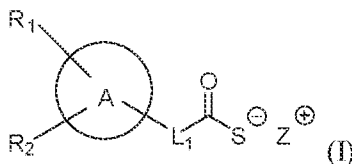
herein, all individual members of the group and all combinations and sub-combinations possible of the group are intended to be individually included in the disclosure. As used herein, “and/or” means that one, all, or any combination of items in a list separated by “and/or” are included in the list; for example, “1, 2 and/or 3” is equivalent to “1, 2, 3, 1 and 2, 1 and 3, 2 and 3, or 1, 2 and 3”.

[0244] Every formulation or combination of components described or exemplified can be used to practice the invention, unless otherwise stated. Specific names of materials are intended to be exemplary, as it is known that one of ordinary skill in the art can name the same material differently. It will be appreciated that methods, device elements, starting materials, and synthetic methods other than those specifically exemplified can be employed in the practice of the invention without resort to undue experimentation. All art-known functional equivalents, of any such methods, device elements, starting materials, and synthetic methods are intended to be included in this invention. Whenever a range is given in the specification, for example, a temperature range, a time range, or a composition range, all intermediate ranges and subranges, as well as all individual values included in the ranges given are intended to be included in the disclosure.

[0245] The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by examples, embodiments, and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Z^+ is Na^+ , K^+ , or H^+ ;

A is substituted or unsubstituted C_6 - C_{20} aryl or substituted or unsubstituted C_3 - C_{20} heteroaryl;

L_1 is a bond, $-(CH_2)_n-$, C_2 - C_6 branched alkyl, $-O-(CH_2)_n-C(CH_3)_2-$, $-R_5C(=O)NHR_6-$, $-O-(CH_2)_n-$, or $-O-(CH_2)_n-O-$;

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

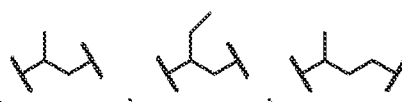
each R_1 and R_2 are independently hydrogen, halogen, $-CN$, $-NO_2$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-SO_2NR_3R_4-$, C_6 - C_{10} aryl, or C_3 - C_{10} heteroaryl, wherein each R_3 , R_4 , R_5 , and R_6 are independently hydrogen or C_1 - C_6 alkyl.

2. The compound of claim 1, wherein A is substituted or unsubstituted C_6 - C_{10} aryl or substituted or unsubstituted C_3 - C_{10} heteroaryl.

3. The compound of claim 1 or claim 2, wherein A is phenyl, naphthyl, anthracenyl, oxazolyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, thiazolyl, pyrazolyl, pyrimidyl, quinolyl, isoquinolyl, purinyl, acridyl, carbazolyl, cinnolyl, quinazolinyl, indolyl, benzyltriazolyl, benzothiophenyl, benzo(f)uranyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, tetrazolyl, trizinyl, or carbazolyl.

4. The compound of any one of claims 1 to 3, wherein L_1 is a bond, $-(CH_2)_n-$, C_2 - C_6 branched alkyl, $-O-(CH_2)_n-C(CH_3)_2-$, or $-R_5C(=O)NHR_6-$.

5. The compound of any one of claims 1 to 4, wherein:

L_1 is a bond, $-(CH_2)_n-$, $-CH(CH_3)-$, , $-O-(CH_2)_n-C(CH_3)_2-$, or $-R_5C(=O)NHR_6-$.

6. The compound of any one of claims 1 to 4, wherein n is 0, 1, 2, 3, or 4.

7. The compound of any one of claims 1 to 6, wherein R_1 is hydrogen, halogen, -CN, -NO₂, C₁-C₆ alkyl, C₆-C₁₀ aryl, or C₃-C₁₀ heteroaryl.

8. The compound of any one of claims 1 to 7, wherein R_1 is hydrogen, halogen, -CN, -NO₂, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, phenyl, naphthyl, anthracenyl, oxazolyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, or thiazolyl.

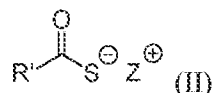
9. The compound of any one of claims 1 to 8, wherein R_2 is hydrogen, halogen, -CN, -NO₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₂NR₃R₄-, C₆-C₁₀ aryl, or C₃-C₁₀ heteroaryl.

10. The compound of any one of claims 1 to 9, wherein R_2 is hydrogen, halogen, -CN, -NO₂, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, methoxy, ethoxy, propoxy, propoxyl, butoxy, cyclopropoxy, cyclobutoxy, -CH₂Cl, -CF₃, -CH₂CF₃, -CH₂CCl₃, -SO₂NR₃R₄-, phenyl, naphthyl, anthracenyl, oxazolyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, or thiazolyl.

11. The compound of any one of claims 1 to 10, wherein each R_3 , R_4 , R_5 , R_6 are each independently C₁-C₆ alkyl.

12. The compound of any one of claims 1 to 11, wherein each R_3 , R_4 , R_5 , R_6 are each independently methyl, ethyl, propyl, isopropyl, butyl, or tert-butyl.

13. A compound of Formula II:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

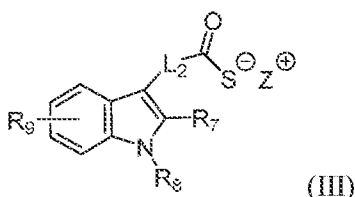
Z^+ is Na⁺, K⁺, or H⁺; and

R' is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted bridged cycloalkyl, or substituted or unsubstituted spirocycloalkyl.

14. The compound of claim 13, wherein each R' has at least one substituent and wherein the at least one substituent is selected from the group consisting of halogen, -OH, -CN, -NO₂, and C₁-C₆ alkyl.

15. The compound of claim 13 or claim 14, wherein R' is substituted or unsubstituted C₂-C₆ branched alkyl, substituted or unsubstituted C₁-C₂₀ straight chain alkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, or substituted or unsubstituted C₈-C₁₆ bridged cycloalkyl.

16. A compound of Formula III:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Z⁺ is Na⁺, K⁺, or H⁺;

L₂ is a bond, -(CH₂)_n-, or C₂-C₆ branched alkyl;

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

R₇ is hydrogen or C₁-C₆ alkyl;

R₈ is hydrogen, -C(=O)-R₁₀, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, or C₁-C₆ haloalkoxy, wherein R₁₀ is substituted or unsubstituted C₆-C₁₀ aryl or substituted or unsubstituted C₃-C₁₀ heteroaryl, wherein when substituted by a substituent, the substituent is selected from the group consisting of halogen, -OH, -CN, -NO₂, C₁-C₄ alkyl, C₁-C₄ alkoxy, and C₁-C₄ haloalkyl; and

R₉ is hydrogen, halogen, -CN, -NO₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, or C₁-C₆ haloalkoxy.

17. The compound of claim 16, wherein:

L₂ is -(CH₂)_n-; and

n is 0, 1, 2 or 3.

18. The compound of claim 16 or claim 17, wherein R₇ is hydrogen or C₁-C₄ alkyl.

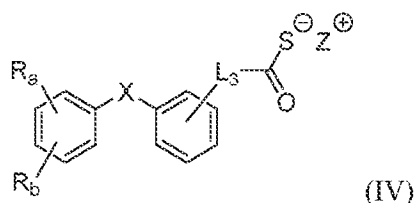
19. The compound of any one of claims 16 to 18, wherein R₇ is methyl, ethyl, propyl, isopropyl, butyl, or tert-butyl.

20. The compound of any one of claims 16 to 19, wherein:

R_8 is hydrogen or $-C(=O)-R_{10}$, wherein R_{10} is substituted or unsubstituted phenyl, substituted or unsubstituted naphthalenyl, substituted or unsubstituted anthracenyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted furyl, substituted or unsubstituted thiophenyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted quinolyl, and wherein when substituted by a substituent, the substituent is selected from the group consisting of halogen, $-OH$, $-CN$, $-NO_2$, methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

21. The compound of any one of claims 16 to 20, wherein R_9 is hydrogen, halogen, $-CN$, $-NO_2$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or C_1 - C_6 haloalkyl.

