microglia and NLRP3 inflammasome pathway activation in the pathogenesis of tauopathies in the Tau22 mouse model of FrontoTemporal Dementia (FTD). Genetic ablation of components of the NLRP3 inflammasome pathway in Tau22 mice reduced Tau aggregation/phosphorylation as well as improved cognition. Stancu *et al.* (*Acta Neuropathol.* 2019; 137(4): 599–617) investigated the role of inflammasome activation in prion-like or templated seeding of Tau pathology. Significant inhibition of exogenously seeded Tau pathology was found in ASC deficient - PS19 Tau transgenic mice. Furthermore, it was demonstrated that chronic intracerebral administration of the NLRP3 inhibitor, MCC950, inhibits exogenously seeded Tau pathology. Finally, ASC deficiency also decreased non-exogenously seeded Tau pathology in PS19 mice.

There is a need to identify and develop specific NLRP3 inflammasome pathway inhibitors and/or modulators of interleukin activity with beneficial pharmacological and/or physiological and/or physicochemical properties.

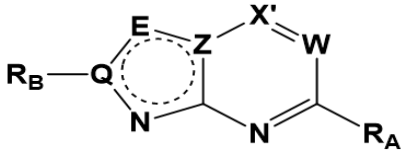
The present invention provides compound of formula (I) which have surprisingly been found to be capable of modulating a component of the NLRP3 inflammasome pathway, in particular inhibiting the activation, of a component of the NLRP3 inflammasome pathway, such as NLRP3 inflammasome. Thus, such compounds are beneficial in the treatment of a disease, disorder, or abnormality which is responsive to the modulation of a component of the NLRP3 inflammasome pathway and/or which is responsive to the modulation of IL-1 beta and/or IL-18 levels that commonly lead to pathological inflammation.

SUMMARY

Accordingly, the present disclosure provides compounds that can be employed in the treatment, alleviation or prevention of a disease, disorder or an abnormality which is responsive to the modulation, in particular inhibition, of a component of the NLRP3 inflammasome pathway, or which is responsive to the modulation, in particular decrease, of IL-1 beta and/or IL-18 levels.

Various examples of the disclosure are described herein.

Within one aspect of the disclosure, provided herein is a compound of formula (I')



(I')

available position with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH, -N$\mathbf{R_5R_6}$ and halo; or

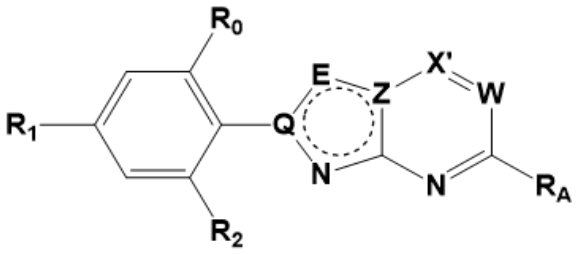
C_3-C_6cycloalkyl optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo; or

C_1-C_6alkyl optionally substituted with one or two substituents independently selected from the group consisting of -OH, halo, haloC_1-C_4alkyl, C_1-C_4alkoxy and -N$\mathbf{R_5R_6}$;

$\mathbf{R_5}$ and $\mathbf{R_6}$ are independently selected from H and C_1-C_3alkyl; and

m is 0, 1 or 2.

Within one aspect of the disclosure, provided herein is a compound having the formula (II')



(II')

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein

X' is selected from CH or N;

W is selected from N, CH or C$\mathbf{R_c}$;

Q is selected from N and C;

E is selected from N$\mathbf{R_a}$ and C$\mathbf{R_a}$;

Z is selected from N and C;

wherein at least one of **Q** and **Z** is C**,** and/or **E** is C$\mathbf{R_a}$;

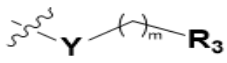
$\mathbf{R_c}$ is selected from the group consisting of C_1-C_4alkyl, -O-C_1-C_4alkyl, C_1-C_4alkyl-OH, halo or haloC_1-C_4alkyl;

$\mathbf{R_a}$ is selected from the group consisting of -H and -C_1-C_3alkyl;

$\mathbf{R_0}$ is selected from the group consisting of -H, C_1-C_3alkyl and halo;

$\mathbf{R_1}$ is selected from the group consisting of -CF_3, -OCF_3, -$OCHF_2$ and halo;

$\mathbf{R_2}$ is selected from the group consisting of -OH, -H and -CF_3;

$\mathbf{R_A}$ is 

;

Y is selected from NH, N$\mathbf{R_d}$, O or is a bond;

$\mathbf{R_d}$ is selected from the group consisting of -C_1-C_4alkyl, -C_1-C_4alkyl-OH or -C_1-C_4alkyl-Hal;

$\mathbf{R_3}$ is selected from the group consisting of

R_0 is selected from the group consisting of -H, C_1-C_3alkyl and halo;

R_1 is selected from the group consisting of -CF_3, -OCF_3, -$OCHF_2$ and halo;

R_2 is selected from the group consisting of -OH, -H and -CF_3;

Y is selected from NH and O; and

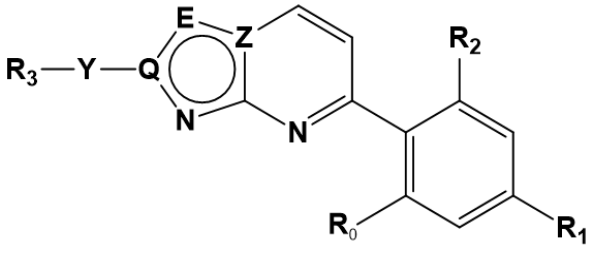
R_3 is selected from the group consisting of

4-, 5- or 6-membered heterocycloalkyl containing one or two heteroatoms, preferably one heteroatom, wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo;

C_3-C_6cycloalkyl optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo; and

C_1-C_6alkyl optionally substituted with one or two substituents independently selected from the group consisting of -OH, halo, haloC_1-C_4alkyl, C_1-C_4alkoxy and -N**R_5R_6**, wherein **R_5** and **R_6** are independently selected from H and C_1-C_3alkyl.

In another example there is provided a compound of formula (III)



(III)

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein

Q is selected from N and C;

E is selected from N**R_a** and C**R_a;**

Z is selected from N and C;

wherein at least one of **Q** and **Z** is C**,** and/or **E** is C**R_a**;

R_a is selected from the group consisting of -H and -C_1-C_3alkyl;

R_0 is selected from the group consisting of -H, C_1-C_3alkyl and halo;

R_1 is selected from the group consisting of -CF_3, -OCF_3, -$OCHF_2$ and halo;

R_2 is selected from the group consisting of -OH, -H and -CF_3;

Y is selected from NH and O; and

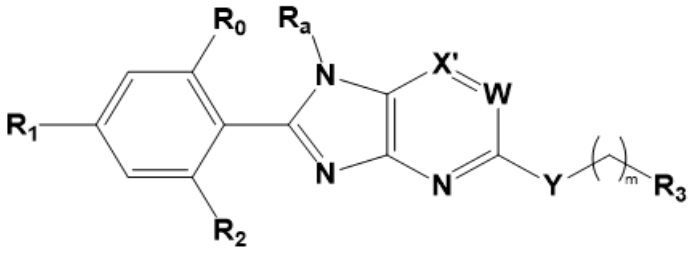
R_3 is selected from the group consisting of

4-, 5- or 6-membered heterocycloalkyl containing one or two heteroatoms, preferably one heteroatom, wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo;

C_3-C_6cycloalkyl optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo; and

C_1-C_6alkyl optionally substituted with one or two substituents independently selected from the group consisting of -OH, halo, haloC_1-C_4alkyl, C_1-C_4alkoxy and -N$\mathbf{R_5R_6}$, wherein $\mathbf{R_5}$ and $\mathbf{R_6}$ are independently selected from H and C_1-C_3alkyl.

In another example there is provided a compound of formula (II'a)



(II'a)

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein

X' is selected from CH or N;

W is selected from N, CH or C$\mathbf{R_c}$;

$\mathbf{R_c}$ is selected from the group consisting of C_1-C_4alkyl, -O-C_1-C_4alkyl, C_1-C_4alkyl-OH, halo or haloC_1-C_4alkyl;

$\mathbf{R_a}$ is selected from the group consisting of -H and -C_1-C_3alkyl;

$\mathbf{R_0}$ is selected from the group consisting of -H, C_1-C_3alkyl and halo;

$\mathbf{R_1}$ is selected from the group consisting of -CF_3, -OCF_3, -$OCHF_2$ and halo;

$\mathbf{R_2}$ is selected from the group consisting of -OH, -H and -CF_3;

Y is selected from NH, N$\mathbf{R_d}$, O or is a bond;

$\mathbf{R_d}$ is selected from the group consisting of -C_1-C_4alkyl, -C_1-C_4alkyl-OH, or -C_1-C_4alkyl-Hal;

$\mathbf{R_3}$ is selected from the group consisting of

4-, 5- or 6-membered heterocycloalkyl containing one or two heteroatoms, preferably one heteroatom, wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH; -N$\mathbf{R_5R_6}$ and halo; or

8-, 9- or 10-membered bicyclic fused heterocycloalkyl containing one to three heteroatoms, wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted at any available position with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH, -N$\mathbf{R_5R_6}$ and halo; or

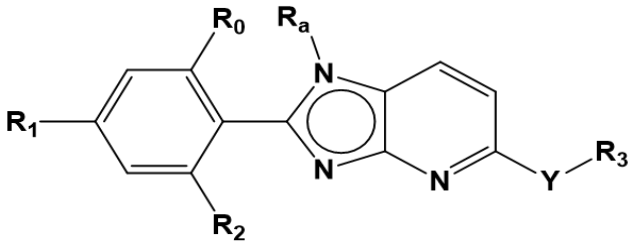
C_3-C_6cycloalkyl optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo; or

C_1-C_6alkyl optionally substituted with one or two substituents independently selected from the group consisting of -OH, halo, haloC_1-C_4alkyl, C_1-C_4alkoxy and -N$\mathbf{R_5R_6}$;

$\mathbf{R_5}$ and $\mathbf{R_6}$ are independently selected from H and C_1-C_3alkyl; and

m is 0, 1 or 2.

