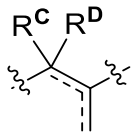
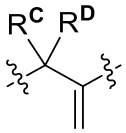
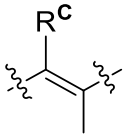
much more reactive DMI. In this latter case, the α,β-unsaturated carboxylic acid is esterified and, as a consequence, the IL-6-lowering and NRF2-activating effects of DMI are reversed by the thiols N-acetylcysteine and GSH, respectively. Through the reaction with KEAP1 and the resulting NRF2 activation, as well as GAPDH inhibition (Liao S.-T. *et al.*, 2019), 4OI has been demonstrated to produce a wide range of interesting biological effects, including: 1) protection of neuronal cells from hydrogen peroxide (Liu H. *et al.*, 2018); 2) inhibition of proinflammatory cytokine production in peripheral blood mononuclear cells of SLE patients (Tang C. *et al.*, 2018); 3) protection of human umbilical vein endothelial cells from high glucose (Tang C. *et al.*, 2019); 4) inhibition of osteoclastogenesis by suppressing the E3 ubiquitin ligase Hrd1 and activating NRF2 signaling (Sun X. *et al.*, 2019); 5) induction of repression of STING by NRF2 and type I IFN production in cells from patients with STING-dependent interferonopathies (Olagnier D. *et al.*, 2018); 6) protection against renal fibrosis via inhibiting the TGF-beta/Smad pathway, autophagy and reducing generation of reactive oxygen species (Tian F. *et al.*, 2020); 7) reduction of brain viral burden in mice intracranially injected with Zika virus (Daniels B. P. *et al.* 2019); and 8) protection against liver ischemia–reperfusion injury (Yi F. *et al.* 2020). Furthermore, itaconate has been reported to modulate tricarboxylic acid and redox metabolism to mitigate reperfusion injury (Cordes T. *et al.*, 2020). In addition, raised plasma itaconate levels demonstrate a clear correlation with reduction in rheumatoid arthritis disease activity scores following commencement of therapy with conventional disease modifying anti-rheumatic drug (cDMARD) therapy (Daly R. *et al.*, 2019).

In spite of the above findings, there remains a need to identify and develop new α,β-unsaturated carboxyl compounds such as itaconate and acrylate derivatives possessing enhanced properties compared to currently marketed anti-inflammatory agents, such as DMF. The present inventors have now discovered, surprisingly, that certain α,β-unsaturated methacrylic acids possessing heteroaryl groups are effective at reducing cytokine release, activating NRF2 in cells and/or have improved metabolic stability. These properties make them potentially more effective than 4-octyl itaconate in particular. Such compounds are therefore expected to possess excellent anti-inflammatory properties.

Summary ~~**of the invention**~~

In a first aspect, the present ~~invention~~ disclosure provides a compound of formula (I):

wherein  in the compound of formula (I) represents:

 or ;

and wherein

the total number of carbon atoms in groups R^{A1} and R^{A2} taken together including their optional substituents is 6–14; and

wherein, when  represents an isoxazole, R^{A1} does not represent phenyl, phenyl substituted by bromo, or phenyl substituted by methyl;

or a pharmaceutically acceptable salt and/or solvate thereof.

~~In a further aspect, t~~The present ~~invention~~ disclosure also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof. In a further aspect, the present disclosure provides a pharmaceutical composition comprising a compound or pharmaceutically acceptable salt and/or solvate thereof as defined herein and one or more pharmaceutically acceptable diluents or carriers.

~~In a further aspect, t~~The present disclosure also ~~invention~~ provides a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof for use as a medicament. In a further aspect, the present disclosure provides the compound or pharmaceutically acceptable salt and/or solvate thereof as defined herein, or a pharmaceutical composition as defined herein for use as a medicament.

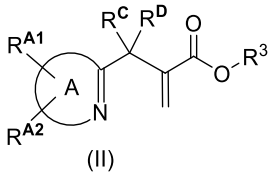
~~In a further aspect, t~~The present disclosure also ~~invention~~ provides a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof for use in treating or preventing an inflammatory disease or a disease associated with an undesirable immune response. In a further aspect, the present disclosure provides the compound or pharmaceutically acceptable salt and/or solvate thereof as defined herein, or a pharmaceutical composition as defined herein for use in treating or preventing an inflammatory disease or a disease associated with an undesirable immune response.

~~In a further aspect, t~~The present disclosure also ~~invention~~ provides the use of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof in the manufacture of a medicament for treating or preventing an inflammatory disease or a disease associated with an immune response. In a further aspect, the present disclosure provides use of a compound or pharmaceutically acceptable salt and/or solvate thereof as defined herein or a pharmaceutical composition as defined herein in the manufacture of a medicament for treating or preventing an inflammatory disease or a disease associated with an undesirable immune response.

~~In a further aspect, t~~The present disclosure also ~~invention~~ provides a method of treating or preventing an inflammatory disease or a disease associated with an undesirable immune response, which comprises administering a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof.

In a further aspect, the present disclosure provides compound selected from the group consisting of:

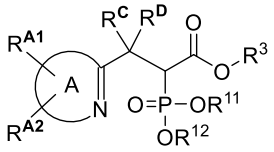
- a compound of formula (II):



(II)

or salt thereof, wherein , R^{A1}, R^{A2}, R^{C} and R^{D} are defined herein and R^{3} represents C_{1-4} alkyl optionally substituted with halo;

- a compound of formula (III):

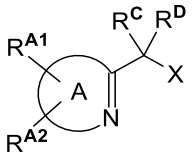


(III)

or salt thereof, wherein R^{A1} is selected from the group consisting of C_{2-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $-(CH_2)_{0-6}-C_{3-10}$ cycloalkyl, $-(CH_2)_{0-6}-C_{5-10}$ spirocycloalkyl, $-(CH_2)_{0-6}$–aryl and O–aryl, and wherein R^{A1} is optionally substituted as defined herein,

, R^{A2}, R^{C} and R^{D} are defined herein and R^{3}, R^{11} and R^{12} independently represent C_{1-4} alkyl optionally substituted with halo;

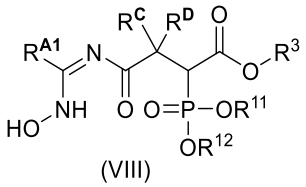
- a compound of formula (V):



(V)

or salt thereof, wherein , R^{A1}, R^{A2}, R^{C} and R^{D} are defined herein, and X is selected from the group consisting of chloro, bromo, iodo, alkanesulfonate and arenesulfonate;

- a compound of formula (VIII):

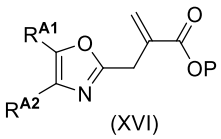


(VIII)

or a salt thereof;

wherein R^{A1}, R^{C} and R^{D} are as defined herein, and R^{3}, R^{11} and R^{12} independently represent C_{1-4} alkyl optionally substituted with halo;

- a compound of formula (XVI):

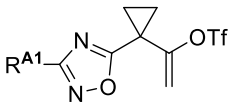


(XVI) ;

or a salt thereof;

wherein R^{A1} and R^{A2} are defined herein and P is a carboxylic acid protecting group; and

- a compound of formula (XXIV):

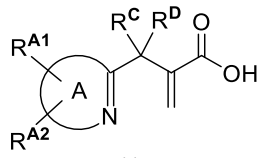


(XXIV) ;

or a salt thereof;

wherein R^{A1} is defined herein.

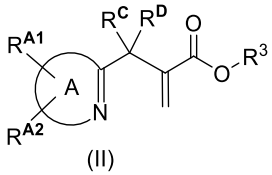
In a further aspect, the present disclosure provides a process for preparing the compound of formula (I):



(I)

or a salt thereof which comprises

(a) hydrolysing the ester moiety in a compound of formula (II):

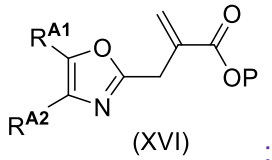


(II)

or a salt thereof,

wherein , R^{A1}, R^{A2}, R^{C} and R^{D} and R^{3} are defined herein and R^{3} represents C_{1-4} alkyl optionally substituted with halo; or

(b) deprotecting a compound of formula (XVI):

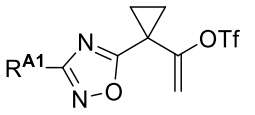


(XVI) ;

or a salt thereof;

wherein R^{A1} and R^{A2} are defined herein and P is a carboxylic acid protecting group; or

(c) reacting a compound of formula (XXIV):



(XXIV) ;

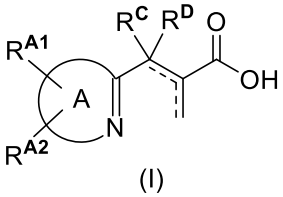
or a salt thereof;

with carbon monoxide in the presence of a metal catalyst, followed by hydrolysis to give the compounds of formula (I);

wherein R^{A1} is defined herein.