22. A compound of Formula IV:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Z^+ is Na^+ , K^+ , or H^+ ;

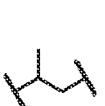
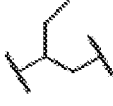
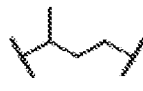
L_3 is a bond, $-(CH_2)_n-$, or C_2 - C_6 branched alkyl;

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

X is $-NH-$ or $-C(=O)-$;

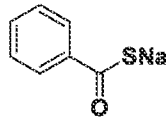
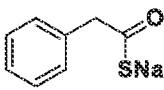
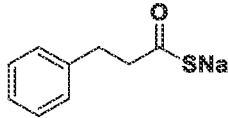
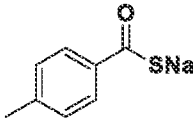
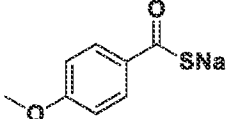
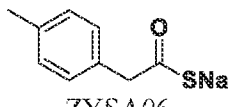
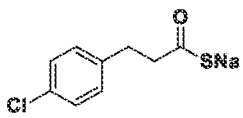
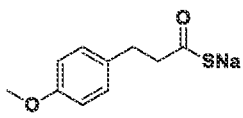
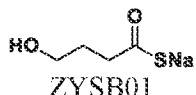
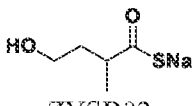
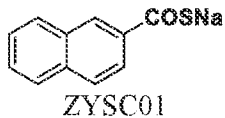
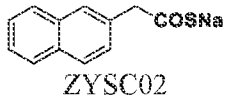
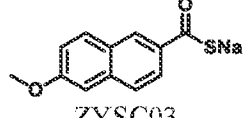
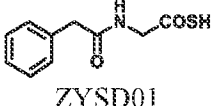
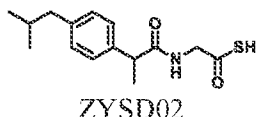
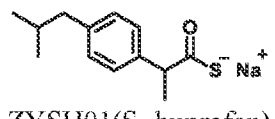
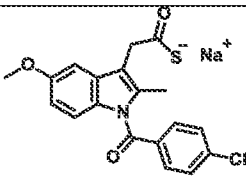
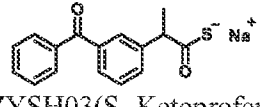
each R_a and R_b are independently hydrogen, halogen, $-CN$, $-NO_2$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, or C_1 - C_6 haloalkoxy.

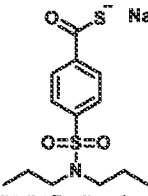
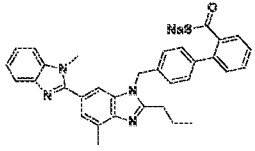
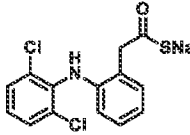
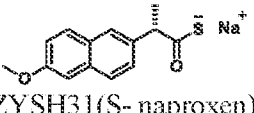
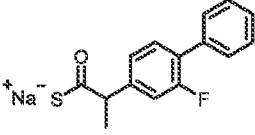
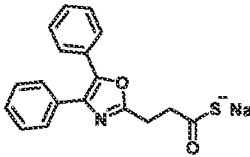
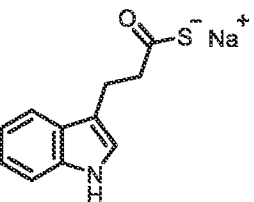
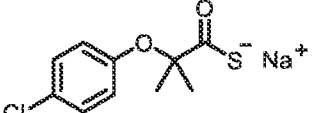
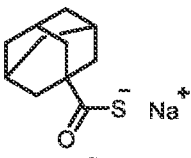
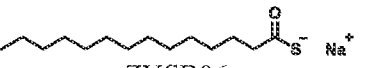
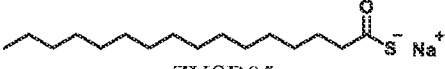
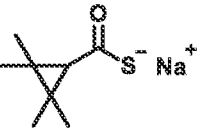
23. The compound of claim 22, wherein:

L_3 is a bond, $-(CH_2)_n-$, $-CH(CH_3)-$, , , or ; and n is 0, 1, 2 or 3.

24. The compound of claim 22 or claim 23, wherein each R_a and R_b are each independently hydrogen, halogen, $-CN$, $-NO_2$, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, or C_1 - C_4 haloalkoxy.

25. A compound selected from the group consisting of:

 ZYSA01	 ZYSA02	 ZYSA03
 ZYSA04	 ZYSA05	 ZYSA06
 ZYSA07	 ZYSA08	 ZYSB01
 ZYSB02	ZYSB03	
 ZYSC01	 ZYSC02	 ZYSC03
 ZYSD01	 ZYSD02	
 ZYSH01(S- buprofen)	 ZYSH02(S- indomethacin)	 ZYSH03(S- Ketoprofen)

 ZYSH04(S- Gemfibrozil)	 ZYSH05(S- Probenecid)	 ZYSH06(S- telmisartan)
 ZYSH21(S- diclofenac)	 ZYSH31(S- naproxen)	 ZYSH07 (Flurbiprofen)
 ZYSH08 (Oxaprozin)	 ZYSA12 (3-indolepropionic acid)	 ZYSA13
 ZYSB04		 ZYSB08
 ZYSB07		 ZYSB06
 ZYSB05		 ZYSB09

and a pharmaceutically acceptable salt or prodrug thereof.

26. A pharmaceutical composition comprising a compound of any one of claims 1 to 25 and a pharmaceutically acceptable carrier.

27. A kit comprising a compound of any one of claims 1 to 25 or a pharmaceutical composition of claim 26.

28. A method of treating or preventing a cerebrovascular disease, an anti-inflammatory condition, rheumatic or rheumatoid arthritis, gout, high blood pressure, a high blood lipids condition, or liver toxicity in a subject, comprising administering to the subject an effective amount of a compound of any one of claims 1 to 25, or a pharmaceutical composition of claim 26.

29. The method of claim 28, wherein the compound is an antipyretic or an analgesic compound.

30. The method of claim 28 or claim 29, wherein the compound reduces liver toxicity on GSH depletion or mitochondrial damage

31. A compound comprising a thiocarboxylic acid moiety, wherein the compound releases hydrogen sulfide under enzyme-catalyzed conditions.

32. The compound of claim 31, wherein the compound is a thiolated sartan compound.

33. The compound of claim 32, wherein the thiolated sartan compound is thiolated valsartan, thiolated eplosartan, or thiolated timosartan.

