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(54) **Title**: FUSED PYRIDINE COMPOUNDS, COMPOSITIONS AND METHODS OF USE

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

FUSED PYRIDINE COMPOUNDS, COMPOSITIONS AND METHODS OF USE

[1] This application claims the priority to the U.S. provisional application No. 62/277,459, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[2] Provided are certain novel fused pyridine compounds or pharmaceutically acceptable salts thereof which can inhibit activity of urate anion transporter 1 (URAT1) and may be useful in 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

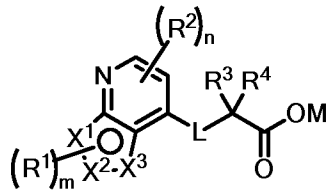
in the *SLC22A12* gene are directly associated with changes in serum uric acid. URAT1-mediated uric acid uptake has been shown by experiments using the *Xenopus* oocyte expression system. Inhibitors of urate transporter, such as URAT1, can prevent reuptake of uric acid at the proximal renal tubule and thus increase renal excretion of uric acid, and are therefore effective in the prevention and treatment of gout.

[7] Although URAT1 inhibitors were disclosed in the arts, e.g. WO 2009070740, WO 2011159839 and WO 2009145456, 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 fused pyridine compounds and pharmaceutical compositions thereof, and their use as pharmaceuticals.

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



(I)

or a pharmaceutically acceptable salt thereof,
wherein:

L is selected from NR^X, O and S;

X^1, X^2 and X^3 are independently selected from C, N, O or S, with the proviso that no more than one of X^1, X^2 and X^3 is O or S;

each R^1 is independently selected from hydrogen, 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, -$NR^{A1}R^{B1}$, -OR^{A1}, -$S(O)_rR^{A1}$, -$S(O)_2OR^{A1}$, -$OS(O)_2R^{A1}$, -$P(O)R^{A1}R^{B1}$, -$P(O)(OR^{A1})(OR^{B1})$, -$C(O)R^{A1}$, -$C(O)OR^{A1}$, -$OC(O)R^{A1}$, -$C(O)NR^{A1}R^{B1}$, -$NR^{A1}C(O)R^{B1}$, -$OC(O)NR^{A1}R^{B1}$, -$NR^{A1}C(O)OR^{B1}$, -$NR^{A1}C(O)NR^{A1}R^{B1}$, -$NR^{A1}C(S)NR^{A1}R^{B1}$, -$S(O)_rNR^{A1}R^{B1}$, -$NR^{A1}S(O)_rR^{B1}$, -$NR^{A1}S(O)_2NR^{A1}R^{B1}$, -$S(O)(=NR^{E1})R^{B1}$, -$N=S(O)R^{A1}R^{B1}$, -$NR^{A1}S(O)(=NR^{E1})R^{B1}$, -$S(O)(=NR^{E1})NR^{A1}R^{B1}$, -$NR^{A1}S(O)(=NR^{E1})NR^{A1}R^{B1}$, -$C(=NR^{E1})R^{A1}$, -$C(=N\text{-}OR^{B1})R^{A1}$, -$C(=NR^{E1})NR^{A1}R^{B1}$, -$NR^{A1}C(=NR^{E1})R^{B1}$ and -$NR^{A1}C(=NR^{E1})NR^{A1}R^{B1}$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and

heteroaryl are each unsubstituted or substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^X;

each R^2 is independently selected from hydrogen, 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}, -$S(O)_rR^{A2}$, -$S(O)_2OR^{A2}$, -$OS(O)_2R^{A2}$, -$P(O)R^{A2}R^{B2}$, -$P(O)(OR^{A2})(OR^{B2})$, -$C(O)R^{A2}$, -$C(O)OR^{A2}$, -$OC(O)R^{A2}$, -$C(O)NR^{A2}R^{B2}$, -$NR^{A2}C(O)R^{B2}$, -$OC(O)NR^{A2}R^{B2}$, -$NR^{A2}C(O)OR^{B2}$, -$NR^{A2}C(O)NR^{A2}R^{B2}$, -$NR^{A2}C(S)NR^{A2}R^{B2}$, -$S(O)_rNR^{A2}R^{B2}$, -$NR^{A2}S(O)_rR^{B2}$, -$NR^{A2}S(O)_2NR^{A2}R^{B2}$, -$S(O)(=NR^{E2})R^{B2}$, -$N=S(O)R^{A2}R^{B2}$, -$NR^{A2}S(O)(=NR^{E2})R^{B2}$, -$S(O)(=NR^{E2})NR^{A2}R^{B2}$, -$NR^{A2}S(O)(=NR^{E2})NR^{A2}R^{B2}$, -$C(=NR^{E2})R^{A2}$, -$C(=N\text{-}OR^{B2})R^{A2}$, -$C(=NR^{E2})NR^{A2}R^{B2}$, -$NR^{A2}C(=NR^{E2})R^{B2}$ and -$NR^{A2}C(=NR^{E2})NR^{A2}R^{B2}$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^X;

R^3 and R^4 are each independently selected from hydrogen, 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 the said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^X;

or R^3 and R^4 together with the carbon atom to which they are attached form a ring of 3 to 7 members containing 0, 1, or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1, 2 or 3 R^X groups;

each R^{A1}, R^{A2}, R^{B1} and R^{B2} are independently selected from hydrogen, 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, such as one, two, three, or four substituents, independently selected from R^X;

or each "R^{A1} and R^{B1}" 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^X groups;

each R^{E1} and R^{E2} are independently selected from hydrogen, C_{1-10} alkyl, CN, NO_2, OR^{a1}, SR^{a1}, -$S(O)_rR^{a1}$, -$S(O)_rNR^{a1}R^{b1}$, -$C(O)R^{a1}$, -$C(O)OR^{a1}$ and -$C(O)NR^{a1}R^{b1}$;

each R^X 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, -$(CR^{c1}R^{d1})_tNR^{a1}R^{b1}$, -$(CR^{c1}R^{d1})_tOR^{b1}$, -$(CR^{c1}R^{d1})_tS(O)_rR^{b1}$, -$(CR^{c1}R^{d1})_tS(O)_2OR^{b1}$, -$(CR^{c1}R^{d1})_tOS(O)_2R^{b1}$, -$(CR^{c1}R^{d1})_tP(O)R^{a1}R^{b1}$,

$-(CR^{c1}R^{d1})_tP(O)(OR^{a1})(OR^{b1})$, $-(CR^{c1}R^{d1})_tC(O)R^{a1}$, $-(CR^{c1}R^{d1})_tC(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tOC(O)R^{b1}$, $-(CR^{c1}R^{d1})_tC(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)R^{b1}$, $-(CR^{c1}R^{d1})_tOC(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(S)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_rNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_rR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_2NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tN=S(O)R^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tC(=NR^{e1})R^{a1}$, $-(CR^{c1}R^{d1})_tC(=N\text{-}OR^{b1})R^{a1}$, $-(CR^{c1}R^{d1})_tC(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(=NR^{e1})R^{b1}$ and $-(CR^{c1}R^{d1})_tNR^{a1}C(=NR^{e1})NR^{a1}R^{b1}$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^Y;

each R^{a1} and each R^{b1} are independently selected from hydrogen, 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, such as one, two, three, or four substituents, 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, 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, such as one, two, three or four substituents, 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, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, CN, NO_2, OR^{a2}, SR^{a2}, $-S(O)_rR^{a2}$, $-S(O)_rNR^{a2}R^{b2}$, $-C(O)R^{a2}$, $-C(O)OR^{a2}$ 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, $-NO_2$, $-(CR^{c2}R^{d2})_tNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tOR^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_rR^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_2OR^{b2}$, $-(CR^{c2}R^{d2})_tOS(O)_2R^{b2}$, $-(CR^{c2}R^{d2})_tP(O)R^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tP(O)(OR^{a2})(OR^{b2})$, $-(CR^{c2}R^{d2})_tC(O)R^{a2}$, $-(CR^{c2}R^{d2})_tC(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)R^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(S)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_rNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_rR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_2NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tN=S(O)R^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})R^{b2}$,

$-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(=N\text{-}OR^{b2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})R^{b2}$ and $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})NR^{a2}R^{b2}$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, such as one, two, three, or four substituents, 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, 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, such as one, two, three, or four 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;

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, 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, such as one, two, three, or four 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;

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, 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)NH_2, -C(O)NH(C_{1-4} alkyl), -C(O)N(C_{1-4} alkyl)$_2$, - C(O)NH(C_{3-10} cycloalkyl), -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$$NH_2$, -S(O)$_2$NH($C_{1-4}$ alkyl), -S(O)$_2$N(C_{1-4} alkyl)$_2$, -S(O)$_2$NH(C_{3-10} cycloalkyl) and -S(O)$_2$N(C_{3-10} cycloalkyl)$_2$;

M is hydrogen, C_{1-4} alkyl or a pharmaceutically acceptable cation;

m is selected from 0, 1, 2 and 3;

n is selected from 0, 1 and 2;

each r is independently selected from 1 and 2;

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

[9] In another aspect, disclosed is a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[10] In yet another aspect, disclosed is a method for decreasing uric acid levels in one or more tissues or organs of a subject in need of decreasing uric acid levels by 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 a pharmaceutical composition thereof.

[11] 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 a pharmaceutical composition thereof, and optionally in combination with a second therapeutic agent, thereby treating said condition. In some embodiments, the subject in need of decreased uric acid levels has a disorder characterized by abnormally high content of uric acid in one or more tissues or organs of the subject. In some embodiments, the disorder is characterized by over production of uric acid, low excretion of uric acid, tumor lysis, a blood disorder or a combination thereof. In some embodiments, the disorder is gout.

[12] Alternatively, disclosed is 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.

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

[14] 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, Kelley-Seegmiller syndrome, urolithiasis, plumbism, hyperparathyroidism, psoriasis, sarcoidosis, and hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency or a combination thereof.

[15] More specifically, the condition disclosed herein is gout.

[16] Alternatively, a compound of formula (I) or a pharmaceutically acceptable salt thereof disclosed herein may be used in the treatment of hyperuricemia where this is present together with one or more other diseases, such as kidney failure, type 2 diabetes, cardiovascular disease (e.g. hypertension, myocardial infarction, heart failure, coronary artery disease, cerebrovascular disease, atherosclerosis, angina, aneurism, hyperlipidemia and stroke), obesity, metabolic syndrome, myeloproliferative disorders, lymphoproliferative disorders and disorders associated with certain medications, such as a diuretic (e.g. a thiazide), an immunosuppressant (e.g. a cyclosporine therapy), a chemotherapeutic agent (e.g. cisplatin) or aspirin.

[17] Furthermore, disclosed is a method 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 a pharmaceutical composition thereof, and optionally in combination with a second therapeutic agent, thereby treating said condition.

[18] Alternatively, disclosed is 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.

[19] 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, Kelley-Seegmiller syndrome, urolithiasis, plumbism, hyperparathyroidism, psoriasis, sarcoidosis, and hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency or a combination thereof.

[20] More specifically, the condition disclosed herein is gout.

[21] In the above method(s) 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 exemplary and 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] Definition of standard chemistry terms may be found in reference works, including Carey and Sundberg "ADVANCED ORGANIC CHEMISTRY 4TH ED." Vols. A (2000) and B (2001), Plenum Press, New York. 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] As used herein, the term "optionally substituted" means unsubstituted or substituted. The term "substituted" means that a hydrogen atom is removed and replaced by a substituent. It is to be understood that substitution at a given atom is limited by valency. Throughout the definitions, the term "C_{i-j}" indicates a range which includes the endpoints, wherein i and j are integers and indicate the number of carbons. Examples include C_{1-4}, C_{1-10}, C_{3-10}, and the like.