In another example there is provided a compound of formula (IIa)



(IIa)

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein

$\mathbf{R_a}$ is selected from the group consisting of -H and -C_1-C_3alkyl;

$\mathbf{R_0}$ is selected from the group consisting of -H, C_1-C_3alkyl and halo;

$\mathbf{R_1}$ is selected from the group consisting of -CF_3, -OCF_3, -$OCHF_2$ and halo;

$\mathbf{R_2}$ is selected from the group consisting of -OH, -H and -CF_3;

Y is selected from NH and O; and

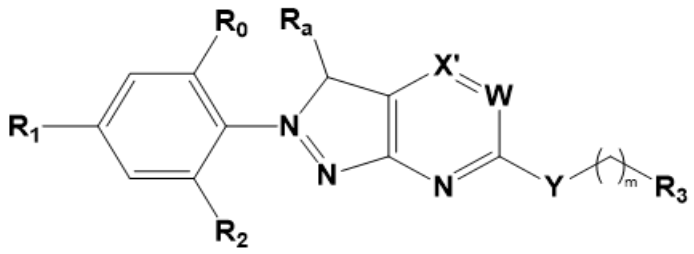
$\mathbf{R_3}$ is selected from the group consisting of

4-, 5- or 6-membered heterocycloalkyl containing one or two heteroatoms, preferably one heteroatom, wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo;

C_3-C_6cycloalkyl optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo; and

C_1-C_6alkyl optionally substituted with one or two substituents independently selected from the group consisting of -OH, halo, haloC_1-C_4alkyl, C_1-C_4alkoxy and -N$\mathbf{R_5R_6}$, wherein $\mathbf{R_5}$ and $\mathbf{R_6}$ are independently selected from H and C_1-C_3alkyl.

In another example there is provided a compound of formula (II'b)



(II'b)

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein

X' is selected from CH or N;

W is selected from N, CH or **CR_c**;

R_c is selected from the group consisting of -C_1-C_4alkyl, -O-C_1-C_4alkyl, -C_1-C_4alkyl-OH, -halo or C_1-C_4alkyl-Hal;

R_a is selected from the group consisting of -H and -C_1-C_3alkyl;

R_0 is selected from the group consisting of -H, C_1-C_3alkyl and halo;

R_1 is selected from the group consisting of -CF_3, -OCF_3, -$OCHF_2$ and halo;

R_2 is selected from the group consisting of -OH, -H and -CF_3;

Y is selected from NH, N**R_d**, O or is a bond;

R_d is selected from the group consisting of -C_1-C_4alkyl, -C_1-C_4alkyl-OH, or -C_1-C_4alkyl-Hal;

R_3 is selected from the group consisting of

4-, 5- or 6-membered heterocycloalkyl containing one or two heteroatoms, wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH; -N**R_5R_6** and halo; or

8-, 9- or 10-membered bicyclic fused heterocycloalkyl containing one to three heteroatoms, wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted at any available position with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH, -N**R_5R_6** and halo; or

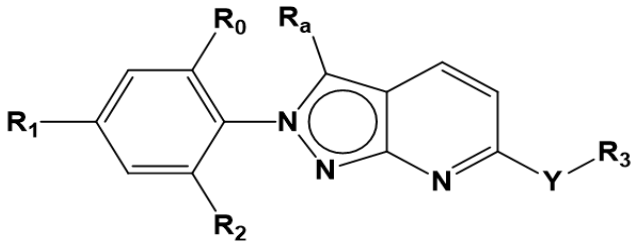
C_3-C_6cycloalkyl optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo; or

C_1-C_6alkyl optionally substituted with one or two substituents independently selected from the group consisting of -OH, halo, haloC_1-C_4alkyl, C_1-C_4alkoxy and -N**R_5R_6**;

R_5 and **R_6** are independently selected from H and C_1-C_3alkyl;

m is 0, 1 or 2.

In another example there is provided a compound of formula (IIb)



(IIb)

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein

R_a is selected from the group consisting of -H and -C_1-C_3alkyl;

R_0 is selected from the group consisting of -H, C_1-C_3alkyl and halo;

R_1 is selected from the group consisting of -CF_3, -OCF_3, -$OCHF_2$ and halo;

R_2 is selected from the group consisting of -OH, -H and -CF_3;

Y is selected from NH and O; and

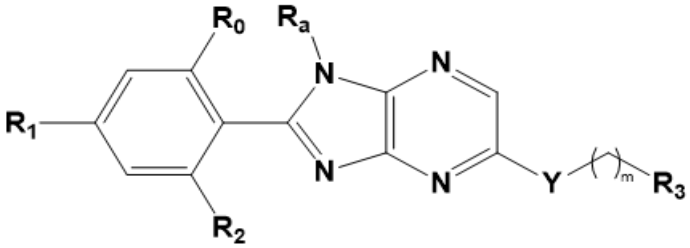
R_3 is selected from the group consisting of

4-, 5- or 6-membered heterocycloalkyl containing one or two heteroatoms, preferably one heteroatom, wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo;

C_3-C_6cycloalkyl optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo; and

C_1-C_6alkyl optionally substituted with one or two substituents independently selected from the group consisting of -OH, halo, haloC_1-C_4alkyl, C_1-C_4alkoxy and -N**R_5R_6**, wherein **R_5** and **R_6** are independently selected from H and C_1-C_3alkyl.

In another example there is provided a compound of formula (IV)



(IV)

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof; wherein

R_a is selected from the group consisting of -H and -C_1-C_3alkyl;

R_0 is selected from the group consisting of -H, C_1-C_3alkyl and halo;

R_1 is selected from the group consisting of -CF_3, -OCF_3, -$OCHF_2$ and halo;

R_2 is selected from the group consisting of -OH, -H and -CF_3;

Y is selected from NH, N**R_d**, O or is a bond;

R_d is selected from the group consisting of -C_1-C_4alkyl, -C_1-C_4alkyl-OH, or -C_1-C_4alkyl-Hal;

R_3 is selected from the group consisting of

4-, 5- or 6-membered heterocycloalkyl containing one or two heteroatoms, wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH; -N**R_5****R_6** and halo; or

8-, 9- or 10-membered bicyclic fused heterocycloalkyl containing one to three heteroatoms, wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted at any available position with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH, -N**R_5****R_6** and halo; or

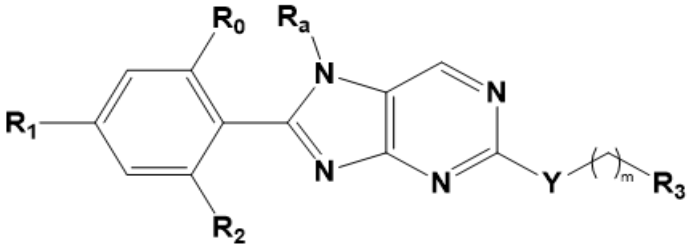
C_3-C_6cycloalkyl optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo; or

C_1-C_6alkyl optionally substituted with one or two substituents independently selected from the group consisting of -OH, halo, haloC_1-C_4alkyl, C_1-C_4alkoxy and -N**R_5****R_6**;

R_5 and **R_6** are independently selected from H and C_1-C_3alkyl;

m is 0, 1 or 2.

In another example there is provided a compound of formula (V)



(V)

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein

R_a is selected from the group consisting of -H and -C_1-C_3alkyl;

R_0 is selected from the group consisting of -H, C_1-C_3alkyl and halo;

R_1 is selected from the group consisting of -CF_3, -OCF_3, -$OCHF_2$ and halo;

R_2 is selected from the group consisting of -OH, -H and -CF_3;

Y is selected from NH, N**R_d**, O or is a bond;

R_d is selected from the group consisting of -C_1-C_4alkyl, -C_1-C_4alkyl-OH, or -C_1-C_4alkyl-Hal;

R_3 is selected from the group consisting of

4-, 5- or 6-membered heterocycloalkyl containing one or two heteroatoms, wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH; -N**R_5R_6** and halo; or

8-, 9- or 10-membered bicyclic fused heterocycloalkyl containing one to three heteroatoms, wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted at any available position with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH, -N**R_5R_6** and halo; or

C_3-C_6cycloalkyl optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo; or

C_1-C_6alkyl optionally substituted with one or two substituents independently selected from the group consisting of -OH, halo, haloC_1-C_4alkyl, C_1-C_4alkoxy and -N**R_5R_6**;

R_5 and **R_6** are independently selected from H and C_1-C_3alkyl;

m is 0, 1 or 2.

Within the present disclosure any reference to the compounds of formula (I'), (I), (II'), (II), (II'a), (II'b), (IIa), (IIb), (III'), (III), (IV) or (V), or the preferred examples thereof is intended to also refer to the stereoisomers, or racemic mixtures, or tautomers, or polymorphs, or pharmaceutically acceptable salts, or prodrugs, or hydrates, or solvates thereof.

Compounds of formula (I'), (I), (II'), (II), (II'a), (II'b), (IIa), (IIb), (III'), (III), (IV) or (V), or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, are suitable for the treatment, alleviation or prevention of a disease, disorder or an abnormality which is responsive to the modulation, in particular inhibition, of a component of the NLRP3 inflammasome pathway, or which is responsive to the modulation, in particular decrease, of IL-1 beta and/or IL-18 levels. In particular, the component of the inflammasome pathway is the NLRP3 inflammasome. Activation of the NLRP3 inflammasome pathway can trigger the formation of ASC specks, cleavage and activation of Caspase-1 and Caspase-8 and subsequent activation and release IL-1 beta, IL-18, gasdermin D cleavage and pore formation, pyroptosis, and release of IL-1alpha, IL-33, IL-17 and High-Mobility Group Box (HMGB) protein. The compounds of formula (I'), (I), (II'), (II), (II'a), (II'b), (IIa), (IIb), (III'), (III), (IV) or (V), or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, have the capability to modulate, in particular decrease, IL-1 beta and/or IL-18 levels.