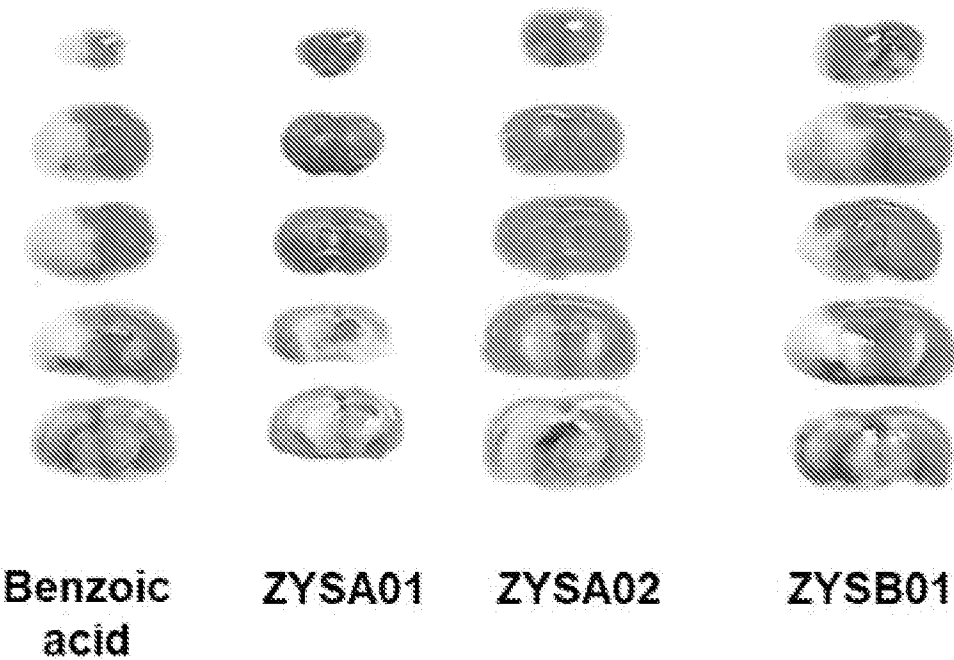


FIG. 1A

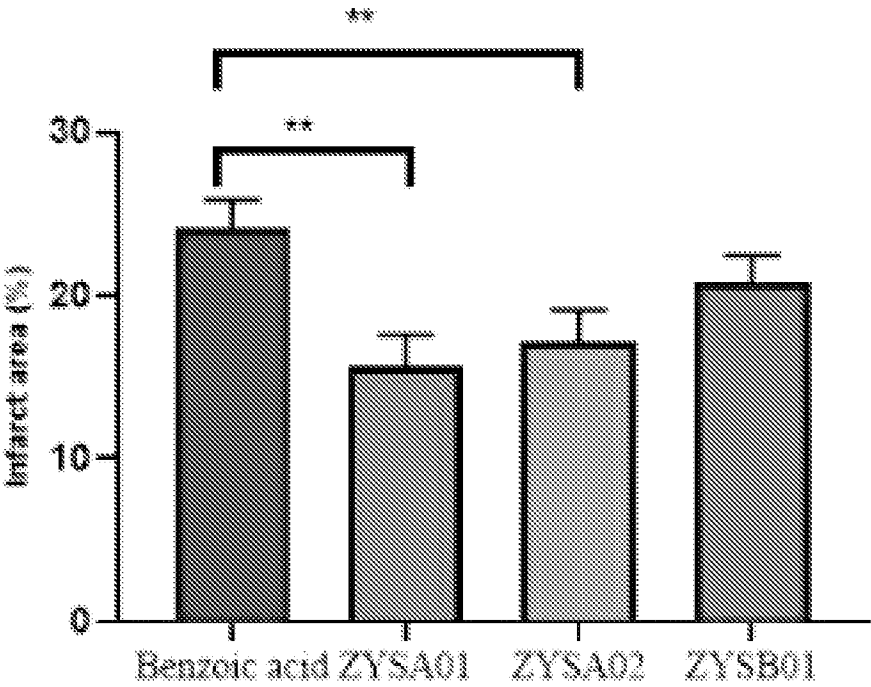


FIG. 1B

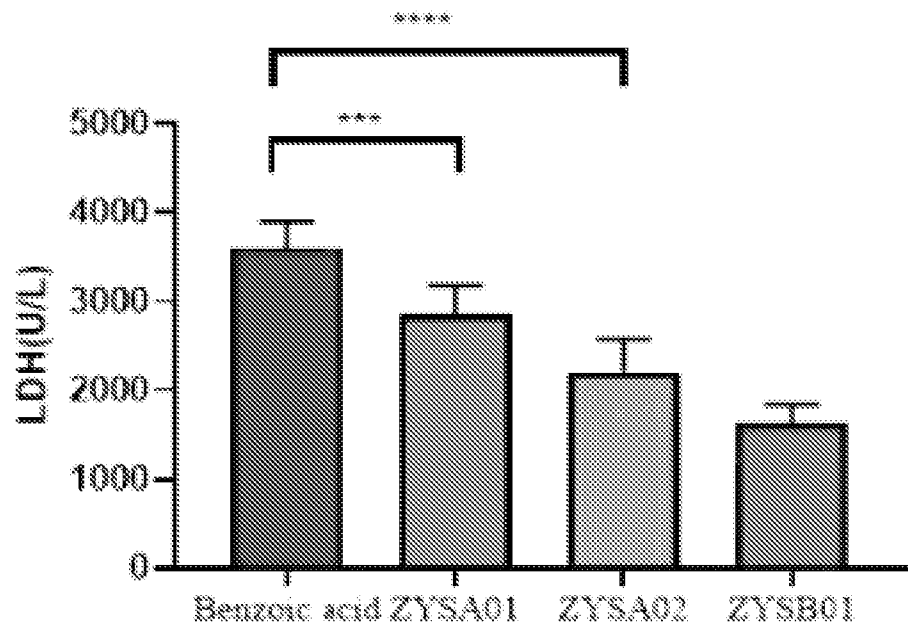


FIG. 1C

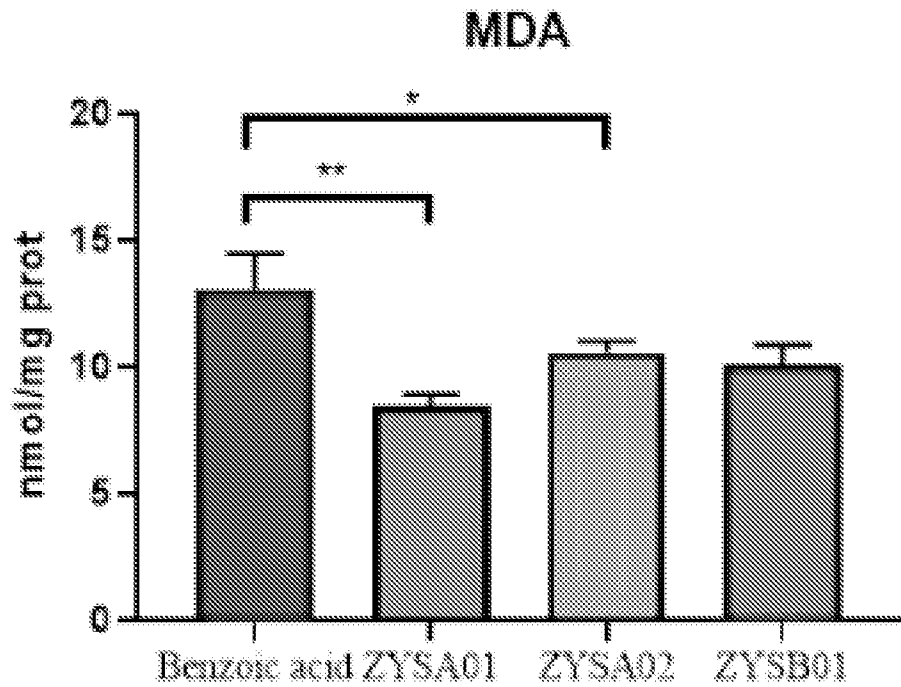
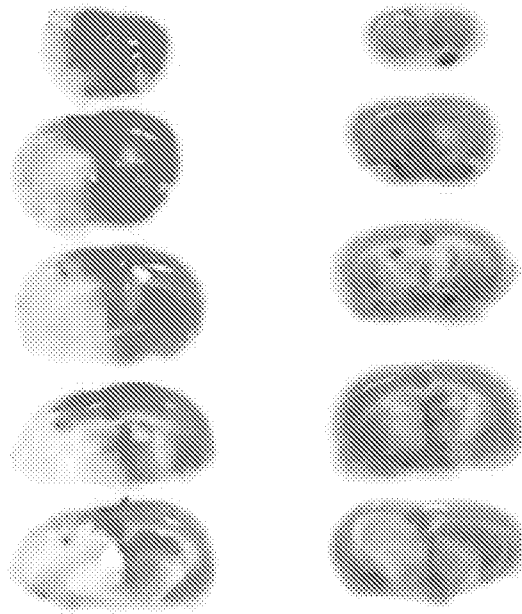


