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(54) Title: GLYCOLATE OXIDASE INHIBITORS AND METHODS OF USE FOR THE TREATMENT OF KIDNEY STONES

(57) Abstract: Provided herein are compounds of Formula I and Formula II, and compositions comprising the same, as well as methods of use thereof for treating kidney stones (e.g., inhibiting the formation of oxalate kidney stones; treating primary hyperoxaluria), inhibiting the production of glyoxylate and/or oxalate, and/or inhibiting glycolate oxidase (GO).
Glycolate Oxidase Inhibitors and Methods of Use
for the Treatment of Kidney Stones

RELATED APPLICATIONS
This application claims the benefit of United States Provisional Patent Application Serial No. 62/263,938, filed December 7, 2015, the disclosure of which is incorporated by reference herein in its entirety.

GOVERNMENT FUNDING
This invention was made with government support under grant numbers DK083527 and DK073732 awarded by National Institutes of Health. The United States government has certain rights in the invention.

BACKGROUND
Kidney stones affect approximately 1 in 11 individuals in the United States. The 2012 National Health and Nutrition and Examination Survey (NHANES), part of the Urological Diseases in America Project, reported that the overall prevalence of kidney stones was 8.8% (10.6 % and 7.1 % for men and women, respectively) (Jiang et al., Am J Physiol Gastrointest Liver Physiol 302. G637-643, 2012). This study and others attest to the significant increase in stone cases in general, but especially in individuals with obesity, diabetes, and following bariatric surgery (Jiang et al., supra; Knight et al., Am J Nephrol 25, 171-175, 2005). The direct and indirect costs associated with kidney stone treatment (i.e., nephrocalcinosis) are significant (Knight et al., Kidney Int 70, 1929-1934, 2006).

Individuals with Primary Hyperoxaluria (PH) have mutations in a variety of genes involved in glyoxylate and hydroxyproline (Hyp) metabolism that result in a significant increase in oxalate production and deposition of calcium oxalate stones, the most common type of stones for all stone formers. The treatments for these individuals range from a combined kidney-liver transplant to a life-long use of potassium citrate, increased fluid intake and dietary restriction of oxalate (Riedel et al., PLoS One 6, e26021, 2011; Knight et al., Am J Physiol-Renal 302, 688-693, 2012). Treatments for the removal of stones currently include shock-wave lithotripsy, ureteroscopic stone removal, and percutaneous nephrolithotomy (Riedel et al., supra). However, the recurrence of stones following the available procedures is over 50%.
Kidney stones are also a significant problem in veterinary medicine. Pets such as dogs and cats can develop stones that lead to painful urination and/or a life-threatening blockage.

Considering that the current treatments only address symptoms, novel treatments to prevent the formation of stones in PH and other idiopathic stone formers are greatly needed.

SUMMARY

Provided herein are compounds of **Formula 1**:

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  OOC
/ \
A   H
|   D
\  /
B   N

I

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wherein:

A is C\(\text{\textgreek{S}}\) or S;
B is CH or N;
D is CH or N; and

R\(^1\) is aryl or heteroaryl, wherein said aryl or heteroaryl has two aromatic rings, which rings are fused or directly adjoining,

or a pharmaceutically acceptable salt or prodrug thereof.

In some embodiments, A is CH\(_2\). In some embodiments, A is S. In some embodiments, B is CH. In some embodiments, B is N. In some embodiments, D is CH. In some embodiments, D is N.

In some embodiments, R\(^1\) is benzothiophene or biphenyl.

In some embodiments, R\(^1\) is selected from the group consisting of:
wherein $R^{10}$, $R^{11}$' and $R^{12}$ are each independently selected from the group consisting of: H, alkyl, halo and haloalkyl, or a pharmaceutically acceptable salt or prodrug thereof.

Also provided are compounds of Formula II:

\[
\begin{align*}
\text{II} & \\
\text{wherein:}
\end{align*}
\]

- $A$ is CH$_2$ or S;
- $R^1$ is aryl or heteroaryl, wherein said aryl or heteroaryl has two aromatic rings, which rings are fused or directly adjoining; and $R^2$ is H or OH,
- or a pharmaceutically acceptable salt or prodrug thereof.

In some embodiments, $A$ is CH$_2$. In some embodiments, $A$ is S. In some embodiments, $R^2$ is H. In some embodiments, $R^2$ is OH.

