BICYCLIC HETEROARYLAMIDES HAVING GPR68 MODULATING ACTIVITY

TECHNICAL FIELD

The present invention relates to novel GPR68 modulators, their pharmaceutically acceptable salts, and pharmaceutical compositions thereof. The present invention also relates to methods of using such compounds and compositions, including to treat various diseases and disorders; particularly cancer and/or proliferative diseases or disorders.

BACKGROUND

GPR68 (also known as ovarian cancer G protein-coupled receptor 1 or OGR1) is a proton-sensing G-protein-coupled receptor (GPCR) that responds to extracellular acidity and regulates a variety of cellular functions. It has been found that GPR68 expression is highly upregulated in numerous types of cancer, such as colon cancer, medulloblastoma, head and neck cancer, pancreatic cancer and prostate cancer, and it has been suggested that GPR68 has key roles in tumour biology. As such, GPR68 is an attractive target for anti-cancer drug development. Until now, however, few compounds have been identified as selective GPR68 ligands/modulators.

An unmet medical need therefore exists for effective and safe GPR68 modulators.

The present invention has been devised to address at least one of the challenges described above.

SUMMARY

Generally, provided herein are compounds and pharmaceutical compositions capable of modulating GPR68. Also provided are method of treatment and therapeutic / medical uses involving compounds or pharmaceutical compositions of this disclosure for for treating diseases, disorders or conditions associated with GPR68.

In an aspect of this disclosure, there is provided a compound of formula (1):

R^5 and R^6 are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more ring members selected from N, O, S and SO_2; or

R^5 and R^6 together with the carbon atoms to which they are attached form a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more ring members selected from N, O, S and SO_2.

In examples,

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkylene having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, C_9-C_{10} bicyclic aryl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, phenoxy, and 5- or 6- membered heteroaryloxy having one or more heteroatoms selected from N, O and S, wherein said alkyl, cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, bicyclic aryl, heteroaryl, bicyclic heteroaryl, phenoxy and heteroaryloxy are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, $NR^{1a}R^{1b}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, phenoxy, halophenoxy, 5- or 6- membered heteroaryloxy having one or more heteroatoms selected from N, O and S, and C_1-C_4 alkyl substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is selected from H, C_1-C_4 alkyl and C_3-C_8 cycloakyl;

R^3 is selected from H, OH, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-

C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2- C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, C_1-C_4 alkyl, and $NR^{3c}R^{3d}$;

R^{3a} is selected from H, C_1-C_4 alkyl, C_1-C_4 alkyl-OH, and C_1-C_4 alkyl-$NR^{3e}R^{3f}$;

R^{3b}, R^{3c}, R^{3d}, R^{3e} and R^{3f} are each independently selected from H and C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6-membered heteroaryl having one or more ring members selected from N, O, S and SO_2;

R^{4a} and R^{4b} are each independently selected from H and C_1-C_4 alkyl;

R^5 and R^6 are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S; or

R^5 and R^6 together with the carbon atoms to which they are attached form a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S.

In examples,

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkylene having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, and phenoxy, wherein said alkyl, cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, bicyclic heteroaryl, and phenoxy are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, $NR^{1a}R^{1b}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, halophenoxy, and C_1-C_4 alkyl

substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, and $NR^{3c}R^{3d}$;

R^{3a} is selected from H, C_1-C_4 alkyl, and C_1-C_4 alkyl-$NR^{3e}R^{3f}$;

R^{3b} is selected from H and C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^{3e} and R^{3f} are each independently selected from C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} is selected from H and C_1-C_4 alkyl;

R^{4b} is H;

R^5 is selected from H, C_1-C_4 alkyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, or C_3-C_6 cycloalkylene;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, and phenoxy, wherein said alkyl, cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, bicyclic heteroaryl, and phenoxy are each optionally substituted by one or more substituents independently selected from halogen, CN, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4

alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, and C_1-C_4 alkyl substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH and $NR^{3c}R^{3d}$;

R^{3a} is selected from H and C_1-C_4 alkyl;

R^{3b} is selected from C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} is selected from H and C_1-C_4 alkyl;

R^{4b} is H ;

R^5 is selected from H, C_1-C_4 alkyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is a bond, C_1-C_6 alkylene, or C_1-C_6 haloalkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, CN, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-

$NR^{1a}R^{1b}$, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH and $NR^{3c}R^{3d}$;

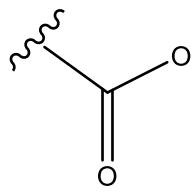
R^{3a} is selected from H and C_1-C_4 alkyl;

R^{3b} is selected from C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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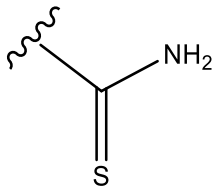

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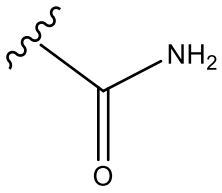

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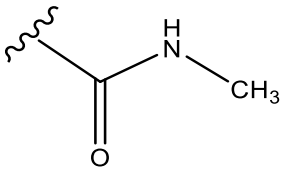


wherein  indicates the point of attachment to the rest of the compound;

R^5 is selected from H and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is a bond, C_1-C_6 alkylene, or C_3-C_6 cycloalkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each

optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy;

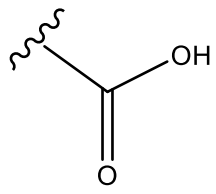
R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl optionally substituted by OH, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 haloalkoxy-C_1-C_4 alkyl,, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl;

R^{3a} is H;

R^{3b} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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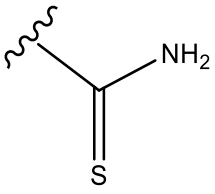

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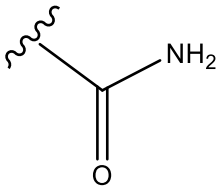


; wherein  indicates the point of attachment to the rest of the compound;

R^5 is H;

R^6 is selected from H and C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is either a bond or C_1-C_6 alkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_8-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy;

R^2 is H;

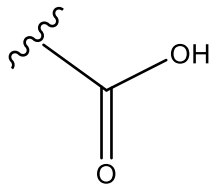
R^3 is selected from $NR^{3a}R^{3b}$, C_1-C_4 alkyl optionally substituted by one or more substituents independently selected from OH and $NR^{3c}R^{3d}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_3-C_8

cycloalkoxy-C_1-C_4 alkyl, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, and alkyl-S-C_1-C_4 alkyl;

R^{3a} is H;

R^{3b} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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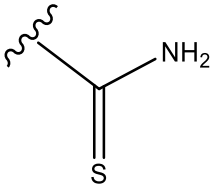

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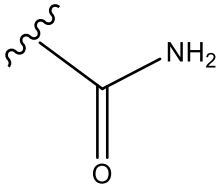


; wherein

indicates the point of attachment to the rest of the compound;

R^5, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H; and

R^6 is selected from H and C_1-C_4 alkyl.

In examples, Q is O.

In examples, L is either a bond or methylene.

In examples, R^1 is selected from:

- C_3-C_8 cycloalkyl optionally substituted by one or more substituents independently selected from halogen and C_1-C_4 haloalkoxy;
- C_8-C_{11} bicyclic cycloalkyl optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl and C_1-C_4 alkoxy;
- 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2;
- 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, optionally substituted by one or more substituents independently selected from halogen;
- phenyl optionally substituted by one or more substituents independently selected from halogen and C_1-C_4 alkyl;
- 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, optionally substituted by one or more substituents independently selected from C_1-C_4 alkyl and C_1-C_4 haloalkyl; and
- 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, optionally substituted substituted by one or more substituents independently selected from halogen and C_1-C_4 alkyl.

In examples, R^2 is H.

In examples, R^3 is selected from:

- $NR^{3a}R^{3b}$;
- C_1-C_4 alkyl optionally substituted by OH;
- C_3-C_8 cycloalkyl;
- 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;
- 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;
- C_1-C_4 alkoxy-C_1-C_4 alkyl;
- C_3-C_8 cycloalkyl-C_1-C_4 alkoxy;
- C_3-C_8 cycloalkoxy-C_1-C_4 alkyl;
- C_1-C_4 haloalkoxy-C_1-C_4 alkyl; and
- C_1-C_4 alkyl-S-C_1-C_4 alkyl;

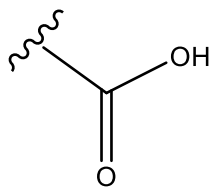
wherein

R^{3a} is H; and

R^{3b} is selected from C_1-C_4 alkyl.

In examples, R^3 is selected from C_1-C_4 alkoxy-C_1-C_4 alkyl.

In examples, R^4 is selected from the following groups:



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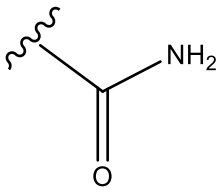

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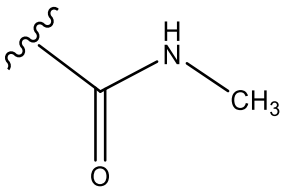

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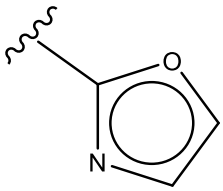

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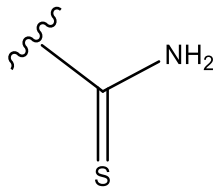


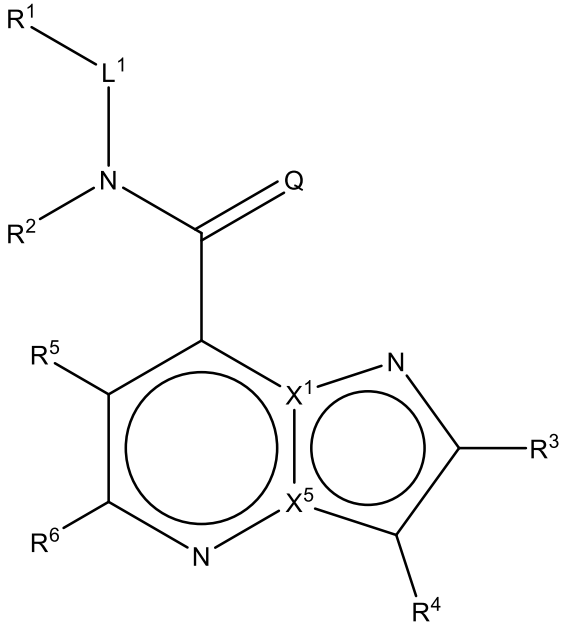
, wherein  indicates the point of attachment to the rest of the compound.