FIG. 1D

3/16



Telmisartan ZYSH06

FIG. 2A

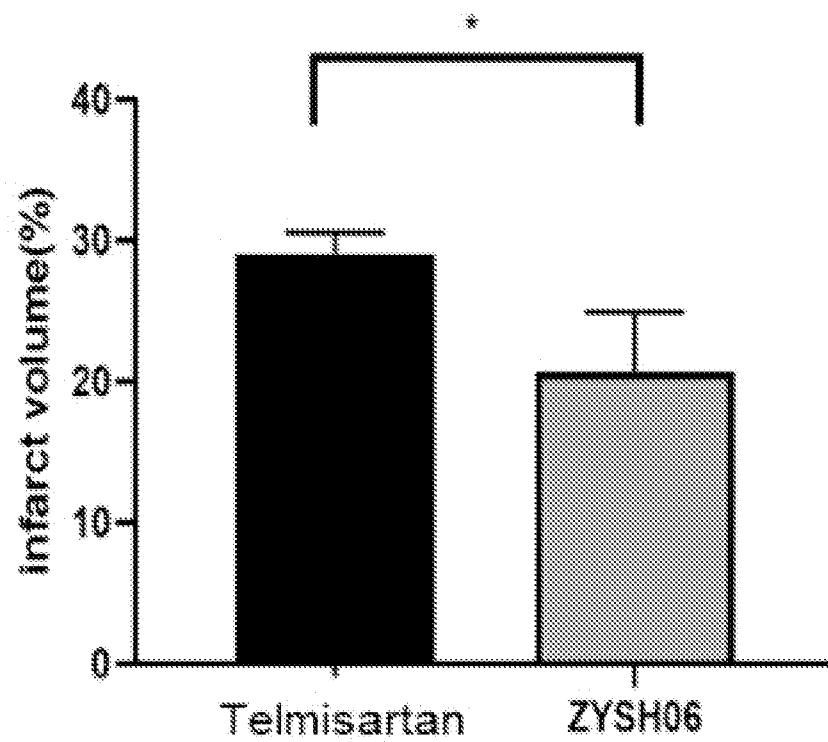


FIG. 2B

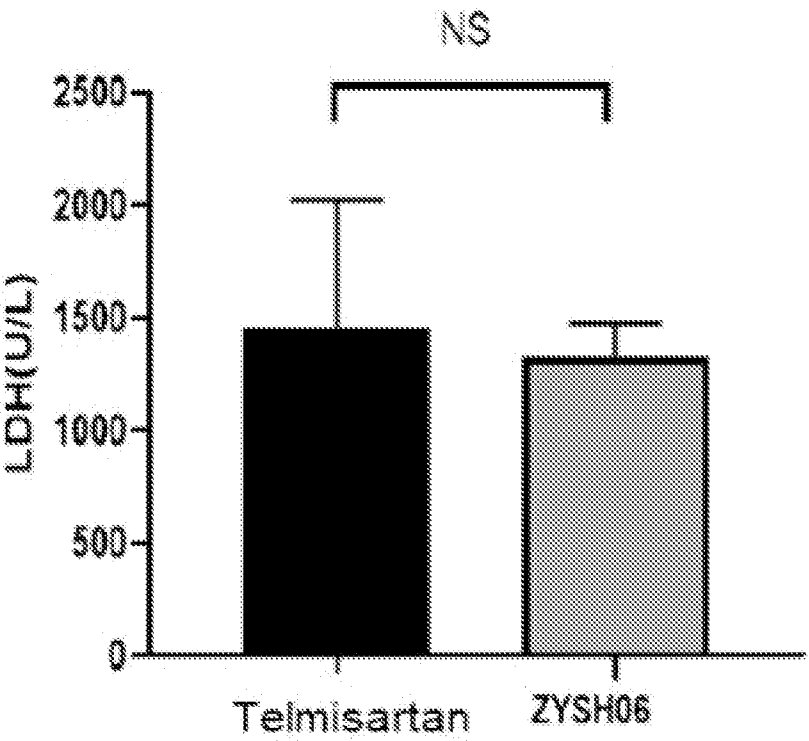


FIG. 2C

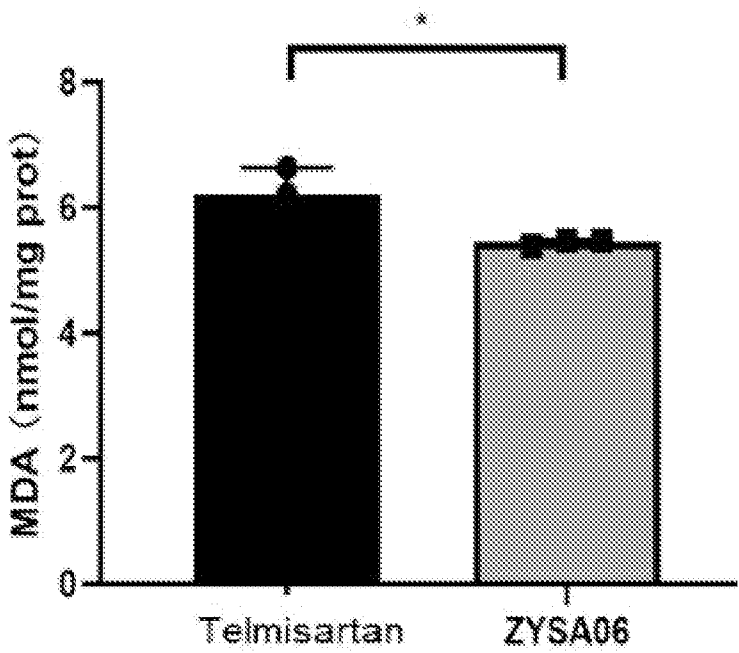


FIG. 2D

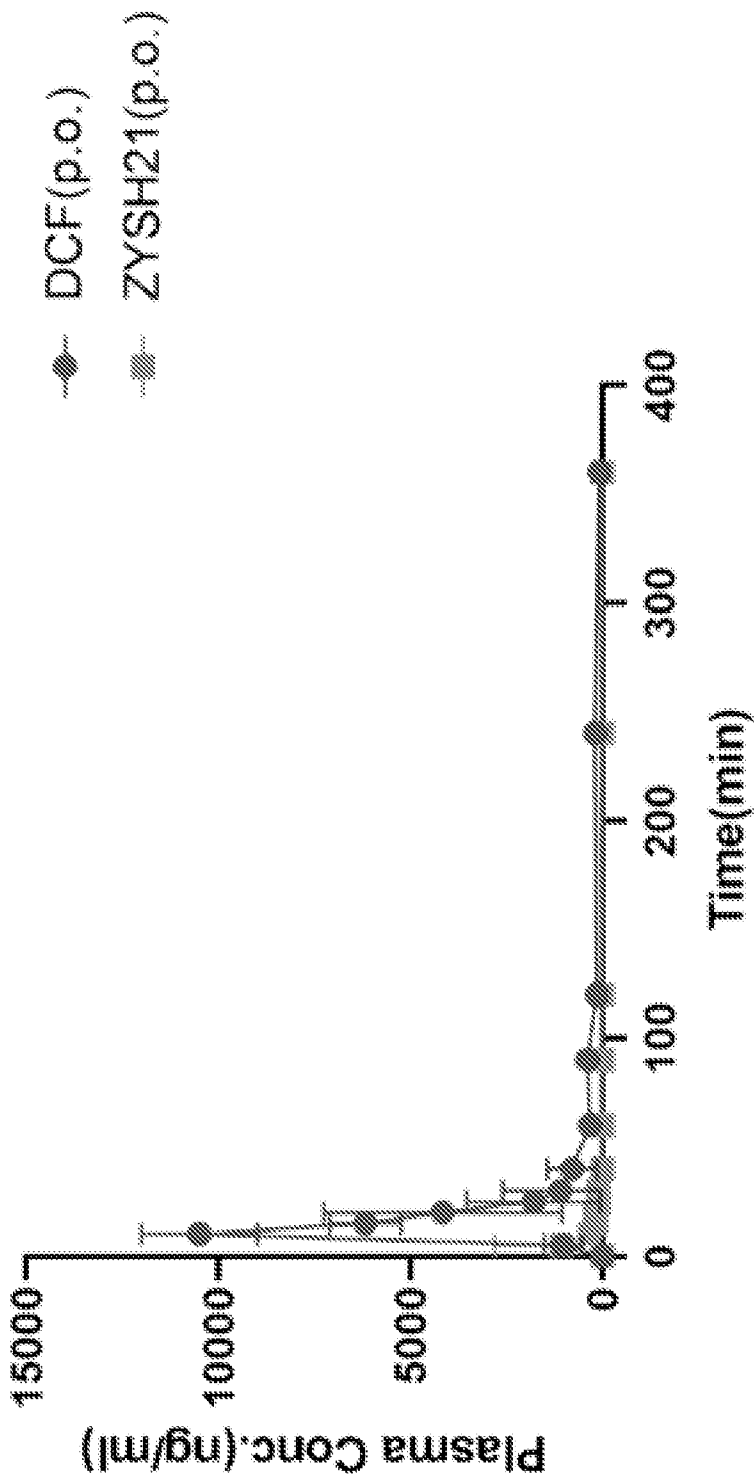


FIG. 3

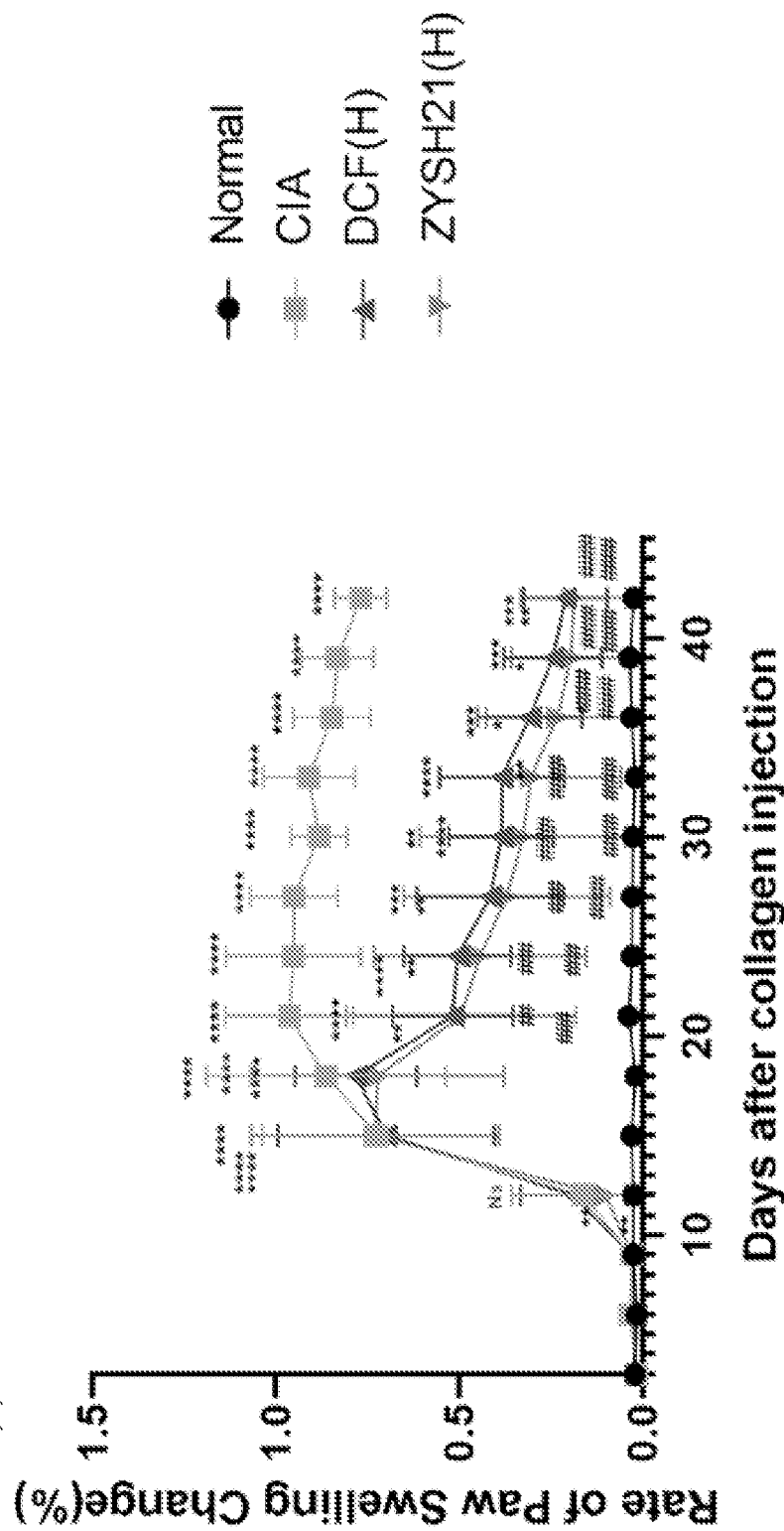


FIG. 4

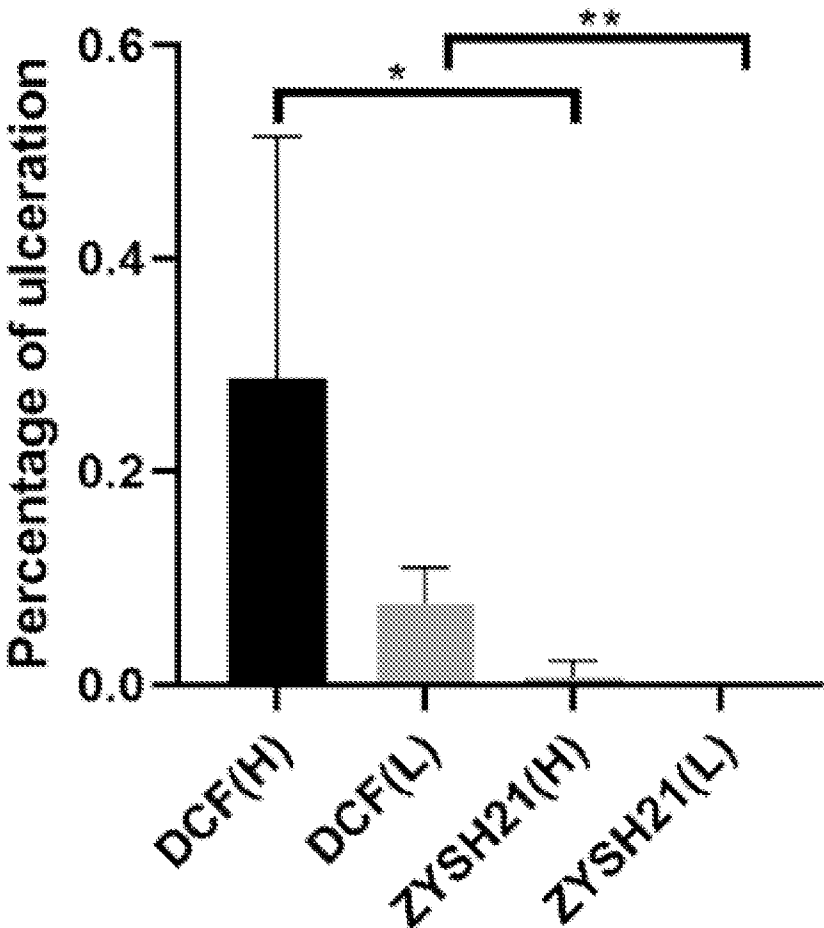


FIG. 5

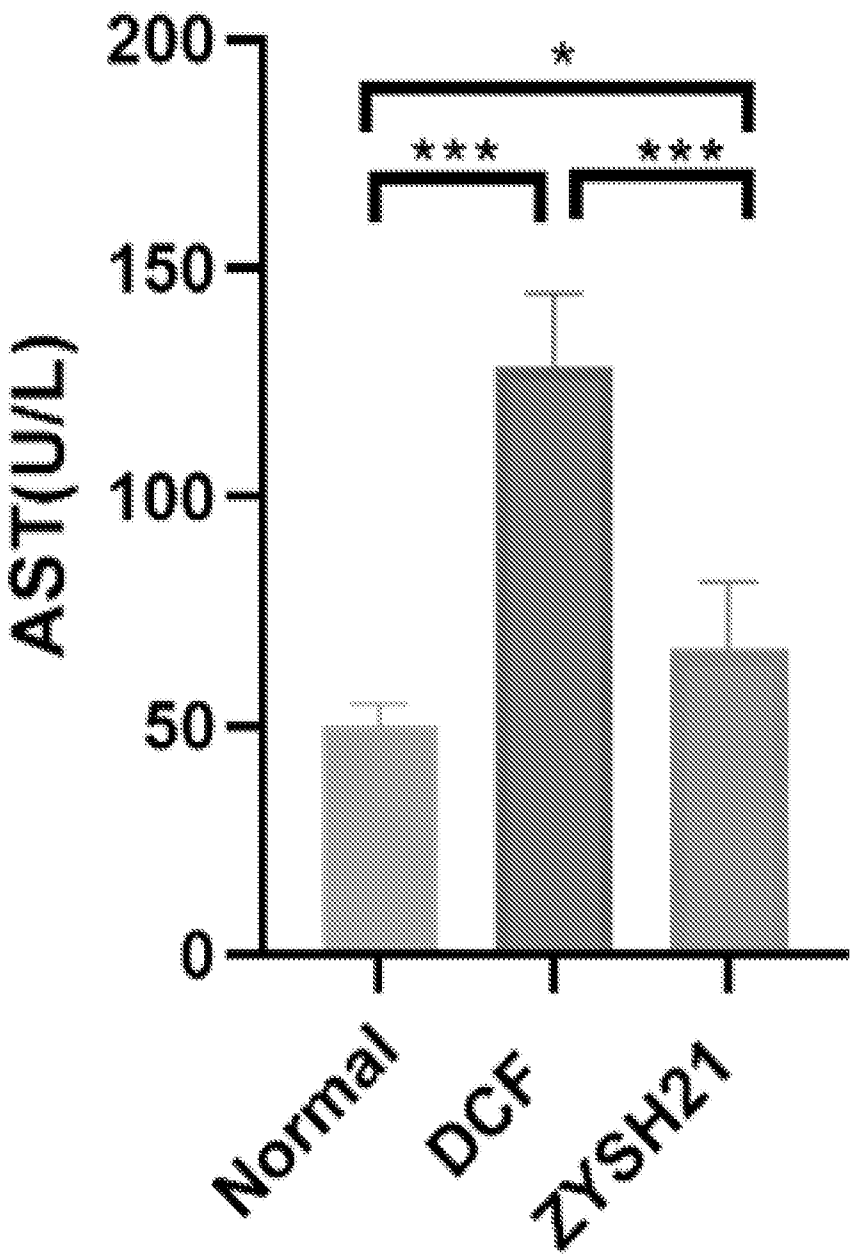


FIG. 6A

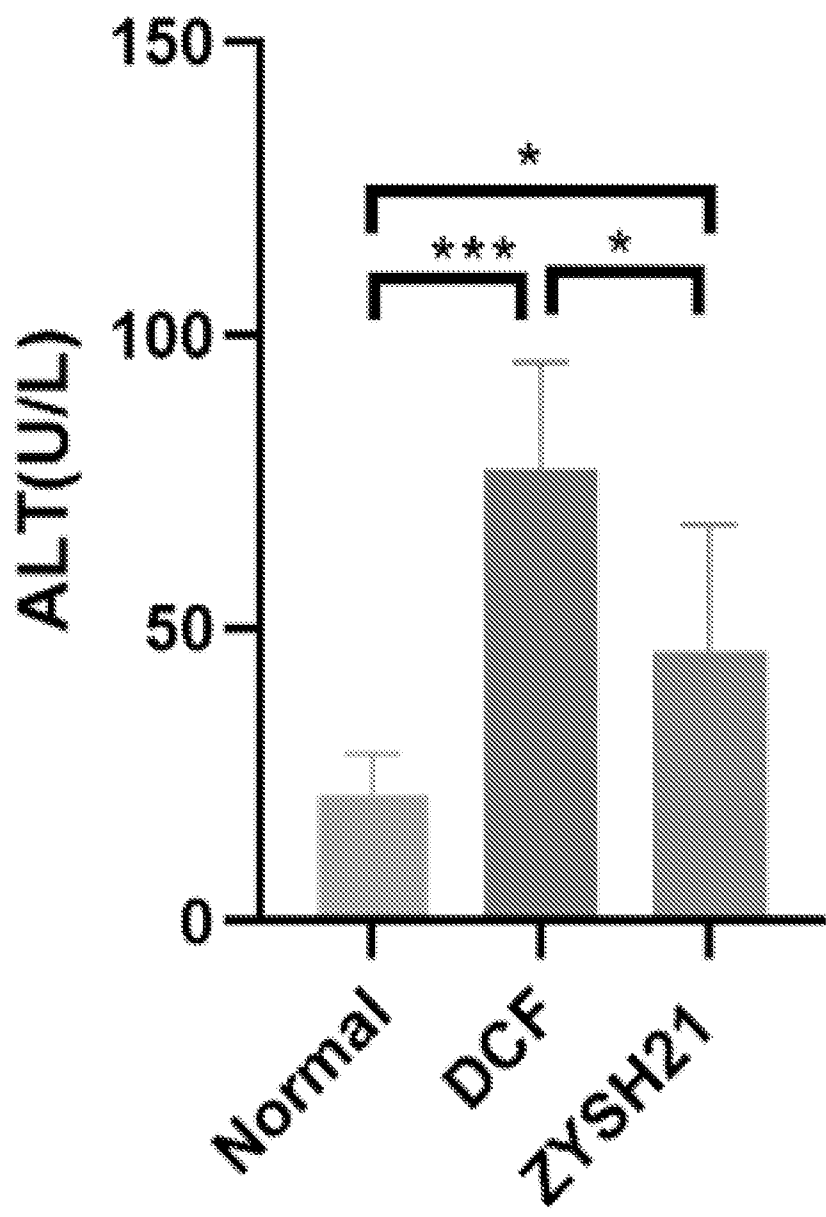


FIG. 6B

10/16

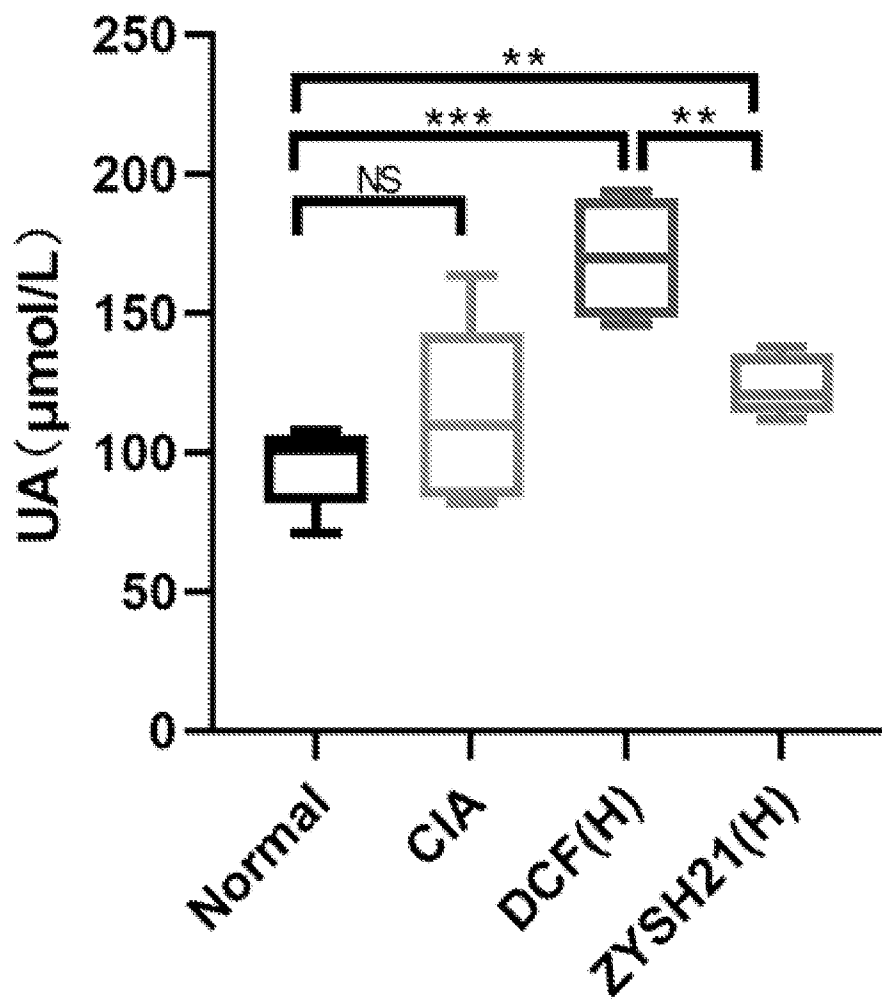


FIG. 7

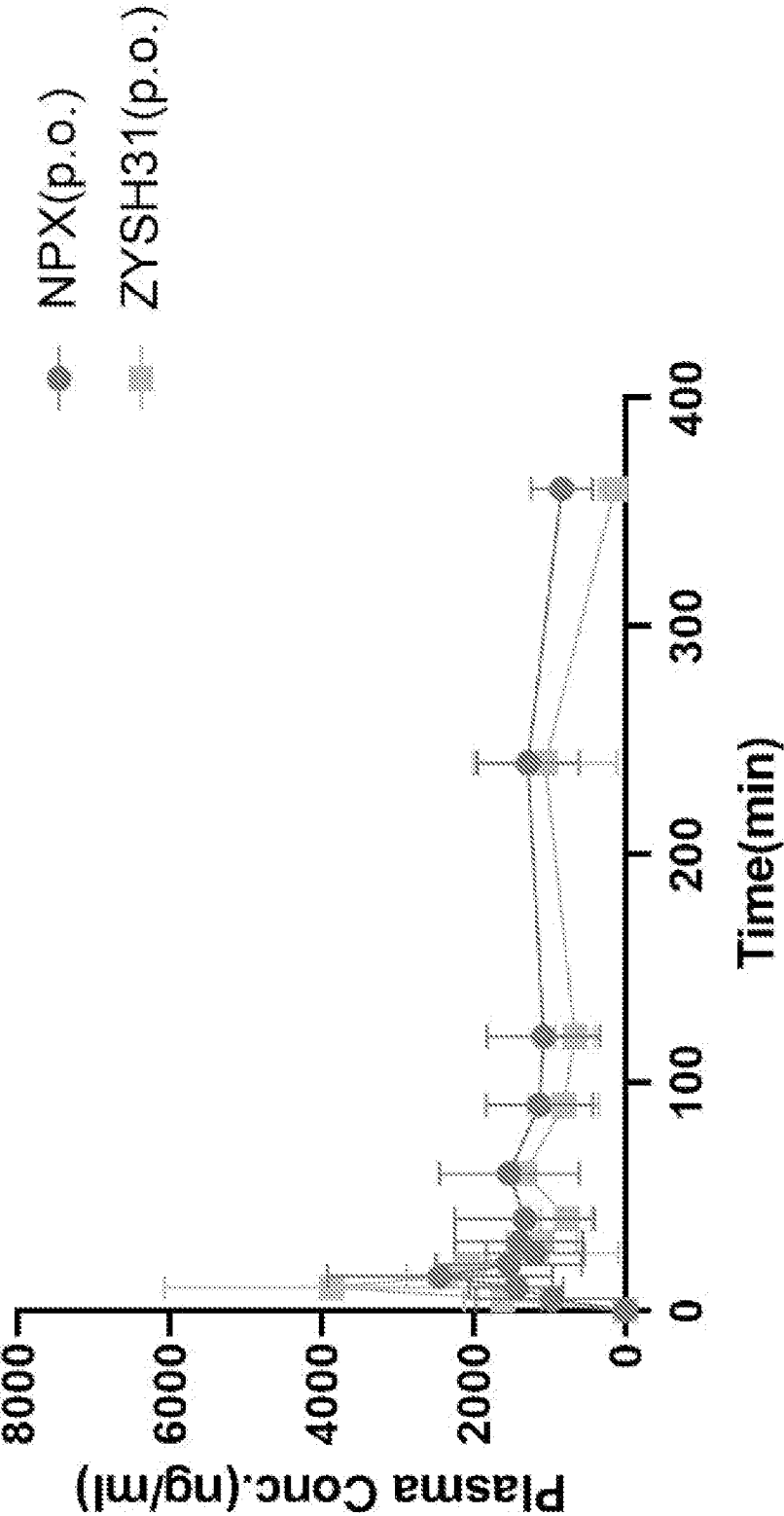


FIG. 8

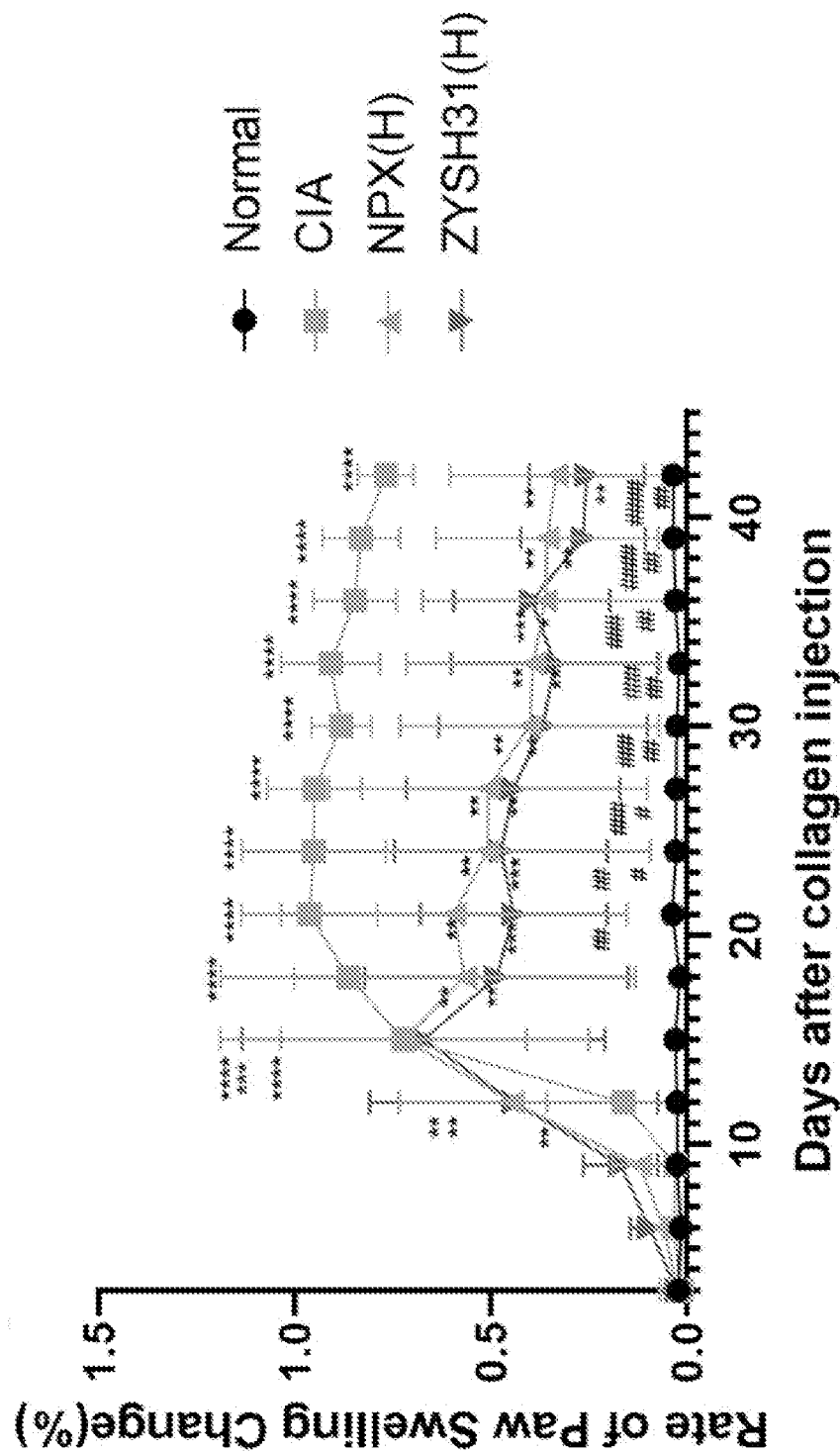


FIG. 9

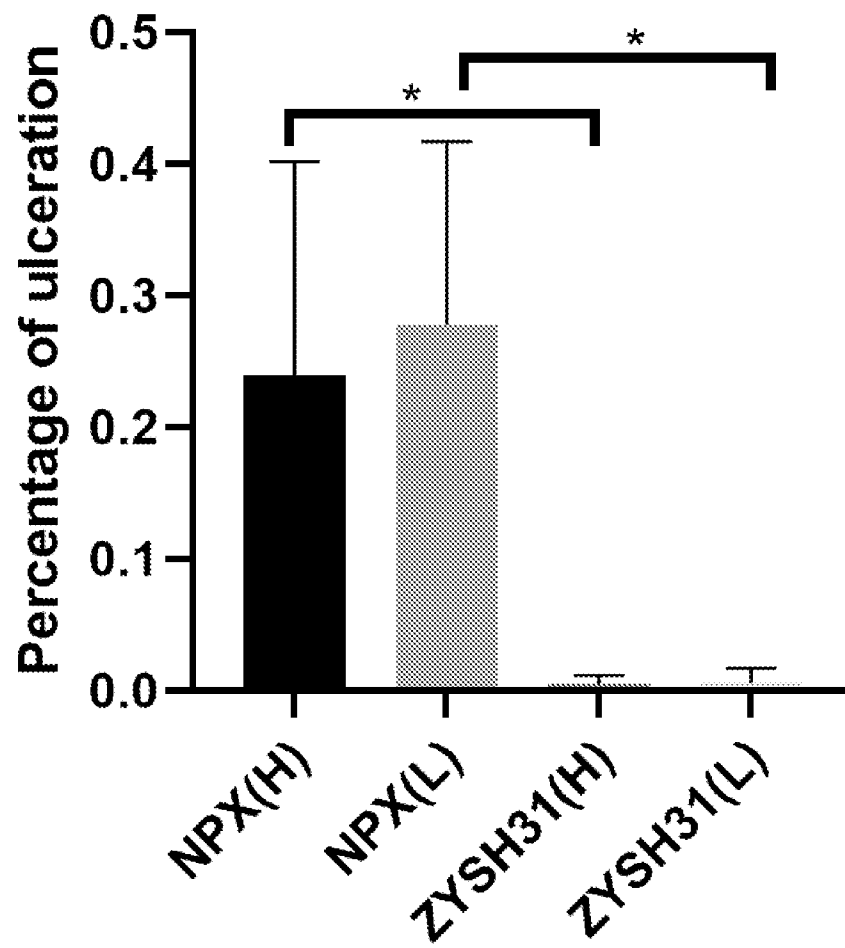


FIG. 10

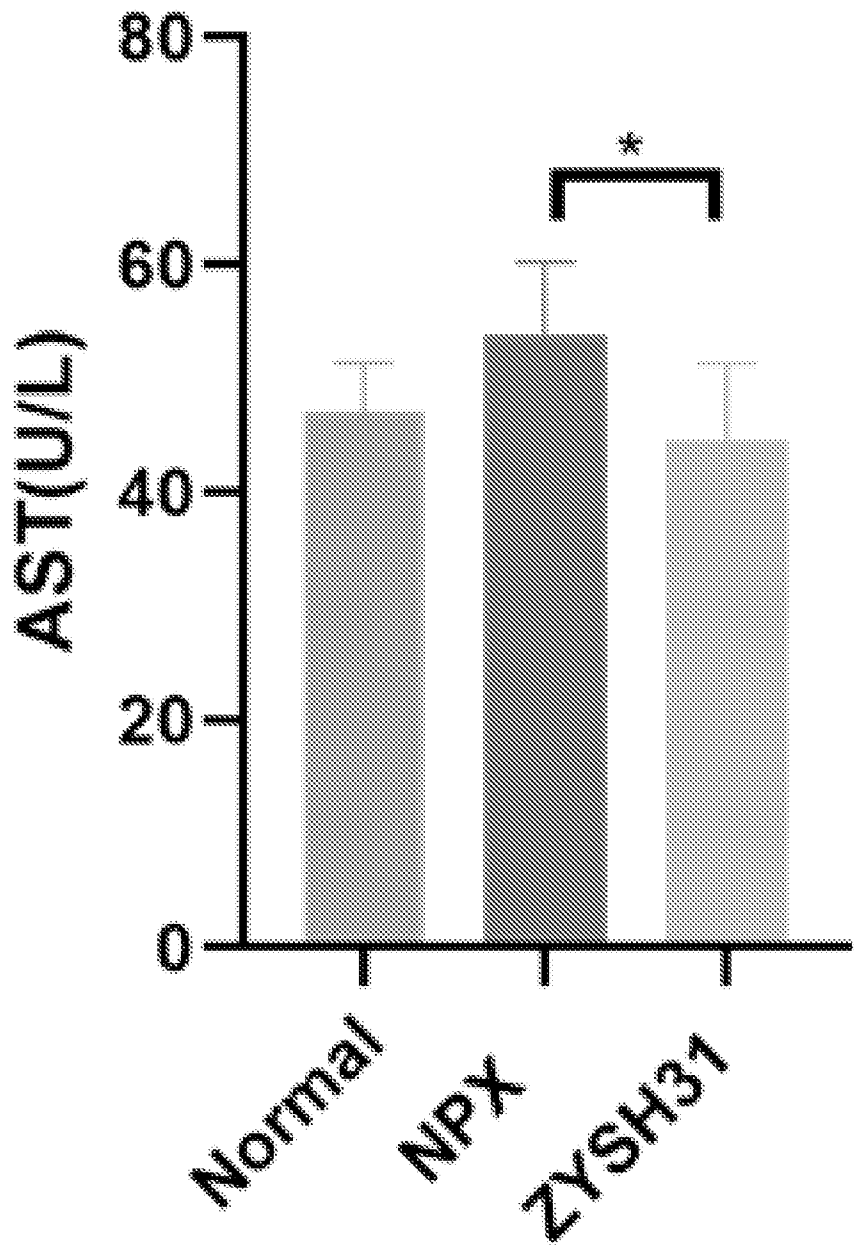


FIG. 11A

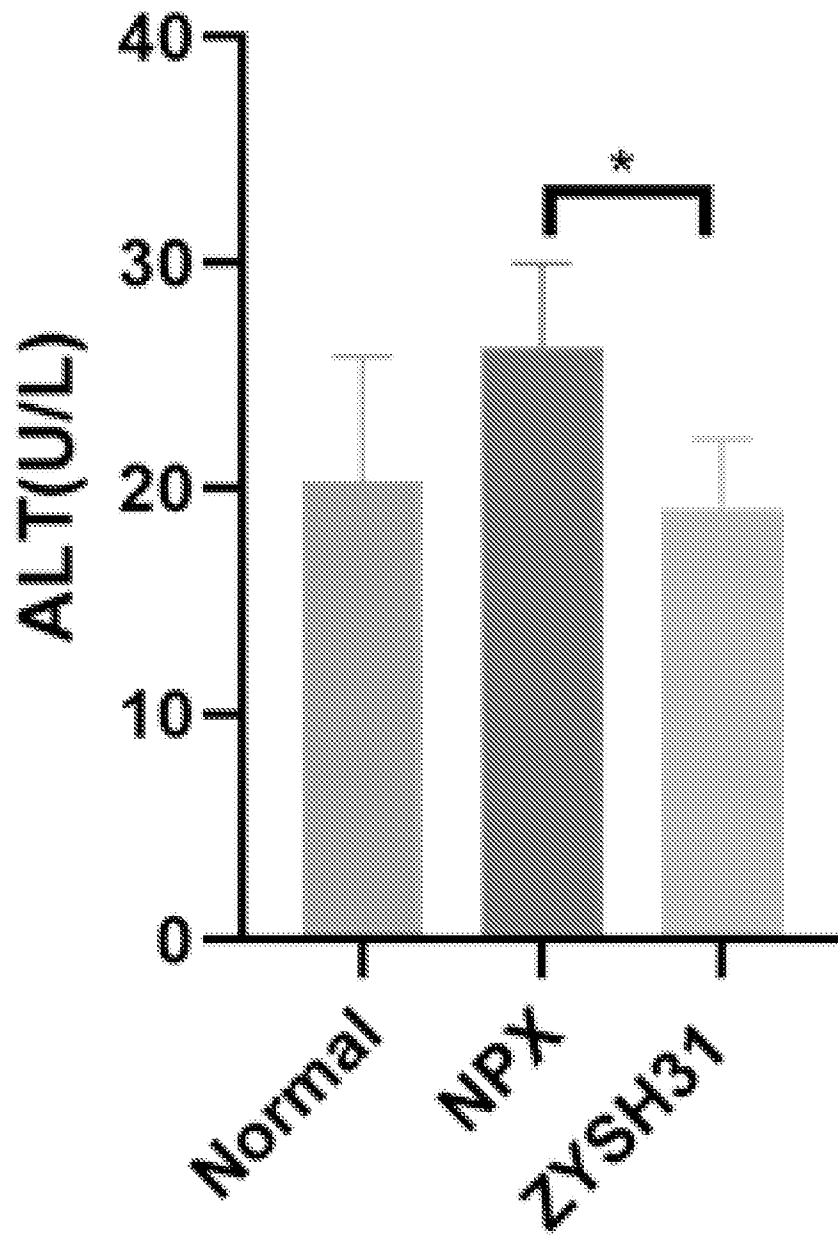


FIG. 11B

16/16

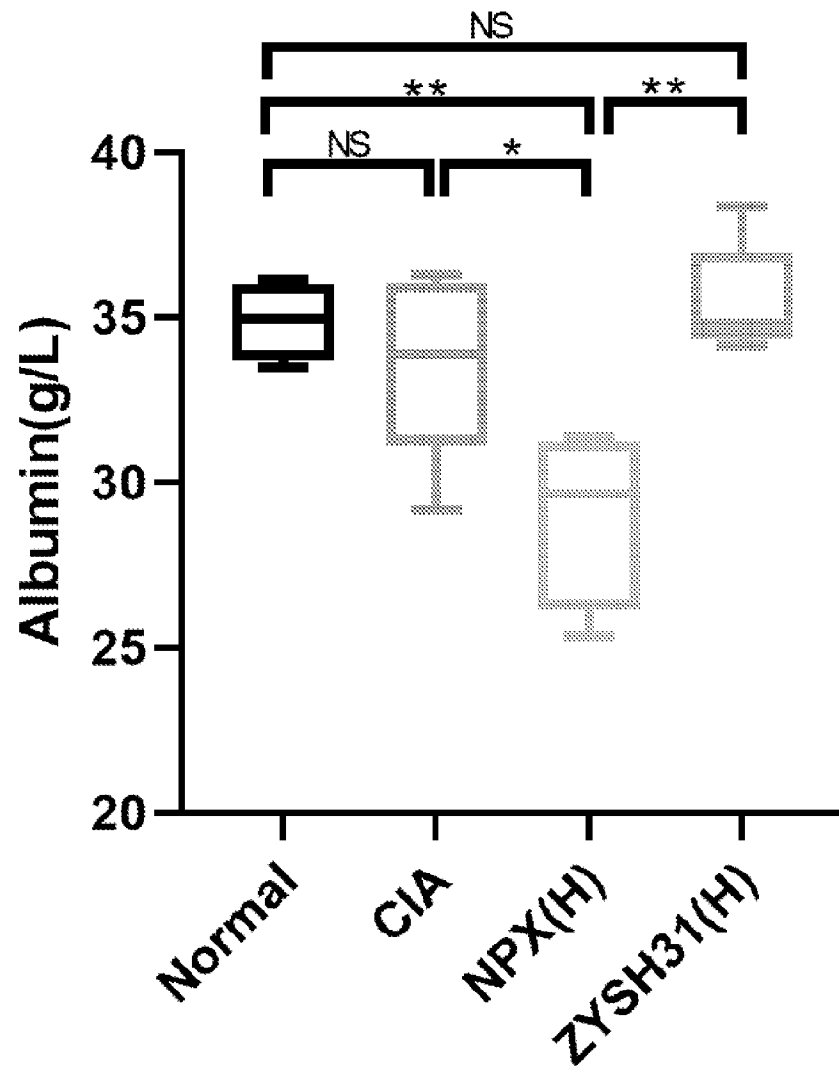


FIG. 12