[27] The term "alkyl" refers to both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Unless otherwise specified, "alkyl" refers to C_1-C_6 alkyl. For example, C_1-C_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.

[28] The term "cycloalkyl" as used herein, means a monocyclic or bridged hydrocarbon ring system. The monocyclic cycloalkyl is a carbocyclic ring system containing three to ten carbon atoms, zero heteroatoms and zero double bonds. Examples of monocyclic ring systems include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The monocyclic ring may contain one or two alkylene bridges, each consisting of one, two, or three carbon atoms, each linking two non-adjacent carbon atoms of the ring system. 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 and bridged cycloalkyl can be attached to the parent molecular moiety through any substitutable atom contained within the ring system.

[29] The term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 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 from 2 to 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.

[30] The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 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 from 2 to 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.

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

[32] The term "alkoxy", employed alone or in combination with other terms, refers to an alkyl radical that 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 from one to ten carbon atoms, having straight or branched moieties. Alkoxy groups, includes but is not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, hexyloxy, and the like.

[33] The term "cycloalkoxy", employed alone or in combination with other terms, refers to cycloalkyl radical that 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 from three to ten carbon atoms. Cycloalkoxy groups, includes but is not limited to, cyclopropoxy, cyclobutoxy, cyclohexyloxy, and the like.

[34] The term "alkylthio", employed alone or in combination with other terms, refers to an alkyl radical that 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 from one to ten carbon atoms, having straight or branched moieties. Alkylthio groups, includes but is not limited to, methylthio, ethylthio, propylthio, isopropylthio, butylthio, hexylthio, and the like.

[35] The term "cycloalkylthio", employed alone or in combination with other terms, refers to cycloalkyl radical that 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 from three to ten carbon atoms. Cycloalkylthio groups, includes but is not limited to, cyclopropylthio, cyclobutylthio, cyclohexylthio, and the like.

[36] The term "alkylamino", employed alone or in combination with other terms, refers to an alkyl radical that 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 from one to ten carbon atoms, having straight or branched moieties. Alkylamino groups, includes but is not limited to, methylamino, ethylamino, propylamino, isopropylamino, butylamino, hexylamoino, and the like.

[37] The term "cycloalkylamino", employed alone or in combination with other terms, refers to cycloalkyl radical that 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 from three to ten carbon atoms. Cycloalkylamino groups, includes but is not limited to, cyclopropylamino, cyclobutylamino, cyclohexylamino, and the like.

[38] The term "di(alkyl)amino", employed alone or in combination with other terms, refers to two alkyl radicals that 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 from one to ten carbon atoms, having straight or branched moieties.

[39] The term "aryl" encompasses: 5- and 6-membered carbocyclic aromatic rings, for example, benzene; bicyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, naphthalene, indane and 1, 2, 3, 4-tetrahydroquinoline; and tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene. In cases where the aryl substituent is bicyclic or tricyclic and at least one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

[40] For example, aryl includes 5- and 6-membered carbocyclic aromatic rings fused to a 5- to 7-membered heterocyclic ring containing one or more heteroatoms selected from N, O, and S, provided that the point of attachment is at the carbocyclic aromatic ring. 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 adding "-idene" to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene. Aryl, however, does not encompass or overlap in any way with heteroaryl, separately defined below. Hence, if one or more carbocyclic aromatic rings are fused with a heterocyclic aromatic ring, the resulting ring system is heteroaryl, not aryl, as defined herein.

[41] The term “heteroaryl” refers to

5- to 8-membered aromatic, monocyclic rings 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;

8- to 12-membered bicyclic rings 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 and wherein at least one heteroatom is present in an aromatic ring; and

11- to 14-membered tricyclic rings 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 and wherein at least one heteroatom is present in an aromatic ring.

[42] 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.

[43] Examples of heteroaryl groups include, but are not limited to, (as numbered from the linkage position assigned priority 1), 2-pyridyl, 3-pyridyl, 4-pyridyl, 2,3-pyrazinyl, 3,4-pyrazinyl, 2,4-pyrimidinyl, 3,5-pyrimidinyl, 1-pyrazolyl, 2,3-pyrazolyl, 2,4-imidazolinyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothienyl, furyl, benzofuryl, benzoimidazolinyl, indolinyl, pyridizinyl, triazolyl, quinolinyl, pyrazolyl, and 5,6,7,8-tetrahydroisoquinoline.

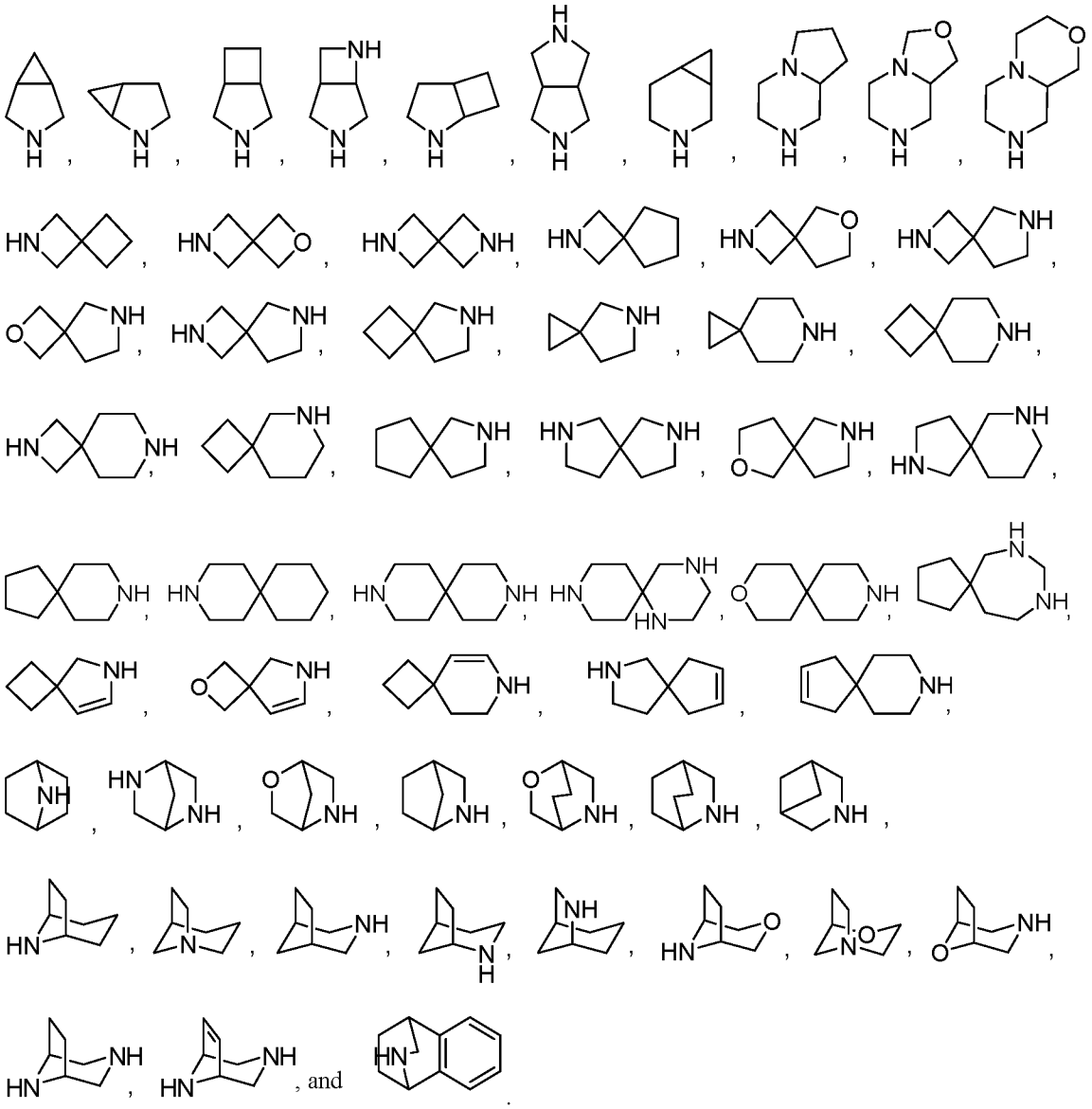
[44] Further heteroaryl groups include, but are not limited to, pyrrolyl, isothiazolyl, triazinyl, pyrazinyl, pyridazinyl, indolyl, benzotriazolyl, quinoxalinyl, and isoquinolinyl,. As with the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl.

[45] 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. Heteroaryl does not encompass or overlap with aryl as defined above.

[46] In cases where the heteroaryl substituent is bicyclic or tricyclic and at least one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively.

[47] The term "heterocycle" (and variations thereof such as "heterocyclic", or "heterocyclyl") broadly refers to a single aliphatic ring, usually with 3 to 12 ring atoms, containing at least 2 carbon atoms in addition to one or more, preferably one to three heteroatoms independently selected from oxygen, sulfur, and nitrogen, as well as combinations comprising at least one of the foregoing heteroatoms. Alternatively , a heterocycle as defined above may be multicyclic ring system (e.g. bicyclic) in which two or more rings may be fused or bridged or spiro together, wherein at least one such ring contains one or more heteroatoms independently selected from oxygen, sulfur, and nitrogen. “Heterocycle” also refers to 5- to 7-membered heterocyclic ring containing one or more heteroatoms selected from N, O, and S fused with 5- and 6-membered carbocyclic aromatic ring, provided that the point of attachment is at the heterocyclic ring. The rings may be saturated or have one or more double bonds (i.e. partially unsaturated). The heterocycle can be substituted by oxo. The nitrogen and sulfur heteroatoms in the heterocycle rings may optionally be oxidized and the nitrogen atoms may optionally be quarternized. The heterocycle is connected to the parent molecular moiety through any substitutable carbon or any substitutable heteroatom contained within the rings, 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 results. Heterocycle does not overlap with heteroaryl.

[48] Suitable heterocycles include, but are not limited to (as numbered from the linkage position assigned priority 1), 1-pyrrolidinyl, 2-pyrrolidinyl, 2,4-imidazolidinyl, 2,3-pyrazolidinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, and 2,5-piperazinyl. Morpholinyl groups are also contemplated, including 2-morpholinyl and 3-morpholinyl (numbered wherein the oxygen is assigned priority 1). Substituted heterocycle also includes ring systems substituted with one or more oxo moieties, such as piperidinyl N-oxide, morpholinyl-*N*-oxide, 1-oxo-1-thiomorpholinyl and 1,1-dioxo-1-thiomorpholinyl. Bicyclic heterocycles include, but are not limited to,



[49] As used herein, "arylalkyl" refers to an alkyl moiety substituted by an aryl group. Example arylalkyl groups include benzyl, phenethyl, and naphthylmethyl groups. In some

embodiments, arylalkyl groups have from 7 to 20 or 7 to 11 carbon atoms. When used in the phrase "arylC_{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. Likewise, when used in the phrase "arylCl_{-10} alkyl", the term "C_{1-10}" refers to the alkyl portion of the moiety and does not describe the number of atoms in the aryl portion of the moiety.