In examples, R^5 is H.

In examples, R^6 is H or methyl.

In examples, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In an example of this disclosure, there is provided a compound of formula (2a):



(2a)

including any stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof, wherein

Q is O or S;

X^1 is selected from C and N;

X^2 is selected from CR^5 and N;

X^3 is selected from CR^6 and N;

X^4 is selected from CR^7 and N;

X^5 is selected from C and N;

wherein X^1, X^2, X^3, X^4 and X^5 are selected so that the ring labelled A is aromatic;

X^6 is selected from CR^8R^9, O and N;

X^7 is selected from CR^{10}, $CR^{11}R^{12}$, O and N;

q is 0 or 1;

wherein when q is 0, X^7 is O or N; and when X^7 is O or N and q is 1, X^6 is CR^8R^9;

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkylene having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O,

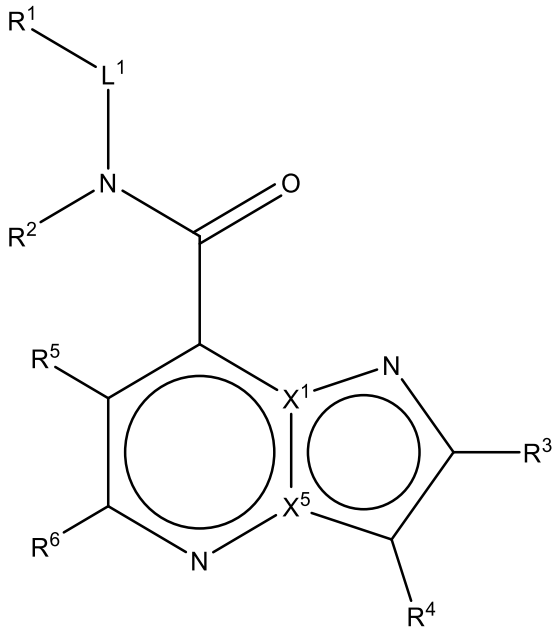
R^{4a} and R^{4b} are each independently selected from H and C_1-C_4 alkyl;

R^5 and R^6 are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S; or

R^5 and R^6 together with the carbon atoms to which they are attached form a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S.

In an aspect of the present disclosure, there is provided a compound of formula (2a):



(2a)

including any stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof, wherein X^1, X^5, L^1, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined as disclosed herein;

wherein one of X^1 and X^5 is C and the other is N.

In examples,

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkylene having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, C_9-C_{10} bicyclic aryl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, phenoxy, and 5- or 6- membered heteroaryloxy having one or more heteroatoms selected from N, O and S, wherein said alkyl, cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, bicyclic aryl, heteroaryl, bicyclic heteroaryl, phenoxy and heteroaryloxy are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, $NR^{1a}R^{1b}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, phenoxy, halophenoxy, 5- or 6- membered heteroaryloxy having one or more heteroatoms selected from N, O and S, and C_1-C_4 alkyl substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is selected from H, C_1-C_4 alkyl and C_3-C_8 cycloakyl;

R^3 is selected from H, OH, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-

C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2- C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, C_1-C_4 alkyl, and $NR^{3c}R^{3d}$;

R^{3a} is selected from H, C_1-C_4 alkyl, C_1-C_4 alkyl-OH, and C_1-C_4 alkyl-$NR^{3e}R^{3f}$;

R^{3b}, R^{3c}, R^{3d}, R^{3e} and R^{3f} are each independently selected from H and C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} and R^{4b} are each independently selected from H and C_1-C_4 alkyl;

R^5 and R^6 are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S; or

R^5 and R^6 together with the carbon atoms to which they are attached form a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S.

In examples,

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkylene having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more S and SO_2.selected from N, O, S and SO_2, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, and phenoxy, wherein said alkyl, cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, bicyclic heteroaryl, and phenoxy are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, $NR^{1a}R^{1b}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl,

halophenoxy, and C_1-C_4 alkyl substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, and $NR^{3c}R^{3d}$;

R^{3a} is selected from H, C_1-C_4 alkyl, and C_1-C_4 alkyl-$NR^{3e}R^{3f}$;

R^{3b} is selected from H and C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^{3e} and R^{3f} are each independently selected from C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} is selected from H and C_1-C_4 alkyl;

R^{4b} is H;

R^5 is selected from H, C_1-C_4 alkyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, or C_3-C_6 cycloalkylene;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more ring members selected from N, O, S and SO_2, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, and phenoxy, wherein said alkyl, cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, bicyclic heteroaryl, and phenoxy are each optionally substituted by one or more substituents independently selected from halogen, CN, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy,

C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, and C_1-C_4 alkyl substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH and $NR^{3c}R^{3d}$;

R^{3a} is selected from H and C_1-C_4 alkyl;

R^{3b} is selected from C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} is selected from H and C_1-C_4 alkyl;

R^{4b} is H ;

R^5 is selected from H, C_1-C_4 alkyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is a bond, C_1-C_6 alkylene, or C_1-C_6 haloalkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, CN, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-

$NR^{1a}R^{1b}$, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH and $NR^{3c}R^{3d}$;

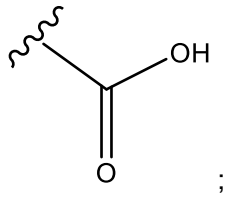
R^{3a} is selected from H and C_1-C_4 alkyl;

R^{3b} is selected from C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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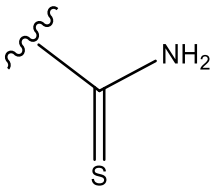

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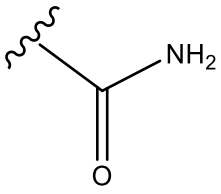

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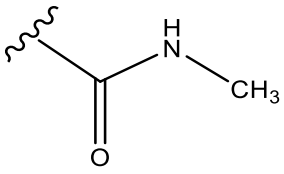


wherein  indicates the point of attachment to the rest of the compound;

R^5 is selected from H and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is a bond, C_1-C_6 alkylene, or C_3-C_6 cycloalkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each

optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy;

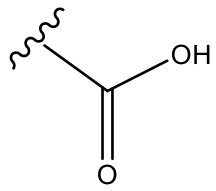
R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl optionally substituted by OH, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 haloalkoxy-C_1-C_4 alkyl,, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl;

R^{3a} is H;

R^{3b} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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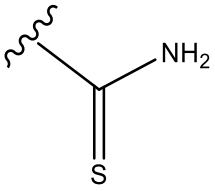

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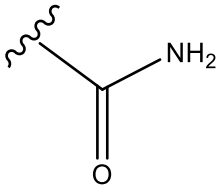


; wherein

indicates the point of attachment to the rest of the compound;

R^5 is H;

R^6 is selected from H and C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is either a bond or C_1-C_6 alkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_8-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy;

R^2 is H;

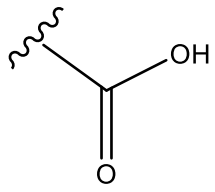
R^3 is selected from $NR^{3a}R^{3b}$, C_1-C_4 alkyl optionally substituted by one or more substituents independently selected from OH and $NR^{3c}R^{3d}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_3-C_8

cycloalkoxy-C_1-C_4 alkyl, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, and alkyl-S-C_1-C_4 alkyl;

R^{3a} is H;

R^{3b} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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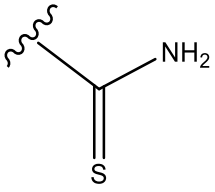

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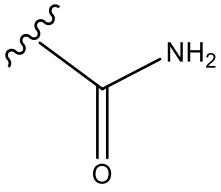


; wherein

indicates the point of attachment to the rest of the compoundR^5, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H; and

R^6 is selected from H and C_1-C_4 alkyl.

In examples, Q is O.

In examples, L is either a bond or methylene.

In examples, R^1 is selected from:

- C_3-C_8 cycloalkyl optionally substituted by one or more substituents independently selected from halogen and C_1-C_4 haloalkoxy;
- C_8-C_{11} bicyclic cycloalkyl optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl and C_1-C_4 alkoxy;
- 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2;
- 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, optionally substituted by one or more substituents independently selected from halogen;
- phenyl optionally substituted by one or more substituents independently selected from halogen and C_1-C_4 alkyl;
- 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, optionally substituted by one or more substituents independently selected from C_1-C_4 alkyl and C_1-C_4 haloalkyl; and
- 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, optionally substituted substituted by one or more substituents independently selected from halogen and C_1-C_4 alkyl.

In examples, R^2 is H.

In examples, R^3 is selected from:

- $NR^{3a}R^{3b}$;
- C_1-C_4 alkyl optionally substituted by OH;
- C_3-C_8 cycloalkyl;
- 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;
- 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;
- C_1-C_4 alkoxy-C_1-C_4 alkyl;
- C_3-C_8 cycloalkyl-C_1-C_4 alkoxy;
- C_3-C_8 cycloalkoxy-C_1-C_4 alkyl;
- C_1-C_4 haloalkoxy-C_1-C_4 alkyl; and
- C_1-C_4 alkyl-S-C_1-C_4 alkyl;

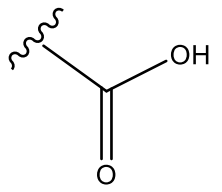
wherein

R^{3a} is H; and

R^{3b} is selected from C_1-C_4 alkyl.

In examples, R^3 is selected from C_1-C_4 alkoxy-C_1-C_4 alkyl.