The compounds of formula (I'), (I), (II'), (II), (II'a), (II'b), (IIa), (IIb), (III'), (III), (IV) or (V), or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, display high capability in modulating and, in particular inhibiting the activation of, a component of the NLRP3 inflammasome pathway, in particular wherein the component of the inflammasome pathway is the NLRP3 inflammasome. Due to their unique design features, these compounds display properties such as modulating or inhibiting the activation of the NLRP3 inflammasome pathway allowing them to be a successful medicament for the treatment, alleviation or prevention of diseases, disorders and abnormalities responsive to the modulation or inhibition of a component of the NLRP3 inflammasome pathway such as, for example, Alzheimer's disease, Parkinson's disease, CAPS, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) and gout.

In a further aspect, the present disclosure provides for a pharmaceutical composition comprising a compound as disclosed herein, or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, and optionally comprising at least one pharmaceutically acceptable carrier, diluent, adjuvant or excipient. In a further example, the disclosure relates to a pharmaceutical composition comprising a compound of formula (I'), (I), (II'), (II), (II'a), (II'b), (IIa), (IIb), (III'), (III), (IV) or (V), or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, and optionally comprising at least one pharmaceutically acceptable carrier, diluent, adjuvant or excipient.

In another example, the present disclosure refers to a compound of formula (I'), (I), (II'), (II), (II'a), (II'b), (IIa), (IIb), (III'), (III), (IV) or (V), or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, for use as a medicament.

In yet another aspect, the present disclosure provides for a use of the compound as disclosed herein, or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, in the manufacture of a medicament for the treatment, alleviation or prevention of a disease, or a disorder or an abnormality which is responsive to the modulation of a component of the NLRP3 inflammasome pathway and/or which is responsive to the modulation of IL-1 beta and/or IL-18 levels. Yet another example, the present disclosure refers to a compound of formula (I'), (I), (II'), (II), (II'a), (II'b), (IIa), (IIb), (III'), (III), (IV) or (V), or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically

acceptable salt, a prodrug, a hydrate, or a solvate thereof, for use in the treatment, alleviation or prevention of a disease, disorder, or abnormality which is responsive to the modulation, in particular inhibition of activation, of a component of the NLRP3 inflammasome pathway and/or which is responsive to the modulation, in particular decrease, of IL-1 beta and/or IL-18 levels.

A further example is concerned with the use of the compound of formula (I'), (I), (II'), (II), (II'a), (II'b), (IIa), (IIb), (III'), (III), (IV) or (V), or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, for the manufacture of a medicament for treating, alleviating or preventing a disease, disorder or abnormality which is responsive to the modulation, in particular inhibition of activation, of a component of the NLRP3

inflammasome pathway and/or which is responsive to the modulation, in particular decrease, of IL-1 beta and/or IL-18 levels.

In yet another example, the present disclosure is directed to a method of treating, alleviating or preventing a disease, disorder or abnormality which is responsive to the modulation, in particular inhibition of activation, of a component of the NLRP3 inflammasome pathway or which is responsive to the modulation, in particular decrease, of IL-1 beta and/or IL-18 levels, the method comprising administering a therapeutically effective amount of a compound of formula (I'), (I), (II'), (II), (II'a), (II'b), (IIa), (IIb), (III'), (III), (IV) or (V), or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, to a subject in need thereof (e.g. a patient).

A pharmaceutical composition comprising a combination of a compound of formula (I'), (I), (II'), (II), (II'a), (II'b), (IIa), (IIb), (III'), (III), (IV) or (V), or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, and at least one further biologically active compound differing from the compound of formula (I'), (I), (II'), (II), (II'a), (II'b), (IIa), (IIb), (III'), (III), (IV) or (V), or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, and optionally comprising at least one pharmaceutically acceptable carrier, diluent, adjuvant or excipient, is also the subject-matter of the present disclosure.

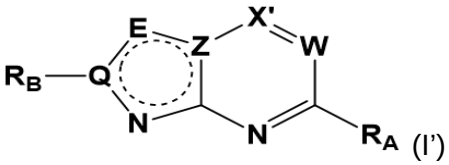
In particular, the further biologically active compound can be one which is used for the treatment of a disease, disorder, or abnormality associated with a disease targeting different pathomechanism, e.g. an anti-amyloid beta antibody, anti-Tau antibody, amyloid beta small molecule inhibitor, Tau aggregation small molecule inhibitor, anti-alpha synuclein antibody or alpha-synuclein aggregation small molecule inhibitor, anti-TDP-43 antibody or anti-TDP-43 aggregation small molecule inhibitor, among others. When a compound of the disclosure is used in combination with a further biologically active compound, the dose of each compound may differ from the dose if the compound is used as monotherapy.

In a further aspect, the present disclosure provides for a use of a compound as disclosed herein, or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, as an analytical reference or an *in vitro* screening tool. An additional example relates to the use of the compound of formula (I'), (I), (II'), (II), (II'a), (II'b), (IIa), (IIb), (III'), (III), (IV) or (V), or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, as an analytical reference or an *in vitro* screening tool.

The present disclosure is described hereinafter.

CLAIMS

1. A compound having the formula (I')



(I')

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein

X' is selected from CH or N;

W is selected from N, CH or **CR_c**;

Q is selected from N and C;

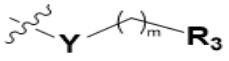
E is selected from **NR_a** and **CR_a**;

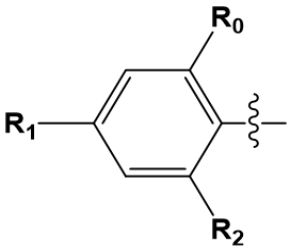
Z is selected from N and C;

wherein at least one of **Q** and **Z** is C**,** and/or **E** is **CR_a**;

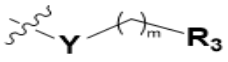
R_c is selected from the group consisting of -C_1-C_4alkyl, -O-C_1-C_4alkyl, -C_1-C_4alkyl-OH, -halo or -C_1-C_4alkyl-Hal;

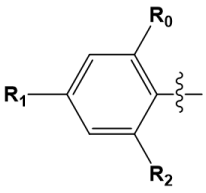
R_a is selected from the group consisting of -H and -C_1-C_3alkyl;

R_A and **R_B** are each selected from 

and 

,

wherein one of **R_A** and **R_B** is 

and the other of **R_A** and **R_B** is 

;

R_0 is selected from the group consisting of -H, C_1-C_3alkyl and halo;

R_1 is selected from the group consisting of -CF_3, -OCF_3, -$OCHF_2$ and halo;

R_2 is selected from the group consisting of -OH, -H and -CF_3;

Y is selected from NH, **NR_d**, O or is a bond;

R_d is selected from the group consisting of -C_1-C_4alkyl, -C_1-C_4alkyl-OH, or -C_1-C_4alkyl-Hal;

R_3 is selected from the group consisting of

4-, 5- or 6-membered heterocycloalkyl containing one or two heteroatoms, wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH; -N$\mathbf{R_5R_6}$ and halo; or

8-, 9- or 10-membered bicyclic fused heterocycloalkyl containing one to three heteroatoms wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted at any available position with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH, -N$\mathbf{R_5R_6}$ and halo; or

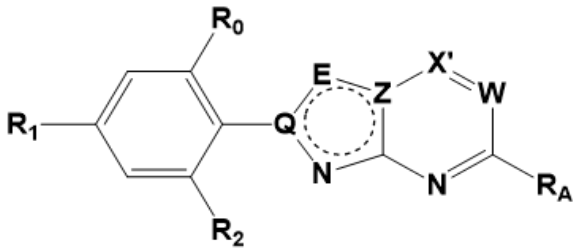
C_3-C_6cycloalkyl optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo; or

C_1-C_6alkyl optionally substituted with one or two substituents independently selected from the group consisting of -OH, halo, haloC_1-C_4alkyl, C_1-C_4alkoxy and -N$\mathbf{R_5R_6}$;

$\mathbf{R_5}$ and $\mathbf{R_6}$ are independently selected from H and C_1-C_3alkyl; and

m is 0, 1 or 2.

2. A compound according to claim 1 having the formula (II')



(II')

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein

X' is selected from CH or N;

W is selected from N, CH or C$\mathbf{R_c}$;

Q is selected from N and C;

E is selected from N$\mathbf{R_a}$ and C$\mathbf{R_a}$;

Z is selected from N and C;

wherein at least one of **Q** and **Z** is C**,** and/or **E** is C$\mathbf{R_a}$;

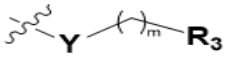
$\mathbf{R_c}$ is selected from the group consisting of C_1-C_4alkyl, -O-C_1-C_4alkyl, C_1-C_4alkyl-OH, halo or haloC_1-C_4alkyl;

$\mathbf{R_a}$ is selected from the group consisting of -H and -C_1-C_3alkyl;

$\mathbf{R_0}$ is selected from the group consisting of -H, C_1-C_3alkyl and halo;

R_1 is selected from the group consisting of $-CF_3$, $-OCF_3$, $-OCHF_2$ and halo;

R_2 is selected from the group consisting of -OH, -H and $-CF_3$;

R_A is  ;

Y is selected from NH, N**R_d**, O or is a bond;

R_d is selected from the group consisting of $-C_1$-C_4alkyl, $-C_1$-C_4alkyl-OH, or $-C_1$-C_4alkyl-Hal;

R_3 is selected from the group consisting of

4-, 5- or 6-membered heterocycloalkyl containing one or two heteroatoms, preferably one heteroatom, wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH; -N**R_5R_6** and halo; or

8-, 9- or 10-membered bicyclic fused heterocycloalkyl containing one to three heteroatoms wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted at any available position with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH, -N**R_5R_6** and halo; or

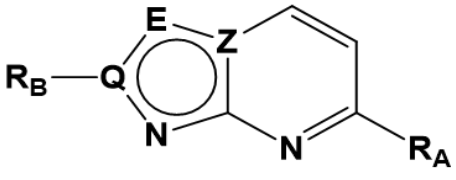
C_3-C_6cycloalkyl optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo; or

C_1-C_6alkyl optionally substituted with one or two substituents independently selected from the group consisting of -OH, halo, haloC_1-C_4alkyl, C_1-C_4alkoxy and -N**R_5R_6**;

R_5 and **R_6** are independently selected from H and C_1-C_3alkyl; and

m is 0, 1 or 2.