[50] As used herein, "heterocyclylalkyl" refers to alkyl substituted by heterocyclyl. When used in the phrase "heterocyclyl-C_{1-6} alkyl", the term "C_{1-6}" refers to the alkyl portion of the moiety and does not describe the number of atoms in the heterocyclyl portion of the moiety.

[51] As used herein, "cycloalkylalkyl" refers to alkyl substituted by cycloalkyl. When used in the phrase "C_{3-10} cycloalkylalkyl", 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. When used in the phrase "C_{3-7} cycloalkylalkyl", the term "C_{3-7}" refers to the cycloalkyl portion of the moiety and does not describe the number of atoms in the alkyl portion of the moiety. When used in the phrase "C_{3-8} cycloalkylalkyl", the term "C_{3-8}" refers to the cycloalkyl portion of the moiety and does not describe the number of atoms in the alkyl portion of the moiety. When used in the phrase "cycloalkyl C_{1-10} alkyl", the term "C_{1-10}" refers to the alkyl portion of the moiety and does not describe the number of atoms in the cycloalkyl portion of the moiety.

[52] As used herein, "heteroarylalkyl" refers to alkyl substituted by heteroaryl. 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. Likewise, when used in the phrase "heteroaryl C_{1-10} alkyl", the term "C_{1-10}" refers to the alkyl portion of the moiety and does not describe the number of atoms in the heteroaryl portion of the moiety.

[53] 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^1 is arylalkyl, 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^{6b} and the alkyl portion may also be unsubstituted or substituted with at least one substituent, such as one, two, three, or four substituens, independently selected from R^{6a}.

[54] 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 crystal structures, and may also be in the form of 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.

[55] When the compound disclosed herein is basic, salts may be prepared using a 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.

[56] 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.

[57] 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*-l,3-dioxol-4-yl-methyl, trimethylsilyl, triethylsilyl, and triphenylsilyl.

[58] 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.

[59] 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.

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

[61] The term "effective amount" means the amount of the a compound and/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.

[62] 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.

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

[64] 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.

[65] 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.

[66] 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.

[67] 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.

[68] 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, 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.

[69] 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. In addition to

the above, relevant procedures and intermediates are disclosed, for instance, in Lizondo, J et al, Drugs Fut, 21(11), 1116 (1996); Brickner, S J et al., J Med Chem, 39(3), 673 (1996); Mallesham, B et al, Org Lett, 5(7), 963 (2003); PCT publications WO1997010223, WO2005099353, WO1995007271, WO2006008754; US Patent Nos. 7538189; 7534814; 7531685; 7528131; 7521421; 7514068; 7511013; and US Patent Application Publication Nos. 20090137457; 20090131485; 20090131363; 20090118238; 20090111840; 20090105338; 20090105307; 20090105147; 20090093422; 20090088416; and 20090082471, the methods are hereby incorporated by reference.

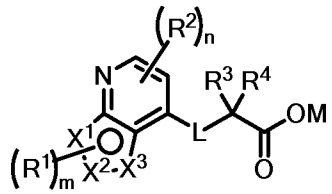
[70] The isotope-labeled compounds of the invention may be used as standards to determine the effectiveness of URAT1 inhibitors in binding assays. Isotope containing compounds have been used in pharmaceutical research to investigate the in vivo metabolic fate of the compounds by evaluation of the mechanism 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 Comp. Radiopharmaceut., 36(10):927-932 (1995); Kushner et al., Can. J. Physiol. Pharmacol, 77, 79-88 (1999).

[71] In addition, non-radio active 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 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 %. Replacement of up to about 15% of normal atom with a heavy isotope has been effected and maintained for a period of days to weeks in mammals, including rodents and dogs, with minimal observed adverse effects (Czajka D M and Finkel A J, Ann. N.Y. Acad. Sci. 1960 84: 770; Thomson J F, Ann. New York Acad. Sci 1960 84: 736; Czakja D M et al., Am. J. Physiol. 1961 201 : 357). Acute replacement of as high as 15%-23% in human fluids with deuterium was found not to cause toxicity (Blagojevic N et al. in "Dosimetry & Treatment Planning for Neutron Capture Therapy", Zamenhof R, Solares G and Harling O Eds. 1994. Advanced Medical Publishing, Madison Wis. pp.125-134; Diabetes Metab. 23: 251 (1997)).

[72] 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.

[73] 1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,
wherein:

L is selected from NR^X, O and S;

X^1, X^2 and X^3 are independently selected from C, N, O or S, with the proviso that no more than one of X^1, X^2 and X^3 is O or S;

each R^1 is independently selected from hydrogen, 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, -$NR^{A1}R^{B1}$, -OR^{A1}, -$S(O)_rR^{A1}$, -$S(O)_2OR^{A1}$, -$OS(O)_2R^{A1}$, -$P(O)R^{A1}R^{B1}$, -$P(O)(OR^{A1})(OR^{B1})$, -$C(O)R^{A1}$, -$C(O)OR^{A1}$, -$OC(O)R^{A1}$, -$C(O)NR^{A1}R^{B1}$, -$NR^{A1}C(O)R^{B1}$, -$OC(O)NR^{A1}R^{B1}$, -$NR^{A1}C(O)OR^{B1}$, -$NR^{A1}C(O)NR^{A1}R^{B1}$, -$NR^{A1}C(S)NR^{A1}R^{B1}$, -$S(O)_rNR^{A1}R^{B1}$, -$NR^{A1}S(O)_rR^{B1}$, -$NR^{A1}S(O)_2NR^{A1}R^{B1}$, -$S(O)(=NR^{E1})R^{B1}$, -$N=S(O)R^{A1}R^{B1}$, -$NR^{A1}S(O)(=NR^{E1})R^{B1}$, -$S(O)(=NR^{E1})NR^{A1}R^{B1}$, -$NR^{A1}S(O)(=NR^{E1})NR^{A1}R^{B1}$, -$C(=NR^{E1})R^{A1}$, -$C(=N\text{-}OR^{B1})R^{A1}$, -$C(=NR^{E1})NR^{A1}R^{B1}$, -$NR^{A1}C(=NR^{E1})R^{B1}$ and -$NR^{A1}C(=NR^{E1})NR^{A1}R^{B1}$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^X;

each R^2 is independently selected from hydrogen, 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}, -$S(O)_rR^{A2}$, -$S(O)_2OR^{A2}$, -$OS(O)_2R^{A2}$, -$P(O)R^{A2}R^{B2}$, -$P(O)(OR^{A2})(OR^{B2})$, -$C(O)R^{A2}$, -$C(O)OR^{A2}$, -$OC(O)R^{A2}$, -$C(O)NR^{A2}R^{B2}$, -$NR^{A2}C(O)R^{B2}$, -$OC(O)NR^{A2}R^{B2}$, -$NR^{A2}C(O)OR^{B2}$, -$NR^{A2}C(O)NR^{A2}R^{B2}$, -$NR^{A2}C(S)NR^{A2}R^{B2}$, -$S(O)_rNR^{A2}R^{B2}$, -$NR^{A2}S(O)_rR^{B2}$, -$NR^{A2}S(O)_2NR^{A2}R^{B2}$, -$S(O)(=NR^{E2})R^{B2}$, -$N=S(O)R^{A2}R^{B2}$, -$NR^{A2}S(O)(=NR^{E2})R^{B2}$, -$S(O)(=NR^{E2})NR^{A2}R^{B2}$, -$NR^{A2}S(O)(=NR^{E2})NR^{A2}R^{B2}$, -$C(=NR^{E2})R^{A2}$, -$C(=N\text{-}OR^{B2})R^{A2}$, -$C(=NR^{E2})NR^{A2}R^{B2}$, -$NR^{A2}C(=NR^{E2})R^{B2}$ and -$NR^{A2}C(=NR^{E2})NR^{A2}R^{B2}$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^X;

R^3 and R^4 are each independently selected from hydrogen, 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 the said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^X;

or R^3 and R^4 together with the carbon atom to which they are attached form a ring of 3 to 7 members containing 0, 1, or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1, 2 or 3 R^X groups;

each R^{A1}, R^{A2}, R^{B1} and R^{B2} are independently selected from hydrogen, 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, such as one, two, three, or four substituents, independently selected from R^X;

or each "R^{A1} and R^{B1}" 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^X groups;

each R^{E1} and R^{E2} are independently selected from hydrogen, C_{1-10} alkyl, CN, NO_2, OR^{a1}, SR^{a1}, $-S(O)_rR^{a1}$, $-S(O)_rNR^{a1}R^{b1}$, $-C(O)R^{a1}$, $-C(O)OR^{a1}$ and $-C(O)NR^{a1}R^{b1}$;

each R^X 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, $-NO_2$, $-(CR^{c1}R^{d1})_tNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tOR^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_rR^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_2OR^{b1}$, $-(CR^{c1}R^{d1})_tOS(O)_2R^{b1}$, $-(CR^{c1}R^{d1})_tP(O)R^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tP(O)(OR^{a1})(OR^{b1})$, $-(CR^{c1}R^{d1})_tC(O)R^{a1}$, $-(CR^{c1}R^{d1})_tC(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tOC(O)R^{b1}$, $-(CR^{c1}R^{d1})_tC(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)R^{b1}$, $-(CR^{c1}R^{d1})_tOC(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(S)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_rNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_rR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_2NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tN=S(O)R^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tC(=NR^{e1})R^{a1}$, $-(CR^{c1}R^{d1})_tC(=N\text{-}OR^{b1})R^{a1}$, $-(CR^{c1}R^{d1})_tC(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(=NR^{e1})R^{b1}$ and $-(CR^{c1}R^{d1})_tNR^{a1}C(=NR^{e1})NR^{a1}R^{b1}$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^Y;

each R^{a1} and each R^{b1} are independently selected from hydrogen, 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, such as one, two, three, or four substituents, 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, 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, such as one, two, three or four substituents, 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, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, CN, NO_2, OR^{a2}, SR^{a2}, $-S(O)_rR^{a2}$, $-S(O)_rNR^{a2}R^{b2}$, $-C(O)R^{a2}$, $-C(O)OR^{a2}$ 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, $-NO_2$, $-(CR^{c2}R^{d2})_tNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tOR^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_rR^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_2OR^{b2}$, $-(CR^{c2}R^{d2})_tOS(O)_2R^{b2}$, $-(CR^{c2}R^{d2})_tP(O)R^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tP(O)(OR^{a2})(OR^{b2})$, $-(CR^{c2}R^{d2})_tC(O)R^{a2}$, $-(CR^{c2}R^{d2})_tC(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)R^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(S)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_rNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_rR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_2NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tN=S(O)R^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(=N\text{-}OR^{b2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})R^{b2}$ and $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})NR^{a2}R^{b2}$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, such as one, two, three, or four substituents, 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, 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, such as one, two, three, or four 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;

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, 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, such as one, two, three, or four 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;

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, 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)NH_2, -C(O)NH(C_{1-4} alkyl), -C(O)N(C_{1-4} alkyl)$_2$, - C(O)NH(C_{3-10} cycloalkyl), -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$$NH_2$, -S(O)$_2$NH($C_{1-4}$ alkyl), -S(O)$_2$N(C_{1-4} alkyl)$_2$, -S(O)$_2$NH(C_{3-10} cycloalkyl) and -S(O)$_2$N(C_{3-10} cycloalkyl)$_2$;

M is hydrogen, C_{1-4} alkyl or a pharmaceutically acceptable cation;

m is selected from 0, 1, 2 and 3;

n is selected from 0, 1 and 2;

each r is independently selected from 1 and 2;

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

[74] 2. A compound of 1 or a pharmaceutically acceptable salt thereof, wherein L is selected from S and O.

