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(54) Title: HETEROCYCLIC DERIVATIVES AND USE THEREOF

(57) Abstract: Provided are certain URAT1 inhibitors, pharmaceutical compositions thereof, and methods of use thereof.

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HETEROCYCLIC DERIVATIVES AND USE THEREOF

[1] This application claims the priority to the U.S. provisional application No. 62/862,164, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[2] Provided are certain compounds or pharmaceutically acceptable salts thereof which can inhibit activity of urate anion transporter 1 (URAT1) and may be useful for the treatment of reducing uric acid levels and treatment of disorders, particularly gout.

BACKGROUND OF THE INVENTION

[3] Uric acid is the final metabolite of endogenous and dietary purine metabolism. The main route of uric acid excretion is the kidney. Approximately two-thirds of uric acid is excreted in the urine and the remaining is excreted in feces. Urate functions as an antioxidant in the blood, but elevated levels of uric acid (a condition known as hyperuricemia) can precipitate gout. Hyperuricemia may result from the overproduction of uric acid or from insufficient renal elimination, or a combination of the both.

[4] Gout is a painful, debilitating and progressive disease caused by abnormally elevated levels of serum uric acid. Gout is associated with elevated levels of uric acid that crystallize and deposit in joints, tendons, and surrounding tissues. This leads to the deposition of painful, needle-like uric acid crystals in and around the connective tissue of the joints and in the kidneys, resulting in inflammation, the formation of disfiguring nodules, intermittent attacks of severe pain and kidney damage. In addition, recent studies suggest that elevated urate levels play a pivotal role in other important diseases such as chronic renal disease, cardiovascular disease, diabetes and hypertension.

[5] Agents that decrease serum uric acid levels may be used to treat the cause of gout. These include agents that: inhibit the enzymes that result in uric acid production, such as xanthine oxidase inhibitors (e.g. allopurinol, febuxostat or tisopurine), or purine nucleoside phosphorylase (PNP) inhitors (e.g. ulodesine); metabolise uric acide, such as urate oxidases, also known as uricase (e.g. pegloticase); or increase the excretion of uric acid in the urine (uricosurics). Uricosurics include agents that inhibit the transporters responsible for renal reabsorption of uric acid back into the blood, such as benziodarone, isobromindione, probenecid and sulphinpyrazone, and URAT1 inhibitors (e.g. lesinuard).

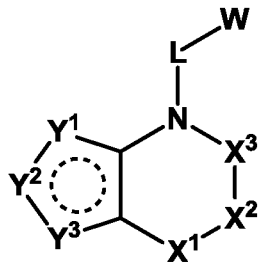
[6] Urate anion transporter 1 (URAT1) is an organic anion transporter, which primarily found in kidney, and it is also known as solute carrier family 22, member 12, and is encoded by the gene *SLC22A12*. Human genetic analysis has demonstrated that polymorphisms in the *SLC22A12* gene are directly associated with changes in serum uric acid. URAT1-mediated uric acid uptake has been shown by experiments using the *Xenopus* oocyte expression system. Inhibitors of urate transporter, such as URAT1, can prevent reuptake of uric acid at the proximal renal tubule and thus increase renal excretion of uric acid, and are therefore effective in the prevention and treatment of gout.

[7] Therefore, a compound having inhibitory activities against URAT1 will a successfully therapeutic approach for dedicated classes of patients with dysregulated URAT1 expression and/or activity. Although URAT1 inhibitors were disclosed in the arts, e.g. WO 2009070740 and WO 2011159839, many suffer from low potency, short half-life or toxicity. Therefore, there is a need for new URAT1 inhibitors that have at least one advantageous property selected from potency, stability, selectivity, toxicity, pharmacokinetics and pharmacodynamics properties as an alternative for the treatment of diseases such as hyperuricemia and gout. In this regard, a novel class of URAT1 inhibitors is provided herein.

DISCLOSURE OF THE INVENTION

[8] Disclosed herein are certain novel compounds, pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, and their use as pharmaceuticals.

[9] In one aspect, disclosed herein is a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

W is selected from aryl and heteroaryl, wherein aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X;

L is selected from $-(CR^{C0}R^{D0})_uC(O)(CR^{C0}R^{D0})_t-$, $-(CR^{C0}R^{D0})_uC(O)NR^{A0}(CR^{C0}R^{D0})_t-$, $-(CR^{C0}R^{D0})_uS(O)_r(CR^{C0}R^{D0})_t-$ and $-(CR^{C0}R^{D0})_uS(O)_rNR^{A0}(CR^{C0}R^{D0})_t-$;

X^1 is selected from $CR^{C1}R^{D1}$, NR^{A1}, O and $S(O)_r$;

X^2 and X^3 are independently selected from $-(CR^{C1}R^{D1})_u-$, $-(CR^{C1}R^{D1})_uO(CR^{C1}R^{D1})_t-$, $-(CR^{C1}R^{D1})_uNR^{A1}(CR^{C1}R^{D1})_t-$, $-(CR^{C1}R^{D1})_uS(CR^{C1}R^{D1})_t-$, $-(CR^{C1}R^{D1})_uC(O)(CR^{C1}R^{D1})_t-$ and $-(CR^{C1}R^{D1})_uS(O)_r(CR^{C1}R^{D1})_t-$;

Y^1, Y^2 and Y^3 are independently selected from N, NR^1, CR^2, O and $S(O)_r$;

R^1 is selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1};

R^2 is selected from hydrogen, deuterium, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, CN, NO_2, $-NR^{A2}R^{B2}$, $-OR^{A2}$, $-C(O)R^{A2}$, $-C(=NR^{E2})R^{A2}$, $-C(=N-OR^{B2})R^{A2}$, $-C(O)OR^{A2}$, $-OC(O)R^{A2}$, $-C(O)NR^{A2}R^{B2}$, $-NR^{A2}C(O)R^{B2}$, $-C(=NR^{E2})NR^{A2}R^{B2}$, $-NR^{A2}C(=NR^{E2})R^{B2}$, $-OC(O)NR^{A2}R^{B2}$, $-NR^{A2}C(O)OR^{B2}$,

$-NR^{A2}C(O)NR^{A2}R^{B2}$, $-NR^{A2}C(S)NR^{A2}R^{B2}$, $-NR^{A2}C(=NR^{E2})NR^{A2}R^{B2}$, $-S(O)_rR^{A2}$, $-S(O)(=NR^{E2})R^{B2}$, $-N=S(O)R^{A2}R^{B2}$, $-S(O)_2OR^{A2}$, $-OS(O)_2R^{A2}$, $-NR^{A2}S(O)_rR^{B2}$, $-NR^{A2}S(O)(=NR^{E2})R^{B2}$, $-S(O)_rNR^{A2}R^{B2}$, $-S(O)(=NR^{E2})NR^{A2}R^{B2}$, $-NR^{A2}S(O)_2NR^{A2}R^{B2}$, $-NR^{A2}S(O)(=NR^{E2})NR^{A2}R^{B2}$, $-P(O)R^{A2}R^{B2}$ and $-P(O)(OR^{A2})(OR^{B2})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X2};

each R^{A0} is independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X0};

each R^{A1} is independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1};

each R^{A2} and R^{B2} are independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl, and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X2};

or "R^{A2} and R^{B2}" together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1 or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus and optionally substituted with 1, 2 or 3 R^{X2} groups;

each R^{C0} and R^{D0} are independently selected from hydrogen, deuterium, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X0};

or each "R^{C0} and R^{D0}" together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen and optionally substituted with 1 2 or 3 R^{X0} groups;

each R^{C1} and R^{D1} are independently selected from hydrogen, deuterium, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1};

or each "R^{C1} and R^{D1}" together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen and optionally substituted with 1 2 or 3 R^{X1} groups;

each R^{E2} are independently selected from hydrogen, deuterium, C_{1-10} alkyl, CN, NO_2, $-OR^{a1}$, $-SR^{a1}$, $-S(O)_rR^{a1}$, $-C(O)R^{a1}$, $-C(O)OR^{a1}$, $-C(O)NR^{a1}R^{b1}$ and $-S(O)_rNR^{a1}R^{b1}$, wherein

alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X2};

each R^X, R^{X0}, R^{X1}, R^{X2} are independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, halogen, CN, NO_2, $-(CR^{c1}R^{d1})_tNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tOR^{b1}$, $-(CR^{c1}R^{d1})_tC(O)R^{a1}$, $-(CR^{c1}R^{d1})_tC(=NR^{e1})R^{a1}$, $-(CR^{c1}R^{d1})_tC(=N\text{-}OR^{b1})R^{a1}$, $-(CR^{c1}R^{d1})_tC(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tOC(O)R^{b1}$, $-(CR^{c1}R^{d1})_tC(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)R^{b1}$, $-(CR^{c1}R^{d1})_tC(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tOC(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(S)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_rR^{b1}$, $-(CR^{c1}R^{d1})_tS(O)(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tN{=}S(O)R^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_2OR^{b1}$, $-(CR^{c1}R^{d1})_tOS(O)_2R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_rR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_rNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_2NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tP(O)R^{a1}R^{b1}$ and $-(CR^{c1}R^{d1})_tP(O)(OR^{a1})(OR^{b1})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y;

each R^{a1} and each R^{b1} are independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y;

or R^{a1} and R^{b1} together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1 or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^Y groups;

each R^{c1} and each R^{d1} are independently selected from hydrogen, deuterium, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y;

or R^{c1} and R^{d1} together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1, 2 or 3 R^Y groups;

each R^{e1} is independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, CN, NO_2, $-OR^{a2}$, $-SR^{a2}$, $-S(O)_rR^{a2}$, $-C(O)R^{a2}$, $-C(O)OR^{a2}$, $-S(O)_rNR^{a2}R^{b2}$ and $-C(O)NR^{a2}R^{b2}$;

each R^Y is independently selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, halogen, CN, NO_2, $-(CR^{c2}R^{d2})_tNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tOR^{b2}$, $-(CR^{c2}R^{d2})_tC(O)R^{a2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(=N\text{-}OR^{b2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(O)NR^{a2}R^{b2}$,

$-(CR^{c2}R^{d2})_tNR^{a2}C(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(S)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_rR^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tN=S(O)R^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_2OR^{b2}$, $-(CR^{c2}R^{d2})_tOS(O)_2R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_rR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_rNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_2NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tP(O)R^{a2}R^{b2}$ and $-(CR^{c2}R^{d2})_tP(O)(OR^{a2})(OR^{b2})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from OH, CN, amino, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

each R^{a2} and each R^{b2} are independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino, di(C_{1-10} alkyl)amino, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylamino, cycloalkylamino, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

or R^{a2} and R^{b2} together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1 or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1 or 2 substituents, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

each R^{c2} and each R^{d2} are independently selected from hydrogen, deuterium, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino, di(C_{1-10} alkyl)amino, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylamino, cycloalkylamino, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

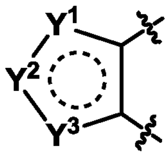
or R^{c2} and R^{d2} together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 or 2 substituents, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

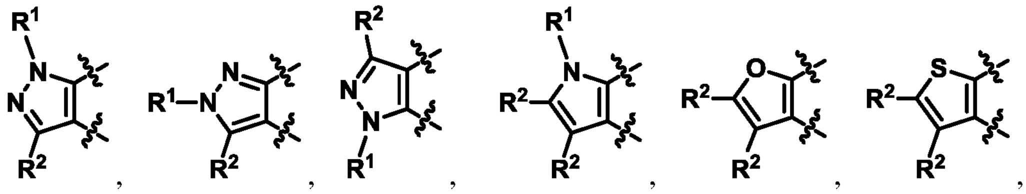
each R^{e2} is independently selected from hydrogen, deuterium, CN, NO_2, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, -C(O)C_{1-4} alkyl, -C(O)C_{3-10} cycloalkyl, -C(O)OC_{1-4} alkyl, -C(O)OC_{3-10} cycloalkyl, -C(O)N(C_{1-4} alkyl)$_2$, -C(O)N(C_{3-10} cycloalkyl)$_2$, -S(O)$_2$$C_{1-4}$ alkyl, -S(O)$_2$$C_{3-10}$ cycloalkyl, -S(O)$_2$N(C_{1-4} alkyl)$_2$ and -S(O)$_2$N(C_{3-10} cycloalkyl)$_2$;

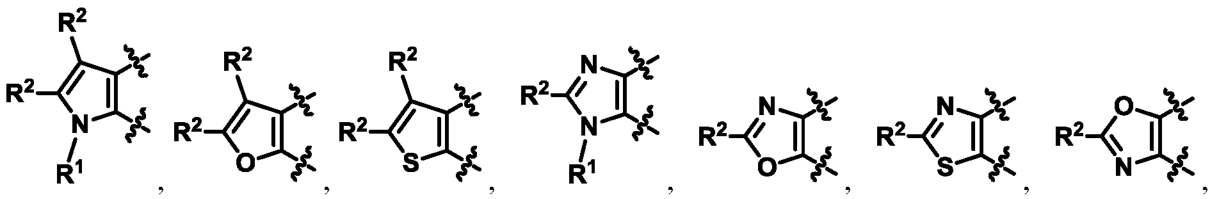
each r is independently selected from 0, 1 and 2;

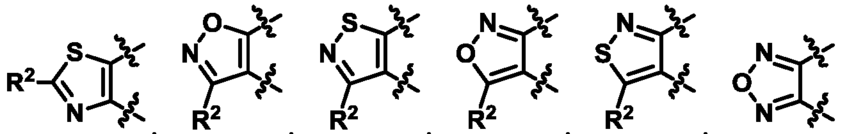
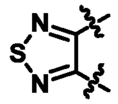
each t is independently selected from 0, 1, 2, 3 and 4;

each u is independently selected from 0, 1, 2, 3 and 4.

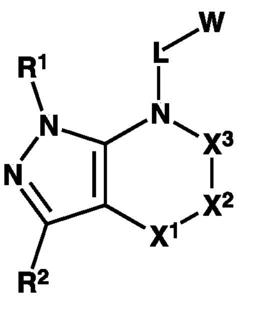
[10] In one embodiment of formula (I), the invention provides a compound or a pharmaceutically acceptable salt thereof, wherein the moiety  in Formula (I) is selected from





 and  , wherein R^1 and R^2 are as defined in formula (I).

[11] In one embodiment of formula (I), the invention provides a compound or a pharmaceutically acceptable salt thereof, wherein Y^1 is NR^1, Y^2 is N and Y^3 is CR^2, the compound has the structure of formula (II),



(II)

wherein R^1, R^2, X^1, X^2, X^3, L and W are as defined in formula (I).

[12] In yet another aspect, the present disclosure provides pharmaceutical compositions comprising a compound of formula (I) or at least one pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[13] In yet another aspect, the disclosure provides methods for modulating URAT1, comprising administering to a system or a subject in need thereof, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof or pharmaceutical compositions thereof, thereby modulating said URAT1.

[14] In yet another aspect, disclosed is a method to treat, ameliorate or prevent a condition which responds to inhibition of URAT1 comprising administering to a system or subject in need of such treatment an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof or pharmaceutical compositions thereof, and optionally in combination with a second therapeutic agent, thereby treating said condition.

[15] Alternatively, the present disclosure provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a condition mediated by URAT1. In particular embodiments, the compounds of the disclosure may be used alone or in combination with a second therapeutic agent to treat a condition mediated by URAT1.

[16] Alternatively, disclosed is a compound of formula (I) or a pharmaceutically acceptable salt thereof for treating a condition mediated by URAT1.

[17] Specifically, the condition herein includes but not limited to, hyperuricaemia, gout, a recurrent gout attach, tophaceous gout, arthritis, gouty arthritis, inflammatory arthritis, joint inflammation, deposition of urate crystals in the joint, kidney disease, kidney stones, kidney failure, urolithiasis, hypertension, a cardiovascular disease, coronary heart disease, Lesch-Nyhan syndrome and Kelley-Seegmiller syndrome.

[18] Furthermore, the disclosure provides methods for treating a condition characterized by abnormal tissue or organ levels of uric acid, comprising administering to a system or subject in need of such treatment an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof or pharmaceutical compositions thereof, and optionally in combination with a second therapeutic agent, thereby treating said condition.

[19] Alternatively, the present disclosure provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a condition characterized by abnormal tissue or organ levels of uric acid. In particular examples, the compounds of the disclosure may be used alone or in combination with a chemotherapeutic agent to treat a condition characterized by abnormal tissue or organ levels of uric acid.

[20] Specifically, the condition disclosed herein includes but not limited to, hyperuricaemia, gout, a recurrent gout attach, tophaceous gout, arthritis, gouty arthritis, inflammatory arthritis, joint inflammation, deposition of urate crystals in the joint, kidney disease, kidney stones, kidney failure, urolithiasis, hypertension, a cardiovascular disease, coronary heart disease, Lesch-Nyhan syndrome and Kelley-Seegmiller syndrome.

[21] In the above methods for using the compounds of the disclosure, a compound of formula (I) or a pharmaceutically acceptable salt thereof may be administered to a system

comprising cells or tissues, or to a subject including a mammalian subject such as a human or animal subject.

Certain Terminology

[22] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. All patents, patent applications, published materials referred to throughout the entire disclosure herein, unless noted otherwise, are incorporated by reference in their entirety. In the event that there is a plurality of definitions for terms herein, those in this section prevail.

[23] It is to be understood that the foregoing general description and the following detailed description are explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. 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. It should also be noted that use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes", and "included" is not limiting. Likewise, use of the term "comprising" as well as other forms, such as "comprise", "comprises", and "comprised" is not limiting.

[24] Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, IR and UV/Vis spectroscopy and pharmacology, within the skill of the art are employed. Unless specific definitions are provided, the nomenclature employed in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those known in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Reactions and purification techniques can be performed e.g., using kits of manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures can be generally performed of conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. Throughout the specification, groups and substituents thereof can be chosen by one skilled in the field to provide stable moieties and compounds.

[25] Where substituent groups are specified by their conventional chemical formulas, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left. As a non-limiting example, CH_2O is equivalent to OCH_2.

[26] The term "substituted" means that a hydrogen atom is replaced by a substituent. It is to be understood that substitution at a given atom is limited by valency.

[27] The term "C_{i-j}" or "i-j membered" used herein means that the moiety has i-j carbon atoms or i-j atoms. For example, "C_{1-6} alkyl" means said alkyl has 1-6 carbon atoms. Likewise, C_{3-10} cycloalkyl means said cycloalkyl has 3-10 carbon atoms.

[28] When any variable (e.g. R) occurs at the structure of a compound over one time, it is defined independently at each case. Therefore, for example, if a group is substituted by 0-2

R, the group may be optionally substituted by at most two R and R has independent option at each case. Additionally, a combination of substituents and/or the variants thereof are allowed only if such a combination will result in a stable compound.