3. A compound according to claim 1 having the formula (I)



(I),

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein

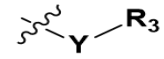
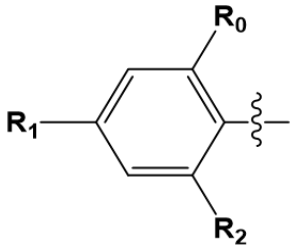
Q is selected from N and C;

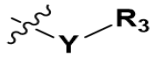
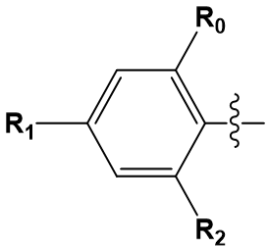
E is selected from N**R_a** and C**R_a**;

Z is selected from N and C;

wherein at least one of **Q** and **Z** is C**,** and/or **E** is C**R_a**; and

R_a is selected from the group consisting of -H and $-C_1$-C_3alkyl;

$\mathbf{R_A}$ and $\mathbf{R_B}$ are each selected from  and ,

wherein one of $\mathbf{R_A}$ and $\mathbf{R_B}$ is  and the other of $\mathbf{R_A}$ and $\mathbf{R_B}$ is ;

$\mathbf{R_0}$ is selected from the group consisting of -H, C_1-C_3alkyl and halo;

$\mathbf{R_1}$ is selected from the group consisting of $-CF_3$, $-OCF_3$, $-OCHF_2$ and halo;

$\mathbf{R_2}$ is selected from the group consisting of -OH, -H and $-CF_3$;

Y is selected from NH and O; and

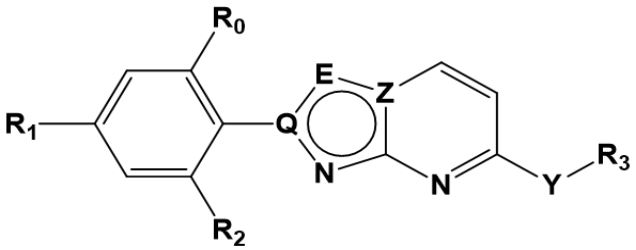
$\mathbf{R_3}$ is selected from the group consisting of

4-, 5- or 6-membered heterocycloalkyl containing one or two heteroatoms, preferably one heteroatom, wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo;

C_3-C_6cycloalkyl optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo; and

C_1-C_6alkyl optionally substituted with one or two substituents independently selected from the group consisting of -OH, halo, haloC_1-C_4alkyl, C_1-C_4alkoxy and -N$\mathbf{R_5R_6}$ wherein $\mathbf{R_5}$ and $\mathbf{R_6}$ are independently selected from H and C_1-C_3alkyl.

4. A compound according to any one of claims 1 to 3 having the formula (II)



(II)

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein

Q is selected from N and C;

E is selected from N$\mathbf{R_a}$ and C$\mathbf{R_a}$;

Z is selected from N and C;

wherein at least one of **Q** and **Z** is C**,** and/or **E** is C$\mathbf{R_a}$;

$\mathbf{R_a}$ is selected from the group consisting of -H and -C_1-C_3alkyl;

$\mathbf{R_0}$ is selected from the group consisting of -H, C_1-C_3alkyl and halo;

$\mathbf{R_1}$ is selected from the group consisting of -CF_3, -OCF_3, -$OCHF_2$ and halo;

$\mathbf{R_2}$ is selected from the group consisting of -OH, -H and -CF_3;

Y is selected from NH and O; and

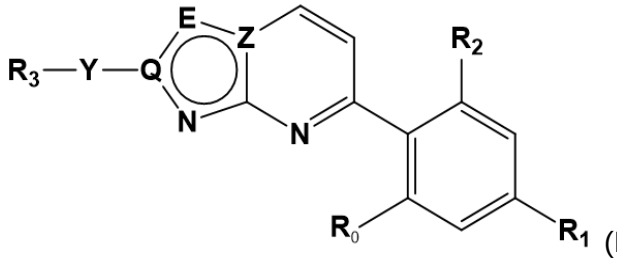
$\mathbf{R_3}$ is selected from the group consisting of

4-, 5- or 6-membered heterocycloalkyl containing one or two heteroatoms, preferably one heteroatom, wherein said heteroatom(s) is/are independently selected from N and O, optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo;

C_3-C_6cycloalkyl optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, -OH and halo; and

C_1-C_6alkyl optionally substituted with one or two substituents independently selected from the group consisting of -OH, halo, haloC_1-C_4alkyl, C_1-C_4alkoxy and -N$\mathbf{R_5R_6}$ wherein $\mathbf{R_5}$ and $\mathbf{R_6}$ are independently selected from H and C_1-C_3alkyl.

5. The compound according to claim 1 or 3 having the formula (III)

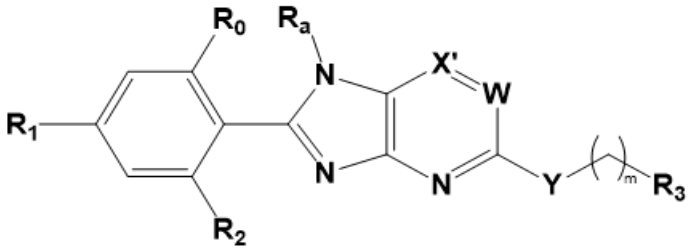


(III)

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein **Q, E, Z**, $\mathbf{R_0}$**,** $\mathbf{R_1}$, $\mathbf{R_2}$, $\mathbf{R_3}$, and **Y** are as defined in claim 1 or 3.

6. The compound according to claim 2 having the formula (II'a)

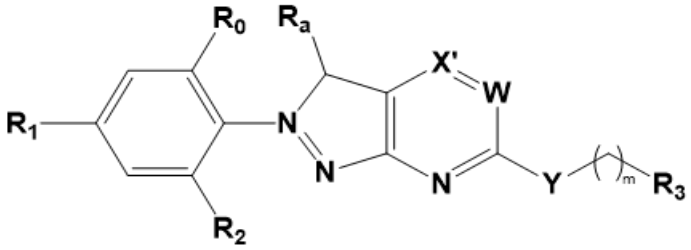


(II'a)

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein **X'**, **W**, **R_0, R_1**, **R_2**, **R_3, R_a, m** and **Y** are as defined in claim 1.

7. The compound according to claim 2 having the formula (II'b)

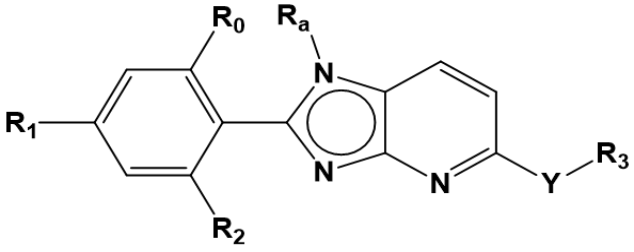


(II'b)

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein **X'**, **W**, **R_0, R_1**, **R_2**, **R_3, R_a, m** and **Y** are as defined in claim 1.

8. The compound according to any one of claims 2 to 4 having the formula (IIa)

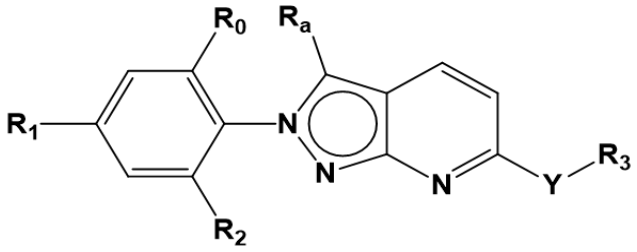


(IIa)

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein **R_0, R_1**, **R_2**, **R_3, R_a** and **Y** are as defined in any one of claims 2 to 4.

9. The compound according to any one of claims 2 to 4 having the formula (IIb)

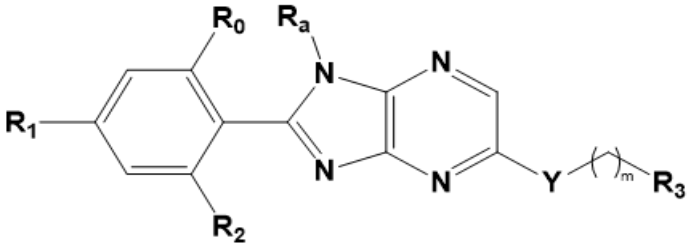


(IIb)

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein **R_0, R_1**, **R_2**, **R_3, R_a** and **Y** are as defined in any one of claims 2 to 4.

10. The compound according to claim 2 having the formula (IV)

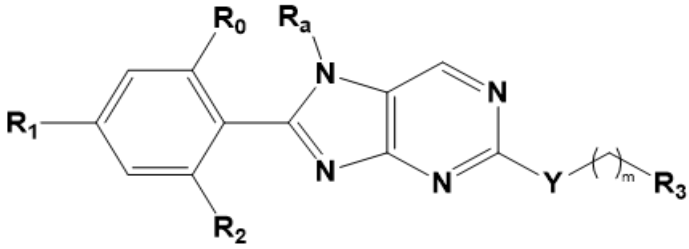


(IV)

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein **R_0, R_1**, **R_2**, **R_3, R_a**, **m** and **Y** are as defined in claim 2.

11. The compound according to claim 2 having the formula (V)



(V)

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof;

wherein **R_0, R_1**, **R_2**, **R_3, R_a**, **m** and **Y** are as defined in claim 2.

