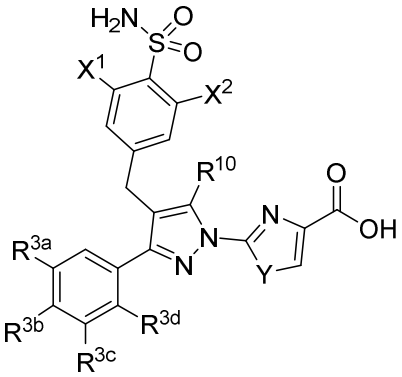
[00012] Several LDH inhibitors have been described in the literature as oncolytic agents (Granchi, J. Med. Chem. 2011, 54, 1599-1612; Ward, J. Med. Chem. 2012, 55, 3285-3306; Kohlmann, J. Med. Chem. 2013, 56, 1023-1040; Fauber, Bioorg. Med. Chem. Lett. 2013, 20, 5533–5539; Purkey, ACS Med. Chem. Lett. 2016, 7, 896-901; Rai, J. Med. Chem. 2017, 60, 9184-9204). The majority of these inhibitors suffer from modest LDH inhibition, poor cellular penetration and poor pharmacokinetic properties, making their application as therapies challenging. Furthermore, the specific requirements of an effective agent for the treatment of hyperoxaluria differ significantly from those required for oncology. Most oncology agents have a systemic tissue distribution profile, ensuring the compound can inhibit cancer cells throughout the body. In addition, for oncology indications, compounds need to exhibit a high degree of cytotoxicity. In contrast, with hyperoxaluria, one desires a liver-targeted tissue distribution profile, with improved activity in hepatocytes and little or no cytotoxicity.

[00013] There remains a need for novel classes of liver-targeted small molecule therapeutics which can inhibit the LDH protein to be utilized for treatment of diseases such as primary hyperoxaluria and secondary hyperoxalurias, where reducing the amount of oxalate synthesis would be beneficial.

SUMMARY

[00014] In certain ~~embodiments~~examples, provided herein are compounds of Formula (I), or a pharmaceutically acceptable salt or solvate thereof. In certain ~~embodiments~~examples, the compounds are inhibitors of the lactate dehydrogenase (LDH) enzyme. In certain ~~embodiments~~examples, the compounds as LDH inhibitors will confer therapeutic benefits associated with reducing oxalate levels including lowering endogenous production of oxalate.

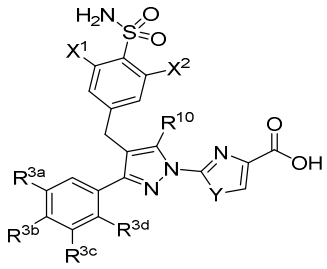
[00015] In certain ~~embodiments~~examples, provided herein are compounds having the Formula (I):



(I),

or a pharmaceutically acceptable salt or solvate thereof, wherein:
Y is O or S;
X^1 is hydrogen, fluoro or chloro;
X^2 is hydrogen, fluoro or chloro;
R^{3a} is hydrogen, fluoro, chloro, cyano, C_{1-3}haloalkyl, C_{1-3}alkoxy or C_{1-3}haloalkoxy;
R^{3b} is hydrogen, fluoro, chloro, cyano or C_{1-3}haloalkyl;
R^{3c} is hydrogen, fluoro or chloro;
R^{3d} is hydrogen, fluoro or chloro;
R^{10} is C_{1-3}alkyl, C_{3-4}cycloalkyl or C_{3-4}cycloalkylC_{1-3}alkyl;
provided (i) when R^{3b} is fluoro, R^{3a} is methoxy and R^{3c} and R^{3d} are each hydrogen, or (ii) when R^{3b} is hydrogen, R^{3a} is isopropyloxy and R^{3c} and R^{3d} are each hydrogen, or (iii) when R^{3a}, R^{3b}, R^{3c} and R^{3d} are all hydrogen, then at least one of X^1 and X^2 is fluoro or chloro; and provided, when R^{3a} is CF_3, R^{3b} is fluoro, and R^{3c} and R^{3d} are each hydrogen, then R^{10} is not cyclopropylmethyl.