In examples, R^4 is selected from the following groups:



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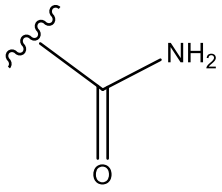

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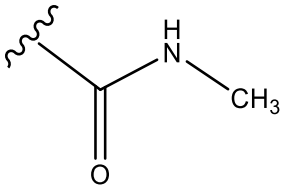

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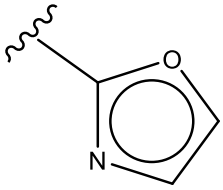

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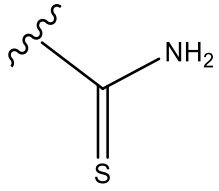


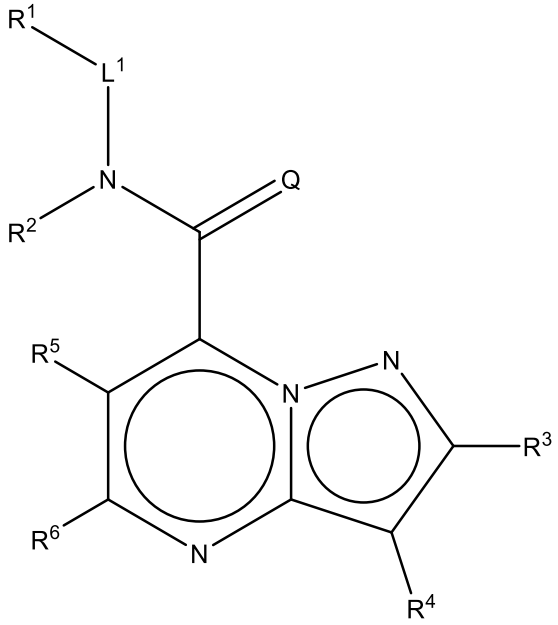
, wherein  indicates the point of attachment to the rest of the compound.

In examples, R^5 is H.

In examples, R^6 is H or methyl.

In examples, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In an example of this disclosure, there is provided a compound of formula (2aa):



(2aa)

including any stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof, wherein

Q is O or S;

X^1 is selected from C and N;

X^2 is selected from CR^5 and N;

X^3 is selected from CR^6 and N;

X^4 is selected from CR^7 and N;

X^5 is selected from C and N;

wherein X^1, X^2, X^3, X^4 and X^5 are selected so that the ring labelled A is aromatic;

X^6 is selected from CR^8R^9, O and N;

X^7 is selected from CR^{10}, $CR^{11}R^{12}$, O and N;

q is 0 or 1;

wherein when q is 0, X^7 is O or N; and when X^7 is O or N and q is 1, X^6 is CR^8R^9;

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkylene having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O,

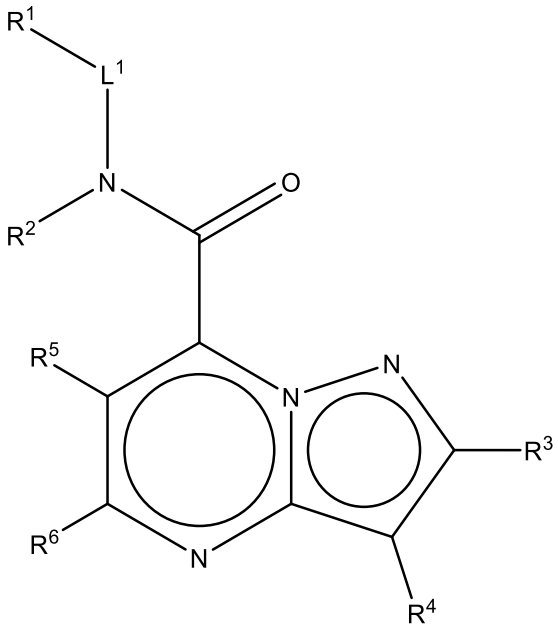
R^{4a} and R^{4b} are each independently selected from H and C_1-C_4 alkyl;

R^5 and R^6 are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S; or

R^5 and R^6 together with the carbon atoms to which they are attached form a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S.

In another aspect of the present disclosure, there is provided a compound of formula (2aa):



(2aa)

including any stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof, wherein L^1, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined herein.

In examples,

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkylene having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, C_9-C_{10} bicyclic aryl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, phenoxy, and 5- or 6- membered heteroaryloxy having one or more heteroatoms selected from N, O and S, wherein said alkyl, cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, bicyclic aryl, heteroaryl, bicyclic heteroaryl, phenoxy and heteroaryloxy are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, $NR^{1a}R^{1b}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, phenoxy, halophenoxy, 5- or 6- membered heteroaryloxy having one or more heteroatoms selected from N, O and S, and C_1-C_4 alkyl substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is selected from H, C_1-C_4 alkyl and C_3-C_8 cycloakyl;

R^3 is selected from H, OH, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-

C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2- C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, C_1-C_4 alkyl, and $NR^{3c}R^{3d}$;

R^{3a} is selected from H, C_1-C_4 alkyl, C_1-C_4 alkyl-OH, and C_1-C_4 alkyl-$NR^{3e}R^{3f}$;

R^{3b}, R^{3c}, R^{3d}, R^{3e} and R^{3f} are each independently selected from H and C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} and R^{4b} are each independently selected from H and C_1-C_4 alkyl;

R^5 and R^6 are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S; or

R^5 and R^6 together with the carbon atoms to which they are attached form a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S.

In examples,

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkylene having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, and phenoxy, wherein said alkyl, cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, bicyclic heteroaryl, and phenoxy are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, $NR^{1a}R^{1b}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, halophenoxy, and C_1-C_4 alkyl

substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, and $NR^{3c}R^{3d}$;

R^{3a} is selected from H, C_1-C_4 alkyl, and C_1-C_4 alkyl-$NR^{3e}R^{3f}$;

R^{3b} is selected from H and C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^{3e} and R^{3f} are each independently selected from C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} is selected from H and C_1-C_4 alkyl;

R^{4b} is H;

R^5 is selected from H, C_1-C_4 alkyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, or C_3-C_6 cycloalkylene;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, and phenoxy, wherein said alkyl, cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, bicyclic heteroaryl, and phenoxy are each optionally substituted by one or more substituents independently selected from halogen, CN, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4

alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, and C_1-C_4 alkyl substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH and $NR^{3c}R^{3d}$;

R^{3a} is selected from H and C_1-C_4 alkyl;

R^{3b} is selected from C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} is selected from H and C_1-C_4 alkyl;

R^{4b} is H ;

R^5 is selected from H, C_1-C_4 alkyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is a bond, C_1-C_6 alkylene, or C_1-C_6 haloalkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, CN, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-

$NR^{1a}R^{1b}$, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH and $NR^{3c}R^{3d}$;

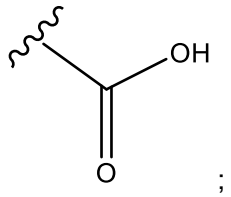
R^{3a} is selected from H and C_1-C_4 alkyl;

R^{3b} is selected from C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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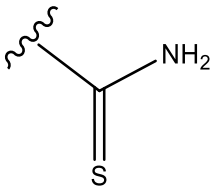

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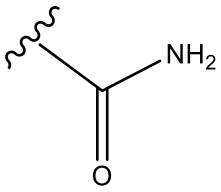

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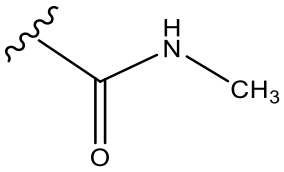


wherein  indicates the point of attachment to the rest of the compound;

R^5 is selected from H and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is a bond, C_1-C_6 alkylene, or C_3-C_6 cycloalkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each

optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy;

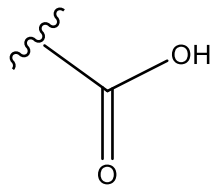
R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl optionally substituted by OH, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 haloalkoxy-C_1-C_4 alkyl,, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl;

R^{3a} is H;

R^{3b} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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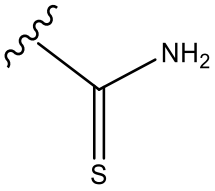
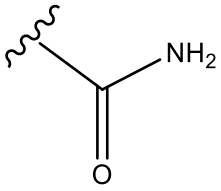


; and


; wherein

indicates the point of attachment to the rest of the compound;

R^5 is H;

R^6 is selected from H and C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is either a bond or C_1-C_6 alkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_8-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy;

R^2 is H;

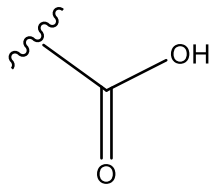
R^3 is selected from $NR^{3a}R^{3b}$, C_1-C_4 alkyl optionally substituted by one or more substituents independently selected from OH and $NR^{3c}R^{3d}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_3-C_8

cycloalkoxy-C_1-C_4 alkyl, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, and alkyl-S-C_1-C_4 alkyl;

R^{3a} is H;

R^{3b} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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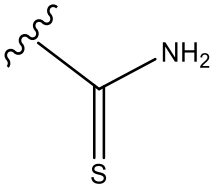

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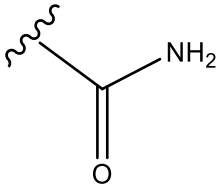


; wherein

indicates the point of attachment to the rest of the compoundR^5, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H; and

R^6 is selected from H and C_1-C_4 alkyl.

In examples, Q is O.

In examples, L is either a bond or methylene.

In examples, R^1 is selected from:

- C_3-C_8 cycloalkyl optionally substituted by one or more substituents independently selected from halogen and C_1-C_4 haloalkoxy;
- C_8-C_{11} bicyclic cycloalkyl optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl and C_1-C_4 alkoxy;
- 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2;
- 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, optionally substituted by one or more substituents independently selected from halogen;
- phenyl optionally substituted by one or more substituents independently selected from halogen and C_1-C_4 alkyl;
- 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, optionally substituted by one or more substituents independently selected from C_1-C_4 alkyl and C_1-C_4 haloalkyl; and
- 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, optionally substituted substituted by one or more substituents independently selected from halogen and C_1-C_4 alkyl.

In examples, R^2 is H.

In examples, R^3 is selected from:

- $NR^{3a}R^{3b}$;
- C_1-C_4 alkyl optionally substituted by OH;
- C_3-C_8 cycloalkyl;
- 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;
- 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;
- C_1-C_4 alkoxy-C_1-C_4 alkyl;
- C_3-C_8 cycloalkyl-C_1-C_4 alkoxy;
- C_3-C_8 cycloalkoxy-C_1-C_4 alkyl;
- C_1-C_4 haloalkoxy-C_1-C_4 alkyl; and
- C_1-C_4 alkyl-S-C_1-C_4 alkyl;

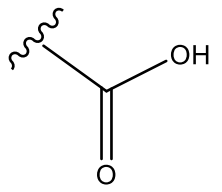
wherein

R^{3a} is H; and

R^{3b} is selected from C_1-C_4 alkyl.

In examples, R^3 is selected from C_1-C_4 alkoxy-C_1-C_4 alkyl.