CLAIMS

1. A compound of formula (I):



(I)

wherein,



represents a 5 membered heteroaryl ring, which in addition to the C=N shown contains one or more further heteroatoms independently selected from N, O and S;

or 

represents a 6 membered heteroaryl ring, which in addition to the C=N shown optionally contains one or more further N atoms;

R^{A1} is selected from the group consisting of $C_{1–10}$ alkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $–(CH_2)_{0–6}–C_{3–10}$ cycloalkyl, $–(CH_2)_{0–6}–C_{5–10}$ spirocycloalkyl, $–(CH_2)_{0–6}–$aryl and O–aryl;

wherein R^{A1} is optionally substituted by one or more substituents selected from the group consisting of halo, $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, hydroxy, cyano, OG^1, $S(O)_{0–2}G^1$, SF_5, $(CH_2)_{0-3}C_{3-7}$ cycloalkyl and 5–7-membered heterocyclyl wherein said C_{3-7} cycloalkyl and said 5–7-membered heterocyclyl are optionally substituted by one or more groups selected from halo, C_{1-3} alkyl and C_{1-3} haloalkyl; wherein two alkyl groups which are attached to the same carbon atom are optionally joined to form a C_{3-7} cycloalkyl ring; wherein the $C_{3–10}$ cycloalkyl group is optionally fused to a phenyl ring which phenyl ring is optionally substituted by one or more halo atoms; or R^{A1} is optionally substituted by one phenyl ring which is optionally substituted by C_{1-2} haloalkyl, C_{1-2} haloalkoxy or one or more halo atoms;

wherein G^1 is $C_{1–6}$ alkyl, $C_{3–7}$ cycloalkyl, $C_{1–6}$ haloalkyl, or $(CH_2)_{0-1}$phenyl wherein G^1 is optionally substituted by one or more substituents selected from the group consisting of halo, $C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, hydroxy, cyano, nitro, $C_{1–2}$ alkoxy and $C_{1–2}$ haloalkoxy;

R^{A2} is selected from the group consisting of halo, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{1–6}$ haloalkyl, hydroxy, cyano, nitro, NR^1R^2, OG^2 and $S(O)_{0–2}G^2$;

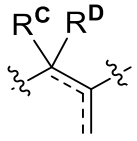
wherein G^2 is $C_{1–6}$ alkyl, $C_{3–7}$ cycloalkyl, $C_{1–6}$ haloalkyl, or phenyl which is optionally substituted by one or more substituents selected from the group consisting of halo, $C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, hydroxy, cyano, nitro, $C_{1–2}$ alkoxy and $C_{1–2}$ haloalkoxy; and

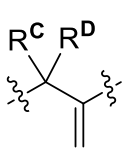
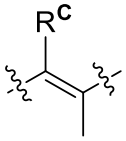
wherein R^1 and R^2 are independently H or C_{1-2} alkyl or, taken together, R^1 and R^2 may combine to form a 5–7-membered heterocyclic ring;

or R^{A2} is absent; and

R^C and R^D are each independently H, $C_{1–2}$ alkyl, hydroxy, fluoro or $C_{1–2}$ alkoxy; or R^C and R^D may

join to form a C_{3-5} cycloalkyl ring;

wherein  in the compound of formula (I) represents:

 or ;

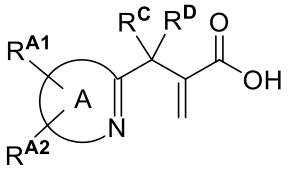
and wherein

the total number of carbon atoms in groups R^{A1} and R^{A2} taken together including their optional substituents is 6–14; and

wherein, when  represents an isoxazole, R^{A1} does not represent phenyl, phenyl substituted by bromo, or phenyl substituted by methyl;

or a pharmaceutically acceptable salt and/or solvate thereof.

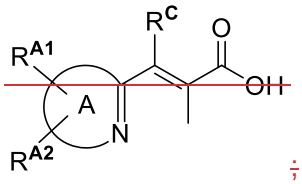
2. The compound or pharmaceutically acceptable salt and/or solvate thereof according to claim 1 wherein the compound of formula (I) is:

;

or a pharmaceutically acceptable salt and/or solvate thereof;

wherein A, R^{A1}, R^{A2}, R^{C} and R^{D} are as defined in claim 1.

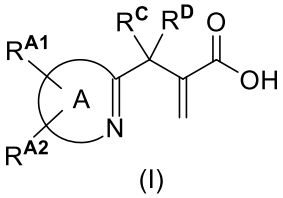
~~3. The compound according to claim 1 wherein the compound of formula (I) is:~~

~~;~~

~~or a pharmaceutically acceptable salt and/or solvate thereof;~~

~~wherein A, R^{A1}, R^{A2} and R^{C} are as defined in claim 1.~~

34. The compound or pharmaceutically acceptable salt and/or solvate thereof according to claim 1 which is a compound of formula (I):



(I)

wherein,



represents a 5 membered heteroaryl ring, which in addition to the C=N shown contains one or more further heteroatoms independently selected from N, O and S;

or 

represents a 6 membered heteroaryl ring, which in addition to the C=N shown optionally contains one or more further N atoms;

R^{A1} is selected from the group consisting of $C_{1–10}$ alkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $–(CH_2)_{0–6}–C_{3–10}$ cycloalkyl, $–(CH_2)_{0–6}–C_{5–10}$ spirocycloalkyl and $–(CH_2)_{0–6}–$aryl; wherein R^{A1} is optionally substituted by one or more substituents selected from the group consisting of halo, $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, hydroxy, cyano, OG^1, $S(O)_{0–2}G^1$, SF_5 and $(CH_2)_{0-3}C_{3-7}$ cycloalkyl wherein said C_{3-7} cycloalkyl is optionally substituted by one or more groups selected from halo, C_{1-3} alkyl and C_{1-3} haloalkyl; wherein two alkyl groups which are attached to the same carbon atom are optionally joined to form a C_{3-7} cycloalkyl ring; or R^{A1} is optionally substituted by one phenyl ring which is optionally substituted by C_{1-2} haloalkyl, C_{1-2} haloalkoxy or one or more halo atoms;

wherein G^1 is $C_{1–6}$ alkyl, $C_{3–7}$ cycloalkyl, $C_{1–6}$ haloalkyl, or $(CH_2)_{0-1}$phenyl which is optionally substituted by one or more substituents selected from the group consisting of halo, $C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, hydroxy, cyano, nitro, $C_{1–2}$ alkoxy and $C_{1–2}$ haloalkoxy;

R^{A2} is selected from the group consisting of halo, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{1–6}$ haloalkyl, hydroxy, cyano, nitro, NR^1R^2, OG^2 and $S(O)_{0–2}G^2$;

wherein G^2 is $C_{1–6}$ alkyl, $C_{3–7}$ cycloalkyl, $C_{1–6}$ haloalkyl, or phenyl which is optionally substituted by one or more substituents selected from the group consisting of halo, $C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, hydroxy, cyano, nitro, $C_{1–2}$ alkoxy and $C_{1–2}$ haloalkoxy; and

wherein R^1 and R^2 are independently H or C_{1-2} alkyl or, taken together, R^1 and R^2 may combine to form a 5–7-membered heterocyclic ring;

or R^{A2} is absent;

R^C and R^D are each independently H, $C_{1–2}$ alkyl, hydroxy, fluoro or $C_{1–2}$ alkoxy; and

wherein,

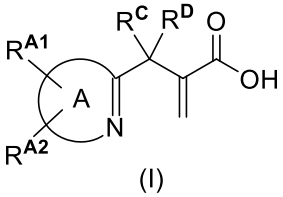
the total number of carbon atoms in groups R^{A1} and R^{A2} taken together including their optional substituents is 6–14; and

wherein, when 

represents an isoxazole, R^{A1} does not represent phenyl, phenyl substituted by bromo, or phenyl substituted by methyl;

or a pharmaceutically acceptable salt and/or solvate thereof.