[29] The expression "one or more" or "at least one" refers to one, two, three, four, five, six, seven, eight, nine or more.

[30] Unless stated otherwise, the term "hetero" means heteroatom or heteroatom radical (i.e. a radical containing heteroatom), i.e. the atoms beyond carbon and hydrogen atoms or the radical containing such atoms. Preferably, the heteroatom(s) is independently selected from the group consisting of O, N, S, P and the like. In an embodiment wherein two or more heteroatoms are involved, the two or more heteroatoms may be the same, or part or all of the two or more heteroatoms may be different.

[31] The term "alkyl", employed alone or in combination with other terms, refers to branched or straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Unless otherwise specified, "alkyl" refers to C_{1-10} alkyl. For example, C_{1-6}, as in "C_{1-6} alkyl" is defined to include groups having 1, 2, 3, 4, 5, or 6 carbons in a linear or branched arrangement. For example, "C_{1-8} alkyl" includes but is not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, i-butyl, pentyl, hexyl, heptyl, and octyl.

[32] The term "cycloalkyl", employed alone or in combination with other terms, refers to a saturated monocyclic or multicyclic (e.g. bicyclic or tricyclic) hydrocarbon ring system, usually with 3 to 16 ring atoms. The ring atoms of cycloalkyl are all carbon and the cycloalkyl contains zero heteroatoms and zero double bonds. In a multicyclic cycloalkyl, two or more rings can be fused or bridged or spiro together. Examples of monocyclic ring systems include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The bridged cycloalkyl is a polycyclic ring system containing 3-10 carbon atoms, which contains one or two alkylene bridges, each alkylene bridge consisting of one, two, or three carbon atoms, each linking two non-adjacent carbon atoms of the ring system. Cycloalkyl can be fused with aryl or heteroaryl group. In some embodiments, cycloalkyl is benzocondensed. Representative examples of such bridged cycloalkyl ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, bicyclo[4.2.1]nonane, tricyclo[3.3.1.03,7]nonane and tricyclo[3.3.1.13,7]decane (adamantane). The monocyclic or bridged cycloalkyl can be attached to the parent molecular moiety through any substitutable atom contained within the ring system.

[33] The term "alkenyl", employed alone or in combination with other terms, refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing 2-10 carbon atoms and at least one carbon to carbon double bond. In some embodiments, one carbon to carbon double bond is present, and up to four non-aromatic carbon-carbon double bonds may be present. Thus, "C_{2-6} alkenyl" means an alkenyl radical having 2-6 carbon atoms. Alkenyl groups include but are not limited to ethenyl, propenyl, butenyl, 2-methylbutenyl and cyclohexenyl. The straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

[34] The term "alkynyl", employed alone or in combination with other terms, refers to a hydrocarbon radical, straight, branched or cyclic, containing 2-10 carbon atoms and at least

one carbon to carbon triple bond. In some embodiments, up to three carbon-carbon triple bonds may be present. Thus, "C_{2-6} alkynyl" means an alkynyl radical having 2-6 carbon atoms. Alkynyl groups include but are not limited to ethynyl, propynyl, butynyl, and 3-methylbutynyl. The straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

[35] The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine.

[36] The term "alkoxy", employed alone or in combination with other terms, refers to an alkyl as defined above, which is single bonded to an oxygen atom. The attachment point of an alkoxy radical to a molecule is through the oxygen atom. An alkoxy radical may be depicted as -O-alkyl. The term "C_{1-10} alkoxy" refers to an alkoxy radical containing 1-10 carbon atoms, having straight or branched moieties. Alkoxy group includes but is not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy, and the like.

[37] The term "cycloalkoxy", employed alone or in combination with other terms, refers to cycloalkyl as defined above, which is single bonded to an oxygen atom. The attachment point of a cycloalkoxy radical to a molecule is through the oxygen atom. A cycloalkoxy radical may be depicted as -O-cycloalkyl. "C_{3-10} cycloalkoxy" refers to a cycloalkoxy radical containing 3-10 carbon atoms. Cycloalkoxy can be fused with aryl or heteroaryl group. In some embodiments, cycloalkoxy is benzocondensed. Cycloalkoxy group includes but is not limited to, cyclopropoxy, cyclobutoxy, cyclopentyloxy, cyclohexyloxy, and the like.

[38] The term "alkylthio", employed alone or in combination with other terms, refers to an alkyl radical as defined above, which is single bonded to a sulfur atom. The attachment point of an alkylthio radical to a molecule is through the sulfur atom. An alkylthio radical may be depicted as -S-alkyl. The term "C_{1-10} alkylthio" refers to an alkylthio radical containing 1-10 carbon atoms, having straight or branched moieties. Alkylthio group includes but is not limited to, methylthio, ethylthio, propylthio, isopropylthio, butylthio, hexylthio, and the like.

[39] The term "cycloalkylthio", employed alone or in combination with other terms, refers to cycloalkyl as defined above, which is single bonded to a sulfur atom. The attachment point of a cycloalkylthio radical to a molecule is through the sulfur atom. A cycloalkylthio radical may be depicted as -S-cycloalkyl. "C_{3-10} cycloalkylthio" refers to a cycloalkylthio radical containing 3-10 carbon atoms. Cycloalkylthio can be fused with aryl or heteroaryl group. In some embodiments, cycloalkylthio is benzocondensed. Cycloalkylthio group includes but is not limited to, cyclopropylthio, cyclobutylthio, cyclohexylthio, and the like.

[40] The term "alkylamino", employed alone or in combination with other terms, refers to an alkyl as defined above, which is single bonded to a nitrogen atom. The attachment point of an alkylamino radical to a molecule is through the nitrogen atom. An alkylamino radical may be depicted as -NH(alkyl). The term "C_{1-10} alkylamino" refers to an alkylamino radical containing 1-10 carbon atoms, having straight or branched moieties. Alkylamino group includes but is not limited to, methylamino, ethylamino, propylamino, isopropylamino, butylamino, hexylamoino, and the like.

[41] The term "cycloalkylamino", employed alone or in combination with other terms, refers to cycloalkyl as defined above, which is single bonded to a nitrogen atom. The attachment point of a cycloalkylamino radical to a molecule is through the nitrogen atom. A

cycloalkylamino radical may be depicted as -NH(cycloalkyl). "C_{3-10} cycloalkylamino" refers to a cycloalkylamino radical containing 3-10 carbon atoms. Cycloalkylamino can be fused with aryl or heteroaryl group. In some embodiments, cycloalkylamino is benzocondensed. Cycloalkylamino group includes but is not limited to, cyclopropylamino, cyclobutylamino, cyclohexylamino, and the like.

[42] The term "di(alkyl)amino", employed alone or in combination with other terms, refers to two alkyl as defined above, which are single bonded to a nitrogen atom. The attachment point of an di(alkyl)amino radical to a molecule is through the nitrogen atom. A di(alkyl)amino radical may be depicted as -N(alkyl)$_2$. The term "di(C_{1-10} alkyl)amino" refers to a di(C_{1-10} alkyl)amino radical wherein the alkyl radicals each independently contains 1-10 carbon atoms, having straight or branched moieties.

[43] The term "aryl", employed alone or in combination with other terms, refers to a monovalent, monocyclic- , bicyclic- or tricyclic aromatic hydrocarbon ring system having 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms (a "C_{6-14} aryl" group), particularly a ring having 6 carbon atoms (a "C_6 aryl" group), e.g. a phenyl group; or a ring having 10 carbon atoms (a "C_{10} aryl" group), e.g. a naphthyl group; or a ring having 14 carbon atoms, (a "C_{14} aryl" group), e.g. an anthranyl group. Aryl can be fused with cycloalkyl or heterocycle group.

[44] Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by removing "-yl" and adding "-idene" to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene.

[45] The term "heteroaryl", employed alone or in combination with other terms, refers to a monovalent, monocyclic- , bicyclic- or tricyclic aromatic ring system having 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 ring atoms (a "5- to 14-membered heteroaryl" group), particularly 5 or 6 or 9 or 10 atoms, and which contains at least one heteroatom which may be identical or different, said heteroatom selected from N, O and S, with the remaining ring atoms being carbon. Heteroaryl can be fused with cycloalkyl or heterocycle group. In some embodiments, "heteroaryl" refers to

a 5- to 8-membered monocyclic aromatic ring containing one or more, for example, from 1 to 4, or, in some embodiments, from 1 to 3, heteroatoms selected from N, O and S, with the remaining ring atoms being carbon; or

a 8- to 12-membered bicyclic aromatic ring system containing one or more, for example, from 1 to 6, or, in some embodiments, from 1 to 4, or, in some embodiments, from 1 to 3, heteroatoms selected from N, O and S, with the remaining ring atoms being carbon; or

a 11- to 14-membered tricyclic aromatic ring system containing one or more, for example, from 1 to 8, or, in some embodiments, from 1 to 6, or, in some embodiments, from 1 to 4, or in some embodiments, from 1 to 3, heteroatoms selected from N, O and S, with the remaining ring atoms being carbon.

[46] When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In some embodiments, the total number of S and

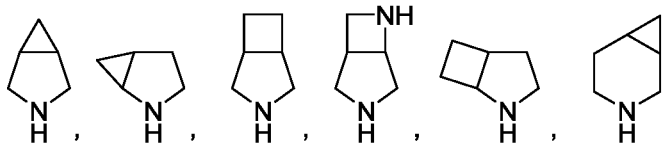
O atoms in the heteroaryl group is not more than 2. In some embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1.

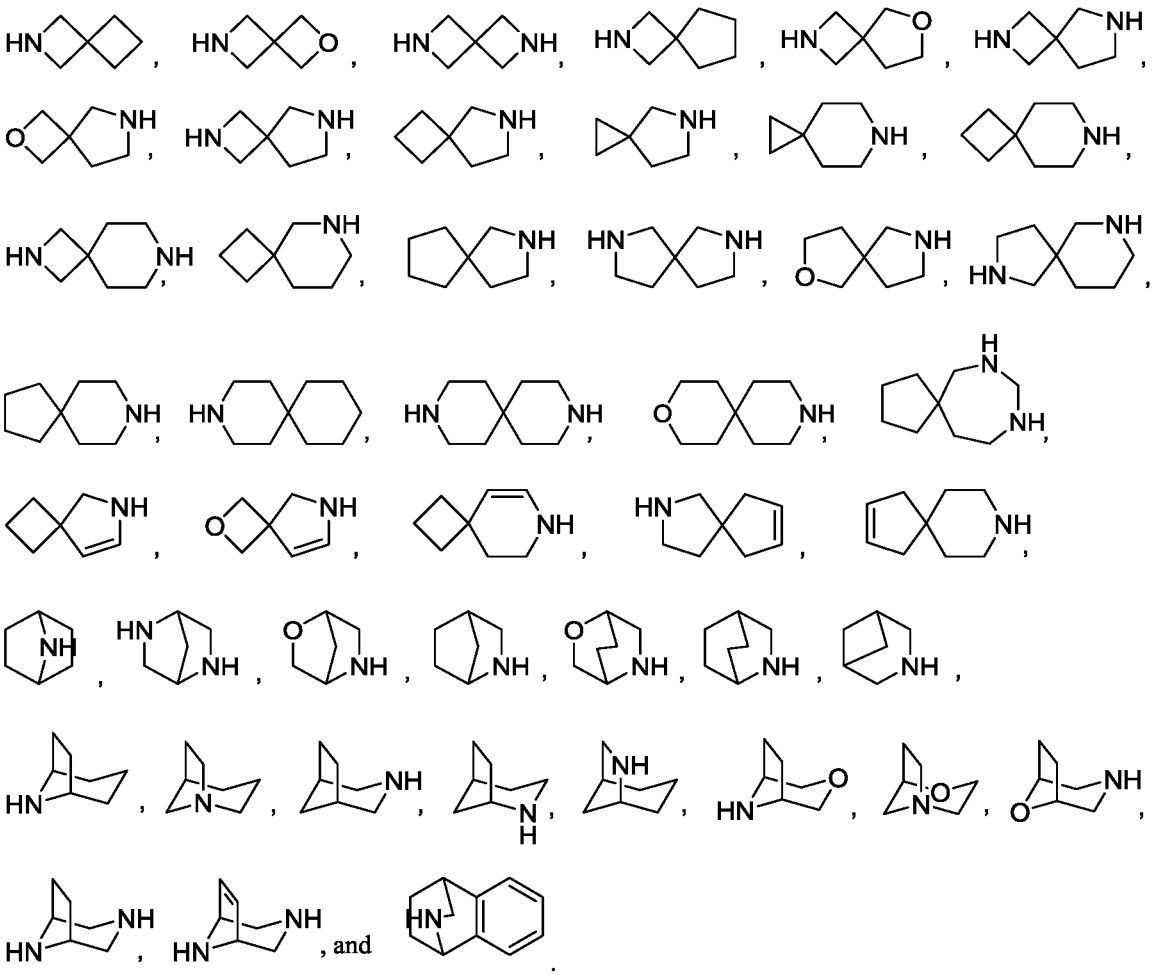
[47] Examples of heteroaryl groups include, but are not limited to, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-6-yl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, pyridazinyl, triazinyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, triazolyl, tetrazolyl, thienyl, furyl.

[48] Further heteroaryl groups include but are not limited to indolyl, benzothienyl, benzofuryl, benzoimidazolyl, benzotriazolyl, quinoxalinyl, quinolinyl, and isoquinolinyl. "Heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl.

[49] Bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a pyridyl group with two points of attachment is a pyridylidene.

[50] The term "heterocycle", employed alone or in combination with other terms, (and variations thereof such as "heterocyclic", or "heterocyclyl") broadly refers to a saturated or unsaturated mono- or multicyclic (e.g. bicyclic) aliphatic ring system, usually with 3 to 12 ring atoms, wherein at least one (e.g. 2, 3 or 4) ring atom is heteroatom independently selected from O, S, N and P (preferably O, S, N), with the remaining ring atoms being carbon. In a multicyclic heterocycle, two or more rings can be fused or bridged or spiro together. Heterocycle can be fused with aryl or heteroaryl group. In some embodiments, heterocycle is benzocondensed. Heterocycle also includes ring systems substituted with one or more oxo or imino moieties. In some embodiments, the C, N, S and P atoms in the heterocycle ring are optionally substituted by oxo. In some embodiments, the C, S and P atoms in the heterocycle ring are optionally substituted by imino, and imino can be unsubstituted or substituted. The point of the attachment may be carbon atom or heteroatom in the heterocyclic ring, provided that attachment results in the creation of a stable structure. When the heterocyclic ring has substituents, it is understood that the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure result.

[51] Suitable heterocycles include, for example, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-3-yl, imidazolidin-4-yl, imidazolidin-5-yl, pyrazolidin-1-yl, pyrazolidin-2-yl, pyrazolidin-3-yl, pyrazolidin-4-yl, pyrazolidin-5-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, hexahydropyridazin-1-yl, hexahydropyridazin-3-yl and hexahydropyridazin-4-yl. Morpholinyl groups are also contemplated, such as morpholin-1-yl, morpholin-2-yl and morpholin-3-yl. Examples of heterocycle with one or more oxo moieties include but are not limited to, piperidinyl N-oxide, morpholinyl-N-oxide, 1-oxo-thiomorpholinyl and 1,1-dioxo-thiomorpholinyl. Bicyclic heterocycles include, for example: 



[52] As used herein, "aryl-alkyl" refers to an alkyl moiety as defined above substituted by an aryl group as defined above. Exemplary aryl-alkyl groups include but are not limited to benzyl, phenethyl and naphthylmethyl groups. In some embodiments, aryl-alkyl groups have 7-20 or 7-11 carbon atoms. When used in the phrase "aryl-C_{1-4} alkyl", the term "C_{1-4}" refers to the alkyl portion of the moiety and does not describe the number of atoms in the aryl portion of the moiety.

[53] As used herein, "heterocyclyl-alkyl" refers to alkyl as defined above substituted by heterocyclyl as defined above. When used in the phrase "heterocyclyl-C_{1-4} alkyl", the term "C_{1-4}" refers to the alkyl portion of the moiety and does not describe the number of atoms in the heterocyclyl portion of the moiety.

[54] As used herein, "cycloalkyl-alkyl" refers to alkyl as defined above substituted by cycloalkyl as defined above. When used in the phrase "C_{3-10} cycloalkyl-C_{1-4} alkyl", the term "C_{3-10}" refers to the cycloalkyl portion of the moiety and does not describe the number of atoms in the alkyl portion of the moiety, and the term "C_{1-4}" refers to the alkyl portion of the moiety and does not describe the number of atoms in the cycloalkyl portion of the moiety.

[55] As used herein, "heteroaryl-alkyl" refers to alkyl as defined above substituted by heteroaryl as defined above. When used in the phrase "heteroaryl-C_{1-4} alkyl", the term "C_{1-4}" refers to the alkyl portion of the moiety and does not describe the number of atoms in the heteroaryl portion of the moiety.

[56] For avoidance of doubt, reference, for example, to substitution of alkyl, cycloalkyl, heterocyclyl, aryl and/or heteroaryl refers to substitution of each of those groups individually as well as to substitutions of combinations of those groups. That is, if R is aryl-C_{1-4} alkyl and may be unsubstituted or substituted with at least one substituent, such as one, two, three, or four substituents, independently selected from R^X, it should be understood that the aryl portion may be unsubstituted or substituted with at least one substituent, such as one, two, three, or four substituents, independently selected from R^X and the alkyl portion may also be unsubstituted or substituted with at least one substituent, such as one, two, three, or four substituents, independently selected from R^X.

[57] The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases may be selected, for example, from aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium and zinc salts. Further, for example, the pharmaceutically acceptable salts derived from inorganic bases may be selected from ammonium, calcium, magnesium, potassium and sodium salts. Salts in the solid form may exist in one or more crystalline forms, or polymorphs, and may also be in the form of solvates, such as hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases may be selected, for example, from salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethyl-morpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine and tripropylamine, tromethamine.

[58] When the compound disclosed herein is basic, salts may be prepared using at least one pharmaceutically acceptable non-toxic acid, selected from inorganic and organic acids. Such acid may be selected, for example, from acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric and p-toluenesulfonic acids. In some embodiments, such acid may be selected, for example, from citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric and tartaric acids.

[59] The terms "administration of" and or "administering" a compound or a pharmaceutically acceptable salt should be understood to mean providing a compound or a pharmaceutically acceptable salt thereof to the individual in recognized need of treatment.

[60] The term "effective amount" means the amount of the a compound or a pharmaceutically acceptable salt that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

[61] The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which

results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to a pharmaceutical composition is intended to encompass a product comprising the active ingredient (s) and the inert ingredient (s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients.