[75] 3. A compound of 2 or a pharmaceutically acceptable salt thereof, wherein L is S.

[76] 4. A compound of any one of 1-3 or a pharmaceutically acceptable salt thereof, wherein X^1, X^2 and X^3 are independently selected from C and S, with the proviso that no more than one of X^1, X^2 and X^3 is S.

[77] 5. A compound of any one of 1-4 or a pharmaceutically acceptable salt thereof, wherein each R^1 is independently selected from hydrogen, halogen, CN, C_{1-10} alkyl and aryl, wherein alkyl and aryl are each unsubstituted or substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^X.

[78] 6. A compound of 5 or a pharmaceutically acceptable salt thereof, wherein each R^1 is independently selected from hydrogen, fluorine, chlorine, bromine, CF_3, phenyl, 4-fluorophenyl and 4-cyanophenyl.

[79] 7. A compound of any one of 1-6 or a pharmaceutically acceptable salt thereof, wherein each R^2 is hydrogen.

[80] 8. A compound of any one of 1-7 or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are each independently selected from C_{1-10} alkyl, wherein alkyl is unsubstituted or substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^X.

[81] 9. A compound of 8 or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are each methyl or methyl substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^X.

[82] 10. A compound of 9 or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are each methyl or methyl substituted with at least one substituent, such as one, two, three or four substituents, independently selected from halogen and $-OR^{a1}$.

[83] 11. A compound of 10 or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are methyl or methyl substituted with at least one substituent, such as one, two, three or four substituents, independently selected from fluorine, OH and OCH_3.

[84] 12. A compound of any one of 1-7 or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 together with the carbon atom to which they are attached form a ring of 3 to 7 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1, 2 or 3 R^X groups.

[85] 13. A compound of 12 or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 together with the carbon atom to which they are attached form cyclobutane, and optionally substituted with 1, 2 or 3 R^X groups.

[86] 14. A compound of 13 or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 together with the carbon atom to which they are attached form cyclobutane, and optionally substituted with 1 or 2 halogen, OH and OCH_3.

[87] 15. A compound of any one of 1 to 14 or a pharmaceutically acceptable salt thereof, wherein M is selected from hydrogen, C_{1-4} alkyl, and a pharmaceutically acceptable cation. Preferably the pharmaceutically acceptable cation is Na^+, Li^+, K^+, Ca^{2+}, Mg^{2+}, NH^{4+}, tetramethylammonium, tetraethylammonium, methylamino, dimethylamino, trimethylamine or triethylamino.

[88] 16. A compound of 15 or a pharmaceutically acceptable salt thereof, wherein M is hydrogen.

[89] 17. A compound, selected from

1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid,

2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-2-methylpropanoic acid,

1-((2-(trifluoromethyl)thieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid,

2-methyl-2-((2-(trifluoromethyl)thieno[2,3-*b*]pyridin-4-yl)thio)propanoic acid,

1-((2-chlorothieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid,

1-((2-phenylthieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid,

1-((2-(4-fluorophenyl)thieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid,

1-((2-(4-cyanophenyl)thieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid,

1-((2-bromothieno[3,2-*b*]pyridin-7-yl)thio)cyclobutane-1-carboxylic acid,

1-(thieno[2,3-*b*]pyridin-4-ylthio)cyclobutane-1-carboxylic acid,

2-methyl-2-(thieno[2,3-*b*]pyridin-4-ylthio)propanoic acid,

2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-hydroxy-2-methylpropanoic acid,

2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-methoxy-2-methylpropanoic acid,

2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-fluoro-2-methylpropanoic acid,

2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3,3-difluoro-2-methylpropanoic acid,

2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3,3,3-trifluoro-2-methylpropanoic acid,

1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-hydroxycyclobutane-1-carboxylic acid,

1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-methoxycyclobutane-1-carboxylic acid,

1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-fluorocyclobutane-1-carboxylic acid,

1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3,3-difluorocyclobutane-1-carboxylic acid,

or pharmaceutically acceptable salts thereof.

[90] 18. A pharmaceutical composition comprising a compound of 1-17, or a pharmaceutically acceptable salts thereof.

[91] 19. A therapeutic method comprising administering a compound of 1-17 or a pharmaceutically acceptable salts thereof to a subject in need.

[92] In yet another of its aspects, provided is a kit comprising a compound disclosed herein, or a pharmaceutically acceptable salts 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.

[93] In still another of its aspects, there is provided an article of manufacture comprising a compound disclosed herein, or a pharmaceutically acceptable salts 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.

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

[95] 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 salts thereof.

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

[97] 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 the URAT1 *in vivo*, the second compound being a compound disclosed herein, or a pharmaceutically acceptable salts thereof, .

[98] 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, comprising causing a compound disclosed herein, or a pharmaceutically acceptable salts thereof, to be present in a subject in a therapeutically effective amount for the disease state.

[99] 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, comprising administering a first compound to a subject that is converted in vivo to a second compound wherein the second compound inhibits the URAT1 *in vivo*. It is noted that the compounds of the present invention may be the first or second compounds.

[100] 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, Kelley-Seegmiller syndrome, urolithiasis, plumbism, hyperparathyroidism, psoriasis, sarcoidosis, and hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency or a combination thereof.

[101] In another of its aspects, there is provided a method of treating a disease state characterized by abnormal tissue or organ levels of uric acid for which activity of URAT1 contributes to the pathology and/or symptomology of the disease state including but not limited to, for example, goat, hyperuricaemia.

[102] In still another of its aspects, the present invention relates to the use of a compound disclosed herein as a medicament. In yet another of its aspects, the present invention relates to the use of a compound disclosed herein, or a pharmaceutically acceptable salts thereof, in the manufacture of a medicament for inhibiting URAT1.

[103] In a further of its aspects, the present invention relates to the use of a compound disclosed herein, or a pharmaceutically acceptable salts thereof, in the manufacture of a medicament for treating a condition characterized by abnormal tissue or organ levels of uric acid for which a URAT1 possesses activity that contributes to the pathology and/or symptomology of the disease state.

Administration and Pharmaceutical Compositions

[104] 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.

[105] 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.

[106] 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.

[107] 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 1000 mg of active substance.

[108] 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).

[109] Suspensions in oil may comprise as the oil component the vegetable, synthetic, or semi-synthetic oils customary for injection purposes. Examples include 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.

[110] 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.

[111] 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.

[112] Suitable carriers as used herein, refers to relatively nontoxic chemical compounds or agents that facilitate the incorporation of a compound into cells or tissues, which 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.

[113] 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 acetylcellulose 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.

[114] 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.

[115] 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.

[116] 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.

[117] The disclosure also provides for a pharmaceutical combinations, e.g. a kit, comprising a) a first agent which is a compound 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

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

[119] 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.

[120] 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.

[121] For example, the compounds or pharmaceutical acceptable salts of the disclosure may be used in accordance with the disclosure in combination with pharmaceutical compositions effective in various diseases as described above. The one or more additional therapeutic agents may be selected from any of the agents or types of agent such as, a xanthine oxidase inhibitor (e.g. allopurinol, febuxostat or tisopurine); a xanthine oxidoreductase inhibitor (e.g. topiroxostat); a purine nucleoside phosphorylase (PNP) inhibitor (e.g. ulodesine); a uricase (e.g. pegloticase or rasburicase); a uricosuric agent, such as an agent that inhibits one or more transporters responsible for reabsorption of uric acid back into the blood, for example uric acid transporter inhibitors, such as another URAT1 inhibitor (e.g. benzbromarone, URC-102 or RDEA3170), a glucose transporter (GLUT) inhibitor, such as a GLUT-9 inhibitor, an organic anion transporter (OAT) inhibitor, such as an OAT-4 inhibitor, a solute carrier family 2 (facilitated glucose transporter), member 9 (SLC2A9) inhibitor, or an agent which inhibits one or more of the above transporters, such as benziodarone, isobromindion, probenecid, sulphinpyrazone, arhalofenate, tranilast, lesinuard or KUX-1151; an agent that otherwise exerts blood uric acid lowering effects, such as amlodipine, atorvastatin, fenofibrate or indomethacin; an anti-inflammatory drug such as nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g. celecoxib), adrnocorticotropic hormone (ACTH), a glucorticoid, colchicine, steroids, an interleukin 1 inhibitor (e.g. rilonacept) or an agent that modulates inflammoson signaling cascades (e.g. an IRAK4 inhibitor); or an agent that reduces pain, such as acetaminophen, an ion channel modulator (e.g. an inhibitor of Nav1.7, TRPV1 or TRPM2).

[122] In some embodiments, the additional agent is, an androgen, a cox-2 inhibitor, a PPAR agonist, naproxen, sevelamer, sibutmaine, troglitazone, proglitazone, another uric acid lowering agent, losartan, fibric acid, salisylate, vitamin C, or combinations thereof.

EXAMPLES

[123] 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.

[124] 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) and/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.

[125] A compound of formula (I) can also be prepared as a pharmaceutically acceptable acid addition salt by, for example, reacting the free base form of a compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of formula (I) can be prepared by, for example, reacting the free acid form of a 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.

[126] 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).

[127] The N-oxides of a compound of formula (I) and/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.

[128] 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.

[129] 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.

[130] 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).

[131] 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.

[132] ^{1}H 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).

[133] 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

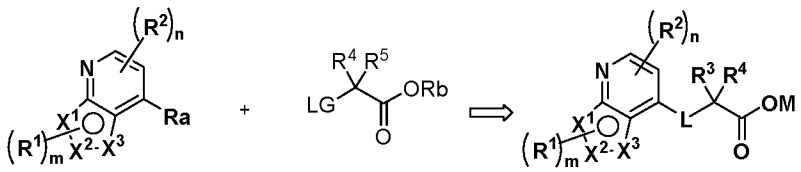
[134] A compound of formula I or a pharmaceutically acceptable salt thereof may be synthesized according to a variety of reaction schemes. Some illustrative schemes are provided below and in the examples. Other reaction schemes could be readily devised by those skilled in the art in view of the present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

[135] In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxyl, amino, imino, thio or carboxyl 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.

[136] 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.

[137] 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.

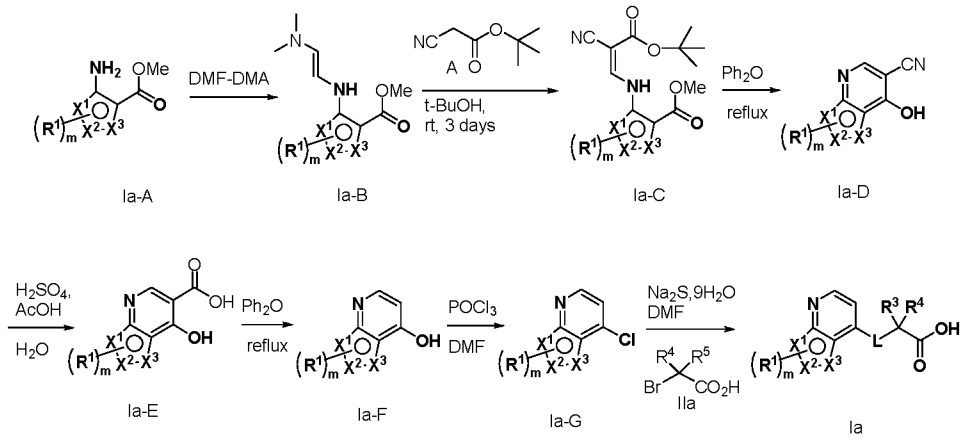
[138] As an illustration, one of the synthetic approach of the compounds of formula I of the present disclosure is outlined in Scheme 1. As shown in the Scheme, the compounds of formula I can be disassembled into the intermediates II and III, which are either known in the literature or may be prepared by a variety of methods familiar to those skilled in the art. Coupling of fused pyridine III with II via nucleophilic substitution reactions leads to compounds of formula I.