In examples, R^4 is selected from the following groups:



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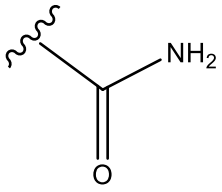

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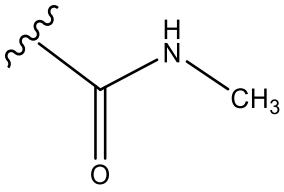

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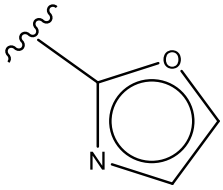

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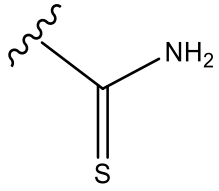


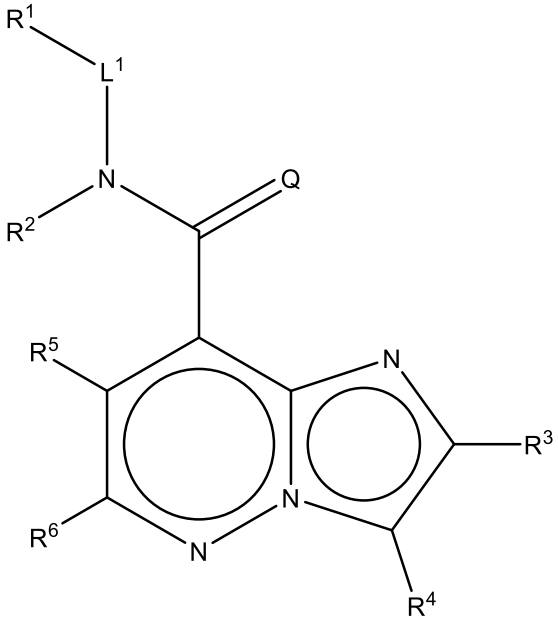
, wherein  indicates the point of attachment to the rest of the compound.

In examples, R^5 is H.

In examples, R^6 is H or methyl.

In examples, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In an example of this disclosure, there is provided a compound of formula (2ab):



(2ab)

including any stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof, wherein

Q is O or S;

X^1 is selected from C and N;

X^2 is selected from CR^5 and N;

X^3 is selected from CR^6 and N;

X^4 is selected from CR^7 and N;

X^5 is selected from C and N;

wherein X^1, X^2, X^3, X^4 and X^5 are selected so that the ring labelled A is aromatic;

X^6 is selected from CR^8R^9, O and N;

X^7 is selected from CR^{10}, $CR^{11}R^{12}$, O and N;

q is 0 or 1;

wherein when q is 0, X^7 is O or N; and when X^7 is O or N and q is 1, X^6 is CR^8R^9;

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkylene having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O,

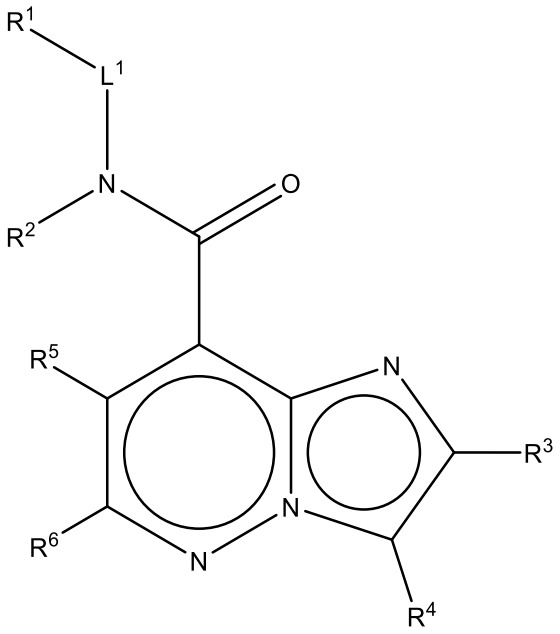
R^{4a} and R^{4b} are each independently selected from H and C_1-C_4 alkyl;

R^5 and R^6 are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S; or

R^5 and R^6 together with the carbon atoms to which they are attached form a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S.

In another aspect of the present disclosure, there is provided a compound of formula (2ab):



(2ab)

including any stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof, wherein L^1, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined herein.

In examples,

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkylene having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, C_9-C_{10} bicyclic aryl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, phenoxy, and 5- or 6- membered heteroaryloxy having one or more heteroatoms selected from N, O and S, wherein said alkyl, cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, bicyclic aryl, heteroaryl, bicyclic heteroaryl, phenoxy and heteroaryloxy are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, $NR^{1a}R^{1b}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, phenoxy, halophenoxy, 5- or 6- membered heteroaryloxy having one or more heteroatoms selected from N, O and S, and C_1-C_4 alkyl substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is selected from H, C_1-C_4 alkyl and C_3-C_8 cycloakyl;

R^3 is selected from H, OH, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-

C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2- C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, C_1-C_4 alkyl, and $NR^{3c}R^{3d}$;

R^{3a} is selected from H, C_1-C_4 alkyl, C_1-C_4 alkyl-OH, and C_1-C_4 alkyl-$NR^{3e}R^{3f}$;

R^{3b}, R^{3c}, R^{3d}, R^{3e} and R^{3f} are each independently selected from H and C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} and R^{4b} are each independently selected from H and C_1-C_4 alkyl;

R^5 and R^6 are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S; or

R^5 and R^6 together with the carbon atoms to which they are attached form a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S.

In examples,

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkylene having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, and phenoxy, wherein said alkyl, cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, bicyclic heteroaryl, and phenoxy are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, $NR^{1a}R^{1b}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, halophenoxy, and C_1-C_4 alkyl

substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, and $NR^{3c}R^{3d}$;

R^{3a} is selected from H, C_1-C_4 alkyl, and C_1-C_4 alkyl-$NR^{3e}R^{3f}$;

R^{3b} is selected from H and C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^{3e} and R^{3f} are each independently selected from C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} is selected from H and C_1-C_4 alkyl;

R^{4b} is H;

R^5 is selected from H, C_1-C_4 alkyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, or C_3-C_6 cycloalkylene;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, and phenoxy, wherein said alkyl, cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, bicyclic heteroaryl, and phenoxy are each optionally substituted by one or more substituents independently selected from halogen, CN, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4

alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, and C_1-C_4 alkyl substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH and $NR^{3c}R^{3d}$;

R^{3a} is selected from H and C_1-C_4 alkyl;

R^{3b} is selected from C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} is selected from H and C_1-C_4 alkyl;

R^{4b} is H ;

R^5 is selected from H, C_1-C_4 alkyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is a bond, C_1-C_6 alkylene, or C_1-C_6 haloalkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, CN, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-

$NR^{1a}R^{1b}$, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH and $NR^{3c}R^{3d}$;

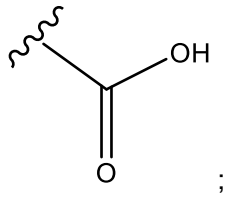
R^{3a} is selected from H and C_1-C_4 alkyl;

R^{3b} is selected from C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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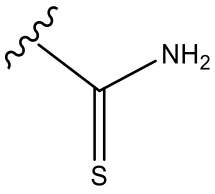

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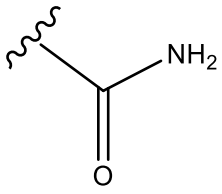

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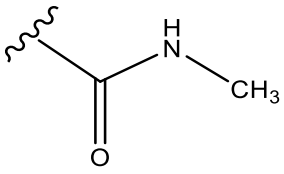


wherein  indicates the point of attachment to the rest of the compound;

R^5 is selected from H and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is a bond, C_1-C_6 alkylene, or C_3-C_6 cycloalkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each

optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy;

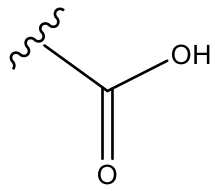
R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl optionally substituted by OH, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 haloalkoxy-C_1-C_4 alkyl,, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl;

R^{3a} is H;

R^{3b} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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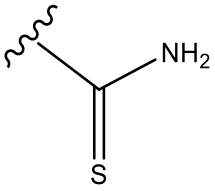

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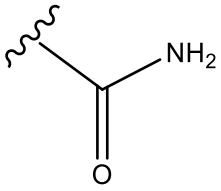


; wherein

indicates the point of attachment to the rest of the compound;

R^5 is H;

R^6 is selected from H and C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is either a bond or C_1-C_6 alkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_8-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy;

R^2 is H;

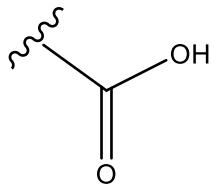
R^3 is selected from $NR^{3a}R^{3b}$, C_1-C_4 alkyl optionally substituted by one or more substituents independently selected from OH and $NR^{3c}R^{3d}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_3-C_8

cycloalkoxy-C_1-C_4 alkyl, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, and alkyl-S-C_1-C_4 alkyl;

R^{3a} is H;

R^{3b} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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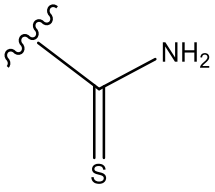

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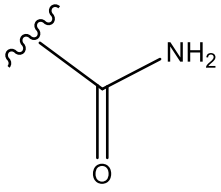


; wherein

indicates the point of attachment to the rest of the compoundR^5, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H; and

R^6 is selected from H and C_1-C_4 alkyl.

In examples, Q is O.

In examples, L is either a bond or methylene.

In examples, R^1 is selected from:

- C_3-C_8 cycloalkyl optionally substituted by one or more substituents independently selected from halogen and C_1-C_4 haloalkoxy;
- C_8-C_{11} bicyclic cycloalkyl optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl and C_1-C_4 alkoxy;
- 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2;
- 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, optionally substituted by one or more substituents independently selected from halogen;
- phenyl optionally substituted by one or more substituents independently selected from halogen and C_1-C_4 alkyl;
- 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, optionally substituted by one or more substituents independently selected from C_1-C_4 alkyl and C_1-C_4 haloalkyl; and
- 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, optionally substituted substituted by one or more substituents independently selected from halogen and C_1-C_4 alkyl.

In examples, R^2 is H.