[62] The term "pharmaceutically acceptable" it is meant compatible with the other ingredients of the formulation and not unacceptably deleterious to the recipient thereof.

[63] The term "subject" as used herein in reference to individuals suffering from a disorder, a condition, and the like, encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non- mammals include, but are not limited to, birds, fish and the like. In one embodiment of the methods and compositions provided herein, the mammal is a human.

[64] The terms "treat," "treating" or "treatment," and other grammatical equivalents as used herein, include alleviating, abating or ameliorating a disease or condition, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition, and are intended to include prophylaxis. The terms further include achieving a therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient may still be afflicted with the underlying disorder. For prophylactic benefit, the compositions may be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[65] The term "protecting group" or "Pg" refers to a substituent that can be commonly employed to block or protect a certain functionality while reacting other functional groups on the compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include but are not limited to acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBZ) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include but are not limited to acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include $-CH_2CH_2SO_2Ph$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfenyl)ethyl,

2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, *John Wiley & Sons*, New York, 1991.

[66] The term "NH protecting group" as used herein includes, but not limited to, trichloroethoxycarbonyl, tribromoethoxycarbonyl, benzyloxycarbonyl, para-nitrobenzylcarbonyl, ortho-bromobenzyloxycarbonyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, phenylacetyl, formyl, acetyl, benzoyl, tert-amyloxycarbonyl, tert-butoxycarbonyl, para-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyl-oxycarbonyl, 4-(phenylazo)-benzyloxycarbonyl, 2-furfuryloxycarbonyl, diphenylmethoxycarbonyl, 1,1-dimethylpropoxy-carbonyl, isopropoxycarbonyl, phthaloyl, succinyl, alanyl, leucyl, 1-adamantyloxycarbonyl, 8-quinolyloxycarbonyl, benzyl, diphenylmethyl, triphenylmethyl, 2-nitrophenylthio, methanesulfonyl, para-toluenesulfonyl, *N,N*-dimethylaminomethylene, benzylidene, 2-hydroxybenzylidene, 2-hydroxy-5-chlorobenzylidene, 2-hydroxy-l-naphthylmethylene, 3-hydroxy-4-pyridylmethylene, cyclohexylidene, 2-ethoxycarbonylcyclohexylidene, 2-ethoxycarbonylcyclopentylidene, 2-acetylcyclohexylidene, 3,3-dimethyl-5-oxycyclo-hexylidene, diphenylphosphoryl, dibenzylphosphoryl, 5-methyl-2-oxo-2*H*-1,3-dioxol-4-yl-methyl, trimethylsilyl, triethylsilyl and triphenylsilyl.

[67] The term "C(O)OH protecting group" as used herein includes, but not limited to, methyl, ethyl, n-propyl, isopropyl, 1,1-dimethylpropyl, n-butyl, tert-butyl, phenyl, naphthyl, benzyl, diphenylmethyl, triphenylmethyl, para-nitrobenzyl, para-methoxybenzyl, bis(para-methoxyphenyl)methyl, acetylmethyl, benzoylmethyl, para-nitrobenzoylmethyl, para-bromobenzoylmethyl, para-methanesulfonylbenzoylmethyl, 2-tetrahydropyranyl, 2-tetrahydrofuranyl, 2,2,2-trichloro-ethyl, 2-(trimethylsilyl)ethyl, acetoxymethyl, propionyloxymethyl, pivaloyloxymethyl, phthalimidomethyl, succinimidomethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxymethyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, benzyloxymethyl, methylthiomethyl, 2-methylthioethyl, phenylthiomethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, diphenylmethylsilyl and tert-butylmethoxyphenylsilyl.

[68] The term "OH or SH protecting group" as used herein includes, but not limited to, benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, isobutyloxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-(phenylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphonio)ethoxycarbonyl, 2-furfuryloxycarbonyl, 1-adamantyloxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, 4-ethoxy-1-naphthyloxycarbonyl, 8-quinolyloxycarbonyl, acetyl, formyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, pivaloyl, benzoyl, methyl, tert-butyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, benzyl (phenylmethyl), para-methoxybenzyl, 3,4-dimethoxybenzyl, diphenylmethyl, triphenylmethyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, methoxymethyl, methylthiomethyl,

benzyloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloro-ethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, 1-ethoxyethyl, methanesulfonyl, para-toluenesulfonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, diphenylmethylsilyl and tert-butylmethoxyphenylsilyl.

[69] Geometric isomers may exist in the present compounds. Compounds of this invention may contain carbon-carbon double bonds or carbon-nitrogen double bonds in the E or Z configuration, wherein the term "E" represents higher order substituents on opposite sides of the carbon-carbon or carbon-nitrogen double bond and the term "Z" represents higher order substituents on the same side of the carbon-carbon or carbon-nitrogen double bond as determined by the Cahn-Ingold-Prelog Priority Rules. The compounds of this invention may also exist as a mixture of "E" and "Z" isomers. Substituents around a cycloalkyl or heterocycloalkyl are designated as being of cis or trans configuration. Furthermore, the invention contemplates the various isomers and mixtures thereof resulting from the disposal of substituents around an adamantane ring system. Two substituents around a single ring within an adamantane ring system are designated as being of Z or E relative configuration. For examples, see C. D. Jones, M. Kaselj, R. N. Salvatore, W. J. le Noble J. Org. Chem. 1998, 63, 2758-2760.

[70] Compounds of this invention may contain asymmetrically substituted carbon atoms in the R or S configuration, in which the terms "R" and "S" are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-10. Compounds having asymmetrically substituted carbon atoms with equal amounts of R and S configurations are racemic at those carbon atoms. Atoms with an excess of one configuration over the other are assigned the configuration present in the higher amount, preferably an excess of about 85-90%, more preferably an excess of about 95-99%, and still more preferably an excess greater than about 99%. Accordingly, this invention includes racemic mixtures, relative and absolute stereoisomers, and mixtures of relative and absolute stereoisomers.

Isotope Enriched or Labeled Compounds.

[71] Compounds of the invention can exist in isotope-labeled or -enriched form containing one or more atoms having an atomic mass or mass number different from the atomic mass or mass number most abundantly found in nature. Isotopes can be radioactive or non- radioactive isotopes. Isotopes of atoms such as hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine and iodine include, but are not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl and ^{125}I. Compounds that contain other isotopes of these and/or other atoms are within the scope of this invention.

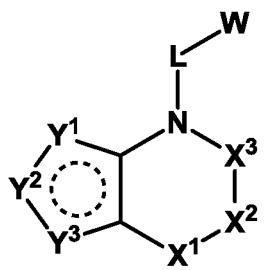
[72] In another embodiment, the isotope-labeled compounds contain deuterium (^{2}H), tritium (^{3}H) or ^{14}C isotopes. Isotope-labeled compounds of this invention can be prepared by the general methods well known to persons having ordinary skill in the art. Such isotope-labeled compounds can be conveniently prepared by carrying out the procedures disclosed in the Examples disclosed herein and Schemes by substituting a readily available isotope-labeled reagent for a non-labeled reagent. In some instances, compounds may be treated with isotope-labeled reagents to exchange a normal atom with its isotope, for example, hydrogen for deuterium can be exchanged by the action of a deuterated acid such as D_2SO_4/D_2O.

[73] The isotope-labeled compounds of the invention may be used as standards to determine the effectiveness of URAT1 inhibitors in binding assays. Isotope containing compounds have been used in pharmaceutical research to investigate the in vivo metabolic fate of the compounds by evaluation of the mechanism of action and metabolic pathway of the nonisotope-labeled parent compound (Blake et al. J. Pharm. Sci. 64, 3, 367-391 (1975)). Such metabolic studies are important in the design of safe, effective therapeutic drugs, either because the in vivo active compound administered to the patient or because the metabolites produced from the parent compound prove to be toxic or carcinogenic (Foster et al., Advances in Drug Research Vol. 14, pp. 2-36, Academic press, London, 1985; Kato et al, J. Labelled Compounds. Radiopharmaceuticals, 36(10):927-932 (1995); Kushner et al., Can. J. Physiol. Pharmacology, 77, 79-88 (1999).

[74] In addition, non-radioactive isotope containing drugs, such as deuterated drugs called "heavy drugs" can be used for the treatment of diseases and conditions related to URAT1 activity. Increasing the amount of an isotope present in a compound above its natural abundance is called enrichment. Examples of the amount of enrichment include but are not limited to from about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 21, 25, 29, 33, 37, 42, 46, 50, 54, 58, 63, 67, 71, 75, 79, 84, 88, 92, 96, to about 100 mol %.

[75] Stable isotope labeling of a drug can alter its physico-chemical properties such as pKa and lipid solubility. These effects and alterations can affect the pharmacodynamic response of the drug molecule if the isotopic substitution affects a region involved in a ligand-receptor interaction. While some of the physical properties of a stable isotope-labeled molecule are different from those of the unlabeled one, the chemical and biological properties are the same, with one important exception: because of the increased mass of the heavy isotope, any bond involving the heavy isotope and another atom will be stronger than the same bond between the light isotope and that atom. Accordingly, the incorporation of an isotope at a site of metabolism or enzymatic transformation will slow said reactions potentially altering the pharmacokinetic profile or efficacy relative to the non-isotopic compound.

[76] In an Embodiment (1), disclosed herein is a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

W is selected from aryl and heteroaryl, wherein aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X;

L is selected from $-(CR^{C0}R^{D0})_uC(O)(CR^{C0}R^{D0})_t-$, $-(CR^{C0}R^{D0})_uC(O)NR^{A0}(CR^{C0}R^{D0})_t-$, $-(CR^{C0}R^{D0})_uS(O)_r(CR^{C0}R^{D0})_t-$ and $-(CR^{C0}R^{D0})_uS(O)_rNR^{A0}(CR^{C0}R^{D0})_t-$;

X^1 is selected from $CR^{C1}R^{D1}$, NR^{A1}, O and $S(O)_r$;

X^2 and X^3 are independently selected from $-(CR^{C1}R^{D1})_u-$, $-(CR^{C1}R^{D1})_uO(CR^{C1}R^{D1})_t-$, $-(CR^{C1}R^{D1})_uNR^{A1}(CR^{C1}R^{D1})_t-$, $-(CR^{C1}R^{D1})_uS(CR^{C1}R^{D1})_t-$, $-(CR^{C1}R^{D1})_uC(O)(CR^{C1}R^{D1})_t-$ and $-(CR^{C1}R^{D1})_uS(O)_r(CR^{C1}R^{D1})_t-$;

Y^1, Y^2 and Y^3 are independently selected from N, NR^1, CR^2, O and $S(O)_r$;

R^1 is selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1};

R^2 is selected from hydrogen, deuterium, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, CN, NO_2, $-NR^{A2}R^{B2}$, $-OR^{A2}$, $-C(O)R^{A2}$, $-C(=NR^{E2})R^{A2}$, $-C(=N\text{-}OR^{B2})R^{A2}$, $-C(O)OR^{A2}$, $-OC(O)R^{A2}$, $-C(O)NR^{A2}R^{B2}$, $-NR^{A2}C(O)R^{B2}$, $-C(=NR^{E2})NR^{A2}R^{B2}$, $-NR^{A2}C(=NR^{E2})R^{B2}$, $-OC(O)NR^{A2}R^{B2}$, $-NR^{A2}C(O)OR^{B2}$, $-NR^{A2}C(O)NR^{A2}R^{B2}$, $-NR^{A2}C(S)NR^{A2}R^{B2}$, $-NR^{A2}C(=NR^{E2})NR^{A2}R^{B2}$, $-S(O)_rR^{A2}$, $-S(O)(=NR^{E2})R^{B2}$, $-N=S(O)R^{A2}R^{B2}$, $-S(O)_2OR^{A2}$, $-OS(O)_2R^{A2}$, $-NR^{A2}S(O)_rR^{B2}$, $-NR^{A2}S(O)(=NR^{E2})R^{B2}$, $-S(O)_rNR^{A2}R^{B2}$, $-S(O)(=NR^{E2})NR^{A2}R^{B2}$, $-NR^{A2}S(O)_2NR^{A2}R^{B2}$, $-NR^{A2}S(O)(=NR^{E2})NR^{A2}R^{B2}$, $-P(O)R^{A2}R^{B2}$ and $-P(O)(OR^{A2})(OR^{B2})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X2};

each R^{A0} is independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X0};

each R^{A1} is independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1};

each R^{A2} and R^{B2} are independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl, and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X2};

or "R^{A2} and R^{B2}" together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1 or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus and optionally substituted with 1, 2 or 3 R^{X2} groups;

each R^{C0} and R^{D0} are independently selected from hydrogen, deuterium, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or

substituted with at least one substituent, independently selected from R^{X0};

or each "R^{C0} and R^{D0}" together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen and optionally substituted with 1 2 or 3 R^{X0} groups;

each R^{C1} and R^{D1} are independently selected from hydrogen, deuterium, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1};

or each "R^{C1} and R^{D1}" together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen and optionally substituted with 1 2 or 3 R^{X1} groups;

each R^{E2} are independently selected from hydrogen, deuterium, C_{1-10} alkyl, CN, NO_2, $-OR^{a1}$, $-SR^{a1}$, $-S(O)_rR^{a1}$, $-C(O)R^{a1}$, $-C(O)OR^{a1}$, $-C(O)NR^{a1}R^{b1}$ and $-S(O)_rNR^{a1}R^{b1}$, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X2};

each R^X, R^{X0}, R^{X1}, R^{X2} are independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, halogen, CN, NO_2, $-(CR^{c1}R^{d1})_tNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tOR^{b1}$, $-(CR^{c1}R^{d1})_tC(O)R^{a1}$, $-(CR^{c1}R^{d1})_tC(=NR^{e1})R^{a1}$, $-(CR^{c1}R^{d1})_tC(=N\text{-}OR^{b1})R^{a1}$, $-(CR^{c1}R^{d1})_tC(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tOC(O)R^{b1}$, $-(CR^{c1}R^{d1})_tC(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)R^{b1}$, $-(CR^{c1}R^{d1})_tC(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tOC(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(S)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_rR^{b1}$, $-(CR^{c1}R^{d1})_tS(O)(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tN{=}S(O)R^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_2OR^{b1}$, $-(CR^{c1}R^{d1})_tOS(O)_2R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_rR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_rNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_2NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tP(O)R^{a1}R^{b1}$ and $-(CR^{c1}R^{d1})_tP(O)(OR^{a1})(OR^{b1})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y;

each R^{a1} and each R^{b1} are independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y;

or R^{a1} and R^{b1} together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1 or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^Y groups;

each R^{c1} and each R^{d1} are independently selected from hydrogen, deuterium, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl,

heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y;

or R^{c1} and R^{d1} together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1, 2 or 3 R^Y groups;

each R^{e1} is independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, CN, NO_2, $-OR^{a2}$, $-SR^{a2}$, $-S(O)_rR^{a2}$, $-C(O)R^{a2}$, $-C(O)OR^{a2}$, $-S(O)_rNR^{a2}R^{b2}$ and $-C(O)NR^{a2}R^{b2}$;

each R^Y is independently selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, halogen, CN, NO_2, $-(CR^{c2}R^{d2})_tNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tOR^{b2}$, $-(CR^{c2}R^{d2})_tC(O)R^{a2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(=N\text{-}OR^{b2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(S)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_rR^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tN=S(O)R^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_2OR^{b2}$, $-(CR^{c2}R^{d2})_tOS(O)_2R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_rR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_rNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_2NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tP(O)R^{a2}R^{b2}$ and $-(CR^{c2}R^{d2})_tP(O)(OR^{a2})(OR^{b2})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from OH, CN, amino, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

each R^{a2} and each R^{b2} are independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino, di(C_{1-10} alkyl)amino, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylamino, cycloalkylamino, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

or R^{a2} and R^{b2} together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1 or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1 or 2 substituents, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

each R^{c2} and each R^{d2} are independently selected from hydrogen, deuterium, halogen,

C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino, di(C_{1-10} alkyl)amino, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylamino, cycloalkylamino, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

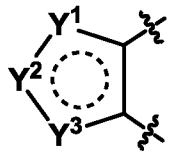
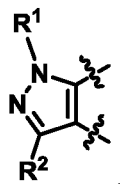
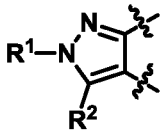
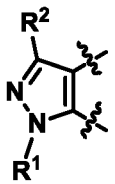
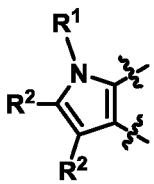
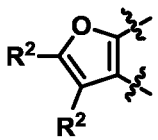
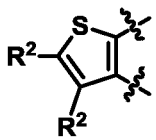
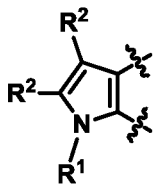
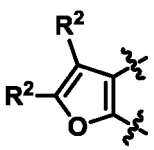
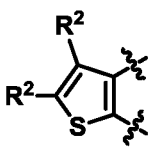
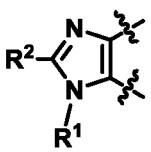
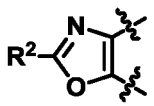
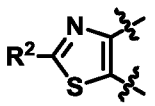
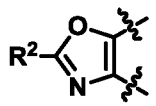
or R^{c2} and R^{d2} together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 or 2 substituents, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

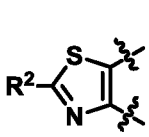
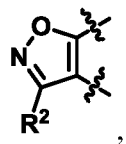
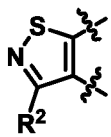
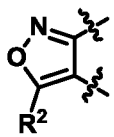
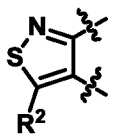
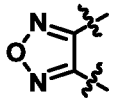
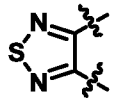
each R^{e2} is independently selected from hydrogen, deuterium, CN, NO_2, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, -C(O)C_{1-4} alkyl, -C(O)C_{3-10} cycloalkyl, -C(O)OC_{1-4} alkyl, -C(O)OC_{3-10} cycloalkyl, -C(O)N(C_{1-4} alkyl)$_2$, -C(O)N(C_{3-10} cycloalkyl)$_2$, -S(O)$_2$$C_{1-4}$ alkyl, -S(O)$_2$$C_{3-10}$ cycloalkyl, -S(O)$_2$N(C_{1-4} alkyl)$_2$ and -S(O)$_2$N(C_{3-10} cycloalkyl)$_2$;

each r is independently selected from 0, 1 and 2;

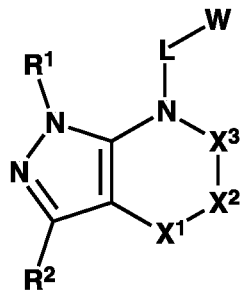
each t is independently selected from 0, 1, 2, 3 and 4;

each u is independently selected from 0, 1, 2, 3 and 4.