Scheme 1

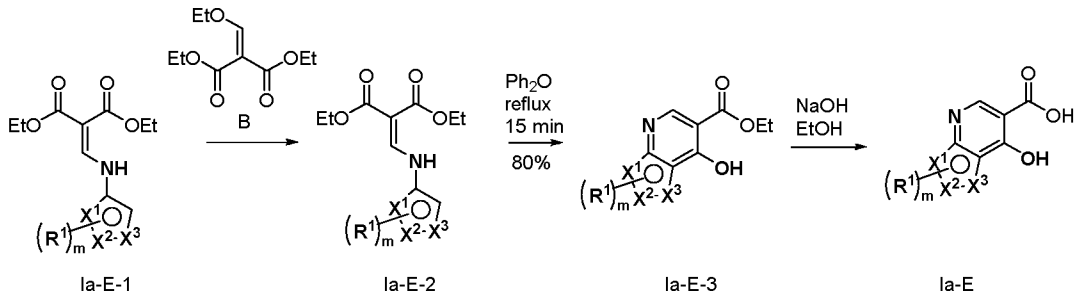
[139] As an illustration of the preparation of compounds of formula I, one synthetic route of compounds of formula Ia is shown in Scheme 2. Starting from amino heteroaryl

compounds of Ia-A, which is either commercially available or known in the literature, enamine Ia-B can be readily prepared by reacting Ia-A with a reagent such as DMF-DMA or through other transformations known in the literature. Treatment of Ia-B with *tert*-butyl cyanoacetate provides Ia-C, the cyclization of which provides Ia-D. Hydrolysis of the cyano group into carboxyl group followed by decarboxylation results in fused hydroxyl pyridine intermediate Ia-F. Treatment of Ia-F with chlorinating reagent such as $POCl_3$ in the presence of DMF gives Ia-G. Transformation of chloride group into thio group and alkylation of the resulting thio group provides compounds of formula Ia.



Scheme 2

[140] Alternatively compounds of formula Ia-E can be prepared through the method outlined in Scheme 3. Starting from compounds of formula Ia-E-1, which can be prepared from the method known in the literature, Ia-E-2 can be prepared by reacting Ia-E-1 with B. Cyclization of Ia-E-2 results in Ia-E-3, hydrolysis of which leads to compounds of Ia-E.



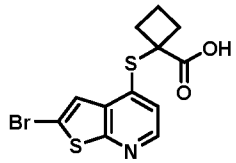
Scheme 3

[141] 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. These examples are illustrative only and should not be construed as limiting the invention in any way.

Preparation of Examples

Example 1

[142] *1-((2-bromothieno[2,3-b]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid* (**1**)



1

[143] *4-hydroxythieno[2,3-b]pyridine-5-carbonitrile* (**1a**)

[144] 4-hydroxythieno[2,3-*b*]pyridine-5-carbonitrile (**1a**) was prepared according to the method described in *US 2008 / 76926.*

[145] *2-bromo-4-hydroxythieno[2,3-b]pyridine-5-carbonitrile* (**1b**)

[146] To a suspension of 4-hydroxythieno[2,3-*b*]pyridine-5-carbonitrile (**1a**) (0.5 g, 2.82 mmol) in acetic acid (8.0 mL) was added bromine (0.3 mL, 5.64 mmol) at room temperature. Then the resulting solution was stirred for 16 h at 80°C. The solvent was evaporated under reduced pressure. The solids were washed with petroleum ether (3 × 20 mL), dried in an oven to give 2-bromo-4-hydroxythieno[2,3-*b*]pyridine-5-carbonitrile (**1b**). MS-ESI (m/z): 255/257 $[M + 1]^+$.

[147] *2-bromo-4-hydroxythieno[2,3-b]pyridine-5-carboxylic acid* (**1c**)

[148] To a suspension of 2-bromo-4-hydroxythieno[2,3-*b*]pyridine-5-carbonitrile (**1b**) (0.6 g, 2.35 mmol) in acetic acid (8.0 mL) were added concentrated sulfuric acid (8 mL) and distilled water (3 mL). Then the reaction mixture was stirred for 16 h at 90°C. The mixture was diluted with water (20 mL). The solids were collected by filtration and dried in an oven to give 2-bromo-4-hydroxythieno[2,3-*b*]pyridine-5-carboxylic acid (**1c**). MS-ESI (m/z): 274/276 $[M + 1]^+$.

[149] *2-bromothieno[2,3-b]pyridin-4-ol* (**1d**)

[150] A suspension of 2-bromo-4-hydroxythieno[2,3-*b*]pyridine-5-carboxylic acid (**1c**) (0.5 g, 1.82 mmol) in diphenyl ether (8.0 mL) was stirred for 1 h at 255°C. The reaction mixture was cooled to room temperature, and petroleum ether (40mL) was added. The solids were collected by filtration, washed with petroleum ether (3 × 10 mL) and dried in an oven to give 2-bromothieno[2,3-*b*]pyridin-4-ol (**1d**). MS-ESI (m/z): 230/232 $[M + 1]^+$.

[151] *2-bromo-4-chlorothieno[2,3-b]pyridine* (**1e**)

[152] To a solution of 2-bromothieno[2,3-*b*]pyridin-4-ol (**1d**) (0.4 g, 1.74 mmol) in phosphorus oxychloride (8.0 mL) was added *N,N*-dimethylformamide (0.1 mL). The resulting solution was stirred for 3 h at 70°C. The reaction mixture was cooled to room temperature, and poured into ice water (40 mL). The resulting mixture was extracted with dichloromethane (3 × 30

mL). The organic layers were combrined, washed with water (3 × 30 mL), brine (30 mL), and dried over anhydrous sodium sulfate. The solids were filtered out and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane/ petroleum ether (1: 4 ~ 1: 2) to give 2-bromo-4-chlorothieno[2,3-*b*]pyridine (**1e**). MS-ESI (m/z): 248/250 $[M+1]^+$.

[153] *ethyl 1-((2-bromothieno[2,3-b]pyridin-4-yl)thio)cyclobutane-1-carboxylate* (**1f**)

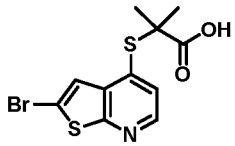
[154] To a solution of 2-bromo-4-chlorothieno[2,3-*b*]pyridine (**1e**) (25.0 mg, 0.10 mmol) in *N*,*N*-dimethylformamide (0.5 mL) was added sodium sulfide nonahydrate (48.0 mg, 0.20 mmol). The resulting solution was stirred for 2 h at 100°C. The reaction mixture was cooled to room temperature, and ethyl 1-bromocyclobutane-1-carboxylate (62.0 mg, 0.3 mmol) was added. Then the resulting solution was stirred for 1 h at 60°C. The reaction was quenched with water (20 mL). The resulting mixture was extracted with ethyl acetate (3 × 10 mL), and the organic layers were combined, washed with water (3 × 20 mL), brine (20 mL), and dried over anhydrous sodium sulfate. The solids were filtered out and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate/ petroleum ether (1: 50 ~ 1: 20) to give ethyl 1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylate (**1f**). MS-ESI (m/z): 372/374 $[M+1]^+$.

[155] *1-((2-bromothieno[2,3-b]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid* (**1**)

[156] To a solution of ethyl 1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylate (**1f**) (28.0 mg, 0.075 mmol) in methanol (3.0 mL) was added aqueous sodium hydroxide (2.5 N, 1.0 mL). The resulting solution was stirred for 2 h at room temperature. The pH value was adjusted to 4~5 with hydrochloric acid (1 N). The resulting mixture was extracted with dichloromethane (3 × 10 mL), and the organic layers were combined, washed with brine (10 mL), and dried over anhydrous sodium sulfate. The solids were filtered out and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with methanol/ dichloromethane (1: 20 ~ 1: 10) to give 1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid (**1**). MS-ESI (m/z): 344/346 $[M+1]^+$.

Example 2

[157] *2-((2-bromothieno[2,3-b]pyridin-4-yl)thio)-2-methylpropanoic acid* (**2**)

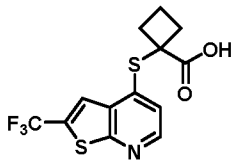


2

[158] 2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-2-methylpropanoic acid (**2**) was prepared according to the synthetic method of **1** by replacing methyl 1-bromocyclobutane-1-carboxylate with methyl 2-bromo-2-methylpropanoate. MS-ESI (m/z): 332/334 $[M+1]^+$.

Example 3

[159] *1-((2-(trifluoromethyl)thieno[2,3-b]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid* (**3**)



3

[160] *4-hydroxy-2-iodothieno[2,3-b]pyridine-5-carbonitrile* (**3a**)

[161] To a solution of 4-hydroxythieno[2,3-*b*]pyridine-5-carbonitrile (**1a**) (1.0 g, 5.65 mmol) in chloroform (112.0 mL) were added iodine (2.2 g, 8.47 mmol) and [bis(trifluoroacetoxy)iodo]benzene (3.6 g, 8.47 mmol). The resulting solution was stirred for 20 h at room temperature. Three quarters of the solvent was evaporated. The solids were collected by filtration, washed with petroleum ether (30 mL) and dried in an oven to give 4-hydroxy-2-iodothieno[2,3-*b*]pyridine-5-carbonitrile (**3a**). MS-ESI (m/z): 303 $[M+1]^+$.

[162] *2-iodo-4-((4-methoxybenzyl)oxy)thieno[2,3-b]pyridine-5-carbonitrile* (**3b**)

[163] To a solution of 4-hydroxy-2-iodothieno[2,3-*b*]pyridine-5-carbonitrile (**3a**) (0.56 g, 1.85 mmol) in *N,N*-dimethylformamide (10.0 mL) were added cesium carbonate (1.2 g, 3.70 mmol) and 1-(chloromethyl)-4-methoxybenzene (0.43 g, 2.77 mmol). The resulting solution was stirred for 16 h at room temperature. The reaction was quenched with water (30 mL). The resulting mixture was extracted with dichloromethane (3 × 30 mL). The organic layers were combined, washed with water (2 × 30 mL), brine (30 mL), and dried over anhydrous sodium sulfate. The solids were filtered out and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with dichloromethane/ petroleum ether (1: 5 ~ 1: 2) to give 2-iodo-4-((4-methoxybenzyl)oxy)-thieno[2,3-*b*]pyridine-5-carbonitrile (**3b**). MS-ESI (m/z): 423 $[M+1]^+$.

