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(71) Applicant: **SITRYX THERAPEUTICS LIMITED** [GB/GB]; 101 Bellhouse Building, Magdalen Centre, The Oxford Science Park, Oxford OX4 4GA (GB).

(72) Inventors: **COOKE, Michael Liam**; c/o Sygnature Discovery Limited, The Discovery Building, Biocity, Pennyfoot Street, Nottingham, Nottinghamshire NG1 1GF (GB). **FYFE, Matthew Colin Thor**; c/o Sitryx Therapeutics Limited, 101 Bellhouse Building, Magdalen Centre, The Oxford Science Park, Oxford OX4 4GA (GB). **TEOBALD, Barry John**; c/o Sitryx Therapeutics Limited, 101 Bellhouse Building, Magdalen Centre, The Oxford Science Park, Oxford OX4 4GA (GB).

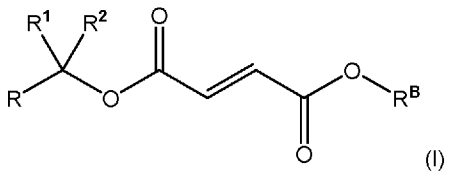
(74) Agent: **KINCH, Alison** et al.; Sagittarius IP, Marlow International, Parkway, Marlow, Buckinghamshire SL7 1YL (GB).

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(54) Title: NOVEL COMPOUNDS



(I)

(57) Abstract: The invention relates to compounds of formula (I) and to their use in treating or preventing an inflammatory disease or a disease associated with an undesirable immune response: wherein R, R^1, R^2 and R^B are as defined herein.

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NOVEL COMPOUNDS

Field of the invention

The present invention relates to compounds and their use in treating or preventing inflammatory diseases or diseases associated with an undesirable immune response, and to related compositions, methods and intermediate compounds.

Background of the invention

Chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), multiple sclerosis, psoriasis, Crohn's disease, ulcerative colitis, uveitis and chronic obstructive pulmonary disease (COPD) represent a significant burden to society because of life-long debilitating illness, increased mortality and high costs for therapy and care (Straub R.H. and Schradin C., 2016). Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widespread medicines employed for treating inflammatory disorders, but these agents do not prevent the progression of the inflammation and only treat the accompanying symptoms. Glucocorticoids are powerful anti-inflammatory agents, making them emergency treatments for acute inflammatory flares, but given longer term these medicines give rise to a plethora of unwanted side-effects and may also be subject to resistance (Straub R. H. and Cutolo M., 2016). Thus, considerable unmet medical need still exists for the treatment of inflammatory disorders and extensive efforts to discover new medicines to alleviate the burden of these diseases is ongoing (Hanke T. *et al.*, 2016).

Dimethyl fumarate (DMF), a diester of the citric acid cycle (CAC) intermediate fumaric acid, is utilised as an oral therapy for treating psoriasis (Brück J. *et al.*, 2018) and multiple sclerosis (Mills E. A. *et al.*, 2018). Importantly, following oral administration, none of this agent is detected in plasma (Dibbert S. *et al.*, 2013), the only drug-related compounds observed being the hydrolysis product monomethyl fumarate (MMF) and glutathione (GSH) conjugates of both the parent (DMF) and metabolite (MMF). DMF's mechanism of action is complex and controversial. This compound's efficacy has been attributed to a multiplicity of different phenomena involving covalent modification of proteins and the conversion of "prodrug" DMF to MMF. In particular, the following pathways have been highlighted as being of relevance to DMF's anti-inflammatory effects: 1) activation of the anti-oxidant, anti-inflammatory, nuclear factor (erythroid-derived 2)-like 2 (NRF2) pathway as a consequence of reaction of the electrophilic α,β-unsaturated ester moiety with nucleophilic cysteine residues on kelch-like ECH-associated protein 1 (KEAP1) (Brennan M. S. *et al.*, 2015); 2) induction of activating transcription factor 3 (ATF3), leading to

suppression of pro-inflammatory cytokines interleukin (IL)-6 and IL-8 (Müller S. *et al.*, 2017); 3) inactivation of the glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH) through succination of its catalytic cysteine residue with a Michael accepting unsaturated ester (Kornberg M. D. *et al.*, 2018; Angiari S. and O'Neill L. A., 2018); 4) inhibition of nuclear factor-kappaB (NF-κB)-driven cytokine production (Gillard G. O. *et al.*, 2015); 5) preventing the association of PKCθ with the costimulatory receptor CD28 to reduce the production of IL-2 and block T-cell activation (Blewett M. M. *et al.*, 2016); 6) reaction of the electrophilic α,β-unsaturated ester with the nucleophilic thiol group of anti-oxidant GSH, impacting cellular responses to oxidative stress (Lehmann J. C. U. *et al.*, 2007); 7) agonism of the hydroxycarboxylic acid receptor 2 (HCA2) by the MMF generated *in vivo* through DMF hydrolysis (von Glehn F. *et al.*, 2018); 8) allosteric covalent inhibition of the p90 ribosomal S6 kinases (Andersen J. L. *et al.*, 2018); 9) inhibition of the expression and function of hypoxia-inducible factor-1α (HIF-1α) and its target genes, such as IL-8 (Zhao G. *et al.*, 2014); and 10) inhibition of Toll-like receptor (TLR)-induced M1 and K63 ubiquitin chain formation (McGuire V. A. *et al.*, 2016). In general, with the exception of HCA2 agonism (Tang H. *et al.*, 2008), membrane permeable diester DMF tends to exhibit much more profound biological effects in cells compared to its monoester counterpart MMF. However, the lack of systemic exposure of DMF *in vivo* has led some researchers to assert that MMF is, in fact, the principal active component following oral DMF administration (Mrowietz U. *et al.*, 2018). As such, it is evident that some of the profound biology exerted by DMF in cells is lost because of hydrolysis *in vivo* to MMF.

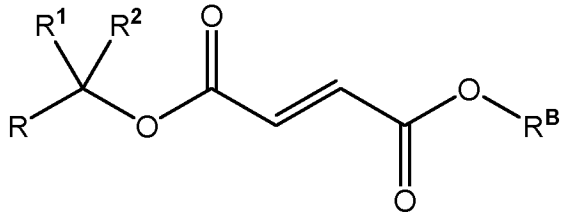
US 2020/0000758 discloses a method of treating psoriasis with sustained release compression coated tablet dosage forms comprising certain methyl hydrogen fumarate prodrugs. WO 2018/191221 discloses GHB (gamma-hydroxybutyrate) prodrug fumarates which are said to decrease or deter the potential for GHB abuse, illicit and illegal use, and overdose. WO 2018/183264 also discloses fumarates which are said to decrease or deter the potential for opioid abuse, addiction, illicit and illegal use, and overdose. WO 2016/061393 discloses monomethyl and monoethyl fumarate prodrugs which are said to have utility in the treatment of neurodegenerative, inflammatory and autoimmune disorders.

In spite of the above findings, there remains a need to identify and develop new therapeutics possessing enhanced properties compared to currently marketed anti-inflammatory agents, such as DMF. The present inventors have now discovered novel fumarate compounds which are more effective at reducing cytokine release in cells and/or in activating NRF2-driven effects than dimethyl fumarate. These properties, amongst others, including enhanced metabolic and hydrolytic stability, make them potentially more effective than dimethyl fumarate and/or diroximel fumarate (WO 2014/152494; Naismith R. T. et al., *CNS Drugs* **2020**, *34*, 185–196). Such

compounds therefore possess excellent anti-inflammatory properties.

Summary of the invention

The present invention provides a compound of formula (I):



(I);

wherein:

R is C_{4-10} alkyl, and R^1 and R^2 are independently selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl or R^1 and R^2 join to form a C_{3-4} cycloalkyl ring; wherein R is optionally substituted by one or more R^a wherein R^a is independently selected from the group consisting of halo, C_{1-2} haloalkyl and C_{1-2} haloalkoxy; or

R is selected from the group consisting of C_{6-10} cycloalkyl, phenyl and 5- or 6-membered heteroaryl, and R^1 and R^2 are independently selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl, or R^1 and R^2 join to form a C_{3-4} cycloalkyl ring or a 4–6-membered heterocyclic ring, wherein the C_{3-4} cycloalkyl ring is optionally substituted by methyl, halo or cyano; wherein R is optionally substituted by one or more R^b wherein R^b is independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy and cyano; or

R is H, methyl or CF_3 and R^1 and R^2 are joined to form a C_{4-10} cycloalkyl ring, wherein the C_{4-10} cycloalkyl ring is optionally substituted by one or more R^c wherein R^c is independently selected from the group consisting of halo, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy and C_{1-2} haloalkoxy, and/or wherein the C_{4-10} cycloalkyl ring is optionally substituted by two R^c groups wherein the two R^C groups are attached to the same carbon atom and are joined to form a C_{4-6} cycloalkyl ring; and

R^B is selected from the group consisting of CH_2COOH, CH_2CH_2COOH, CH_2tetrazolyl and CH_2CH_2tetrazolyl, wherein R^B is optionally substituted on an available carbon atom by one or more $R^{B'}$ wherein $R^{B'}$ is selected from the group consisting of difluoromethyl, trifluoromethyl and methyl, and/or wherein R^B is optionally substituted by two $R^{B'}$ groups, attached to the same carbon atom, that are joined to form a C_{3-6} cycloalkyl or a 4–6-membered heterocyclic ring;

wherein the total number of carbon atoms in groups R, R^1 and R^2 taken together, including their optional substituents, and including the carbon to which R, R^1 and R^2 are attached, is 6 to 14;

or a pharmaceutically acceptable salt and/or solvate thereof.

The present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof.

The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof for use as a medicament.

The present 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.

The present 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 undesirable immune response.

The present 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.

Also provided are intermediate compounds of use in the preparation of compounds of formula (I).

Detailed description of the invention

Compounds of formula (I)

Embodiments and preferences set out herein with respect to the compound of formula (I) apply equally to the pharmaceutical composition, compound for use, use and method aspects of the invention.

As used herein, the term “alkyl”, such as “C_{4-10} alkyl”, “C_{1-4} alkyl” or “C_{1-2} alkyl”, refers to a straight or branched fully saturated hydrocarbon group having the specified number of carbon atoms. The term encompasses methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decyl. Branched variants are also included such as $(n\text{-Bu})_2CH–$, n-pentyl–$CH(CH_2CH_3)–$, n-pentyl-$C(CH_3)_2–$, n-hexyl-$C(CH_3)_2–$ and n-heptyl-$CH(CH_3)–$. The term “alkyl” also encompasses “alkylene” which is a bifunctional straight or branched fully saturated hydrocarbon group having the stated number of carbon atoms. Example “alkylene” groups include methylene, ethylene, n-propylene, n-butylene, n-pentylene, n-

heptylene, n-hexylene and n-octylene.

The term "cycloalkyl", such as "C_{6-10} cycloalkyl" or "C_{3-6} cycloalkyl", refers to a fully saturated cyclic hydrocarbon group having the specified number of carbon atoms. The term encompasses cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl as well as bridged systems such as bicyclo[1.1.1]pentyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl and adamantyl.

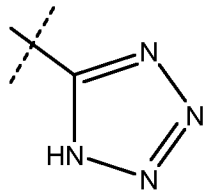
The term "haloalkyl", such as "C_{1-3} haloalkyl", "C_{1-2} haloalkyl" or "C_1 haloalkyl", refers to a straight or a branched fully saturated hydrocarbon chain containing the specified number of carbon atoms and at least one halogen atom, such as fluoro or chloro, especially fluoro. An example of haloalkyl is CF_3. Further examples of haloalkyl are CHF_2, CF_2CH_3 and CH_2CF_3.

The term "haloalkoxy" refers to a haloalkyl group, such as "C_{1-3} haloalkyl", "C_{1-2} haloalkyl" or "C_1 haloalkyl", as defined above, singularly bonded via an oxygen atom. Examples of haloalkoxy groups include OCF_3, $OCHF_2$ and OCH_2CF_3.

The term "halo" refers to fluorine, chlorine, bromine or iodine. Particular examples of halo are fluorine, chlorine and bromine, especially fluorine.

The term "5- or 6-membered heteroaryl" refers to a cyclic group with aromatic character containing the indicated number of atoms (5 or 6) wherein at least one of the atoms in the cyclic group is a heteroatom independently selected from N, O and S. The term encompasses pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, oxazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyradizinyl and pyrazinyl.

The term "tetrazolyl" refers to a 5-(1H-tetrazolyl) substituent where the tetrazole is linked to the rest of the molecule via a carbon atom:



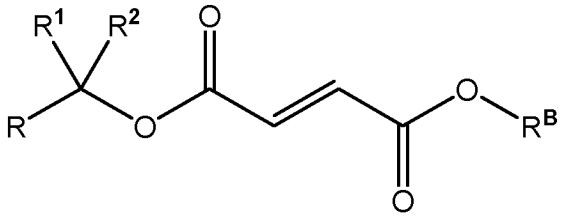
wherein the dashed line indicates the point of attachment to the rest of the molecule.

The term "4–6-membered heterocyclic ring" refers to a non-aromatic cyclic group having 4 to 6 ring atoms and wherein at least one of the ring atoms is a heteroatom selected from N, O, S and B. The term "heterocyclic ring" is interchangeable with "heterocyclyl". The term encompasses

oxetanyl, thietanyl, azetidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl. 4–6-membered heterocyclyl groups can typically be substituted by one or more (e.g. one or two) oxo groups. Suitably, thietanyl is substituted by one or two oxo groups.

Where substituents are indicated as being *optionally substituted* in formula (I) in the embodiments and preferences set out below, the optional substituent may be attached to an available carbon atom, which means a carbon atom which is attached to a hydrogen atom i.e. a C-H group. The optional substituent replaces the hydrogen atom attached to the carbon atom.

In one embodiment, the invention provides a compound of formula (I):



(I);

wherein:

R is C_{4-10} alkyl, and R^1 and R^2 are independently selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl or R^1 and R^2 join to form a C_{3-4} cycloalkyl ring; wherein R is optionally substituted by one or more R^a wherein R^a is independently selected from the group consisting of halo, C_{1-2} haloalkyl and C_{1-2} haloalkoxy; or

R is selected from the group consisting of C_{6-10} cycloalkyl and phenyl, and R^1 and R^2 are independently selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl, or R^1 and R^2 join to form a C_{3-4} cycloalkyl ring; wherein R is optionally substituted by one or more R^b wherein R^b is independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy and C_{1-4} haloalkoxy; or

R is H, methyl or CF_3 and R^1 and R^2 are joined to form a C_{4-10} cycloalkyl ring, wherein the C_{4-10} cycloalkyl ring is optionally substituted by one or more R^c wherein R^c is independently selected from the group consisting of halo, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy and C_{1-2} haloalkoxy, and/or wherein the C_{4-10} cycloalkyl ring is optionally substituted by two R^c groups wherein the two R^c groups are attached to the same carbon atom and are joined to form a C_{4-6} cycloalkyl ring; and

R^B is selected from the group consisting of CH_2COOH, CH_2CH_2COOH, CH_2tetrazolyl and CH_2CH_2tetrazolyl, wherein R^B is optionally substituted on an available carbon atom by one or more $R^{B'}$ wherein $R^{B'}$ is selected from the group consisting of difluoromethyl, trifluoromethyl and methyl, and/or wherein R^B is optionally substituted by two $R^{B'}$ groups, attached to the same carbon atom, that are joined to form a C_{3-6} cycloalkyl or a 4–6-membered heterocyclic ring;

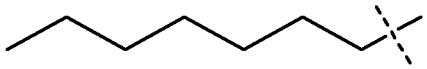
wherein the total number of carbon atoms in groups R, R^1 and R^2 taken together, including their optional substituents, and including the carbon to which R, R^1 and R^2 are attached, is 6 to 14;

or a pharmaceutically acceptable salt and/or solvate thereof.

In one embodiment, R is C_{4-10} alkyl, and R^1 and R^2 are independently selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl or R^1 and R^2 join to form a C_{3-4} cycloalkyl ring.

In one embodiment, R is C_4 alkyl. In another embodiment, R is C_5 alkyl. In another embodiment , R is C_6 alkyl. In another embodiment, R is C_7 alkyl. In another embodiment, R is C_8 alkyl. In another embodiment, R is C_9 alkyl. In another embodiment, R is C_{10} alkyl. Most suitably, R is C_7 alkyl.

Suitably, the C_7 alkyl group is linear such that the following group forms:



wherein the dashed bond indicates the point of attachment to the C atom attached to R^1 and R^2.

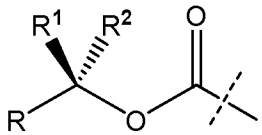
In one embodiment, R^1 is H. In another embodiment, R^1 is C_{1-4} alkyl such as methyl. In another embodiment, R^1 is C_{1-4} haloalkyl such as CF_3.

In one embodiment, R^2 is H. In another embodiment, R^2 is C_{1-4} alkyl such as methyl. In another embodiment, R^2 is C_{1-4} haloalkyl such as CF_3.

In one embodiment, R^1 and R^2 join to form a C_{3-4} cycloalkyl ring. Suitably, R^1 and R^2 join to form a C_3 cycloalkyl ring. Alternatively, R^1 and R^2 join to form a C_4 cycloalkyl ring.

Suitably, R^1 is CF_3 and R^2 is H. Alternatively, R^1 is methyl and R^2 is methyl. Most suitably, R^1 is methyl and R^2 is H.

When R^1 and R^2 are different, suitably the groups have the following configuration:



wherein the dashed line indicates the point of attachment to the rest of the molecule.

In one embodiment, R is not substituted. In another embodiment, R is substituted by one or more R^a. In one embodiment, R is substituted by one R^a group. In another embodiment, R is substituted

by two R^a groups. In another embodiment, R is substituted by three R^a groups. In another embodiment, R is substituted by four R^a groups.

In one embodiment, R^a is halo such as fluoro. In another embodiment, R^a is C_{1-2} haloalkyl such as CF_3. In another embodiment, R^a is C_{1-2} haloalkoxy such as OCF_3.

In another embodiment, R is selected from the group consisting of C_{6-10} cycloalkyl, phenyl and 5- or 6-membered heteroaryl, and R^1 and R^2 are independently selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl, or R^1 and R^2 join to form a C_{3-4} cycloalkyl ring or a 4–6-membered heterocyclic ring, wherein the C_{3-4} cycloalkyl ring is optionally substituted by methyl, halo or cyano.

Suitably, R is selected from the group consisting of C_{6-10} cycloalkyl and phenyl, and R^1 and R^2 are independently selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl, or R^1 and R^2 join to form a C_{3-4} cycloalkyl ring.

In one embodiment, R is C_{6-10} cycloalkyl such as C_{6-8} cycloalkyl. Suitably, R is C_6 cycloalkyl. Alternatively, R is C_7 cycloalkyl. Alternatively, R is C_8 cycloalkyl. Alternatively, R is C_9 cycloalkyl. Alternatively, R is C_{10} cycloalkyl.

In another embodiment, R is phenyl.

In another embodiment, R is 5- or 6-membered heteroaryl.

In one embodiment, R^1 is H. In another embodiment, R^1 is C_{1-4} alkyl such as methyl. In another embodiment, R^1 is C_{1-4} haloalkyl such as CF_3.

In one embodiment, R^2 is H. In another embodiment, R^2 is C_{1-4} alkyl such as methyl. In another embodiment, R^2 is C_{1-4} haloalkyl such as CF_3.

In one embodiment, R^1 and R^2 join to form a C_{3-4} cycloalkyl ring. Suitably, R^1 and R^2 join to form a C_3 cycloalkyl ring. Alternatively, R^1 and R^2 join to form a C_4 cycloalkyl ring.

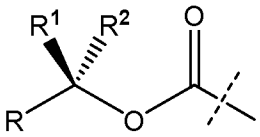
In an embodiment, the C_{3-4} cycloalkyl ring is not substituted. In another embodiment, the C_{3-4} cycloalkyl ring is substituted by methyl, halo or cyano.

In another embodiment, R^1 and R^2 join to form a 4–6-membered heterocyclic ring. In one

embodiment, R^1 and R^2 join to form a 4-membered heterocyclic ring such as oxetanyl or thietanyl. In another embodiment, R^1 and R^2 join to form a 5-membered heterocyclic ring. In another embodiment, R^1 and R^2 join to form a 6-membered heterocyclic ring.

Suitably, R^1 is CF_3 and R^2 is H. Alternatively, R^1 is methyl and R^2 is methyl. Most suitably, R^1 is methyl and R^2 is H.

When R^1 and R^2 are different, suitably the groups have the following configuration:



wherein the dashed line indicates the point of attachment to the rest of the molecule.

In one embodiment, R is not substituted. In another embodiment, R is substituted by one or more R^b. In one embodiment, R is substituted by one R^b group. In another embodiment, R is substituted by two R^b groups. In another embodiment, R is substituted by three R^b groups. In another embodiment, R is substituted by four R^b groups.

In one embodiment, R^b is halo such as chloro or bromo. In another embodiment, R^b is C_{1-4} alkyl such as methyl. In another embodiment, R^b is C_{1-4} haloalkyl such as CF_3. In another embodiment, R^b is C_{1-4} alkoxy such as OCH_3. In another embodiment, R^b is C_{1-4} haloalkoxy, such as OCF_3. In another embodiment, R^b is cyano.

Suitably, when R^1 and R^2 join to form a C_3 cycloalkyl ring, R is phenyl and is substituted by one R^b wherein R^b is halo, e.g., bromo.

Suitably, when R^1 and R^2 join to form a C_4 cycloalkyl ring, R is phenyl and is substituted by two R^b wherein R^b is halo, e.g., chloro.

In one embodiment, R is H, methyl or CF_3 and R^1 and R^2 are joined to form a C_{4-10} cycloalkyl ring. Suitably, R is H. Alternatively, R is methyl. Alternatively, R is CF_3. Most suitably, R is H.

In this embodiment, R^1 and R^2 are joined to form a C_{4-10} cycloalkyl ring such as a C_{6-8} cycloalkyl ring. In one embodiment, R^1 and R^2 are joined to form a C_4 cycloalkyl ring. In another embodiment, R^1 and R^2 are joined to form a C_5 cycloalkyl ring. In another embodiment, R^1 and R^2 are joined to form a C_6 cycloalkyl ring. In another embodiment, R^1 and R^2 are joined to form a C_7 cycloalkyl ring. In another embodiment, R^1 and R^2 are joined to form a C_8 cycloalkyl ring. In another

embodiment, R^1 and R^2 are joined to form a C_9 cycloalkyl ring. In another embodiment, R^1 and R^2 are joined to form a C_{10} cycloalkyl ring. Most suitably, R^1 and R^2 are joined to form a C_8 cycloalkyl ring.

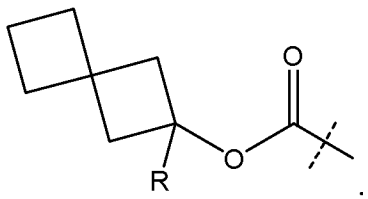
In one embodiment, the C_{4-10} cycloalkyl ring is not substituted. In another embodiment, the C_{4-10} cycloalkyl ring is substituted by one or more R^c. In one embodiment, the C_{4-10} cycloalkyl ring is substituted by one R^c group. In another embodiment, the C_{4-10} cycloalkyl ring is substituted by two R^c groups. In another embodiment, the C_{4-10} cycloalkyl ring is substituted by three R^c groups. In another embodiment, the C_{4-10} cycloalkyl ring is substituted by four R^c groups.

In one embodiment, R^c is halo such as fluoro. In another embodiment, R^c is C_{1-2} alkyl such as methyl. In another embodiment, R^c is C_{1-2} haloalkyl such as CF_3. In another embodiment, R^c is C_{1-2} alkoxy such as methoxy. In another embodiment, R^c is C_{1-2} haloalkoxy such as OCF_3.

In one embodiment, C_{4-10} cycloalkyl ring is substituted by two R^c groups wherein the two R^C groups are attached to the same carbon atom and are joined to form a C_{4-6} cycloalkyl ring. Suitably, the two R^C groups join to form a C_4 cycloalkyl ring. Alternatively, the two R^C groups join to form a C_5 cycloalkyl ring. Alternatively, the two R^C groups join to form a C_6 cycloalkyl ring.

Most suitably, R^1 and R^2 are joined to form a C_4 cycloalkyl ring substituted by two R^C groups which are attached to the same carbon atom and are joined to form a C_4 cycloalkyl ring. In this embodiment, suitably R is H.

Suitably, the two R^c groups are attached to the 3-position of the C_4 cycloalkyl ring so that the following moiety forms:



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In any of the above embodiments, and unless otherwise stated, the substituent groups R^a, R^b and R^c may be attached to the same carbon atom, or may be attached to different carbon atoms.

The total number of carbon atoms in groups R, R^1 and R^2 taken together, including their optional substituents, and including the carbon to which R, R^1 and R^2 are attached, is 6 to 14. In one embodiment, the total number of carbon atoms is 6 carbon atoms. In another embodiment, the total number of carbon atoms is 7 carbon atoms. In another embodiment, the total number of

carbon atoms is 8 carbon atoms. In another embodiment, the total number of carbon atoms is 9 carbon atoms. In another embodiment, the total number of carbon atoms is 10 carbon atoms. In another embodiment, the total number of carbon atoms is 11 carbon atoms. In another embodiment, the total number of carbon atoms is 12 carbon atoms. In another embodiment, the total number of carbon atoms is 13 carbon atoms. In another embodiment, the total number of carbon atoms is 14 carbon atoms.

In one embodiment, R^B is CH_2COOH. In another embodiment, R^B is CH_2CH_2COOH. In another embodiment, R^B is CH_2tetrazolyl. In another embodiment, R^B is CH_2CH_2tetrazolyl. Suitably, R^B is CH_2COOH or CH_2CH_2COOH.

In one embodiment, R^B is not substituted.

In another embodiment, R^B is substituted on an available carbon atom by one or more such as one, two, three or four, e.g., one $R^{B'}$ wherein $R^{B'}$ is selected from the group consisting of difluoromethyl, trifluoromethyl and methyl, and/or wherein R^B is optionally substituted by two $R^{B'}$ groups, attached to the same carbon atom, that are joined to form a C_{3-6} cycloalkyl or a 4–6-membered heterocyclic ring.

In one embodiment, R^B is substituted by one $R^{B'}$. In another embodiment, R^B is substituted by two $R^{B'}$. In another embodiment, R^B is substituted by three $R^{B'}$. In another embodiment, R^B is substituted by four $R^{B'}$.

In one embodiment, $R^{B'}$ is difluoromethyl. In another embodiment, $R^{B'}$ is trifluoromethyl. In another embodiment, $R^{B'}$ is methyl. Suitably, R^B is substituted by one methyl group. Alternatively, R^B is substituted by two $R^{B'}$ groups, attached to the same carbon atom, that are joined to form a C_{3-6} cycloalkyl or a 4–6-membered heterocyclic ring. Suitably, the two $R^{B'}$ groups join to form a C_{3-6} cycloalkyl ring such as a C_3 cycloalkyl ring. Alternatively, the two $R^{B'}$ groups join to form a 4–6-membered heterocyclic ring.

Suitably, $R^{B'}$ is attached to the same or different carbon to the carbon attached to the COOH or tetrazolyl group. When R^B is CH_2CH_2COOH or CH_2CH_2tetrazolyl, suitably $R^{B'}$ is attached to the carbon atom linked to the oxygen atom of the carboxylate group attached to R^B.

Suitably, the two $R^{B'}$ groups, attached to the same carbon atom, that are joined to form a C_{3-6} cycloalkyl or a 4–6-membered heterocyclic ring are attached to the same or different carbon to the carbon attached to the COOH or tetrazolyl group. When R^B is CH_2CH_2COOH or

CH_2CH_2tetrazolyl, suitably the two $R^{B'}$ groups are attached to the carbon atom linked to the oxygen atom of the carboxylate group attached to R^B.

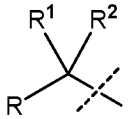
In one embodiment, the molecular weight of the compound of formula (I) is 150 Da – 450 Da, suitably 200 Da – 400 Da.

In one embodiment there is provided a compound of formula (I), selected from the group consisting of:
(E)-2-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)acetic acid;
(*E*)-2-((4-(cyclohexyloxy)-4-oxobut-2-enoyl)oxy)acetic acid;
(E)-3-((4-(Cyclooctyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid;
(*E*)-3-((4-(cyclohexyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid;
2-(1H-tetrazol-5-yl)ethyl cyclooctyl fumarate;
(*S,E*)-2-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid;
(*E*)-3-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)-2,2-dimethylpropanoic acid;
(*E*)-1-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)cyclopropane-1-carboxylic acid;
(*E*)-2-((4-oxo-4-(spiro[3.3]heptan-2-yloxy)but-2-enoyl)oxy)acetic acid;
(*E*)-2-((4-(cycloheptyloxy)-4-oxobut-2-enoyl)oxy)acetic acid;
(*E*)-3-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)butanoic acid;
(*R,E*)-2-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid;
(*E*)-2-((4-(cycloheptyloxy)-4-oxobut-2-enoyl)oxy)acetic acid; and
(*R,E*)-3-((4-(octan-2-yloxy)-4-oxobut-2-enoyl)oxy)propanoic acid;
or a pharmaceutically acceptable salt and/or solvate of any one thereof.

In another embodiment there is provided a compound of formula (I) which is:
(E)-2-((4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoyl)oxy) acetic acid;
or a pharmaceutically acceptable salt and/or solvate of any one thereof.

In another embodiment, there is provided a compound of formula (I) which is:
(E)-3-(4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoyloxy)propanoic acid;
or a pharmaceutically acceptable salt and/or solvate of any one thereof.