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/043214

A. CLASSIFICATION OF SUBJECT MATTERIPC: **A61K 31/395** (2024.01); **A61K 31/095** (2024.01); **A61K 31/145** (2024.01); **A61K 31/33** (2024.01)CPC: **A61K 31/395**; **A61K 31/095**; **A61K 31/145**; **A61K 31/33**

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)

See Search History Document

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

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2013/0253051 A1 (XIAN, et.al.) 26 September 2013 (26.09.2013) ENTIRE DOCUMENT	1-3;25
A	US 11,078,157 B1 (UNIVERSITY OF OREGON) 03 August 2021 (03.08.2021) ENTIRE DOCUMENT	1-3;25
X	Pubchem 376395434 deposited on 30 November 2018 pp. 1-6. Pg. 2, structure	1-3;25

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“D” document cited by the applicant in the international application

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“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

“&” document member of the same patent family

Date of the actual completion of the international search

07 October 2024 (07.10.2024)

Date of mailing of the international search report

17 December 2024 (17.12.2024)

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/043214

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: **4-12, 19-21 and 26-30**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I+: Claims 1-3, 13-18, and 22-25 directed to a compound of formula I-IV or a pharmaceutically acceptable salt or prodrug thereof. The compound will be searched to the extent that it encompasses the first species of a compound represented by the structure of formula I, wherein Z+ is Na+, A is a substituted C6-aryl; L1 is a bond; R1 and R2 is H. It is believed that claims 1-3 and 