In examples, R^3 is selected from:

- $NR^{3a}R^{3b}$;
- C_1-C_4 alkyl optionally substituted by OH;
- C_3-C_8 cycloalkyl;
- 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;
- 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;
- C_1-C_4 alkoxy-C_1-C_4 alkyl;
- C_3-C_8 cycloalkyl-C_1-C_4 alkoxy;
- C_3-C_8 cycloalkoxy-C_1-C_4 alkyl;
- C_1-C_4 haloalkoxy-C_1-C_4 alkyl; and
- C_1-C_4 alkyl-S-C_1-C_4 alkyl;

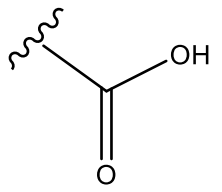
wherein

R^{3a} is H; and

R^{3b} is selected from C_1-C_4 alkyl.

In examples, R^3 is selected from C_1-C_4 alkoxy-C_1-C_4 alkyl.

In examples, R^4 is selected from the following groups:



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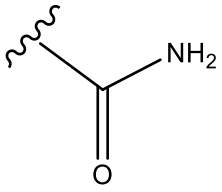

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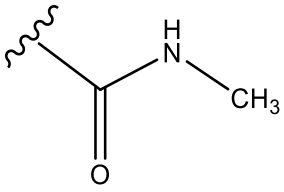

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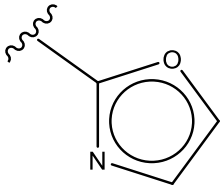

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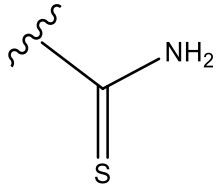


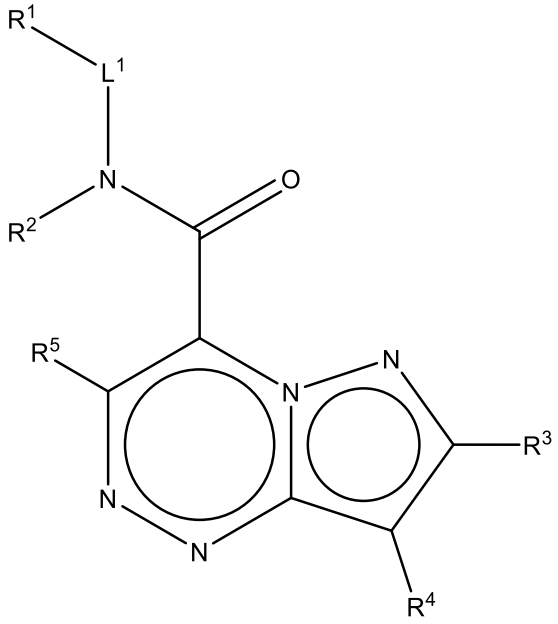
, wherein  indicates the point of attachment to the rest of the compound.

In examples, R^5 is H.

In examples, R^6 is H or methyl.

In examples, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In an example of this disclosure, there is provided a compound of formula (2ad):



(2ad)

including any stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof, wherein

Q is O or S;

X^1 is selected from C and N;

X^2 is selected from CR^5 and N;

X^3 is selected from CR^6 and N;

X^4 is selected from CR^7 and N;

X^5 is selected from C and N;

wherein X^1, X^2, X^3, X^4 and X^5 are selected so that the ring labelled A is aromatic;

X^6 is selected from CR^8R^9, O and N;

X^7 is selected from CR^{10}, $CR^{11}R^{12}$, O and N;

q is 0 or 1;

wherein when q is 0, X^7 is O or N; and when X^7 is O or N and q is 1, X^6 is CR^8R^9;

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkylene having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S;

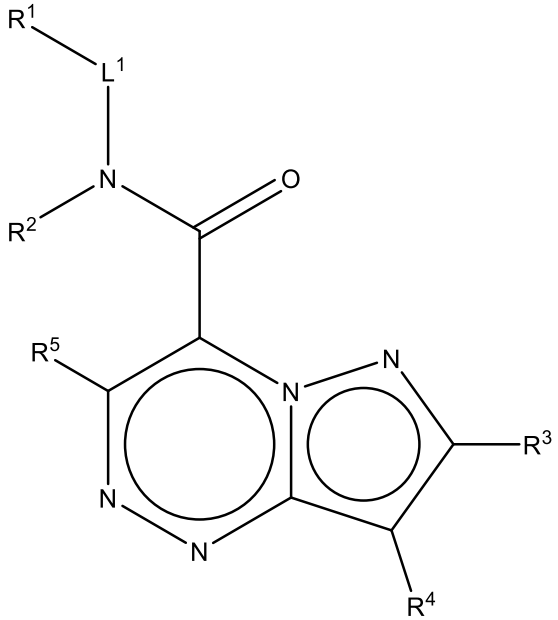
R^{4a} and R^{4b} are each independently selected from H and C_1-C_4 alkyl;

R^5 and R^6 are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S; or

R^5 and R^6 together with the carbon atoms to which they are attached form a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S.

In another aspect of the present disclosure, there is provided a compound of formula (2ad):



(2ad)

Including any stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof, wherein L^1, R^1, R^2, R^3, R^4, and R^5 are as defined herein.

In examples,

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkylene having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, C_9-C_{10} bicyclic aryl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, phenoxy, and 5- or 6- membered heteroaryloxy having one or more heteroatoms selected from N, O and S, wherein said alkyl, cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, bicyclic aryl, heteroaryl, bicyclic heteroaryl, phenoxy and heteroaryloxy are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, $NR^{1a}R^{1b}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, phenoxy, halophenoxy, 5- or 6- membered heteroaryloxy having one or more heteroatoms selected from N, O and S, and C_1-C_4 alkyl substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is selected from H, C_1-C_4 alkyl and C_3-C_8 cycloakyl;

R^3 is selected from H, OH, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2- C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, C_1-C_4 alkyl, and $NR^{3c}R^{3d}$;

R^{3a} is selected from H, C_1-C_4 alkyl, C_1-C_4 alkyl-OH, and C_1-C_4 alkyl-$NR^{3e}R^{3f}$;

R^{3b}, R^{3c}, R^{3d}, R^{3e} and R^{3f} are each independently selected from H and C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} and R^{4b} are each independently selected from H and C_1-C_4 alkyl;

R^5 and R^6 are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S; or

R^5 and R^6 together with the carbon atoms to which they are attached form a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S.

In examples,

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkylene having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, and phenoxy, wherein said alkyl, cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, bicyclic heteroaryl, and phenoxy are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, $NR^{1a}R^{1b}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or

more heteroatoms selected from N, O and S, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, halophenoxy, and C_1-C_4 alkyl substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, and $NR^{3c}R^{3d}$;

R^{3a} is selected from H, C_1-C_4 alkyl, and C_1-C_4 alkyl-$NR^{3e}R^{3f}$;

R^{3b} is selected from H and C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^{3e} and R^{3f} are each independently selected from C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} is selected from H and C_1-C_4 alkyl;

R^{4b} is H;

R^5 is selected from H, C_1-C_4 alkyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, or C_3-C_6 cycloalkylene;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, and phenoxy, wherein said alkyl, cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, bicyclic heteroaryl, and

phenoxy are each optionally substituted by one or more substituents independently selected from halogen, CN, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, and C_1-C_4 alkyl substituted by a 5- or 6- membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH and $NR^{3c}R^{3d}$;

R^{3a} is selected from H and C_1-C_4 alkyl;

R^{3b} is selected from C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} is selected from H and C_1-C_4 alkyl;

R^{4b} is H ;

R^5 is selected from H, C_1-C_4 alkyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is a bond, C_1-C_6 alkylene, or C_1-C_6 haloalkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each optionally substituted by one or more substituents independently selected from

halogen, CN, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH and $NR^{3c}R^{3d}$;

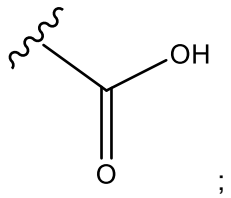
R^{3a} is selected from H and C_1-C_4 alkyl;

R^{3b} is selected from C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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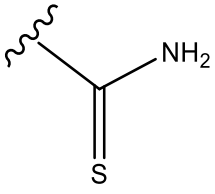

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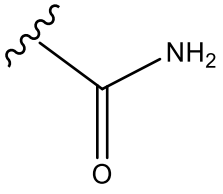

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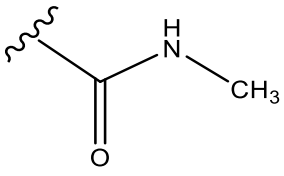


wherein  indicates the point of attachment to the rest of the compound;

R^5 is selected from H and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is a bond, C_1-C_6 alkylene, or C_3-C_6 cycloalkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, heterocycloalkyl, bicyclic

cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy;

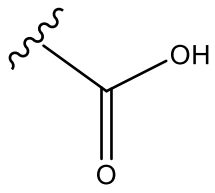
R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl optionally substituted by OH, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 haloalkoxy-C_1-C_4 alkyl,, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl;

R^{3a} is H;

R^{3b} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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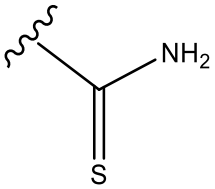

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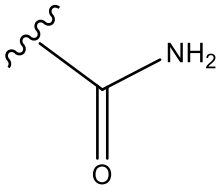


; wherein

indicates the point of attachment to the rest of the compound;

R^5 is H;

R^6 is selected from H and C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In examples,

L^1 is either a bond or C_1-C_6 alkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_8-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy;

R^2 is H;

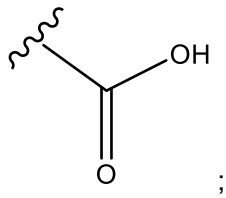
R^3 is selected from $NR^{3a}R^{3b}$, C_1-C_4 alkyl optionally substituted by one or more substituents independently selected from OH and $NR^{3c}R^{3d}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6-

membered heteroaryl having one or more heteroatoms selected from N, O and S, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, and alkyl-S-C_1-C_4 alkyl;

R^{3a} is H;

R^{3b} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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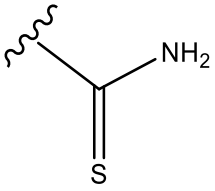

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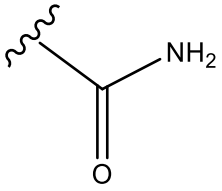


; wherein

indicates the point of attachment to the rest of the compoundR^5, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H; and

R^6 is selected from H and C_1-C_4 alkyl.