In some embodiments, $R^1$ is benzothiophene or biphenyl.
In some embodiments, R is selected from the group consisting of:

```
\[
\begin{align*}
\text{R}^{10} & \quad \text{R}^{11} & \quad \text{R}^{12} \\
\text{S} & \quad \text{R}^{10} & \quad \text{R}^{11} \\
\end{align*}
\]
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wherein R\(^{10}\), R\(^{11}\) and R\(^{12}\) are each independently selected from the group consisting of: H, alkyl, halo and haloalkyl, or a pharmaceutically acceptable salt or prodrug thereof.

Also provided are pharmaceutical compositions comprising a compound, pharmaceutically acceptable salt or prodrug as taught herein. In some embodiments, the composition is formulated for oral administration. In some embodiments, the composition is a food product formulation.

Further provided are methods of treating kidney stones (e.g., inhibiting the formation of oxalate kidney stones; treating primary hyperoxaluria), comprising: administering to a subject in need thereof a therapeutically effective amount of a compound, pharmaceutically acceptable salt or prodrug as taught herein.

Still further provided are methods of inhibiting the production of glyoxylate and/or oxalate, and/or inhibiting glycolate oxidase (GO), in a subject in need thereof, comprising: administering to said subject a therapeutically effective amount of a compound, pharmaceutically acceptable salt or prodrug as taught herein.

Also provided is the use of the compound, pharmaceutically acceptable salt or prodrug as taught herein, or a pharmaceutical composition as taught herein, for treating kidney stones (e.g., inhibiting the formation of oxalate kidney stones; treating primary hyperoxaluria), inhibiting the production of glyoxylate and/or oxalate, and/or inhibiting glycolate oxidase (GO), in a human or non-human animal subject in need thereof.

Further provided is the use of a compound, pharmaceutically acceptable salt or prodrug as taught herein in the preparation of a medicament for treating kidney stones (e.g., inhibiting the formation of oxalate kidney stones; treating primary hyperoxaluria), inhibiting the production of
glyoxylate and/or oxalate, and/or inhibiting glycolate oxidase (GO), in a human or non-human animal subject in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 presents a schematic of the metabolism of 4-hydroxyproline. Glycolate and glyoxylate within a hepatocyte. Four mitochondrial enzymes are responsible for Hyp breakdown: hydroxyproline dehydrogenase (HYPDH), A'-pyrrole-S-carboxylate dehydrogenase (1P5CDH), aspartate aminotransferase (AspAT), and 4-hydroxy-2-oxoglutarate aldolase (HOGA). A variety of enzymes, including alanine-glyoxylate aminotransferase (AGT), D-amino acid oxidase (DAO), glyoxylate reductase (GR), and lactate dehydrogenase (LDH), can act on the glyoxylate produced from HOG cleavage. AGT, GR, and HOGA are mutated within primary hyperoxaluria patients (PH type 1, 2, and 3, respectively). Glycolate oxidase (GO) can readily convert glycolate back into glyoxylate within the peroxisome; a feature that is particularly problematic for PH2 patients.

DETAILED DESCRIPTION

Provided herein are methods of treatment for controlling or inhibiting the formation of kidney stones comprising administering to a subject in need thereof an inhibitor of glycolate oxidase (GO), as well as compounds and compositions useful for the same.

The disclosures of all patent references cited herein are hereby incorporated by reference to the extent they are consistent with the disclosure set forth herein. As used herein in the description of the invention and the appended claims, the singular forms "a," "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise.

"Subject" or "patient" as used herein are generally mammalian subjects, including both human subjects and non-human mammalian subjects (e.g., dog, cat, horse, etc.) for research or veterinary purposes. Subjects may be male or female and may be of any suitable age, including neonate, infant, juvenile, adolescent, adult, and geriatric subjects.

"Treat" as used herein refers to any type of treatment that imparts a benefit to a subject, particularly slowing or inhibiting the formation of glycolate and/or oxalate, decreasing urinary oxalate, slowing or inhibiting the formation of calcium oxalate stones in the kidneys and/or urinary tract (kidneys, ureters, bladder, and urethra), and/or the deposition of calcium oxalate in other tissues such as the heart. For example, the treatment may reduce the size of and/or decrease the number of such stones, inhibit or slow the growth of such stones or calcium oxalate
deposition in tissues such as the heart, alleviate symptoms of such stones or deposition, etc. Treatment may also include prophylactic treatment of a subject deemed to be at risk of kidney stone formation (e.g., after bariatric surgery and recurrent idiopathic "stone formers").

"Kidney stones" are hard deposits of minerals that form a stone or crystal aggregation, which may result in damage or failure of the kidney and/or urinary tract function. Most kidney stones are calcium stones, usually in the form of calcium oxalate.

"Oxalate" or "oxalic acid" is a dianion of the formula \( \text{C}_2\text{O}_4^{2-} \) produced by the body and also commonly ingested in the diet. Oxalate can combine with calcium in the kidneys or urinary tract to form calcium oxalate, which is the main component of most kidney stones.