[164] *4-((4-methoxybenzyl)oxy)-2-(trifluoromethyl)thieno[2,3-b]pyridine-5-carbonitrile* **(3c)**

[165] To a solution of 2-iodo-4-((4-methoxybenzyl)oxy)thieno[2,3-*b*]pyridine-5-carbonitrile (**3b**) (1.15 g, 2.72 mmol) in dimethyl sulfoxide (25.0 mL) were added (trifluoromethyl)trimethylsilane (1.93 g, 13.60 mmol), copper(I) iodide (0.62 g, 3.26 mmol), potassium fluoride (0.16 g, 8.15 mmol), 1,10-phenanthroline (0.59 g, 3.26 mmol) and trimethyl borate (0.85 g, 8.15 mmol) under an inert atmosphere of nitrogen. The resulting solution was stirred for 16 h at 100°C. The reaction was quenched with water (200 mL). The resulting mixture was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined, washed with water (3 × 50 mL), brine (50 mL), and dried over anhydrous sodium sulfate. The solids were filtered out and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with tetrahydrofuran/ petroleum ether (1: 2 ~ 1: 1) to give 4-((4-methoxybenzyl)oxy)-2-(trifluoromethyl)thieno[2,3-*b*]pyridine-5-carbonitrile (**3c**). MS-ESI (m/z): 365 $[M+1]^+$.

[166] *4-hydroxy-2-(trifluoromethyl)thieno[2,3-b]pyridine-5-carboxylic acid* **(3d)**

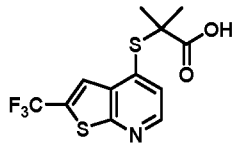
[167] To a suspension of 4-((4-methoxybenzyl)oxy)-2-(trifluoromethyl)thieno[2,3-*b*]pyridine-5-carbonitrile (**3c**) (0.1g, 0.27 mmol) in acetic acid (1.0 mL) were added concentrated sulfuric acid (1.0 mL) and distilled water (0.4 mL). Then the reaction mixture was stirred for 16 h at 90°C. The mixture was diluted with water (5.0 mL). The solids were collected by filtration and dried in an oven to give 4-hydroxy-2-(trifluoromethyl)-thieno[2,3-*b*]pyridine-5-carboxylic acid (**3d**). MS-ESI (m/z): 264 $[M+1]^+$.

[168] *1-((2-(trifluoromethyl)thieno[2,3-b]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid* **(3)**

[169] The title compound 1-((2-(trifluoromethyl)thieno[2,3-*b*]pyridin-4-yl)thio)-cyclobutane-1-carboxylic acid (**3**) was prepared according to the synthetic method of **1** by replacing 2-bromo-4-hydroxythieno[2,3-*b*]pyridine-5-carboxylic acid (**1c**) with 4-hydroxy-2-(trifluoromethyl)-thieno[2,3-*b*]pyridine-5-carboxylic acid (**3d**). MS-ESI (m/z): 334 $[M+1]^+$.

Example 4

[170] *2-methyl-2-((2-(trifluoromethyl)thieno[2,3-b]pyridin-4-yl)thio)propanoic acid* **(4)**

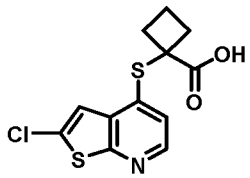


4

[171] The title compound 2-methyl-2-((2-(trifluoromethyl)thieno[2,3-*b*]pyridin-4-yl)thio)propanoic acid (**4**) was prepared according to the synthetic method of **3** by replacing methyl 1-bromocyclobutane-1-carboxylate with methyl 2-bromo-2-methylpropanoate. MS-ESI (m/z): 322 $[M + 1]^+$.

Example 5

[172] *1-((2-chlorothieno[2,3-b]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid* (**5**)



5

[173] *2-chloro-4-hydroxythieno[2,3-b]pyridine-5-carbonitrile* (**5a**)

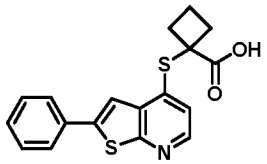
[174] To a suspension of **1a** (0.1 g, 0.57 mmol) in acetic acid (3.0 mL) was added *N*-chlorosuccinimide (0.15 g, 1.14 mmol) at room temperature. Then the resulting suspension was stirred for 2 h at 80°C. The solvent was evaporated under reduced pressure. The solids were washed with dichloromethane (10 mL), and dried in an oven to give 2-chloro-4-hydroxythieno[2,3-*b*]pyridine-5-carbonitrile (**5a**). MS-ESI (m/z): 211/213 $[M + 1]^+$.

[175] *1-((2-chlorothieno[2,3-b]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid* (**5**)

[176] The title compound 1-((2-chlorothieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid (**5**) was prepared according to the synthetic method of **1** by replacing 2-bromo-4-hydroxythieno[2,3-*b*]pyridine-5-carbonitrile (**1b**) with 2-chloro-4-hydroxythieno[2,3-*b*]pyridine-5-carbonitrile (**5a**). MS-ESI (m/z): 300 $[M + 1]^+$.

Example 6

[177] *1-((2-phenylthieno[2,3-b]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid* (**6**)



6

[178] *4-chloro-2-phenylthieno[2,3-b]pyridine* (**6a**)

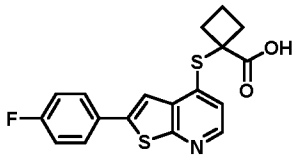
[179] To a solution of 2-bromo-4-chlorothieno[2,3-*b*]pyridine (**1e**) (20.0 mg, 0.08 mmol) in dioxane (0.5 mL) were added phenylboronic acid (10.0 mg, 0.08 mmol), cesium carbonate (52.0 mg, 0.16 mmol) and bis(triphenylphosphine)palladium(II) chloride (6.0 mg, 0.008 mmol) under an inert atmosphere of nitrogen. The resulting solution was stirred for 2 h at 80°C. The reaction was quenched with water (10.0 mL). The resulting mixture was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, washed with water (3 × 10 mL), brine (10 mL), and dried over anhydrous sodium sulfate. The solids were filtered out and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate/ petroleum ether (1: 20) to give 4-chloro-2-phenylthieno[2,3-*b*]pyridine (**6a**). MS-ESI (m/z): 246/248 $[M + 1]^+$.

[180] *1-((2-phenylthieno[2,3-b]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid* (**6**)

[181] The title compound 1-((2-phenylthieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid (**6**) was prepared according to the synthetic method of **1** by replacing 2-bromo-4-chlorothieno[2,3-*b*]pyridine (**1e**) with 4-chloro-2-phenylthieno[2,3-*b*]pyridine (**6a**). MS-ESI (m/z): 342 $[M + 1]^+$.

Example 7

[182] *1-((2-(4-fluorophenyl)thieno[2,3-b]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid* (**7**)

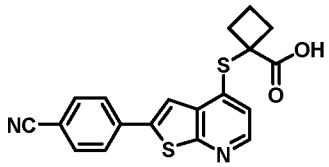


7

[183] The title compound 1-((2-(4-fluorophenyl)thieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid (**7**) was prepared according to the synthetic method of **6** by replacing phenylboronic acid with 2-(4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. MS-ESI (m/z): 360 $[M + 1]^+$.

Example 8

[184] *1-((2-(4-cyanophenyl)thieno[2,3-b]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid* (**8**)

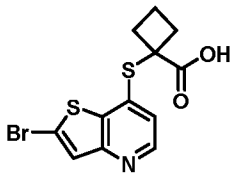


8

[185] The title compound 1-((2-(4-cyanophenyl)thieno[2,3-*b*]pyridin-4-yl)thio)-cyclobutane-1-carboxylic acid (**8**) was prepared according to the synthetic method of **6** by replacing phenylboronic acid with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile. MS-ESI (m/z): 367 $[M+1]^+$.

Example 9

[186] *1-((2-bromothieno[3,2-b]pyridin-7-yl)thio)cyclobutane-1-carboxylic acid* (**9**)



9

[187] *ethyl 7-hydroxythieno[3,2-b]pyridine-6-carboxylate* (**9a**)

[188] The title compound ethyl 7-hydroxythieno[3,2-*b*]pyridine-6-carboxylate (**9a**) was prepared according to the method described in *Tetrahedron, 1987, 43(14), 3295-3302.*

[189] *ethyl 2-bromo-7-hydroxythieno[3,2-b]pyridine-6-carboxylate* (**9b**)

[190] To a suspension of ethyl 7-hydroxythieno[3,2-*b*]pyridine-6-carboxylate (**9a**) (0.48 g, 2.15 mmol) in acetic acid (10.0 mL) was added bromine (4.0 mL) at room temperature. Then the resulting solution was stirred for 16 h at 80°C. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with methanol/ dichloromethane (1: 60 ~ 1: 40) to give ethyl 2-bromo-7-hydroxythieno[3,2-*b*]pyridine-6-carboxylate (**9b**). MS-ESI (m/z): 302/304 $[M+1]^+$.

[191] *2-bromo-7-hydroxythieno[3,2-b]pyridine-6-carboxylic acid* (**9c**)

[192] To a solution of ethyl 2-bromo-7-hydroxythieno[3,2-*b*]pyridine-6-carboxylate (**9b**) (200.0 mg, 0.66 mmol) in ethanol (15.0 mL) was added aqueous sodium hydroxide (2.5 N, 5.0 mL) at room temperature. Then the resulting solution was stirred for 1.5 h at 80°C. The solvent was evaporated under reduced pressure. The pH value was adjusted to 4~5 with hydrochloric acid

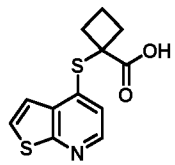
(2 N). The solids were collected by filtration and dried in an oven to give 2-bromo-7-hydroxythieno[3,2-*b*]pyridine-6-carboxylic acid (**9c**). MS-ESI (m/z): 274/276 [M + 1]$^+$.

[193] *1-((2-bromothieno[3,2-b]pyridin-7-yl)thio)cyclobutane-1-carboxylic acid* (**9**)

[194] The title compound 1-((2-bromothieno[3,2-*b*]pyridin-7-yl)thio)cyclobutane-1-carboxylic acid (**9**) was prepared according to the synthetic method of **1** by replacing 2-bromo-4-hydroxythieno[2,3-*b*]pyridine-5-carboxylic acid (**1c**) with 2-bromo-7-hydroxythieno[3,2-*b*]pyridine-6-carboxylic acid (**9c**). MS-ESI (m/z): 344/346 [M + 1]$^+$.

Example 10

[195] *1-(thieno[2,3-b]pyridin-4-ylthio)cyclobutane-1-carboxylic acid* (**10**)

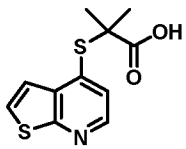


10

[196] The title compound 1-(thieno[2,3-*b*]pyridin-4-ylthio)cyclobutane-1-carboxylic acid (**10**) was prepared according to the synthetic method of **1** by replacing 2-bromo-4-hydroxythieno[2,3-*b*]pyridine-5-carbonitrile (**1b**) with 4-hydroxythieno[2,3-*b*]pyridine-5-carbonitrile (**1a**). MS-ESI (m/z): 266 [M + 1]$^+$.

Example 11

[197] *2-methyl-2-(thieno[2,3-b]pyridin-4-ylthio)propanoic acid* (**11**)

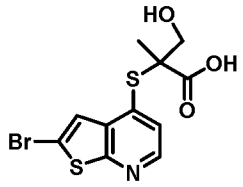


11

[198] The title compound 2-methyl-2-(thieno[2,3-*b*]pyridin-4-ylthio)propanoic acid (**11**) was prepared according to the synthetic method of **10** by replacing methyl 1-bromocyclobutane-1-carboxylate with methyl 2-bromo-2-methylpropanoate. MS-ESI (m/z): 254 [M + 1]$^+$.