[77] In another Embodiment (2), the invention provides a compound of Embodiment (1) or a pharmaceutically acceptable salt thereof, wherein the moiety  in Formula (I) is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

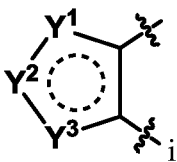
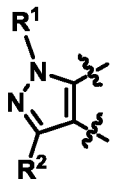
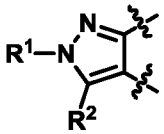
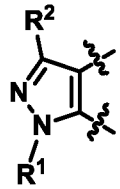
 ,  ,  ,  ,  ,  and  , wherein R^1 and R^2 are as defined in formula (I).

[78] In another Embodiment (3), the invention provides a compound of Embodiment (1) or a pharmaceutically acceptable salt thereof, wherein Y^1 is NR^1, Y^2 is N and Y^3 is CR^2, the compound has the structure of formula (II),



(II)

wherein R^1, R^2, X^1, X^2, X^3, L and W are as defined in formula (I).

[79] In another Embodiment (4), the invention provides a compound of any one of Embodiments (1)-(2) or a pharmaceutically acceptable salt thereof, wherein the moiety  in Formula (I) is selected from  ,  and  , wherein R^1 and R^2 are as defined in formula (I).

[80] In another Embodiment (5), the invention provides a compound of any one of Embodiments (1)-(4) or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from hydrogen, deuterium, C_{1-10} alkyl and C_{3-10} cycloalkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.

[81] In another Embodiment (6), the invention provides a compound of Embodiment (5) or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from hydrogen and C_{1-10} alkyl, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.

[82] In another Embodiment (7), the invention provides a compound of Embodiment (6) or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from hydrogen and methyl.

[83] In another Embodiment (8), the invention provides a compound of any one of Embodiments (1)-(4) or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from hydrogen, deuterium, OH, CN, NO_2 NH_2, C_{1-10} alkyl and C_{3-10} cycloalkyl, wherein alkyl

and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X2}.

[84] In another Embodiment (9), the invention provides a compound of Embodiment (8) or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from hydrogen and C_{1-10} alkyl, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X2}.

[85] In another Embodiment (10), the invention provides a compound of Embodiment (9) or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from hydrogen and methyl.

[86] In another Embodiment (11), the invention provides a compound of any one of Embodiments (1)-(10) or a pharmaceutically acceptable salt thereof, wherein X^1 is selected from $CR^{C1}R^{D1}$, NR^{A1}, O, S and $S(O)_2$.

[87] In another Embodiment (12), the invention provides a compound of Embodiment (11) or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^1 are independently selected from hydrogen, deuterium, halogen, C_{1-10} alkyl and C_{3-10} cycloalkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.

[88] In another Embodiment (13), the invention provides a compound of Embodiment (11) or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^1 together with the carbon atom(s) to which they are attached form a ring of 3 to 8 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen and optionally substituted with 1, 2 or 3 R^{X1} groups.

[89] In another Embodiment (14), the invention provides a compound of Embodiment (12) or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^1 are independently selected from hydrogen, deuterium and C_{1-10} alkyl, wherein alkyl is each unsubstituted or substituted with at least one substituent, independently selected from R^Y.

[90] In another Embodiment (15), the invention provides a compound of Embodiment (11) or a pharmaceutically acceptable salt thereof, wherein the R^{A1} in X^1 is selected from deuterium, halogen, OH, C_{1-10} alkyl and C_{3-10} cycloalkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.

[91] In another Embodiment (16), the invention provides a compound of Embodiment (15) or a pharmaceutically acceptable salt thereof, wherein the R^{A1} in X^1 is selected from hydrogen, deuterium, and C_{1-10} alkyl, wherein alkyl is each unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.

[92] In another Embodiment (17), the invention provides a compound of any one of Embodiments (11)-(16) or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^1 are independently selected from hydrogen and deuterium, wherein the R^{A1} in X^1 is selected from hydrogen, deuterium and methyl.

[93] In another Embodiment (18), the invention provides a compound of any one of Embodiments (1)-(17) or a pharmaceutically acceptable salt thereof, wherein X^2 and X^3 are independently selected from $-(CR^{C1}R^{D1})_u-$.

[94] In another Embodiment (19), the invention provides a compound of Embodiment (18) or a pharmaceutically acceptable salt thereof, wherein each u is independently selected from 0, 1 and 2.

[95] In another Embodiment (20), the invention provides a compound of any one of Embodiments (18)-(19) or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^2 or X^3 are independently selected from hydrogen, deuterium, halogen, C_{1-10} alkyl and C_{3-10} cycloalkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.

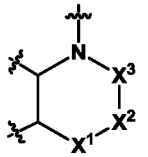
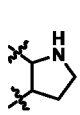
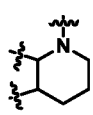
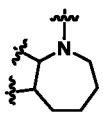
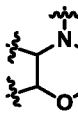
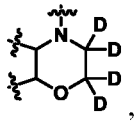
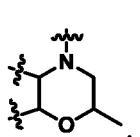
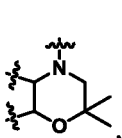
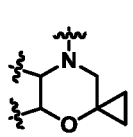
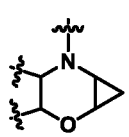
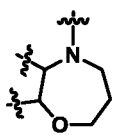
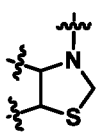
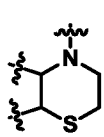
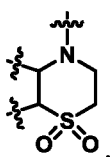
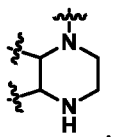
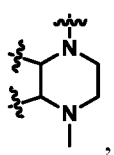
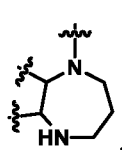
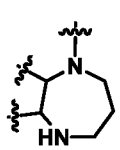
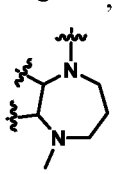
[96] In another Embodiment (21), the invention provides a compound of Embodiment (20) or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^2 or X^3 are independently selected from hydrogen, deuterium, halogen and C_{1-10} alkyl, wherein alkyl is each unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.

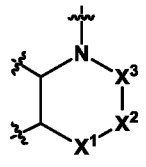
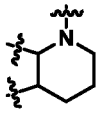
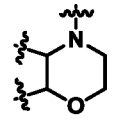
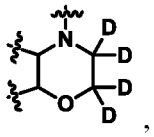
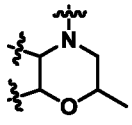
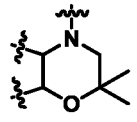
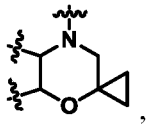
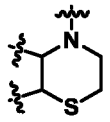
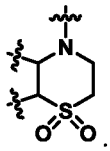
[97] In another Embodiment (22), the invention provides a compound of Embodiment (21) or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^2 or X^3 are independently selected from hydrogen, deuterium and methyl.

[98] In another Embodiment (23), the invention provides a compound of any one of Embodiments (18)-(19) or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^2 or X^3 together with the carbon atom(s) to which they are attached form a ring of 3 to 8 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen and optionally substituted with 1, 2 or 3 R^{X1} groups.

[99] In another Embodiment (24), the invention provides a compound of Embodiment (23) or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^2 or X^3 together with the carbon atom(s) to which they are attached form3- to 5- membered cycloalkyl.

[100] In another Embodiment (25), the invention provides a compound of Embodiment (24) or a pharmaceutically acceptable salt thereof, wherein R^{C1} and R^{D1} in X^2 or X^3 together with the carbon atom(s) to which they are attached form cyclopropyl.

[101] In another Embodiment (26), the invention provides a compound of any one of Embodiments (1)-(25) or a pharmaceutically acceptable salt thereof, wherein the moiety  in Formula (I) is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  .

[102] In another Embodiment (27), the invention provides a compound of Embodiment (26) or a pharmaceutically acceptable salt thereof, wherein the moiety  in Formula (I) is selected from  ,  ,  ,  ,  ,  ,  and  .

[103] In another Embodiment (28), the invention provides a compound of any one of Embodiments (1)-(27) or a pharmaceutically acceptable salt thereof, wherein L is $-(CR^{C0}R^{D0})_uC(O)(CR^{C0}R^{D0})_t-$.

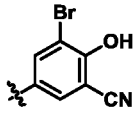
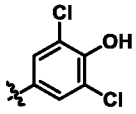
[104] In another Embodiment (29), the invention provides a compound of Embodiment (28) or a pharmaceutically acceptable salt thereof, wherein L is -C(O)-.

[105] In another Embodiment (30), the invention provides a compound of any one of Embodiments (1)-(29) or a pharmaceutically acceptable salt thereof, wherein W is aryl, wherein aryl is unsubstituted or substituted with at least one substituent, independently selected from R^X.

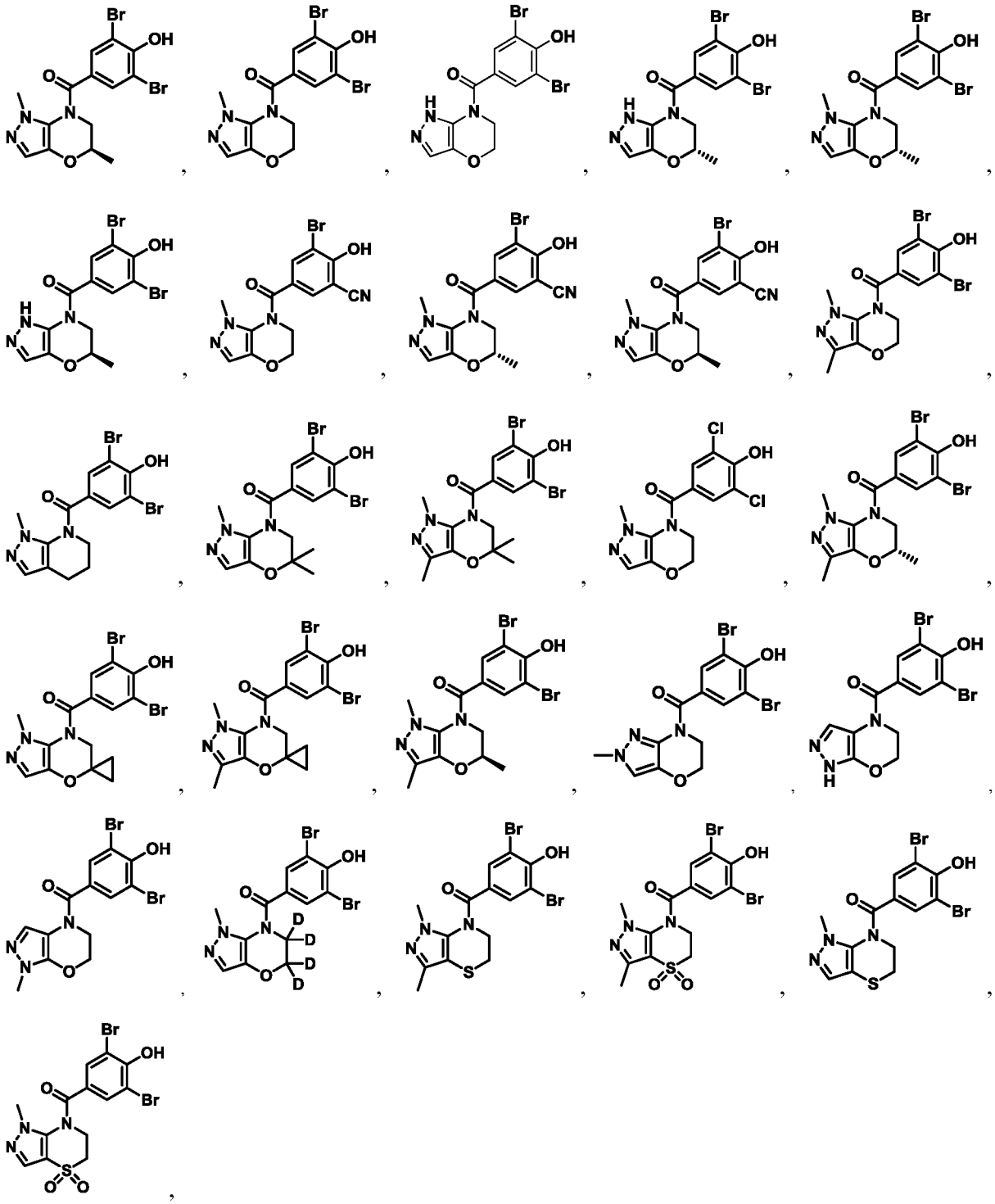
[106] In another Embodiment (31), the invention provides a compound of any one of Embodiments (1)-(29) or a pharmaceutically acceptable salt thereof, wherein W is heteroaryl wherein heteroaryl is unsubstituted or substituted with at least one substituent, independently selected from R^X.

[107] In another Embodiment (32), the invention provides a compound of Embodiment (30) or a pharmaceutically acceptable salt thereof, wherein W is phenyl, the substituent R^X of phenyl is selected from halogen, CN and $-(CR^{c1}R^{d1})_tOR^{b1}$.

[108] In another Embodiment (33), the invention provides a compound of Embodiment (32) or a pharmaceutically acceptable salt thereof, wherein the substituent R^X of phenyl is selected from Cl, Br, CN and OH.

[109] In another Embodiment (34), the invention provides a compound of Embodiment (33) or a pharmaceutically acceptable salt thereof, wherein the moiety  in Formula (I) is selected from  ,  and  .

[110] In another Embodiment (35), the invention provides a compound selected from



and pharmaceutically acceptable salts thereof.

[111] In another Embodiment (36), the invention provides a pharmaceutical composition comprising a compound of any one of Embodiments (1) to (35) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

[112] In another Embodiment (37), the invention provides a method of treating, ameliorating or preventing a condition, which responds to inhibition of URAT1, comprising administering to a subject in need of such treatment an effective amount of a compound of any one of Embodiments (1) to (35), or a pharmaceutically acceptable salt thereof, or a

pharmaceutical composition thereof, and optionally in combination with a second therapeutic agent.

[113] In another Embodiment (38), the invention provides a use of a compound of any one of Embodiments (1) to (35) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating a condition mediated by URAT1.

[114] In yet another of its aspects, there is provided a kit comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof; and instructions which comprise one or more forms of information selected from the group consisting of indicating a disease state for which the composition is to be administered, storage information for the composition, dosing information and instructions regarding how to administer the composition. In one particular variation, the kit comprises the compound in a multiple dose form.

[115] In still another of its aspects, there is provided an article of manufacture comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof; and packaging materials. In one variation, the packaging material comprises a container for housing the compound. In one particular variation, the container comprises a label indicating one or more members of the group consisting of a disease state for which the compound is to be administered, storage information, dosing information and/or instructions regarding how to administer the compound. In another variation, the article of manufacture comprises the compound in a multiple dose form.

[116] In a further of its aspects, there is provided a therapeutic method comprising administering a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

[117] In another of its aspects, there is provided a method of inhibiting URAT1 comprising contacting the URAT1 with a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

[118] In yet another of its aspects, there is provided a method of inhibiting URAT1 comprising causing a compound disclosed herein, or a pharmaceutically acceptable salt thereof to be present in a subject in order to inhibit URAT1 *in vivo*.

[119] In a further of its aspects, there is provided a method of inhibiting URAT1 comprising administering a first compound to a subject that is converted *in vivo* to a second compound wherein the second compound inhibits URAT1 *in vivo*, the second compound being a compound according to any one of the above embodiments and variations.

[120] In another of its aspects, there is provided a method of treating a disease state for which URAT1 possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising causing a compound disclosed herein, or a pharmaceutically acceptable salt thereof to be present in a subject in a therapeutically effective amount for the disease state.

[121] In a further of its aspects, there is provided a method of treating a disease state for which URAT1 possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising administering a first compound to a subject that is converted in vivo to a second compound wherein the second compound inhibits URAT1 *in*

vivo. It is noted that the compounds of the present invention may be the first or second compounds.

[122] In one variation of each of the above methods the disease state is selected from the group consisting of hyperuricaemia, gout, a recurrent gout attach, tophaceous gout, arthritis, gouty arthritis, inflammatory arthritis, joint inflammation, deposition of urate crystals in the joint, kidney disease, kidney stones, kidney failure, urolithiasis, hypertension, a cardiovascular disease, coronary heart disease, Lesch-Nyhan syndrome and Kelley-Seegmiller syndrome.

[123] In another of its aspects, there is provided a method of treating a disease state for which a mutation in URAT1 gene contributes to the pathology and/or symptomology of the disease state including, goat, hyperuricaemia.

[124] In still another of its aspects, the present invention relates to the use of a compound of any of the above embodiments and variations as a medicament. In yet another of its aspects, the present invention relates to the use of a compound according to any one of the above embodiments and variations in the manufacture of a medicament for inhibiting URAT1.

[125] In a further of its aspects, the present invention relates to the use of a compound according to any one of the above embodiments and variations in the manufacture of a medicament for treating a disease state for which URAT1 possesses activity that contributes to the pathology and/or symptomology of the disease state.

Administration and Pharmaceutical Compositions

[126] In general, compounds of the disclosure will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors known to those of ordinary skill in the art. For example, for the treatment of neoplastic diseases and immune system disorders, the required dosage will also vary depending on the mode of administration, the particular condition to be treated and the effect desired.

[127] In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.001 to about 100 mg/kg per body weight, or particularly, from about 0.03 to 2.5 mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, may be in the range from about 0.5 mg to about 2000 mg, or more particularly, from about 0.5 mg to about 1000 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50 mg active ingredient.

[128] Compounds of the disclosure may be administered as pharmaceutical compositions by any conventional route; for example, enterally, e.g., orally, e.g., in the form of tablets or capsules; parenterally, e.g., in the form of injectable solutions or suspensions; or topically, e.g., in the form of lotions, gels, ointments or creams, or in a nasal or suppository form.

[129] Pharmaceutical compositions comprising a compound of the present disclosure in free form or in a pharmaceutically acceptable salt form in association with at least one

pharmaceutically acceptable carrier or diluent may be manufactured in a conventional manner by mixing, granulating, coating, dissolving or lyophilizing processes. For example, pharmaceutical compositions comprising a compound of the disclosure in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent. Unit dosage forms for oral administration contain, for example, from about 0.1 mg to about 500 mg of active substance.

[130] In one embodiment, the pharmaceutical compositions are solutions of the active ingredient, including suspensions or dispersions, such as isotonic aqueous solutions. In the case of lyophilized compositions comprising the active ingredient alone or together with a carrier such as mannitol, dispersions or suspensions can be made up before use. The pharmaceutical compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. Suitable preservatives include but are not limited to antioxidants such as ascorbic acid, or microbicides, such as sorbic acid or benzoic acid. The solutions or suspensions may further comprise viscosity-increasing agents, including but not limited to, sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone, gelatins, or solubilizers, e.g. Tween 80 (polyoxyethylene(20)sorbitan mono-oleate).