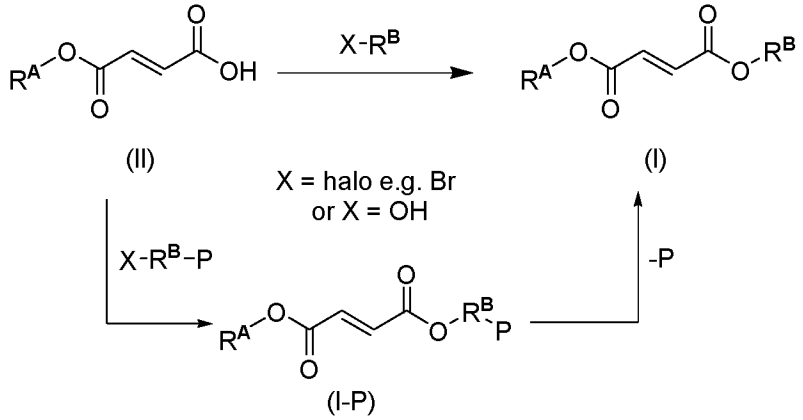
Compounds of formula (I) may be prepared as set out in the Examples and as set out in the following schemes. As used herein, R^A is equivalent to the following group:



wherein R, R^1 and R^2 are defined elsewhere herein and the dashed line indicates the

connection to the remainder of the compound of formula (I).

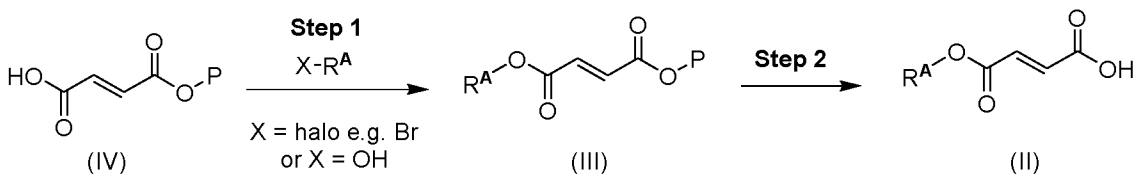
Scheme 1: Synthesis of compound of formula (I)



Compounds of formula (I) may be prepared from compounds of formula (II) under standard ester forming conditions which are well known to the person skilled in the art. For example, when X = halo, such as Br, compounds of formula (I) can be prepared from compounds of formula (II) using X-R^B in the presence of base e.g. K_2CO_3 in solvent such as acetone. When X = OH, compounds of formula (I) may be accessed via condensation reactions employing a coupling agent e.g. EDCI/DMAP in presence of a base e.g. DIPEA in a solvent such as DCM. Alternatively, when X = OH, the carboxyl group may be activated with an activating agent such as $(COCl)_2$ in a solvent, e.g., a dimethylformamide/DCM mixture, following by addition of a base e.g. Et_3N in a solvent, e.g., DCM, to provide compounds of formula (I).

Compounds of formula (II) may be reacted with a protected derivative of X-R^B such as X-R^B-P, wherein P is a carboxylic acid protecting group such as C_{1-6} alkyl e.g. *tert*-butyl, or para-methoxybenzyl (Scheme 1). In such instances, the protecting group may be removed as the final step using conditions known to the person skilled in the art. For example, a carboxylic acid protecting group such as C_{1-6} alkyl e.g. *tert*-butyl, or para-methoxybenzyl may be removed under acidic conditions such as TFA in DCM.

Scheme 2: Synthesis of compound of formula (II)



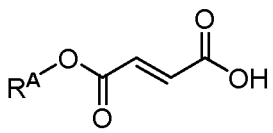
Compounds of formula (II) may be prepared from compounds of formula (IV), wherein P is a carboxylic acid protecting group such as C_{1-6} alkyl e.g. *tert*-butyl, or para-methoxybenzyl. P may also be Fmoc.

Step 1: When X = halo such as Br, compounds of formula (III) can be prepared from compounds of formula (IV) using X-R^A in the presence of base e.g. K_2CO_3 in solvent such as acetone. When X = OH, compounds of formula (III) may be accessed via condensation reactions employing a coupling agent e.g. EDCI/DMAP in presence of a base e.g. DIPEA in a solvent such as DCM. Alternatively, when X = OH, the carboxyl group may be activated with an activating agent such as $(COCl)_2$ in a solvent e.g. a dimethylformamide/DCM mixture, following by addition of a base e.g. Et_3N in a solvent e.g. DCM to give compounds of formula (III).

Step 2: Compounds of formula (II) may be obtained by removal of protecting group P using conditions known to the person skilled in the art. For example, when P is C_{1-6} alkyl e.g. *tert*-butyl, or para-methoxybenzyl P may be removed under acidic conditions such as TFA in DCM. When P is Fmoc, the protecting group may be removed using basic conditions such as TEA in dimethylformamide.

The skilled person will appreciate that protecting groups may be used throughout the synthetic schemes described herein to give protected derivatives of any of the above compounds or generic formulae. Protective groups and the means for their removal are described in "*Protective Groups in Organic Synthesis*", by Theodora W. Greene and Peter G. M. Wuts, published by John Wiley & Sons Inc; 4th Rev Ed., 2006, ISBN-10: 0471697540. Examples of nitrogen protecting groups include trityl (Tr), tert-butyloxycarbonyl (BOC), 9-fluorenylmethyloxycarbonyl (Fmoc), acetyl (Ac), benzyl (Bn) and para-methoxybenzyl (PMB). Examples of oxygen protecting groups include acetyl (Ac), methoxymethyl (MOM), para-methoxybenzyl (PMB), benzyl, tert-butyl, methyl, ethyl, tetrahydropyranyl (THP), and silyl ethers and esters (such as trimethylsilyl (TMS), tert-butyldimethylsilyl (TBDMS), tri-iso-propylsilyloxymethyl (TOM), and triisopropylsilyl (TIPS) ethers and esters). Specific examples of carboxylic acid protecting groups include alkyl esters (such as C_{1-6} alkyl e.g. C_{1-4} alkyl esters), benzyl esters and silyl esters. Specific examples of carboxylic acid protecting groups include alkyl esters (such as C_{1-6} alkyl e.g. C_{1-4} alkyl esters), benzyl esters (e.g. para-methoxybenzyl) and silyl esters.

In one embodiment, there is provided a process for the preparation of compounds of formula (I) or a salt, such as a pharmaceutically acceptable salt thereof, which comprises reacting a compound of formula (II):



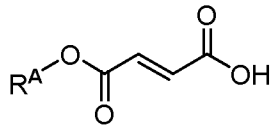
(II)

or a salt such as a pharmaceutically acceptable salt thereof, wherein R^A is defined elsewhere

herein;

with X-R^B or a salt, such as a pharmaceutically acceptable salt thereof, wherein X is halo e.g. Br, or OH, and R^B is defined elsewhere herein.

In another embodiment, there is provided a process for the preparation of compounds of formula (I) or a salt, such as a pharmaceutically acceptable salt thereof, which comprises reacting a compound of formula (II):



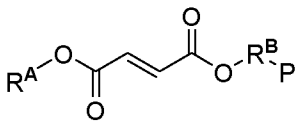
(II)

or a salt such as a pharmaceutically acceptable salt thereof, wherein R^A is defined elsewhere herein;

with X-R^B-P or a salt, such as a pharmaceutically acceptable salt thereof, followed by removal of protecting group P, wherein P is a carboxylic acid protecting group such as C_{1-6} alkyl e.g. *tert*-butyl, or para-methoxybenzyl, X is halo e.g. Br, or OH, and R^B is defined elsewhere herein.

Protecting group P may be removed under conditions known to the skilled person. When P is C_{1-6} alkyl, e.g., *tert*-butyl, P may be removed using acidic conditions such as TFA in DCM. When P is *para*-methoxybenzyl, P may also be removed using acidic conditions, such as hydrogen chloride in dioxane.

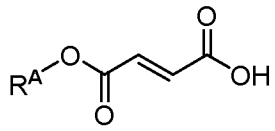
In one embodiment, there is provided a compound of formula (I-P):



(I-P)

or a salt such as a pharmaceutically acceptable salt thereof, wherein R^A, R^B and P are defined elsewhere herein.

In one embodiment, there is provided a compound of formula (II):

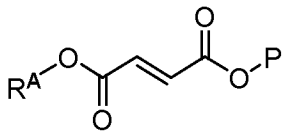


(II)

or a salt such as a pharmaceutically acceptable salt thereof, wherein R^A is defined elsewhere herein.

Suitably, the compound of formula (II) is other than 1-octyl fumarate and *(E)*-4-(cycloheptyloxy)-4-oxobut-2-enoic acid.

In one embodiment, there is provided a compound of formula (III):



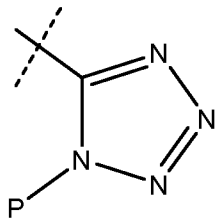
(III)

or a salt such as a pharmaceutically acceptable salt thereof, wherein R^A is defined elsewhere herein and P is a carboxylic acid protecting group such as C_{1-6} alkyl e.g. *tert*-butyl, or para-methoxybenzyl.

The moiety "-R^B-P" as used herein means that R^B is protected with protecting group P. The location and specific protecting group will depend on the identity of R^B which will be understood by the skilled person.

For example, when R^B comprises CH_2COOH or CH_2CH_2COOH, suitably P is a carboxylic acid protecting group and suitably replaces the hydrogen atom attached to an oxygen atom, i.e., CH_2COO-P or CH_2CH_2COO-P.

When R^B comprises CH_2tetrazolyl or CH_2CH_2tetrazolyl, suitably P is a tetrazolyl protecting group which replaces the hydrogen atom attached to a nitrogen atom:



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Certain intermediates are novel and are claimed as an aspect of the invention:

2-(*tert*-butoxy)-2-oxoethyl cyclooctyl fumarate;

2-(*tert*-butoxy)-2-oxoethyl cyclohexyl fumarate;

3-(*tert*-butoxy)-3-oxopropyl cyclooctyl fumarate;

3-(*tert*-butoxy)-3-oxopropyl cyclohexyl fumarate;

(*S*)-1-(*tert*-butoxy)-1-oxopropan-2-yl cyclooctyl fumarate;

Cyclooctyl (3-((4-methoxybenzyl)oxy)-2,2-dimethyl-3-oxopropyl) fumarate;

2-(*tert*-butoxy)-2-oxoethyl spiro[3.3]heptan-2-yl fumarate;

2-(*tert*-butoxy)-2-oxoethyl cycloheptyl fumarate;

Cyclooctyl (4-((4-methoxybenzyl)oxy)-4-oxobutan-2-yl) fumarate;
(*R*)-1-(*tert*-butoxy)-1-oxopropan-2-yl cyclooctyl fumarate;
(*R*)-2-(*tert*-butoxy)-2-oxoethyl octan-2-yl fumarate;
(*R*)-3-(*tert*-butoxy)-3-oxopropyl octan-2-yl fumarate;
or a salt thereof.

Such intermediates may be considered prodrugs of compounds of formula (I).

Also provided is a compound selected from the group consisting of:
(*E*)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid;
(*E*)-4-(1-methylcyclobutoxy)-4-oxobut-2-enoic acid;
octyl fumarate;
(E)-4-(cyclooctyloxy)-4-oxobut-2-enoic acid;
(*E*)-4-oxo-4-(spiro[3.3]heptan-2-yloxy)but-2-enoic acid; and
(E)-4-(cycloheptyloxy)-4-oxobut-2-enoic acid;
or a salt, such as a pharmaceutically acceptable salt, thereof.

Suitably, there is provided a compound selected from the group consisting of:
(*E*)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid;
(*E*)-4-(1-methylcyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-(cyclooctyloxy)-4-oxobut-2-enoic acid; and
(*E*)-4-oxo-4-(spiro[3.3]heptan-2-yloxy)but-2-enoic acid;
or a salt, such as a pharmaceutically acceptable salt, thereof.

Also provided is a compound selected from the group consisting of:
(E)-4-oxo-4-(1-(5-(trifluoromethyl)pyridin-2-yl)cyclobutoxy)but-2-enoic acid;
(E)-4-oxo-4-(1-(3-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid;
(E)-4-oxo-4-(1-(2-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid;
(E)-4-(1-(4-bromophenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-(1-(4-chlorophenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-(1-(3,5-dichlorophenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-oxo-4-(1-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)but-2-enoic acid;
(*E*)-4-(1-(3-fluoro-4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(*E*)-4-oxo-4-((3-(4-(trifluoromethyl)phenyl)thietan-3-yl)oxy)but-2-enoic acid;
(*E*)-4-oxo-4-((3-(4-(trifluoromethyl)phenyl)oxetan-3-yl)oxy)but-2-enoic acid;
(*S*,E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)ethoxy)but-2-enoic acid;
(*R*,E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)ethoxy)but-2-enoic acid;

(E)-4-oxo-4-((2-(4-(trifluoromethyl)phenyl)propan-2-yl)oxy)but-2-enoic acid;
(E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-(1-(5-chloropyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-(1-(3,5-dichloro-4-fluorophenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-(1-(3-chloro-4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-(1-(4-cyanophenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-oxo-4-(1-(3,4,5-trifluorophenyl)cyclobutoxy)but-2-enoic acid;
(E)-4-(3-methyl-1-(4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-oxo-4-((4-(4-(trifluoromethyl)phenyl)tetrahydro-2H-pyran-4-yl)oxy)but-2-enoic acid;
(E)-4-(3-cyano-1-(4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-oxo-4-(1-(5-(trifluoromethyl)thiophen-2-yl)cyclobutoxy)but-2-enoic acid;
(E)-4-(1-(3,5-difluoro-4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-oxo-4-(1-(4-(trifluoromethoxy)phenyl)cyclobutoxy)but-2-enoic acid;
(E)-4-(3,3-difluoro-1-(4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid; and
(E)-4-(1-(4-(difluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
or a salt, such as a pharmaceutically acceptable salt, thereof.

There is also provided a compound selected from the group consisting of:
(E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclopropoxy)but-2-enoic acid;
(E)-4-oxo-4-(1-(5-(trifluoromethyl)pyrimidin-2-yl)cyclobutoxy)but-2-enoic acid;
(E)-4-(1-(3,5-dimethoxyphenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-(1-(3-chloro-5-(trifluoromethoxy)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-oxo-4-(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethoxy)but-2-enoic acid; and
(E)-4-oxo-4-(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethoxy)but-2-enoic acid;
or a salt, such as a pharmaceutically acceptable salt, thereof.

Suitably, the compound is:
(*E*)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid;
or a salt, such as a pharmaceutically acceptable salt, thereof.

It will be appreciated that for use in therapy the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art. Pharmaceutically acceptable salts include acid addition salts, suitably salts of compounds of the invention comprising a basic group such as an amino group, formed with inorganic acids, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid. Also included are salts formed with organic acids e.g. succinic acid, maleic acid, acetic acid, fumaric acid, citric acid, tartaric acid, benzoic acid, p-toluenesulfonic acid, methanesulfonic acid,

naphthalenesulfonic acid and 1,5-naphthalenedisulfonic acid. Other salts, e.g., oxalates or formates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention, as are basic addition salts such as sodium, potassium, calcium, aluminium, zinc, magnesium and other metal salts.

Pharmaceutically acceptable salts may also be formed with organic bases such as basic amines e.g. with ammonia, meglumine, tromethamine, piperazine, arginine, choline, diethylamine, benzathine or lysine. Thus, in one embodiment there is provided a compound of formula (I) in the form of a pharmaceutically acceptable salt. Alternatively, there is provided a compound of formula (I) in the form of a free acid. When the compound contains a basic group as well as the free acid it may be Zwitterionic.

Suitably, the compound of formula (I) is not a salt e.g. is not a pharmaceutically acceptable salt.

Compounds of formula (II) may be in the form of a salt, such as a pharmaceutically acceptable salt, such as those defined above. Suitably, the compound of formula (II) is not a salt, e.g., is not a pharmaceutically acceptable salt.

Suitably, where the compound of formula (I) or the compound of formula (II) is in the form of a salt, the pharmaceutically acceptable salt is a basic addition salt such as a carboxylate salt formed with a group 1 metal (e.g. a sodium or potassium salt), a group 2 metal (e.g. a magnesium or calcium salt) or an ammonium salt of a basic amine (e.g. an NH_4^+ salt), such as a sodium salt.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form and, if crystalline, may optionally be solvated, e.g., as the hydrate. This invention includes within its scope stoichiometric solvates (e.g., hydrates) as well as compounds containing variable amounts of solvent (e.g., water). Suitably, the compound of formula (I) is not a solvate.

The compounds of formula (II) may be prepared in crystalline or non-crystalline form and, if crystalline, may optionally be solvated, e.g., as the hydrate. This invention includes within its scope stoichiometric solvates (e.g., hydrates) as well as compounds containing variable amounts of solvent (e.g., water). Suitably, the compound of formula (II) is not a solvate.

The invention extends to a pharmaceutically acceptable derivative thereof, such as a pharmaceutically acceptable prodrug of compounds of formula (I). The invention also extends to a pharmaceutically acceptable derivative of compounds of formula (II), such as a pharmaceutically acceptable prodrug of compounds of formula (II). Typical prodrugs of

compounds of formula (I) which comprise a carboxylic acid, and compounds of formula (II), include ester (e.g. C_{1-6} alkyl e.g. C_{1-4} alkyl ester) derivatives thereof. Thus, in one embodiment, the compound of formula (I) is provided as a pharmaceutically acceptable prodrug. In another embodiment, the compound of formula (I) is not provided as a pharmaceutically acceptable prodrug. In one embodiment, the compound of formula (II) is provided as a pharmaceutically acceptable prodrug. In another embodiment, the compound of formula (II) is not provided as a pharmaceutically acceptable prodrug.

Certain compounds of formula (I) may metabolise under certain conditions such as by hydrolysis of the R^B ester group. Without wishing to be bound by theory, formation of an active metabolite (such as in vivo) of a compound of formula (I) may be beneficial by contributing to the biological activity observed of the compound of formula (I). Thus, in one embodiment, there is provided an active metabolite of the compound of formula (I) and its use as a pharmaceutical e.g. for the treatment or prevention of the diseases mentioned herein.

It is to be understood that the present invention encompasses all isomers of compounds of formula (I) including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The present invention also encompasses all isomers of compounds of formula (II) including all geometric, tautomeric and optical forms, and mixtures thereof (e.g., racemic mixtures). Where additional chiral centres are present in compounds of formula (II), the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The present invention also includes all isotopic forms of the compounds provided herein, whether in a form (i) wherein all atoms of a given atomic number have a mass number (or mixture of mass numbers) which predominates in nature (referred to herein as the “natural isotopic form”) or (ii) wherein one or more atoms are replaced by atoms having the same atomic number, but a mass number different from the mass number of atoms which predominates in nature (referred to herein as an “unnatural variant isotopic form”). It is understood that an atom may naturally exist as a

mixture of mass numbers. The term “unnatural variant isotopic form” also includes embodiments in which the proportion of an atom of given atomic number having a mass number found less commonly in nature (referred to herein as an “uncommon isotope”) has been increased relative to that which is naturally occurring e.g. to the level of >20%, >50%, >75%, >90%, >95% or >99% by number of the atoms of that atomic number (the latter embodiment referred to as an "isotopically enriched variant form"). The term “unnatural variant isotopic form” also includes embodiments in which the proportion of an uncommon isotope has been reduced relative to that which is naturally occurring. Isotopic forms may include radioactive forms (i.e. they incorporate radioisotopes) and non-radioactive forms. Radioactive forms will typically be isotopically enriched variant forms.

An unnatural variant isotopic form of a compound may thus contain one or more artificial or uncommon isotopes such as deuterium (^{2}H or D), carbon-11 (^{11}C), carbon-13 (^{13}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), nitrogen-15 (^{15}N), oxygen-15 (^{15}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), phosphorus-32 (^{32}P), sulphur-35 (^{35}S), chlorine-36 (^{36}Cl), chlorine-37 (^{37}Cl), fluorine-18 (^{18}F) iodine-123 (^{123}I), iodine-125 (^{125}I) in one or more atoms or may contain an increased proportion of said isotopes as compared with the proportion that predominates in nature in one or more atoms.

Unnatural variant isotopic forms comprising radioisotopes may, for example, be used for drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Unnatural variant isotopic forms which incorporate deuterium i.e. ^{2}H or D may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Further, unnatural variant isotopic forms may be prepared which incorporate positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, and would be useful in positron emission topography (PET) studies for examining substrate receptor occupancy.

In one embodiment, the compounds of formula (I) are provided in a natural isotopic form. In one embodiment, the compounds of formula (II) are provided in a natural variant isotopic form. In one embodiment, the compounds of formula (I) are provided in an unnatural variant isotopic form. In one embodiment, the compounds of formula (II) are provided in an unnatural variant isotopic form. In a specific embodiment, the unnatural variant isotopic form is a form in which deuterium (i.e. ^{2}H or D) is incorporated where hydrogen is specified in the chemical structure in one or more atoms of a compound of formula (I) or (II). In one embodiment, the atoms of the compounds of formula (I) or (II) are in an isotopic form which is not radioactive. In one embodiment, one or more atoms

of the compounds of formula (I) or (II) are in an isotopic form which is radioactive. Suitably radioactive isotopes are stable isotopes. Suitably the unnatural variant isotopic form is a pharmaceutically acceptable form.

In one embodiment, a compound of formula (I) is provided whereby a single atom of the compound exists in an unnatural variant isotopic form. In one embodiment, a compound of formula (II) is provided whereby a single atom of the compound exists in an unnatural variant isotopic form. In another embodiment, a compound of formula (I) is provided whereby two or more atoms exist in an unnatural variant isotopic form. In another embodiment, a compound of formula (II) is provided whereby two or more atoms exist in an unnatural variant isotopic form.

Unnatural isotopic variant forms can generally be prepared by conventional techniques known to those skilled in the art or by processes described herein e.g. processes analogous to those described in the accompanying Examples for preparing natural isotopic forms. Thus, unnatural isotopic variant forms could be prepared by using appropriate isotopically variant (or labelled) reagents in place of the normal reagents employed in the Examples. Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

Therapeutic indications

Compounds of formula (I) are of use in therapy, particularly for treating or preventing an inflammatory disease or a disease associated with an undesirable immune response. Compounds of formula (II) are also of use in therapy, particularly for treating or preventing an inflammatory disease or a disease associated with an undesirable immune response. As shown in Biological Example 1 below, example compounds of formula (I) reduced cytokine release more effectively than dimethyl fumarate and in some cases, 2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate, as demonstrated by lower IC_{50} values. Compounds of formula (II) reduced cytokine release more effectively than monomethyl fumarate and preferred compounds of formula (II) reduced cytokine release more effectively than dimethyl fumarate and 2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate, as demonstrated by lower IC_{50} values. Cytokines are important mediators of inflammation and immune-mediated disease as evidenced by the therapeutic benefit delivered by antibodies targeting them.

Thus, in a first aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, for use as a medicament. In a second aspect, the present invention provides a compound of formula (II) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, for use as a medicament. In a third aspect the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein. Such a pharmaceutical composition contains the compound of formula (I) and a pharmaceutically acceptable carrier or excipient. In a fourth aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (II) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein. Such a pharmaceutical composition contains the compound of formula (II) and a pharmaceutically acceptable carrier or excipient.

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, 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, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, 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, the present 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, as defined herein.

In a further aspect, the present invention provides a compound of formula (II) or a pharmaceutically acceptable salt and/or solvate thereof, 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, the present invention provides the use of a compound of formula (II) or a pharmaceutically acceptable salt and/or solvate thereof, 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, the present 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 (II) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein.

For all aspects of the invention, suitably the compound is administered to a subject in need thereof, wherein the subject is suitably a human subject.

In one embodiment is provided a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, for use in treating an inflammatory disease or disease associated with an undesirable immune response. In one embodiment of the invention is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, in the manufacture of a medicament for treating an inflammatory disease or a disease associated with an undesirable immune response. In one embodiment of the invention is provided a method of treating 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, as defined herein.

In one embodiment is provided a compound of formula (II) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, for use in treating an inflammatory disease or disease associated with an undesirable immune response. In one embodiment of the invention is provided the use of a compound of formula (II) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, in the manufacture of a medicament for treating an inflammatory disease or a disease associated with an undesirable immune response. In one embodiment of the invention is provided a method of treating an inflammatory disease or a disease associated with an undesirable immune response, which comprises administering a compound of formula (II) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein.

In one embodiment is provided a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, for use in preventing an inflammatory disease or a disease associated with an undesirable immune response. In one embodiment of the invention is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, in the manufacture of a medicament for preventing an inflammatory disease or a disease associated with an undesirable immune response. In one embodiment of the invention is provided a method of 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, as defined herein.

In one embodiment is provided a compound of formula (II) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, for use in preventing an inflammatory disease or a disease associated with an undesirable immune response. In one embodiment of the invention is provided the use of a compound of formula (II) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, in the manufacture of a medicament for preventing an inflammatory disease or a disease associated with an undesirable immune response. In one

embodiment of the invention is provided a method of preventing an inflammatory disease or a disease associated with an undesirable immune response, which comprises administering a compound of formula (II) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein.

In one embodiment is provided a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, for use in treating or preventing an inflammatory disease. In one embodiment of the invention is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, in the manufacture of a medicament for treating or preventing an inflammatory disease. In one embodiment of the invention is provided a method of treating or preventing an inflammatory disease, which comprises administering a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein.

In one embodiment is provided a compound of formula (II) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, for use in treating or preventing an inflammatory disease. In one embodiment of the invention is provided the use of a compound of formula (II) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, in the manufacture of a medicament for treating or preventing an inflammatory disease. In one embodiment of the invention is provided a method of treating or preventing an inflammatory disease, which comprises administering a compound of formula (II) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein.

In one embodiment is provided a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, for use in treating or preventing a disease associated with an undesirable immune response. In one embodiment of the invention is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, in the manufacture of a medicament for treating or preventing a disease associated with an undesirable immune response. In one embodiment of the invention is provided a method of treating or preventing 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, as defined herein.

In one embodiment is provided a compound of formula (II) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein, for use in treating or preventing a disease associated with an undesirable immune response. In one embodiment of the invention is provided the use of a compound of formula (II) or a pharmaceutically acceptable salt and/or solvate thereof, as

defined herein, in the manufacture of a medicament for treating or preventing a disease associated with an undesirable immune response. In one embodiment of the invention is provided a method of treating or preventing a disease associated with an undesirable immune response, which comprises administering a compound of formula (II) or a pharmaceutically acceptable salt and/or solvate thereof, as defined herein.

An undesirable immune response will typically be an immune response which gives rise to a pathology, i.e., is a pathological immune response or reaction.

In one embodiment, the inflammatory disease or disease associated with an undesirable immune response is an auto-immune disease.

In one embodiment, 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), familial 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).

In one embodiment, the inflammatory disease or disease associated with an undesirable immune response is, or is associated with, a disease selected from the following autoinflammatory diseases: familial 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, and 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, and 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) and Schnitzler syndrome.

In one embodiment, the inflammatory disease or disease associated with an undesirable immune response is, or is associated with, a disease selected from the following diseases mediated by excess NF-κB or gain of function in the NF-κB signalling pathway or in which there is a major contribution to the abnormal pathogenesis therefrom (including non-canonical NF-κB signalling): 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), asthma, COPD, type 1 diabetes mellitus, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease (including ulcerative colitis and Crohn's disease), and SLE.

In one embodiment, the disease 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.

In one embodiment, the disease is multiple sclerosis.

In one embodiment, the disease is psoriasis.

In one embodiment, the disease is asthma.

In one embodiment, the disease is chronic obstructive pulmonary disease.

In one embodiment, the disease is systemic lupus erythematosus.

In one embodiment, the compound of formula (I) exhibits a lower IC_{50} compared with dimethyl fumarate when tested in a cytokine assay e.g. as described in Biological Example 1. In one embodiment, the compound of formula (I) exhibits a lower IC_{50} compared with dimethyl fumarate when tested in a cytokine assay e.g. as described in Biological Example 1. In one embodiment, the compound of formula (I) exhibits a lower IC_{50} compared with 2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate when tested in a cytokine assay e.g. as described in Biological Example 1. In one embodiment, the compound of formula (I) exhibits a lower IC_{50} compared with 2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate when tested in a cytokine assay e.g. as described in Biological Example 1.

In one embodiment, the compound of formula (I) exhibits a lower EC_{50} compared with dimethyl fumarate when tested in an NRF2 assay e.g. as described in Biological Example 2. In one embodiment, the compound of formula (I) exhibits a higher E_{max} compared with dimethyl fumarate when tested in an NRF2 assay e.g. as described in Biological Example 2. In one embodiment, the compound of formula (I) exhibits a lower EC_{50} and/or higher E_{max} compared with dimethyl fumarate when tested in an NRF2 assay e.g. as described in Biological Example 2. In one embodiment, the compound of formula (I) exhibits a lower EC_{50} and higher E_{max} compared with

dimethyl fumarate when tested in an NRF2 assay e.g. as described in Biological Example 2.

In one embodiment, the compound of formula (I) exhibits lower intrinsic clearance (Cl_{int}) compared with 2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate when tested in a hepatocyte stability assay (such as in human hepatocytes), e.g., as described in Biological Example 3. In one embodiment, the compound of formula (I) exhibits a longer half-life (T1/2) compared with 2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate when tested in a hepatocyte stability assay (such as in human hepatocytes), e.g. as described in Biological Example 3.

Administration

The compound of formula (I) is usually administered as a pharmaceutical composition. Thus, in one embodiment, is provided a pharmaceutical composition comprising a compound of formula (I) and one or more pharmaceutically acceptable diluents or carriers.

Furthermore, the compound of formula (II) is usually administered as a pharmaceutical composition. Thus, in one embodiment, is provided a pharmaceutical composition comprising a compound of formula (II) and one or more pharmaceutically acceptable diluents or carriers.

Details below regarding pharmaceutical compositions and administration thereof in respect of compounds of formula (I) apply equally to compounds of formula (II).