"Glyoxylate" is a precursor of oxalate, as shown in FIG. 1.

"Glycolate oxidase" or "GO" is an enzyme that catalyzes the oxidation of glycolate. Multiple GO isoforms exist, such as GO1 (predominantly in liver) and G02 (located in kidney and liver) (Jones et al. J Biol Chem 275, 12590-12597, 2000). GO1 catalyzes the FMN-dependent oxidation of glycolate to glyoxylate, and glyoxylate to oxalate, although the latter occurs with a 100-fold lower keat/Km value (Murray et al. Biochemistry 47, 2439-2449, 2008).

"Primary hyperoxaluria" is a condition characterized by the overproduction of oxalate and/or defective production or function of one or more enzymes that regulate the levels of oxalate in the body. Sufferers of Type 1 primary hyperoxaluria have a defect or shortage of the alanine:glyoxylate aminotransferase enzyme (AGT). Type 2 primary hyperoxaluria sufferers have a defect or shortage of the glyoxylate reductase enzyme (GR). Type 3 primary hyperoxaluria sufferers have a defect or shortage of the 4-hydroxy-2-oxoglutarate aldolase (HOGA).

"Hydroxyproline" or "Hyp" has the structure:

![Hydroxyproline](image-url)

Hydroxyproline is produced in the body primarily from endogenous collagen turnover (Miyata et al., Proc Natl Acad Sci USA 111, 14406-14411, 2014). Using a unique metabolic tracer, \(^{13}\text{C}_5,^{15}\text{N}\)-Hyp (all five carbons isotope and nitrogen atom labeled), it was determined that the level of Hyp turnover could be as high as 6-7 g/day (Riedel et al., Biochim Biophys Acta 1822, 1544-1552, 2012). Less than 5 mg of free Hyp is excreted in urine each day, indicating that most of the Hyp is metabolized (Belostotsky et al., J Mol Med (Berl) 90, 1497-1504, 2012). This

The biological reason why Hyp metabolism occurs is not clear, although it does enable some pyruvate to feed back into other pathways.

Hyp is metabolized primarily in the mitochondria of the liver and renal cortical tissue (Kivirikko, Int Rev Connect Tissue Res 5, 93-163, 1970; Atlante et al., Biochem Biophys Res Commun 202, 58-64, 1994; Monico et al., Clin J Am Soc Nephrol 6, 2289-2295, 2011; Wold et al., J Food Sc 64, 377-383, 1999). Diet can also be a source of collagen. For example, a quarter pound hamburger rich in gristle could contain as much as 6 grams of collagen, yielding 780 mg of Hyp (Khan et al., J Urol 184, 1189-1196, 2010). In fact, dietary Hyp can significantly increase oxalate production in humans and lead to hyperoxaluria in mouse and rat models (Khan et al., Kidney Int 70, 914-923, 2006; Valle et al., J Clin Invest 64, 1365-1370, 1979; Adams et al, Annu Rev Biochem 49, 1005-1061, 1980).

**FIG. 1** presents the Hyp catabolic pathway and the metabolism of glyoxylate and glycolate. The Hyp pathway involves four enzymatic reactions (Miyata et al., Proc Natl Acad Sci USA 111, 14406-14411, 2014; Efron et al., New Engl J Med 272, 1299-1309, 1965; Pelkonen et al, New Engl J Med 283, 451-456, 1970). The first step of the pathway is the flavin FAD-dependent oxidation of Hyp to A'-pyrroline-3-hydroxy-5-carboxylate (3-OH-P5C) by HYPDH. The 3-OH-P5C intermediate is converted to 4-hydroxy-glutamate (4-OH-Glu) by 1P5CDH, an NAD+-dependent enzyme shared with the proline degradation pathway (Efron et al., supra). Aspartate aminotransferase (AspAT) utilizes oxaloacetate to convert 4-OH-Glu to 4-hydroxy-2-oxoglutarate (HOG). HOG is then cleaved by the unique HOG aldolase (HOGA) into two fragments, glyoxylate and pyruvate. The glyoxylate can then be converted to glycolate and glycine via glyoxylate reductase (GR) and alanine:glyoxylate aminotransferase (AGT), respectively. Glycolate can be converted back into glyoxylate by glycolate oxidase (GO).

AGT, GR, and HOGA are mutated within primary hyperoxaluria patients (PH type 1, 2, and 3, respectively). For PHI and PH2 patients, the glyoxylate produced from Hyp could exacerbate the already high levels of glyoxylate, and increase oxalate production via the lactate dehydrogenase (LDH). For PH3 patients, HOGA is inactivated, leading to a buildup of HOG (Riedel et al., Biochim Biophys Acta 1822, 1544-1552, 2012; Belostotsky et al., J Mol Med (Berl) 90, 1497-1504, 2012). Recent studies identified that HOG can inhibit GR, potentially
leading to a PH2-like phenotype (Riedel et al., Biochim Biophys Acta 1822, 1544-1552, 2012). In contrast, glycolic aciduria, caused by deficiencies in GO, is not associated with any overt consequences, and glycolate can be excreted (Frishberg et al. J Med Genet 51, 526-529, 2014).

Thus, and without wishing to be bound by theory, inhibition of GO by a small molecule inhibitor that targets the enzyme active site is not expected to lead to any adverse side effects, and will block the formation of glyoxylate and oxalate from glycolate for all PH patient types. Inhibition of GO is also expected to help idiopathic stone formers and other individuals with high urinary oxalate levels, such as those that have undergone gastric bypass surgery. For the latter, there is a significant increase in stone formation that may benefit from prophylactic treatment post surgery. While the exact origins of the oxalate in these patients has not been determined, inhibition of HYPDH will decrease glyoxylate and oxalate levels, which will ultimately reduce the glyoxylate and oxalate burden in them.

1. Active compounds.

Active compounds as described herein can be prepared in accordance with known procedures or variations thereof that will be apparent to those skilled in the art.