In examples, Q is O.

In examples, L is either a bond or methylene.

In examples, R^1 is selected from:

- C_3-C_8 cycloalkyl optionally substituted by one or more substituents independently selected from halogen and C_1-C_4 haloalkoxy;
- C_8-C_{11} bicyclic cycloalkyl optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl and C_1-C_4 alkoxy;
- 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2;
- 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, optionally substituted by one or more substituents independently selected from halogen;
- phenyl optionally substituted by one or more substituents independently selected from halogen and C_1-C_4 alkyl;
- 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, optionally substituted by one or more substituents independently selected from C_1-C_4 alkyl and C_1-C_4 haloalkyl; and
- 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, optionally substituted substituted by one or more substituents independently selected from halogen and C_1-C_4 alkyl.

In examples, R^2 is H.

In examples, R^3 is selected from:

- $NR^{3a}R^{3b}$;
- C_1-C_4 alkyl optionally substituted by OH;
- C_3-C_8 cycloalkyl;
- 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;
- 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;
- C_1-C_4 alkoxy-C_1-C_4 alkyl;
- C_3-C_8 cycloalkyl-C_1-C_4 alkoxy;
- C_3-C_8 cycloalkoxy-C_1-C_4 alkyl;
- C_1-C_4 haloalkoxy-C_1-C_4 alkyl; and
- C_1-C_4 alkyl-S-C_1-C_4 alkyl;

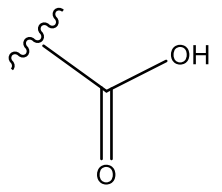
wherein

R^{3a} is H; and

R^{3b} is selected from C_1-C_4 alkyl.

In examples, R^3 is selected from C_1-C_4 alkoxy-C_1-C_4 alkyl.

In examples, R^4 is selected from the following groups:



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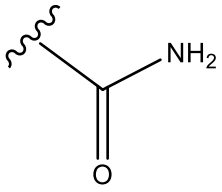

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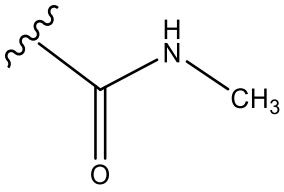

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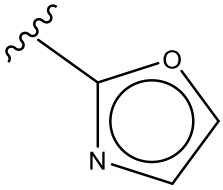

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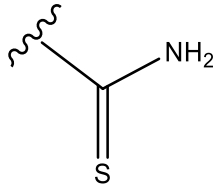


, wherein  indicates the point of attachment to the rest of the compound.

In examples, R^5 is H.

In examples, R^6 is H or methyl.

In examples, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

In another example of this disclosure, there is provided a compound of formula (1) selected from Table 1. In another example there is provided a compound according to any one of compounds 1 to 242, or a stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof;

for example a compound selected from compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, and 242;

for example a compound selected from 1, 2, 4, 5, 6, 7, 8, 9, 11, 14, 15, 18, 19, 20, 21, 22, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, and 242;

for example a compound selected from 1, 2, 4, 5, 6, 9, 14, 18, 21, 22, 25, 26, 27, 29, 30, 32, 33, 34, 35, 36, 37, 39, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 91, 92, 93, 94, 95, 97, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111,

112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, and 242;

for example a compound selected from 1, 2, 4, 6, 21, 26, 27, 33, 34, 37, 42, 43, 44, 46, 48, 53, 54, 55, 56, 57, 58, 59, 60, 61, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 83, 85, 86, 87, 88, 91, 92, 93, 94, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 126, 127, 128, 129, 130, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 189, 190, 191, 192, 193, 194, 195, 196, 198, 199, 200, 201, 202, 203, 204, 205, 206, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, and 242;

for example a compound selected from 27, 33, 34, 37, 46, 54, 56, 57, 58, 59, 60, 61, 64, 66, 68, 70, 72, 73, 74, 75, 79, 80, 82, 83, 85, 87, 88, 91, 92, 93, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 123, 128, 129, 130, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 144, 145, 147, 148, 150, 151, 152, 153, 157, 158, 159, 160, 163, 164, 166, 167, 168, 169, 170, 173, 174, 175, 176, 177, 178, 179, 182, 183, 184, 189, 191, 192, 193, 194, 195, 196, 200, 201, 202, 208, 209, 210, 211, 214, 216, 217, 219, 222, 223, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, and 242.

In another example of this disclosure, there is provided a compound of formula (1) as described above for use in medicine. In another example of this disclosure, there is provided a compound of formula (2aa) as described above for use in medicine. In another example of this disclosure, there is provided a compound of formula (2ab) as described above for use in medicine. In another example of this disclosure, there is provided a compound of formula (2ad) as described above for use in medicine. In another aspect of this disclosure, there is provided a compound as disclosed herein for use in medicine.

In examples, the compound of formula (1), formula (2aa), (2ab), or (2ad) is for use in the treatment or prophylaxis of a cancer or proliferative disease or disorder.

In another aspect of the present disclosure, there is provided use of a compound as disclosed herein in the manufacture of a medicament for the treatment or prophylaxis of a cancer or proliferative disease or disorder. In another aspect of the present disclosure, there is provided use of a compound as disclosed herein in the manufacture of a medicament for the treatment or prophylaxis of fibrotic disease or inflammatory disease.

In examples, the cancer or proliferative disease or disorder is selected from: adrenal gland cancer, anal cancer, angiosarcoma, bladder cancer, blastic plasmacytoid dendritic cell neoplasm, bone cancer, brain cancer, breast cancer, bronchogenic carcinoma, central nervous system (CNS) cancer, cervical cancer, chondrosarcoma, colon cancer, colorectal cancer, cancer of connective tissue, esophageal cancer, embryonal carcinoma, fibrosarcoma, glioblastomas, medulloblastoma, head and neck cancer, hematological cancer, kidney cancer, leukemias (e.g., acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia), myelodysplastic syndrome, liposarcoma, liver cancer, lung cancer, lymphoid cancers (e.g., Hodgkin's and non-Hodgkin's lymphomas), mesothelioma, multiple myeloma, muscular cancer, myxosarcoma, neuroblastomas, ocular cancer, oral/digestive tract cancer, osteogenic sarcoma, ovarian cancer, papillary carcinoma, pancreatic cancer, polycythemia vera, prostate cancer, renal cancer, retinal cancer, skin cancer, small cell lung carcinoma, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, vulvar cancer, gliomas, melanoma, non-small cell lung cancer and acute myeloid leukemia (AML).

In another example of this disclosure, there is provided a pharmaceutical composition comprising a compound of formula (1), formula (2aa), formula (2ab) or formula (2ad) as described above, or a stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof, and at least one pharmaceutically acceptable diluent, excipient or carrier. In another aspect of the present disclosure, there is provided a a pharmaceutical composition as disclosed herein, or a stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof, and at least one pharmaceutically acceptable diluent, excipient or carrier.

In another example of this disclosure, there is provided a pharmaceutical composition comprising a compound of formula (1), formula (2aa), formula (2ab), or formula (2ad) as described above, or a stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof, and at least one pharmaceutically acceptable diluent, excipient or carrier for use for use in medicine. In another aspect of the present disclosure, there is provided a pharmaceutical composition as disclosed herein for use in medicine.

In examples, the pharmaceutical composition comprising a compound of formula (1), formula (2aa), formula (2ab), or formula (2ad) is for use in the treatment or prophylaxis of a cancer or proliferative disease or disorder.

In another aspect of the present disclosure, there is provided use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for the treatment or prophylaxis of a cancer, proliferative disease or disorder, fibrotic disease or inflammatory disease.

In examples, the cancer or proliferative disease or disorder is selected from: adrenal gland cancer, anal cancer, angiosarcoma, bladder cancer, blastic plasmacytoid dendritic cell neoplasm, bone cancer, brain cancer, breast cancer, bronchogenic carcinoma, central nervous system (CNS) cancer, cervical cancer, chondrosarcoma, colon cancer, colorectal cancer, cancer of connective tissue, esophageal cancer, embryonal carcinoma, fibrosarcoma, glioblastomas, medulloblastoma, head and neck cancer, hematological cancer, kidney cancer, leukemias (e.g., acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia), myelodysplastic syndrome, liposarcoma, liver cancer, lung cancer, lymphoid cancers (e.g., Hodgkin's and non-Hodgkin's lymphomas), mesothelioma, multiple myeloma, muscular cancer, myxosarcoma, neuroblastomas, ocular cancer, oral/digestive tract cancer, osteogenic sarcoma, ovarian cancer, papillary carcinoma, pancreatic cancer, polycythemia vera, prostate cancer, renal cancer, retinal cancer, skin cancer, small cell lung carcinoma, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, vulvar cancer, gliomas, melanoma, non-small cell lung cancer and acute myeloid leukemia (AML).

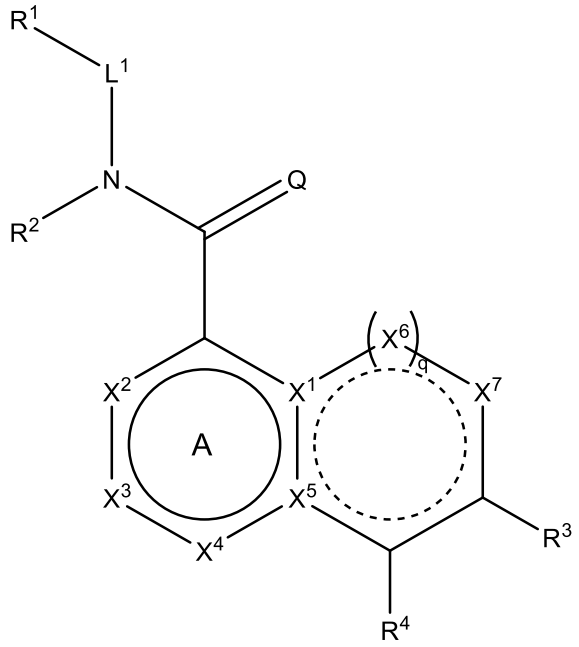
Within the scope of this disclosure it is expressly intended that the various examples, examples, examples and alternatives set out in the preceding paragraphs, in the claims and/or in the following description and drawings, and in particular the individual features thereof, may be taken independently or in any combination. That is, all examples and/or features of any example can be combined in any way and/or combination, unless such features are incompatible. More particularly, it is specifically intended that any example of any example may form an example of any other example, and all such combinations are encompassed within the scope of the disclosure. The applicant reserves the right to change any originally filed claim or file any new claim accordingly, including the right to amend any originally filed claim to depend from and/or incorporate any feature of any other claim although not originally claimed in that manner.