45. The compound or pharmaceutically acceptable salt and/or solvate thereof according to claim 34 which is a compound of formula (I):



(I)

wherein,



represents a 5 membered heteroaryl ring, which in addition to the C=N shown contains one or more further heteroatoms independently selected from N, O and S;

or 

represents a 6 membered heteroaryl ring, which in addition to the C=N shown optionally contains one or more further N atoms;

R^{A1} is selected from the group consisting of $C_{1–10}$ alkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $–(CH_2)_{0–6}–C_{3–10}$ cycloalkyl, $–(CH_2)_{0–6}–C_{5–10}$ spirocycloalkyl and $–(CH_2)_{0–6}–$aryl; wherein R^{A1} is optionally substituted by one or more substituents selected from the group consisting of halo, $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, hydroxy, cyano, OG^1 and $S(O)_{0–2}G^1$, wherein two alkyl groups which are attached to the same carbon atom are optionally joined to form a C_{3-7} cycloalkyl ring, or R^{A1} is optionally substituted by one phenyl ring which is optionally substituted by C_{1-2} haloalkyl, C_{1-2} haloalkoxy or one or more halo atoms;

wherein G^1 is $C_{1–6}$ alkyl, $C_{3–7}$ cycloalkyl, $C_{1–6}$ haloalkyl, or phenyl which is optionally substituted by one or more substituents selected from the group consisting of halo, $C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, hydroxy, cyano, nitro, $C_{1–2}$ alkoxy and $C_{1–2}$ haloalkoxy;

R^{A2} is selected from the group consisting of halo, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{1–6}$ haloalkyl, hydroxy, cyano, nitro, NR^1R^2, OG^2 and $S(O)_{0–2}G^2$;

wherein G^2 is $C_{1–6}$ alkyl, $C_{3–7}$ cycloalkyl, $C_{1–6}$ haloalkyl, or phenyl which is optionally substituted by one or more substituents selected from the group consisting of halo, $C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, hydroxy, cyano, nitro, $C_{1–2}$ alkoxy and $C_{1–2}$ haloalkoxy; and

wherein R^1 and R^2 are independently H or C_{1-2} alkyl or, taken together, R^1 and R^2 may combine to form a 5–7-membered heterocyclic ring;

or R^{A2} is absent;

R^C and R^D are each independently H, $C_{1–2}$ alkyl, hydroxy or fluoro; and

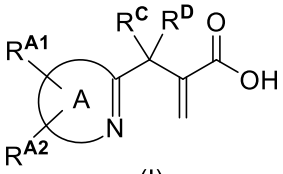
wherein,

the total number of carbon atoms in groups R^{A1} and R^{A2} taken together including their optional substituents is 6–14; and

wherein, when  represents an isoxazole, R^{A1} does not represent phenyl, phenyl substituted by bromo, or phenyl substituted by methyl;

or a pharmaceutically acceptable salt and/or solvate thereof.

56. The compound or pharmaceutically acceptable salt and/or solvate thereof according to claim 45 which is a compound of formula (I):



(I)

wherein,

 represents a 5 membered heteroaryl ring, which in addition to the C=N shown contains one or more further heteroatoms independently selected from N, O and S;

or  represents a 6 membered heteroaryl ring, which in addition to the C=N shown optionally contains one or more further N atoms;

R^{A1} is selected from the group consisting of $C_{1–10}$ alkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $–(CH_2)_{1–6}–C_{3–10}$ cycloalkyl, $–(CH_2)_{0–6}–C_{5–10}$ spirocycloalkyl and $–(CH_2)_{0–6}–$aryl; wherein R^{A1} is optionally substituted by one or more substituents selected from the group consisting of halo, $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, hydroxy, cyano, OG^1 and $S(O)_{0–2}G^1$ and wherein two alkyl groups which are attached to the same carbon atom are optionally joined to form a C_{3-7} cycloalkyl ring;

wherein G^1 is $C_{1–6}$ alkyl, $C_{3–7}$ cycloalkyl, $C_{1–6}$ haloalkyl, or phenyl which is optionally substituted by one or more substituents selected from the group consisting of halo, $C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, hydroxy, cyano, nitro, $C_{1–2}$ alkoxy and $C_{1–2}$ haloalkoxy;

R^{A2} is selected from the group consisting of halo, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{1–6}$ haloalkyl, hydroxy, cyano, nitro, NR^1R^2, OG^2 and $S(O)_{0–2}G^2$;

wherein G^2 is $C_{1–6}$ alkyl, $C_{3–7}$ cycloalkyl, $C_{1–6}$ haloalkyl, or phenyl which is optionally substituted by one or more substituents selected from the group consisting of halo, $C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, hydroxy, cyano, nitro, $C_{1–2}$ alkoxy and $C_{1–2}$ haloalkoxy; and

wherein R^1 and R^2 are independently H or C_{1-2} alkyl;

or R^{A2} is absent;

R^C and R^D are each independently H, $C_{1–2}$ alkyl, hydroxy or fluoro; and

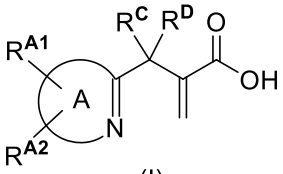
wherein,

the total number of carbon atoms in groups R^{A1} and R^{A2} taken together including their optional substituents is 6–12; and

wherein, when  represents an isoxazole, R^{A1} does not represent phenyl, phenyl substituted by bromo, or phenyl substituted by methyl;

or a pharmaceutically acceptable salt and/or solvate thereof.

67. The compound or pharmaceutically acceptable salt and/or solvate thereof according to claim 56 which is a compound of formula (I):



(I)

wherein,

 represents a 5 membered heteroaryl ring, which in addition to the C=N shown contains one or more further heteroatoms independently selected from N, O and S;

or  represents a 6 membered heteroaryl ring, which in addition to the C=N shown optionally contains one or more further N atoms;

R^{A1} is selected from the group consisting of $C_{1–10}$ alkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $–(CH_2)_{0–6}–C_{3–10}$ cycloalkyl, $–(CH_2)_{0–6}–C_{5–10}$ spirocycloalkyl and $–(CH_2)_{0–6}–$aryl; wherein R^{A1} is optionally substituted by one or more substituents selected from the group consisting of halo, $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, hydroxy, cyano, OG^1 and $S(O)_{0–2}G^1$;

wherein G^1 is $C_{1–6}$ alkyl, $C_{3–7}$ cycloalkyl, $C_{1–6}$ haloalkyl, or phenyl which is optionally substituted by one or more substituents selected from the group consisting of halo, $C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, hydroxy, cyano, nitro, $C_{1–2}$ alkoxy and $C_{1–2}$ haloalkoxy;

R^{A2} is selected from the group consisting of halo, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{1–6}$ haloalkyl, hydroxy, cyano, nitro, NR^1R^2, OG^2 and $S(O)_{0–2}G^2$;

wherein G^2 is $C_{1–6}$ alkyl, $C_{3–7}$ cycloalkyl, $C_{1–6}$ haloalkyl, or phenyl which is optionally substituted by one or more substituents selected from the group consisting of halo, $C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl, hydroxy, cyano, nitro, $C_{1–2}$ alkoxy and $C_{1–2}$ haloalkoxy; and

wherein R^1 and R^2 are independently H or C_{1-2} alkyl;

or R^{A2} is absent;

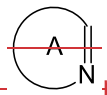
R^C and R^D are each independently H, $C_{1–2}$ alkyl, hydroxy or fluoro; and

wherein,

the total number of carbon atoms in groups R^{A1} and R^{A2} taken together including their optional substituents is 6–12; and

wherein, when  represents an isoxazole, R^{A1} does not represent phenyl, phenyl substituted by bromo, or phenyl substituted by methyl;
or a pharmaceutically acceptable salt and/or solvate thereof.

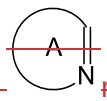
78. The compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 67, wherein  represents a 5 membered heteroaryl ring, which in addition to the C=N shown contains one or more (e.g. one or two) further heteroatoms independently selected from N, O and S.

9. The compound according to any one of claims 1 to 7, wherein  represents a 6 membered heteroaryl ring, which in addition to the C=N shown optionally contains one or more (e.g. one or two) further N atoms.

810. The compound or pharmaceutically acceptable salt and/or solvate thereof according to claim 78, wherein  represents a 5 membered heteroaryl ring selected from the group consisting of imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole and tetrazole.

911. The compound or pharmaceutically acceptable salt and/or solvate thereof according to claim 810, wherein  represents an oxadiazole, in particular 1,2,4-oxadiazole.

10. The compound or pharmaceutically acceptable salt and/or solvate thereof according to claim 9, wherein  is 1,2,4-oxadiazole.

12. The compound according to claim 9, wherein  represents a 6 membered heteroaryl ring selected from the group consisting of pyridine, pyridazine, pyrimidine, pyrazine and triazine.

1113. The compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 1012, wherein R^{A1} is selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $-(CH_2)_{0-6}-C_{3-10}$ cycloalkyl, $-(CH_2)_{0-6}-C_{5-10}$ spirocycloalkyl and $-(CH_2)_{0-}$

$_{6}$–phenyl.

~~14. The compound according to claim 13 wherein R^{A1} is C_{1-10} alkyl e.g. C_{7-8} alkyl e.g. n-octyl.~~

~~15. The compound according to any one of claims 1 to 14 wherein R^{A1} represents $-(CH_2)_{0-6}-C_{3-10}$ cycloalkyl, in particular $-(CH_2)_{0-6}-C_{4-10}$ cycloalkyl, $-(CH_2)_{0-6}-C_{5-10}$ cycloalkyl or $-(CH_2)_{0-6}-C_{5-8}$ cycloalkyl; or R^{A1} is selected from the group consisting of $-(CH_2)_{0-6}-$cyclopropyl, $-(CH_2)_{0-6}-$cyclobutyl, $-(CH_2)_{0-6}-$cyclopentyl, $-(CH_2)_{0-6}-$cyclohexyl, $-(CH_2)_{0-6}-$cycloheptyl, $-(CH_2)_{0-6}-$cyclooctyl and $-(CH_2)_{0-6}-$bicyclo[2.2.1]heptyl; and in particular is $-(CH_2)_{0-6}-$cyclopentyl, $-(CH_2)_{0-6}-$cyclohexyl, $-(CH_2)_{0-6}-$cycloheptyl, $-(CH_2)_{0-6}-$cyclooctyl or $-(CH_2)_{0-6}-$bicyclo[2.2.1]heptyl.~~

~~16. The compound according to claim 15 wherein R^{A1} is $-(CH_2)_0-C_{3-10}$ cycloalkyl.~~

12~~17~~. The compound or pharmaceutically acceptable salt and/or solvate thereof according to ~~any one of~~ claim~~s 1 to 12~~11 wherein R^{A1} is $-(CH_2)_{0-2}-$phenyl ~~such as $-(CH_2)_{0-1}-$phenyl~~.