As will be appreciated by those of skill in the art, the active compounds of the various formulas disclosed herein may contain chiral centers, e.g., asymmetric carbon atoms, and the present disclosure is inclusive of both: (i) racemic mixtures of the active compounds, and (ii) enantiomeric forms of the active compounds. The resolution of racemates into enantiomeric forms can be done in accordance with known procedures in the art. For example, the racemate may be converted with an optically active reagent into a diastereomeric pair, and the diastereomeric pair subsequently separated into the enantiomeric forms.

Also included in active compounds disclosed herein are tautomers (e.g., tautomers of triazole and/or pyrazole) and rotamers.

As described herein, certain groups or portions of the compounds of the invention may optionally be substituted with one or more substituents, such as those illustrated generally herein. In general, the term "substituted" refers to the replacement of hydrogen in a given structure with a substituent. Unless otherwise indicated, a substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable compounds. "Stable" as used herein refers to a chemically feasible compound that is not substantially altered when kept
at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

As used herein in the accompanying chemical structures, "H" refers to a hydrogen atom. "C" refers to a carbon atom. "N" refers to a nitrogen atom. "S" refers to a sulfur atom.

The term "hydroxy," as used herein, refers to a group -OH.

"Carbonyl" is a group having a carbon atom double-bonded to an oxygen atom (C=O).

"Carboxy" as used herein refers to a group -COOH or -COO -.

"Amine" or "amino" refers to a group –NH₂.

"Halo" is a halogen group selected from the group consisting of fluoro (-F), choro (-Cl), bromo (-Br), and iodo (-I). "Haloalkyl" is a halogen group connected to the parent compound by an alkyl group.

"Alkyl," as used herein, refers to a saturated straight or branched chain, or cyclic hydrocarbon containing from 1 to 10 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, n-decyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. "Lower alkyl" as used herein, is a subset of alkyl and refers to a straight or branched chain hydrocarbon group containing from 1 to 4 carbon atoms. Representative examples of lower alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, and the like. The alkyl groups may be optionally substituted with one or more suitable substituents, such as halo, hydroxy, carboxy, amine, etc.

"Aryl," as used herein, refers to a monocyclic carbocyclic ring system or a bicyclic carbocyclic fused or directly adjoining ring system having one or more aromatic rings. Examples include, but are not limited to, phenyl, indanyl, indenyl, tetrahydronaphthyl, and the like. As noted, in some embodiments, the aryl has two aromatic rings, which rings are fused or directly adjoining. Examples include, but are not limited to, biphcnyl, naphthyl. azulenyl, etc. The aryl may be optionally substituted with one or more suitable substituents, such as alkyl, halo, hydroxy, carboxy, amine, etc.

"Heteroaryl," as used herein, refers to a monovalent aromatic group having a single ring or two fused or directly adjoining rings and containing in at least one of the rings at least one heteroatom (typically 1 to 3) independently selected from nitrogen, oxygen and sulfur. Examples include, but are not limited to, pyrrole, imidazole, thiazole, oxazole, furan, thiophene, triazole, pyrazole, isoxazole, isothiazole, pyridine, pyrazine, pyridazine, pyrimidine, triazine, and the like. As noted, in some embodiments, the heteroaryl has two aromatic rings, which rings are fused or
directly adjoining. Examples include, but are not limited to, benzothiophene, benzofuran, indole, benzoimidazole, benzthiazole, quinoline, isoquinoline, quinazoline, quinoxaline, phenyl-pyrrole, phenyl-thiophene, etc. The heteroaryl may be optionally substituted with one or more suitable substituents, such as alkyl, halo, hydroxy, carboxy, amine, etc.

A "pharmaceutically acceptable salt" is a salt that retains the biological effectiveness of the free acids or bases of a specified compound and that is not biologically or otherwise undesirable. Examples of pharmaceutically acceptable salts may include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, gamma-hydroxybutyrates, glycollates, tartrates, methanesulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

A "prodrug" is a compound that is converted under physiological conditions or by solvolysis or metabolically to a compound that is pharmaceutically active. A thorough discussion is provided in T. Higuehi and V. Stella, Prodrugs as Novel delivery Systems. Vol. 14 of the A.C.S. Symposium Series and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated by reference herein in their entirety. See also Huttunen et al., "Prodrugs - from Serendipity to Rational Design." Pharmacological Reviews 63(3):750-771 (2011), which is incorporated by reference herein. Example prodrugs include, but are not limited to, the addition of/conversion to phosphate(s), amino acid esters, amino acid amides, sugar derivatives, alkyl or aryl esters, etc., at an -OH, -SH, -NH or -COOH group of the parent active compound.

Provided herein as active compounds according to some embodiments are compounds of Formula I:

```
OOC

H

A

D

B

R

1
```
wherein:

A is CH₂ or S;
B is CH or N;
D is CH or N; and
R¹ is aryl or heteroaryl, wherein said aryl or heteroaryl has two aromatic rings, which rings are fused or directly adjoining,
or a pharmaceutically acceptable salt or prodrug thereof.

In some embodiments of **Formula I**, A is C₃. In some embodiments, A is S. In some embodiments, B is CH. In some embodiments, B is N. In some embodiments, D is CH. In some embodiments, D is N.

In some embodiments of **Formula I**, R¹ is benzothiophene or biphenyl.

In some embodiments of **Formula I**, R¹ is selected from the group consisting of:

wherein R¹₀, R¹¹ and R¹² are each independently selected from the group consisting of: H, alkyl, halo and haloalkyl.

Also provided are GO inhibitor compounds of **Formula II**:
wherein:

5 A is CH₂ or S;

R¹ is aryl or heteroaryl, wherein said aryl or heteroaryl has two aromatic rings, which rings are fused or directly adjoining; and

R² is H or OH,

or a pharmaceutically acceptable salt or prodrug thereof.

10 In some embodiments of Formula II, A is CH₂. In some embodiments, A is S.

In some embodiments of Formula II, R¹ is benzothiophene or biphenyl.

15 In some embodiments of Formula II, R¹ is selected from the group consisting of:

wherein R¹⁰, R¹¹, and R¹² are each independently selected from the group consisting of: H, alkyl, halo and haloalkyl.

20 2. Formulations.

The active compounds described herein may be formulated for administration in a pharmaceutical carrier in accordance with known techniques. See, e.g., Remington, *The Science*
and Practice of Pharmacy (9th Ed. 1995). In the manufacture of a pharmaceutical formulation according to the invention, the active compound (including the physiologically acceptable salts or prodrugs thereof) is typically admixed with, *inter alia*, an acceptable carrier. The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the patient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose formulation, for example, a tablet, which may contain from 0.01 or 0.5% to 95% or 99% by weight of the active agent. One or more active agents may be incorporated in the formulations of the invention, which may be prepared by any of the well-known techniques of pharmacy comprising admixing the components, optionally including one or more accessory ingredients.

The pharmaceutical compositions may also contain other additives, such as pH-adjusting additives. In particular, useful pH-adjusting agents include acids, such as hydrochloric acid, bases and/or buffers, such as sodium lactate, sodium acetate, sodium phosphate, sodium citrate, sodium borate, or sodium gluconate. Further, the compositions may contain preservatives. Useful preservatives include methyl paraben, propyl paraben, benzoic acid and benzyl alcohol.

The formulations may comprise nanoparticles, such as biodegradable polymers and/or liposome-forming material, for encapsulation and/or delivery of the active agent(s). *See, e.g.*, WO 2014/201312 to Wang et al.; Cho and Jung. "Supramolecular Complexation of Carbohydrates for the Bioavailability Enhancement of Poorly Soluble Drugs," *Molecules* 20:19620-19646, 2015; Nogueira et al., "Design of liposomal formulations for cell targeting," *Colloids Surf B Biointerfaces* 136:514-526, 2015. In some embodiments, liver-targeting nanoparticles may be used for specific delivery of active agent(s) acting at the liver. *See, e.g.*, U.S. 2015/0150994 to Hahn et al.; U.S. 2008/0138394 to Kim et al. In some embodiments, kidney-targeting nanoparticles may be used for specific delivery of active agent(s) acting at the kidney. *See, e.g.*, U.S. Patent No. 8,318,199 to Kim et al.; U.S. 2012/0196807 to Nakamura et al.


Formulations of the invention may include those suitable for oral, buccal (sub-lingual), parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous), topical (i.e., both skin and mucosal surfaces, including airway surfaces) and transdermal administration, although the
most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular active compound being used.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of the active compound(s); as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients as noted above). In general, the formulations of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, a tablet may be prepared by compressing or molding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

Formulations suitable for oral administration also include food product formulations, such as a nutritional bar or an animal feed (e.g., pet food such as dog or cat food). Food product formulations may include one or more of carbohydrates such as wheat, corn rice, barley or oats, dairy products such as milk, oils such as canola oil or soybean oil, flavorants such as sugar or syrup, coloring, chocolate, preservatives, etc. Pet food formulations, in particular, may include meat, poultry, fish or other animal-derived components such as eggs.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising the active compound in a flavored base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration comprise sterile aqueous and non-aqueous injection solutions, which preparations are preferably isotonic with the blood of the intended recipient. These preparations may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient. Aqueous and non-aqueous sterile suspensions may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition.