12. The compound according to any one of the preceding claims, wherein

R_3 is selected from the group consisting of

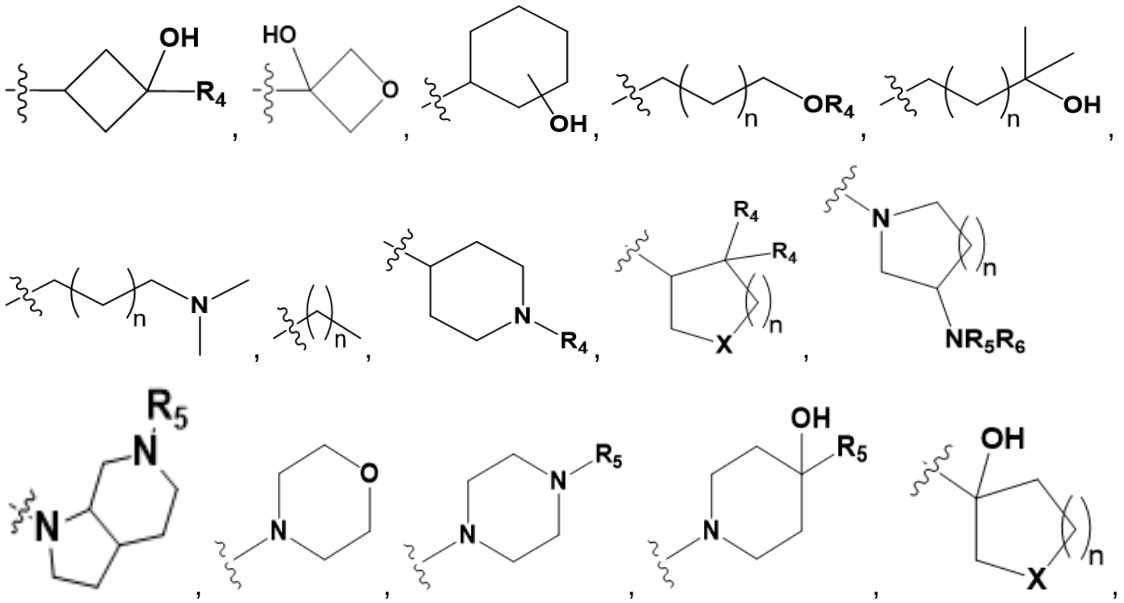
4-, 5- or 6-membered heterocycloalkyl containing one heteroatom, wherein said heteroatom is N or O, optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl;

C_3-C_6cycloalkyl optionally substituted with one or two substituents independently selected from the group consisting of C_1-C_4alkyl, -OH and halo;

hydroxyC_1-C_6alkyl; and

C_1-C_6alkyl optionally substituted with -N$\mathbf{R_5R_6}$ wherein $\mathbf{R_5}$ and $\mathbf{R_6}$ are independently selected from H and C_1-C_3alkyl.

13. The compound according to any one of the preceding claims, wherein $\mathbf{R_3}$ is selected from the group consisting of



Me, and CF_3;

wherein

X is selected from O and N$\mathbf{R_4}$;

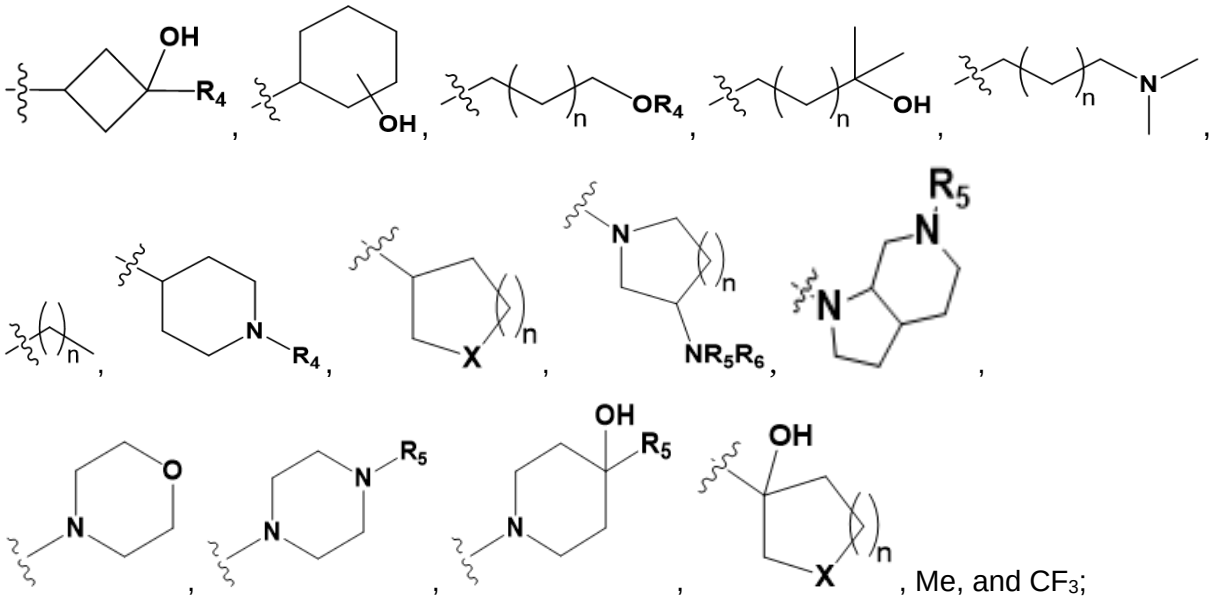
$\mathbf{R_4}$ is independently selected from H, halo or C_1-C_3alkyl;

$\mathbf{R_5}$ is independently selected from H or C_1-C_3alkyl, preferably H or Me;

$\mathbf{R_6}$ is selected from the group consisting of C_1-C_4alkyl; and

n is selected from 0, 1 or 2.

14. The compound according to any one of claims 1 to 10, wherein $\mathbf{R_3}$ is selected from the group consisting of



wherein

X is selected from O and N**R4**;

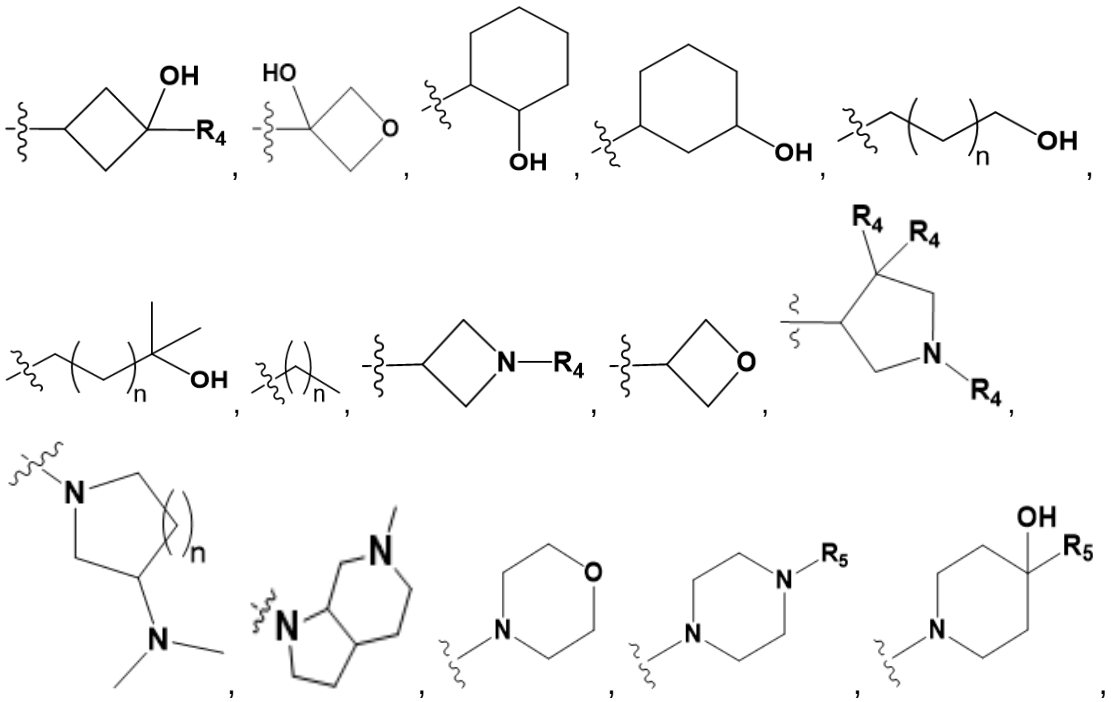
R4 is independently selected from H, halo or C_1-C_3alkyl;

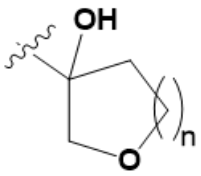
R5 is independently selected from -H or -Me;

R6 is selected from the group consisting of C_1-C_4alkyl; and

n is selected from 0, 1 or 2.

15. The compound according to claim 11, wherein **R3** is selected from the group consisting of




, Me, and CF_3;

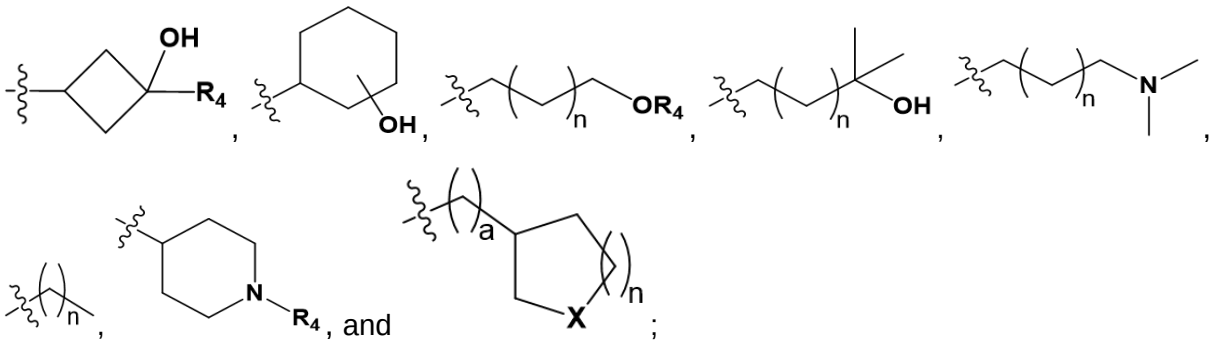
wherein

$\mathbf{R_4}$ is independently selected from H, F, or C_1-C_3alkyl; and

$\mathbf{R_5}$ is methyl; and

n is selected from 0, 1 or 2.