[131] Suspensions in oil may comprise as the oil component the vegetable, synthetic, or semi-synthetic oils customary for injection purposes. Examples include but are not limited to liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to 22 carbon atoms, or in some embodiments, from 12 to 22 carbon atoms. Suitable liquid fatty acid esters include but are not limited to lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brassidic acid and linoleic acid, and if desired, may contain antioxidants, for example vitamin E, 3-carotene or 3,5-di-tert-butyl-hydroxytoluene. The alcohol component of these fatty acid esters may have six carbon atoms and may be monovalent or polyvalent, for example a mono-, di- or trivalent, alcohol. Suitable alcohol components include but are not limited to methanol, ethanol, propanol, butanol or pentanol or isomers thereof; glycol and glycerol.

[132] Other suitable fatty acid esters include but are not limited ethyl-oleate, isopropyl myristate, isopropyl palmitate, LABRAFIL® M 2375, (polyoxyethylene glycerol), LABRAFIL® M 1944 CS (unsaturated polyglycolized glycerides prepared by alcoholysis of apricot kernel oil and comprising glycerides and polyethylene glycol ester), LABRASOL™ (saturated polyglycolized glycerides prepared by alcoholysis of TCM and comprising glycerides and polyethylene glycol ester; all available from GaKefosse, France), and/or MIGLYOL® 812 (triglyceride of saturated fatty acids of chain length C8 to C12 from Hüls AG, Germany), and vegetable oils such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil, or groundnut oil.

[133] Pharmaceutical compositions for oral administration may be obtained, for example, by combining the active ingredient with one or more solid carriers, and if desired, granulating a resulting mixture, and processing the mixture or granules by the inclusion of additional excipients, to form tablets or tablet cores.

[134] Suitable carriers include but are not limited to fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, carboxymethyl starch, crosslinked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients include flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

[135] Tablet cores may be provided with suitable, optionally enteric, coatings through the use of, inter alia, concentrated sugar solutions which may comprise gum arable, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as cellulose acetate phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or tablet coatings, for example for identification purposes or to indicate different doses of active ingredient.

[136] Pharmaceutical compositions for oral administration may also include hard capsules comprising gelatin or soft-sealed capsules comprising gelatin and a plasticizer, such as glycerol or sorbitol. The hard capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders, and/or glidants, such as talc or magnesium stearate, and optionally stabilizers. In soft capsules, the active ingredient may be dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene or propylene glycol, to which stabilizers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type, may also be added.

[137] Pharmaceutical compositions suitable for rectal administration are, for example, suppositories comprising a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

[138] Pharmaceutical compositions suitable for parenteral administration may comprise aqueous solutions of an active ingredient in water-soluble form, for example of a water-soluble salt, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilizers. The active ingredient, optionally together with excipients, can also be in the form of a lyophilizate and can be made into a solution before parenteral administration by the addition of suitable solvents. Solutions such as are used, for example, for parenteral administration can also be employed as infusion solutions. The manufacture of injectable preparations is usually carried out under sterile conditions, as is the filling, for example, into ampoules or vials, and the sealing of the containers.

[139] The disclosure also provides for a pharmaceutical combinations, e.g. a kit, comprising a) a first agent which is a compound of the disclosure as disclosed herein, in free

form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

Combination therapies

[140] The compounds or pharmaceutical acceptable salts of the disclosure may be administered as the sole therapy, or together with other therapeutic agent or agents.

[141] For example, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e. by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the individual is enhanced). Or, by way of example only, the benefit experienced by an individual may be increased by administering one of the compounds described herein with another therapeutic agent that also has therapeutic benefit. By way of example only, in a treatment for gout involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the individual with another therapeutic agent for gout. Or, by way of example only, if one of the side effects experienced by an individual upon receiving one of the compounds described herein is nausea, then it may be appropriate to administer an anti-nausea agent in combination with the compound. Or, the additional therapy or therapies include, but are not limited to physiotherapy, psychotherapy, radiation therapy, application of compresses to a diseased area, rest, altered diet, and the like. Regardless of the disease, disorder or condition being treated, the overall benefit experienced by the individual may be additive of the two therapies or the individual may experience a synergistic benefit.

[142] In the instances where the compounds described herein are administered in combination with other therapeutic agents, the compounds described herein may be administered in the same pharmaceutical composition as other therapeutic agents, or because of different physical and chemical characteristics, be administered by a different route. For example, the compounds described herein may be administered orally to generate and maintain good blood levels thereof, while the other therapeutic agent may be administered intravenously. Thus the compounds described herein may be administered concurrently, sequentially or dosed separately to other therapeutic agents.

EXAMPLES

[143] Various methods may be developed for synthesizing a compound of formula (I) or a pharmaceutically acceptable salt thereof. Representative methods for synthesizing a compound of formula (I) or a pharmaceutically acceptable salt thereof are provided in the Examples. It is noted, however, that a compound of formula (I) or a pharmaceutically acceptable salt thereof may also be synthesized by other synthetic routes that others may devise.

[144] It will be readily recognized that certain compounds of formula (I) have atoms with linkages to other atoms that confer a particular stereochemistry to the compound (e.g., chiral centers). It is recognized that synthesis of a compound of formula (I) or a pharmaceutically acceptable salt thereof may result in the creation of mixtures of different stereoisomers

(enantiomers, diastereomers). Unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all of the different possible stereoisomers.

[145] Ae compound of formula (I) can also be prepared as a pharmaceutically acceptable acid addition salt by, for example, reacting the free base form of the at least one compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of the at least one compound of formula (I) can be prepared by, for example, reacting the free acid form of the at least one compound with a pharmaceutically acceptable inorganic or organic base. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of formula (I) are set forth in the definitions section of this Application. Alternatively, the salt forms of the compounds of formula (I) can be prepared using salts of the starting materials or intermediates.

[146] The free acid or free base forms of the compounds of formula (I) can be prepared from the corresponding base addition salt or acid addition salt form. For example, a compound of formula (I) in an acid addition salt form can be converted to the corresponding free base thereof by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of formula (I) in a base addition salt form can be converted to the corresponding free acid thereof by, for example, treating with a suitable acid (e.g., hydrochloric acid, etc).

[147] The N-oxides of the a compound of formula (I) or a pharmaceutically acceptable salt thereof can be prepared by methods known to those of ordinary skill in the art. For example, N-oxides can be prepared by treating an unoxidized form of the compound of formula (I) with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, meta-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as dichloromethane) at approximately 0 to 80 °C. Alternatively, the N-oxides of the compounds of formula (I) can be prepared from the N-oxide of an appropriate starting material.

[148] Compounds of formula (I) in an unoxidized form can be prepared from N-oxides of compounds of formula (I) by, for example, treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, and the like) in an suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, and the like) at 0 to 80 °C.

[149] Protected derivatives of the compounds of formula (I) can be made by methods known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, Protecting Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, Inc. 1999.

[150] As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. For example, the following abbreviations may be used in the

examples and throughout the specification: g (grams); mg (milligrams); L (liters); mL (milliliters); μL (microliters); psi (pounds per square inch); M (molar); mM (millimolar); i.v. (intravenous); Hz (Hertz); MHz (megahertz); mol (moles); mmol (millimoles); RT (room temperature); min (minutes); h (hours); mp (melting point); TLC (thin layer chromatography); Rt (retention time); RP (reverse phase); MeOH (methanol); i-PrOH (isopropanol); TEA (triethylamine); TFA (trifluoroacetic acid); TFAA (trifluoroacetic anhydride); THF (tetrahydrofuran); DMSO (dimethyl sulfoxide); EtOAc (ethyl acetate); DME (1,2-dimethoxyethane); DCM (dichloromethane); DCE (dichloroethane); DMF (N,N-dimethylformamide); DMPU (N,N'-dimethylpropyleneurea); CDI (1,1-carbonyldiimidazole); IBCF (isobutyl chloroformate); HOAc (acetic acid); HOSu (N-hydroxysuccinimide); HOBT (1-hydroxybenzotriazole); Et_2O (diethyl ether); EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride); BOC (tert-butyloxycarbonyl); FMOC (9-fluorenylmethoxycarbonyl); DCC (dicyclohexylcarbodiimide); CBZ (benzyloxycarbonyl); Ac (acetyl); atm (atmosphere); TMSE (2-(trimethylsilyl)ethyl); TMS (trimethylsilyl); TIPS (triisopropylsilyl); TBS (t-butyldimethylsilyl); DMAP (4-dimethylaminopyridine); Me (methyl); OMe (methoxy); Et (ethyl); tBu (tert-butyl); HPLC (high pressure liquid chomatography); BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride); TBAF (tetra-n-butylammonium fluoride); m-CPBA (meta-chloroperbenzoic acid).

[151] References to ether or Et_2O are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions were conducted under an inert atmosphere at RT unless otherwise noted.

[152] ^1H NMR spectra were recorded on a Varian Mercury Plus 400. Chemical shifts are expressed in parts per million (ppm). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad).

[153] Low-resolution mass spectra (MS) and compound purity data were acquired on a Shimadzu LC/MS single quadrapole system equipped with electrospray ionization (ESI) source, UV detector (220 and 254 nm), and evaporative light scattering detector (ELSD). Thin-layer chromatography was performed on 0.25 mm Superchemgroup silica gel plates (60F-254), visualized with UV light, 5% ethanolic phosphomolybdic acid, ninhydrin, or p-anisaldehyde solution. Flash column chromatography was performed on silica gel (200-300 mesh, Branch of Qingdao Haiyang Chemical Co.,Ltd).

Synthetic Schemes

[154] A compound of formula I and/or a pharmaceutically acceptable salt thereof may be synthesized according to a variety of reaction schemes. Some illustrative schemes are provided below and in the examples. Other reaction schemes could be readily devised by those skilled in the art in view of the present disclosure.

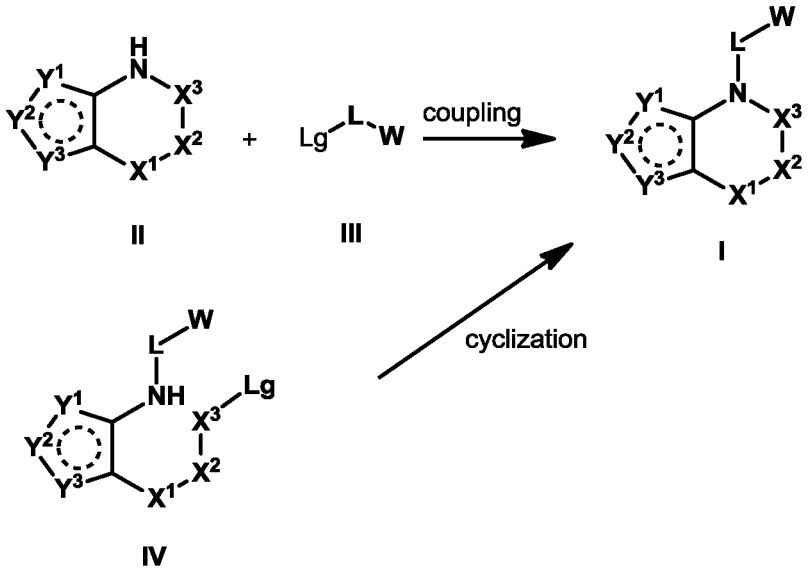
[155] In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions.

Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

[156] Synthetic methods for preparing the compounds of the present disclosure are illustrated in the following Schemes and Examples. Starting materials are commercially available or may be made according to procedures known in the art or as illustrated herein.

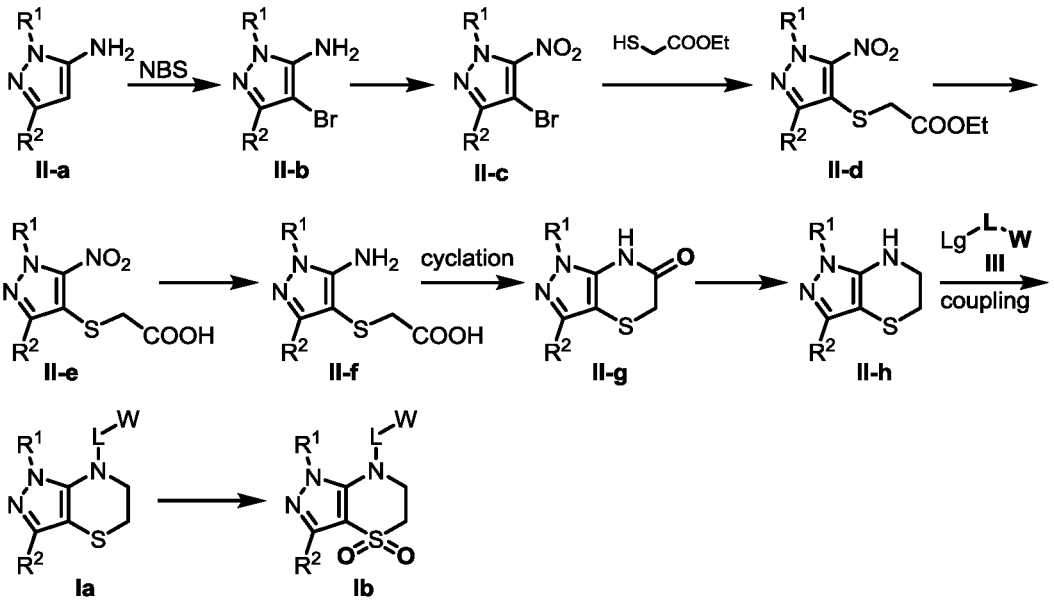
[157] The intermediates shown in the following schemes are either known in the literature or may be prepared by a variety of methods familiar to those skilled in the art.

[158] Two synthetic approaches for the construction of the compounds of formula I are shown in Scheme 1. Coupling of fused heterocyclic amines of formula II with intermediates of formula III gives compounds of formula I, which can also be synthesized by via the intramolecular cyclization of intermediates of formula IV.



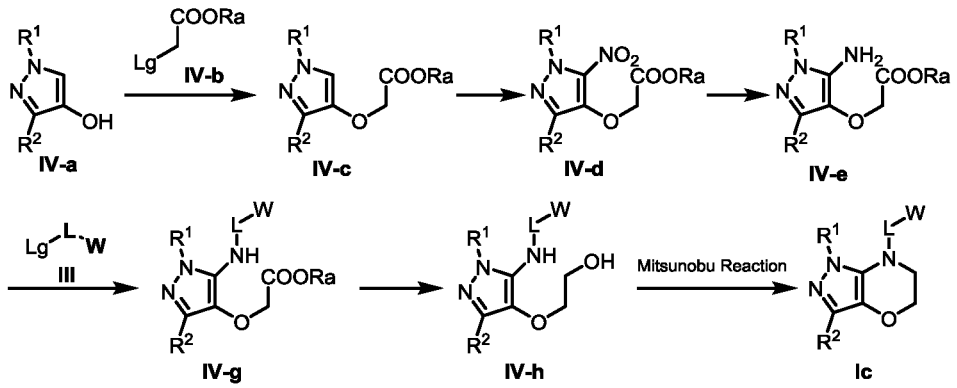
Scheme 1

[159] As an illustration of the synthesis of compounds of formula I, one of the synthetic approach of the compounds of formula Ia and Ib is outlined in Scheme 2. Halogenation of II-a with reagents such as NBS gives bromide II-b. Oxidation of amine II-b by H_2O_2 gives nitro compounds of formula II-c. S_NAr substitutions of II-c with ethyl 2-mercaptoacetate provides II-d. Hydrolysis of Ester II-d followed by the reduction of the resulting acid with reducing reagents such as ferrous powder gives amino acid II-f. Intramolecular cyclization of II-f with reagents such as $POCl_3$ gives lactam II-g which can be reduced with BH_3 to give amine II-h. Condensation of amine II-h with III followed by other necessary derivatization reactions leads to compounds of formula Ib. Compounds of formula Ib can be prepared by the oxidization of Ia.



Scheme 2

[160] As a further illustration of the preparation of I. One synthetic route of Ic is shown in Scheme 3. The preparation starts with IV-a, which is commercially available or can be synthesized following the procedure known in the literature. Alkylation of IV-a with IV-b in the presence of a base such as Cs_2CO_3 provides ethers of formula IV-c. Nitration of IV-c leads to nitro intermediates of formula IV-d which can converted into intermediates IV-g via reduction of the nitro group and coupling of the resulting amine with III. Ester IV-g can be converted into alcohol IV-h via $NaBH_4/CaCl_2$ reduction. Cyclization of IV-h via mitsunobu reaction followed by other necessary derivatization reactions to give compounds of formula Ic.

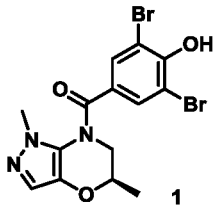


Scheme 3

[161] In some cases, the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood.

Example 1

[162] *(R)-(3,5-dibromo-4-hydroxyphenyl)(1,5-dimethyl-5,6-dihydropyrazolo[4,3-b][1,4] oxazin-7(1H)-yl)methanone* (**1**)



1

[163] *Methyl (R)-2-((1-methyl-1H-pyrazol-4-yl)oxy)propanoate* (**1a**)

[164] To a mixture of 1-methyl-1H-pyrazol-4-ol (400 mg, 4.08 mmol) and Cs_2CO_3 (2.60 g, 8.00 mmol) in DMF (6.0 mL) was added a solution of methyl (*S*)-2-((methylsulfonyl)oxy)propanoate (1.00 g, 5.50 mmol) (*WO2015/164643, **2015**, A1*) in DMF (4.0 mL) at 80°C. The mixture was stirred at 80°C for 45 min. The mixture was diluted with H_2O (100 mL), extracted with EtOAc (3 × 50 mL), washed with brine, dried over Na_2SO_4, filtered, concentrated and purified by column chromatography on silica gel eluting with Petroleum/ EtOAc (10:1 ~ 2:1) to give the title compound methyl (*R*)-2-((1-methyl-1*H*-pyrazol- 4-yl)oxy)propanoate (**1a**). MS-ESI (m/z): 185 $[M + 1]^+$.

[165] *Methyl (R)-2-((1-methyl-5-nitro-1H-pyrazol-4-yl)oxy)propanoate* (**1b**)

[166] To a mixture of methyl (*R*)-2-((1-methyl-1*H*-pyrazol-4-yl)oxy)propanoate (**1a**) (3.68 g, 20.0 mmol) in Con.H_2SO_4 (30.0 mL) was added KNO_3 (3.23 g, 32.0 mmol) in portions under ice-water bath. The mixture was stirred at 0°C for 20 min. Then the mixture was poured into ice water (350 mL) and extracted with DCM (3 × 100 mL), The organic phase was washed with saturated $NaHCO_3$ aqueous solution, concentrated and purified by column chromatography on silica gel eluting with Petroleum/ EtOAc (10:1 ~ 4:1) to give the title compound methyl (*R*)-2-((1-methyl-5-nitro-1*H*-pyrazol-4-yl)oxy)propanoate (**1b**). MS-ESI (m/z): 230 $[M + 1]^+$.