requiring only the addition of the sterile liquid carrier, for example, saline or water-for-injection immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. For example, in one aspect of the present invention, there is provided an injectable, stable, sterile composition comprising an active compound(s) in a unit dosage form in a sealed container. The active compound(s) may be provided in the form of a lyophilizate which is capable of being reconstituted with a suitable pharmaceutically acceptable carrier to form a liquid composition suitable for injection thereof into a subject.

When the active compound(s) is substantially water-insoluble, a sufficient amount of emulsifying agent which is physiologically acceptable may be employed in sufficient quantity to emulsify the compound or salt in an aqueous carrier. One such useful emulsifying agent is phosphatidyl choline.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include petroleum jelly, lanoline, polyethylene glycols, alcohols, transdermal enhancers, and combinations of two or more thereof.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Formulations suitable for transdermal administration may also be delivered by iontophoresis (see, for example. *Pharmaceutical Research* 3 (6):318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. Suitable formulations comprise citrate or bisXtris buffer (pH 6) or ethanol/water and contain from 0.1 to 0.2M active ingredient.

The unit dosage form typically comprises from about 1 mg, 5 mg, 10 mg, 100 mg, 250 mg, 500 mg, 1 gram, 5 grams, 10 grams, or any ranges therein, of the active compound(s), depending on the subject being treated (e.g., human or non-human mammalian subject). In some embodiments, the unit dosage form is in the range of 500 mg to 10 grams, keeping in mind that a good portion of the active compound(s) may not be absorbed upon administration (e.g., oral administration).

The present invention is explained in greater detail in the following non-limiting examples.

EXAMPLES
Example 1. Glycolate oxidase (GO) inhibitor design. Based on crystal structures of human GO1 with CCPST and CDST as well as other biochemical data, GO inhibitors are designed to exploit one or more of the following interactions:

1. Force W110 to "flip" out of the active site, causing loop 4 to become disordered;
2. Protonated nitrogen at position 3 directly interacts with the catalytic residue His260;
3. Carboxylate interaction with one or both of two conserved Arg residues.

Example 2. Example GO inhibitors. With the above considerations in mind, the following compounds are designed as GO inhibitors.
\[ a. \quad R = OH \]
\[ b. \quad R = H \]
**Example 3. Testing of inhibitors of GO.** The inhibition of recombinant, human liver GO (the \( \text{HAO1} \) gene product) is readily determined by a coupled assay that contains 2,6-dichloroindophenol (DCIP) (Murray et al., Biochemistry 47, 2439-2449, 2008). Briefly, GO is pre-incubated at 37 °C with or without inhibitor in 100 mM potassium phosphate pH 7.5 (0.1% DMSO final) for 5 min. An aliquot of pre-warmed DCIP and glycolate is added to start the reaction (final concentration 75 \( \mu \)M DCIP, 3 mM glycolate). The reaction rate is determined by monitoring the decrease at 600 nm (extinction coefficient of 21 mM\(^{-1}\) cm\(^{-1}\)). COST inhibits GO with an apparent Ki of \(~15\) nM.

**Example 4. Therapy with GO inhibitor.** Subjects are administered a GO inhibitor to treat kidney stones.

---

**Literature Cited.**


Example 5. Mouse model. Mice that do not express GO have been generated. The Haol (GO) deficient animals developed normally and exhibited similar behavior to wild-type litter mates. The genotype of each mouse was confirmed by PGR analysis from a tail snip. Liver was analyzed by western analysis. These tests confirmed that the Haol homozygous mouse did not contain GO in any of the samples. As expected, GO is not present in the kidney of all mouse strains.

Mice lacking GO appear normal apart from an increased urinary glycolate excretion and elevated plasma glycolate level. Male mice lacking GO excreted 1.4 fold more urinary oxalate than wild type litter mates; however, female Haol deficient mice show no significant difference in urinary oxalate excretion compared to Wt litter mates. It is noted that this finding with male Haol deficient mice is not consistent with data recently published by Dr. Salido’s group that showed no difference in urinary oxalate excretion between Wt and Haol deficient male mice. However, the diet used by Dr. Salido’s group was different from that used in this study.

The heterozygous (Htz) Haol mouse strain showed reduced expression of protein as measured by western Blot.