The compound of formula (I) may be administered by any convenient method, e.g. by oral, parenteral, buccal, sublingual, nasal, rectal, intrathecal or transdermal administration, and the pharmaceutical compositions adapted accordingly.

The compound of formula (I) may be administered topically to the target organ e.g. topically to the eye, lung, nose or skin. Hence the invention provides a pharmaceutical composition comprising a compound of formula (I) optionally in combination with one or more topically acceptable diluents or carriers.

A compound of formula (I) which is active when given orally can be formulated as a liquid or solid, e.g. as a syrup, suspension, emulsion, tablet, capsule or lozenge.

A liquid formulation will generally consist of a suspension or solution of the compound of formula (I) in a suitable liquid carrier(s). Suitably the carrier is non-aqueous e.g. polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or

colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations, such as magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures, e.g. pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatine capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), e.g. aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatine capsule.

Typical parenteral compositions consist of a solution or suspension of the compound of formula (I) in a sterile aqueous carrier or parenterally acceptable oil, e.g. polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the compound of formula (I) in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container which can take the form of a cartridge or refill for use with an atomising device. Alternatively, the sealed container may be a disposable dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas e.g. air, or an organic propellant such as a chlorofluorocarbon (CFC) or a hydrofluorocarbon (HFC). Aerosol dosage forms can also take the form of pump-atomisers.

Topical administration to the lung may be achieved by use of an aerosol formulation. Aerosol formulations typically comprise the active ingredient suspended or dissolved in a suitable aerosol propellant, such as a chlorofluorocarbon (CFC) or a hydrofluorocarbon (HFC).

Topical administration to the lung may also be achieved by use of a non-pressurised formulation such as an aqueous solution or suspension. These may be administered by means of a nebuliser e.g. one that can be hand-held and portable or for home or hospital use (i.e. non-portable). The formulation may comprise excipients such as water, buffers, tonicity adjusting agents, pH adjusting agents, surfactants and co-solvents.

Topical administration to the lung may also be achieved by use of a dry-powder formulation. The formulation will typically contain a topically acceptable diluent such as lactose, glucose or mannitol (preferably lactose).

The compound of the invention may also be administered rectally, for example in the form of suppositories or enemas, which include aqueous or oily solutions as well as suspensions and emulsions and foams. Such compositions are prepared following standard procedures, well known by those skilled in the art. For example, suppositories can be prepared by mixing the active ingredient with a conventional suppository base such as cocoa butter or other glycerides. In this case, the drug is mixed with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Generally, for compositions intended to be administered topically to the eye in the form of eye drops or eye ointments, the total amount of the compound of the present invention will be about 0.0001 to less than 4.0% (w/w).

Preferably, for topical ocular administration, the compositions administered according to the present invention will be formulated as solutions, suspensions, emulsions and other dosage forms.

The compositions administered according to the present invention may also include various other ingredients, including, but not limited to, tonicity agents, buffers, surfactants, stabilizing polymer, preservatives, co-solvents and viscosity building agents. Suitable pharmaceutical compositions of the present invention include a compound of the invention formulated with a tonicity agent and a buffer. The pharmaceutical compositions of the present invention may further optionally include a surfactant and/or a palliative agent and/or a stabilizing polymer.

Various tonicity agents may be employed to adjust the tonicity of the composition, preferably to that of natural tears for ophthalmic compositions. For example, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, simple sugars such as dextrose, fructose, galactose, and/or simply polyols such as the sugar alcohols mannitol, sorbitol, xylitol, lactitol, isomaltitol, maltitol, and hydrogenated starch hydrolysates may be added to the composition to approximate physiological tonicity. Such an amount of tonicity agent will vary, depending on the particular agent to be added. In general, however, the compositions will have a tonicity agent in an amount sufficient to cause the final composition to have an ophthalmically acceptable

osmolality (generally about 150-450 mOsm, preferably 250-350 mOsm and most preferably at approximately 290 mOsm). In general, the tonicity agents of the invention will be present in the range of 2 to 4% w/w. Preferred tonicity agents of the invention include the simple sugars or the sugar alcohols, such as D-mannitol.

An appropriate buffer system (e.g. sodium phosphate, sodium acetate, sodium citrate, sodium borate or boric acid) may be added to the compositions to prevent pH drift under storage conditions. The particular concentration will vary, depending on the agent employed. Preferably however, the buffer will be chosen to maintain a target pH within the range of pH 5 to 8, and more preferably to a target pH of pH 5 to 7.

Surfactants may optionally be employed to deliver higher concentrations of compound of the present invention. The surfactants function to solubilise the compound and stabilise colloid dispersion, such as micellar solution, microemulsion, emulsion and suspension. Examples of surfactants which may optionally be used include polysorbate, poloxamer, polyosyl 40 stearate, polyoxyl castor oil, tyloxapol, Triton, and sorbitan monolaurate. Preferred surfactants to be employed in the invention have a hydrophile/lipophile/balance "HLB" in the range of 12.4 to 13.2 and are acceptable for ophthalmic use, such as TritonX114 and tyloxapol.

Additional agents that may be added to the ophthalmic compositions of compounds of the present invention are demulcents which function as a stabilising polymer. The stabilizing polymer should be an ionic/charged example with precedence for topical ocular use, more specifically, a polymer that carries negative charge on its surface that can exhibit a zeta-potential of (–)10–50 mV for physical stability and capable of making a dispersion in water (i.e. water soluble). A preferred stabilising polymer of the invention would be polyelectrolyte, or polyelectrolytes if more than one, from the family of cross-linked polyacrylates, such as carbomers and Pemulen(R), specifically Carbomer 974p (polyacrylic acid), at 0.1–0.5% w/w.

Other compounds may also be added to the ophthalmic compositions of the compound of the present invention to increase the viscosity of the carrier. Examples of viscosity enhancing agents include, but are not limited to: polysaccharides, such as hyaluronic acid and its salts, chondroitin sulfate and its salts, dextrans, various polymers of the cellulose family; vinyl polymers; and acrylic acid polymers.

Topical ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, chlorobutanol, benzododecinium bromide, methyl paraben, propyl

paraben, phenylethyl alcohol, edentate disodium, sorbic acid, polyquaternium-1, or other agents known to those skilled in the art. Such preservatives are typically employed at a level of from 0.001 to 1.0% w/v. Unit dose compositions of the present invention will be sterile, but typically unpreserved. Such compositions, therefore, generally will not contain preservatives.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles where the compound of formula (I) is formulated with a carrier such as sugar and acacia, tragacanth, or gelatine and glycerine.

Compositions suitable for transdermal administration include ointments, gels and patches.

The composition may contain from 0.1% to 100% by weight, for example from 10 to 60% by weight, of the compound of formula (I), depending on the method of administration. The composition may contain from 0% to 99% by weight, for example 40% to 90% by weight, of the carrier, depending on the method of administration. The composition may contain from 0.05mg to 1000mg, for example from 1.0 mg to 500 mg, such as from 1.0 mg to 50 mg, e.g. about 10 mg of the compound of formula (I), depending on the method of administration. The composition may contain from 50 mg to 1000 mg, for example from 100mg to 400mg of the carrier, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 500mg, such as from 1.0 mg to 50 mg, e.g. about 10 mg and such unit doses may be administered more than once a day, for example two or three times a day. Such therapy may extend for a number of weeks or months.

In one embodiment of the invention, the compound of formula (I) is used in combination with a further therapeutic agent or agents. When the compound of formula (I) is used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route. Alternatively, the compounds may be administered separately.

Therapeutic agents which may be used in combination with the present invention include: corticosteroids (glucocorticoids), retinoids (e.g. acitretin, isotretinoin, tazarotene), anthralin, vitamin D analogues (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, thiopurines (e.g. azathioprine, 6-mercaptopurine), methotrexate, anti-TNFα agents (e.g. infliximab, etanercept, adalimumab,

certolizumab, golimumab and biosimilars), phosphodiesterase-4 (PDE4) inhibition (e.g. apremilast, crisaborole), anti-IL-17 agents (e.g. brodalumab, ixekizumab, secukinumab), anti-IL12/IL-23 agents (e.g. ustekinumab, briakinumab), anti-IL-23 agents (e.g. guselkumab, tildrakizumab), JAK (Janus Kinase) inhibitors (e.g. tofacitinib, ruxolitinib, baricitinib, filgotinib, upadacitinib), plasma exchange, intravenous immune globulin (IVIG), cyclophosphamide, anti-CD20 B cell depleting agents (e.g. rituximab, ocrelizumab, ofatumumab, obinutuzumab), anthracycline analogues (e.g. mitoxantrone), cladribine, sphingosine 1-phosphate receptor modulators or sphingosine analogues (e.g. fingolimod, siponimod, ozanimod, etrasimod), interferon beta preparations (including interferon beta 1b/1a), glatiramer, anti-CD3 therapy (e.g. OKT3), anti-CD52 targeting agents (e.g. alemtuzumab), leflunomide, teriflunomide, gold compounds, laquinimod, potassium channel blockers (e.g. dalfampridine/4-aminopyridine), mycophenolic acid, mycophenolate mofetil, purine analogues (e.g. pentostatin), mTOR (mechanistic target of rapamycin) pathway inhibitors (e.g. sirolimus, everolimus), anti-thymocyte globulin (ATG), IL-2 receptor (CD25) inhibitors (e.g. basiliximab, daclizumab), anti-IL-6 receptor or anti-IL-6 agents (e.g. tocilizumab, siltuximab), Bruton's tyrosine kinase (BTK) inhibitors (e.g. ibrutinib), tyrosine kinase inhibitors (e.g. imatinib), ursodeoxycholic acid, hydroxychloroquine, chloroquine, B cell activating factor (BAFF, also known as BLyS, B lymphocyte stimulator) inhibitors (e.g. belimumab, blisibimod), other B cell targeted therapy including fusion proteins targeting both APRIL (A PRoliferation-Inducing Ligand) and BLyS (e.g. atacicept), PI3K inhibitors including pan-inhibitors or those targeting the p110δ and/or p110γ containing isoforms (e.g. idelalisib, copanlisib, duvelisib), interferon α receptor inhibitors (e.g. anifrolumab, sifalimumab), T cell co-stimulation blockers (e.g. abatacept, belatacept), thalidomide and its derivatives (e.g. lenalidomide), dapsone, clofazimine, leukotriene antagonists (e.g. montelukast), theophylline, anti-IgE therapy (e.g. omalizumab), anti-IL-5 agents (e.g. mepolizumab, reslizumab), long-acting muscarinic agents (e.g. tiotropium, aclidinium, umeclidinium), PDE4 inhibitors (e.g. roflumilast), riluzole, free radical scavengers (e.g. edaravone), proteasome inhibitors (e.g. bortezomib), complement cascade inhibitors including those directed against C5 (e.g. eculizumab), immunoadsor, antithymocyte globulin, 5-aminosalicylates and their derivatives (e.g. sulfasalazine, balsalazide, mesalamine), anti-integrin agents including those targeting α4β1 and/or α4β7 integrins (e.g. natalizumab, vedolizumab), anti-CD11-α agents (e.g. efalizumab), non-steroidal anti-inflammatory drugs (NSAIDs) including the salicylates (e.g. aspirin), propionic acids (e.g. ibuprofen, naproxen), acetic acids (e.g. indomethacin, diclofenac, etodolac), oxicams (e.g. meloxicam) and fenamates (e.g. mefenamic acid), selective or relatively selective COX-2 inhibitors (e.g. celecoxib, etroxicoxib, valdecoxib and etodolac, meloxicam, nabumetone), colchicine, IL-4 receptor inhibitors (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, specific

antibiotics 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, cystic fibrosis transmembrane conductance regulator (CFTR) modulators, VEGF (vascular endothelial growth factor) inhibitors (e.g. bevacizumab, ranibizumab, pegaptanib, aflibercept), pirfenidone, and mizoribine.

Compounds of formula (I) and (II) may display one or more of the following desirable properties:

- low IC_{50} values for inhibiting release of cytokines e.g. IL-1β and/or IL-6, from cells;
- low EC_{50} and/or high E_{max} values for activating the NRF2 pathway;
- enhanced efficacy through improved hydrolytic stability of carboxylic acid esters and/or augmented maximum response;
- reduced dose and dosing frequency through improved pharmacokinetics;
- improved oral systemic bioavailability;
- reduced plasma clearance following intravenous dosing;
- improved metabolic stability e.g. as demonstrated by improved stability in plasma and/or hepatocytes;
- augmented cell permeability;
- enhanced aqueous solubility;
- good tolerability, for example, by limiting the flushing and/or gastrointestinal side effects provoked by oral DMF (Hunt T. *et al.*, 2015; WO2014/152494A1, incorporated herein by reference), possibly by reducing or eliminating HCA2 activity;
- low toxicity at the relevant therapeutic dose;
- distinct anti-inflammatory profiles resulting from varied electrophilicities, leading to differential targeting of the cysteine proteome (van der Reest J. *et al.*, 2018) and, therefore, modified effects on gene activation).

In addition, compounds of formula (II) may be advantageous because their biological activities are not glutathione sensitive.

Abbreviations

Ac	acetyl
Ac_2O	acetic anhydride
ADEM	acute disseminated encephalomyelitis
AIDP	acute inflammatory demyelinating polyneuropathy

ALPS	autoimmune lymphoproliferative syndrome
AMAN	acute motor axonal neuropathy
AMD	age related macular degeneration
AMSAN	acute motor and sensory axonal neuropathy
APEX	autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome
APRIL	A PRoliferation-Inducing Ligand
aq.	aqueous
ATF3	activating transcription factor 3
ATG	anti-thymocyte
BAFF	B cell activating factor
BBFO	broadband fluorine observe
Bn	benzyl
BEH	ethylene bridged hybrid
BOC	tertiary-butoxycarbonyl
BSA	bovine serum albumin
BTK	Bruton's tyrosine kinase
CAC	citric acid cycle
CANDLE	chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
CAPS	cryopyrin-associated periodic syndromes
CFC	chlorofluorocarbon
CFTR	cystic fibrosis transmembrane conductance regulator
CIDP	chronic inflammatory demyelinating polyneuropathy
CLE	cutaneous lupus erythematosus
CLIPPERS	chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids
CLL	chronic lymphocytic leukaemia
COPD	chronic obstructive pulmonary disease
CRMO	chronic recurrent multifocal osteomyelitis
CRVO	central retinal vein occlusion
CSH	charged surface hybrid
DABCO	1,4-diazabicyclo[2.2.2]octane
DAD	diode array detector
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DCM	dichloromethane
DIPEA	N,N-diisopropylethylamine

DIRA	deficiency of interleukin-1 receptor antagonist
DITRA	deficiency of the interleukin-36-receptor antagonist
DLBCL	diffuse large B cell lymphoma
DMAP	4-dimethylaminopyridine
DMF	dimethyl fumarate
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	ethylenediaminetetraacetic acid
EGPA	eosinophilic granulomatosis with polyangiitis
EtOAc	ethyl acetate
FBS	fetal bovine serum
FCAS	familial cold autoinflammatory syndrome
Fmoc	9-fluorenylmethyloxycarbonyl
FMF	familial Mediterranean fever
GAPDH	glyceraldehyde 3-phosphate dehydrogenase
GPA	granulomatosis with polyangiitis
GSH	glutathione
GVHD	graft versus host disease
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HCA2	hydroxycarboxylic acid receptor 2
HCV	hepatitis C
HFC	hydrofluorocarbon
HIF-1α	hypoxia-inducible factor-1α
HIV	human immunodeficiency virus
HMDMs	human monocyte derived macrophages
HOBt	1-hydroxybenzotriazole
IL	interleukin
IPEX	immune dysregulation polyendocrinopathy enteropathy X-linked
IRG1	immune-responsive gene 1
IVIG	intravenous immune globulin
JAK	Janus kinase
KEAP1	kelch-like ECH-associated protein 1
LCMS	liquid chromatography–mass spectrometry
LDA	lithium diisopropylamide
LPS	lipopolysaccharide

MALT	mucosa-associated lymphoid tissue
mCPBA	meta-chloroperoxybenzoic acid
M-CSF	macrophage-colony stimulating factor
MMF	monomethyl fumarate
MMN	multifocal motor neuropathy
MOG	myelin oligodendrocyte glycoprotein
MOM	methoxymethyl
MS	mass spectrometry
MSD	mass selective detector
MTBE	methyl tertiary-butyl ether
NLRP12AD	NLRP12-associated autoinflammatory disorders
NMM	N-methylmorpholine
NMR	nuclear magnetic resonance
NOMID	neonatal onset multisystem inflammatory disease
NRF2	nuclear factor (erythroid-derived 2)-like 2
NSAIDs	non-steroidal anti-inflammatory drugs
O/N	overnight
PAH	pulmonary arterial hypertension
PANDAS	paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
PANS	paediatric acute-onset neuropsychiatric syndrome
PAPA	pyogenic arthritis, pyoderma gangrenosum, severe cystic acne
PMB	4-methoxybenzyl
PBMCs	primary peripheral blood mononuclear cells
PBS	phosphate buffered saline
PDA	photodiode array
PDE4	phosphodiesterase-4
PET	positron emission topography
PFAPA	periodic fever aphthous stomatitis
PLEVA	pityriasis lichenoides et varioliformis acuta
PMA	phorbol 12-myristate 13-acetate
PSC	primary sclerosing cholangitis
PUVA	psoralen ultraviolet irradiation
p-TsOH	*p*-toluenesulfonic acid
4OI	4-octyl itaconic acid
RT	room temperature
sat.	saturated

SDH	succinate dehydrogenase
SFC	supercritical fluid chromatography
SLE	systemic lupus erythematosus
STING	stimulator of interferon genes
TBDMS	tert-butyldimethylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TLR	Toll-like receptor
TMS	trimethylsilyl
TNF	tumour necrosis factor
TOM	tri-iso-propylsilyloxymethyl
Tr	trityl
TRAPS	tumour necrosis factor receptor-associated periodic fever
Trt	trityl, triphenylmethyl
TTP	thrombotic thrombocytopenic purpura
UPLC	ultra performance liquid chromatography
VEGF	vascular endothelial growth factor
VWD	variable wavelength detector
wt.	weight

EXAMPLES

Analytical Equipment

NMR spectra were recorded using a Bruker 400 MHz Avance III spectrometer fitted with a BBFO 5 mm probe, or a Bruker 500 MHz Avance III HD spectrometer equipped with a Bruker 5 mm SmartProbeTM. Spectra were measured at 298 K, unless indicated otherwise, and were referenced relative to the solvent resonance. The chemical shifts are reported in parts per million. Data were acquired using Bruker TopSpin software.

UPLC/MS analysis was carried out on a Waters Acquity UPLC system using either a Waters Acquity CSH C18 or BEH C18 column (2.1 x 30 mm) maintained at a temperature of 40 °C and eluted with a linear acetonitrile gradient appropriate for the lipophilicity of the compound over 3 or 10 minutes at a constant flow rate of 0.77 mL/min. The aqueous portion of the mobile phase was either 0.1 % Formic Acid (CSH C18 column) or 10 mM Ammonium Bicarbonate (BEH C18

column). LC-UV chromatograms were recorded using a Waters Acquity PDA detector between 210 and 400 nm. Mass spectra were recorded using a Waters Acquity Qda detector with electrospray ionisation switching between positive and negative ion mode. Sample concentration was adjusted to give adequate UV response.

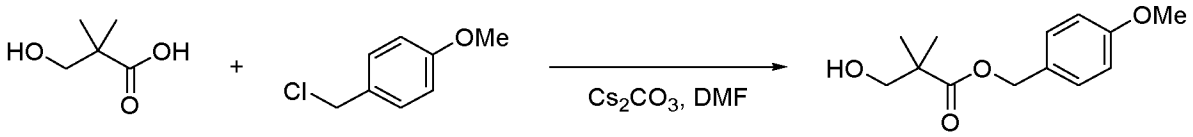
LCMS analysis was carried out on an Agilent LCMS system using either a Waters Acquity CSH C18 or BEH C18 column (4.6 x 30 mm) maintained at a temperature of 40 °C and eluted with a linear acetonitrile gradient appropriate for the lipophilicity of the compound over 4 or 15 minutes at a constant flow rate of 2.5 mL/min. The aqueous portion of the mobile phase was either 0.1 % Formic Acid (CSH C18 column) or 10 mM Ammonium Bicarbonate (BEH C18 column). LC-UV chromatograms were recorded using an Agilent VWD or DAD detector at 254 nm. Mass spectra were recorded using an Agilent MSD detector with electrospray ionisation switching between positive and negative ion mode. Sample concentration was adjusted to give adequate UV response.

Commercial Materials

All starting materials disclosed herein are commercially available. Dimethyl fumarate is commercially available, for example from Sigma Aldrich. 2-(2,5-Dioxopyrrolidin-1-yl)ethyl methyl fumarate (diroximel fumarate) is commercially available, for example from Angene. Monomethyl fumarate is commercially available, for example from Sigma Aldrich.

Unless otherwise stated all reactions were stirred. Organic solutions were routinely dried over anhydrous magnesium sulfate. Hydrogenations were performed on a Thales H-cube flow reactor under the conditions stated or under pressure in a gas autoclave (bomb).

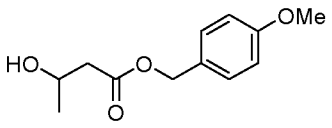
Intermediate 1: 4-methoxybenzyl 3-hydroxy-2,2-dimethylpropanoate



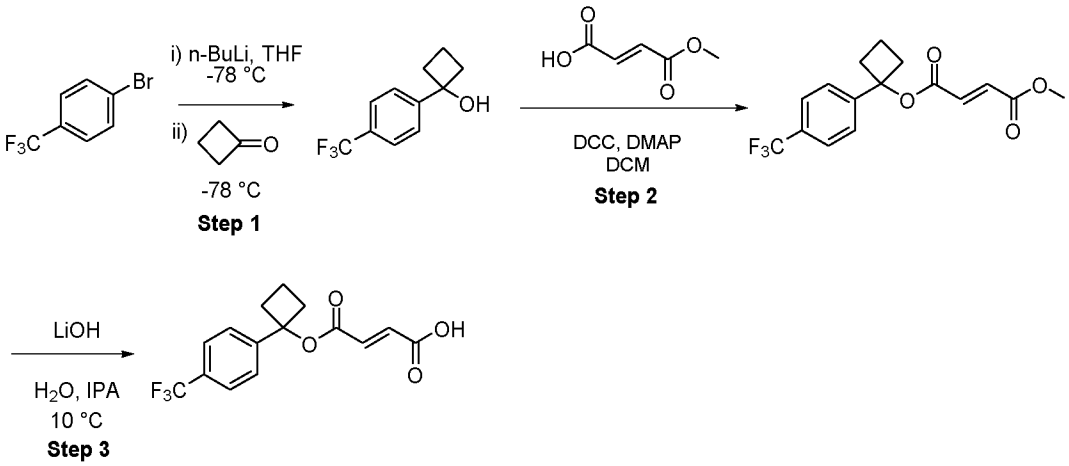
1-(chloromethyl)-4-methoxybenzene (1.0 mL, 7.4 mmol) was added to a mixture of 3-hydroxy-2,2-dimethylpropanoic acid (1.0 g, 8.5 mmol) and cesium carbonate (2.76 g, 8.5 mmol) in dimethylformamide (40 mL). The mixture was stirred at RT for 3 h, then heated to 70 °C for 2 h, then cooled to RT and stirred for 18 h. The mixture was poured onto water (50 mL) and extracted with EtOAc (3x50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography on silica gel (0-50% EtOAc/isohexane) to afford 4-methoxybenzyl 3-hydroxy-2,2-dimethylpropanoate (1.45 g,

5.78 mmol) as a colourless oil. ^{1}H NMR (400 MHz, DMSO) δ 7.32 - 7.27 (m, 2H), 6.97 - 6.90 (m, 2H), 5.01 (s, 2H), 4.85 (t, J = 5.5 Hz, 1H), 3.76 (s, 3H), 3.42 (d, J = 5.5 Hz, 2H), 1.08 (s, 6H).

The following compounds were synthesised using the same procedure.

Int. Number	Structure	Name
2		4-methoxybenzyl 3-hydroxybutanoate
		LCMS m/z 247.1 $(M+Na)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO) δ 7.34 - 7.25 (m, 2H), 6.97 - 6.86 (m, 2H), 5.00 (s, 2H), 4.72 (d, J = 5.1 Hz, 1H), 4.05 - 3.95 (m, 1H), 3.75 (s, 3H), 2.37 (d, J = 6.6 Hz, 2H), 1.08 (d, J = 6.2 Hz, 3H)

Intermediate 3: (*E*)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid



Step 1

To a solution of 1-bromo-4-(trifluoromethyl)benzene (22.3 g, 99.5 mmol) in THF (180 mL) at -78 °C was added n-BuLi solution in hexane (2.5 M, 43.7 mL, 109.2 mmol) and the mixture was stirred at -78 °C for 1 h. Cyclobutanone (7.6 g, 109.2 mmol) was added, and the mixture was stirred at -78 °C for 5 h, then quenched with saturated aqueous NH_4Cl solution (200 mL). The phases were separated and the aqueous layer was extracted with MTBE (2 x 80 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure at 30 °C, and the residue was purified by flash column chromatography (120 g silica, 0-14% MTBE/petroleum ether) to give 1-(4-(trifluoromethyl)phenyl)cyclobutan-1-ol (16.5 g, 76.3 mmol, 77 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (s, 4H), 2.59-2.48 (m, 2H), 2.43-2.32 (m, 2H), 2.12-1.98 (m, 1H), 1.81-1.66 (m, 1H). One exchangeable proton not observed.

Step 2

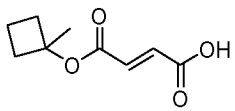
A mixture of 1-(4-(trifluoromethyl)phenyl)cyclobutan-1-ol (300 mg, 1.39 mmol), (*E*)-4-methoxy-4-oxobut-2-enoic acid (181 mg, 1.39 mmol), DCC (430 mg, 2.09 mmol) and DMAP (17 mg, 0.14 mmol) in DCM (3 mL) was stirred at room temperature for 30 min. The mixture was filtered, and

the filtrate was concentrated under reduced pressure at 35 °C. The residue was purified by flash column chromatography (12 g silica, 0-10% MTBE/petroleum ether) to give methyl (1-(4-(trifluoromethyl)phenyl)cyclobutyl) fumarate (360 mg, 1.10 mmol, 79 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65-7.55 (m, 4H), 6.87-6.76 (m, 2H), 3.80 (s, 3H), 2.79-2.59 (m, 4H), 2.13-1.97 (m, 1H), 1.87-1.71 (m, 1H).

Step 3

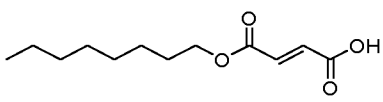
To a solution of methyl (1-(4-(trifluoromethyl)phenyl)cyclobutyl) fumarate (360 mg, 1.10 mmol) in IPA (3 mL) was added aqueous LiOH solution (2 M, 0.6 mL, 1.20 mmol), and the reaction mixture was stirred at 10 °C for 20 min. The reaction mixture was acidified with dilute aqueous HCl (0.5 M) to pH = 3, and extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure at 30 °C. The residue was purified by preparative HPLC (Column: Waters X-Bridge C18 OBD 10 µm 19x250 mm; Flow Rate: 20 mL/min; solvent system: MeCN/(0.2% formic acid/water); gradient: 65-95% MeCN; collection wavelength: 214 nm). The collected fractions were concentrated under reduced pressure at 30 °C to remove MeCN, and the residue was lyophilized to give (*E*)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid (110 mg, 0.35 mmol, 32 %) as an off-white solid. LCMS m/z 336.8 $(M+Na)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d6) δ: 13.26 (br, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 6.74-6.62 (m, 2H), 2.68-2.59 (m, 4H), 2.05-1.92 (m, 1H), 1.85-1.69 (m, 1H).

Intermediate 4: (*E*)-4-(1-methylcyclobutoxy)-4-oxobut-2-enoic acid



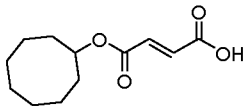
Fumaroyl dichloride (0.071 mL, 0.654 mmol) was dissolved in DCM (2 mL) and treated with 1-methylcyclobutanol (0.113 g, 1.308 mmol) and TEA (0.310 ml, 2.223 mmol). The reaction mixture was stirred for 3 hours at room temperature, then it was diluted with water.The organic layer was collected and dried (phase separator), then the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel (12 g cartridge, 0-10% MeOH/DCM), yielding only (E)-4-(1-methylcyclobutoxy)-4-oxobut-2-enoic acid (60 mg, 0.319 mmol, 48.8 % yield) as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.51 (s, 1H), 6.64 (d, J = 7.3 Hz, 2H), 2.36 - 2.24 (m, 2H), 2.11 (ddq, J = 12.1, 8.2, 2.4 Hz, 2H), 1.83 - 1.73 (m, 1H), 1.72 - 1.62 (m, 1H), 1.53 (s, 3H).

Intermediate 5: octyl fumarate



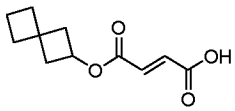
This compound is commercially available and may be purchased, for example, from Aurora Fine Chemicals Ltd.

Intermediate 6: (E)-4-(cyclooctyloxy)-4-oxobut-2-enoic acid



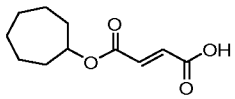
The synthesis of Intermediate 6 is described in Example 3.

Intermediate 7: (E)-4-oxo-4-(spiro[3.3]heptan-2-yloxy)but-2-enoic acid



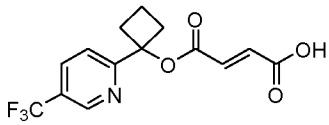
The synthesis of Intermediate 7 is described in Example 9.