[167] *Methyl (R)-2-((5-amino-1-methyl-1H-pyrazol-4-yl)oxy)propanoate* (**1c**)

[168] A mixture of methyl (*R*)-2-((1-methyl-5-nitro-1*H*-pyrazol-4-yl)oxy)propanoate (**1b**) (2.80 g, 12.2 mmol) and Pd/C (1.00 g) in MeOH (50.0 mL) was stirred at RT under H_2 atmosphere for 6 hours. The reaction mixture was filtered through celite and concentrated to give the crude product of title compound methyl (*R*)-2-((5-amino-1-methyl-1*H*-pyrazol-4-yl)oxy)propanoate (**1c**) which was used directly for next step. MS-ESI (m/z): 200 $[M + 1]^+$.

[169] *2,6-Dibromo-4-methoxybenzoic acid* (**1d**)

[170] 2,6-dibromo-4-methoxybenzoic acid (**1d**) was prepared according to the method described in *European Journal of Inorganic Chemistry, 2015, 3, 534 - 541.*

[171] *Methyl (R)-2-((5-(3,5-dibromo-4-methoxybenzamido)-1-methyl-1H-pyrazol-4-yl)oxy)propanoate* (**1e**)

[172] To a mixture of 2,6-dibromo-4-methoxybenzoic acid (**1d**) (2.92 g, 14.0 mmol) in DCM (25 mL) was added $(COCl)_2$ (2M in DCM, 15.0 mL) followed by DMF (0.05 mL), The mixture was stirred at RT for 2 hours. The mixture was concentrated and the residue was

dissolved in DCM (10 mL). To a solution of methyl (*R*)-2-((5-amino-1-methyl-1*H*-pyrazol-4- yl)oxy)propanoate (**1c**) (2.50 g, 12.6 mmol) and pyridine (5mL) in DCM (20 mL) was added the mixture of above solution dropwise under ice-bath, after addition, the mixture was stirred at RT for overnight. The mixture was quenched with H_2O, sequentially washed with 1N HCl (2 × 50 mL), saturated $NaHCO_3$ aqueous solution (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by column chromatography on silica gel eluting with Petroleum/ EtOAc (10:1 ~ 1:1) to give the title compound methyl (*R*)-2-((5-(3,5-dibromo-4-methoxybenzamido)-1-methyl-1*H*-pyrazol- 4-yl)oxy)propanoate (**1e**). MS-ESI (m/z): 490, 492, 494 (1:2:1) $[M + 1]^+$.

[173] *(R)-3,5-dibromo-N-(4-((1-hydroxypropan-2-yl)oxy)-1-methyl-1H-pyrazol-5-yl)-4-methoxybenzamide* (**1f**)

[174] To a mixture of methyl (*R*)-2-((5-(3,5-dibromo-4-methoxybenzamido)-1-methyl-1*H*-pyrazol-4-yl)oxy)propanoate (**1e**) (3.90 g, 8.00 mmol) and $CaCl_2$ (1.76 g, 15.9 mmol) in EtOH (50.0 mL) was added $NaBH_4$ (1.20 g, 31.7 mmol) in portions under ice-water bath. The mixture was stirred at 0°C for 2 h. The reaction was quenched with water, filtered and the filtrate was extracted with DCM (2 × 100 mL). The extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel, eluting with DCM/MeOH (20:1) to give the title compound (*R*)-3,5-dibromo-*N*-(4-((1-hydroxypropan- 2-yl)oxy)-1-methyl-1*H*-pyrazol-5-yl)-4-methoxybenzamide (**1f**). MS-ESI (m/z): 462, 464, 466 (1:2:1) $[M + 1]^+$.

[175] *(R)-(3,5-dibromo-4-methoxyphenyl)(1,5-dimethyl-5,6-dihydropyrazolo[4,3-b][1,4]oxazin-7(1H)-yl)methanone* (**1g**)

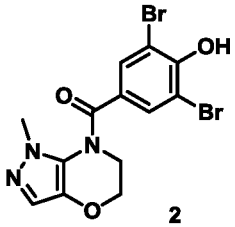
[176] The mixture of (*R*)-3,5-dibromo-*N*-(4-((1-hydroxypropan-2-yl)oxy)-1-methyl-1*H*-pyrazol-5-yl)-4-methoxybenzamide (**1f**) (2.30 g, 5.00 mmol), PPh_3 (4.58 g, 17.5 mmol) and DIAD (3.03 g, 15.0 mmol) in THF (40.0 mL) was stirred at 0°C ~ RT for 3 h. Then the mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel eluting with Petroleum/ EtOAc (10:1 ~ 5:1) to give the title compound (*R*)-(3,5-dibromo-4-methoxyphenyl)(1,5-dimethyl-5,6-dihydropyrazolo[4,3-*b*][1,4] oxazin-7(1*H*)-yl)methanone (**1g**). MS-ESI (m/z): 444, 446, 448 (1:2:1) $[M + 1]^+$.

[177] *(R)-(3,5-dibromo-4-hydroxyphenyl)(1,5-dimethyl-5,6-dihydropyrazolo[4,3-b][1,4]oxazin-7(1H)-yl)methanone* (**1**)

[178] The mixture of (*R*)-(3,5-dibromo-4-methoxyphenyl)(1,5-dimethyl-5,6-dihydropyrazolo[4,3-*b*][1,4]oxazin-7(1*H*)-yl)methanone (**1g**) (3.00 g, 6.77 mmol) and BBr_3 (1M in DCM, 30.0 mL) in DCM (10.0 mL) was stirred at 0°C ~ RT for 2 h. The reaction was quenched with ice water (300 g) and extracted with DCM (2 × 100 mL). The extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel eluting with DCM/MeOH (100:1 ~ 20:1) to give the title compound (*R*)-(3,5-dibromo-4-hydroxyphenyl)(1,5-dimethyl-5,6-dihydropyrazolo[4,3-*b*][1,4]oxazin-7(1*H*)-yl)methanone (**1**). MS-ESI (m/z): 430, 432, 434 (1:2:1) $[M + 1]^+$.

Example 2

[179] *(3,5-Dibromo-4-hydroxyphenyl)(1-methyl-5,6-dihydropyrazolo[4,3-b][1,4]oxazin-7(1H)-yl)methanone* (**2**)

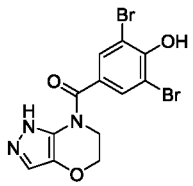
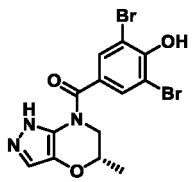
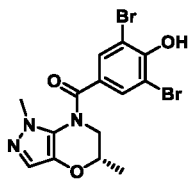
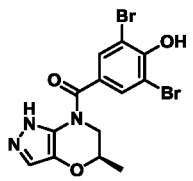


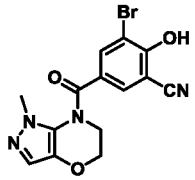
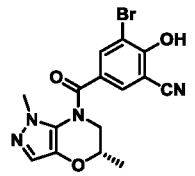
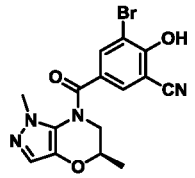
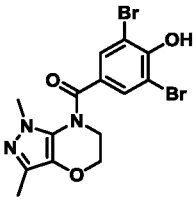
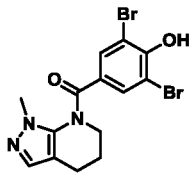
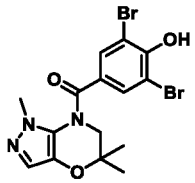
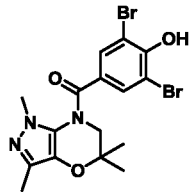
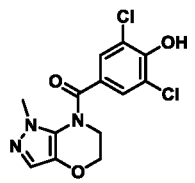
2

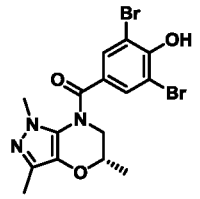
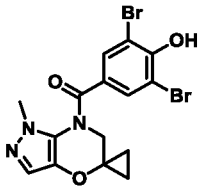
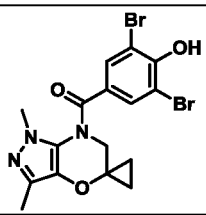
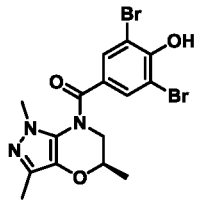
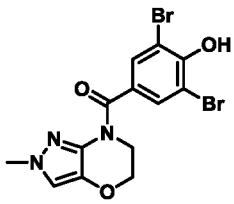
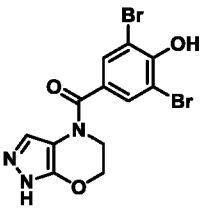
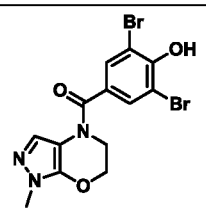
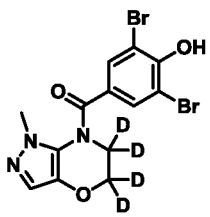
[180] The title compound **2** was prepared according to the synthetic method of **1** by replacing methyl (*S*)-2-((methylsulfonyl)oxy)propanoate with methyl 2-bromoacetate. MS-ESI (m/z): 416, 418, 420 (1:2:1) $[M + 1]^+$.

[181] Following essentially the same procedures described for Examples **1~2** or using similar synthetic methods or strategies, Examples **3~18** listed in Table 1 were prepared. The structures and names of Examples **3 ~ 19** are given in Table 1.

Table 1

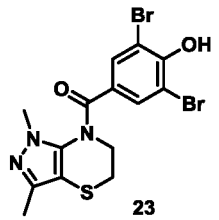
EXAMPLE	STRUCTURE	NAME	DATA
3		(3,5-dibromo-4-hydroxyphenyl)(5,6-dihydropyrazolo[4,3-*b*][1,4]oxazin-7(1*H*)-yl)methanone	MS-ESI (m/z): 402, 404, 406 (1:2:1) $[M + 1]^+$
4		(*S*)-(3,5-dibromo-4-hydroxyphenyl)(5-methyl-5,6-dihydropyrazolo[4,3-*b*][1,4]oxazin-7(1*H*)-yl)methanone	MS-ESI (m/z): 416, 418, 420 (1:2:1) $[M + 1]^+$
5		(*S*)-(3,5-dibromo-4-hydroxyphenyl)(1,5-dimethyl-5,6-dihydropyrazolo[4,3-*b*][1,4]oxazin-7(1*H*)-yl)methanone	MS-ESI (m/z): 430, 432, 434 (1:2:1) $[M + 1]^+$
6		(*R*)-(3,5-dibromo-4-hydroxyphenyl)(5-methyl-5,6-dihydropyrazolo[4,3-*b*][1,4]oxazin-7(1*H*)-yl)methanone	MS-ESI (m/z): 416, 418, 420 (1:2:1) $[M + 1]^+$

EXAMPLE	STRUCTURE	NAME	DATA
7		3-bromo-2-hydroxy-5-(1-methyl-1,5,6,7-tetrahydropyrazolo[4,3-*b*][1,4]oxazine-7-carbonyl)benzonitrile	MS-ESI (m/z): 363, 365 (1:1) [M + 1]+.
8		(*S*)-3-bromo-5-(1,5-dimethyl-1,5,6,7-tetrahydropyrazolo[4,3-*b*][1,4]oxazine-7-carbonyl)-2-hydroxybenzonitrile	MS-ESI (m/z): 377, 379 (1: 1) $[M + 1]^+$
9		(*R*)-3-bromo-5-(1,5-dimethyl-1,5,6,7-tetrahydropyrazolo[4,3-*b*][1,4]oxazine-7-carbonyl)-2-hydroxybenzonitrile	MS-ESI (m/z): 377, 379 (1: 1) $[M + 1]^+$
10		(3,5-dibromo-4-hydroxyphenyl)(1,3-dimethyl-5,6-dihydropyrazolo[4,3-*b*][1,4]oxazin-7(1*H*)-yl)methanone	MS-ESI (m/z): 430, 432, 434 (1:2:1) $[M + 1]^+$.
11		(3,5-dibromo-4-hydroxyphenyl)(1-methyl-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*b*]pyridin-7-yl)methanone	MS-ESI (m/z): 414, 416, 418 (1:2:1) $[M + 1]^+$.
12		(3,5-dibromo-4-hydroxyphenyl)(1,5,5-trimethyl-5,6-dihydropyrazolo[4,3-*b*][1,4]oxazin-7(1*H*)-yl)methanone	MS-ESI (m/z): 444, 446, 448 (1:2:1) $[M + 1]^+$.
13		(3,5-dibromo-4-hydroxyphenyl)(1,3,5,5-tetramethyl-5,6-dihydropyrazolo[4,3-*b*][1,4]oxazin-7(1*H*)-yl)methanone	MS-ESI (m/z): 458, 460, 462 (1:2:1) $[M + 1]^+$.
14		(3,5-dichloro-4-hydroxyphenyl)(1-methyl-5,6-dihydropyrazolo[4,3-*b*][1,4]oxazin-7(1*H*)-yl)methanone	MS-ESI (m/z): 328 $[M + 1]^+$.

EXAMPLE	STRUCTURE	NAME	DATA
15		(*S*)-(3,5-dibromo-4-hydroxyphenyl)(1,3,5-trimethyl-5,6-dihydropyrazolo[4,3-*b*][1,4]oxazin-7(1*H*)-yl)methanone	MS-ESI (m/z): 444, 446, 448 (1:2:1) [M + 1]$^+$.
16		(3,5-dibromo-4-hydroxyphenyl)(1'-methyl-1'*H*-spiro[cyclopropane-1,5'-pyrazolo[4,3-*b*][1,4]oxazin]-7'(6'*H*)-yl)methanone	MS-ESI (m/z): 442, 444, 446 (1:2:1) [M + 1]$^+$.
17		(3,5-dibromo-4-hydroxyphenyl)(1',3'-dimethyl-1'*H*-spiro[cyclopropane-1,5'-pyrazolo[4,3-*b*][1,4]oxazin]-7'(6'*H*)-yl)methanone	MS-ESI (m/z): 456, 458, 460 (1:2:1) [M + 1]$^+$.
18		(*R*)-(3,5-dibromo-4-hydroxyphenyl)(1,3,5-trimethyl-5,6-dihydropyrazolo[4,3-*b*][1,4]oxazin-7(1*H*)-yl)methanone	MS-ESI (m/z): 444, 446, 448 (1:2:1) [M + 1]$^+$.
19		(3,5-dibromo-4-hydroxyphenyl)(2-methyl-5,6-dihydropyrazolo[4,3-*b*][1,4]oxazin-7(2*H*)-yl)methanone	MS-ESI (m/z): 416, 418, 420 (1:2:1) [M + 1]$^+$.
20		(3,5-dibromo-4-hydroxyphenyl)(5,6-dihydropyrazolo[3,4-*b*][1,4]oxazin-4(1*H*)-yl)methanone	MS-ESI (m/z): 402, 404, 406 (1:2:1) [M + 1]$^+$.
21		(3,5-dibromo-4-hydroxyphenyl)(1-methyl-5,6-dihydropyrazolo[3,4-*b*][1,4]oxazin-4(1*H*)-yl)methanone	MS-ESI (m/z): 416, 418, 420 (1:2:1) [M + 1]$^+$.
22		(3,5-dibromo-4-hydroxyphenyl)(1-methyl-5,6-dihydropyrazolo[4,3-*b*][1,4]oxazin-7(1*H*)-yl-5,5,6,6-d_4)methanone	MS-ESI (m/z): 420, 422, 424 (1:2:1) [M + 1]$^+$.

Example 23

[182] *(3,5-dibromo-4-hydroxyphenyl)(1,3-dimethyl-5,6-dihydropyrazolo[4,3-b][1,4]thiazin-7(1H)-yl)methanone* (**23**)



23

[183] *4-bromo-1,3-dimethyl-1H-pyrazol-5-amine* (**23a**)

[184] To a stirred solution of 1,3-dimethyl-1*H*-pyrazol-5-amine (10 g, 90.0 mmol) in DCM (150 mL) was added NBS(16 g, 90 mmol) in 5 portions at 0 ~ 5℃. The resulting mixture was stirred at the same temperature for 1 h under nitrogen atmosphere. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (100 mL). The aqueous layer was extracted with DCM (50 mL × 2). The combined DCM phase was washed sequentially with saturated aqueous Na_2SO_3 solution, water and brine, concentrated to give 4-bromo-1,3-dimethyl-1*H*-pyrazol-5-amine (**23a**) as crude, which was used in the next step without further purification. MS-ESI(m/z): 190, 192 $[M+1]^+$.

[185] *4-bromo-1,3-dimethyl-5-nitro-1H-pyrazole* (**23b**)

[186] To a stirred solution of 4-bromo-1,3-dimethyl-1*H*-pyrazol-5-amine (**23a**) (5.0 g, 26.3 mmol) in con. H_2SO_4 (100 mL) was added H_2O_2 / H_2O (30%, 40 mL) dropwise at 5 ~ 30℃. The resulting mixture was stirred at RT for 2 h. Additional H_2O_2/H_2O (30%, 8 mL) was added dropwise to the reaction at 5 ~ 30℃. The mixture was stirred at RT for 2 h before being poured into ice-water. The mixture was extracted with EA (100 mL × 3), the combined extracts were washed sequentially with saturated aqueous Na_2SO_3 solution (100 mL) , saturated aqueous $NaHCO_3$ solution (100 mL), water (100 mL) ,brine (100 mL), dried over Na_2SO_4 and concentrated to give the title compound 4-bromo-1,3-dimethyl-5-nitro-1*H*-pyrazole (**23b**) as crude, which was used in the next step without further purification.

[187] *ethyl 2-((1,3-dimethyl-5-nitro-1H-pyrazol-4-yl)thio)acetate* (**23c**)

[188] To a stirred solution of 4-bromo-1,3-dimethyl-5-nitro-1*H*-pyrazole (**23b**) (1.0 g, 4.55 mmol) in DMF (10 mL) was added K_2CO_3 (1.26 g, 9.12 mmol), followed by the addition of ethyl 2-mercaptoacetate (0.820 g,6.82 mmol) at RT. The resulting mixture was stirred at RT for 1.5 h under nitrogen atmosphere. Additional ethyl 2-mercaptoacetate (0.547 g, 4.55 mmol) was added to the reaction. The resulting mixture was stirred at RT for 1 h before being diluted with water. The mixture was extracted with EA for 3 times, the extracts were washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel, eluting with PE/EA (20:1 ~ 5:1) to give the title compound ethyl 2-((1,3-dimethyl-5-nitro-1*H*-pyrazol-4-yl)thio)acetate (**23c**). MS-ESI(m/z):260 $[M+1]^+$.