~~18. The compound according to any one of claims 1 to 17 wherein R^{A1} is not substituted.~~

13~~19~~. The compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 12~~17~~, wherein R^{A1} is substituted by one or more ~~such as one, two, three or four, e.g., one~~ substituent(s) selected from the group consisting of halo, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxy, cyano, OG^1, $S(O)_{0-2}G^1$, SF_5, C_{3-7} cycloalkyl and 5–7-membered heterocyclyl, wherein said C_{3-7} cycloalkyl and said 5–7-membered heterocyclyl are optionally substituted by one or more groups selected from halo ~~(e.g. F)~~, C_{1-3} alkyl ~~(e.g. methyl or n-propyl)~~ and C_{1-3} haloalkyl ~~(e.g. CF_3)~~.

~~20. The compound according to any one of claims 1 to 17, wherein R^{A1} is substituted by one or more such as one, two, three or four, e.g., one substituent(s) selected from the group consisting of halo (e.g. chloro or bromo), C_{1-6} alkyl, C_{1-6} haloalkyl (e.g. CF_3), hydroxy, cyano, OG^1, $S(O)_{0-2}G^1$ (e.g. SG^1), SF_5 and $(CH_2)_{0-3}C_{3-7}$ cycloalkyl (e.g. cyclopropyl or cyclopentyl) wherein said C_{3-7} cycloalkyl is optionally substituted by one or more groups selected from halo (e.g. F), C_{1-3} alkyl (e.g. methyl or n-propyl) and C_{1-3} haloalkyl (e.g. CF_3).~~

14~~21~~. The compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to ~~17, 19 or 20~~13, wherein R^{A1} is substituted by one or more ~~such as one, two, three or four, e.g., one~~ substituent(s) selected from the group consisting of halo ~~(e.g. chloro or bromo)~~, C_{1-2} alkyl, C_{1-2} haloalkyl ~~(e.g. CF_3)~~, hydroxy, cyano, $O(C_{1-2}$ alkyl) and $S(O)_2C_{1-2}$ alkyl.

~~22. The compound according to any one of claims 1 to 17 or 19 to 21, wherein R^{A1} is substituted by one phenyl ring which is optionally substituted by C_{1-2} haloalkyl (e.g., CF_3), C_{1-2} haloalkoxy (e.g., OCF_3), or one or more such as one, two, three or four, e.g., one halo atoms (e.g., chloro and/or fluoro).~~

~~23. The compound according to any one of claims 1 to 17, or 19 to 22, wherein R^{A1} is substituted by two alkyl groups such as C_{1-6} alkyl, for example C_{1-2} alkyl, wherein the two alkyl groups are attached to the same carbon atom in R^{A1} and are joined to form a C_{3-7} cycloalkyl group, such as a cyclopropyl ring.~~

~~24. The compound according to any one of claims 1 to 17 wherein R^{A1} is substituted by one C_{1-6} alkyl group e.g. n-butyl.~~

15~~25~~. The compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 13~~17~~ wherein R^{A1} is substituted by one OG^1 group.

16~~26~~. The compound or pharmaceutically acceptable salt and/or solvate thereof according to claim 15~~25~~ wherein G^1 is $C_{1–6}$ alkyl ~~e.g. n-butyl~~.

~~27. The compound according to any one of claims 1 to 17 wherein R^{A1} is substituted by one SF_5 group.~~

~~28. The compound according to any one of claims 1 to 17 wherein R^{A1} is substituted by one SG^1 group.~~

~~29. The compound according to claim 28 wherein G^1 is C_{1-6} haloalkyl e.g. CF_3.~~

17~~30~~. The compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 16~~29~~, wherein R^{A2} is absent.

~~31. The compound according to any one of claims 1 to 29, wherein R^{A2} is C_{1-6} alkyl.~~

18~~32~~. The compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 17~~31~~, wherein R^C is H and~~/or~~ ~~wherein~~ R^D is H.

19~~33~~. The compound according to claim 1, selected from the group consisting of:
2-((3-octyl-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((5-octyl-1,3,4-oxadiazol-2-yl)methyl)acrylic acid;
2-((5-octyl-1,2,4-oxadiazol-3-yl)methyl)acrylic acid;
2-((3-(4-chlorobenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-chlorophenethyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-heptyl-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(octan-2-yl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(naphthalen-2-ylmethyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(4-chlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(8,8,8-trifluorooctyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(2-methylheptan-2-yl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((1-octyl-1H-1,2,4-triazol-3-yl)methyl)acrylic acid;
2-((3-(3,4-dichlorobenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-(tert-butyl)benzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(3,5-dichlorobenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(7,7,8,8,8-pentafluorooctyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-butylphenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-((4'-chloro-[1,1'-biphenyl]-4-yl)methyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-butylbenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(3-chlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(4-(trifluoromethyl)phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-pentylphenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(2-chlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(4-chlorophenyl)cyclobutyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(2-methyloctan-2-yl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(3-butylphenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-pentylbenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(3-butylbenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(2-(4-chlorophenyl)propan-2-yl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(7,7-difluorooctyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(cyclohexylmethyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(3-(4-chlorophenyl)propyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(octyl-d17)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(oct-7-yn-1-yl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-propylphenethyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((5-octyl-1,3,4-thiadiazol-2-yl)methyl)acrylic acid;
2-((4-octylthiazol-2-yl)methyl)acrylic acid;
2-((4-octyloxazol-2-yl)methyl)acrylic acid;

(R)-2-((3-(octan-2-yl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(4-ethylphenethyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(4-(trifluoromethyl)benzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

(S)-2-((3-(octan-2-yl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(1-(4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(1-(4-methoxyphenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(4-(trifluoromethoxy)benzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(7,7,8-trifluorooctyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(4-(1-(trifluoromethyl)cyclopropyl)benzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(1-(4-(trifluoromethoxy)phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(1-(4-bromophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(4-butoxybenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(1-(4-chloro-3-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-nonyl-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(8,8,8-trifluorooctan-2-yl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((5-octylthiazol-2-yl)methyl)acrylic acid;

2-((3-undecyl-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(oct-3-yn-1-yl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(8,8-difluorooctyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((5-octyloxazol-2-yl)methyl)acrylic acid;