DETAILED DESCRIPTION

Described herein are compounds and compositions (e.g. organic molecules, research tools, pharmaceutical formulations and therapeutics); uses for the compounds and compositions of the disclosure (*in vitro* and *in vivo*); as well as corresponding methods, whether diagnostic,

CLAIMS:

1. A compound of formula (1):



(1)

including any stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof, wherein:

Q is O or S;

X^1 is selected from C and N;

X^2 is selected from CR^5 and N;

X^3 is selected from CR^6 and N;

X^4 is selected from CR^7 and N;

X^5 is selected from C and N;

wherein X^1, X^2, X^3, X^4 and X^5 are selected so that the ring labelled A is aromatic;

X^6 is selected from CR^8R^9, O and N;

X^7 is selected from CR^{10}, $CR^{11}R^{12}$, O and N;

q is 0 or 1;

wherein when q is 0, X^7 is O or N; and when X^7 is O or N and q is 1, X^6 is CR^8R^9;

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O,

S and SO_2, phenyl, C_9-C_{10} bicyclic aryl, 5- or 6- membered heteroaryl having one or more ring members selected from N, O, S and SO_2, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, phenoxy, and 5- or 6- membered heteroaryloxy having one or more heteroatoms selected from N, O and S, wherein said alkyl, cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, bicyclic aryl, heteroaryl, bicyclic heteroaryl, phenoxy and heteroaryloxy are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, $NR^{1a}R^{1b}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, phenoxy, halophenoxy, 5- or 6- membered heteroaryloxy having one or more heteroatoms selected from N, O and S, and C_1-C_4 alkyl substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is selected from H, C_1-C_4 alkyl and C_3-C_8 cycloakyl;

or R^1, R^2 and L^1 and the nitrogen atom to which R^2 and L^1 are attached form a 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 8- to 11-membered bicyclic heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, or 8- to 10-membered bicyclic heteroaryl having one or more heteroatoms selected from N, O and S, wherein said heterocycloalkyl, bicyclic heterocycloalkyl, heteroaryl and bicyclic heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, $NR^{1a}R^{1b}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy and C_1-C_4 alkyl-$NR^{1a}R^{1b}$;

R^3 is selected from H, OH, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2- C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, C_1-C_4 alkyl, and $NR^{3c}R^{3d}$;

R^{3a} is selected from H, C_1-C_4 alkyl, C_1-C_4 alkyl-OH, and C_1-C_4 alkyl-$NR^{3e}R^{3f}$;

R^{3b}, R^{3c}, R^{3d}, R^{3e} and R^{3f} are each independently selected from H and C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} and R^{4b} are each independently selected from H and C_1-C_4 alkyl;

R^5 and R^6 are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S; or R^5 and R^6 together with the carbon atoms to which they are attached form a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S; and R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S.

2. The compound of claim 1, wherein

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, C_9-C_{10} bicyclic aryl, 5- or 6- membered heteroaryl having one or more ring members selected from N, O, S and SO_2, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, phenoxy, and 5- or 6- membered heteroaryloxy having one or more heteroatoms selected from N, O and S, wherein said alkyl, cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, bicyclic aryl, heteroaryl, bicyclic heteroaryl, phenoxy and heteroaryloxy are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, $NR^{1a}R^{1b}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, phenoxy, halophenoxy, 5- or 6- membered heteroaryloxy having one or more heteroatoms selected from N, O and S, and C_1-C_4 alkyl substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is selected from H, C_1-C_4 alkyl and C_3-C_8 cycloakyl;

R^3 is selected from H, OH, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2- C_1-C_4 alkyl, wherein

said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, C_1-C_4 alkyl, and $NR^{3c}R^{3d}$;

R^{3a} is selected from H, C_1-C_4 alkyl, C_1-C_4 alkyl-OH, and C_1-C_4 alkyl-$NR^{3e}R^{3f}$;

R^{3b}, R^{3c}, R^{3d}, R^{3e} and R^{3f} are each independently selected from H and C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} and R^{4b} are each independently selected from H and C_1-C_4 alkyl;

R^5 and R^6 are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S; or

R^5 and R^6 together with the carbon atoms to which they are attached form a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each independently selected from H, halogen, OH, CN, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S.

3. The compound of claim 1 or claim 2, wherein

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, C_3-C_6 cycloalkylene, or a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more ring members selected from N, O, S and SO_2, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, and phenoxy, wherein said alkyl, cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, bicyclic heteroaryl, and phenoxy are each optionally substituted by one or more substituents independently selected from halogen, OH, CN, $NR^{1a}R^{1b}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, halophenoxy, and C_1-C_4 alkyl substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, and $NR^{3c}R^{3d}$;

R^{3a} is selected from H, C_1-C_4 alkyl, and C_1-C_4 alkyl-$NR^{3e}R^{3f}$;

R^{3b} is selected from H and C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^{3e} and R^{3f} are each independently selected from C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} is selected from H and C_1-C_4 alkyl;

R^{4b} is H;

R^5 is selected from H, C_1-C_4 alkyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

4. The compound of any preceding claim, wherein

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, or C_3-C_6 cycloalkylene;

R^1 is selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more ring members selected from N, O, S and SO_2, 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, and phenoxy, wherein said alkyl, cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, bicyclic heteroaryl, and phenoxy are each optionally substituted by one or more substituents independently selected from halogen, CN, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, C_3-C_8 cycloalkyl, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, benzyl, and C_1-C_4 alkyl substituted by a 5- or 6-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH and $NR^{3c}R^{3d}$;

R^{3a} is selected from H and C_1-C_4 alkyl;

R^{3b} is selected from C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^4 is selected from C(O)OH, $C(O)NR^{4a}R^{4b}$, $C(S)NR^{4a}R^{4b}$ and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{4a} is selected from H and C_1-C_4 alkyl;

R^{4b} is H ;

R^5 is selected from H, C_1-C_4 alkyl, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

5. The compound of any preceding claim, wherein

L^1 is a bond, C_1-C_6 alkylene, C_1-C_6 haloalkylene, or C_3-C_6 cycloalkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more ring members selected from N, O, S and SO_2, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, CN, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkyl-$NR^{1a}R^{1b}$, and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^{1a} and R^{1b} are each independently selected from H and C_1-C_4 alkyl;

R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, phenyl, 5- or 6-

membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl, wherein said alkyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH and $NR^{3c}R^{3d}$;

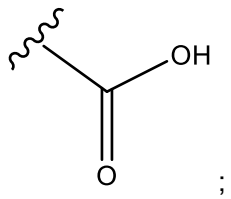
R^{3a} is selected from H and C_1-C_4 alkyl;

R^{3b} is selected from C_1-C_4 alkyl;

R^{3c} is selected from H and C_1-C_4 alkyl;

R^{3d} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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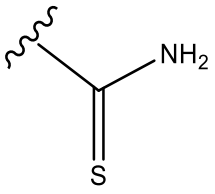

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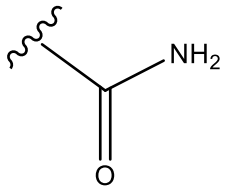

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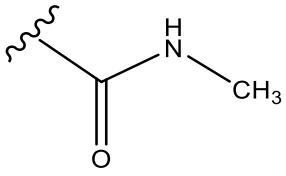


wherein  indicates the point of attachment to the rest of the compound;

R^5 is selected from H and 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;

R^6 is selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkoxy-C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

6. The compound of any preceding claim, wherein

L^1 is a bond, C_1-C_6 alkylene, or C_3-C_6 cycloalkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_7-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more ring members selected from N, O, S and SO_2, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, heterocycloalkyl, bicyclic cycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy;

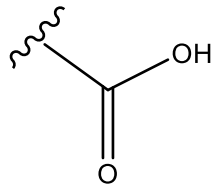
R^2 is H;

R^3 is selected from H, CN, $NR^{3a}R^{3b}$, C_1-C_4 alkyl optionally substituted by OH, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, C_1-C_4 haloalkoxy-C_1-C_4 alkyl,, C_1-C_4 alkyl-S-C_1-C_4 alkyl, and C_1-C_4 alkyl-SO_2-C_1-C_4 alkyl;

R^{3a} is H;

R^{3b} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



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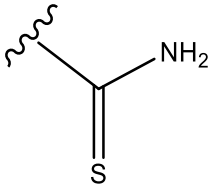

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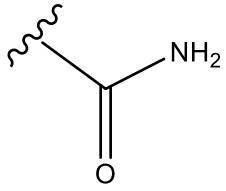


; wherein

indicates the point of attachment to the rest of the compound;

R^5 is H;

R^6 is selected from H and C_1-C_4 alkyl; and

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

7. The compound of any preceding claim, wherein

L^1 is either a bond or C_1-C_6 alkylene;

R^1 is selected from C_3-C_8 cycloalkyl, C_8-C_{11} bicyclic cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, phenyl, 5- or 6- membered heteroaryl having one or more ring members selected from N, O, S and SO_2, and 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, wherein said cycloalkyl, bicyclic cycloalkyl, heterocycloalkyl, bicyclic heterocycloalkyl, phenyl, heteroaryl, and bicyclic heteroaryl are each optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy;

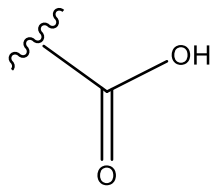
R^2 is H;

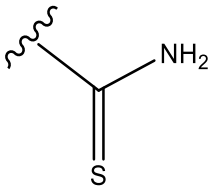
R^3 is selected from $NR^{3a}R^{3b}$, C_1-C_4 alkyl optionally substituted by one or more substituents independently selected from OH and $NR^{3c}R^{3d}$, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S, 5- or 6-membered heteroaryl having one or more heteroatoms selected from N, O and S, C_3-C_8 cycloalkoxy-C_1-C_4 alkyl, C_1-C_4 alkoxy-C_1-C_4 alkyl, C_1-C_4 haloalkoxy-C_1-C_4 alkyl, C_3-C_8 cycloalkyl-C_1-C_4 alkoxy, and alkyl-S-C_1-C_4 alkyl;

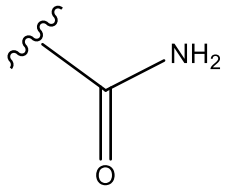
R^{3a} is H;

R^{3b} is selected from C_1-C_4 alkyl;

R^4 is selected from the following groups:



; 

; and 

; wherein  indicates the point of attachment to the rest of the compoundR^5, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H; and

R^6 is selected from H and C_1-C_4 alkyl.