Intermediate 8: (E)-4-(cycloheptyloxy)-4-oxobut-2-enoic acid



The synthesis of Intermediate 8 is described in Example 10.

Intermediate 9: (E)-4-oxo-4-(1-(5-(trifluoromethyl)pyridin-2-yl)cyclobutoxy)but-2-enoic acid



Prepared from of 2-bromo-5-(trifluoromethyl)pyridine and cyclobutanone using a similar procedure to (*E*)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (s, 1H), 7.99 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 4.73 (s, 1H), 2.61-2.49 (m, 4H), 2.17-2.07 (m, 1H), 1.98-1.86 (m, 1H).

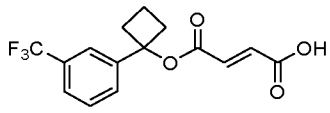
Step 2

LCMS m/z 330.0 $(M+H)^+$ (ES^+).

Step 3

LCMS m/z 316.0 $(M+H)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO-d6) δ: 13.27 (br s, 1H), 9.00 (s, 1H), 8.20 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 6.75 (s, 2H), 2.77-2.70 (m, 2H), 2.64-2.54 (m, 2H), 2.03-1.89 (m, 2H).

Intermediate 10: (E)-4-oxo-4-(1-(3-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid



Prepared from 1-bromo-3-(trifluoromethyl)benzene and cyclobutanone using a similar procedure to (E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, CDCl3) δ: 7.77 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.56-7.48 (m, 2H), 3.21-2.54 (m, 2H), 2.44-2.37 (m, 2H), 2.13-2.04 (m, 1H), 1.79-1.72 (m, 1H).

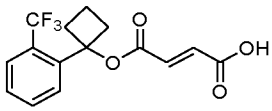
Step 2

LCMS m/z 351.0 $(M+Na)^+$ (ES+).

Step 3

LCMS m/z 336.9 (M+Na)+ (ES+). ^{1}H NMR (400 MHz, DMSO-d6) δ: 13.17 (br s, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.74 (s, 1H), 7.71-7.60 (m, 2H), 6.73-6.62 (m, 2H,), 2.69-2.59 (m, 4H), 2.04-1.92 (m, 1H), 1.80-1.66 (m, 1H).

Intermediate 11: (E)-4-oxo-4-(1-(2-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid



Prepared from 1-bromo-2-(trifluoromethyl)benzene and cyclobutanone using a similar procedure to (E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, CDCl3) δ: 7.68-7.52 (m, 2H), 7.45-7.37 (m, 2H), 2.68-2.61 (m, 2H), 2.46-2.42 (m, 2H), 2.33-2.28 (m, 2H).

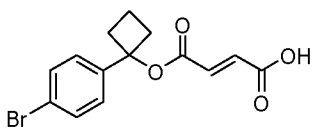
Step 2

LCMS m/z 351.0 $(M+Na)^+$ (ES+).

Step 3

LCMS m/z 337.0 (M+Na)+ (ES+). ^{1}H NMR (400 MHz, DMSO-d6) δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.72 (t, *J* = 7.2 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 6.63-6.55 (m, 2H), 2.79-2.75 (m, 2H), 2.68-2.61 (m, 2H), 1.97-1.91 (m, 1H), 1.74-1.67 (m, 1H).

Intermediate 12: (E)-4-(1-(4-bromophenyl)cyclobutoxy)-4-oxobut-2-enoic acid



Prepared from 1,4-dibromobenzene and cyclobutanone using a similar procedure to (E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, CDCl3) δ: 7.48 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 2.53-2.46 (m, 2H), 2.37-2.30 (m, 2H), 2.06-1.97 (m, 1H), 1.71-1.64 (m, 1H).

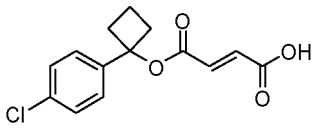
Step 2

LCMS m/z 361.0 $(M+Na)^+$ (ES+).

Step 3

LCMS m/z 346.9 (M+Na)+. (ES+). ^{1}H NMR (400 MHz, DMSO-d6) δ: 13.21 (br s, 1H), 7.59-7.54 (m, 2H), 7.45-7.42 (m, 2H), 6.71-6.61 (m, 2H), 2.65-2.55 (m, 4H), 2.00-1.89 (m, 1H), 1.77-1.63 (m, 1H).

Intermediate 13: (E)-4-(1-(4-chlorophenyl)cyclobutoxy)-4-oxobut-2-enoic acid



Prepared from of 1-bromo-4-chlorobenzene and cyclobutanone using a similar procedure to (E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, CDCl3) δ: 7.46-7.42 (m, 2H), 7.35-7.32 (m, 2H), 2.56-2.45 (m, 2H), 2.40-2.33 (m, 2H), 2.06-1.99 (m, 1H), 1.73-1.66 (m, 1H).

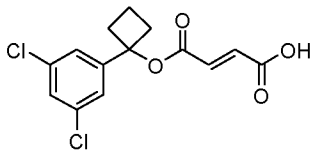
Step 2

LCMS m/z 316.8 $(M+Na)^+$ (ES+).

Step 3

LCMS m/z 302.9 (M+Na)+. (ES+).^{1}H NMR (400 MHz, DMSO-d6) δ: 13.21 (br s, 1H), 7.51 (dd, *J* = 6.4 Hz, 2.0 Hz, 2H), 7.43 (dd, *J* = 6.8 Hz, 2.0Hz, 2H), 6.70-6.62 (m, 2H), 2.62-2.59 (m, 4H), 2.00-1.92 (m, 1H), 1.74-1.69 (m, 1H).

Intermediate 14: (E)-4-(1-(3,5-dichlorophenyl)cyclobutoxy)-4-oxobut-2-enoic acid



Prepared from 1,3-dichloro-5-iodobenzene and cyclobutanone using a similar procedure to (E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, CDCl3) δ 7.38 (d, *J* = 2.0 Hz, 2H), 7.27 (t, *J* = 2.0 Hz, 1H), 2.54-2.48 (m, 2H), 2.40-2.32 (m, 2H), 2.12-2.06 (m, 1H), 1.81-1.70 (m, 1H).

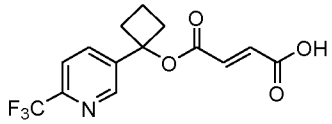
Step 2

LCMS m/z 351.0 (M+Na)+ (ES+).

Step 3

^{1}H NMR (400 MHz, DMSO-d6) δ: 13.26 (br s, 1H), 7.56 (t, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 1.2 Hz, 2H), 6.74-6.64 (m, 2H), 2.68-2.54 (m, 4H), 1.98-1.92 (m, 1H), 1.77-1.70 (m, 1H).

Intermediate 15: (E)-4-oxo-4-(1-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)but-2-enoic acid



Prepared from 5-bromo-2-(trifluoromethyl)pyridine and cyclobutanone using a similar procedure to (E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90 (d, *J* = 2.0 Hz, 1H), 8.01 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 2.62-2.55 (m, 2H), 2.49-2.41 (m, 2H), 2.18-2.09 (m, 1H), 1.88-1.76 (m, 1H).

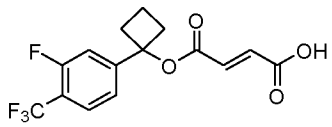
Step 2

LCMS m/z 330.2 $(M+H)^+$ (ES+).

Step 3

LCMS m/z 316.0 $(M+H)^+$.^{1}H NMR (400 MHz, DMSO-d6) δ: 13.25 (br s, 1H), 8.92 (d, *J* = 2.0 Hz, 1H), 7.43 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 6.74-6.65 (m, 2H), 2.72-2.65 (m, 4H), 2.03-1.98 (m, 1H), 1.84-1.76 (m, 1H).

Intermediate 16: (*E*)-4-(1-(3-fluoro-4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid



Prepared from 4-bromo-2-fluoro-1-(trifluoromethyl)benzene and cyclobutanone using a similar procedure to (E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid.

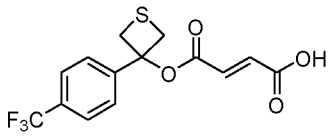
Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (t, *J* = 8.0 Hz, 1H), 7.40-7.35 (m, 2H), 2.57-2.50 (m, 2H), 2.44-2.37 (m, 2H), 2.11-2.09 (m, 1H), 1.80-1.77 (m, 1H).

Step 3

^{1}H NMR (400 MHz, DMSO-d6) δ: 13.24 (br s, 1H), 7.79 (t, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 12.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 6.75-6.66 (m, 2H), 2.67-2.61 (m, 4H), 2.01-1.95 (m, 1H), 1.83-1.75 (m, 1H).

Intermediate 17: (*E*)-4-oxo-4-((3-(4-(trifluoromethyl)phenyl)thietan-3-yl)oxy)but-2-enoic acid



Prepared from 1-iodo-4-(trifluoromethyl)benzene and thietan-3-one using a similar procedure to (E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 3.60 (s, 4H), 2.84 (s, 1H).

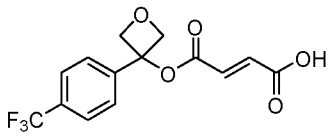
Step 2

LCMS m/z 368.9 $(M+Na)^+$ (ES+).

Step 3

^{1}H NMR (400 MHz, DMSO-d6) δ: 13.30 (br s, 1H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 15.8 Hz, 1H), 6.66 (d, *J* = 15.8 Hz, 1H), 4.05-3.99 (m, 2H), 3.59-3.53 (m, 2H).

Intermediate 18: (*E*)-4-oxo-4-((3-(4-(trifluoromethyl)phenyl)oxetan-3-yl)oxy)but-2-enoic acid



Prepared from 1-bromo-4-(trifluoromethyl)benzene and oxetan-3-one using a similar procedure to (E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 4.95 (d, *J* = 7.6 Hz, 2H), 4.89 (d, *J* = 7.6 Hz, 2H).

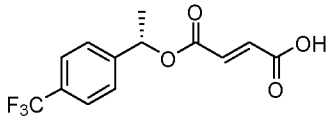
Step 2

LCMS m/z 331.0 $(M+H)^+$ (ES+).

Step 3

LCMS m/z 316.9 $(M+H)^+$.^{1}H NMR (400 MHz, DMSO-d6) δ: 13.35 (br s, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 6.87-6.74 (m, 2H), 5.04 (d, *J* = 8.0 Hz, 2H), 4.89 (d, *J* = 8.0 Hz, 2H).

Intermediate 19: (*S*,E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)ethoxy)but-2-enoic acid

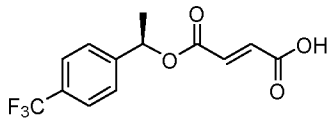


Prepared from (S)-1-(4-(trifluoromethyl)phenyl)ethanol using a similar procedure to (E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid (Step 2 and Step 3 only).

Step 3

^{1}H NMR (400 MHz, DMSO-d6) δ: 12.27 (br, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 6.80-6.72 (m, 2H), 5.99 (q, *J* = 6.4 Hz, 1H), 1.55 (d, *J* = 6.4 Hz, 3H).

Intermediate 20: (*R*,E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)ethoxy)but-2-enoic acid

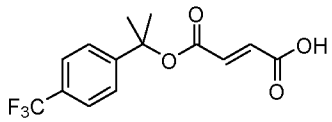


Prepared from (*R*)-1-(4-(trifluoromethyl)phenyl)ethanol using a similar procedure to (E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid (Step 2 and Step 3 only).

Step 3

^{1}H NMR (400 MHz, DMSO-d6) δ: 13.27 (br s, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 6.80-6.71 (m, 2H), 5.99 (q, *J* = 6.4 Hz, 1H), 1.55 (d, *J* = 6.8 Hz, 3H).

Intermediate 21: (E)-4-oxo-4-((2-(4-(trifluoromethyl)phenyl)propan-2-yl)oxy)but-2-enoic acid



Prepared from 2-(4-(trifluoromethyl)phenyl)propan-2-ol using a similar procedure to (E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid (Step 2 and Step 3 only).

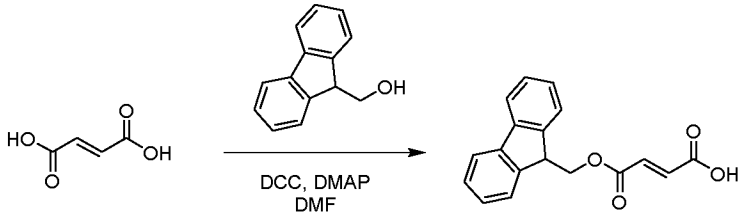
Step 2

LCMS m/z 339.0 $(M+Na)^+$ (ES+).

Step 3

^{1}H NMR (400 MHz, DMSO-d6) δ: 13.26 (br s, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 6.69 (s, 2H), 1.77 (s, 6H).

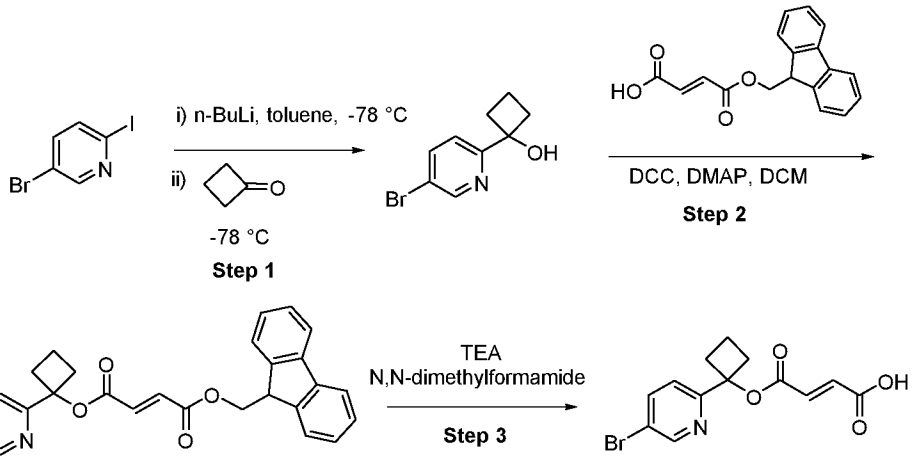
Intermediate 22: (E)-4-((9H-fluoren-9-yl)methoxy)-4-oxobut-2-enoic acid



To the solution of fumaric acid (10.0 g, 86.1 mmol), (9*H*-fluoren-9-yl)methanol (5.6 g, 28.7 mmol) and DMAP (350 mg, 2.9 mmol) in DCM (150 mL) was added DCC (8.9 g, 43.1 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction mixture was filtered and the

filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica (0-30% *tert*-butyl methyl ether/petroleum ether) to give a mixture of (9*H*-fluoren-9-yl)methanol and (*E*)-4-((9*H*-fluoren-9-yl)methoxy)-4-oxobut-2-enoic acid. The mixture was dissolved with EtOAc (50 mL) and the solution extracted with saturated potassium carbonate (100 mL). The aqueous layer was separated and washed with EtOAc (2 x 20 mL), acidified with 2N HCl until pH 4-5, and extracted with EtOAc (3 x 30 mL). The EtOAc layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (*E*)-4-((9*H*-fluoren-9-yl)methoxy)-4-oxobut-2-enoic acid (7.50 g, 89%) as a white solid. LCMS m/z 317.0 $(M+Na)^+$ (ES+). ^1H NMR (400 MHz, $CDCl_3$) δ: 13.29 (br s, 1H), 7.91 (d, *J* = 7.6 Hz, 2H), 7.68 (d, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 6.68 (q, *J* = 15.6 Hz, 2H), 4.54 (d, *J* = 6.8 Hz, 2H), 4.35 (t, *J* = 6.4 Hz, 1H).

Intermediate 23: (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid



Step 1

To the solution of 5-bromo-2-iodopyridine (5.0 g, 17.67 mmol) in toluene (50 mL) was added n-BuLi (7.07 mL, 17.67 mmol, 2.5 M in n-hexane) at -78 °C; and the mixture was stirred for 1 h at this temperature. Cyclobutanone (1.24 g, 17.67 mmol) and added and the mixture was stirred at -78 °C for further 2 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (50 mL), the organic layer was separated and the aqueous layer was extracted with MTBE (2 x 50 mL). The combined organic layers were washed by brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica (0-15% tert-butyl methyl ether/petroleum ether) to give 1-(5-bromopyridin-2-yl)cyclobutan-1-ol (3.0 g, 75% yield) as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.58 (d, *J* = 2.2 Hz, 1H), 7.86 (dd, *J* = 8.4, 2.4 Hz,, 1H), 7.49 (d, *J* = 8.4 Hz,, 1H), 4.67 (s, 1H), 2.57-2.45 (m, 4H), 2.12-2.04 (m, 1H), 1.92-1.82 (m, 1H).

Step 2

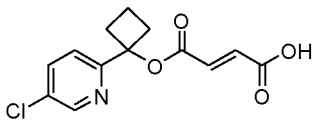
A mixture of 1-(5-bromopyridin-2-yl)cyclobutan-1-ol (300 mg, 1.32 mmol), (*E*)-4-((9*H*-fluoren-9-yl)methoxy)-4-oxobut-2-enoic acid (Intermediate 22, 388 mg, 1.32 mmol), DCC (407 mg, 1.98

mmol) and DMAP (16 mg, 0.13 mmol) in DCM (4 mL) was stirred at room temperature for 3 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica (0-18% *tert*-butyl methyl ether /petroleum ether) to give (9*H*-fluoren-9-yl)methyl (1-(5-bromopyridin-2-yl)cyclobutyl) fumarate (400 mg, 60% yield) as a colorless oil. LCMS m/z 504.0 $(M+H)^+$ (ES+).

Step 3

A solution of (9*H*-fluoren-9-yl)methyl (1-(5-bromopyridin-2-yl)cyclobutyl) fumarate (400 mg, 0.79 mmol) in dimethylformamide (2 mL) and triethylamine (0.4 mL) was stirred at room temperature for 2 h. The reaction mixture was acidified with 0.5 N HCl until pH = 6 and extracted with EtOAc (2 x 3 mL). The EtOAc layer was washed by brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Column: Waters X-Bridge C18 OBD 10µm 19x250mm; Flow Rate: 20 mL/min; solvent system: MeCN/[0.2% formic acid/water] gradient: 55-95% MeCN; collection wavelength: 214 nm). The fractions were concentrated under reduced pressure to remove MeCN, and lyophilized to give (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid (135.8 mg, 52% yield) as white solid. LCMS m/z 326.0 $(M+H)^+$ (ES+). ^{1}H NMR (400 MHz, DMSO-d6) δ: 13.32 (br s, 1H), 8.71 (d, *J* = 1.6 Hz, 1H), 8.03 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.41 (dd, *J* = 8.4, 0.4 Hz, 1H), 6.76-6.67 (m, 2H), 2.73-2.66 (m, 2H), 2.59-2.51 (m, 2H), 2.00-1.92 (m, 1H), 1.90-1.83 (m, 1H).

Intermediate 24: (E)-4-(1-(5-chloropyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid



Prepared from 2-bromo-5-chloropyridine and cyclobutanone using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.48 (d, *J* = 2.4 Hz, 1H), 7.72 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.54 (d, *J* = 8.4Hz, 1H), 4.67 (s, 1H), 2.57-2.44 (m, 4H), 2.13-2.02 (m, 1H), 2.10.2.05 (m, 1H), 1.91-1.80 (m, 1H).

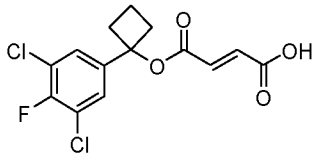
Step 2

LCMS m/z 460.0 $(M+H)^+$ (ES+).

Step 3

LCMS m/z 282.1 $(M+H)^+$.^{1}H NMR (400 MHz, DMSO-d6) δ: 13.31 (br, 1H), 8.63 (d, *J* = 2.0 Hz, 1H), 7.91 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.47 (d, *J* = 8.8, Hz, 1H), 6.76-6.67 (m, 2H), 2.73-2.67 (m, 2H), 2.60-2.51 (m, 2H), 2.01-1.92 (m, 1H), 1.90-1.83 (m, 1H).

Intermediate 25: (E)-4-(1-(3,5-dichloro-4-fluorophenyl)cyclobutoxy)-4-oxobut-2-enoic acid



Prepared from 5-bromo-1,3-dichloro-2-fluorobenzene and cyclobutanone using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (d, *J* = 6.4 Hz, 2H), 2.55-2.44 (m, 2H), 2.41-2.30 (m, 2H), 2.11-2.04 (m, 1H), 1.80-1.66 (m, 1H).

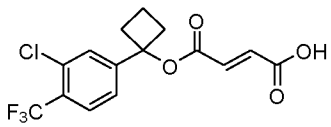
Step 2

LCMS m/z 532.8 $(M+Na)^+$ (ES+).

Step 3

^{1}H NMR (400 MHz, DMSO-d6) δ: 13.25 (br s, 1H), 7.69 (d, *J* = 6.4 Hz, 2H), 6.75-6.62 (m, 2H), 2.70-2.50 (m, 4H), 2.00-1.91 (m, 1H), 1.77-1.68 (m, 1H).

Intermediate 26: (E)-4-(1-(3-chloro-4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid



Prepared from 4-bromo-2-chloro-1-(trifluoromethyl)benzene and cyclobutanone using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (t, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 1H), 2.57-2.50 (m, 2H), 2.43-2.35 (m, 2H), 2.14-2.04 (m, 1H), 1.83-1.74 (m, 1H).

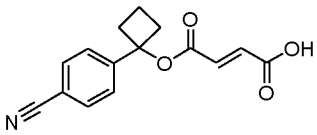
Step 2

LCMS m/z 559.0 $(M+Na)^+$ (ES+).

Step 3

^{1}H NMR (400 MHz, DMSO-d6) δ: 13.29 (br s, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.78 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 6.78 – 6.64 (m, 2H), 2.70-2.58 (m, 4H), 2.08-1.94 (m, 1H), 1.84-1.728 (m, 1H).

Intermediate 27: (E)-4-(1-(4-cyanophenyl)cyclobutoxy)-4-oxobut-2-enoic acid



Prepared from 4-iodobenzonitrile and cyclobutanone using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66-7.61 (m, 4H), 2.56-2.50 (m, 2H), 2.44-2.36 (m, 2H), 2.13-2.05 (m, 1H), 1.85-1.71 (m, 1H).

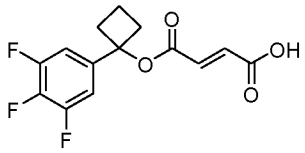
Step 2

LCMS m/z 472.0 $(M+Na)^+$ (ES+).

Step 3

LCMS m/z 294.1 $(M+Na)^+$ (ES+). ^{1}H NMR (400 MHz, DMSO-d6) δ: 13.26 (br s, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.71-7.63 (m, 2H), 2.64-2.60 (m, 4H), 2.01-1.95 (m, 1H), 1.80-1.73 (m, 1H)

Intermediate 28: (E)-4-oxo-4-(1-(3,4,5-trifluorophenyl)cyclobutoxy)but-2-enoic acid



Prepared from 5-bromo-1,2,3-trifluorobenzene and cyclobutanone using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14-7.04 (m, 1H), 6.97-6.90 (m,1H), 2.66-2.59 (m, 2H), 2.46-2.31 (m, 2H), 2.21-2.10 (m, 1H), 1.82-1.68 (m, 1H).

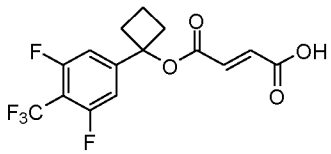
Step 2

LCMS m/z 501.0 $(M+Na)^+$ (ES+).

Step 3

NMR (400 MHz, DMSO-d6) δ: 13.24 (br s, 1H), 7.52-7.46 (m, 1H), 7.36-7.29 (m, 2H), 6.69-6.55 (m, 2H), 2.79-2.73 (m, 2H), 2.67-2.59 (m, 2H), 2.02-1.95 (m, 1H), 1.71-1.64 (m, 1H)

Intermediate 29: (E)-4-(1-(3,5-difluoro-4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid



Prepared from 5-bromo-1,3-difluoro-2-(trifluoromethyl)benzene and cyclobutanone using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (d, *J* = 11.2 Hz, 2H), 2.53-2.46 (m, 2H), 2.43-2.36 (m, 2H), 2.15-2.07 (m, 1H), 1.84-1.77 (m, 1H)

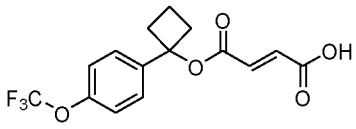
Step 2

LCMS m/z 550.8 $(M+Na)^+$ (ES+).

Step 3

NMR (400 MHz, DMSO-d6) δ: 13.26 (br s, 1H), 7.50 (d, *J* = 11.2 Hz, 2H), 6.78-6.64 (m, 2H), 2.68-2.56 (m, 4H), 2.02-1.93 (m, 1H), 1.87-1.76 (m, 1H).

Intermediate 30: (E)-4-oxo-4-(1-(4-(trifluoromethoxy)phenyl)cyclobutoxy)but-2-enoic acid



Prepared from 1-bromo-4-(trifluoromethoxy)benzene and cyclobutanone using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (d, *J*= 7 Hz, 2H), 7.20 (d, *J*= 4 Hz, 2H), 2.57-2.50 (m, 2H), 2.40-2.31 (m, 2H), 2.07-1.99 (m, 1H), 1.74-1.66 (m, 1H).

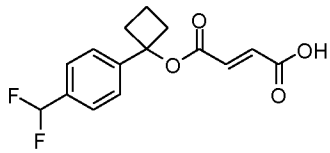
Step 2

LCMS m/z 530.9 $(M+Na)^+$ (ES+).

Step 3

^{1}H NMR (400 MHz, DMSO-d6) δ: 13.21 (br s, 1H), 7.63-7.59 (m, 2H), 7.37-7.35 (m, 2H), 6.73-6.63 (m, 2H), 2.62 (m, 4H), 1.99-1.90 (m, 1H), 1.76-1.65 (m, 1H).

Intermediate 31: (E)-4-(1-(4-(difluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid



Prepared from 1-bromo-4-(difluoromethyl)benzene and cyclobutanone using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (m, 4H), 6.65 (t, *J* = 56.4 Hz, 1H), 2.60-2.53 (m, 2H), 2.43-2.35 (m, 2H), 2.09-2.02 (m, 1H), 1.76-1.71 (m, 1H).

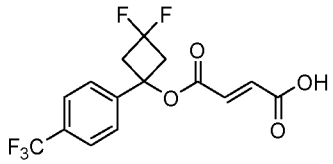
Step 2

LCMS m/z 497.0 $(M+Na)^+$ (ES+).

Step 3

LCMS m/z 319.3 $(M+Na)^+$ (ES+). ^{1}H NMR (400 MHz, DMSO-d6) δ: 13.22 (br s, 1H), 7.63-7.56 (m, 4H), 7.03 (t, *J* = 55.6 Hz, 1H), 6.73-6.63 (m, 2H), 2.63 (m, 4H), 2.00-1.94 (m, 1H), 1.78-1.68 (m, 1H).

Intermediate 32: (E)-4-(3,3-difluoro-1-(4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid



Prepared from 1-iodo-4-(trifluoromethyl)benzene and 3,3-difluorocyclobutanone using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67-7.63 (m, 2H), 7.62-7.25 (m, 2H), 3.20-3.01 (m, 4H).

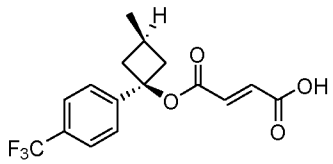
Step 2

LCMS m/z 550.8 $(M+Na)^+$ (ES+).

Step 3

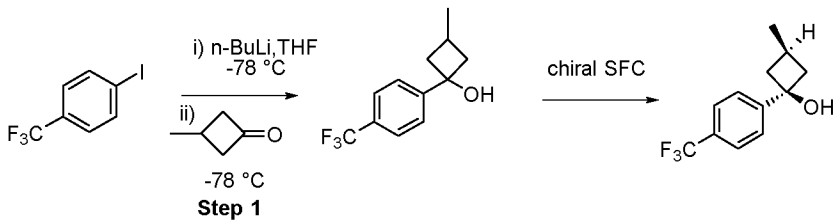
^{1}H NMR (400 MHz, DMSO-d6) δ: 13.42 (br s, 1H), 7.78-7.71 (m, 4H), 6.77 (d, *J* = 15.8 Hz, 1H), 6.66 (d, *J* = 15.8 Hz, 1H), 3.50-3.33 (m, 4H).

Intermediate 33: (E)-4-((cis)-3-methyl-1-(4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid



Prepared from 1-iodo-4-(trifluoromethyl)benzene and 3-methylcyclobutan-1-one using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid.

Step 1



Step 1

3-methyl-1-(4-(trifluoromethyl)phenyl)cyclobutan-1-ol (700 mg, 3.0 mmol) was separated by SFC (Column: CHIRALPAK AD-5 (30x250mm 5µm) (Daicel). Column temperature: 35 °C. CO_2 flow rate: 36 mL/min; cosolvent flow rate: 9 mL/min; total flow rate: 45 mL/min. Cosolvent: methanol. Gradient: methanol 20%. Collection wavelength: 215 nm). Trans isomer (minor): Rt = 0.898 min; cis isomer (major): Rt =1.039 min. The SFC fractions containing the cis isomer were concentrated under reduced pressure to to give (cis)-3-methyl-1-(4-(trifluoromethyl)phenyl)cyclobutan-1-ol (500 mg, 71% yield, stereochemistry arbitrarily assigned) which was used in Step 2. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65-7.60 (m, 4H), 2.80-2.69 (m, 2H), 2.14-1.97 (m, 3H), 1.20 (d, *J* = 6.0 Hz, 3H).