Example 12

[199] *2-((2-bromothieno[2,3-b]pyridin-4-yl)thio)-3-hydroxy-2-methylpropanoic acid* **(12)**



12

[200] *ethyl 2-((2-bromothieno[2,3-b]pyridin-4-yl)thio)propanoate* **(12a)**

[201] To a solution of 2-bromo-4-chlorothieno[2,3-*b*]pyridine (**1e**) (645.0 mg, 2.60 mmol) in *N*,*N*-dimethylformamide (15 mL) was added sodium sulfide nonahydrate (1.25 g, 5.20 mmol). The resulting solution was stirred for 1 h at 100°C. The reaction mixture was cooled to room temperature, and ethyl 2-bromopropanoate (1.4 g, 7.8 mmol) was added. Then the resulting solution was stirred for 1 h at r.t.. The reaction was quenched with water (100 mL). The resulting mixture was extracted with ethyl acetate (3 × 60 mL), and the organic layers were combined, washed sequentially with water (2 × 80 mL) and brine (80 mL), and dried over anhydrous sodium sulfate. The solids were filtered out and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate/ petroleum ether (1: 50 ~ 1: 10) to give ethyl 2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)propanoate (**12a**). MS-ESI (m/z): 346/348 $[M+1]^+$.

[202] *ethyl 2-((2-bromothieno[2,3-b]pyridin-4-yl)thio)-3-hydroxy-2-methylpropanoate* ***(12b)***

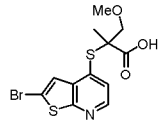
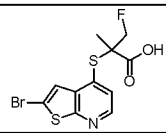
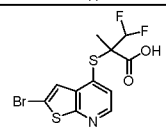
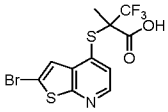
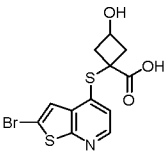
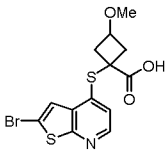
[203] To a solution of ethyl 2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)propanoate (**12a**). (703.0 mg, 2.03 mmol) in *N*,*N*-dimethylformamide (8.5 mL) was added para HCHO (183 mg, 6.1 mmol). The resulting solution was stirred at r.t., and NaH (18 mg, 0.4 mmol) was added. Then the resulting solution was stirred for 1 h at r.t.. The reaction was quenched with water (50 mL). The resulting mixture was extracted with ethyl acetate (3 × 60 mL), and the organic layers were combined, washed sequentially with water (2 × 80 mL) and brine (80 mL), and dried over anhydrous sodium sulfate. The solids were filtered out and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate/ petroleum ether (1: 25~ 1: 3) to give ethyl 2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-hydroxy-2-methylpropanoate (**12b**). MS-ESI (m/z): 376/378 $[M+1]^+$.

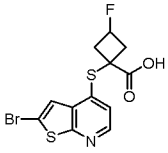
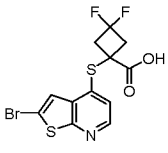
[204] *2-((2-bromothieno[2,3-b]pyridin-4-yl)thio)-3-hydroxy-2-methylpropanoic acid* **(12)**

[205] To a solution of ethyl 2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-hydroxy-2-methylpropanoate **(12b)**. (80.0 mg, 0.213 mmol) in THF (8 mL) ,MeOH (3 ml) and H_2O (1.5 ml) was added $LiOH.H_2O$ (52 mg). The resulting solution was stirred at r.t. for 3 h The reaction was quenched with water (30 mL) and the mixture was adjusted to pH = 3 using 1 N HCl (aq). The resulting mixture was extracted with DCM (3 × 60 mL), and the organic layers were combined, washed with brine (50 mL), and dried over anhydrous sodium sulfate. The solids were filtered out and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with DCM/MeOH (1:50 ~ 1:10) to give 2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-hydroxy-2-methylpropanoic acid **(12)**. MS-ESI (m/z): 348/350 $[M + 1]^+$.

[206] Following essentially the same procedures described for Examples 1-12, Examples 13-20 listed in Table 1 were prepared by using the appropriate starting materials and making necessary functional group manipulations when needed.

TABLE 1

EXAMPLE	STRUCTURE	NAME	DATA
13		2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-methoxy-2-methylpropanoic acid	MS-ESI (m/z): 362/364 $[M + 1]^+$
14		2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-fluoro-2-methylpropanoic acid	MS-ESI (m/z): 350/352 $[M + 1]^+$
15		2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3,3-difluoro-2-methylpropanoic acid	MS-ESI (m/z): 368/370 $[M + 1]^+$
16		2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3,3,3-trifluoro-2-methylpropanoic acid	MS-ESI (m/z): 386/388 $[M + 1]^+$
17		1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-hydroxycyclobutane-1-carboxylic acid	MS-ESI (m/z): 360/362 $[M + 1]^+$
18		1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-methoxycyclobutane-1-carboxylic acid	MS-ESI (m/z): 374/376 $[M + 1]^+$

EXAMPLE	STRUCTURE	NAME	DATA
19		1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-fluorocyclobutane-1-carboxylic acid	MS-ESI (m/z): 362/364 $[M+1]^+$
20		1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3,3-difluorocyclobutane-1-carboxylic acid	MS-ESI (m/z): 380/382 $[M+1]^+$

URAT1 inhibitor activity

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

[208] Cell Lines were generated in WuXi AppTec (HEK293-URAT-4: Stable cell line of HEK293 which was transfected with pcDNA3.1-URAT (Human SLC22A12 cDNA Clone, Abgent-DC07943). HEK293-PCDNA-5: Negative control cell of HEK293 which was transfected with pcDNA3.1 empty vector.

URAT1 *in vitro* inhibition activity-Method A

[209] Cells were seeded onto 24-well plates at the density of 2.0×10^5 cells per well. The cells were incubated at 37°C, 5% CO_2 overnight. After approximately 24 hours culture, cells were used for uptake experiments. The culture medium were removed from the wells and the cells were incubated in 0.4 ml/well of Hank's balanced salt solution (HBSS) for 10 min. HBSS was replaced with 0.18 ml/well fresh HBSS. Compounds were 5 folds serial diluted in DMSO, and then 25 folds diluted in HBSS. Compounds diluted with HBSS (10 µl) were added to relevant well of cell plates, and plates were incubated at 37°C, 5% CO_2 for 15 min. The final concentration of DMSO in the assay was 0.2%. 10 µl HBSS containing radioactively labeled Urate (^{14}C-uric acid) was added to each well. The final concentration of ^{14}C-uric acid in the assay medium was 50 µM. After 10 min, the assay medium was immediately removed. The cells were washed quickly with 0.5 ml pre-chilled HBSS twice. 0.1 M NaOH (0.4 ml) was added to lyse the cells for at least 20 min. The cell lysate was collected to a scintillation vial, and scintillant (4 ml) was added and the radioactivity was counted by a liquid scintillation counter. Inhibiton% data were calculated using the fomular

$$inhibiton\% = \frac{HC - CPD}{HC - LC} \times 100$$

, and analyzed using Prism5 software. (*CN 101679251*)

CPD: Signal from a well containing a test compound

HC (high control): Average of signals from HEK293-URAT-4 cells

LC(low control): Average of signals from HEK293- PCDNA-5.

[210] Select compounds prepared as described above were assayed according to the biological procedures described in Method A. The results are given in the Table 2.

TABLE 2

Example	IC_{50} (nM)	Example	IC_{50} (nM)
1	30	6	793
2	62	7	1380
3	1081	9	250

URAT1 *in vitro* inhibition activity-Method B

[211] 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.

[212] 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.

[213] 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 = $[100 \times (U-U_0)/(U_c-U_0)]$%, 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.

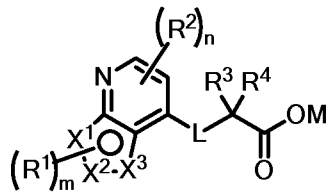
[214] Select compounds prepared as described above were assayed according to the biological procedures described Method B. The results are given in the Table 3.

TABLE 3

Example	**IC_{50} (nM)**	**Example**	**IC_{50} (nM)**
12	67	16	462
14	146	19	482

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,
wherein:

L is selected from NR^X, O and S;

X^1, X^2 and X^3 are independently selected from C, N, O or S, with the proviso that no more than one of X^1, X^2 and X^3 is O or S;

each R^1 is independently selected from hydrogen, 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, -$NR^{A1}R^{B1}$, -OR^{A1}, -$S(O)_rR^{A1}$, -$S(O)_2OR^{A1}$, -$OS(O)_2R^{A1}$, -$P(O)R^{A1}R^{B1}$, -$P(O)(OR^{A1})(OR^{B1})$, -$C(O)R^{A1}$, -$C(O)OR^{A1}$, -$OC(O)R^{A1}$, -$C(O)NR^{A1}R^{B1}$, -$NR^{A1}C(O)R^{B1}$, -$OC(O)NR^{A1}R^{B1}$, -$NR^{A1}C(O)OR^{B1}$, -$NR^{A1}C(O)NR^{A1}R^{B1}$, -$NR^{A1}C(S)NR^{A1}R^{B1}$, -$S(O)_rNR^{A1}R^{B1}$, -$NR^{A1}S(O)_rR^{B1}$, -$NR^{A1}S(O)_2NR^{A1}R^{B1}$, -$S(O)(=NR^{E1})R^{B1}$, -$N=S(O)R^{A1}R^{B1}$, -$NR^{A1}S(O)(=NR^{E1})R^{B1}$, -$S(O)(=NR^{E1})NR^{A1}R^{B1}$, -$NR^{A1}S(O)(=NR^{E1})NR^{A1}R^{B1}$, -$C(=NR^{E1})R^{A1}$, -$C(=N\text{-}OR^{B1})R^{A1}$, -$C(=NR^{E1})NR^{A1}R^{B1}$, -$NR^{A1}C(=NR^{E1})R^{B1}$, and -$NR^{A1}C(=NR^{E1})NR^{A1}R^{B1}$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^X;

each R^2 is independently selected from hydrogen, 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}, -$S(O)_rR^{A2}$, -$S(O)_2OR^{A2}$, -$OS(O)_2R^{A2}$, -$P(O)R^{A2}R^{B2}$, -$P(O)(OR^{A2})(OR^{B2})$, -$C(O)R^{A2}$, -$C(O)OR^{A2}$, -$OC(O)R^{A2}$, -$C(O)NR^{A2}R^{B2}$, -$NR^{A2}C(O)R^{B2}$, -$OC(O)NR^{A2}R^{B2}$, -$NR^{A2}C(O)OR^{B2}$, -$NR^{A2}C(O)NR^{A2}R^{B2}$, -$NR^{A2}C(S)NR^{A2}R^{B2}$, -$S(O)_rNR^{A2}R^{B2}$, -$NR^{A2}S(O)_rR^{B2}$, -$NR^{A2}S(O)_2NR^{A2}R^{B2}$, -$S(O)(=NR^{E2})R^{B2}$, -$N=S(O)R^{A2}R^{B2}$, -$NR^{A2}S(O)(=NR^{E2})R^{B2}$, -$S(O)(=NR^{E2})NR^{A2}R^{B2}$, -$NR^{A2}S(O)(=NR^{E2})NR^{A2}R^{B2}$, -$C(=NR^{E2})R^{A2}$, -$C(=N\text{-}OR^{B2})R^{A2}$, -$C(=NR^{E2})NR^{A2}R^{B2}$, -$NR^{A2}C(=NR^{E2})R^{B2}$, and -$NR^{A2}C(=NR^{E2})NR^{A2}R^{B2}$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^X;