2-((3-(9,9,9-trifluorononyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(4-butoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(dispiro[3.1.3^{6}.1^{4}]decan-2-yl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-cyclooctyl-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-cyclohexyl-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-cycloheptyl-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(adamantan-1-yl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(1-(3,5-dichlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(6-methylheptyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(4-neopentylbenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(4-propylbenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(4-(1,1-difluoropropyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(4-(1-propylcyclopropyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(4-(3,3,3-trifluoropropyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-((4-chlorophenyl)difluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(4-(5,5,5-trifluoropentyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(4-(2-cyclopropylethyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(1-(4-(pentafluoro-λ^{6}-sulfaneyl)phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(1-(4-(difluoromethoxy)phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-(1,1-difluoropentyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(4-butoxyphenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-(1,1,2,2-tetrafluoroethoxy)benzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(4-(1,1,2,2-tetrafluoroethoxy)phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((5-(1,1-difluorooctyl)-1,2,4-oxadiazol-3-yl)methyl)acrylic acid;
2-((5-((4-chlorophenyl)difluoromethyl)-1,2,4-oxadiazol-3-yl)methyl)acrylic acid;
2-((5-((4-bromophenyl)difluoromethyl)-1,2,4-oxadiazol-3-yl)methyl)acrylic acid;
2-((3-(1-(4-((trifluoromethyl)thio)phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(6,6,8,8,8-pentafluorooctyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1,1-difluorooctyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((5-((4-chlorophenyl)difluoromethyl)-1,2,4-oxadiazol-3-yl)methyl)acrylic acid;
2-((3-((4-bromophenyl)difluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-((4-butylphenyl)difluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(difluoro(4-(trifluoromethyl)phenyl)methyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-(1,1-difluoropentyl)benzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(difluoro(4-(trifluoromethoxy)phenyl)methyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((5-(4-butylbenzyl)-1,2,4-oxadiazol-3-yl)methyl)acrylic acid;
2-((5-(4-butoxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)acrylic acid;
2-((5-(difluoro(4-(trifluoromethyl)phenyl)methyl)-1,2,4-oxadiazol-3-yl)methyl)acrylic acid;
2-((3-(4-(1,1-difluorobutyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((5-(1-(4-(trifluoromethoxy)phenyl)cyclopropyl)-1,2,4-oxadiazol-3-yl)methyl)acrylic acid;
2-((3-(4-(benzyloxy)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((4-(4-butylphenyl)oxazol-2-yl)methyl)acrylic acid;
2-((5-octylisoxazol-3-yl)methyl)acrylic acid;
2-((4-(1-(4-(trifluoromethyl)phenyl)cyclopropyl)oxazol-2-yl)methyl)acrylic acid;
2-((4-octylpyridin-2-yl)methyl)acrylic acid trifluoroacetic acid salt;
2-((5-octylpyridin-2-yl)methyl)acrylic acid trifluoroacetic acid salt;
2-((5-octylpyrimidin-2-yl)methyl)acrylic acid;
2-((5-octylpyrazin-2-yl)methyl)acrylic acid;
2-((6-octylpyridazin-3-yl)methyl)acrylic acid;
2-((5-methyl-4-octyloxazol-2-yl)methyl)acrylic acid;
2-(hydroxy(3-octyl-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((5-butyl-4-(4-chlorophenyl)oxazol-2-yl)methyl)acrylic acid;
2-(methoxy(3-octyl-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(4-cyclobutoxyphenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-cyclopentylbenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-(1-(4-cyclopropoxyphenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(4-cyclopentylphenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(4-iodophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-iodophenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(difluoro(4-iodophenyl)methyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-(pentafluoro-λ^6-sulfaneyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-(pentafluoro-λ^6-sulfaneyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((4,5-dibutyloxazol-2-yl)methyl)acrylic acid;
2,2-((3-(difluoro(4-(pentafluoro-λ^6-sulfaneyl)phenyl)methyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2,2-((3-(difluoro(4-fluorophenyl)methyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-butylphenoxy)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((4-(4-butylbenzyl)oxazol-2-yl)methyl)acrylic acid;
2-((3-(4-cyclobutylbenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-butoxy-3-fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(4-cyclobutylphenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-(pyrrolidin-1-yl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(3,5-dichloro-4-fluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(3,5-dichloro-4-fluorobenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(4-chloro-3,5-difluorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(3-chloro-4-(trifluoromethyl)phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(3-chloro-4-(trifluoromethyl)benzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(4-bromo-3-chlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-bromo-3-chlorobenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(3-chloro-4-methoxyphenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(3-chloro-4-methylphenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-cyclobutoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-cyclopentyloxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
(R)-2-((3-(4-(sec-butoxy)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
(S)-2-((3-(4-(sec-butoxy)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-(4,4,4-trifluorobutoxy)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-(1-propylcyclopropyl)benzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4,6-dichloro-2,3-dihydro-1H-inden-1-yl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-propoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-((3-chloro-4-methoxyphenyl)difluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-((3-chloro-4-methylphenyl)difluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;

2-((3-((4-chlorophenyl)fluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-((3,5-dichloro-4-fluorophenyl)difluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-((4-bromo-3-chlorophenyl)difluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(difluoro(4-((trifluoromethyl)thio)phenyl)methyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-(1-(3-(1-(4-(trifluoromethyl)phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)cyclopropyl)acrylic acid;
3-methyl-2-methylene-3-(3-(1-(4-(trifluoromethyl)phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)butanoic acid;
2-((3-(1-(4-((trifluoromethyl)sulfinyl)phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-((trifluoromethyl)thio)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-(3-methoxypropoxy)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-butoxy-3-chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-butoxy-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-butoxy-3,5-difluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(3-chloro-4-methoxybenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-chloro-3,5-difluorobenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(3-chloro-4-methylbenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
(E)-2-methyl-3-(3-octyl-1,2,4-oxadiazol-5-yl)acrylic acid;
(E)-3-(3-(4-butoxyphenyl)-1,2,4-oxadiazol-5-yl)-2-methylacrylic acid;
(E)-3-(3-(1-(4-bromophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)-2-methylacrylic acid;
(E)-2-methyl-3-(3-(1-(4-(pentafluoro-λ^6-sulfaneyl)phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)acrylic acid;
(E)-2-methyl-3-(3-(1-(4-((trifluoromethyl)thio)phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)acrylic acid;
2-((6-(4-chlorobenzyl)pyridin-2-yl)methyl)acrylic acid trifluoroacetic acid salt;
2-(1-(3-(difluoro(4-(trifluoromethyl)phenyl)methyl)-1,2,4-oxadiazol-5-yl)cyclopropyl)acrylic acid;
2-methylene-3-(3-(1-(4-(trifluoromethyl)phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)butanoic acid;
2-((6-(1-(4-chlorophenyl)cyclopropyl)pyridin-2-yl)methyl)acrylic acid; and
2-((3-(1-(4-bromo-3,5-dichlorophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
or a pharmaceutically acceptable salt and/or solvate of any one thereof.

~~34. The compound according to claim 33, selected from the group consisting of:~~
~~2-((3-octyl-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;~~
~~2-((5-octyl-1,3,4-oxadiazol-2-yl)methyl)acrylic acid; and~~
~~2-((5-octyl-1,2,4-oxadiazol-3-yl)methyl)acrylic acid;~~
~~or a pharmaceutically acceptable salt and/or solvate thereof.~~

~~35. The compound according to claim 34, which is 2-((3-octyl-1,2,4-oxadiazol-5-yl)methyl)acrylic acid or a pharmaceutically acceptable salt and/or solvate thereof.~~

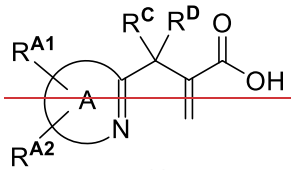
2036. The compound according to claim 3319, selected from the group consisting of:
2-((3-(4-butylbenzyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(4-bromophenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(4-butoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
2-((3-(1-(4-((trifluoromethyl)thio)phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid; and
2-((3-(1-(4-(pentafluoro-λ^6-sulfaneyl)phenyl)cyclopropyl)-1,2,4-oxadiazol-5-yl)methyl)acrylic acid;
or a pharmaceutically acceptable salt and/or solvate of any one thereof.

2137. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 2036 and one or more pharmaceutically acceptable diluents or carriers.

3822. The compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 3620, or a pharmaceutical composition according to claim 37 21 for use as a medicament.

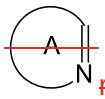
3923. The compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 3620, or a pharmaceutical composition according to claim 37 21 for use in treating or preventing an inflammatory disease or a disease associated with an undesirable immune response.

~~40. A compound of formula (I):~~

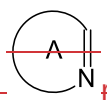


(I)

~~wherein,~~



~~represents a 5 membered heteroaryl ring, which in addition to the C=N shown contains one or more further heteroatoms independently selected from N, O and S;~~

~~or~~ 

~~represents a 6 membered heteroaryl ring, which in addition to the C=N shown optionally contains one or more further N atoms;~~

~~R^{A1} is selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $-(CH_2)_{0-6}-C_{3-10}$ cycloalkyl, $-(CH_2)_{0-6}-C_{5-10}$ spirocycloalkyl and $-(CH_2)_{0-6}-$aryl; wherein R^{A1} is optionally substituted by one or more substituents selected from the group consisting of halo, C_{1-6} alkyl, C_{1-}~~

$_{6}$-haloalkyl, hydroxy, cyano, OG^1 and $S(O)_{0-2}G^1$, wherein two alkyl groups which are attached to the same carbon atom are optionally joined to form a C_{3-7} cycloalkyl ring, or R^{A1} is optionally substituted by one phenyl ring which is optionally substituted by C_{1-2} haloalkyl, C_{1-2} haloalkoxy or one or more halo atoms;

wherein G^1 is C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, or phenyl which is optionally substituted by one or more substituents selected from the group consisting of halo, C_{1-2} alkyl, C_{1-2} haloalkyl, hydroxy, cyano, nitro, C_{1-2} alkoxy and C_{1-2} haloalkoxy;

R^{A2} is selected from the group consisting of halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, hydroxy, cyano, nitro, NR^1R^2, OG^2 and $S(O)_{0-2}G^2$;

wherein G^2 is C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, or phenyl which is optionally substituted by one or more substituents selected from the group consisting of halo, C_{1-2} alkyl, C_{1-2} haloalkyl, hydroxy, cyano, nitro, C_{1-2} alkoxy and C_{1-2} haloalkoxy; and

wherein R^1 and R^2 are independently H or C_{1-2} alkyl or, taken together, R^1 and R^2 may combine to form a 5–7-membered heterocyclic ring;

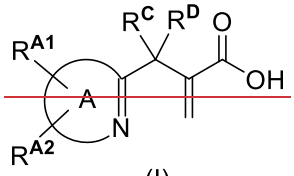
or R^{A2} is absent;

R^C and R^D are each independently H, C_{1-2} alkyl, hydroxy or fluoro;

or a pharmaceutically acceptable salt and/or solvate thereof;

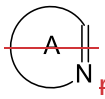
for use in treating or preventing an inflammatory disease or a disease associated with an undesirable immune response.