16. The compound according to any one of claims 1 to 10, wherein $\mathbf{R_3}$ is selected from the group consisting of


; wherein

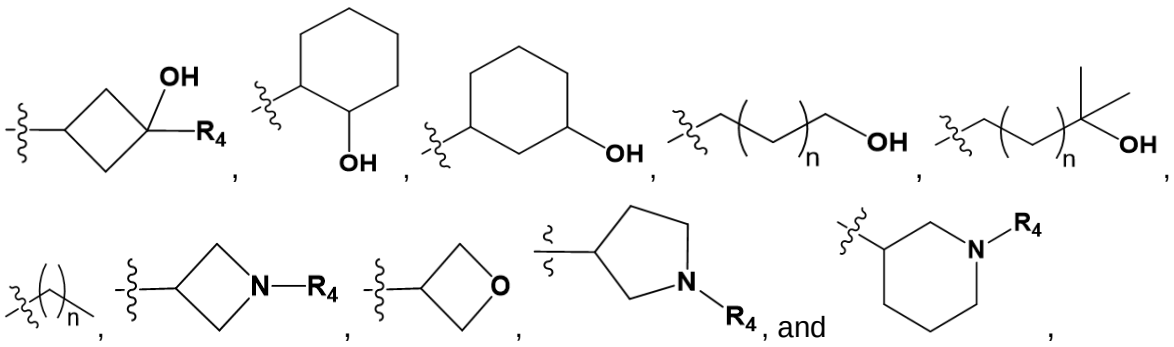
X is selected from O and N$\mathbf{R_4}$;

$\mathbf{R_4}$ is independently selected from -H or -C_1-C_3alkyl;

a is selected from 0 and 1; and

n is selected from 0, 1 or 2.

17. The compound according to claim 16, wherein $\mathbf{R_3}$ is selected from the group consisting of


wherein $\mathbf{R_4}$ is independently selected from -H or -C_1-C_3alkyl; and

n is selected from 0, 1 or 2.

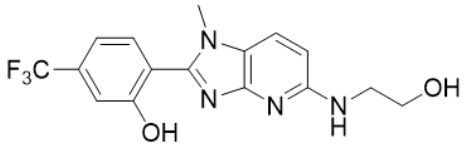
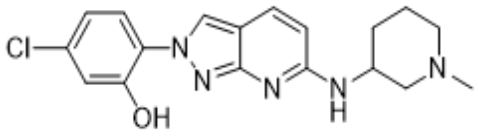
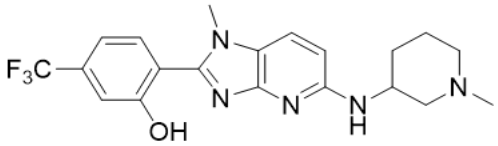
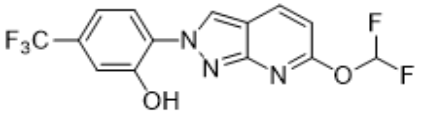
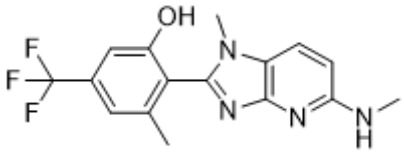
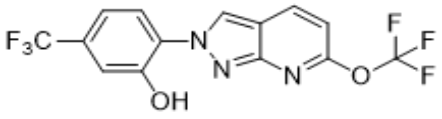
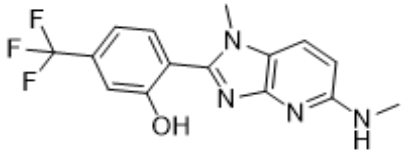
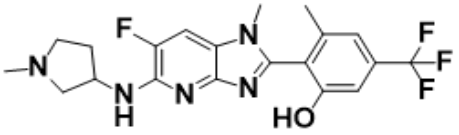
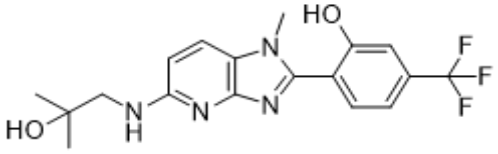
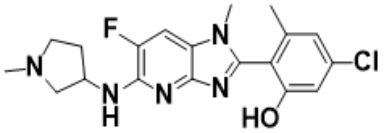
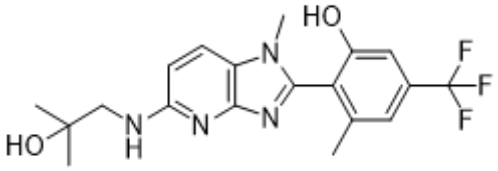
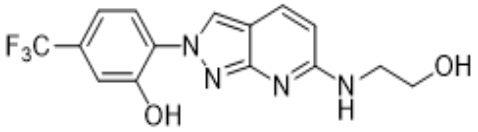
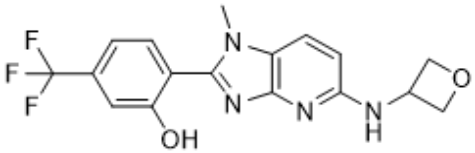
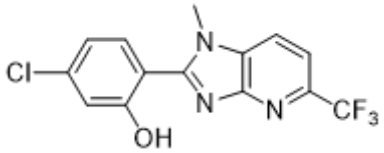
18. The compound according to any one of the preceding claims, wherein

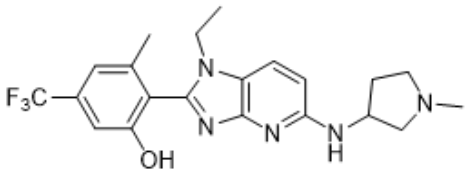
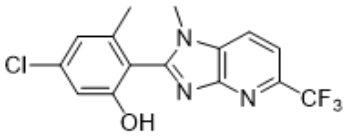
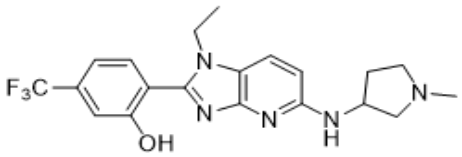
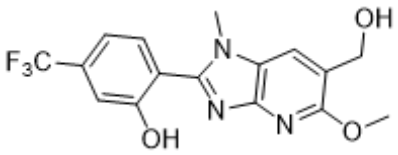
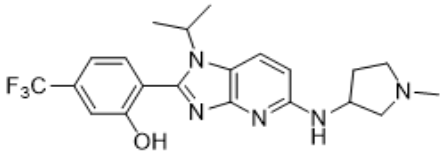
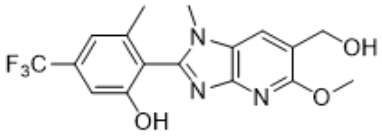
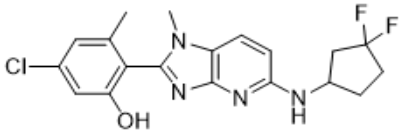
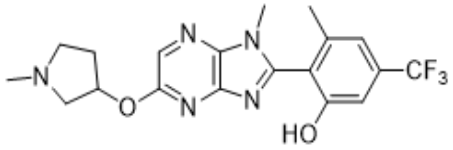
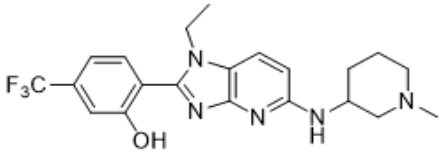
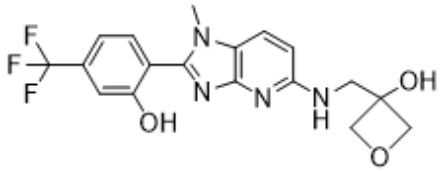
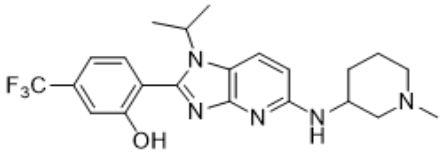
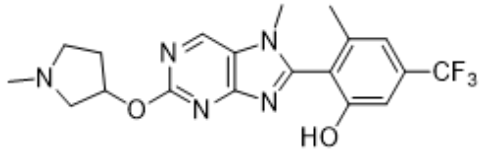
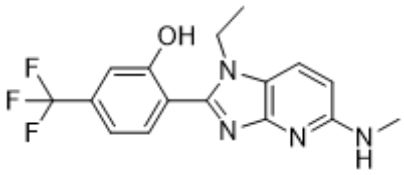
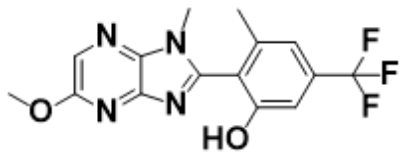
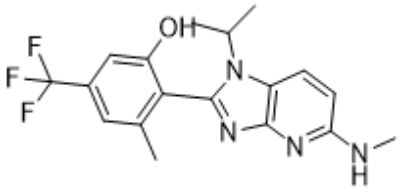
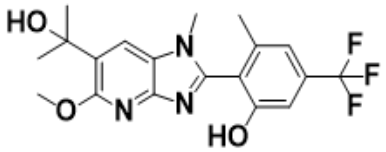
$\mathbf{R_0}$ is -H or -CH_3;