[00015a] In one aspect, the present disclosure refers to a compound of Formula (I):



(I),
or a pharmaceutically acceptable salt or solvate thereof, wherein:
Y is O or S;
X^1 is hydrogen, fluoro or chloro;
X^2 is hydrogen, fluoro or chloro;
R^{3a} is hydrogen, fluoro, chloro, cyano, C_{1-3}haloalkyl, C_{1-3}alkoxy or C_{1-3}haloalkoxy;
R^{3b} is hydrogen, fluoro, chloro, cyano or C_{1-3}haloalkyl;
R^{3c} is hydrogen, fluoro or chloro;
R^{3d} is hydrogen, fluoro or chloro;
R^{10} is C_{1-3}alkyl, C_{3-4}cycloalkyl or C_{3-4}cycloalkylC_{1-3}alkyl;
provided (i) when R^{3b} is fluoro, R^{3a} is methoxy and R^{3c} and R^{3d} are each hydrogen, or (ii) when R^{3b} is hydrogen, R^{3a} is isopropyloxy and R^{3c} and R^{3d} are each hydrogen, or (iii) when R^{3a}, R^{3b}, R^{3c} and R^{3d} are all hydrogen, then at least one of X^1 and X^2 is fluoro or chloro; and provided, when R^{3a} is CF_3, R^{3b} is fluoro, and R^{3c} and R^{3d} are each hydrogen, then R^{10} is not cyclopropylmethyl.

[00016] Also provided are pharmaceutical compositions formulated for administration by an appropriate route and means containing therapeutically effective concentrations of one or more of the compounds provided herein, or pharmaceutically acceptable salts or solvates thereof, and optionally comprising at least one pharmaceutical carrier. In one aspect, the present disclosure refers to a pharmaceutical composition comprising any one of the compounds disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier. In certain ~~embodiments~~examples, the pharmaceutical compositions deliver amounts effective for lowering oxalate levels in a subject in need thereof. In certain ~~embodiments~~examples, the pharmaceutical compositions deliver amounts effective for reducing kidney stone formation in a subject in need thereof.

[00017] In another ~~aspect~~example, provided herein are methods of treating a disease or disorder associated with elevated oxalate levels, comprising administering to a subject having such disease or disorder, a therapeutically effective amount of one or more compounds disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical compositions disclosed herein. In one aspect, the present disclosure refers to use of any one of the compounds disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a disease or disorder associated with elevated oxalate levels in a subject having such disease and disorder. In certain ~~embodiments~~examples, the disease or disorder is hyperoxaluria, chronic kidney disease (CKD), end stage renal disease (ESRD) or kidney stone disease. In yet certain ~~embodiments~~examples, the disease or disorder is primary hyperoxaluria, idiopathic hyperoxaluria or idiopathic oxalate kidney stone disease. In yet certain ~~embodiments~~examples, the disease or disorder is associated with the *AGXT*, *GRHPR* or *HOGA1* mutation, or a combination of mutations thereof.

[00018] Also provided herein are combination therapies using one or more compounds or compositions provided herein, in combination with other pharmaceutical agents for the treatment of the diseases and disorders described herein.

[00019] These and other ~~aspects~~ examples of the subject matter described herein will become evident upon reference to the following detailed description and drawings.

BRIEF DESCRIPTION OF THE DRAWING(S)

[00020] FIG. 1 depicts the percent reduction in urinary oxalate levels in AGXT knockdown mouse model of primary hyperoxaluria 1 (PH1) following administration of compounds of Formula (I) disclosed herein, at 5 mg/kg QD PO for 5 days.

[00021] FIG. 2 depicts the XlogP distribution of the compounds of Formula (I) disclosed herein.

DETAILED DESCRIPTION

A. DEFINITIONS

[00022] 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. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise. The term "subject" refers to an animal which includes mammals such as mice, rats, cows, sheep, pigs, rabbits, goats, horses, monkeys, dogs, cats, and humans, including neonatal, infant, juvenile, adolescent, adult or geriatric patients.

[00023] The term "halo", "halogen" or "halide" as used herein and unless otherwise indicated, refers to any radical of fluorine, chlorine, bromine or iodine.

[00024] The term "alkyl" as used herein and unless otherwise indicated, refers to a saturated hydrocarbon chain radical that may be a straight chain or branched chain, containing the indicated number of carbon atoms or otherwise having from one to ten, one to eight, one to six or one to four carbon atoms, and which is attached to the rest of the molecule by a single bond. In certain embodiments, the hydrocarbon chain is optionally deuterated. For example, C_{1-3} alkyl