41. A compound of formula (I):

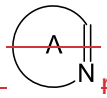


(I)

wherein,



represents a 5 membered heteroaryl ring, which in addition to the C=N shown contains one or more further heteroatoms independently selected from N, O and S;

or 

represents a 6 membered heteroaryl ring, which in addition to the C=N shown optionally contains one or more further N atoms;

R^{A1} is selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $-(CH_2)_{0-6}-C_{3-10}$ cycloalkyl, $-(CH_2)_{0-6}-C_{5-10}$ spirocycloalkyl and $-(CH_2)_{0-6}-$aryl; wherein R^{A1} is optionally substituted by one or more substituents selected from the group consisting of halo, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxy, cyano, OG^1 and $S(O)_{0-2}G^1$;

wherein G^1 is C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, or phenyl which is optionally

substituted by one or more substituents selected from the group consisting of halo, C_{1-2} alkyl, C_{1-2} haloalkyl, hydroxy, cyano, nitro, C_{1-2} alkoxy and C_{1-2} haloalkoxy;

R^{A2} is selected from the group consisting of halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, hydroxy, cyano, nitro, NR^1R^2, OG^2 and $S(O)_{0-2}G^2$;

wherein G^2 is C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, or phenyl which is optionally substituted by one or more substituents selected from the group consisting of halo, C_{1-2} alkyl, C_{1-2} haloalkyl, hydroxy, cyano, nitro, C_{1-2} alkoxy and C_{1-2} haloalkoxy; and

wherein R^1 and R^2 are independently H or C_{1-2} alkyl;

or R^{A2} is absent;

R^C and R^D are each independently H, C_{1-2} alkyl, hydroxy or fluoro;

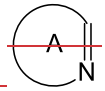
or a pharmaceutically acceptable salt and/or solvate thereof;

for use in treating or preventing an inflammatory disease or a disease associated with an undesirable immune response.

42. The compound for use according to claim 40 or 41 wherein R^{A1} is $-(CH_2)_{1-6}-C_{3-10}$ cycloalkyl.

43. The compound for use according to any one of claims 40 to 42 wherein R^{A1} is optionally substituted by one or more (such as one, two, three or four e.g., one) substituents selected from the group consisting of halo, C_{1-6} alkyl, C_{1-6} haloalkyl, hydroxy, cyano, OG^1 and $S(O)_{0-2}G^1$ and wherein two alkyl groups which are attached to the same carbon atom are optionally joined to form a C_{3-7} cycloalkyl ring.

44. The compound for use according to any one of claims 40 to 43 wherein the total number of carbon atoms in groups R^{A1} and R^{A2} taken together including their optional substituents is 6–14 e.g. 6–12.

45. The compound for use according to any one of claims 40 to 44 wherein, when 

represents an isoxazole, R^{A1} does not represent phenyl, phenyl substituted by bromo, or phenyl substituted by methyl.

4624. Use of a compound or pharmaceutically acceptable salt and/or solvate thereof according to any one of claims 1 to 2036 or a pharmaceutical composition according to claim 2137 in the manufacture of a medicament for treating or preventing an inflammatory disease or a disease associated with an undesirable immune response.

47. A method of treating or preventing an inflammatory disease or a disease associated with

~~an undesirable immune response, which comprises administering a compound according to any one of claims 1 to 36 or a pharmaceutical composition according to claim 37.~~

~~48. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 1 to 47, for treating an inflammatory disease or a disease associated with an undesirable immune response.~~

~~49. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 1 to 47, for preventing an inflammatory disease or a disease associated with an undesirable immune response.~~

~~50. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 1 to 47, for treating or preventing an inflammatory disease.~~

~~51. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 1 to 47, for treating or preventing a disease associated with an undesirable immune response.~~

~~52~~25. The compound, pharmaceutical composition, compound for use~~,~~ or use ~~or method~~ according to any one of claims 1 to ~~51~~24, wherein the inflammatory disease or disease associated with an undesirable immune response is, or is associated with, a disease selected from the group consisting of: psoriasis (including chronic plaque, erythrodermic, pustular, guttate, inverse and nail variants), asthma, chronic obstructive pulmonary disease (COPD, including chronic bronchitis and emphysema), heart failure (including left ventricular failure), myocardial infarction, angina pectoris, other atherosclerosis and/or atherothrombosis-related disorders (including peripheral vascular disease and ischaemic stroke), a mitochondrial and neurodegenerative disease ~~(such as Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, retinitis pigmentosa or mitochondrial encephalomyopathy)~~, autoimmune paraneoplastic retinopathy, transplantation rejection (including antibody-mediated and T cell-mediated forms), multiple sclerosis, transverse myelitis, ischaemia-reperfusion injury ~~(e.g. during elective surgery such as cardiopulmonary bypass for coronary artery bypass grafting or other cardiac surgery, following percutaneous coronary intervention, following treatment of acute ST-elevation myocardial infarction or ischaemic stroke, organ transplantation, or acute compartment syndrome)~~, AGE-induced genome damage, an inflammatory bowel disease ~~(e.g. Crohn's disease or ulcerative colitis)~~, primary sclerosing cholangitis (PSC), PSC-autoimmune hepatitis overlap syndrome, non-alcoholic fatty liver disease (non-alcoholic steatohepatitis), rheumatica, granuloma annulare, cutaneous lupus erythematosus (CLE), systemic lupus erythematosus (SLE), lupus nephritis, drug-induced lupus, autoimmune myocarditis or myopericarditis,

Dressler’s syndrome, giant cell myocarditis, post-pericardiotomy syndrome, drug-induced hypersensitivity syndromes (including hypersensitivity myocarditis), eczema, sarcoidosis, erythema nodosum, acute disseminated encephalomyelitis (ADEM), neuromyelitis optica spectrum disorders, MOG (myelin oligodendrocyte glycoprotein) antibody-associated disorders (including MOG-EM), optic neuritis, CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids), diffuse myelinoclastic sclerosis, Addison's disease, alopecia areata, ankylosing spondylitis, other spondyloarthritides (including peripheral spondyloarthritis, that is associated with psoriasis, inflammatory bowel disease, reactive arthritis or juvenile onset forms), antiphospholipid antibody syndrome, autoimmune hemolytic anaemia, autoimmune hepatitis, autoimmune inner ear disease, pemphigoid (including bullous pemphigoid, mucous membrane pemphigoid, cicatricial pemphigoid, herpes gestationis or pemphigoid gestationis, ocular cicatricial pemphigoid), linear IgA disease, Behçet's disease, celiac disease, Chagas disease, dermatomyositis, diabetes mellitus type I, endometriosis, Goodpasture's syndrome, Graves' disease, Guillain-Barre syndrome and its subtypes (including acute inflammatory demyelinating polyneuropathy, AIDP, acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), pharyngeal-cervical-brachial variant, Miller-Fisher variant and Bickerstaff's brainstem encephalitis), progressive inflammatory neuropathy, Hashimoto's disease, hidradenitis suppurativa, inclusion body myositis, necrotising myopathy, Kawasaki disease, IgA nephropathy, Henoch-Schonlein purpura, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura (TTP), Evans’ syndrome, interstitial cystitis, mixed connective tissue disease, undifferentiated connective tissue disease, morphea, myasthenia gravis (including MuSK antibody positive and seronegative variants), narcolepsy, neuromyotonia, pemphigus vulgaris, pernicious anaemia, psoriatic arthritis, polymyositis, primary biliary cholangitis (also known as primary biliary cirrhosis), rheumatoid arthritis, palindromic rheumatism, schizophrenia, autoimmune (meningo-)encephalitis syndromes, scleroderma, Sjogren's syndrome, stiff person syndrome, polymylagia rheumatica, giant cell arteritis (temporal arteritis), Takayasu arteritis, polyarteritis nodosa, Kawasaki disease, granulomatosis with polyangitis (GPA; formerly known as Wegener’s granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss syndrome), microscopic polyarteritis/polyangiitis, hypocomplementaemic urticarial vasculitis, hypersensitivity vasculitis, cryoglobulinemia, thromboangiitis obliterans (Buerger’s disease), vasculitis, leukocytoclastic vasculitis, vitiligo, acute disseminated encephalomyelitis, adrenoleukodystrophy, Alexander’s disease, Alper's disease, balo concentric sclerosis or Marburg disease, cryptogenic organising pneumonia (formerly known as bronchiolitis obliterans organizing pneumonia), Canavan disease, central nervous system vasculitic syndrome, Charcot-Marie-Tooth disease, childhood ataxia with central nervous system hypomyelination, chronic inflammatory demyelinating polyneuropathy (CIDP), diabetic retinopathy, globoid cell leukodystrophy (Krabbe disease), graft-versus-host disease (GVHD) (including acute and chronic