R^3 and R^4 are each independently selected from hydrogen, 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 the said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^X;

or R^3 and R^4 together with the carbon atom to which they are attached form a ring of 3 to 7 members containing 0, 1, or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1, 2 or 3 R^X groups;

each R^{A1}, R^{A2}, R^{B1} and R^{B2} are independently selected from hydrogen, 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, such as one, two, three, or four substituents, independently selected from R^X;

or each "R^{A1} and R^{B1}" 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 and nitrogen, and optionally substituted with 1, 2 or 3 R^X groups;

each R^{E1} and R^{E2} are independently selected from hydrogen, C_{1-10} alkyl, CN, NO_2, OR^{a1}, SR^{a1}, $-S(O)_rR^{a1}$, $-S(O)_rNR^{a1}R^{b1}$, $-C(O)R^{a1}$, $-C(O)OR^{a1}$ and $-C(O)NR^{a1}R^{b1}$;

each R^X 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, $-NO_2$, $-(CR^{c1}R^{d1})_tNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tOR^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_rR^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_2OR^{b1}$, $-(CR^{c1}R^{d1})_tOS(O)_2R^{b1}$, $-(CR^{c1}R^{d1})_tP(O)R^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tP(O)(OR^{a1})(OR^{b1})$, $-(CR^{c1}R^{d1})_tC(O)R^{a1}$, $-(CR^{c1}R^{d1})_tC(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tOC(O)R^{b1}$, $-(CR^{c1}R^{d1})_tC(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)R^{b1}$, $-(CR^{c1}R^{d1})_tOC(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(S)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_rNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_rR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_2NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tN=S(O)R^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tC(=NR^{e1})R^{a1}$, $-(CR^{c1}R^{d1})_tC(=N\text{-}OR^{b1})R^{a1}$, $-(CR^{c1}R^{d1})_tC(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(=NR^{e1})R^{b1}$ and $-(CR^{c1}R^{d1})_tNR^{a1}C(=NR^{e1})NR^{a1}R^{b1}$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^Y;

each R^{a1} and each R^{b1} are independently selected from hydrogen, 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, such as one, two, three, or four substituents, 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, 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, such as one, two, three or four substituents, 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, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4} alkyl, CN, NO_2, OR^{a2}, SR^{a2}, $-S(O)_rR^{a2}$, $-S(O)_rNR^{a2}R^{b2}$, $-C(O)R^{a2}$, $-C(O)OR^{a2}$ 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, $-NO_2$, $-(CR^{c2}R^{d2})_tNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tOR^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_rR^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_2OR^{b2}$, $-(CR^{c2}R^{d2})_tOS(O)_2R^{b2}$, $-(CR^{c2}R^{d2})_tP(O)R^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tP(O)(OR^{a2})(OR^{b2})$, $-(CR^{c2}R^{d2})_tC(O)R^{a2}$, $-(CR^{c2}R^{d2})_tC(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)R^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(S)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_rNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_rR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_2NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tN=S(O)R^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(=N\text{-}OR^{b2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})R^{b2}$ and $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})NR^{a2}R^{b2}$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, such as one, two, three, or four substituents, 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, 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, such as one, two, three, or four 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;

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, 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, such as one, two, three, or four 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;

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, 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)NH_2, -C(O)NH(C_{1-4} alkyl), -C(O)N(C_{1-4} alkyl)$_2$, - C(O)NH(C_{3-10} cycloalkyl), -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$$NH_2$, -S(O)$_2$NH($C_{1-4}$ alkyl), -S(O)$_2$N(C_{1-4} alkyl)$_2$, -S(O)$_2$NH(C_{3-10} cycloalkyl) and -S(O)$_2$N(C_{3-10} cycloalkyl)$_2$;

M is hydrogen, C_{1-4} alkyl or a pharmaceutically acceptable cation;

m is selected from 0, 1, 2 and 3;

n is selected from 0, 1 and 2;

each r is independently selected from 1 and 2;

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

2. A compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein L is selected from S and O.

3. A compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein L is S.

4. A compound of any one of claims 1-3 or a pharmaceutically acceptable salt thereof, wherein X^1, X^2 and X^3 are independently selected from C and S, with the proviso that no more than one of X^1, X^2 and X^3 is S.

5. A compound of any one of claims 1-4 or a pharmaceutically acceptable salt thereof, wherein each R^1 is independently selected from hydrogen, halogen, CN, C_{1-10} alkyl and aryl, wherein alkyl and aryl are each unsubstituted or substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^X.

6. A compound of claim 5 or a pharmaceutically acceptable salt thereof, wherein each R^1 is independently selected from hydrogen, chlorine, fluorine, bromine, CF_3, phenyl, 4-fluorophenyl and 4-cyanophenyl.

7. A compound of any one of claims 1-6 or a pharmaceutically acceptable salt thereof, wherein each R^2 is hydrogen.

8. A compound of any one of claims 1-7 or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are each independently selected from C_{1-10} alkyl, wherein alkyl is unsubstituted or substituted with at least one substituent, such as one, two, three or four substituents, independently selected from R^X.

9. A compound of claim 8 or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are each methyl or methyl substituted with at least one substituent, such as one, two, three, or four substituents, independently selected from R^X.

10. A compound of claim 9 or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are each methyl or methyl substituted with at least one substituent, such as one, two, three or four substituents, independently selected from halogen and $-OR^{a1}$.

11. A compound of claim 10 or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are each methyl or methyl substituted with at least one substituent, such as one, two, three or four substituents, independently selected from fluorine, OH and OCH_3.

12. A compound of any one of claims 1-7 or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 together with the carbon atom to which they are attached form a ring of 3 to 7 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1, 2 or 3 R^X groups.

13. A compound of claim 12 or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 together with the carbon atom to which they are attached form cyclobutane, and optionally substituted with 1, 2 or 3 R^X groups.

14. A compound of claim 13 or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 together with the carbon atom to which they are attached form cyclobutane, and optionally substituted with 1 or 2 halogen, OH and OCH_3.

15. A compound of any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof, wherein M is selected from hydrogen, C_{1-4} alkyl, and a pharmaceutically acceptable cation. Preferably the pharmaceutically acceptable cation is Na^+, Li^+, K^+, Ca^{2+}, Mg^{2+}, NH^{4+}, tetramethylammonium, tetraethylammonium, methylamino, dimethylamino, trimethylamine or triethylamino.

16. A compound of claim 15 or a pharmaceutically acceptable salt thereof, wherein M is hydrogen.

17. A compound, selected from

1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid,

2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-2-methylpropanoic acid,

1-((2-(trifluoromethyl)thieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid,

2-methyl-2-((2-(trifluoromethyl)thieno[2,3-*b*]pyridin-4-yl)thio)propanoic acid,

1-((2-chlorothieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid,

1-((2-phenylthieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid,

1-((2-(4-fluorophenyl)thieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid,

1-((2-(4-cyanophenyl)thieno[2,3-*b*]pyridin-4-yl)thio)cyclobutane-1-carboxylic acid,

1-((2-bromothieno[3,2-*b*]pyridin-7-yl)thio)cyclobutane-1-carboxylic acid,

1-(thieno[2,3-*b*]pyridin-4-ylthio)cyclobutane-1-carboxylic acid,

2-methyl-2-(thieno[2,3-*b*]pyridin-4-ylthio)propanoic acid,

2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-hydroxy-2-methylpropanoic acid,

2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-methoxy-2-methylpropanoic acid,

2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-fluoro-2-methylpropanoic acid,

2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3,3-difluoro-2-methylpropanoic acid,

2-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3,3,3-trifluoro-2-methylpropanoic acid,

1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-hydroxycyclobutane-1-carboxylic acid,

1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-methoxycyclobutane-1-carboxylic acid,

1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3-fluorocyclobutane-1-carboxylic acid,

1-((2-bromothieno[2,3-*b*]pyridin-4-yl)thio)-3,3-difluorocyclobutane-1-carboxylic acid,

or pharmaceutically acceptable salts thereof.

18. A pharmaceutical composition, comprising a compound of any one of claims 1 to 17 or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

19. A method of treating, ameliorating or preventing a condition, which responds to inhibition of urate anion transporter 1, comprising administering to a subject in need of such treatment an effective amount of a compound of any one of claims 1 to 17 or a pharmaceutically acceptable salt thereof, or of at least one pharmaceutical composition thereof, and optionally in combination with a second therapeutic agent.

20. Use of a compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating hyperuricemia or gout.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2017/070720

A. CLASSIFICATION OF SUBJECT MATTER

C07D 495/04(2006.01)i; A61K 31/4353(2006.01)i; A61P 9/12(2006.01)i; A61P 19/06(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

CNABS;DWPI;CNKI;REGISTRY;CAPLUS:substructure search according to formula (I),URAT1, urate anion transport, thieno[2,3-b]pyridin+, thieno,pyridin+

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 102143746 A (EXELIXIS INC) 03 August 2011 (2011-08-03) page 50, compound in the left up cornner	1, 7, 15-16, 18
X	WO 2007056281 A2 (ILYPSA INCET AL.) 18 May 2007 (2007-05-18) page 187, compound 8	1-2, 5, 7, 15, 18
X	WO 2006044821 A1 (SB PHARMCO INCET AL.) 27 April 2006 (2006-04-27) page 45, compound 14-13, page 53, ccompound 19-1, page 54, compound 19-2	1-2, 5-8, 15-16, 18
X	WO 2004074284 A1 (PFIZERET AL.) 02 September 2004 (2004-09-02) page 9, the last compound	1-2, 5, 7, 15-16, 18
X	CN 1027369 C (MERRELL DOW PHARMA) 11 January 1995 (1995-01-11) column 21, example 18, column 22, example 20	1-2, 4-7, 15-16, 18
X	Saxena, Abhishek S. et al. "A convenient and expeditious synthesis of annulated N, S-heterocycles" *Journal of the Indian Chemical Society*, Vol. 80, No. 4, 31 December 2003 (2003-12-31), ISSN: 0019-4522, page 312, compounds 3a, 3b, 3c	1-4, 15

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

* Special categories of cited documents:

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

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

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

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 March 2017	**17 April 2017**
Name and mailing address of the ISA/CN **STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China**	Authorized officer **ZHAO,Zhenzhen**
Facsimile No. **(86-10)62019451**	Telephone No. **(86-10)62086358**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2017/070720

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 103068801 B (ARDEA BIOSCIENCES INC) 14 May 2014 (2014-05-14) claim 1, table	1-20
PX	WO 2016040419 A1 (SQUIBB BRISTOL MYERS CO) 17 March 2016 (2016-03-17) page 76, example 50, page 94, example 127A	1-3, 5-6, 15, 18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2017/070720

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

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

1. ☑ Claims Nos.: **19**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claim 19 is directed to a method of treatment of the human/animal body (Rule 39.1(iv) PCT). Nonetheless, the search has been carried out based on the corresponding use of the compounds/ composition in the manufacture of medicaments.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2017/070720

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
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WO	2004074284	A1	02 September 2004	UY	28200	A1	30 September 2004
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				NL	1025542	A1	24 August 2004
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				IL	94377	A	10 January 1997
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International application No.
PCT/CN2017/070720

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				IL	236039	D0	31 May 2015
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International application No.
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WO 2016040419 A1	17 March 2016	None	