Given the cycle of glycolate-glyoxylate interconversion that will occur via GO and glyoxylate reductase activities in hepatocytes lacking alanine-glyoxylate aminotransferase (AGT), inhibition of GO is likely to reduce oxalate synthesis in PHI patients. The contribution of glycolate to oxalate synthesis in humans with functional AGT activity is not known; however, individuals lacking GO appear normal. Frishberg et al., J Med Genet 51(8):526-9 (2014). Therefore, strategies to reduce GO activity may provide benefit for reducing urinary oxalate excretion in patients with calcium oxalate kidney stone disease.

The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.
That which is claimed is:

1. A compound of Formula I:

   ![Formula I diagram]

   I

   wherein:
   - A is \( \text{CH}_2 \) or S;
   - B is \( \text{CH} \) or N;
   - D is \( \text{CH} \) or N; and
   - \( R^1 \) is aryl or heteroaryl, wherein said aryl or heteroaryl has two aromatic rings, which rings are fused or directly adjoining,
     or a pharmaceutically acceptable salt or prodrug thereof.

2. The compound of claim 1, wherein A is \( \text{C}^{34} \).

3. The compound of claim 1, wherein A is S.

4. The compound of claim 1, claim 2 or claim 3, wherein B is CH.

5. The compound of claim 1, claim 2 or claim 3, wherein B is N.

6. The compound of any one of claims 1-5, wherein D is CH.

7. The compound of any one of claims 1-5, wherein D is N.

8. The compound of any one of claims 1-7, wherein \( R^1 \) is benzothiophene or biphenyl.
9. The compound of any one of claims 1-7, wherein \( R^1 \) is selected from the group consisting of:

\[
\begin{align*}
\text{alkyl, halo and haloalkyl,} \\
\text{or a pharmaceutically acceptable salt or prodrug thereof.}
\end{align*}
\]

10. The compound of claim 1, wherein said compound is selected from the group consisting of:

\[
\begin{align*}
\text{or a pharmaceutically acceptable salt thereof.}
\end{align*}
\]

25
11. The compound of claim 1, wherein said compound is selected from the group consisting of:

![Chemical structures]

or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1, wherein said compound is selected from the group consisting of:

![Chemical structures]

or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1, wherein said compound is selected from the group consisting of:
or a pharmaceutically acceptable salt thereof.

14. The compound of claim 1, wherein said compound is selected from the group consisting of:

or a pharmaceutically acceptable salt thereof.

15. The compound of claim 1, wherein said compound is selected from the group consisting of:
or a pharmaceutically acceptable salt thereof.

16. The compound of claim 1, wherein said compound is selected from the group consisting of:

or a pharmaceutically acceptable salt thereof.

17. The compound of claim 1, wherein said compound is selected from the group consisting of:
or a pharmaceutically acceptable salt thereof.

18. The compound of claim 1, wherein said compound is selected from the group consisting of:

or a pharmaceutically acceptable salt thereof.

19. A compound of **Formula II**:

wherein:

A is C\&sup; or S;
R\textsuperscript{1} is aryl or heteroaryl, wherein said aryl or heteroaryl has two aromatic rings, which rings are fused or directly adjoining; and
R\textsuperscript{2} is H or OH,
or a pharmaceutically acceptable salt or prodrug thereof.

20. The compound of claim 19, wherein A is C\textsubscript{3}4.

21. The compound of claim 19, wherein A is S.

22. The compound of claim 19, claim 20 or claim 21, wherein R\textsuperscript{2} is H.

23. The compound of claim 19, claim 20 or claim 21, wherein R\textsuperscript{2} is O\textsubscript{1}1.

24. The compound of any one of claims 19-23, wherein R\textsuperscript{1} is benzothiophene or biphenyl.

25. The compound of any one of claims 19-23, wherein R\textsuperscript{1} is selected from the group consisting of:

\[ \text{wherein } R^{10}, R^{11} \text{ and } R^{12} \text{ are each independently selected from the group consisting of: H, alkyl, halo and haloalkyl,} \]
\[ \text{or a pharmaceutically acceptable salt or prodrug thereof.} \]

26. The compound of claim 19, wherein said compound is selected from the group consisting of:
or a pharmaceutically acceptable salt thereof.

27. The compound of claim 19, wherein said compound is selected from the group consisting of:

or a pharmaceutically acceptable salt thereof.
28. The compound of claim 19, wherein said compound is selected from the group consisting of:

![Chemical structures](image)

or a pharmaceutically acceptable salt thereof.

29. The compound of claim 19, wherein said compound is selected from the group consisting of:
or a pharmaceutically acceptable salt thereof.

30. A pharmaceutical composition comprising a compound, pharmaceutically acceptable salt or prodrug of any one of claims 1-29.

31. The pharmaceutical composition of claim 30, wherein said composition is formulated for oral administration.

32. The pharmaceutical composition of claim 30, wherein said composition is a food product formulation.

33. The pharmaceutical composition of claim 30, wherein said composition is a capsule, cachet, lozenge, or tablet.
34. The pharmaceutical composition of any one of claims 30-33, wherein said formulation is provided in unit dosage form of from 1 mg to 10 grams of the compound, pharmaceutically acceptable salt or prodrug.