forms, as well as intestinal GVHD), hepatitis C (HCV) infection or complication, herpes simplex viral infection or complication, human immunodeficiency virus (HIV) infection or complication, lichen planus, monomelic amyotrophy, cystic fibrosis, pulmonary arterial hypertension (PAH, including idiopathic PAH), lung sarcoidosis, idiopathic pulmonary fibrosis, paediatric asthma, atopic dermatitis, allergic dermatitis, contact dermatitis, allergic rhinitis, rhinitis, sinusitis, conjunctivitis, allergic conjunctivitis, keratoconjunctivitis sicca, dry eye, xerophthalmia, glaucoma, macular oedema, diabetic macular oedema, central retinal vein occlusion (CRVO), macular degeneration (including dry and/or wet age related macular degeneration, AMD), post-operative cataract inflammation, uveitis (including posterior, anterior, intermediate and pan uveitis), iridocyclitis, scleritis, corneal graft and limbal cell transplant rejection, gluten sensitive enteropathy (coeliac disease), dermatitis herpetiformis, eosinophilic esophagitis, achalasia, autoimmune dysautonomia, autoimmune encephalomyelitis, autoimmune oophoritis, autoimmune orchitis, autoimmune pancreatitis, aortitis and periaortitis, autoimmune retinopathy, autoimmune urticaria, Behcet's disease, (idiopathic) Castleman's disease, Cogan's syndrome, IgG4-related disease, retroperitoneal fibrosis, juvenile idiopathic arthritis including systemic juvenile idiopathic arthritis (Still's disease), adult-onset Still's disease, ligneous conjunctivitis, Mooren's ulcer, pityriasis lichenoides et varioliformis acuta (PLEVA, also known as Mucha-Habermann disease), multifocal motor neuropathy (MMN), paediatric acute-onset neuropsychiatric syndrome (PANS) (including paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)), paraneoplastic syndromes (including paraneoplastic cerebellar degeneration, Lambert-Eaton myaesthenic syndrome, limbic encephalitis, brainstem encephalitis, opsoclonus myoclonus ataxia syndrome, anti-NMDA receptor encephalitis, thymoma-associated multiorgan autoimmunity), perivenous encephalomyelitis, reflex sympathetic dystrophy, relapsing polychondritis, sperm & testicular autoimmunity, Susac's syndrome, Tolosa-Hunt syndrome, Vogt-Koyanagi-Harada Disease, anti-synthetase syndrome, autoimmune enteropathy, immune dysregulation polyendocrinopathy enteropathy X-linked (IPEX), microscopic colitis, autoimmune lymphoproliferative syndrome (ALPS), autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APEX), gout, pseudogout, amyloid (including AA or secondary amyloidosis), eosinophilic fasciitis (Shulman syndrome) progesterone hypersensitivity (including progesterone dermatitis), amilial Mediterranean fever (FMF), tumour necrosis factor (TNF) receptor-associated periodic fever syndrome (TRAPS), hyperimmunoglobulinaemia D with periodic fever syndrome (HIDS), PAPA (pyogenic arthritis, pyoderma gangrenosum, severe cystic acne) syndrome, deficiency of interleukin-1 receptor antagonist (DIRA), deficiency of the interleukin-36-receptor antagonist (DITRA), cryopyrin-associated periodic syndromes (CAPS) (including familial cold autoinflammatory syndrome [FCAS], Muckle-Wells syndrome, neonatal onset multisystem inflammatory disease [NOMID]), NLRP12-associated autoinflammatory disorders (NLRP12AD), periodic fever aphthous stomatitis (PFAPA), chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), Majeed syndrome, Blau

syndrome (also known as juvenile systemic granulomatosis), macrophage activation syndrome, chronic recurrent multifocal osteomyelitis (CRMO), familial cold autoinflammatory syndrome, mutant adenosine deaminase 2 and monogenic interferonopathies (including Aicardi-Goutières syndrome, retinal vasculopathy with cerebral leukodystrophy, spondyloenchondrodysplasia, STING [stimulator of interferon genes]-associated vasculopathy with onset in infancy, proteasome associated autoinflammatory syndromes, familial chilblain lupus, dyschromatosis symmetrica hereditaria), Schnitzler syndrome; familial cylindromatosis, congenital B cell lymphocytosis, OTULIN-related autoinflammatory syndrome, type 2 diabetes mellitus, insulin resistance and the metabolic syndrome (including obesity-associated inflammation), atherosclerotic disorders ~~(e.g. myocardial infarction, angina, ischaemic heart failure, ischaemic nephropathy, ischaemic stroke, peripheral vascular disease, aortic aneurysm)~~, renal inflammatory disorders ~~(e.g. diabetic nephropathy, membranous nephropathy, minimal change disease, crescentic glomerulonephritis, acute kidney injury, renal transplantation)~~.

~~53. The compound or pharmaceutical composition for use according to claim 52, wherein the inflammatory disease or disease associated with an undesirable immune response is selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, multiple sclerosis, psoriasis, Crohn's disease, ulcerative colitis, uveitis, cryopyrin-associated periodic syndromes, Muckle-Wells syndrome, juvenile idiopathic arthritis and chronic obstructive pulmonary disease.~~

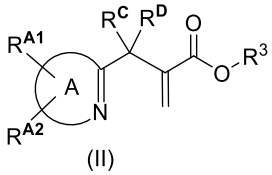
~~54. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 1 to 53, wherein the compound is for administration to a human subject.~~

~~55~~26. The compound, pharmaceutical composition, compound for use~~,~~ or use ~~or method~~ according to any one of claims 1 to ~~54~~25, for use in combination with a further therapeutic agent, ~~such as~~selected from a corticosteroid (glucocorticoid), retinoid ~~(e.g. acitretin, isotretinoin, tazarotene)~~, anthralin, vitamin D analogue ~~(e.g. cacitriol, calcipotriol)~~, calcineurin inhibitors ~~(e.g. tacrolimus, pimecrolimus)~~, phototherapy or photochemotherapy ~~(e.g. psoralen ultraviolet irradiation, PUVA)~~ or other form of ultraviolet light irradiation therapy, ciclosporine, a thiopurine ~~(e.g. azathioprine, 6-mercaptopurine)~~, methotrexate, an anti-TNFα agents ~~(e.g. infliximab, etanercept, adalimumab, certolizumab, golimumab or a biosimilar)~~, phosphodiesterase-4 (PDE4) inhibition ~~(e.g. apremilast, crisaborole)~~, anti-IL-17 agent ~~(e.g. brodalumab, ixekizumab, secukinumab)~~, anti-IL12/IL-23 agent ~~(e.g. ustekinumab, briakinumab)~~, anti-IL-23 agent ~~(e.g. guselkumab, tildrakizumab)~~, JAK (Janus Kinase) inhibitor ~~(e.g. tofacitinib, ruxolitinib, baricitinib, filgotinib, upadacitinib)~~, plasma exchange, intravenous immune globulin (IVIG), cyclophosphamide, anti-CD20 B cell depleting agent ~~(e.g. rituximab, ocrelizumab, ofatumumab, obinutuzumab)~~, anthracycline analogue ~~(e.g. mitoxantrone)~~, cladribine, sphingosine 1-phosphate