[189] *2-((1,3-dimethyl-5-nitro-1H-pyrazol-4-yl)thio)acetic acid* (**23d**)

[190] To a solution of ethyl 2-((1,3-dimethyl-5-nitro-1*H*-pyrazol-4-yl)thio)acetate (**23c**) (0.760 g, 2.93 mmol) in THF (10 mL) and H_2O (10 mL) was added $LiOH{\cdot}H_2O$(1.5 g, 35.7

mmol) at RT. The resulting mixture was stirred at RT for 1.5 h. The mixture was then acidified to pH 2 ~ 3 with HCl (2 N), then extracted with DCM, the extracts was washed with water and brine, dried over Na_2SO_4 and concentrated to give 2-((1,3-dimethyl-5-nitro-1*H*-pyrazol-4-yl)thio)acetic acid (**23d**) as crude, which was used in the next step without further purification. MS-ESI(m/z): 232 $[M+1]^+$.

[191] *2-((5-amino-1,3-dimethyl-1H-pyrazol-4-yl)thio)acetic acid* (**23e**)

[192] To a solution of 2-((1,3-dimethyl-5-nitro-1*H*-pyrazol-4-yl)thio)acetic acid (**23d**) (0.62 g, 2.68 mmol) in EtOH (13 mL) and H_2O (3 mL) was added NH_4Cl (1.16 g, 21.7 mmol) followed by the adding of ferrous powder (1.50 g, 26.9 mmol). The resulting mixture was warmed to 45℃ and stirred for 30 min under nitrogen atmosphere. The mixture was filtered and the filtrate was concentrated. The residue was slurried in DCM/MeOH (10:1), then filtered. The filtrate was concentrated to give 2-((5-amino-1,3-dimethyl-1*H*-pyrazol-4-yl)thio)acetic acid (**23e**) as crude, which was used in the next step without further purification. MS-ESI(m/z):202 $[M+1]^+$.

[193] *1,3-dimethyl-1,7-dihydropyrazolo[4,3-b][1,4]thiazin-6(5H)-one* (**23f**)

[194] A solution of 2-((5-amino-1,3-dimethyl-1*H*-pyrazol-4-yl)thio)acetic acid (**23e**) (234 mg, 1.16 mmol) in $POCl_3$ (5.9 mL) was stirred at RT for 18 h under nitrogen atmosphere. The mixture was warmed to 40℃ and stirred for 1 h, then warmed to 60 ~ 70℃ and stirred for 1.5 h. After being cooled to RT, the mixture was concentrated in vacuo. The residue was added DCM (15 mL) and saturated aqueous Na_2CO_3 solution (21 mL). After the mixture was basified to pH 8 with Na_2CO_3 (solid), the aqueous layer was extracted with DCM/MeOH (10:1) (15 mL × 5). The combined organic phase was dried over Na_2SO_4 and concentrated to give the title compound 1,3-dimethyl-1,7-dihydropyrazolo[4,3-*b*][1,4]thiazin-6(5*H*)-one (**23f**) as crude, which was used in the next step without further purification. MS-ESI(m/z):184 $[M+1]^+$.

[195] *1,3-dimethyl-1,5,6,7-tetrahydropyrazolo[4,3-b][1,4]thiazine* (**23g**)

[196] To a stirred suspension of 1,3-dimethyl-1,7-dihydropyrazolo[4,3-b][1,4]thiazin-6(5*H*)-one (**23f**) (225 mg, 1.23 mmol) in THF (9.0 mL) was added Borane-methyl sulfide complex (0.98 mL, 9.8 mmol) dropwise at RT under nitrogen atmosphere. The resulting mixture was stirred at RT for 2.5 h. After being cooled to 0℃, the reaction was quenched with MeOH (5.0 mL). The resulting mixture was stirred at 0℃ for 5 min, then added HCl (2 M, 0.87 mL). The mixture was stirred at 0℃ for 5 min. After being neutralized with saturated aqueous Na_2CO_3 solution, the mixture was concentrated and the residue was added DCM/MeOH (10:1) (26 mL) and sonicated for 1 min then filtered, the filtrate was concentrated. The residue was purified by column chromatography on silica gel, eluting with DCM/MeOH (30:1) to give the title compound 1,3-dimethyl-1,5,6,7-tetrahydropyrazolo[4,3-*b*][1,4]thiazine (**23g**). MS-ESI(m/z):170 $[M+1]^+$.

[197] *(3,5-dibromo-4-methoxyphenyl)(1,3-dimethyl-5,6-dihydropyrazolo[4,3-b][1,4]thiazin-7(1H)-yl)methanone* (**23h**)

[198] To a solution of 1,3-dimethyl-1,5,6,7-tetrahydropyrazolo[4,3-*b*][1,4]thiazine (**23g**) (151 mg, 0.892 mmol) in THF(15mL) was added HMDSLi / THF(1.0 M, 1.57 mmol) dropwise at -72℃ under nitrogen atmosphere. After addition, the reaction mixture was added 3,5-dibromo-4-methoxybenzoyl chloride (439 mg,1.34 mmol). The resulting mixture was

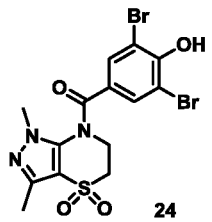
stirred at -72℃ for 10 min and quenched with H_2O (30 mL). The mixture was warmed to RT and extracted with EA (17 mL × 3). The extracts were washed sequentially with water (8 mL) and saturated aqueous $NaHCO_3$ solution (8 mL × 3), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel, eluting with PE/EA (4:1) to give the title compound (3,5-dibromo-4-methoxyphenyl)(1,3-dimethyl-5,6-dihydropyrazolo[4,3-b][1,4]thiazin-7(1*H*)-yl)methanone (**23h**). MS-ESI(m/z): 460, 462, 464 (1:2:1) $[M+1]^+$.

[199] *(3,5-dibromo-4-hydroxyphenyl)(1,3-dimethyl-5,6-dihydropyrazolo[4,3-b][1,4]thiazin-7(1H)-yl)methanone* (**23**)

[200] To a solution of (3,5-dibromo-4-methoxyphenyl)(1,3-dimethyl-5,6-dihydropyrazolo[4,3-*b*][1,4]thiazin-7(1*H*)-yl)methanone (**23h**) (360 mg, 0.781 mmol) in DMF (14.4 mL) was added LiBr (312 mg,3.59 mmol) and piperazine (155.0 mg, 1.80 mmol). The resulting mixture was warmed to 100℃ and stirred for overnight under nitrogen atmosphere. After being cooled to RT, the mixture was poured in to water (75 mL). The resulting mixture was acidified to pH 5 ~ 6 with HCl (1 M). The solid was filtered and washed with H_2O (10 mL × 2). The solid was dissolved in a mixed solvent of DCM (200 mL) and MeOH (50 mL). The resulting solution was concentrated to about 20 mL. The solid was filtered and washed with MTBE (2 mL × 2), and then dried to give (3,5-dibromo-4-hydroxyphenyl)(1,3-dimethyl-5,6-dihydropyrazolo[4,3-*b*][1,4]thiazin-7(1*H*)-yl)methanone (**23**). MS-ESI(m/z): 446, 448, 450 (1:2:1) $[M+1]^+$.

Example 24

[201] *(3,5-dibromo-4-hydroxyphenyl)(1,3-dimethyl-4,4-dioxido-5,6-dihydropyrazolo[4,3-b][1,4]thiazin-7(1H)-yl)methanone* (**24**)

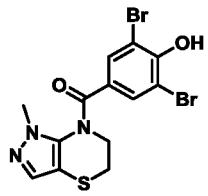
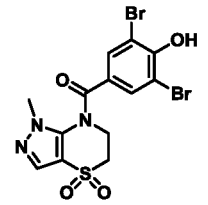


24

[202] To a suspension of (3,5-dibromo-4-hydroxyphenyl)(1,3-dimethyl-4,4-dioxido-5,6-dihydropyrazolo[4,3-*b*][1,4]thiazin-7(1*H*)-yl)methanone (**23**) (35 mg, 0.0783 mmol) in THF (10 mL) and H_2O (4 mL) was added $NaIO_4$ (87.2 mg, 0.408 mmol) and $RuCl_3.H_2O$ (4.80 mg,0.0231 mmol) at 0 ~ 5℃. The resulting mixture was warmed to RT and stirred for 2.5 h. The mixture was concentrated and the residue was purified by preparative TLC eluting with DCM/MeOH (15:1) to give the title compound (3,5-dibromo-4-hydroxyphenyl)(1,3-dimethyl-4,4-dioxido-5,6-dihydropyrazolo[4,3-*b*][1,4]thiazin-7(1*H*)-yl)methanone (**24**). MS-ESI(m/z): 478, 480, 482 (1:2:1) $[M+1]^+$.

[203] Following essentially the same procedures described for Examples **23 ~ 24** or using similar synthetic methods or strategies. Examples **25~26** listed in Table 2 were prepared. The structures and names of Examples **25 ~ 26** are given in Table 2.

Table 2

EXAMPLE	STRUCTURE	NAME	DATA
25		(3,5-dibromo-4-hydroxyphenyl)(1-methyl-5,6-dihydropyrazolo[4,3-*b*][1,4]thiazin-7(1*H*)-yl)methanone	MS-ESI (m/z): 432, 434, 436 (1:2:1) [M + 1]$^+$.
26		(3,5-dibromo-4-hydroxyphenyl)(1-methyl-4,4-dioxido-5,6-dihydropyrazolo[4,3-*b*][1,4]thiazin-7(1*H*)-yl)methanone	MS-ESI (m/z): 464, 466, 468 (1:2:1) [M + 1]$^+$.

URAT1 inhibitor activity

[204] The potency of the compounds of formula (I) as inhibitors of the URAT1 was determined as follow.

[205] HEK293-URAT1 cell Lines were donated by Japan Fuji Biomedical Research Institute. Negative control cell of HEK293 (MOCK cells) which was transfected with pcDNA3.1 empty vector. HEK293-URAT1 cell lines and MOCK cell lines were cultured in complete growth medium consisting of DMEM supplemented with 10% FBS, penicillin and streptomycin.

[206] Preparation of working solution: Each stock solutions was diluted to different concentrations (6, 20, 60, 200 and 600 μmol/L) with DMSO as 200× working solution, which was then diluted to 2×compound working solution with HBSS (Cl^- free) buffer. Radiolabeled substrate ^{14}C-Uric acid solution was diluted with HBSS (Cl^- free) buffer to obtain 2× working solution which was mixed with an equal volume of 2× compound working solution to obtain the mixture of radiolabeled substrate and compound working solution.

[207] HER293-URAT1 and MOCK cells were seeded onto 24-well plates at the density of 1.5 × 10^6 cells per well. The cells were incubated at 37°C, 5% CO_2 overnight. After cultured for approximately 2 to 3 days, cells were used for the experiments. The culture medium were removed from the wells, and cells were washed with HBSS (Cl^- free) and incubated in 37°C HBSS (Cl^- free) for 10 min. HBSS was replaced with 500 μL of the mixture of radiolabeled substrate and compound working solution. The final concentration of ^{14}C-Uric acid in the assay was 5.0 μmol/L. Plates were incubated at 37°C, 5% CO_2 for 2 min, and the reaction was stopped by the addition of pre-chilled HBSS (Cl^- free) by washing three times. 400 μL NaOH (0.1 mmol/L) was added to lyse the cells and the cell lysate was collected to scintillation vials, and 3 ml scintillant (Aquasol-2, PerkinElmer) was added and after mixing completely, the radioactivity was counted by Tri-Carb 2910TR liquid scintillation counter. Each concentration of compounds, positive control and negative control were repeated in two wells (n=2). Inhibition% data were calculated using the formula:

Inhibition = [100 × (U-U_0)/(U_c-U_0)]%, and analyzed using Prism5 software.

U_0: Average of signals of MOCK cells;

U_c: Average of signals of radiolabeled substrate. The half inhibition concentration of the tested compounds to URAT1 were analyzed using Prism 5 software.

[208] Select compounds prepared as described above were assayed according to the biological procedures described herein. The results are given in the Table 3.

Table 3

Example	MDCK IC_{50} (nM)	HEK293 IC_{50} (nM)
1	25	62
2	29	69
3	/	130
5	93	40
10	85	< 30
11	/	100
12	80	/
13	84	/
14	252	/
15	126	/
16	48	/
17	60	/
18	37	/
19	/	339
20	/	235
21	/	297
23	189	/

CYP inhibition assay

[209] The CYP inhibition assay was conducted using human liver microsomes at 0.200 mg/mL with a marker substrate for CYP2C9. The substrate concentrations employed were similar to published Michaelis-Menten constants (K_m) for each of the respective reactions. The test compounds were added at 8 concentrations (0, 0.0500, 0.150, 0.500, 1.50, 5.00, 15.0, and 50.0 μM). A known inhibitor for the isozyme, at a single concentration (3.00 μM) in duplicates, was selected as the positive control. The reaction in the presence of the organic solvent instead of test compounds served as vehicle control. The final content of organic solvent in all the reactions was up to 0.5% DMSO and 0.5% methanol.

[210] Reactions were initiated by adding NADPH followed by incubation at 37°C for 10 minutes. And reactions were terminated by adding a 2-fold volume ice-cold acetonitrile with

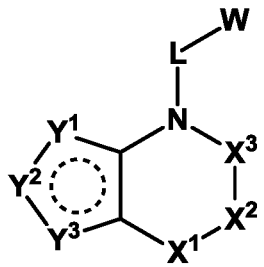
internal standards. Samples were processed and analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS).The results are given in the Table 4.

Table 4

Example	**CYP2C9 IC_{50} (μM)**
1	15.5
2	>50
5	18.9
10	16.2
16	4.25
17	10.4
18	16.0

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

W is selected from aryl and heteroaryl, wherein aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X;

L is selected from $-(CR^{C0}R^{D0})_uC(O)(CR^{C0}R^{D0})_t-$, $-(CR^{C0}R^{D0})_uC(O)NR^{A0}(CR^{C0}R^{D0})_t-$, $-(CR^{C0}R^{D0})_uS(O)_r(CR^{C0}R^{D0})_t-$ and $-(CR^{C0}R^{D0})_uS(O)_rNR^{A0}(CR^{C0}R^{D0})_t-$;

X^1 is selected from $CR^{C1}R^{D1}$, NR^{A1}, O and $S(O)_r$;

X^2 and X^3 are independently selected from $-(CR^{C1}R^{D1})_u-$, $-(CR^{C1}R^{D1})_uO(CR^{C1}R^{D1})_t-$, $-(CR^{C1}R^{D1})_uNR^{A1}(CR^{C1}R^{D1})_t-$, $-(CR^{C1}R^{D1})_uS(CR^{C1}R^{D1})_t-$, $-(CR^{C1}R^{D1})_uC(O)(CR^{C1}R^{D1})_t-$ and $-(CR^{C1}R^{D1})_uS(O)_r(CR^{C1}R^{D1})_t-$;

Y^1, Y^2 and Y^3 are independently selected from N, NR^1, CR^2, O and $S(O)_r$;

R^1 is selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1};

R^2 is selected from hydrogen, deuterium, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, CN, NO_2, $-NR^{A2}R^{B2}$, $-OR^{A2}$, $-C(O)R^{A2}$, $-C(=NR^{E2})R^{A2}$, $-C(=N\text{-}OR^{B2})R^{A2}$, $-C(O)OR^{A2}$, $-OC(O)R^{A2}$, $-C(O)NR^{A2}R^{B2}$, $-NR^{A2}C(O)R^{B2}$, $-C(=NR^{E2})NR^{A2}R^{B2}$, $-NR^{A2}C(=NR^{E2})R^{B2}$, $-OC(O)NR^{A2}R^{B2}$, $-NR^{A2}C(O)OR^{B2}$, $-NR^{A2}C(O)NR^{A2}R^{B2}$, $-NR^{A2}C(S)NR^{A2}R^{B2}$, $-NR^{A2}C(=NR^{E2})NR^{A2}R^{B2}$, $-S(O)_rR^{A2}$, $-S(O)(=NR^{E2})R^{B2}$, $-N=S(O)R^{A2}R^{B2}$, $-S(O)_2OR^{A2}$, $-OS(O)_2R^{A2}$, $-NR^{A2}S(O)_rR^{B2}$, $-NR^{A2}S(O)(=NR^{E2})R^{B2}$, $-S(O)_rNR^{A2}R^{B2}$, $-S(O)(=NR^{E2})NR^{A2}R^{B2}$, $-NR^{A2}S(O)_2NR^{A2}R^{B2}$, $-NR^{A2}S(O)(=NR^{E2})NR^{A2}R^{B2}$, $-P(O)R^{A2}R^{B2}$ and $-P(O)(OR^{A2})(OR^{B2})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X2};

each R^{A0} is independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X0};

each R^{A1} is independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1};

each R^{A2} and R^{B2} are independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl, and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X2};

or "R^{A2} and R^{B2}" together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1 or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus and optionally substituted with 1, 2 or 3 R^{X2} groups;

each R^{C0} and R^{D0} are independently selected from hydrogen, deuterium, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X0};

or each "R^{C0} and R^{D0}" together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen and optionally substituted with 1 2 or 3 R^{X0} groups;

each R^{C1} and R^{D1} are independently selected from hydrogen, deuterium, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1};

or each "R^{C1} and R^{D1}" together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen and optionally substituted with 1 2 or 3 R^{X1} groups;

each R^{E2} are independently selected from hydrogen, deuterium, C_{1-10} alkyl, CN, NO_2, $-OR^{a1}$, $-SR^{a1}$, $-S(O)_rR^{a1}$, $-C(O)R^{a1}$, $-C(O)OR^{a1}$, $-C(O)NR^{a1}R^{b1}$ and $-S(O)_rNR^{a1}R^{b1}$, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X2};

each R^{X}, R^{X0}, R^{X1}, R^{X2} are independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, halogen, CN, NO_2, $-(CR^{c1}R^{d1})_tNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tOR^{b1}$, $-(CR^{c1}R^{d1})_tC(O)R^{a1}$, $-(CR^{c1}R^{d1})_tC(=NR^{e1})R^{a1}$, $-(CR^{c1}R^{d1})_tC(=N\text{-}OR^{b1})R^{a1}$, $-(CR^{c1}R^{d1})_tC(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tOC(O)R^{b1}$, $-(CR^{c1}R^{d1})_tC(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)R^{b1}$, $-(CR^{c1}R^{d1})_tC(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tOC(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(S)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_rR^{b1}$, $-(CR^{c1}R^{d1})_tS(O)(=NR^{e1})R^{b1}$,