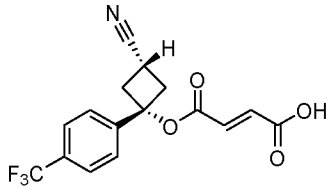
Step 2

LCMS m/z 528.9 $(M+Na)^+$ (ES+).

Step 3

^{1}H NMR (400 MHz, DMSO-d6) δ: 13.22 (br s, 1H), 7.75-7.69 (m, 4H), 6.73-6.63 (m, 2H), 2.85-2.77 (m, 2H), 2.27-2.06 (m, 3H), 1.15 (d, *J* = 6.0 Hz, 3H).

Intermediate 34: (E)-4-((cis)-3-cyano-1-(4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid



Prepared from 1-iodo-4-(trifluoromethyl)benzene and 3-oxocyclobutane-1-carbonitrile using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid.

Step 1

3-hydroxy-3-(4-(trifluoromethyl)phenyl)cyclobutane-1-carbonitrile was obtained as a single isomer (cis). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 3.05-2.96 (m, 2H), 2.86-2.77 (m, 3H).

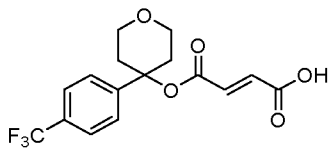
Step 2

LCMS m/z 539.8 $(M+Na)^+$ (ES+).

Step 3

LCMS m/z 362.1 $(M+Na)^+$ (ES+). ^{1}H NMR (400 MHz, DMSO-d6) δ: 13.31 (br s, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 6.76 (d, *J* = 15.8 Hz, 1H), 6.66 (d, *J* = 15.8 Hz, 1H), 3.36-3.23 (m, 1H), 3.18-3.08 (m, 2H), 3.05-2.95 (m, 2H).

Intermediate 35: (E)-4-oxo-4-((4-(4-(trifluoromethyl)phenyl)tetrahydro-2H-pyran-4-yl)oxy)but-2-enoic acid



Prepared from 1-iodo-4-(trifluoromethyl)benzene and dihydro-2H-pyran-4(3H)-one using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66-7.60 (m, 4H), 3.97-3.89 (m, 4H), 2.19 (ddd, *J* = 13.7, 12.0, 6.3 Hz, 2H), 1.70-1.63 (m, 2H).

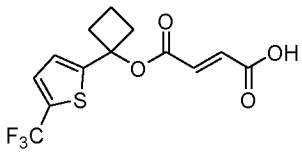
Step 2

LCMS m/z 523.0 $(M+H)^+$ (ES+).

Step 3

LCMS m/z 323.2 $(M+Na)^+$ (ES+). ^1H NMR (400 MHz, DMSO-d6) δ: 13.28 (br s, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.79-7.68 (m, 2H), 3.86-3.78 (m, 2H), 3.70 (td, *J* = 11.7, 1.9 Hz, 2H), 2.38-2.30 (m, 2H), 2.19-2.07 (m, 2H).

Intermediate 36: (E)-4-oxo-4-(1-(5-(trifluoromethyl)thiophen-2-yl)cyclobutoxy)but-2-enoic acid



Prepared from 2-bromo-5-(trifluoromethyl)thiophene and cyclobutanone using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid.

Step 1

^1H NMR (400 MHz, $CDCl_3$) δ: 7.30-7.29 (m, 1H), 7.00-6.99 (m, 1H), 2.56-2.41 (m, 4H), 2.03-1.95 (m, 1H), 1.82-1.75 (m, 1H).

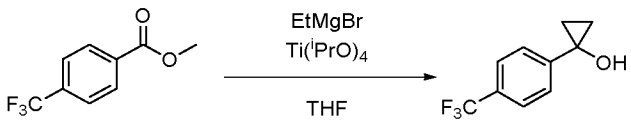
Step 2

LCMS m/z 520.8 $(M+Na)^+$ (ES+).

Step 3

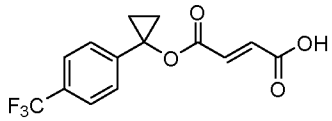
^1H NMR (400 MHz, DMSO-d6) δ: 13.10 (br s, 1H), 7.63-7.62 (m, 1H), 7.38-7.37 (m, 1H), 6.72 (d, *J* = 15.8 Hz, 1H), 6.65 (d, *J* = 15.8 Hz, 1H), 2.75-2.63 (m, 4H), 1.97-1.92 (m, 1H), 1.84-1.76 (m, 1H).

Intermediate 37: 1-(4-(trifluoromethyl)phenyl)cyclopropan-1-ol



To the solution of methyl 4-(trifluoromethyl)benzoate (3 g, 14.7 mmol) and titanium tetraisopropoxide (5.8 g, 20.1 mmol) in THF (30 mL) was added ethyl magnesium bromide (15 mL, 45 mmol, 3M in ether) slowly at 0 °C; and the mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with water (30 mL), and stirred for 1 h until a gray precipitate was formed. The solid was filtered off and filtrate extracted with tert-butyl methyl ether (3 x 40 mL). The combined organic layer was washed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified column chromatography (40 g silica, 0-20% ethyl acetate / petroleum ether) to give a mixture (1:1) of 1-(4-(trifluoromethyl)phenyl)cyclopropan-1-ol and 1-(4-(trifluoromethyl)phenyl)propan-1-ol (1 g, 32% yield) as colorless oil. which was used in the next step directly. ^1H NMR (400 MHz, CDCl3) δ: 7.62-7.57 (m, 4H), 2.42 (s, 1H), 1.38-1.35 (m, 2H), 1.13-1.10 (m, 2H).

Intermediate 38: (E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclopropoxy)but-2-enoic acid



Prepared from 1-(4-(trifluoromethyl)phenyl)cyclopropan-1-ol using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid (Step 2 and 3).

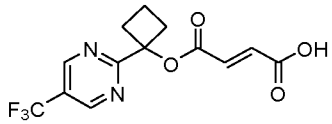
Step 2

LCMS m/z 501.1 $(M+Na)^+$ (ES+).

Step 3

LCMS m/z 301.1 $(M+H)^+$ (ES+). ^{1}H NMR (400 MHz, DMSO-d6) δ: 13.30 (br s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 6.77 (m, 2H), 1.49-1.39 (m, 4H).

Intermediate 39: (E)-4-oxo-4-(1-(5-(trifluoromethyl)pyrimidin-2-yl)cyclobutoxy)but-2-enoic acid



Prepared from 2-iodo-5-(trifluoromethyl)pyrimidine and cyclobutanone using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.00 (s, 2H), 4.76 (s, 1H), 2.67-2.63 (m, 2H), 2.62-2.50 (m, 2H), 2.16-2.00 (m, 2H).

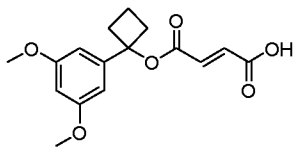
Step 2

LCMS m/z 495.0 $(M+H)^+$ (ES+).

Step 3

LCMS m/z 317.2 $(M+H)^+$ (ES+). ^{1}H NMR (400 MHz, DMSO-d6) δ: 9.02 (d, *J* = 0.4 Hz, 2H), 7.05 (d, *J* = 15.6 Hz, 1H), 6.87 (d, *J* = 15.6 Hz, 1H), 2.94-2.87 (m, 2H), 2.72-2.64 (m, 2H), 2.20-2.12 (m, 2H).

Intermediate 40: (E)-4-(1-(3,5-dimethoxyphenyl)cyclobutoxy)-4-oxobut-2-enoic acid



Prepared from 1-bromo-3,5-dimethoxybenzene and cyclobutanone using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid.

Step 1

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.65 (d, *J* = 2.4 Hz, 2H), 6.38 (t, *J* = 2.0 Hz, 1H), 3.81 (s, 6H), 2.50-2.57 (m, 2H), 2.38-2.31 (m, 2H), 2.03-2.00 (m, 2H), 1.73-1.68 (m, 1H).

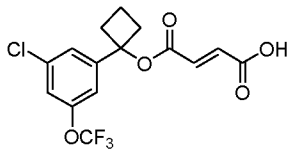
Step 2

LCMS m/z 506.9 $(M+Na)^+$ (ES+).

Step 3

LCMS m/z 329.2 $(M+Na)^+$ (ES+). ^1H NMR (400 MHz, DMSO-d6) δ: 13.20 (br s, 1H), 6.67 (s, 2H), 6.55 (d, *J* = 2.0 Hz, 2H), 6.43 (d, *J* = 2.0 Hz, 1H), 3.74 (s, 6H), 2.59-2.55 (m, 4H), 1.95-1.92 (m, 1H), 1.76-1.71 (m, 1H).

Intermediate 41: (E)-4-(1-(3-chloro-5-(trifluoromethoxy)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid



Prepared from 1-bromo-3-chloro-5-(trifluoromethyl)benzene and cyclobutanone using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid.

Step 1

^1H NMR (400 MHz, $CDCl_3$) δ: 7.67 (s, 1H), 7.57 (s, 1H), 7.50 (s,1H), 2.62-2.56 (m, 2H), 2.50-2.41 (m, 2H), 2.21-2.02 (m, 1H), 1.82-1.68 (m, 1H).

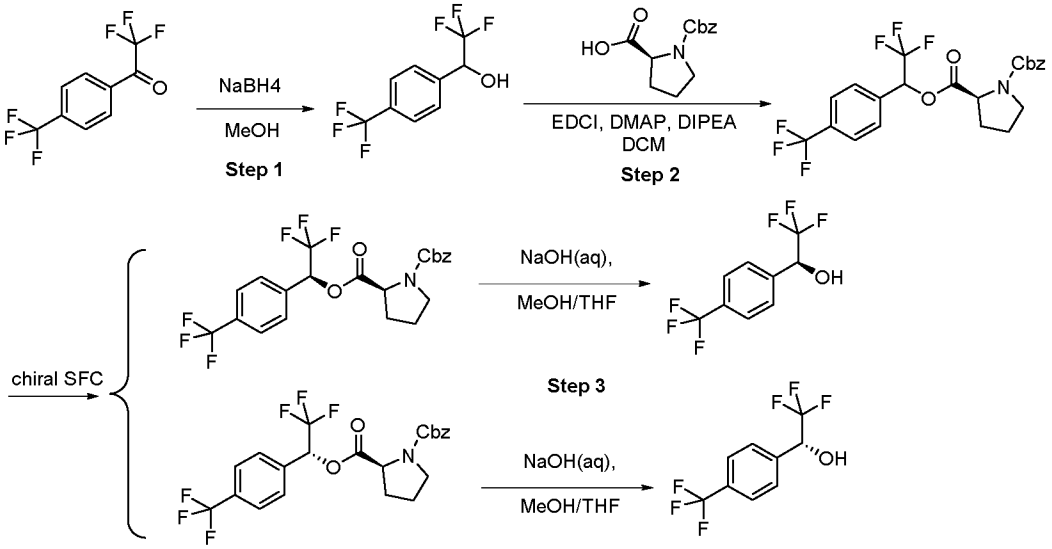
Step 2

LCMS m/z 548.8 $(M+Na)^+$ (ES+).

Step 3

^1H NMR (400 MHz, DMSO-d6) δ: 13.26 (br s, 1H), 7.86 (s, 1H), 7.82 (s, 1H), 7.72 (s, 1H), 6.77 – 6.62 (m, 2H), 2.73-2.58 (m, 4H), 2.02-1.95 (m, 1H), 1.78-1.71 (m, 1H).

Intermediate 42 and Intermediate 43: (S)-2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethan-1-ol and (R)-2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethan-1-ol



Step 1

To a solution of 2,2-dimethylcyclohexanone (2.0 g) in MeOH (40 mL) was added $NaBH_4$ (628 mg, 16.52 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with 2M HCl and concentrated under reduced pressure. The residue was extracted with MTBE (3 x 40 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (0-20% *tert*-Butyl methyl ether / petroleum ether) to give 2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl) ethanol (1.20 g, 60% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.70-7.62 (m, 4H), 5.11 (q, *J* = 6.8 Hz, 1H).

Step 2

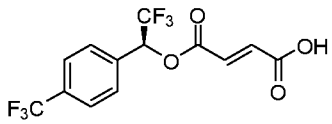
To a solution of 2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethanol (1.20 g, 4.92 mmol), (*S*)-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid (1.84 g, 7.38 mmol), DMAP (720 mg, 5.9 mmol) and DIPEA (1.90 g, 14.76 mmol) in DCM (18 mL) was added EDCI (1.41 g, 7.38 mmol) at 0 °C, and the resulting light yellow mixture was stirred at room temperature for 2 h. The mixture was quenched with 0.5 N HCl (10 mL), the organic phase separated and the aquoes phase extracted with DCM (2 x 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (0-20% *tert*-Butyl methyl ether / petroleum ether) to give (2S)-1-benzyl 2-(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethyl) pyrrolidine-1,2-dicarboxylate (1.60 g, 68% yield) as colorless oil. LCMS m/z 476.2 $(M+H)^+$ (ES+). (2*S*)-1-benzyl 2-(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethyl) pyrrolidine-1,2-dicarboxylate (1.60 g, 3.36 mmol) was separated by SFC (Column: CHIRALPAK AD-5(30x250mm 5µm) (Daicel). Column temperature: 35 °C. Flow Rate: CO_2 flow Rate: 36 mL/min; co solvent flow rate: 9 mL/min; total flow rate: 45 mL/min. Co solvent: iso-propanol. Gradient: iso-propanol 20%. Collection wavelength: 215 nm). The SFC fractions were concentrated under reduced pressure to remove isopropanol to give (S)-1-benzyl 2-((2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethyl) pyrrolidine-1,2-dicarboxylate ISOMER 1 (750 mg, 100% ee, 47% yield) and (S)-1-benzyl 2-((2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethyl) pyrrolidine-1,2-dicarboxylate ISOMER 2 (720 mg, 97.8% ee, 45% yiled). (*R*) or (*S*) configuration were assigned arbitrarily. Chiral HPLC: (Column: CHIRALPAK AD-3 (4.6x100mm); Flow Rate: 2 mL/min; Cosolvent: 15% isopropanol; collection wavelength: 200-400 nm) (S) isomer Rt = 0.904 min; (R) isomer Rt =1.108 min.

Step 3

A solution of (*S*)-1-benzyl 2-(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethyl) pyrrolidine-1,2-dicarboxylate ISOMER 1 (750 mg, 1.58 mmol) and NaOH (126 mg, 3.16 mmol) in MeOH/THF (5 mL/2.5 mL) was stirred at room temperature for 12 h. The mixture was concentrated under reduced pressure, quenched with 0.5 N HCl and extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated under reduced

pressure to give 2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethanol ISOMER 1 (350 mg, 90% yield) as yellow solid. 2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethanol ISOMER 2 (330 mg, 89% yield) was obtained as yellow solid using a similar procedure.

Intermediate 44: (E)-4-oxo-4-(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethoxy)but-2-enoic acid



Prepared from 2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethanol ISOMER 1 using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid (Step 2 and 3 only).

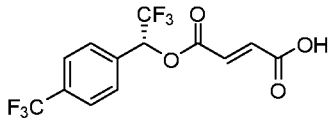
Step 2

LCMS m/z 542.8 $(M+Na)^+$ (ES+).

Step 3

^{1}H NMR (400 MHz, DMSO-d6) δ: 13.41 (s, 1H), 7.86 (s, 4H), 6.95-6.77 (m, 3H).

Intermediate 45: (E)-4-oxo-4-(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethoxy)but-2-enoic acid



Prepared from 2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethanol ISOMER 2 using a similar procedure to (E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid (Step 2 and 3 only).

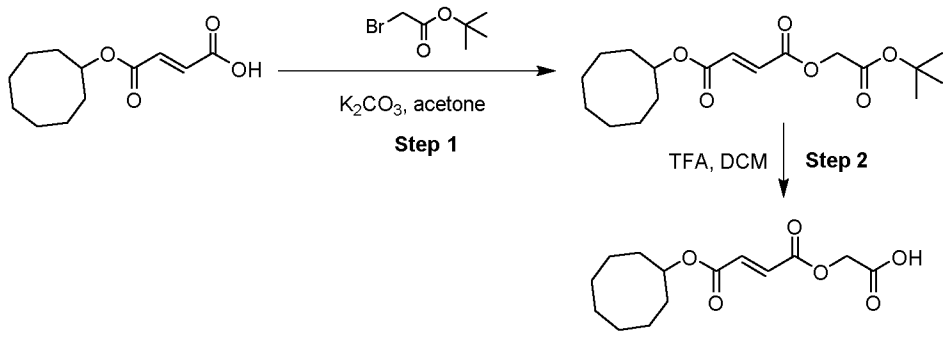
Step 2

LCMS m/z 542.7 $(M+Na)^+$ (ES+).

Step 3

^{1}H NMR (400 MHz, DMSO-d6) δ: 13.41 (s, 1H), 7.86 (s, 4H), 6.92-6.77 (m, 3H).

Example 1: *(E)*-2-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)acetic acid



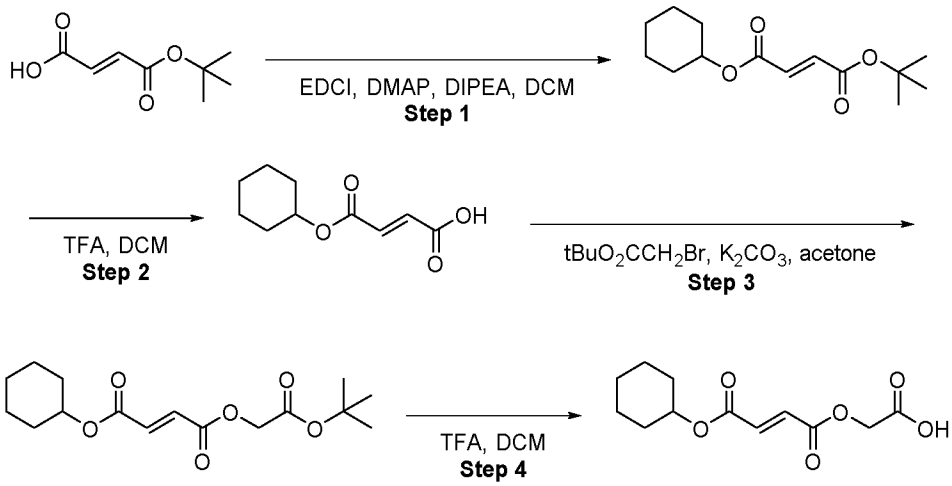
Step 1

To a solution of crude *(E)*-4-(cyclooctyloxy)-4-oxobut-2-enoic acid (Intermediate 6, the synthesis of which is described in Example 3, 115 g, 508 mmol) in acetone (690 mL) was added *tert*-butyl 2-bromoacetate (99.1 g, 508 mmol) and K_2CO_3 (140 g, 1.02 mol). The mixture was stirred at 15 °C for 12 h, then the mixture was added into water (800 mL) and extracted with EtOAc (3 x 600 mL). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 2-20% EtOAc/petroleum ether) to give 2-(*tert*-butoxy)-2-oxoethyl cyclooctyl fumarate (80.0 g, 235 mmol, 46 %) as a yellow oil. ^{1}H NMR (400 MHz, DMSO) δ: 6.83-6.72 (m, 2H), 5.00-4.94 (m, 1H), 4.69 (s, 2H), 1.81-1.42 (m, 23H).

Step 2

To a mixture of 2-(*tert*-butoxy)-2-oxoethyl cyclooctyl fumarate (80.0 g, 235 mmol) in DCM (240 mL) was added TFA (240 mL). The mixture was degassed and purged with N_2 three times, and then stirred at 20 °C for 2 h under a N_2 atmosphere. The reaction mixture was added into ice water (50 mL), and the organic phase was extracted with dichloromethane (2 x 20 mL). The combined organic phases were washed with brine (30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 1-100% MeOH/dichloromethane) to give the crude product which still contained TFA and so was lyophilised to give *(E)*-2-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)acetic acid (50.5 g, 178 mmol, 76 %) as an off-white solid. LCMS m/z 283 $(M-H)^-$ (API^-). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77 (br. s, 1H), 6.99-6.87 (m, 2H), 5.10-5.04 (m, 1H), 4.79 (s, 2H), 1.84-1.79 (m, 6H), 1.59-1.53 (m, 8H).

Example 2: (*E*)-2-((4-(cyclohexyloxy)-4-oxobut-2-enoyl)oxy)acetic acid



Step 1

EDCI (2.12 g, 11 mmol) was added to a mixutre of (E)-4-(tert-butoxy)-4-oxobut-2-enoic acid (1.00 g, 5.52 mmol), DIPEA (1.9 mL, 11 mmol), DMAP (0.067 g, 0.55 mmol) and cyclohexanol (0.58

mL, 5.52 mmol) in DCM (30 mL). The mixture was stirred at RT for 16 h, then concentrated onto silica and purified by chromatography on silica gel (0-20% EtOAc/DCM) to afford tert-butyl cyclohexyl fumarate (920 mg, 3.55 mmol) as a clear colourless oil. LCMS m/z 254.7 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO) δ 6.64 (d, J = 1.3 Hz, 2H), 4.89 - 4.66 (m, 1H), 1.84 - 1.77 (m, 2H), 1.71 - 1.60 (m, 2H), 1.54 - 1.19 (m, 15H).

Step 2

TFA (8 mL, 104 mmol) was added to a solution of tert-butyl cyclohexyl fumarate (920 mg, 3.55 mmol) in DCM (8 mL) at RT. The reaction mixture was stirred for 1 h, diluted with toluene (50 mL) and concentrated. The residue was co-evaporated with toluene (2x20 mL), then taken up in EtOAc (100 mL), washed with brine (50 mL), dried ($MgSO_4$) and concentrated to afford (E)-4-(cyclohexyloxy)-4-oxobut-2-enoic acid (680 mg, 3.40 mmol) as a colourless solid. LCMS m/z 196.7 $(M-H)^-$ (ES^-). ^1H NMR (400 MHz, DMSO) δ 13.20 (s, 1H), 6.92 - 5.83 (m, 2H), 5.02 - 4.46 (m, 1H), 1.96 - 1.04 (m, 10H).

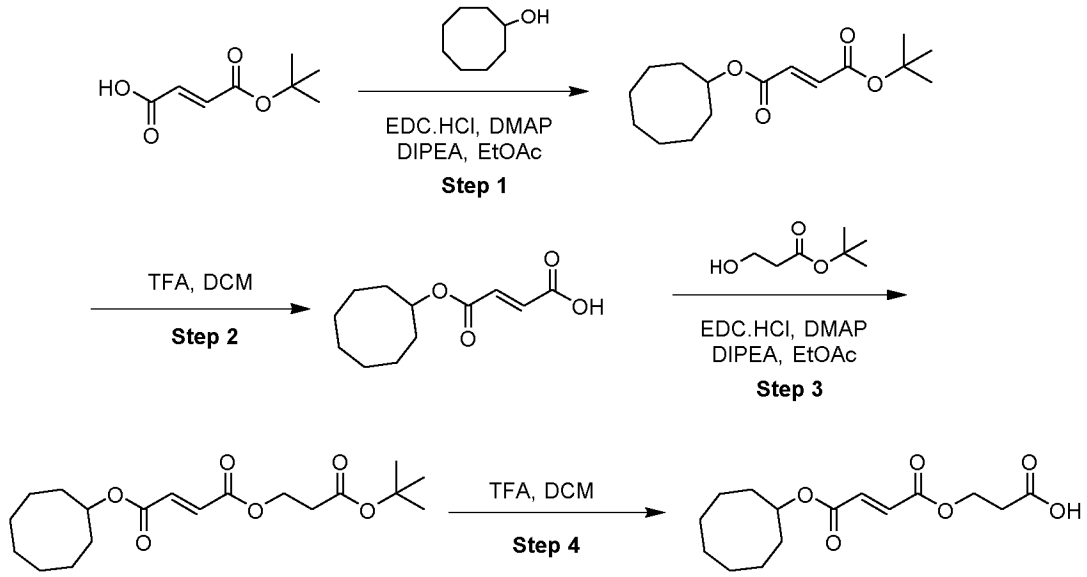
Step 3

Tert-butyl bromoacetate (0.22 mL, 1.46 mmol) was added to a mixture of (E)-4-(cyclohexyloxy)-4-oxobut-2-enoic acid (340 mg, 1.72 mmol) and potassium carbonate (308 mg, 2.23 mmol) in acetone (10 mL). The reaction mixture was stirred for 16 h at RT. The mixture was diluted with EtOAc (20 mL), filtered and concentrated. The residue was taken up in EtOAc (100 mL) and washed with sat. aq. $NaHCO_3$ (3x50 mL). The organic layer was dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography on silica gel (0-20% EtOAc/DCM) to afford 2-(tert-butoxy)-2-oxoethyl cyclohexyl fumarate (486 mg, 1.54 mmol) as a colourless oil. LCMS m/z 335.2 $(M+Na)^+$ (ES^+). ^1H NMR (400 MHz, DMSO) δ 6.88 - 6.54 (m, 2H), 4.88 - 4.77 (m, 1H), 4.69 (s, 2H), 1.88 - 1.78 (m, 2H), 1.74 - 1.51 (m, 2H), 1.56 - 1.11 (m, 15H).

Step 4

TFA (5mL, 65 mmol) was added to a solution of 2-(tert-butoxy)-2-oxoethyl cyclohexyl fumarate (486 mg, 1.54 mmol) in DCM (5 mL) at RT. The reaction mixture was stirred for 1 h, then diluted with toluene (50 mL) and concentrated. The residue was taken up in EtOAc (100 mL),washed with brine (50 mL), dried ($MgSO_4$) and concentrated to afford (E)-2-((4-(cyclohexyloxy)-4-oxobut-2-enoyl)oxy)acetic acid (312 mg, 1.21 mmol) as a colourless solid. LCMS m/z 254.8 $(M-H)^-$ (ES^-). ^1H NMR (400 MHz, DMSO) δ 6.81 (s, 2H), 4.86 - 4.74 (m, 1H), 4.71 (s, 2H), 1.85 - 1.76 (m, 2H), 1.73 - 1.60 (m, 2H), 1.52 - 1.16 (m, 6H) (1 exchangeable proton not observed).

Example 3: *(E)*-3-((4-(Cyclooctyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid



Step 1

A mixture of cyclooctanol (177 g, 1.38 mol), *(E)*-4-(*tert*-butoxy)-4-oxobut-2-enoic acid (238 g, 1.38 mol), DMAP (16.9 g, 138 mmol) and DIPEA (357 g, 2.76 mol) in EtOAc (1.43 L) was degassed and purged with N_2 three times. EDC.HCl (530 g, 2.76 mol) was added into the mixture, and the mixture was stirred at 20 °C for 12 h under a N_2 atmosphere. The mixture was then added into water (1.50 L), and the mixture was extracted with EtOAc (2 x 1.00 L). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 2-20% EtOAc/petroleum ether) to give *tert*-butyl cyclooctyl fumarate (245 g, 868 mmol, 63 %) as a yellow oil. ^{1}H NMR (400 MHz, DMSO) δ: 6.72-6.58 (m, 2H), 4.97-4.91 (m, 1H), 1.79-1.38 (m, 23H).

Step 2

To a solution of *tert*-butyl cyclooctyl fumarate (142 g, 503 mmol) in DCM (426 mL) was added TFA (656 g, 5.75 mol), and the mixture was stirred at 20 °C for 2 h. The mixture was concentrated under reduced pressure and the residue was diluted with water (600 mL) and extracted with EtOAc (3 x 600 mL). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude *(E)*-4-(cyclooctyloxy)-4-oxobut-2-enoic acid (Intermediate 6, 135 g, >100 %, crude) as a grey oil. ^{1}H NMR (400 MHz, DMSO) δ: 6.72-6.62 (m, 2H), 4.97-4.91 (m, 1H), 1.79-1.50 (m, 14H). One exchangeable proton not observed.

Step 3

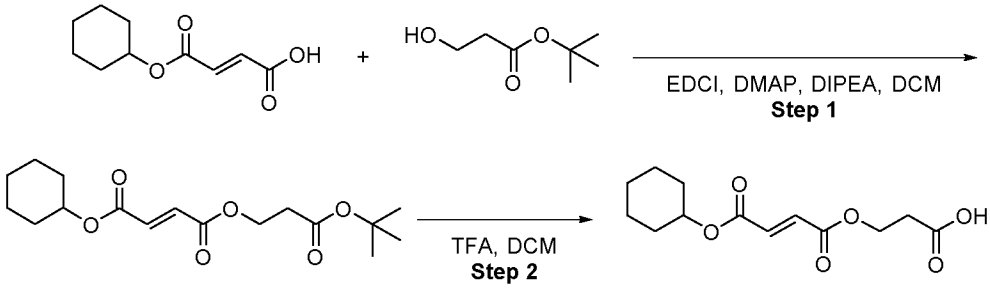
To a solution of crude *(E)*-4-(cyclooctyloxy)-4-oxobut-2-enoic acid (Intermediate 6, 40.0 g, 177 mmol) in EtOAc (240 mL) was added DMAP (2.16 g, 17.7 mmol), DIPEA (45.7 g, 354 mmol) and *tert*-butyl 3-hydroxypropanoate (25.8 g, 177 mmol), followed by EDC.HCl (67.8 g, 354 mmol). The mixture was stirred at 15 °C for 12 h, then the mixture was added into water (300 mL) and extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine (200

mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 2-20% EtOAc/petroleum ether) to give 3-(*tert*-butoxy)-3-oxopropyl cyclooctyl fumarate (36.0 g, 102 mmol, 57 %) as a white oil. ^{1}H NMR (400 MHz, DMSO) δ: 6.81-6.67 (m, 2H), 4.99-4.93 (m, 1H), 4.33 (t, *J* = 6.0 Hz, 2H), 2.63 (t, *J* = 6.0 Hz, 2H), 1.80-1.40 (m, 23H).