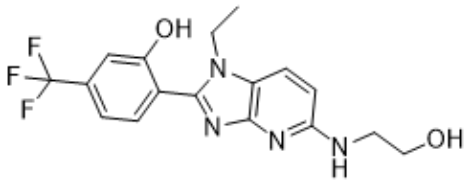
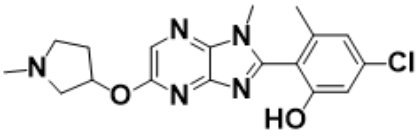
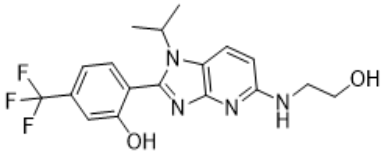
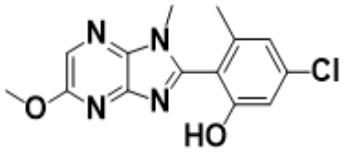
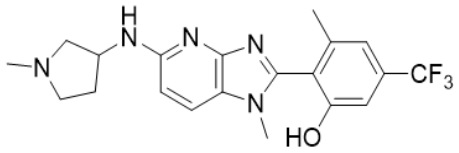
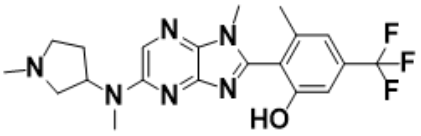
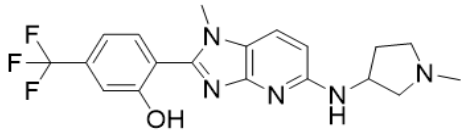
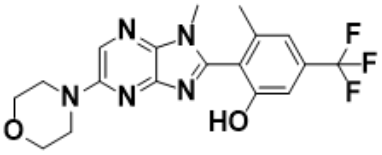
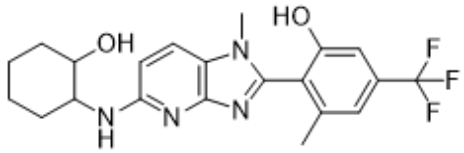
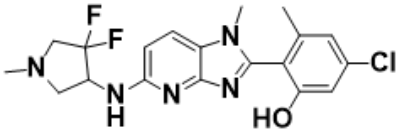
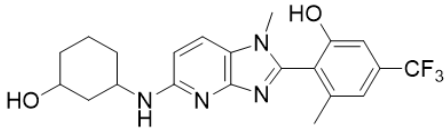
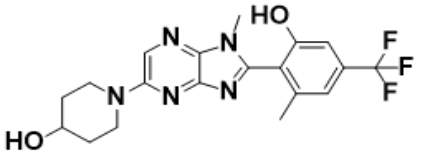
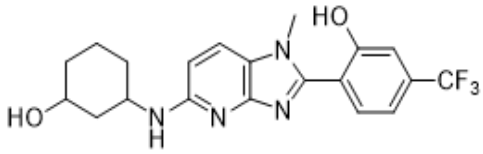
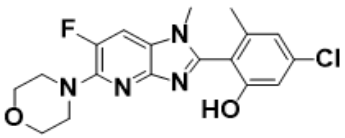
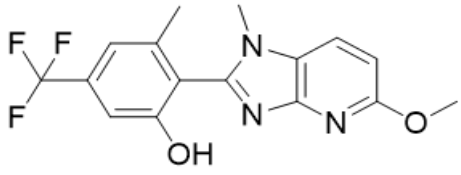
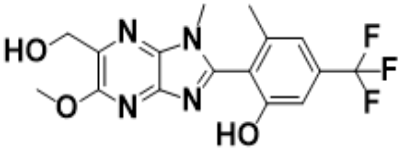
$\mathbf{R_1}$ is -CF_3 or -halo, preferably -Cl; and

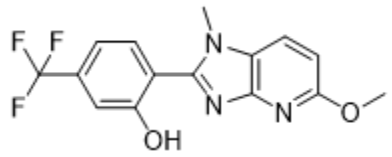
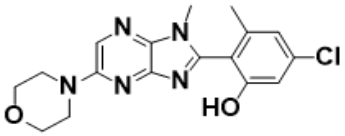
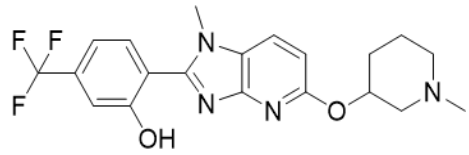
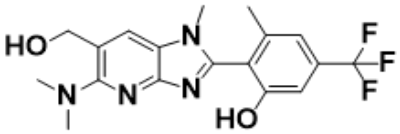
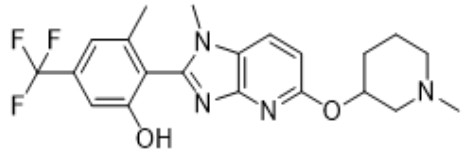
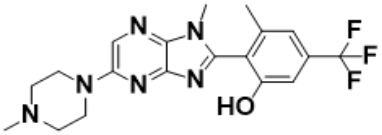
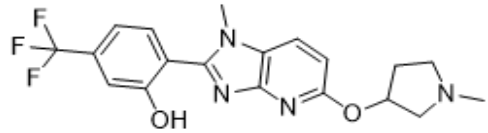
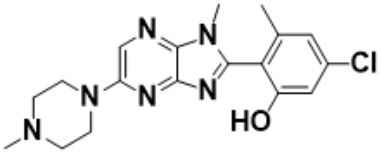
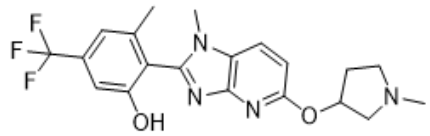
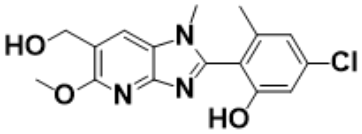
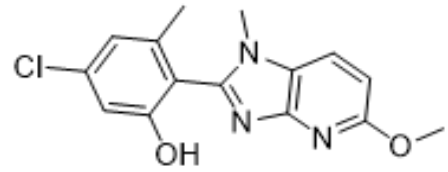
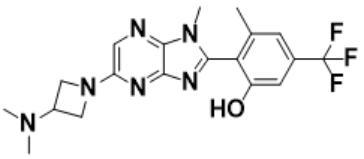
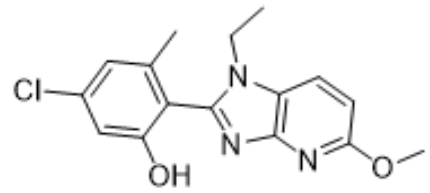
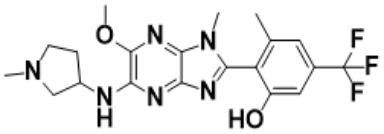
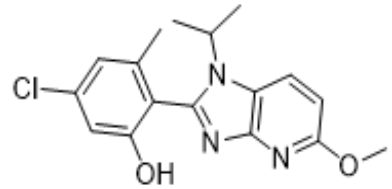
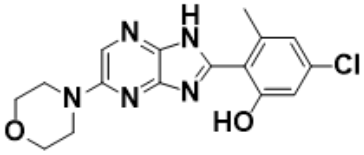
$\mathbf{R_2}$ is -OH.

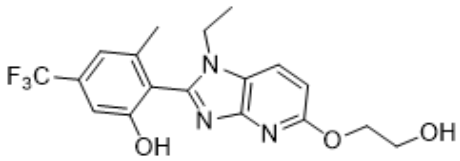
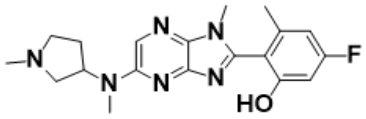
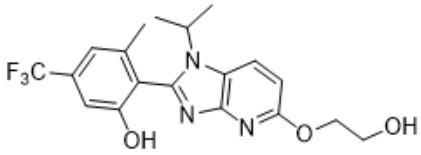
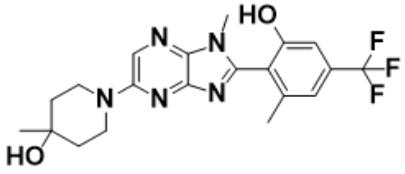
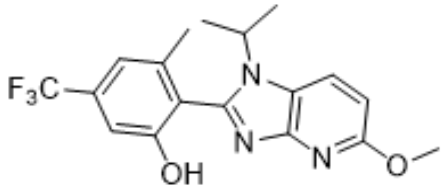
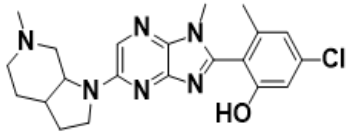
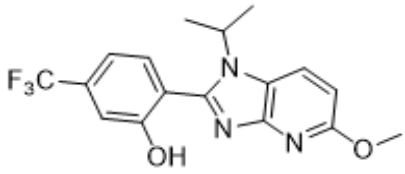
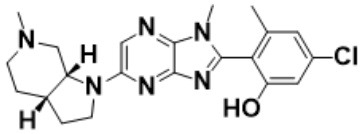
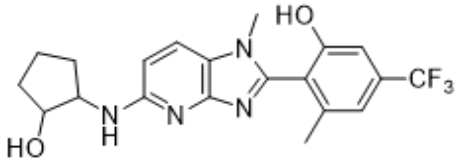
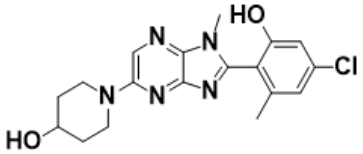
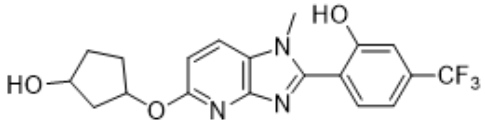
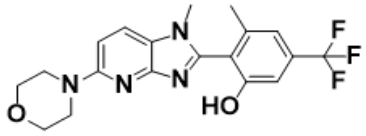
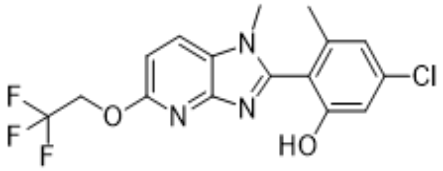
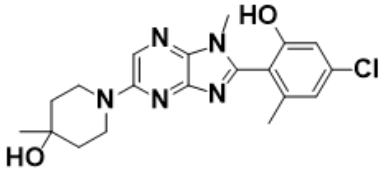
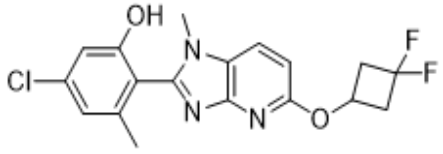
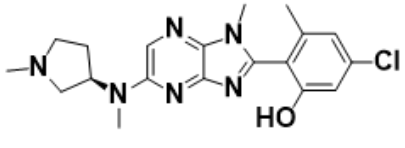
19. The compound according to any of the preceding claims, which is selected from