receptor modulator or sphingosine analogue ~~(e.g. fingolimod, siponimod, ozanimod, etrasimod)~~, interferon beta preparation (including interferon beta 1b/1a), glatiramer, anti-CD3 therapy ~~(e.g. OKT3)~~, anti-CD52 targeting agent ~~(e.g. alemtuzumab)~~, leflunomide, teriflunomide, gold compound, laquinimod, potassium channel blocker ~~(e.g. dalfampridine/4-aminopyridine)~~, mycophenolic acid, mycophenolate mofetil, purine analogue ~~(e.g. pentostatin)~~, mTOR (mechanistic target of rapamycin) pathway inhibitor ~~(e.g. sirolimus, everolimus)~~, anti-thymocyte globulin (ATG), IL-2 receptor (CD25) inhibitor ~~(e.g. basiliximab, daclizumab)~~, anti-IL-6 receptor or anti-IL-6 agent ~~(e.g. tocilizumab, siltuximab)~~, Bruton's tyrosine kinase (BTK) inhibitor ~~(e.g. ibrutinib)~~, tyrosine kinase inhibitor ~~(e.g. imatinib)~~, ursodeoxycholic acid, hydroxychloroquine, chloroquine, B cell activating factor (BAFF, also known as BLyS, B lymphocyte stimulator) inhibitor ~~(e.g. belimumab, blisibimod)~~, other B cell targeted therapy including a fusion protein targeting both APRIL (A PRoliferation-Inducing Ligand) and BLyS ~~(e.g. atacicept)~~, PI3K inhibitor including pan-inhibitor or one targeting the p110δ and/or p110γ containing isoforms ~~(e.g. idelalisib, copanlisib, duvelisib)~~, an interferon α receptor inhibitor ~~(e.g. anifrolumab, sifalimumab)~~, T cell co-stimulation blocker ~~(e.g. abatacept, belatacept)~~, thalidomide and its derivatives ~~(e.g. lenalidomide)~~, dapsone, clofazimine, a leukotriene antagonist ~~(e.g. montelukast)~~, theophylline, anti-IgE therapy ~~(e.g. omalizumab)~~, an anti-IL-5 agent ~~(e.g. mepolizumab, reslizumab)~~, a long-acting muscarinic agent ~~(e.g. tiotropium, aclidinium, umeclidinium)~~, a PDE4 inhibitor ~~(e.g. roflumilast)~~, riluzole, a free radical scavenger ~~(e.g. edaravone)~~, a proteasome inhibitor ~~(e.g. bortezomib)~~, a complement cascade inhibitor including one directed against C5 ~~(e.g. eculizumab)~~, immunoadsor, antithymocyte globulin, 5-aminosalicylates and their derivatives ~~(e.g. sulfasalazine, balsalazide, mesalamine)~~, an anti-integrin agent including one targeting α4β1 and/or α4β7 integrins ~~(e.g. natalizumab, vedolizumab)~~, an anti-CD11-α agent ~~(e.g. efalizumab)~~, a non-steroidal anti-inflammatory drug (NSAID) including a salicylate ~~(e.g. aspirin)~~, a propionic acid ~~(e.g. ibuprofen, naproxen)~~, an acetic acid ~~(e.g. indomethacin, diclofenac, etodolac)~~, an oxicam, ~~(e.g. meloxicam)~~ a fenamate ~~(e.g. mefenamic acid)~~, a selective or relatively selective COX-2 inhibitor ~~(e.g. celecoxib, etroxicoxib, valdecoxib and etodolac, meloxicam, nabumetone)~~, colchicine, an IL-4 receptor inhibitor ~~(e.g. dupilumab)~~, topical/contact immunotherapy ~~(e.g. diphenylcyclopropenone, squaric acid dibutyl ester)~~, anti-IL-1 receptor therapy ~~(e.g. anakinra)~~, IL-1β inhibitor ~~(e.g. canakinumab)~~, IL-1 neutralising therapy ~~(e.g. rilonacept)~~, chlorambucil, a specific antibiotic with immunomodulatory properties and/or ability to modulate NRF2 ~~(e.g. tetracyclines including minocycline, clindamycin, macrolide antibiotics)~~, anti-androgenic therapy ~~(e.g. cyproterone, spironolactone, finasteride)~~, pentoxifylline, ursodeoxycholic acid, obeticholic acid, fibrate, a cystic fibrosis transmembrane conductance regulator (CFTR) modulator, a VEGF (vascular endothelial growth factor) inhibitor ~~(e.g. bevacizumab, ranibizumab, pegaptanib, aflibercept)~~, pirfenidone ~~or~~ and mizoribine.

~~56~~27. A compound selected from the group consisting of:

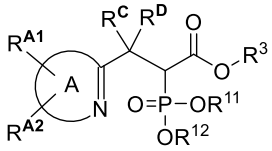
- ~~A~~ a compound of formula (II):



(II)

or salt thereof, wherein , R^{A1}, R^{A2}, R^C and R^D are defined in any one of claims 1 to 20~~36~~ and R^3 represents C_{1-4} alkyl optionally substituted with halo~~.~~;

- ~~57. A~~ a compound of formula (III):

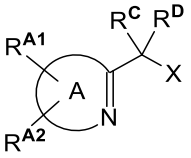


(III)

or salt thereof, wherein R^{A1} is selected from the group consisting of $C_{2–10}$ alkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $–(CH_2)_{0–6}–C_{3–10}$ cycloalkyl, $–(CH_2)_{0–6}–C_{5–10}$ spirocycloalkyl, $–(CH_2)_{0–6}–$aryl and O–aryl, and wherein R^{A1} is optionally substituted as defined in any one of claims 1 to 6,

- , ~~R^{A1},~~ R^{A2}, R^C and R^D are defined in any one of claims 1 to 20~~36~~ and R^3, R^{11} and R^{12} independently represent C_{1-4} alkyl optionally substituted with halo~~.~~;

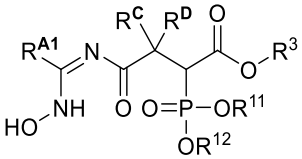
- ~~58. A~~ a compound of formula (V):



(V)

or salt thereof, wherein , R^{A1}, R^{A2}, R^C and R^D are defined in any one of claims 1 to 20~~36~~, and X ~~represents a leaving group~~is selected from the group consisting of chloro, bromo, iodo, alkanesulfonate and arenesulfonate~~.~~;

- ~~59. A~~ a compound of formula (VIII):

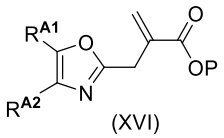


(VIII)

or a salt thereof;

wherein R^{A1}, R^{C} and R^{D} are as defined in any one of claims 1 to 2036, and R^{3}, R^{11} and R^{12} independently represent C_{1-4} alkyl ~~such as methyl or *tert*-butyl~~ optionally substituted with halo~~.~~;

- ~~60. A~~ a compound of formula (XVI):

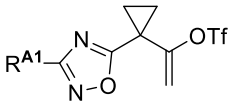


(XVI) ;

or a salt thereof;

wherein R^{A1} and R^{A2} are defined in any one of claims 1 to 2036 and P is a carboxylic acid protecting group ~~such as *para*-methoxybenzyl.~~; and

- ~~61. A~~ a compound of formula (XXIV):

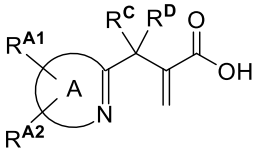


(XXIV) ;

or a salt thereof;

wherein R^{A1} is defined in any one of claims 1 to 2036.

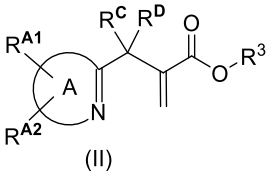
~~62~~28. A process for preparing the compound of formula (I):



(I)

or a salt ~~, such as a pharmaceutically acceptable salt~~ thereof which comprises

(a) hydrolysing the ester moiety in a compound of formula (II):



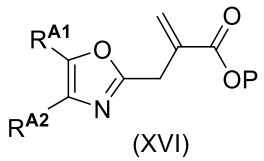
(II)

or a salt thereof,

wherein , R^{A1}, R^{A2}, R^{C} and R^{D} and R^{3} are defined in any one of claims 1 to 2036 and R^{3} represents C_{1-4} alkyl optionally substituted with halo; or~~.~~

(b)

~~63. A process for preparing a compound of formula (I) or a salt, such as pharmaceutically acceptable salt thereof, which comprises~~ deprotecting a compound of formula (XVI):



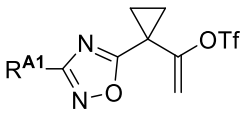
(XVI) ;

or a salt thereof;

wherein R^{A1} and R^{A2} are defined in any one of claims 1 to 20~~36~~ and P is a carboxylic acid protecting group ~~such as *para*-methoxy benzyl~~; or

(c)~~.~~

~~64. A process for preparing a compound of formula (I) or a salt, such as pharmaceutically acceptable salt thereof, which comprises~~ reacting a compound of formula (XXIV):



(XXIV) ;

or a salt thereof;

with carbon monoxide in the presence of a metal catalyst ~~such as a palladium catalyst~~, followed by hydrolysis ~~(such as basic hydrolysis e.g. aqueous K_2CO_3, followed by acidification)~~ to give the compounds of formula (I);

wherein R^{A1} is defined in any one of claims 1 to 20~~36~~.

29. The compound, pharmaceutical composition, compound for use or use according to any one of claims 1 to 26, which is a compound of formula (I).

30. The compound, pharmaceutical composition, compound for use or use according to any one of claims 1 to 26, which is a pharmaceutically acceptable salt of a compound of formula (I).

~~65. A compound according to any one of claims 1 to 64 which is in natural isotopic form.~~

~~66. The compound, pharmaceutical composition, compound for use, use, method or process according to any one of claims 1 to 65 wherein the compound of formula (I) is in the form of a salt, such as a pharmaceutically acceptable salt (e.g., a tromethamine salt) thereof.~~

~~67. The compound according to claim 1 which is a tromethamine salt of 2-((3-octyl-1,2,4-oxadiazol-5-yl)methyl)acrylic acid.~~

~~68. The compound according to claim 67 wherein the tromethamine salt of 2-((3-octyl-1,2,4-oxadiazol-5-yl)methyl)acrylic acid is in crystalline form.~~

~~69. The compound according to claim 68 wherein the crystalline form has an X-ray powder diffraction pattern with at least one (for example, one, two, three, four, five, six, seven, eight, nine, ten, eleven or twelve) peaks selected from peaks at 12.9, 13.5, 17.0, 18.0, 19.9, 20.1, 20.6, 21.0, 23.0, 23.4, 23.6 or 29.3 (± 0.2 degrees, 2-theta values) such as at least one (for example, one, two, three, four, five or six) peaks selected from peaks at 12.9, 17.0, 19.9, 20.1, 23.0, and 23.4 (± 0.2 degrees, 2-theta values).~~