Step 4

To a solution of 3-(*tert*-butoxy)-3-oxopropyl cyclooctyl fumarate (31.0 g, 87.5 mmol) in DCM (93.0 mL) was added TFA (93.0 mL) and the mixture was degassed and purged with N_2 three times, and then stirred at 20 °C for 2 h under a N_2 atmosphere. The reaction mixture was poured to ice water (50 mL), and the organic phase was extracted with dichloromethane (2 x 20 mL). The combined organic phases were washed with brine (30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 1-100% MeOH/dichloromethane) to give the crude product which still contained TFA and so was lyophilised to give *(E)*-3-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid (10.1 g, 33.9 mmol, 39 %) as an off-white solid. LCMS m/z 619 $(2M+Na)^+$ (API^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.88-6.79 (m, 2H), 5.09-5.02 (m, 1H), 4.48 (t, *J* = 6.0 Hz, 2H), 2.78 (t, *J* = 6.0 Hz, 2H), 1.85-1.71 (m, 6H), 1.59-1.55 (m, 8H). One exchangeable proton not observed.

Example 4: (*E*)-3-((4-(cyclohexyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid



Step 1

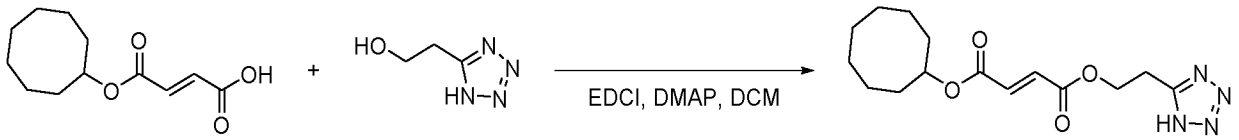
EDCI (658 mg, 3.43 mmol) was added to a solution of (E)-4-(cyclohexyloxy)-4-oxobut-2-enoic acid (340 mg, 1.72 mmol), tert-butyl 3-hydroxypropanoate (0.25 mL, 1.72 mmol), DIPEA (0.6 mL, 3.4 mmol), and DMAP (21 mg, 0.17 mmol) in DCM (16 mL) at RT. The mixture was stirred at RT for 16 h. The reaction mixture was concentrated and purified by chromatography on silica gel (0-20% EtOAc/DCM) to afford 3-(tert-butoxy)-3-oxopropyl cyclohexyl fumarate (357 mg, 1.08 mmol) as a clear colourless oil. LCMS m/z 348.8 $(M+Na)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO) δ 6.72 (d, J = 1.1 Hz, 2H), 4.85 - 4.74 (m, 1H), 4.32 (t, J = 6.5 Hz, 2H), 2.62 (t, J = 5.5 Hz, 2H), 1.93 - 1.15 (m, 19H).

Step 2

TFA (3.4 mL, 44 mmol) was added to a solution of 3-(tert-butoxy)-3-oxopropyl cyclohexyl fumarate (357 mg, 1.08 mmol) in DCM (3 mL) at RT. The mixture was stirred for 1 h at RT, diluted with

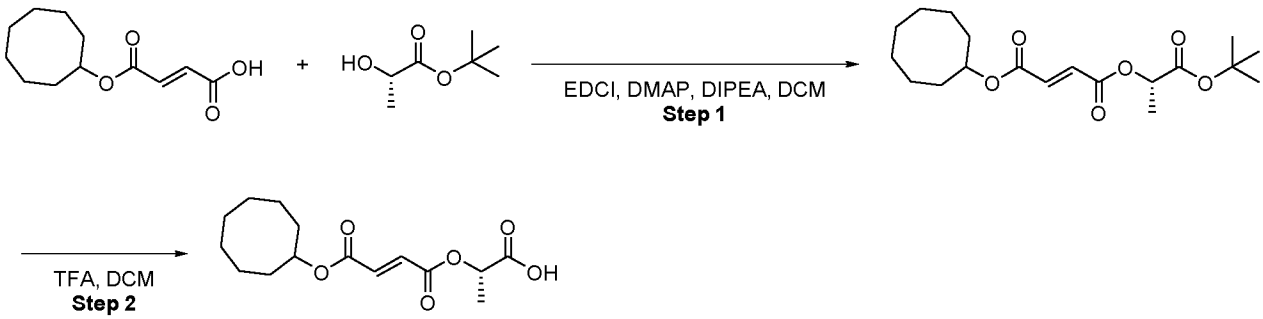
toluene (20 mL) and concentrated. The residue was taken up in EtOAc (50 mL) and washed with brine (20 mL), dried ($MgSO_4$) and concentrated to afford (E)-3-((4-(cyclohexyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid (132 mg, 0.48 mmol) as a colourless solid. LCMS m/z 293.2 $(M+Na)^+$ (ES^+). ^1H NMR (400 MHz, DMSO) δ 12.44 (s, 1H), 6.72 (s, 2H), 4.85 - 4.70 (m, 1H), 4.33 (t, J = 6.1 Hz, 2H), 2.64 (t, J = 6.1 Hz, 2H), 1.87 - 1.76 (m, 2H), 1.74 - 1.57 (m, 2H), 1.54 - 1.10 (m, 6H).

Example 5: 2-(1H-tetrazol-5-yl)ethyl cyclooctyl fumarate



A slurry of EDCI (345 mg, 1.8 mmol) in DCM (3 mL) was added slowly to a solution of (*E*)-4-(cyclooctyloxy)-4-oxobut-2-enoic acid (Intermediate 6, 272 mg, 1.2 mmol), 2-(1H-tetrazol-5-yl)ethanol (164 mg, 1.44 mmol) and DMAP (220 mg, 1.8 mmol) in DCM (3 mL) at 0 °C. The mixture was allowed to warm slowly to RT and stirred for 18 h. The reaction mixture was diluted with 1 M HCl (5 mL) and the phases were separated. The aqueous phase was extracted with DCM (2x5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography on silica gel (0-100% EtOAc/isohexane) to afford 2-(1H-tetrazol-5-yl)ethyl cyclooctyl fumarate (183 mg, 0.56 mmol) as a white solid. LCMS m/z 323.2 $(M+H)^+$ (ES^+). ^1H NMR (400 MHz, DMSO) δ 6.72 (s, 2H), 4.99 - 4.92 (m, 1H), 4.50 (t, J = 6.2 Hz, 2H), 3.32 (t, J = 6.2 Hz, 2H), 1.85 - 1.43 (m, 14H) (1 exchangeable proton not observed).

Example 6: (*S,E*)-2-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid



Prepared using a similar procedure to (E)-3-((4-(cyclohexyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid using (S)-tert-butyl 2-hydroxypropanoate.

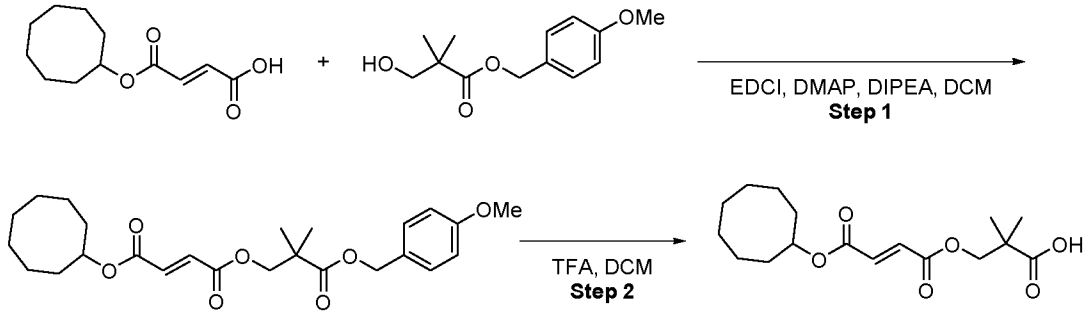
Step 1

LCMS m/z 377.4 $(M+Na)^+$ (ES^+). ^1H NMR (400 MHz, DMSO) δ 6.80 (d, J = 17.3 Hz, 1H), 6.76 (d, J = 17.1 Hz, 1H), 5.02 – 4.92 (m, 2H), 1.86 – 1.45 (m, 14H), 1.43 (d, J = 7.0 Hz, 3H), 1.40 (s, 9H).

Step 2

LCMS m/z 321.2 $(M+Na)^+$ (ES^+). ^1H NMR (400 MHz, DMSO) δ 13.19 (s, 1H), 6.80 (d, J = 16.6 Hz, 1H), 6.75 (d, J = 16.6 Hz, 1H), 5.04 (q, J = 7.1 Hz, 1H), 4.96 (tt, J = 8.2, 4.3 Hz, 1H), 1.87 – 1.38 (m, 17H).

Example 7: (*E*)-3-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)-2,2-dimethylpropanoic acid



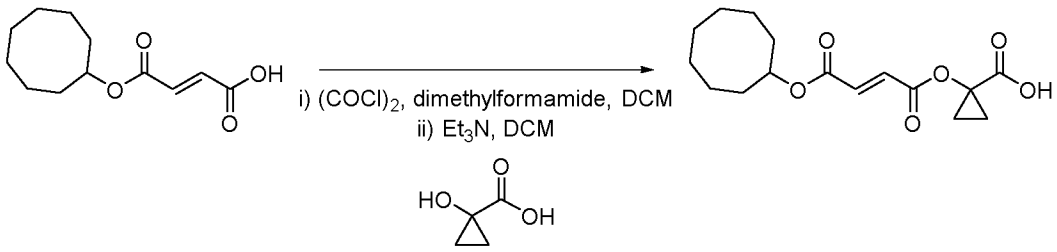
Step 1

EDCI (0.424 g, 2.21 mmol) was added to a solution of (*E*)-4-(cyclooctyloxy)-4-oxobut-2-enoic acid (Intermediate 6, 0.25 g, 1.10 mmol), 4-methoxybenzyl 3-hydroxy-2,2-dimethylpropanoate (0.263 g, 1.11 mmol), DIPEA (0.39 mL, 2.2 mmol) and DMAP (0.013 g, 0.11 mmol) in DCM (5 mL) at RT. The mixture was stirred at RT for 18 h, then concentrated. The crude product was purified by chromatography on silica gel (0-20% EtOAc/isohexane) to afford cyclooctyl (3-((4-methoxybenzyl)oxy)-2,2-dimethyl-3-oxopropyl) fumarate (0.265 g, 0.58 mmol) as a clear colourless oil. LCMS m/z 469.2 $(M+Na)^+$ (ES^+). ^1H NMR (400 MHz, DMSO) δ 7.30 – 7.21 (m, 2H), 6.91 – 6.84 (m, 2H), 6.62 (d, J = 17.6 Hz, 1H), 6.57 (d, J = 17.5 Hz, 1H), 5.04 (s, 2H), 4.95 (tt, J = 8.2, 4.2 Hz, 1H), 4.18 (s, 2H), 3.72 (s, 3H), 1.88 – 1.38 (m, 14H), 1.19 (s, 6H).

Step 2

TFA (0.14 mL, 1.78 mmol) was added dropwise to a solution of cyclooctyl (3-((4-methoxybenzyl)oxy)-2,2-dimethyl-3-oxopropyl) fumarate (0.265 g, 0.59 mmol) in DCM (6 mL). The reaction was slowly allowed to warm to RT and the mixture was stirred at RT for 18 h. The mixture was concentrated and the residue co-evaporated with toluene (2x10 mL). The crude product was purified by chromatography on silica gel (0-10% MeOH/DCM)1 to afford (*E*)-3-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)-2,2-dimethylpropanoic acid (0.165 g, 0.495 mmol) as a slightly yellow oil. LCMS m/z 349.1 $(M+Na)^+$ (ES^+). ^1H NMR (400 MHz, DMSO) δ 12.50 (s, 1H), 6.74 (d, J = 18.5 Hz, 1H), 6.69 (d, J = 18.5 Hz, 1H), 4.96 (tt, J = 8.2, 4.3 Hz, 1H), 4.17 (s, 2H), 1.92 – 1.35 (m, 14H), 1.16 (s, 6H).

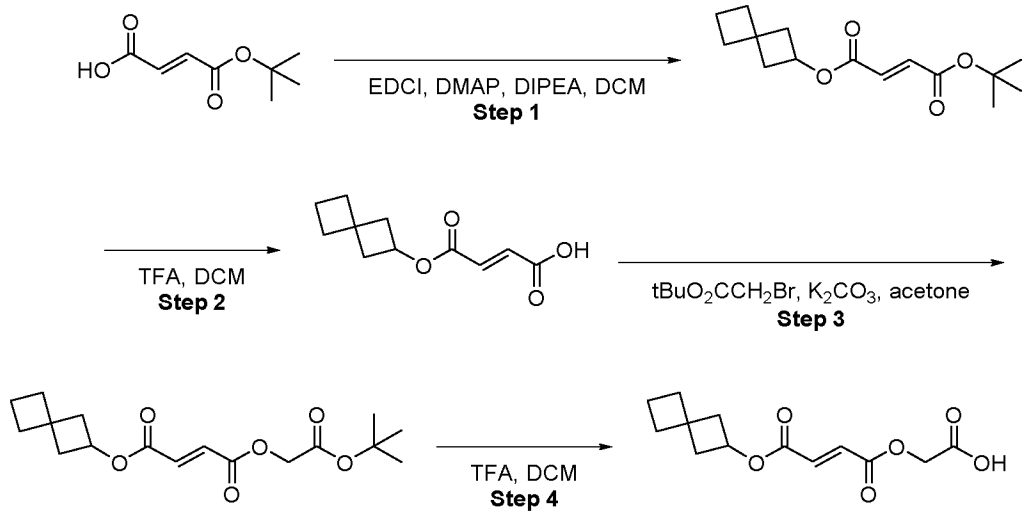
Example 8: (*E*)-1-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)cyclopropane-1-carboxylic acid



Oxalyl chloride (0.23 mL, 2.6 mmol) was added to a solution of (*E*)-4-(cyclooctyloxy)-4-oxobut-2-enoic acid (Intermediate 6, 0.20 g, 0.85 mmol) and dimethylformamide (1 drop) in DCM (5 mL) at 0 °C. The mixture was warmed to RT, stirred for 2.5 h and concentrated. The residue was taken

up in DCM (5 mL) and cooled to 0 °C. 1-Hydroxycyclopropanecarboxylic acid (0.102 g, 1.0 mmol) and triethylamine (0.54 mL, 3.87 mmol were added and the mixture was warmed to RT and stirred for 18 h. 1M HCl (30 mL) was added and the mixture extracted with DCM (3x30 mL). The combined organic extracts were dried (phase separator) and concentrated. The crude product was purified by chromatography on RP Flash C18 (5-100% MeCN/Water, 0.1% Formic Acid) to afford (*E*)-1-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)cyclopropanecarboxylic acid (0.117 g, 0.36 mmol) as a white solid. LCMS m/z 333.2 $(M+Na)^+$ (ES^+). ^1H NMR (400 MHz, DMSO) δ 13.09 (s, 1H), 6.84 – 6.68 (m, 2H), 5.03 – 4.91 (m, 1H), 1.88 – 1.38 (m, 16H), 1.32 – 1.24 (m, 2H).

Example 9: (*E*)-2-((4-oxo-4-(spiro[3.3]heptan-2-yloxy)but-2-enoyl)oxy)acetic acid



Prepared using a similar procedure to (*E*)-2-((4-(cyclohexyloxy)-4-oxobut-2-enoyl)oxy)acetic acid.

Step 1

^1H NMR (400 MHz, DMSO) δ 6.64 (s, 2H), 4.96 – 4.84 (m, 1H), 2.48 – 2.41 (m, 2H), 2.07 – 1.92 (m, 6H), 1.84 – 1.75 (m, 2H), 1.46 (s, 9H).

Step 2, Intermediate 7: (*E*)-4-oxo-4-(spiro[3.3]heptan-2-yloxy)but-2-enoic acid

LCMS m/z 209.1 $(M-H)^-$ (ES^-). ^1H NMR (400 MHz, DMSO) δ 13.21 (s, 1H), 6.75 – 6.58 (m, 2H), 4.97 – 4.83 (m, 1H), 2.49 – 2.41 (m, 2H), 2.08 – 1.93 (m, 6H), 1.85 – 1.75 (m, 2H).

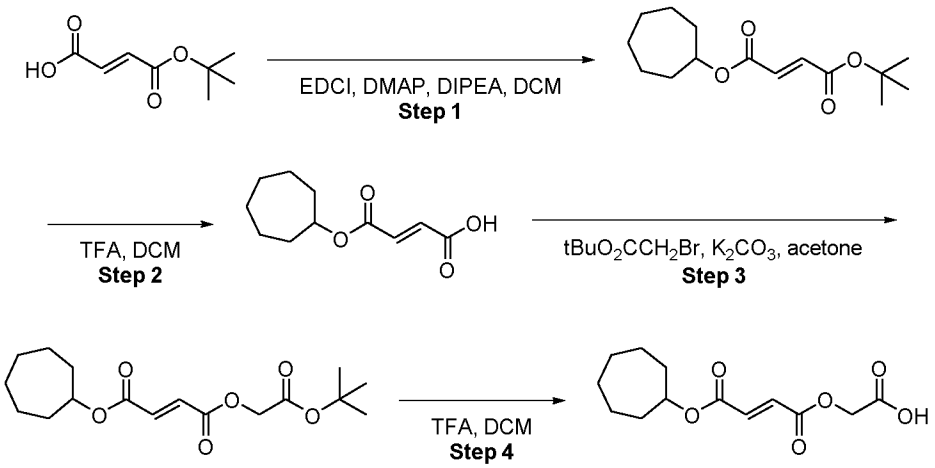
Step 3

^1H NMR (400 MHz, DMSO) δ 6.81 (d, J = 1.9 Hz, 2H), 4.97 – 4.86 (m, 1H), 4.69 (s, 2H), 2.49 – 2.42 (m, 2H), 2.10 – 1.94 (m, 6H), 1.85 – 1.76 (m, 2H), 1.43 (s, 9H).

Step 4

LCMS m/z 267.0 $(M-H)^-$ (ES^-). ^1H NMR (400 MHz, DMSO) δ 13.22 (s, 1H), 6.81 (d, J = 2.9 Hz, 2H), 4.97 – 4.86 (m, 1H), 4.72 (s, 2H), 2.49 – 2.42 (m, 2H), 2.10 – 1.93 (m, 6H), 1.85 – 1.76 (m, 2H).

Example 10: (*E*)-2-((4-(cycloheptyloxy)-4-oxobut-2-enoyl)oxy)acetic acid



Prepared using a similar procedure to (*E*)-2-((4-(cyclohexyloxy)-4-oxobut-2-enoyl)oxy)acetic acid.

Step 1

^{1}H NMR (400 MHz, DMSO) δ 6.64 (d, J = 1.7 Hz, 2H), 4.95 (tt, J = 8.0, 4.5 Hz, 1H), 1.94 – 1.84 (m, 2H), 1.72 – 1.42 (m, 19H).

Step 2, Intermediate 8: *(E)*-4-(cycloheptyloxy)-4-oxobut-2-enoic acid

LCMS m/z 211.0 $(M-H)^-$ (ES^-). ^{1}H NMR (400 MHz, DMSO) δ 13.19 (s, 1H), 6.67 (d, J = 1.2 Hz, 2H), 4.96 (tt, J = 8.2, 4.4 Hz, 1H), 1.95 – 1.82 (m, 2H), 1.73 – 1.37 (m, 10H).

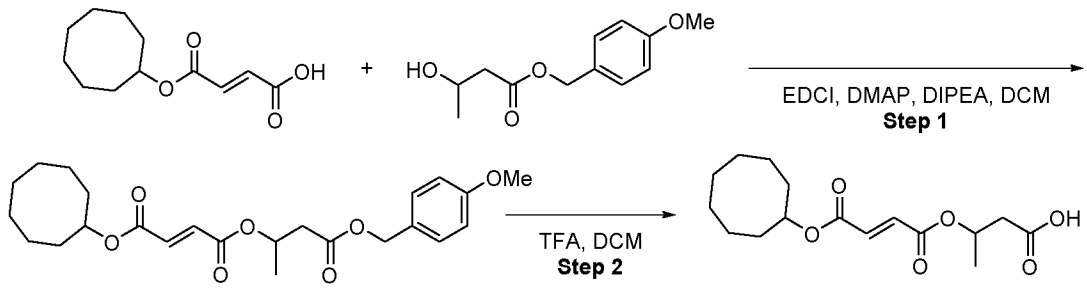
Step 3

LCMS m/z 349.2 $(M+Na)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO) δ 6.82 (s, 2H), 4.98 (tt, J = 8.3, 4.5 Hz, 1H), 4.70 (s, 2H), 1.95 – 1.83 (m, 2H), 1.75 – 1.44 (m, 10H), 1.43 (s, 9H).

Step 4

LCMS m/z 269.0 $(M-H)^-$ (ES^-). ^{1}H NMR (400 MHz, DMSO) δ 13.22 (s, 1H), 6.81 (s, 2H), 4.98 (tt, J = 8.2, 4.4 Hz, 1H), 4.72 (s, 2H), 1.96 – 1.84 (m, 2H), 1.76 – 1.38 (m, 10H).

Example 11: (*E*)-3-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)butanoic acid



Prepared using a similar procedure to (*E*)-3-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)-2,2-dimethylpropanoic acid using 4-methoxybenzyl 3-hydroxybutanoate.

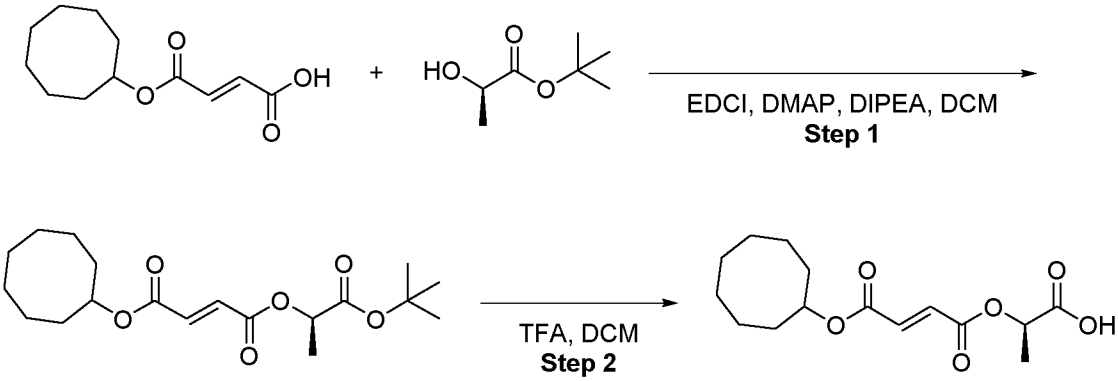
Step 1

LCMS m/z 454.6 $(M+Na)^+$ (ES^+). ^{1}H NMR (400 MHz, DMSO) δ 7.30 – 7.21 (m, 2H), 6.93 – 6.84 (m, 2H), 6.64 (d, J = 15.8 Hz, 1H), 6.59 (d, J = 15.8 Hz, 1H), 5.29 – 5.18 (m, 1H), 5.07 – 4.89 (m, 3H), 3.73 (s, 3H), 2.80 – 2.63 (m, 2H), 1.86 – 1.37 (m, 14H), 1.25 (d, J = 6.3 Hz, 3H).

Step 2

LCMS m/z 334.9 $(M+Na)^+$ (ES^+). ^1H NMR (400 MHz, DMSO) δ 12.38 (s, 1H), 6.71 (d, J = 18.4 Hz, 1H), 6.66 (d, J = 18.4 Hz, 1H), 5.21 (h, J = 6.4 Hz, 1H), 4.95 (tt, J = 8.2, 4.3 Hz, 1H), 2.60 (d, J = 6.6 Hz, 2H), 1.86 – 1.38 (m, 14H), 1.26 (d, J = 6.3 Hz, 3H).

Example 12: (*R,E*)-2-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid



Prepared using a similar procedure to (*E*)-3-((4-(cyclohexyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid using (R)-tert-butyl 2-hydroxypropanoate.

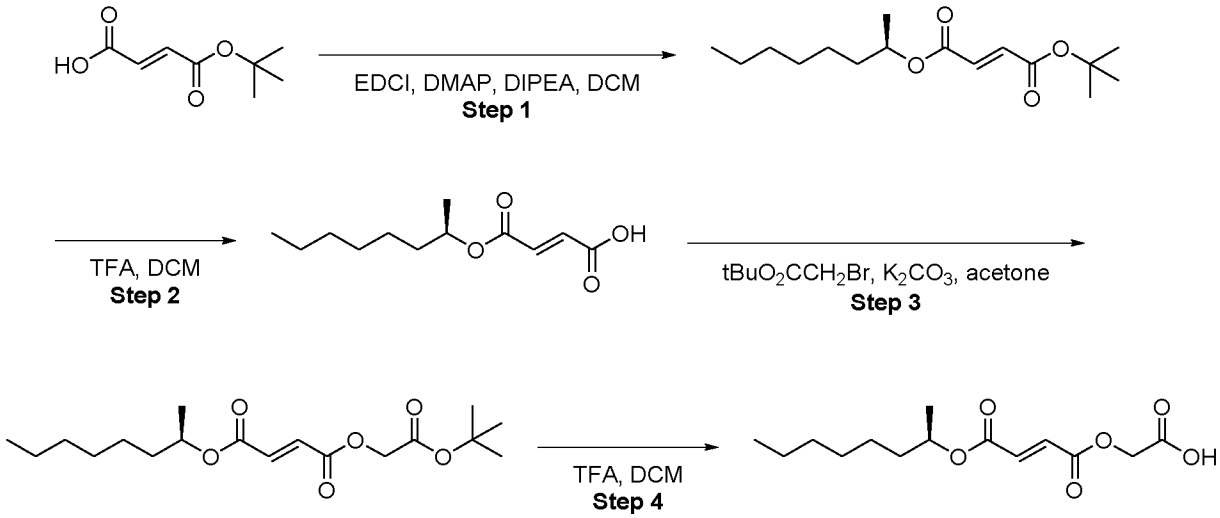
Step 1

LCMS m/z 377.0 $(M+Na)^+$ (ES^+). ^1H NMR (400 MHz, DMSO) δ 6.80 (d, J = 17.3 Hz, 1H), 6.76 (d, J = 17.1 Hz, 1H), 5.02 – 4.92 (m, 2H), 1.86 – 1.45 (m, 14H), 1.43 (d, J = 7.0 Hz, 3H), 1.40 (s, 9H).

Step 2

LCMS m/z 321.2 $(M+Na)^+$ (ES^+). ^1H NMR (400 MHz, DMSO) δ 13.19 (s, 1H), 6.80 (d, J = 16.6 Hz, 1H), 6.75 (d, J = 16.5 Hz, 1H), 5.04 (q, J = 7.0 Hz, 1H), 4.96 (tt, J = 8.2, 4.3 Hz, 1H), 1.87 – 1.38 (m, 17H).

Example 13: (*E*)-2-((4-(cycloheptyloxy)-4-oxobut-2-enoyl)oxy)acetic acid



Prepared using a similar procedure to (*E*)-2-((4-(cyclohexyloxy)-4-oxobut-2-enoyl)oxy)acetic acid.

Step 1

^{1}H NMR (400 MHz, DMSO) δ 6.64 (d, J = 2.1 Hz, 2H), 4.96 – 4.87 (m, 1H), 1.47 (s, 9H), 1.30 – 1.23 (m, 10H), 1.21 (d, J = 6.3 Hz, 3H), 0.89 – 0.83 (m, 3H).

Step 2

LCMS m/z 227.3 $(M-H)^-$ (ES^-). ^{1}H NMR (400 MHz, DMSO) δ 6.67 (s 2H), 4.96 – 4.87 (m, 1H), 1.66 – 1.48 (m, 2H), 1.24 (m, 11H), 0.90 – 0.82 (m, 3H).

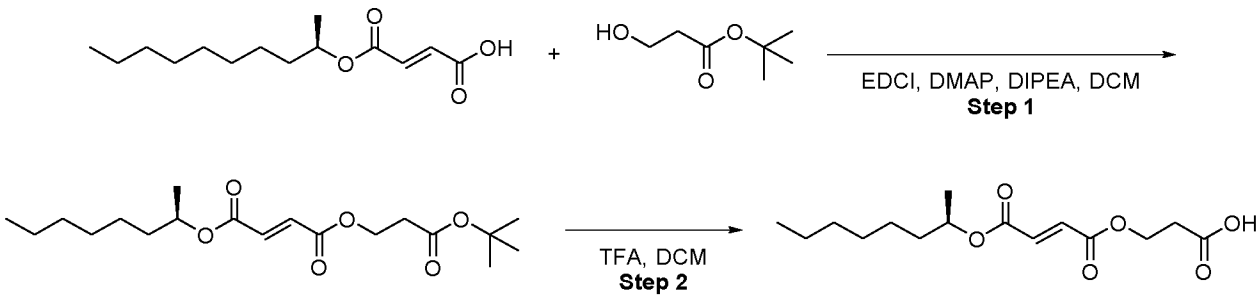
Step 3

^{1}H NMR (400 MHz, DMSO) δ 6.82 (s, 2H), 4.98 – 4.89 (m, 1H), 4.69 (s, 2H), 1.66 – 1.48 (m, 2H), 1.43 (s, 9H), 1.32 – 1.22 (m, 11H), 0.89 – 0.82 (m, 3H).

Step 4

LCMS m/z 285.0 $(M-H)^-$ (ES^-). ^{1}H NMR (400 MHz, DMSO) δ 13.20 (s, 1H), 6.81 (s, 2H), 5.00 – 4.89 (m, 1H), 4.72 (s, 2H), 1.65 – 1.49 (m, 2H), 1.34 – 1.21 (m, 11H), 0.89 – 0.83 (m, 3H).

Example 14: (*R,E*)-3-((4-(octan-2-yloxy)-4-oxobut-2-enoyl)oxy)propanoic acid



Prepared using a similar procedure to (E)-3-((4-(cyclohexyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid.