$-(CR^{c1}R^{d1})_tN=S(O)R^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_2OR^{b1}$, $-(CR^{c1}R^{d1})_tOS(O)_2R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_rR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_rNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_2NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tP(O)R^{a1}R^{b1}$ and $-(CR^{c1}R^{d1})_tP(O)(OR^{a1})(OR^{b1})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y;

each R^{a1} and each R^{b1} are independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y;

or R^{a1} and R^{b1} together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1 or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^Y groups;

each R^{c1} and each R^{d1} are independently selected from hydrogen, deuterium, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y;

or R^{c1} and R^{d1} together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1, 2 or 3 R^Y groups;

each R^{e1} is independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, CN, NO_2, $-OR^{a2}$, $-SR^{a2}$, $-S(O)_rR^{a2}$, $-C(O)R^{a2}$, $-C(O)OR^{a2}$, $-S(O)_rNR^{a2}R^{b2}$ and $-C(O)NR^{a2}R^{b2}$;

each R^Y is independently selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl, heteroaryl-C_{1-4} alkyl, halogen, CN, NO_2, $-(CR^{c2}R^{d2})_tNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tOR^{b2}$, $-(CR^{c2}R^{d2})_tC(O)R^{a2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(=N\text{-}OR^{b2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(S)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_rR^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tN=S(O)R^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_2OR^{b2}$, $-(CR^{c2}R^{d2})_tOS(O)_2R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_rR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_rNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_2NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tP(O)R^{a2}R^{b2}$ and $-(CR^{c2}R^{d2})_tP(O)(OR^{a2})(OR^{b2})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from OH, CN, amino, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10}

alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

each R^{a2} and each R^{b2} are independently selected from hydrogen, deuterium, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino, di(C_{1-10} alkyl)amino, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylamino, cycloalkylamino, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

or R^{a2} and R^{b2} together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1 or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1 or 2 substituents, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

each R^{c2} and each R^{d2} are independently selected from hydrogen, deuterium, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino, di(C_{1-10} alkyl)amino, heterocyclyl, heterocyclyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylamino, cycloalkylamino, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

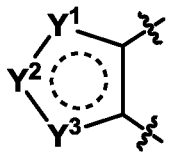
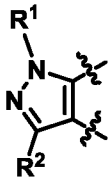
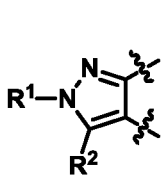
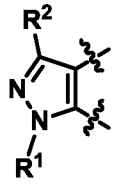
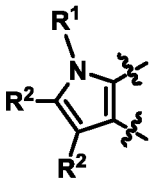
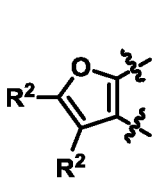
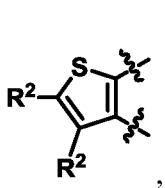
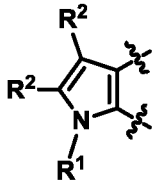
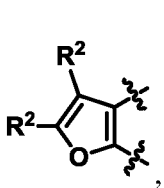
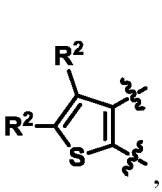
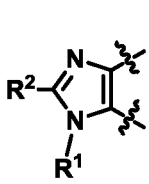
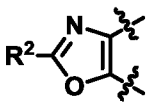
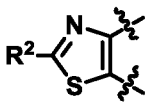
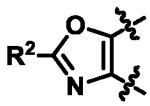
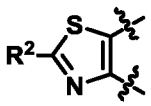
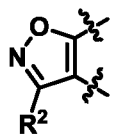
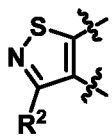
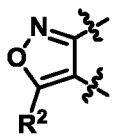
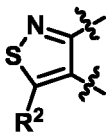
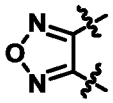
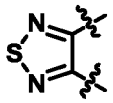
or R^{c2} and R^{d2} together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 or 2 substituents, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

each R^{e2} is independently selected from hydrogen, deuterium, CN, NO_2, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, -C(O)C_{1-4} alkyl, -C(O)C_{3-10} cycloalkyl, -C(O)OC_{1-4} alkyl, -C(O)OC_{3-10} cycloalkyl, -C(O)N(C_{1-4} alkyl)$_2$, -C(O)N(C_{3-10} cycloalkyl)$_2$, -S(O)$_2$$C_{1-4}$ alkyl, -S(O)$_2$$C_{3-10}$ cycloalkyl, -S(O)$_2$N(C_{1-4} alkyl)$_2$ and -S(O)$_2$N(C_{3-10} cycloalkyl)$_2$;

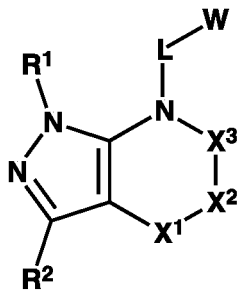
each r is independently selected from 0, 1 and 2;

each t is independently selected from 0, 1, 2, 3 and 4;

each u is independently selected from 0, 1, 2, 3 and 4.

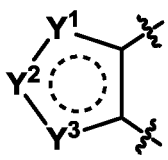
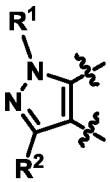
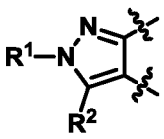
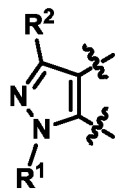
2. A compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the moiety  in Formula (I) is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  ,wherein R^1 and R^2 are as defined in formula (I).

3. A compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein Y^1 is NR^1, Y^2 is N and Y^3 is CR^2, the compound has the structure of formula (Ⅱ),



(Ⅱ)

wherein R^1, R^2, X^1, X^2, X^3, L and W are as defined in formula (I).

4. A compound of any one of claims 1-2 or a pharmaceutically acceptable salt thereof, wherein the moiety  in Formula (I) is selected from  ,  and  , wherein R^1 and R^2 are as defined in formula (I).

5. A compound of any one of claims 1-4 or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from hydrogen, deuterium, C_{1-10} alkyl and C_{3-10} cycloalkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.

6. A compound of claim 5 or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from hydrogen and C_{1-10} alkyl, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.

7. A compound of claim 6 or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from hydrogen and methyl.

8. A compound of any one of claims 1-4 or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from hydrogen, deuterium, halogen, OH, CN, NO_2 NH_2, C_{1-10} alkyl and C_{3-10} cycloalkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X2}.

9. A compound of claim 8 or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from hydrogen and C_{1-10} alkyl, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X2}.

10. A compound of claim 9 or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from hydrogen and methyl.

11. A compound of any one of claims 1-10 or a pharmaceutically acceptable salt thereof, wherein X^1 is selected from $CR^{C1}R^{D1}$, NR^{A1}, O, S and $S(O)_2$.

12. A compound of claim 11 or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^1 are independently selected from hydrogen, deuterium, halogen, C_{1-10} alkyl and C_{3-10} cycloalkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.

13. A compound of claim 12 or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^1 are independently selected from hydrogen, deuterium and C_{1-10} alkyl, wherein alkyl is each unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.

14. A compound of claim 11 or a pharmaceutically acceptable salt thereof, wherein the R^{A1} in X^1 is selected from hydrogen, deuterium, C_{1-10} alkyl and C_{3-10} cycloalkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.

15. A compound of claim 14 or a pharmaceutically acceptable salt thereof, wherein the R^{A1} in X^1 is selected from hydrogen, deuterium and C_{1-10} alkyl, wherein alkyl is each unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.

16. A compound of any one of claims 11-15 or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^1 are independently selected from hydrogen and deuterium, wherein the R^{A1} in X^1 is selected from hydrogen, deuterium and methyl.

17. A compound of any one of claims 1-16 or a pharmaceutically acceptable salt thereof, wherein X^2 and X^3 are independently selected from $-(CR^{C1}R^{D1})_u-$.

18. A compound of claim 17 or a pharmaceutically acceptable salt thereof, wherein each u is independently selected from 0, 1 and 2.

19. A compound of any one of claims 17-18 or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^2 or X^3 are independently selected from hydrogen, deuterium, halogen, C_{1-10} alkyl and C_{3-10} cycloalkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.

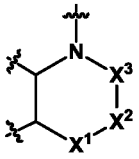
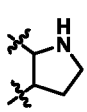
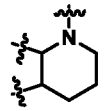
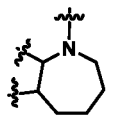
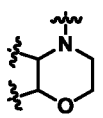
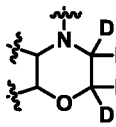
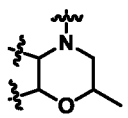
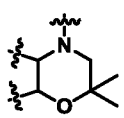
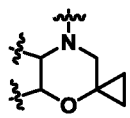
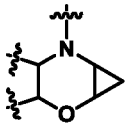
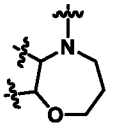
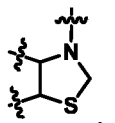
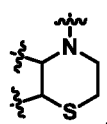
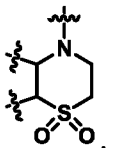
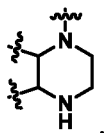
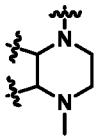
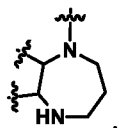
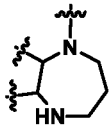
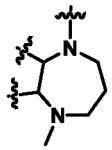
20. A compound of claim 19 or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^2 or X^3 are independently selected from hydrogen, deuterium, halogen and C_{1-10} alkyl, wherein alkyl is each unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.

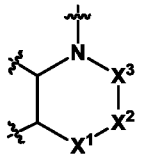
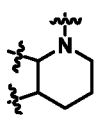
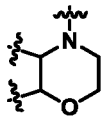
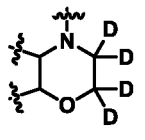
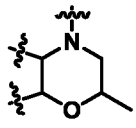
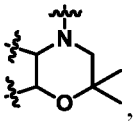
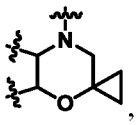
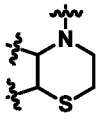
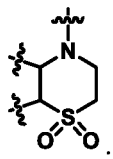
21. A compound of claim 20 or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^2 or X^3 are independently selected from hydrogen, deuterium and methyl.

22. A compound of any one of claims 17-18 or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^2 or X^3 together with the carbon atom(s) to which they are attached form a ring of 3 to 8 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen and optionally substituted with 1, 2 or 3 R^{X1} groups.

23. A compound of claim 22 or a pharmaceutically acceptable salt thereof, wherein the R^{C1} and R^{D1} in X^2 or X^3 together with the carbon atom(s) to which they are attached form3- to 5- membered cycloalkyl.

24. A compound of claim 23 or a pharmaceutically acceptable salt thereof, wherein R^{C1} and R^{D1} in X^2 or X^3 together with the carbon atom(s) to which they are attached form cyclopropyl.

25. A compound of any one of claims 1-24 or a pharmaceutically acceptable salt thereof, wherein the moiety  in Formula (I) is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  .

26. A compound of claim 25 or a pharmaceutically acceptable salt thereof, wherein the moiety  in Formula (I) is selected from  ,  ,  ,  ,  ,  ,  and  .

27. A compound of any one of claims 1-26 or a pharmaceutically acceptable salt thereof, wherein L is $-(CR^{C0}R^{D0})_uC(O)(CR^{C0}R^{D0})_t-$.

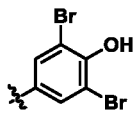
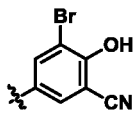
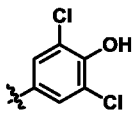
28. A compound of claim 27 or a pharmaceutically acceptable salt thereof, wherein L is -C(O)-.

29. A compound of any one of claims 1-28 or a pharmaceutically acceptable salt thereof, wherein W is aryl, wherein aryl is unsubstituted or substituted with at least one substituent, independently selected from R^X.

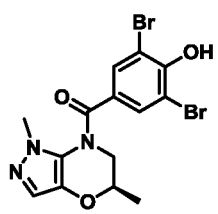
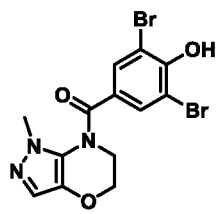
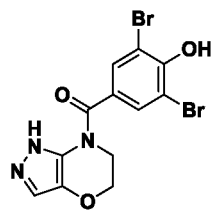
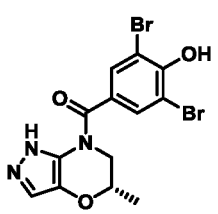
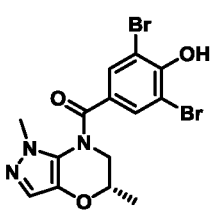
30. A compound of any one of claims 1-28 or a pharmaceutically acceptable salt thereof, wherein W is heteroaryl, wherein heteroaryl is unsubstituted or substituted with at least one substituent, independently selected from R^X.

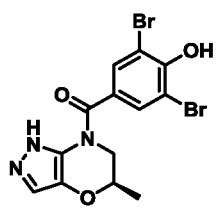
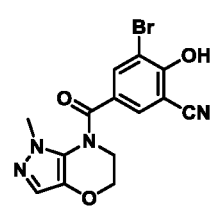
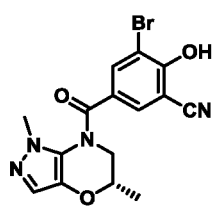
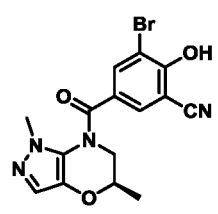
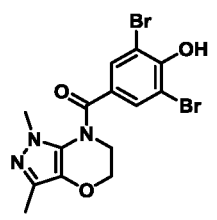
31. A compound of claim 29 or a pharmaceutically acceptable salt thereof, wherein W is phenyl, the substituent R^X of phenyl is selected from halogen, CN and $-(CR^{c1}R^{d1})_tOR^{b1}$.

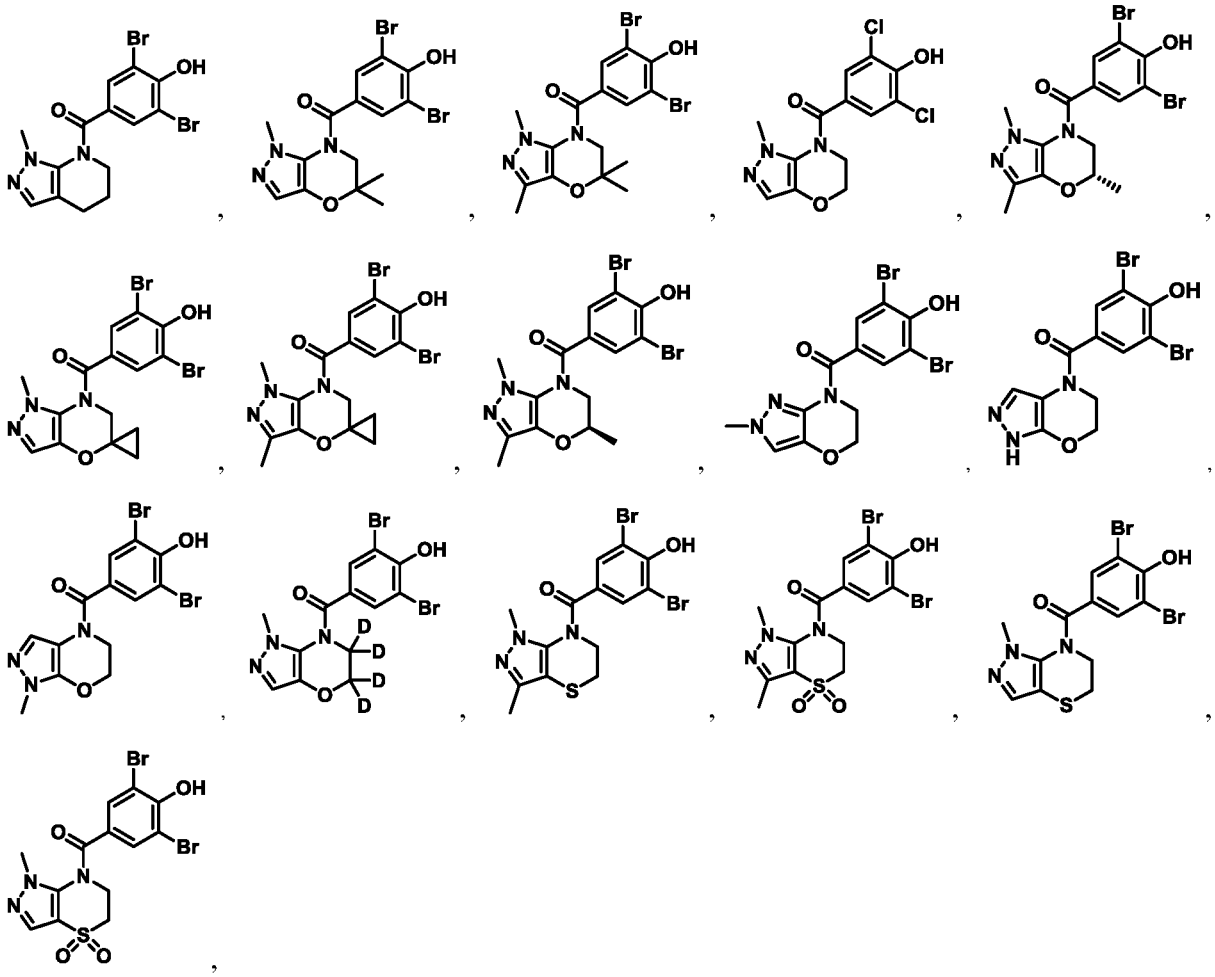
32. A compound of claim 31 or a pharmaceutically acceptable salt thereof, wherein the substituent R^X of phenyl is selected from Cl, Br, CN and OH.

33. A compound of claim 32 or a pharmaceutically acceptable salt thereof, wherein the moiety  in Formula (I) is selected from  ,  and  .

34. A compound selected from

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,



and pharmaceutically acceptable salts thereof.

35. A pharmaceutical composition comprising a compound of any one of claims 1 to 34 or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

36. A method of treating, ameliorating or preventing a condition, which responds to inhibition of URAT1, comprising administering to a subject in need of such treatment an effective amount of a compound of any one of claims 1 to 34 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, and optionally in combination with a second therapeutic agent.

37. Use of a compound of any one of Embodiments claims 1 to 34 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating a condition mediated by URAT1.