25 (in part) read on this first named invention, and thus these claims will be searched without fee. This first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be the compound represented by the structure of formula I, wherein Z+ is Na+, A is a substituted C3-C20 heteroaryl; L1 is a bond; R1 and R2 is H (Claims 1-3, 16-18).

Group II: Claims 31-33 directed to a compound comprising a thiocarboxylic acid moiety, wherein the compound releases hydrogen sulfide under enzyme-catalyzed conditions.

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound represented by the structure of formula I, which is not required by any other invention of Group I+ or Group II.

Group II includes the technical feature of a unique compound that can release hydrogen sulfide under enzyme-catalyzed conditions, which is not required by any other invention of Group I+

Common Technical Features:

The inventions of Group I+ and Group II share the technical feature of a compound represented by the structure of formula I.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/043214

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by Pubchem 376395434 (hereinafter "Pubchem"). Pubchem discloses a compound of formula I, wherein Z+ is Na+, A is a substituted C6-aryl; L1 is a bond; and each of R1 and R2 is H (pg. 2, structure).

As said compound and compositions were known in the art, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+ and Group II. The inventions of Group I+ and Group II thus lack unity under PCT Rule 13.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-3; 25**

- Remark on Protest**
- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - ☐ No protest accompanied the payment of additional search fees.