8. The compound of any preceding claim, wherein Q is O.

9. The compound of any preceding claim, wherein L^1 is either a bond or methylene.

10. The compound of any preceding claim, wherein

R^1 is selected from:

- C_3-C_8 cycloalkyl optionally substituted by one or more substituents independently selected from halogen and C_1-C_4 haloalkoxy;
- C_8-C_{11} bicyclic cycloalkyl optionally substituted by one or more substituents independently selected from halogen, OH, C_1-C_4 alkyl and C_1-C_4 alkoxy;
- 3- to 8-membered heterocycloalkyl having one or more ring members selected from N, O, S and SO_2;
- 8- to 11-membered bicyclic heterocycloalkyl having one or more ring members selected from N, O, S and SO_2, optionally substituted by one or more substituents independently selected from halogen;
- phenyl optionally substituted by one or more substituents independently selected from halogen and C_1-C_4 alkyl;
- 5- or 6- membered heteroaryl having one or more ring members selected from N, O, S and SO_2, optionally substituted by one or more substituents independently selected from C_1-C_4 alkyl and C_1-C_4 haloalkyl; and
- 8- to 10-membered bicyclic heteroaryl having one or more ring members selected from N, O, S and SO_2, optionally substituted substituted by one or more substituents independently selected from halogen and C_1-C_4 alkyl.

11. The compound of any preceding claim, wherein

R^2 is H.

12. The compound of any preceding claim, wherein

R^3 is selected from:

- $NR^{3a}R^{3b}$;

- C_1-C_4 alkyl optionally substituted by OH;
- C_3-C_8 cycloalkyl;
- 3- to 8-membered heterocycloalkyl having one or more heteroatoms selected from N, O and S;
- 5- or 6- membered heteroaryl having one or more heteroatoms selected from N, O and S;
- C_1-C_4 alkoxy-C_1-C_4 alkyl;
- C_3-C_8 cycloalkyl-C_1-C_4 alkoxy;
- C_3-C_8 cycloalkoxy-C_1-C_4 alkyl;
- C_1-C_4 haloalkoxy-C_1-C_4 alkyl; and
- C_1-C_4 alkyl-S-C_1-C_4 alkyl;

wherein

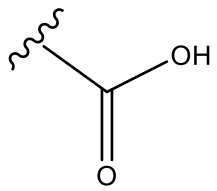
R^{3a} is H; and

R^{3b} is selected from C_1-C_4 alkyl.

13. The compound of any preceding claim, wherein R^3 is selected from C_1-C_4 alkoxy-C_1-C_4 alkyl.

14. The compound of any one of claims 1 to 3 or 8 to 13, wherein

R^4 is selected from the following groups:



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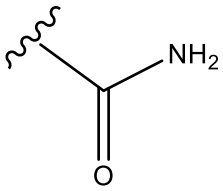

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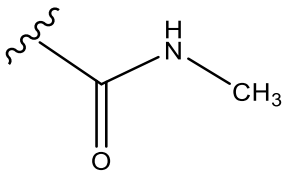

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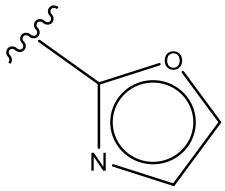

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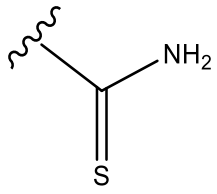


, wherein  indicates the point of attachment to the rest of the compound.

15. A compound of any preceding claim, wherein

R^5 is H.

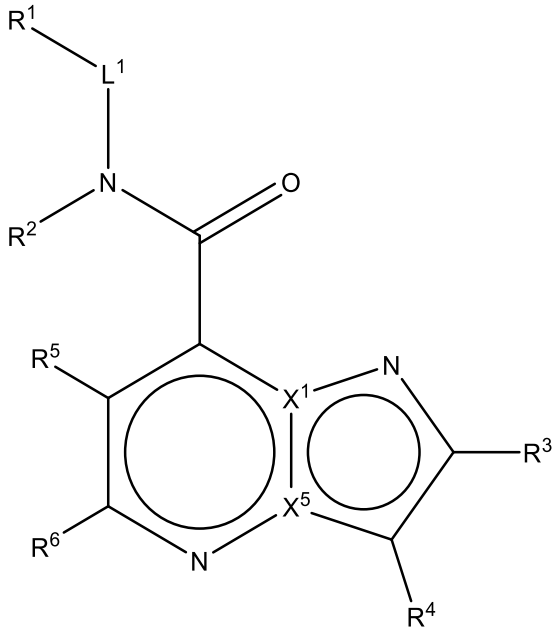
16. The compound of any preceding claim, wherein

R^6 is H or methyl.

17. A compound according to any preceding claim, wherein

R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are each H.

18. A compound of formula (2a):

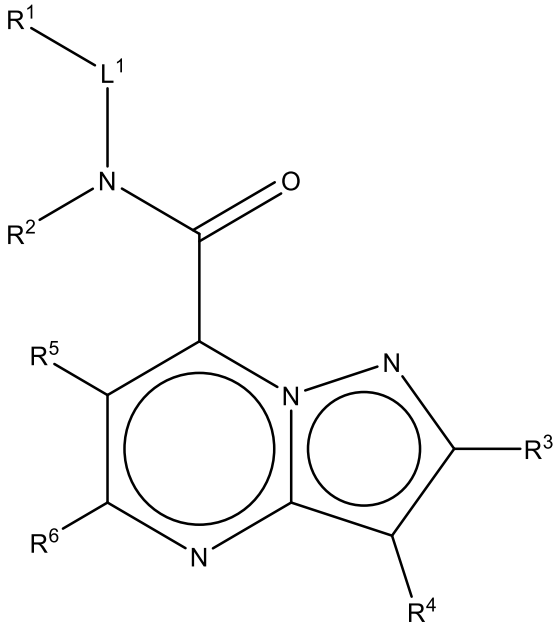


(2a)

including any stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof, wherein X^1, X^5, L^1, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in any one of claims 1 to 16;

wherein one of X^1 and X^5 is C and the other is N.

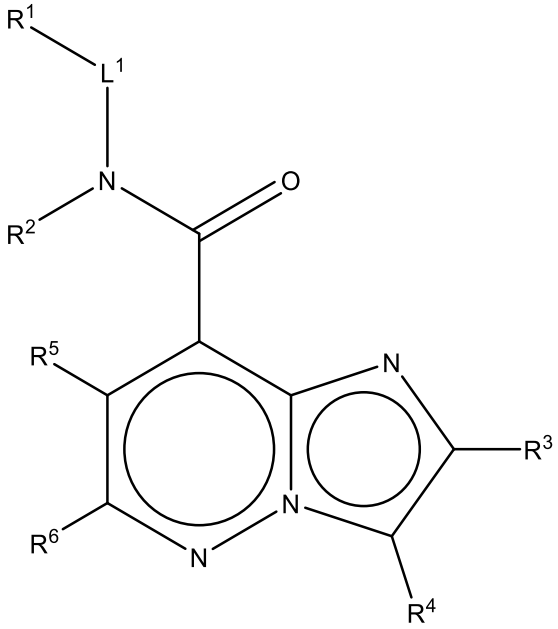
19. A compound of formula (2aa):



(2aa)

including any stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof, wherein L^1, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in any one of claims 1 to 16.

20. A compound of formula (2ab):

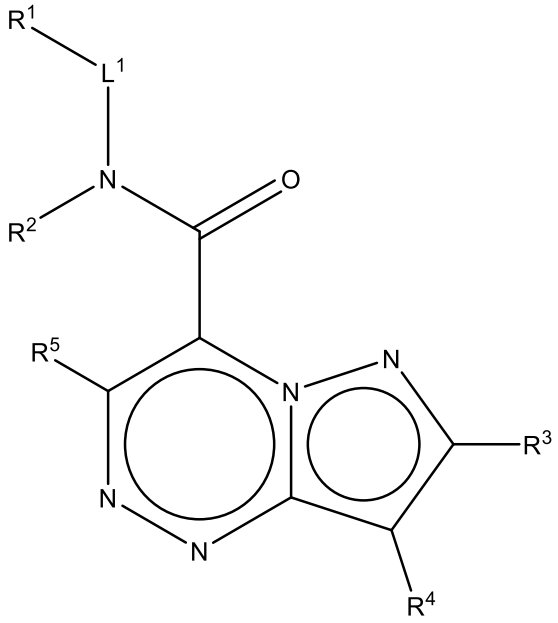


(2ab)

including any stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or

pharmaceutically active metabolite thereof, or combinations thereof, wherein L^1, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in any one of claims 1 to 16.

21. A compound of formula (2ad):



(2ad)

Including any stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or pharmaceutically active metabolite thereof, or combinations thereof, wherein L^1, R^1, R^2, R^3, R^4, and R^5 are as defined in any one of claims 1 to 16.

22. The compound of claim 1, wherein the compound is selected from compounds 1 to 242.

23. The compound of any of claims 1 to 22 for use in medicine.

24. Use of a compound of any of claims 1 to 22 in the manufacture of a medicament for the treatment or prophylaxis of a cancer or proliferative disease or disorder.

25. Use of a compound of any of claims 1 to 22 in the manufacture of a medicament for the treatment or prophylaxis of fibrotic disease or inflammatory disease.

26. A pharmaceutical composition comprising a compound of any of claims 1 to 22, or a stereoisomer or mixture of stereoisomers including diastereomers and enantiomers, tautomer, isotopic form, pharmaceutically acceptable salt, solvate, prodrug, or

pharmaceutically active metabolite thereof, or combinations thereof, and at least one pharmaceutically acceptable diluent, excipient or carrier.

27. The pharmaceutical composition of claim 26 for use in medicine.

28. Use of a pharmaceutical composition of claim 26 in the manufacture of a medicament for the treatment or prophylaxis of a cancer, proliferative disease or disorder, fibrotic disease or inflammatory disease.