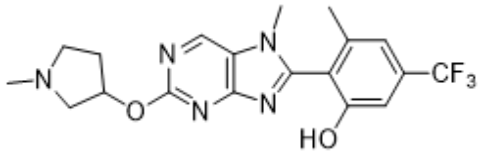
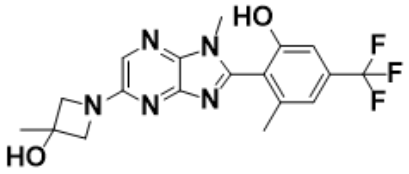
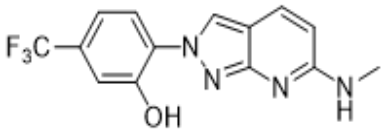
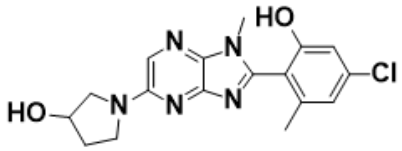
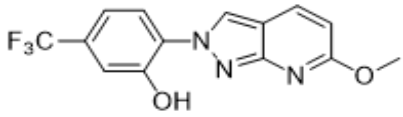
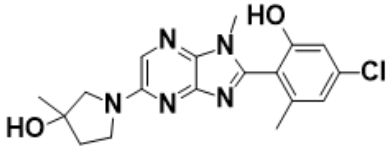
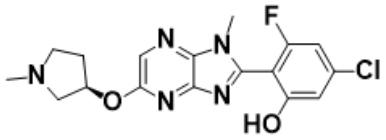
1 	**43** 
2 	**44** 
3 	**45** 
4 	**46** 
5 	**47** 
6 	**48** 
7 	**49** 

8 	50 
9 	51 
10 	52 
11 	53 
12 	54 
13 	55 
14 	56 
15 	57 

16 	58 
17 	59 
18 	60 
19 	61 
20 	62 
21 	63 
22 	64 
23 	65 

24 	66 
25 	67 
26 	68 
27 	69 
28 	70 
29 	71 
30 	72 
31 	73 

32 	74 
33 	75 
34 	76 
35 	77 
36 	78 
37 	79 
38 	80 
39 	81 

40 	**84** 
41 	**85** 
42 	**86** 
	87 

or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof.

20. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 19, or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, and optionally comprising at least one pharmaceutically acceptable carrier, diluent, adjuvant or excipient.

21. The compound according to any one of claims 1 to 19, or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, for use as a medicament.

22. Use of the compound according to any one of claims 1 to 19, or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, in the manufacture of a medicament for the treatment, alleviation or prevention of a disease, or a disorder or an abnormality which is responsive to the modulation of a component of the NLRP3 inflammasome pathway and/or which is responsive to the modulation of IL-1 beta and/or IL-18 levels.

23. The use according to claim 22, wherein the modulation is the reduction and/or inhibition of IL-1 beta.

24. The use according to claim 22, wherein the component of the inflammasome pathway is NLRP3 inflammasome.

25. The use according to claim 22 or 24, wherein the activation of NLRP3 inflammasome pathway is inhibited.

26. The use according to any one of claims 22 to 25, wherein the disease, the disorder or the abnormality selected from Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, demyelination, viral encephalitis, epilepsy, stroke, atherosclerosis, allergic inflammation, cryopyrin-associated periodic syndromes (CAPS), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), neonatal-onset multisystem inflammatory disease (NOMID), gout, pseudo-gout, inflammatory bowel disease (IBD) (including Crohn's disease, ulcerative colitis), hepatitis, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, hypertension, myocardial infarction, heart failure, coronary artery disease, oxalate-induced nephropathy, graft-versus host disease, type 1 diabetes, type 2 diabetes, Edema (DME), Geographic Atrophy (GA), rheumatoid arthritis, myelodysplastic syndrome, familial Mediterranean fever (FMF), TNF receptor associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD), hyperimmunoglobulinemia D, periodic fever syndrome (HIDS), deficiency of interleukin 1 receptor (DIRA) antagonist, Majeed syndrome, pyogenic arthritis pyoderma gangrenosum and acne (PAPA), haploinsufficiency of A20 (HA20), PLCG2-associated antibody deficiency and immune dysregulation (PLAID), pediatric granulomatous arthritis (PGA), PLCG2-associated autoinflammation, antibody deficiency and immune dysregulation (APLAID), sideroblastic anemia with B-cell immunodeficiency, periodic fevers, developmental delay (SIFD), chronic nonbacterial osteomyelitis (CNO), Sweet's syndrome, chronic recurrent multifocal osteomyelitis (CRMO), synovitis, pustulosis, skin contact hypersensitivity, sunburn, psoriasis, hidradenitis suppurativa (HS), epidermolysis bullosa, acne, eczema, alopecia areata, actinic keratosis, hyperostosis, osteitis syndrome (SAPHO), vitiligo, atopic dermatitis, cutaneous lupus, multiple sclerosis (MS), psoriasis, Behcet's disease, Sjogren's syndrome, Schnitzler syndrome, chronic obstructive pulmonary disorder (COPD), asthma, steroid-resistant asthma, Coronavirus-associated inflammatory pathologies including Coronavirus-associated respiratory distress syndrome (CARDS), asbestosis, silicosis, cystic fibrosis, motor neuron disease, Huntington's disease, cerebral

malaria, brain injury from pneumococcal meningitis, obesity, age-related macular degeneration (AMD), corneal infection, uveitis, dry eye, acute kidney disease, chronic kidney disease, lupus nephritis, diabetic nephropathy, alcoholic liver disease, skin contact hypersensitivity, sunburn, osteoarthritis, systemic juvenile idiopathic arthritis, adult-onset Still's disease, relapsing polychondritis, Chikungunya virus, Ross River virus, influenza, HIV, Coronaviruses, Dengue, Zika virus, primary biliary cholangitis, antiphospholipid syndrome, refractory celiac disease, pancreatitis, autoimmune pancreatitis, mucocutaneous lymph node syndrome, lung cancer metastasis, pancreatic cancers, gastric cancers, myelodisplastic syndrome, leukemia; polymyositis, colitis, helminth infection, bacterial infection, abdominal aortic aneurism, wound healing, migraine, depression, psychological stress, pain, neuropathic pain, pericarditis including Dressler's syndrome, ischaemia reperfusion injury, frontotemporal dementia, HIV-associated neurocognitive disorder, traumatic spinal cord injury, traumatic brain injury, inflammatory pain, chronic pain, neuropathic pain, metastatic cancer-induced bone pain, chemotherapy induced peripheral neuropathy and migraine; ankylosing spondylitis and cytokine release syndrome; preferably the disorder is selected from Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, demyelination, multiple sclerosis, encephalomyelitis, leukoencephalopathy, viral encephalitis, epilepsy, stroke, traumatic brain injury, spinal cord injury, atherosclerosis, asthma, allergic inflammation, cryopyrin-associated periodic syndromes (CAPS), gout, inflammatory bowel disease (IBD), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), hypertension, myocardial infarction, oxalate-induced nephropathy, graft-versus host disease, type 1 diabetes, type 2 diabetes, rheumatoid arthritis, myelodysplastic syndrome, anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), acute kidney disease, chronic kidney disease, lupus nephritis, anti-glomerular basement membrane (GMB) disease, IgA nephropathy, glomerulonephritis (GN), systemic lupus erythematosus (SLE), Focal Segmental Glomerulosclerosis, Minimal change disease (MCD), Psoriatic Arthritis, Hereditary Recurrent Fevers (HRFs), acne, atopic dermatitis, hidradenitis suppurativa (HS), and amyloidosis (including AL amyloidosis, AA amyloidosis, ATTR amyloidosis, hereditary amyloidoses (including apolipoprotein A-I (AApoAI), apolipoprotein A-II (AApoAII), gelsolin (AGel), fibrinogen (AFib), and lysozyme (ALys)), Beta-2 microglobulin amyloidosis, iAPP amyloidosis).

27. The use according to claim 26, wherein the disease, the disorder or the abnormality is selected from Alzheimer’s disease, Parkinson’s disease and multiple sclerosis.

28. The use according to claim 26, wherein the disease, the disorder or the abnormality is selected from cryopyrin-associated periodic syndromes (CAPS), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), chronic kidney disease and gout.

29. The use according to claim 26, wherein the disease, the disorder or the abnormality is a skin disease, disorder, or abnormality selected from hidradenitis suppurativa (HS), dermatitis, psoriasis, skin contact hypersensitivity, acne, periodic fever syndrome (HIDS), Sweet's syndrome, eczema, skin lesions, burn, wound, wound healing, trauma, sunburn, actinic keratosis, deficiency of interleukin 1 receptor (DIRA) antagonist, epidermolysis bullosa, vitiligo, atopic dermatitis, cutaneous lupus, and alopecia areata.

30. The use according to claim 29, wherein the disease, the disorder or the abnormality is hidradenitis suppurativa (HS).

31. Use of a compound according to any one of claims 1 to 19, or a stereoisomer, a racemic mixture, a tautomer, a polymorph, a pharmaceutically acceptable salt, a prodrug, a hydrate, or a solvate thereof, as an analytical reference or an *in vitro* screening tool.