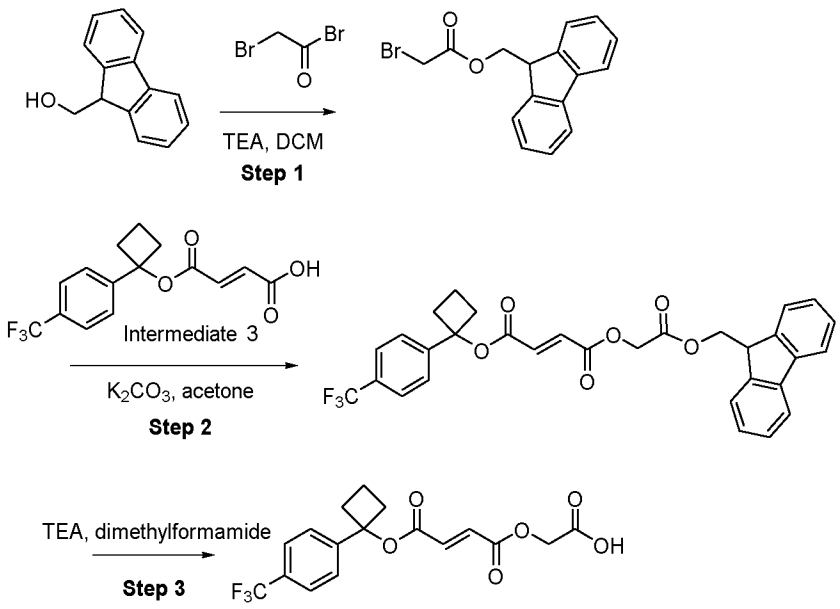
Step 1

^{1}H NMR (400 MHz, DMSO) δ 6.72 (s, 2H), 4.98 – 4.87 (m, 1H), 4.33 (t, J = 6.1 Hz, 2H), 2.63 (t, J = 6.1 Hz, 2H), 1.66 – 1.48 (m, 2H), 1.40 (s, 9H), 1.36 – 1.17 (m, 11H), 0.92 – 0.81 (m, 3H).

Step 2

LCMS m/z 284.8 $(M-H)^-$ (ES^-). ^{1}H NMR (400 MHz, DMSO) δ 13.20 (s, 1H), 6.81 (s, 2H), 5.00 – 4.89 (m, 1H), 4.72 (s, 2H), 1.65 – 1.49 (m, 2H), 1.34 – 1.21 (m, 11H), 0.89 – 0.83 (m, 3H).

Example 15: (E)-2-((4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoyl)oxy) acetic acid



Step 1

To the solution of (9H-fluoren-9-yl)methanol (2.0 g, 10.2 mmol) and 2-bromoacetyl bromide (4.08 g, 20.4 mmol) in DCM (40 mL) was added TEA (3.09 g, 30.6 mmol), and the mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with water (40 mL), the organic layer was separated, and the aqueous layer extracted with DCM (3 x 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica (0-15% *tert*-butyl methyl ether /petroleum ether) to give (9H-fluoren-9-yl)methyl 2-bromoacetate (2.0 g, 62% yield) as yellow oil. LCMS m/z 339.0 $(M+Na)^+$ (ES^+).

Step 2

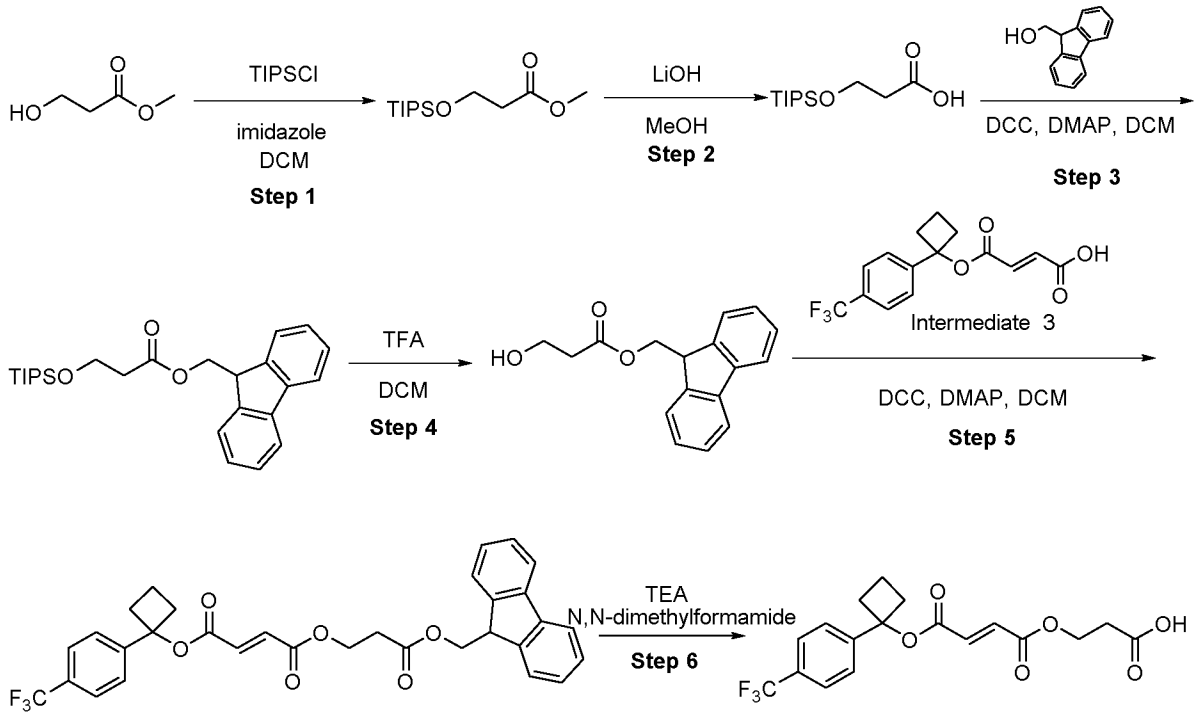
A mixture of (9H-fluoren-9-yl)methyl 2-bromoacetate (310 mg, 0.98 mmol), (E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid (Intermediate 3, 308 mg, 0.98 mmol) and K_2CO_3 (203 mg, 1.47 mmol) in acetone (4 mL) was stirred at room temperature for 18 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica (0-10% *tert*-butyl methyl ether/ petroleum ether) to give 2-((9H-fluoren-9-yl)methoxy)-2-oxoethyl 1-(4-(trifluoromethyl)phenyl)cyclobutyl fumarate (250 mg, 46% yield) as a light yellow oil. LCMS m/z 572.8 $(M+Na)^+$ (ES^+).

Step 3

A solution of 2-((9H-fluoren-9-yl)methoxy)-2-oxoethyl 1-(4-(trifluoromethyl)phenyl)cyclobutyl fumarate (250 mg, 0.45 mmol) in dimethylformamide (2 mL) and TEA (0.4 mL) was stirred at room temperature for 3 h. The reaction mixture was acidified with 0.5 N HCl until pH 5, and extracted with EtOAc (2 x 3 mL). The organic layer was washed by brine, dried over Na_2SO_4, filtered and

concentrated under reduced pressure. The residue was purified by prep-HPLC (Column: Waters SUNFIRE Prep C18 OBD 10µm 19 x 250mm; Flow Rate: 20 mL/min; solvent system: MeCN/(0.2% formic acid/water) gradient: 58-95% MeCN; collection wavelength: 214 nm). The fractions were concentrated under reduced pressure to remove MeCN, and lyophilized to give (*E*)-2-(4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoyloxy)acetic acid (77.2 mg, 46% yield) as white solid. LCMS m/z 394.9 $(M+Na)^+$ (ES^+). ^1H NMR (400 MHz, DMSO) δ 13.24 (br, 1H), 7.78-7.68 (m, 4H), 6.89-7.79 (m, 2H), 4.72 (s, 2H), 2.70-2.60 (m, 4H), 2.04-1.97 (m, 1H), 1.82-1.74 (m, 1H).

Example 16: *(E)*-3-(4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoyloxy)propanoic acid



Step 1

To the solution of methyl 3-hydroxypropanoate (SCP-29-0, 5.00 g, 48.08 mmol) and triisopropylsilyl chloride (18.60 g, 96.16 mmol) in DCM (200 mL) was added imidazole (9.80 g, 144.24 mmol), and the reaction mixture was stirred at room temperature overnight. The mixture was quenched with water (150 mL) and extracted with DCM (3 x 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4. and concentrated under reduced pressure. The residue was purified by flash column chromatography (0-8% *tert*-butyl methyl ether/ petroleum ether) to give methyl 3-(triisopropylsilyloxy)propanoate (11.00 g, 88% yield) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.99 (t, *J* = 6.4 Hz, 2H), 3.68 (s, 3H), 2.56 (t, *J* = 6.4 Hz, 2H), 1.11-1.03 (m, 21H).

Step 2

To a solution of methyl 3-(triisopropylsilyloxy)propanoate (11.00 g, 42.31 mmol) in MeOH (150 mL) was added 2N LiOH aqueous solution (23.27 mL, 46.54 mmol), and the reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure to give the residue, which was quenched with water (100 ml), extracted with MTBE (2 x 150 ml). The MTBE layer was washed by brine, dried over Na_2SO_4, and concentrated under reduced pressure to give 3-(triisopropylsilyloxy)propanoic acid (10.3 g, 99% yield) as light yellow oil, which was used in the next step directly. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.00 (t, *J* = 6.4 Hz, 2H), 2.60 (t, *J* = 6.4 Hz, 2H), 1.14-1.03 (m, 21H). A mixture of 3-(triisopropylsilyloxy)propanoic acid (10.3 g, 41.87 mmol), (9H-fluoren-9-yl)methanol (8.21 g, 41.87 mmol), DCC (12.94 g, 62.805 mmol) and DMAP (511 mg, 4.187 mmol) in DCM (150 mL) was stirred at room temperature for 3 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (0-5% *tert*-butyl methyl ether/ petroleum ether) to give (9H-fluoren-9-yl)methyl 3-(triisopropylsilyloxy)propanoate (17 g, 95% yield) as a light yellow oil. LCMS m/z 447.0 $(M+Na)^+$ (ES^+).

Step 3

A mixture of (9H-fluoren-9-yl)methyl 3-(triisopropylsilyloxy)propanoate (1.3 g, 3.07 mmol) in DCM (4.5 mL) and TFA (1.5 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (0-20% *tert*-butyl methyl ether/ petroleum ether) to give (9H-fluoren-9-yl)methyl 3-hydroxypropanoate (240 mg, 29% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (d, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 6.4 Hz, 2H), 4.48 (d, *J* = 6.8 Hz, 2H), 4.24 (t, *J* = 6.4 Hz, 1H), 3.83 (t, *J* = 6 Hz, 2H), 2.63 (t, *J* = 5.6 Hz, 2H).

Step 4

A mixture of (9H-fluoren-9-yl)methyl 3-hydroxypropanoate (240 mg, 0.89 mmol), (*E*)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid (Intermediate 3, 281 mg, 0.89 mmol), DCC (275 mg, 1.335 mmol) and DMAP (11 mg, 0.09 mmol) in DCM (3 mL) was stirred at room temperature overnight. The the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (0-10% *tert*-butyl methyl ether/ petroleum ether) to give 3-((9H-fluoren-9-yl)methoxy)-3-oxopropyl 1-(4-(trifluoromethyl)phenyl)cyclobutyl fumarate (300 mg, 59% yield) as a light yellow oil. LCMS m/z 586.8 $(M+Na)^+$ (ES^+).

Step 5

A mixture of 3-((9H-fluoren-9-yl)methoxy)-3-oxopropyl 1-(4-(trifluoromethyl)phenyl)cyclobutyl fumarate (300 mg, 0.53 mmol) in N,N-Dimethylformamide (2 mL) and triethylamine (0.4 mL) was stirred at 20 °C for 3 h. The reaction mixture was acidified with 0.5N HCl until pH = 5, and extracted with EtOAc (3 x 3 mL). The EtOAc layer was washed by brine, dried over Na_2SO_4 and

concentrated under reduced pressure. The residue was purified by prep-HPLC (Column: Waters SUNFIRE Prep C18 OBD 10µm 19x250mm; Flow Rate: 20 mL/min; solvent system: MeCN/(0.2% formic acid/water) : MeCN gradient: 58-95%; collection wavelength: 214 nm). The fractions were concentrated under reduced pressure to remove MeCN, and lyophilized to give (E)-3-(4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoyloxy)propanoic acid (108.21 mg, 52% yield) as light yellow oil. LCMS m/z 394.9 $(M+Na)^+$ (ES^+). ^1H NMR (400 MHz, DMSO-d_6) δ: 12.45 (br s, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.79-7.68 (m, 2H), 4.33 (t, *J* = 6 Hz, 2H), 2.66-2.62 (m, 6H), 2.01-1.98 (m, 1H), 1.81-1.73 (m, 1H).

Biological Example 1 – THP-1 AlphaLISA IL-1β and IL-6 Cytokine Assay

Measuring inhibitory effects on IL-1β and IL-6 cytokine output from THP-1s

The cytokine inhibition profiles of compounds of formula (I) were determined in a differentiated THP-1 cell assay. All assays were performed in RPMI-1640 growth medium (Gibco), supplemented with 10% fetal bovine serum (FBS; Gibco), 1% penicillin-streptomycin and 1% sodium pyruvate unless specified otherwise. The IL-1β and IL-6 cytokine inhibition assays were each run in a background of differentiated THP-1 cells as described below. All reagents described were from Sigma-Aldrich unless specified otherwise. Compounds were prepared as 10mM DMSO stocks.

Assay Procedure

THP-1 cells were expanded as a suspension up to 80% confluence in appropriate growth medium. Cells were harvested, suspended, and treated with an appropriate concentration of phorbol 12-myristate 13-acetate (PMA) over a 72hr period (37°C/5% CO_2).

Following 72hrs of THP-1 cell incubation, cellular medium was removed and replaced with fresh growth media containing 1% of FBS. Working concentrations of compounds were prepared separately in 10% FBS treated growth medium and pre-incubated with the cells for 30 minutes (37°C/5% CO_2). Following the 30 minute compound pre-incubation, THP-1s were treated with an appropriate concentration of LPS and the THP-1s were subsequently incubated for a 24hr period (37°C/5% CO_2). An appropriate final concentration of Nigericin was then dispensed into the THP-1 plates and incubated for 1 hour (37°C/5% CO_2) before THP-1 supernatants were harvested and collected in separate polypropylene 96-well holding plates.

Reagents from each of the IL-1β and IL-6 commercial kits (Perkin Elmer) were prepared and run according to the manufacturer's instructions. Subsequently, fluorescence signal detection in a microplate reader was measured (EnVision® Multilabel Reader, Perkin Elmer).

Percentage inhibition was calculated per cytokine by normalizing the sample data to the high and low controls used within each plate (+/- LPS respectively). Percentage inhibition was then plotted against compound concentration and the 50% inhibitory concentration (IC_{50}) was determined from the resultant concentration-response curve.

The data for all compounds of formula (I) tested in this assay are presented in Table 1 below. Dimethyl fumarate and 2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate (diroximel fumarate) were included as comparator compounds.

Table 1 – THP-1 cell IL-1β and IL-6 IC_{50} values (μM) *(++++ indicates IC_{50} of <2.5 μM; +++ indicates IC_{50} of 2.5 to 6.1 μM; ++ indicates IC_{50} of 6.2 to 9.2 μM; + indicates IC_{50} of 9.3 to 14.3 μM)*

Compound	IL-1β (IC_{50})	IL-6 (IC_{50})
dimethyl fumarate	14.4	9.3
2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate	6.2	NT*
Example 1	+++	++++
Example 2	+	++
Example 3	++++	++++
Example 4	+++	++++
		+++[a]
Example 5	+++	NT
Example 6	++++	NT
Example 7	++++	NT
Example 8	++++	NT
Example 9	+++	NT
Example 10	++++	NT
Example 11	++++	NT
Example 12	++++	NT
Example 13	+++	NT
Example 14	++++	NT
Example 15	++++	+++
Example 16	+++	++++

NT* = not tested; [a]from repeated experiments

These results reveal that compounds of formula (I) are expected to have anti-inflammatory activity as shown by their IC_{50} values for inhibition of IL-1β and IL-6 release in this assay. All compounds of the invention tested exhibited improved IL-1β and IL-6 lowering properties (IC_{50} values) compared to dimethyl fumarate. Certain compounds of the invention tested exhibited improved IL-1β lowering properties (IC_{50} values) compared to 2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate (diroximel fumarate).

The data for all compounds of formula (II) tested in this assay are presented in Table 2 below. Monomethyl fumarate was included as a comparator compound.

Table 2 – THP-1 cell IL-1β and IL-6 IC_{50} values (μM) *(++++ indicates IC_{50} of <6 μM, +++ indicates IC_{50} of 6-30 μM, ++ indicates IC_{50} of >30-50 μM; + indicates IC_{50} of >50-100 μM)*

Compound	IL-1β (IC_{50})	IL-6 (IC_{50})
monomethyl fumarate	>100	>100
Intermediate 3	++++	++++
Intermediate 4	>100	NT
Intermediate 6	+++	NT*
Intermediate 7	+++	NT
Intermediate 8	++	NT
Intermediate 9	+++	+++
Intermediate 10	+++	+++
Intermediate 11	+	>100
Intermediate 12	+++	+++
Intermediate 13	+++	+++
Intermediate 14	+++	++++
Intermediate 15	++	>100
Intermediate 16	++++	++++
Intermediate 17	+++	+++
Intermediate 18	+++	+++
Intermediate 19	+++	+++
Intermediate 20	+++	+++
Intermediate 21	+++	>100
Intermediate 23	+++	+++
Intermediate 24	++	+++
Intermediate 25	+++	++++

Compound	IL-1β (IC_{50})	IL-6 (IC_{50})
monomethyl fumarate	>100	>100
Intermediate 26	++++	++++
Intermediate 27	+	+++
Intermediate 28	+++	+++
Intermediate 29	++++	++++
Intermediate 30	++++	+++
Intermediate 31	+++	+++
Intermediate 32	++++	++++
Intermediate 33	++++	++++
Intermediate 34	+++	++
Intermediate 35	+	>100
Intermediate 36	++++	NT
Intermediate 38	++++	+++
Intermediate 39	++	++
Intermediate 40	>100	++
Intermediate 41	+++	+++
Intermediate 44	++++	++++
Intermediate 45	++++	++++

*NT means not tested

The compounds of formula (II) shown in Table 2 exhibited improved cytokine-lowering potencies compared to monomethyl fumarate, as shown by the lower IL-1β and/or IL-6 IC_{50} values (where tested), and thus are expected to exhibit anti-inflammatory activity. Intermediate 4 was not active in these assays. Preferred compounds of formula (II) are also more potent than dimethyl fumarate and 2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate, the values for which are shown in Table 1.

Biological Example 2 – NRF2 activation assay

Measuring compound activation effects on the anti-inflammatory transcription factor NRF2 in DiscoverX PathHunter NRF2 translocation kit

Potency and efficacy of compounds of formula (I) against the target of interest to activate NRF2 (nuclear factor erythroid 2-related factor 2) were determined using the PathHunter NRF2 translocation kit (DiscoverX). The NRF2 translocation assay was run using an engineered recombinant cell line, utilising enzyme fragment complementation to determine activation of the

Keap1-NRF2 protein complex and subsequent translocation of NRF2 into the nucleus. Enzyme activity was quantified using a chemiluminescent substrate consumed following the formation of a functional enzyme upon PK-tagged NRF2 translocation into the nucleus.

Additionally, a defined concentration of dimethyl fumarate was used as the 'High' control to normalise test compound activation responses to.

Assay Procedure

U2OS PathHunter eXpress cells were thawed from frozen prior to plating. Following plating, U2OS cells were incubated for 24hrs (37°C/5%CO_2) in commercial kit provided cell medium.

Following 24hrs of U2OS incubation, cells were directly treated with an appropriate final concentration of compound.

Following compound treatment, the U2OS plates were incubated for a further 6 hours (37°C/5%CO_2) before detection reagent from the PathHunter NRF2 commercial kit was prepared and added to test plates according to the manufacturer's instructions. Subsequently, the luminescence signal detection in a microplate reader was measured (PHERAstar®, BMG Labtech).

Percentage activation was calculated by normalising the sample data to the high and low controls used within each plate (+/- DMF). Percentage activation/response was then plotted against compound concentration and the 50% activation concentration (EC_{50}) was determined from the plotted concentration-response curve.

The data for all compounds of formula (I) tested in this assay are presented in Table 3 below. Dimethyl fumarate was included as the comparator compound.

Table 3 – NRF2 activation *(For EC_{50} values, ++++ means <2.0, +++ means 2.1-6.0 µM, ++ means >6.0-20 µM and + means >20-100 µM; for E_{max} values ++++ means 200-250%, +++ means 150-199%, ++ means 100-149 and + means >17.1-99)*

Compound	-GSH		+GSH	
	EC_{50} (µM)	E_{max} (%)	EC_{50} (µM)	E_{max} (%)
dimethyl fumarate	6.1	100	>100	17.1
Example 1	++++	++++	++	++
Example 2	+++	++++	+	+

Compound	-GSH		+GSH	
	EC_{50} (μM)	E_{max} (%)	EC_{50} (μM)	E_{max} (%)
dimethyl fumarate	6.1	100	>100	17.1
Example 3	++++	++++	+	++
Example 4	+++	+++	++	+
Example 5	+++	+++	+	+
Example 6	++++	++++	++	+
Example 7	++++	++++	++	+
Example 8	++++	++++	+	++
Example 11	++++	++++	+	+
Example 12	++++	++++	++	++
Example 13	++++	+++	+	++
Example 14	+++	+++	++	++
Example 15	+++	+++	>100	+

NT means not tested

These results reveal that compounds of formula (I) are expected to have anti-inflammatory activity as shown by their EC_{50} and E_{max} values for NRF2 activation in this assay. All Examples tested exhibited higher potency, as shown by lower EC_{50} values and higher E_{max} in -GSH and/or +GSH assays, compared to dimethyl fumarate.

The data for all compounds of formula (II) tested in this assay are presented in Table 4 below. Monomethyl fumarate was included as the comparator compound.

Table 4 – NRF2 activation *(For EC_{50} values, +++ means <23.0 uM, ++ means 23.0-<48.4 μM; for E_{max} values ++++ means >150%, +++ means >114-150%, ++ means >87-114%, + means >50-<87%)*

Compound	-GSH		+GSH	
	EC_{50} (μM)	E_{max} (%)	EC_{50} (μM)	E_{max} (%)
monomethyl fumarate	23.0	114	48.4	87
Intermediate 3	+++	+++	+++	+++
Intermediate 4	+++	+++	++	+
Intermediate 5	+++	++++	+++	++++
Intermediate 6	+++	++++	+++	++++
Intermediate 7	+++	++++	+++	+++

Compound	-GSH		+GSH	
	EC_{50} (μM)	E_{max} (%)	EC_{50} (μM)	E_{max} (%)
monomethyl fumarate	23.0	114	48.4	87
Intermediate 8	+++	++++	++	+++
Intermediate 10	+++	+++	+++	+++
Intermediate 12	+++	++	+++	++
Intermediate 14	+++	++++	+++	++++
Intermediate 16	+++	++++	+++	+++
Intermediate 19	+++	++++	+++	+++
Intermediate 20	+++	+++	++	+
Intermediate 21	+++	+++	+++ ++[a]	++
Intermediate 25	+++	++++	+++	++
Intermediate 26	+++	+++	+++	++
Intermediate 30	+++	+++	++	++
Intermediate 36	+++	+++	+++	++
Intermediate 38	+++	++++	+++	+

[a]from repeated experiments

These results reveal that compounds of formula (II) are expected to have anti-inflammatory activity as shown by their EC_{50} and E_{max} values for NRF2 activation in this assay. All compounds tested exhibited higher potency, as shown by lower EC_{50} values and/or higher E_{max} values in the -GSH and/or +GSH assay, compared to dimethyl fumarate. In addition, the activities of the compounds of formula (II) shown in Table 4 were much less susceptible to the effects of added GSH. Preferred compounds have +++ EC_{50} values and at least +++ E_{max} values in the -GSH and +GSH assays.

Biological Example 3 – Hepatocyte stability assay

Defrosted cryo-preserved hepatocytes (viability > 70%) are used to determine the metabolic stability of a compound via calculation of intrinsic clearance (Cl_{int}; a measure of the removal of a compound from the liver in the absence of blood flow and cell binding). Clearance data are particularly important for *in vitro* work as they can be used in combination with *in vivo* data to predict the half-life and oral bioavailability of a drug.

The metabolic stability in hepatocytes assay involves a time-dependent reaction using both positive and negative controls. The cells must be pre-incubated at 37 °C then spiked with test compound (and positive control); samples taken at pre-determined time intervals are analysed to monitor the change in concentration of the initial drug compound over 60 minutes. A buffer incubation reaction (with no hepatocytes present) acts as a negative control and two cocktail solutions, containing compounds with known high and low clearance values (verapamil/7-hydroxycoumarin and propranolol/diltiazem), act as positive controls.

1. The assay is run with a cell concentration of 0.5 x 10^6 cells/mL in Leibovitz buffer.
2. All compounds and controls are run in duplicate.
3. Compound concentration is 10µM.
4. All compounds and controls are incubated with both cells and buffer to show turnover is due to hepatic metabolism.
5. All wells on the incubation plate will have 326.7µL of either cells or buffer added.
6. Prior to assay, cell and buffer-only incubation plates are preincubated for 10 mins at 37 °C.
7. The assay is initiated by adding compounds, 3.3µL of 1mM in 10%DMSO–90%Buffer; final DMSO concentration is 0.1%.
8. Samples are taken at regular timepoints (0, 5, 10, 20, 40, 60 min) until 60 mins.
9. Sample volume is 40µL and it is added to 160µL of crash solvent (acetonitrile with internal standard) and stored on ice.
10. At the end of the assay, the crash plates are centrifuged at 3500rpm for 20mins at 4 °C.
11. 80µL of clear supernatant is removed and mixed with 80µL of deionised water before being analysed by LC-MS/MS.

Raw LC-MS/MS data are exported to, and analysed in, Microsoft Excel for determination of intrinsic clearance. The percentage remaining of a compound is monitored using the peak area of the initial concentration as 100%. Intrinsic clearance and half-life values are calculated using a graph of the natural log of percentage remaining versus the time of reaction in minutes. Half-life (min) and intrinsic clearance (Cl_{int} in µL min^{-1} 10^{-6} cells) values are calculated using the gradient of the graph (the elimination rate constant, k) and Equations 1 and 2.

$$t_{\frac{1}{2}} = \frac{ln2}{k} \qquad \{\text{Equation 1}\}$$

$$Cl_{int} = \left(\frac{ln2}{t_{\frac{1}{2}}}\right) \times \left(\frac{350}{0.175}\right) \qquad \{\text{Equation 2}\}$$

The data for all compounds of formula (I) tested in this assay are presented in Table 5 below. 2-(2,5-Dioxopyrrolidin-1-yl)ethyl methyl fumarate (diroximel fumarate) was included as the comparator compound.

Table 5 – Hepatocyte stability *(For Cl_{int} (µL min^{-1} 10^{-6} cells; mouse), ++ means 200-277 and + means >277; For Cl_{int} (µL min^{-1} 10^{-6} cells; human), ++++ means <50, +++ means 50-149, ++ means 150-277, and + means >277; For T½ (min; mouse), ++ means 5-10, and + means <5; For T½ (min; human), ++++ means >100, +++ means 30-100, ++ means 5-29, and + means <5)*

Compound	Species	Cl_{int} (µL min^{-1} 10^{-6} cells)	T½ (min)
2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate	Human	>277	<5
	Mouse	>277	<5
Example 1	Human	++++	+++
	Mouse	+	+
Example 2	Human	++++	+++
	Mouse	++	++
Example 3	Human	+++	++
	Mouse	+	+
Example 4	Human	+++	++
	Mouse	+	+
Example 5	Human	++	++
	Mouse	+	+
Example 6	Human	++++	+++
	Mouse	++	++
Example 7	Human	+++	++
	Mouse	+	+
Example 8	Human	+++	++
	Mouse	+	+
Example 9	Human	++++	+++
	Mouse	+	+
Example 10	Human	++++	+++
	Mouse	+	+
Example 11	Human	+++	++
	Mouse	+	+
Example 12	Human	++++	++++
	Mouse	+	+
Example 13	Human	+++	++
	Mouse	+	+

Compound	Species	Cl_{int} (µL min^{-1} 10^{-6} cells)	T½ (min)
2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate	Human	>277	<5
	Mouse	>277	<5
Example 14	Human	+	+
	Mouse	+	+
Example 15	Human	+++	++
	Mouse	+	+
Example 16	Human	+++	++
	Mouse	+	+

These results reveal that compounds of the invention are expected to have improved metabolic stabilities, as shown by their intrinsic clearance (Cl_{int}) and half-life ($T_{1/2}$) values in this assay. All the compounds of formula (I), except Example 14, shown in Table 5 were more stable, i.e., they exhibited lower intrinsic clearance (Cl_{int}) and longer half-life ($T_{1/2}$) values compared with 2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate (diroximel fumarate) in at least human hepatocytes. Preferred compounds exhibited lower intrinsic clearance (Cl_{int}) and longer half-life ($T_{1/2}$) values compared with 2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate (diroximel fumarate) in both human and mouse species.