35. A method of treating kidney stones (e.g., inhibiting the formation of oxalate kidney stones; treating primary hyperoxaluria), comprising: administering to a subject in need thereof a therapeutically effective amount of the compound, pharmaceutically acceptable salt or prodrug of any one of claims 1-29, or the pharmaceutical composition of any one of claims 30-34.

36. A method of inhibiting the production of glyoxylate and/or oxalate, and/or inhibiting glycolate oxidase (GO), in a subject in need thereof, comprising: administering to said subject a therapeutically effective amount of the compound, pharmaceutically acceptable salt or prodrug of any one of claims 1-29, or the pharmaceutical composition of any one of claims 30-34.

37. The method of claim 35 or claim 36, wherein said subject is a human subject.

38. The method of claim 35 or claim 36, wherein said subject is a non-human animal subject.

39. The use of the compound, pharmaceutically acceptable salt or prodrug of any one of claims 1-29, or the pharmaceutical composition of any one of claims 30-33, for controlling or inhibiting the formation of calcium oxalate kidney stones, inhibiting the production of glyoxylate and/or oxalate, and/or inhibiting glycolate oxidase (GO), in a human or non-human animal subject in need thereof.

40. The use of the compound, pharmaceutically acceptable salt or prodrug of any one of claims 1-29, in the preparation of a medicament for controlling or inhibiting the formation of calcium oxalate kidney stones, inhibiting the production of glyoxylate and/or oxalate, and/or inhibiting glycolate oxidase (GO), in a human or non-human animal subject in need thereof.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/65300

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07D 207/327 (2017.01)
CPC - C07D207/327; C07C21 01/06

B. FIELDS SEARCHED

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 database and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>US 2007/0142452 A1 (BANNER et al.) 21 June 2007 (21.06.2007) para [01 15], [01 19], [0269], Example 64</td>
<td>1-2, 4</td>
</tr>
<tr>
<td>Y</td>
<td>US 2009/0298905 A1 (COSSIO et al.) 03 December 2009 (03.12.2009) para [0073], [0108], Example 8</td>
<td>1-2, 4</td>
</tr>
<tr>
<td>A</td>
<td>Pubchem-SID 234035183 Deposit Date: 12 February 2015 (12.02.2015) pg 3, Fig.</td>
<td>1-2, 4</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "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
"Q" document member of the same patent family

Date of the actual completion of the international search 19 March 2017
Date of mailing of the international search report 13 APR 2017

Name and mailing address of the ISA/US
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Form PCT/ISA/2 10 (second sheet) (January 2015)
INTERNATIONAL SEARCH REPORT

**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.: 6-9, 24-25 and 30-40
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 64(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:
- Please see attached sheet-

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.: 1-2, 4

**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.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2015)
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 1-5 and 10-18, directed to compounds of Formula I of claim 1, selected from the various structures listed in claims 10-18. The compound of claim 1 will be searched to the extent that it encompasses the first species of claim 1, represented by Formula I, wherein A is \( \text{CH}2 \); B is CH; D is CH; and R1 is aryl, wherein said aryl has two aromatic rings, which rings are fused. It is believed that claims 1-2 and 4 read on this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1. Applicant is invited to elect additional compounds of Formula I, 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 "I" 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 a compound of claim 1, represented by the compound listed in row 1, col 1 of claim 10, wherein A is S; B is N; D is N; and R1 is heteroaryl, wherein said heteroaryl has two aromatic rings which are fused (i.e., claims 1, 3, 5, 10).

Group II: Claims 19-23 and 26-29, directed to a compound of Formula II.

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 of Formula I, which is not required by any other invention of Group I+.

Group II includes the technical feature of a compound of Formula II, not required by Group I+.

Common technical features:

The inventions of Group I+ share the technical feature of a compound having the core structure of Formula I of claim 1.

Groups I+ and II share the technical feature of a compound having a heterocyclic ring attached to \( -\text{A-R1} \).

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by Pubchem-SID 234035183 Deposit 'Hewi' 17 FR/niary '7ni5 (12.07.2015) (hereinafter "Pubchem") which teaches a compound of Formula I wherein A is \( \text{CH}2 \); B is CH; D is CH; and R1 is aryl, wherein said aryl has two aromatic rings, which rings are directly adjoining (pg 3, Fig).

As said compound was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions of Groups I+ and II.

The inventions of Group I+ and II thus lack unity under PCT Rule 13.