Table 6 – Hepatocyte stability *(For Cl_{int} (µL min^{-1} 10^{-6} cells), ++++ means 5-15, +++ means >15-30, ++ means >30-110, + means >110-277 and ± means >277; For T½ (min), ++++ means >100, +++ means 30-100, ++ means 5-29, and + means <5)*

Compound	Species	Cl_{int} (µL min^{-1} 10^{-6} cells)	T½ (min)
2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate	Human	>277	<5
	Mouse	>277	<5
Intermediate 3	Human	++++	++++
	Mouse	+++	+++
Intermediate 6	Human	++++	++++
	Mouse	++	++
Intermediate 7	Human	+++	+++
	Mouse	++	++
Intermediate 8	Human	+++	+++
	Mouse	++	+++
Intermediate 10	Human	++	++
	Mouse	++	+++
Intermediate 12	Human	+++	+++
	Mouse	+++	+++

Compound	Species	Cl_{int} (µL min^{-1} 10^{-6} cells)	T½ (min)
2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate	Human	>277	<5
	Mouse	>277	<5
Intermediate 14	Human	++++	++++
	Mouse	++	++
Intermediate 16	Human	+++	++++
	Mouse	+++	+++
Intermediate 17	Human	++	++
	Mouse	+	++
Intermediate 18	Human	++	+++
	Mouse	++	+++
Intermediate 19	Human	++++	++++
	Mouse	++	++
Intermediate 20	Human	++++	++++
	Mouse	+++	+++
Intermediate 21	Human	++++	++++
	Mouse	++++	++++
Intermediate 25	Human	+++	++++
	Mouse	++	+++
Intermediate 26	Human	+++	+++
	Mouse	++	+++
Intermediate 29	Human	++++	++++
	Mouse	+++	+++
Intermediate 30	Human	++++	++++
	Mouse	+++	+++
Intermediate 32	Human	+++	+++
	Mouse	+++	+++
Intermediate 33	Human	++++	++++
	Mouse	+++	+++
Intermediate 36	Human	++++	++++
	Mouse	++	+++
Intermediate 38	Human	+++	+++
	Mouse	++	++
Intermediate 41	Human	++++	++++
	Mouse	++	+++

Compound	Species	Cl_{int} (µL min^{-1} 10^{-6} cells)	T½ (min)
2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate	Human	>277	<5
	Mouse	>277	<5
Intermediate 44	Human	++	++
	Mouse	±	+
Intermediate 45	Human	++	++
	Mouse	+	*4*

All the compounds of formula (II) shown in Table 6 were more stable, i.e., they exhibited lower intrinsic clearance (Cl_{int}) and longer half-life ($T_{1/2}$) values compared with 2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate (diroximel fumarate) in at least human hepatocytes.

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Miscellaneous

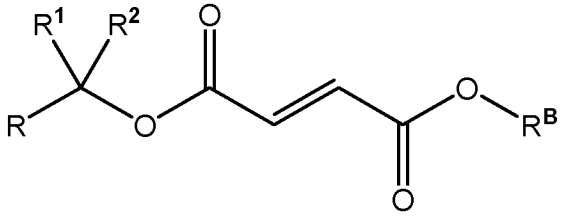
All references referred to in this application, including patent and patent applications, are incorporated herein by reference to the fullest extent possible.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer, step, group of integers or group of steps but not to the exclusion of any other integer, step, group of integers or group of steps.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims.

CLAIMS

1. A compound of formula (I):



(I);

wherein:

R is C_{4-10} alkyl, and R^1 and R^2 are independently selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl or R^1 and R^2 join to form a C_{3-4} cycloalkyl ring; wherein R is optionally substituted by one or more R^a wherein R^a is independently selected from the group consisting of halo, C_{1-2} haloalkyl and C_{1-2} haloalkoxy; or

R is selected from the group consisting of C_{6-10} cycloalkyl, phenyl and 5- or 6-membered heteroaryl, and R^1 and R^2 are independently selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl, or R^1 and R^2 join to form a C_{3-4} cycloalkyl ring or a 4–6-membered heterocyclic ring, wherein the C_{3-4} cycloalkyl ring is optionally substituted by methyl, halo or cyano; wherein R is optionally substituted by one or more R^b wherein R^b is independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy and cyano; or

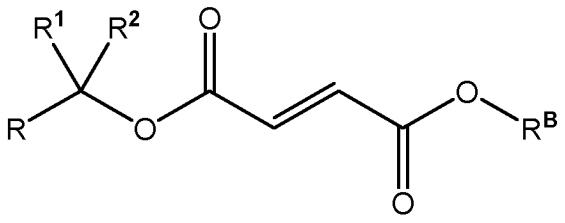
R is H, methyl or CF_3 and R^1 and R^2 are joined to form a C_{4-10} cycloalkyl ring, wherein the C_{4-10} cycloalkyl ring is optionally substituted by one or more R^c wherein R^c is independently selected from the group consisting of halo, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy and C_{1-2} haloalkoxy, and/or wherein the C_{4-10} cycloalkyl ring is optionally substituted by two R^c groups wherein the two R^C groups are attached to the same carbon atom and are joined to form a C_{4-6} cycloalkyl ring; and

R^B is selected from the group consisting of CH_2COOH, CH_2CH_2COOH, CH_2tetrazolyl and CH_2CH_2tetrazolyl, wherein R^B is optionally substituted on an available carbon atom by one or more $R^{B'}$ wherein $R^{B'}$ is selected from the group consisting of difluoromethyl, trifluoromethyl and methyl, and/or wherein R^B is optionally substituted by two $R^{B'}$ groups, attached to the same carbon atom, that are joined to form a C_{3-6} cycloalkyl or a 4–6-membered heterocyclic ring;

wherein the total number of carbon atoms in groups R, R^1 and R^2 taken together, including their optional substituents, and including the carbon to which R, R^1 and R^2 are attached, is 6 to 14;

or a pharmaceutically acceptable salt and/or solvate thereof.

2. The compound according to claim 1 which is a compound of formula (I):



(I);

wherein:

R is C_{4-10} alkyl, and R^1 and R^2 are independently selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl or R^1 and R^2 join to form a C_{3-4} cycloalkyl ring; wherein R is optionally substituted by one or more R^a wherein R^a is independently selected from the group consisting of halo, C_{1-2} haloalkyl and C_{1-2} haloalkoxy; or

R is selected from the group consisting of C_{6-10} cycloalkyl and phenyl, and R^1 and R^2 are independently selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl, or R^1 and R^2 join to form a C_{3-4} cycloalkyl ring; wherein R is optionally substituted by one or more R^b wherein R^b is independently selected from the group consisting of halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy and C_{1-4} haloalkoxy; or

R is H, methyl or CF_3 and R^1 and R^2 are joined to form a C_{4-10} cycloalkyl ring, wherein the C_{4-10} cycloalkyl ring is optionally substituted by one or more R^c wherein R^c is independently selected from the group consisting of halo, C_{1-2} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy and C_{1-2} haloalkoxy, and/or wherein the C_{4-10} cycloalkyl ring is optionally substituted by two R^c groups wherein the two R^c groups are attached to the same carbon atom and are joined to form a C_{4-6} cycloalkyl ring; and

R^B is selected from the group consisting of CH_2COOH, CH_2CH_2COOH, CH_2tetrazolyl and CH_2CH_2tetrazolyl, wherein R^B is optionally substituted on an available carbon atom by one or more $R^{B'}$ wherein $R^{B'}$ is selected from the group consisting of difluoromethyl, trifluoromethyl and methyl, and/or wherein R^B is optionally substituted by two $R^{B'}$ groups, attached to the same carbon atom, that are joined to form a C_{3-6} cycloalkyl or a 4–6-membered heterocyclic ring;

wherein the total number of carbon atoms in groups R, R^1 and R^2 taken together, including their optional substituents, and including the carbon to which R, R^1 and R^2 are attached, is 6 to 14;

or a pharmaceutically acceptable salt and/or solvate thereof.

3. The compound according to claim 1 or claim 2 wherein R is C_{4-10} alkyl, and R^1 and R^2 are independently selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl or R^1 and R^2 join to form a C_{3-4} cycloalkyl ring.

4. The compound according to claim 3 wherein R is C_7 alkyl.

5. The compound according to claim 3 or claim 4 wherein R^1 is H.

6. The compound according to claim 3 or claim 4 wherein R^1 is C_{1-4} alkyl e.g. methyl.

7. The compound according to claim 3 or claim 4 wherein R^1 is C_{1-4} haloalkyl e.g. CF_3.

8. The compound according to any one of claims 3 to 7 wherein R^2 is H.

9. The compound according to any one of claims 3 to 7 wherein R^2 is C_{1-4} alkyl e.g. methyl.

10. The compound according to any one of claims 3 to 7 wherein R^2 is C_{1-4} haloalkyl e.g. CF_3.

11. The compound according to claim 3 or claim 4 wherein R^1 is C_{1-4} alkyl e.g. methyl and R^2 is H.

12. The compound according to claim 3 or claim 4 wherein R^1 and R^2 join to form a C_{3-4} cycloalkyl ring e.g. a C_3 cycloalkyl ring.

13. The compound according to any one of claims 3 to 12 wherein R is not substituted.

14. The compound according to any one of claims 3 to 11 wherein R is substituted by one or more e.g. one R^a.

15. The compound according to claim 14 wherein R^a is halo e.g. fluoro.

16. The compound according to claim 14 wherein R^a is C_{1-2} haloalkyl e.g. CF_3.

17. The compound according to claim 14 wherein R^a is C_{1-2} haloalkoxy e.g. OCF_3.

18. The compound according to claim 1 wherein R is selected from the group consisting of C_{6-10} cycloalkyl, phenyl and 5- or 6-membered heteroaryl, and R^1 and R^2 are independently selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl, or R^1 and R^2 join to form a C_{3-4} cycloalkyl ring or a 4–6-membered heterocyclic ring, wherein the C_{3-4} cycloalkyl ring is optionally substituted by methyl, halo or cyano.

19. The compound according to claim 2 wherein R is selected from the group consisting of C_{6-10} cycloalkyl and phenyl, and R^1 and R^2 are independently selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl, or R^1 and R^2 join to form a C_{3-4} cycloalkyl ring.

20. The compound according to claim 18 or claim 19 wherein R is C_{6-10} cycloalkyl.

21. The compound according to claim 18 or claim 19 wherein R is phenyl.

22. The compound according to claim 18 wherein R is 5-membered heteroaryl.

23. The compound according to claim 18 wherein R is 6-membered heteroaryl.

24. The compound according to any one of claims 18 to 23 wherein R^1 is H.

25. The compound according to any one of claims 18 to 23 wherein R^1 is C_{1-4} alkyl e.g. methyl.

26. The compound according to any one of claims 18 to 23 wherein R^1 is C_{1-4} haloalkyl e.g. CF_3.

27. The compound according to any one of claims 18 to 26 wherein R^2 is H.

28. The compound according to any one of claims 18 to 26 wherein R^2 is C_{1-4} alkyl e.g. methyl.

29. The compound according to any one of claims 18 to 26 wherein R^2 is C_{1-4} haloalkyl e.g. CF_3.

30. The compound according to any one of claims 18 to 23 wherein R^1 and R^2 join to form a C_{3-4} cycloalkyl ring.

31. The compound according to claim 30 wherein R^1 and R^2 join to form a C_3 cycloalkyl ring.

32. The compound according to claim 30 wherein R^1 and R^2 join to form a C_4 cycloalkyl ring.

33. The compound according to any one of claims 30 to 32 wherein the C_{3-4} cycloalkyl ring is not substituted.

34. The compound according to any one of claims 30 to 32 wherein the C_{3-4} cycloalkyl ring is substituted by methyl, halo or cyano.

35. The compound according to claim 34 wherein the C_{3-4} cycloalkyl ring is substituted by methyl.

36. The compound according to claim 34 wherein the C_{3-4} cycloalkyl ring is substituted by halo.

37. The compound according to claim 34 wherein the C_{3-4} cycloalkyl ring is substituted by cyano.

38. The compound according to any one of claims 18 to 23 wherein R^1 and R^2 join to form a 4–6-membered heterocyclic ring.

39. The compound according to claim 38 wherein R^1 and R^2 join to form a 4-membered heterocyclic ring such as oxetanyl or thietanyl.

40. The compound according to claim 38 wherein R^1 and R^2 join to form a 5-membered heterocyclic ring.

41. The compound according to claim 38 wherein R^1 and R^2 join to form a 6-membered heterocyclic ring.

42. The compound according to any one of claims 18 to 41 wherein R is not substituted.

43. The compound according to any one of claims 18 to 41 wherein R is substituted by one or more such as one or two e.g. one R^b.

44. The compound according to claim 43 wherein R^b is halo e.g. chloro or bromo.

45. The compound according to claim 43 wherein R^b is C_{1-4} alkyl e.g. methyl.

46. The compound according to claim 43 wherein R^b is C_{1-4} haloalkyl e.g. CF_3.

47. The compound according to claim 43 wherein R^b is C_{1-4} alkoxy e.g. methoxy.

48. The compound according to claim 43 wherein R^b is C_{1-4} haloalkoxy e.g. OCF_3.

49. The compound according to claim 43 wherein R^b is cyano.

50. The compound according to claim 1 or claim 2 wherein R is H, methyl or CF_3 and R^1 and R^2 are joined to form a C_{4-10} cycloalkyl ring.

51. The compound according to claim 50 wherein R is H.

52. The compound according to claim 50 wherein R is methyl.

53. The compound according to claim 50 wherein R is CF_3.

54. The compound according to any one of claims 50 to 53 wherein R^1 and R^2 are joined to form a C_4 cycloalkyl ring.

55. The compound according to any one of claims 50 to 53 wherein R^1 and R^2 are joined to form a C_6 cycloalkyl ring.

56. The compound according to any one of claims 50 to 53 wherein R^1 and R^2 are joined to form a C_7 cycloalkyl ring.

57. The compound according to any one of claims 50 to 53 wherein R^1 and R^2 are joined to form a C_8 cycloalkyl ring.

58. The compound according to any one of claims 50 to 57 wherein the C_{4-10} cycloalkyl ring is not substituted.

59. The compound according to any one of claims 50 to 57 wherein the C_{4-10} cycloalkyl ring is substituted by one or more e.g. one R^c.

60. The compound according to claim 59 wherein R^c is halo e.g. fluoro.

61. The compound according to claim 59 wherein R^c is C_{1-2} alkyl e.g. methyl.

62. The compound according to claim 59 wherein R^c is C_{1-2} haloalkyl e.g. CF_3.

63. The compound according to claim 59 wherein R^c is C_{1-2} alkoxy e.g. methoxy.

64. The compound according to claim 59 wherein R^c is C_{1-2} haloalkoxy e.g. OCF_3.

65. The compound according to claim 59 wherein the C_{4-10} cycloalkyl ring is substituted by two R^c groups wherein the two R^C groups are attached to the same carbon atom and are joined to form a C_{4-6} cycloalkyl ring e.g. a C_4 cycloalkyl ring.

66. The compound according to any one of claims 1 to 65 wherein R^B is CH_2COOH.

67. The compound according to any one of claims 1 to 65 wherein R^B is CH_2CH_2COOH.

68. The compound according to any one of claims 1 to 65 wherein R^B is CH_2tetrazolyl.

69. The compound according to any one of claims 1 to 65 wherein R^B is CH_2CH_2tetrazolyl.

70. The compound according to any one of claims 66 to 69 wherein R^B is not substituted.

71. The compound according to any one of claims 66 to 69 wherein R^B is substituted on an available carbon atom by one or more such as one, two, three or four, e.g., one $R^{B'}$ wherein $R^{B'}$ is selected from the group consisting of difluoromethyl, trifluoromethyl and methyl, and/or wherein R^B is optionally substituted by two $R^{B'}$ groups, attached to the same carbon atom, that are joined to form a C_{3-6} cycloalkyl or a 4–6-membered heterocyclic ring.

72. The compound according to claim 71 wherein $R^{B'}$ is difluoromethyl.

73. The compound according to claim 71 wherein $R^{B'}$ is trifluoromethyl.

74. The compound according to claim 71 wherein $R^{B'}$ is methyl.

75. The compound according to claim 71 wherein R^B is optionally substituted by two $R^{B'}$ groups, attached to the same carbon atom, that are joined to form a C_{3-6} cycloalkyl or a 4–6-membered heterocyclic ring.

76. The compound according to claim 75 wherein the two $R^{B'}$ groups join to form a C_{3-6} cycloalkyl ring e.g. C_3 cycloalkyl ring.

77. The compound according to claim 75 wherein the two $R^{B'}$ groups join to form a 4–6-membered heterocyclic ring.

78. The compound according to claim 1 which is a compound selected from the group consisting of:
(E)-2-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)acetic acid;
(*E*)-2-((4-(cyclohexyloxy)-4-oxobut-2-enoyl)oxy)acetic acid;
(E)-3-((4-(Cyclooctyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid;
(*E*)-3-((4-(cyclohexyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid;
2-(1H-tetrazol-5-yl)ethyl cyclooctyl fumarate;
(*S,E*)-2-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid;
(*E*)-3-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)-2,2-dimethylpropanoic acid;
(*E*)-1-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)cyclopropane-1-carboxylic acid;
(*E*)-2-((4-oxo-4-(spiro[3.3]heptan-2-yloxy)but-2-enoyl)oxy)acetic acid;
(*E*)-2-((4-(cycloheptyloxy)-4-oxobut-2-enoyl)oxy)acetic acid;
(*E*)-3-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)butanoic acid;
(*R,E*)-2-((4-(cyclooctyloxy)-4-oxobut-2-enoyl)oxy)propanoic acid;
(*E*)-2-((4-(cycloheptyloxy)-4-oxobut-2-enoyl)oxy)acetic acid;
(*R,E*)-3-((4-(octan-2-yloxy)-4-oxobut-2-enoyl)oxy)propanoic acid;
(E)-2-((4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoyl)oxy) acetic acid; and
(E)-3-(4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoyloxy)propanoic acid;
or a pharmaceutically acceptable salt and/or solvate of any one thereof.

79. A pharmaceutical composition comprising the compound of formula (I) according to any one of claims 1 to 78, and one or more pharmaceutically acceptable diluents or carriers.

80. The compound according to any one of claims 1 to 78 or the pharmaceutical composition according to claim 79 for use as a medicament.

81. A compound according to any one of claims 1 to 78 or a pharmaceutical composition according to claim 79 for use in treating or preventing an inflammatory disease or a disease associated with an undesirable immune response.

82. Use of a compound according to any one of claims 1 to 78 or a pharmaceutical composition according to claim 79 in the manufacture of a medicament for treating or preventing an inflammatory disease or a disease associated with an undesirable immune response.

83. 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 78 or a pharmaceutical composition according to claim 79.

84. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 1 to 83, for treating an inflammatory disease or a disease associated with an undesirable immune response.

85. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 1 to 83, for preventing an inflammatory disease or a disease associated with an undesirable immune response.

86. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 1 to 83, for treating or preventing an inflammatory disease.

87. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 1 to 83, for treating or preventing a disease associated with an undesirable immune response.

88. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 1 to 87, 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).

89. The compound for use according to claim 88, 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.

90. The compound, pharmaceutical composition, compound for use, use or method according to claim 89, wherein the inflammatory disease or disease associated with an undesirable immune response is multiple sclerosis.

91. The compound, pharmaceutical composition, compound for use, use or method according to claim 89, wherein the inflammatory disease or disease associated with an undesirable immune response is psoriasis.

92. The compound, pharmaceutical composition, compound for use, use or method according to claim 88, wherein the inflammatory disease or disease associated with an undesirable immune response is asthma.

93. The compound, pharmaceutical composition, compound for use, use or method according to claim 89, wherein the inflammatory disease or disease associated with an undesirable immune response is chronic obstructive pulmonary disease.

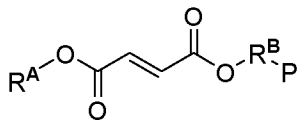
94. The compound, pharmaceutical composition, compound for use, use or method according to claim 89, wherein the inflammatory disease or disease associated with an undesirable immune response is systemic lupus erythematosus.

95. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 1 to 94, wherein the compound is for administration to a human subject.

96. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 1 to 95, for use in combination with a further therapeutic agent, such as 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 mizoribine.

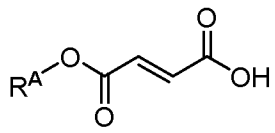
97. A compound of formula (I-P):



(I-P)

or a salt such as a pharmaceutically acceptable salt thereof, wherein R^A and R^B are defined in claim 1 and P is a carboxylic acid protecting group such as C_{1-6} alkyl e.g. *tert*-butyl, or para-methoxybenzyl.

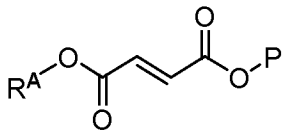
98. A compound of formula (II):



(II)

or a salt such as a pharmaceutically acceptable salt thereof, wherein R^A is defined in claim 1.

99. A compound of formula (III):



(III)

or a salt such as a pharmaceutically acceptable salt thereof, wherein R^A is defined in claim 1 and P is a carboxylic acid protecting group such as C_{1-6} alkyl e.g. *tert*-butyl, para-methoxybenzyl or Fmoc.

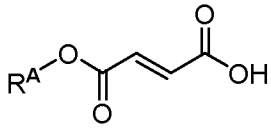
100. The compound according to claim 99 wherein P is C_{1-6} alkyl e.g. *tert*-butyl or para-methoxybenzyl.

101. A compound selected from the group consisting of:
2-(*tert*-butoxy)-2-oxoethyl cyclooctyl fumarate;
2-(tert-butoxy)-2-oxoethyl cyclohexyl fumarate;
3-(*tert*-butoxy)-3-oxopropyl cyclooctyl fumarate;
3-(tert-butoxy)-3-oxopropyl cyclohexyl fumarate;
(*S*)-1-(*tert*-butoxy)-1-oxopropan-2-yl cyclooctyl fumarate;
Cyclooctyl (3-((4-methoxybenzyl)oxy)-2,2-dimethyl-3-oxopropyl) fumarate;
2-(*tert*-butoxy)-2-oxoethyl spiro[3.3]heptan-2-yl fumarate;
2-(*tert*-butoxy)-2-oxoethyl cycloheptyl fumarate;
Cyclooctyl (4-((4-methoxybenzyl)oxy)-4-oxobutan-2-yl) fumarate;
(*R*)-1-(*tert*-butoxy)-1-oxopropan-2-yl cyclooctyl fumarate;
(*R*)-2-(*tert*-butoxy)-2-oxoethyl octan-2-yl fumarate;
(*R*)-3-(*tert*-butoxy)-3-oxopropyl octan-2-yl fumarate;
or a salt thereof.

102. A compound selected from the group consisting of:
(*E*)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid;
(*E*)-4-(1-methylcyclobutoxy)-4-oxobut-2-enoic acid;
octyl fumarate;

(E)-4-(cyclooctyloxy)-4-oxobut-2-enoic acid;
(*E*)-4-oxo-4-(spiro[3.3]heptan-2-yloxy)but-2-enoic acid;
(E)-4-(cycloheptyloxy)-4-oxobut-2-enoic acid;
(E)-4-oxo-4-(1-(5-(trifluoromethyl)pyridin-2-yl)cyclobutoxy)but-2-enoic acid;
(E)-4-oxo-4-(1-(3-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid;
(E)-4-oxo-4-(1-(2-(trifluoromethyl)phenyl)cyclobutoxy)but-2-enoic acid;
(E)-4-(1-(4-bromophenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-(1-(4-chlorophenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-(1-(3,5-dichlorophenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-oxo-4-(1-(6-(trifluoromethyl)pyridin-3-yl)cyclobutoxy)but-2-enoic acid;
(*E*)-4-(1-(3-fluoro-4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(*E*)-4-oxo-4-((3-(4-(trifluoromethyl)phenyl)thietan-3-yl)oxy)but-2-enoic acid;
(*E*)-4-oxo-4-((3-(4-(trifluoromethyl)phenyl)oxetan-3-yl)oxy)but-2-enoic acid;
(*S*,E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)ethoxy)but-2-enoic acid;
(*R*,E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)ethoxy)but-2-enoic acid;
(E)-4-oxo-4-((2-(4-(trifluoromethyl)phenyl)propan-2-yl)oxy)but-2-enoic acid;
(E)-4-(1-(5-bromopyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-(1-(5-chloropyridin-2-yl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-(1-(3,5-dichloro-4-fluorophenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-(1-(3-chloro-4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-(1-(4-cyanophenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-oxo-4-(1-(3,4,5-trifluorophenyl)cyclobutoxy)but-2-enoic acid;
(E)-4-(3-methyl-1-(4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-oxo-4-((4-(4-(trifluoromethyl)phenyl)tetrahydro-2H-pyran-4-yl)oxy)but-2-enoic acid;
(E)-4-(3-cyano-1-(4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-oxo-4-(1-(5-(trifluoromethyl)thiophen-2-yl)cyclobutoxy)but-2-enoic acid;
(E)-4-(1-(3,5-difluoro-4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-oxo-4-(1-(4-(trifluoromethoxy)phenyl)cyclobutoxy)but-2-enoic acid;
(E)-4-(3,3-difluoro-1-(4-(trifluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-(1-(4-(difluoromethyl)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-oxo-4-(1-(4-(trifluoromethyl)phenyl)cyclopropoxy)but-2-enoic acid;
(E)-4-oxo-4-(1-(5-(trifluoromethyl)pyrimidin-2-yl)cyclobutoxy)but-2-enoic acid;
(E)-4-(1-(3,5-dimethoxyphenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-(1-(3-chloro-5-(trifluoromethoxy)phenyl)cyclobutoxy)-4-oxobut-2-enoic acid;
(E)-4-oxo-4-(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethoxy)but-2-enoic acid; and
(E)-4-oxo-4-(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethoxy)but-2-enoic acid;
or a salt thereof.

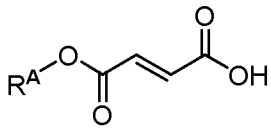
103. A process for the preparation of compounds of formula (I) or a salt, such as a pharmaceutically acceptable salt thereof, which comprises reacting a compound of formula (II):



(II)

or a salt such as a pharmaceutically acceptable salt thereof, wherein R^A is defined in claim 1; with X-R^B or a salt, such as a pharmaceutically acceptable salt thereof, wherein X is halo e.g. Br, or OH, and R^B is defined in claim 1.

104. A process for the preparation of compounds of formula (I) or a salt, such as a pharmaceutically acceptable salt thereof, which comprises reacting a compound of formula (II):



(II)

or a salt such as a pharmaceutically acceptable salt thereof, wherein R^A is defined in claim 1; with X-R^B-P or a salt, such as a pharmaceutically acceptable salt thereof, followed by removal of protecting group P, wherein R^B is defined in claim 1, P is a carboxylic acid protecting group such as C_{1-6} alkyl e.g. *tert*-butyl, para-methoxybenzyl or Fmoc, and X is halo e.g. Br, or OH.

105. The process according to claim 104 wherein P is C_{1-6} alkyl e.g. *tert*-butyl or para-methoxybenzyl.

106. A compound according to any one of claims 1 to 102 which is in natural isotopic form.

107. A pharmaceutical composition comprising a compound according to claim 98 or claim 102.

108. A compound according to claim 98 or claim 102 or a pharmaceutical composition according to claim 107 for use as a medicament.

109. A compound according to claim 98 or claim 102 or a pharmaceutical composition according to claim 107 for use in treating or preventing an inflammatory disease or a disease associated with an undesirable immune response.

110. Use of a compound according to claim 98 or claim 102 or a pharmaceutical composition

according to claim 107 in the manufacture of a medicament for treating or preventing an inflammatory disease or a disease associated with an undesirable immune response.

111. 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 claim 98 or claim 102 or a pharmaceutical composition according to claim 107.

112. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 98, 102 or 107 to 111, for treating an inflammatory disease or a disease associated with an undesirable immune response.

113. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 98, 102 or 107 to 111, for preventing an inflammatory disease or a disease associated with an undesirable immune response.

114. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 98, 102 or 107 to 111, for treating or preventing an inflammatory disease.

115. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 98, 102 or 107 to 111, for treating or preventing a disease associated with an undesirable immune response.

116. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 98, 102 or 107 to 115, 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).

117. The compound for use according to claim 116, 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.

118. The compound, pharmaceutical composition, compound for use, use or method according to claim 117, wherein the inflammatory disease or disease associated with an undesirable immune response is multiple sclerosis.

119. The compound, pharmaceutical composition, compound for use, use or method according to claim 117, wherein the inflammatory disease or disease associated with an undesirable immune response is psoriasis.

120. The compound, pharmaceutical composition, compound for use, use or method according

to claim 116, wherein the inflammatory disease or disease associated with an undesirable immune response is asthma.

121. The compound, pharmaceutical composition, compound for use, use or method according to claim 117, wherein the inflammatory disease or disease associated with an undesirable immune response is chronic obstructive pulmonary disease.

122. The compound, pharmaceutical composition, compound for use, use or method according to claim 117, wherein the inflammatory disease or disease associated with an undesirable immune response is systemic lupus erythematosus.

123. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 98, 102 or 107 to 94, wherein the compound is for administration to a human subject.

124. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 98, 102 or 107 to 123, for use in combination with a further therapeutic agent, such as 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),

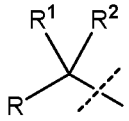
ursodeoxycholic acid, hydroxychloroquine, chloroquine, B cell activating factor (BAFF, also known as BLyS, B lymphocyte stimulator) inhibitor (e.g. belimumab, blisibimod), other B cell targeted therapy including a fusion protein targeting both APRIL (A PRoliferation-Inducing Ligand) and BLyS (e.g. atacicept), 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 mizoribine.

125. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 98, 102, and 107 to 124, wherein the compound of formula (II) is in the form of a pharmaceutically acceptable salt.

126. The compound, pharmaceutical composition, compound for use, use or method according to any one of claims 98, 102, and 107 to 124, wherein the compound of formula (II) is not in the form of a pharmaceutically acceptable salt.

127. The compound or process according to any one of claims 97 to 100 and 103 to 105

wherein R^A is:



wherein R, R^1 and R^2 are defined in claim 1.