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(54) Title: BENZIMIDAZOLONE DERIVATIVES, AND ANALOGUES THEREOF, AS IL-17 MODULATORS

(57) Abstract: A series of substituted benzimidazol-2-one derivatives, and analogues thereof, being potent modulators of human IL-17 activity, are accordingly of benefit in the treatment and/or prevention of various human ailments, including inflammatory and autoimmune disorders.



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BENZIMIDAZOLONE DERIVATIVES, AND ANALOGUES
THEREOF, AS IL-17 MODULATORS

The present invention relates to heterocyclic compounds, and to their use in
5 therapy. More particularly, this invention is concerned with pharmacologically active
benzimidazole derivatives, and analogues thereof. These compounds act as modulators of
IL-17 activity, and are accordingly of benefit as pharmaceutical agents for the treatment
and/or prevention of pathological conditions, including adverse inflammatory and
autoimmune disorders.

10 IL-17A (originally named CTLA-8 and also known as IL-17) is a pro-
inflammatory cytokine and the founder member of the IL-17 family (Rouvier *et al.*, *J.*
Immunol., 1993, **150**, 5445-5456). Subsequently, five additional members of the family
(IL-17B to IL-17F) have been identified, including the most closely related, IL-17F
(ML-1), which shares approximately 55% amino acid sequence homology with IL-17A
15 (Moseley *et al.*, *Cytokine Growth Factor Rev.*, 2003, **14**, 155-174). IL-17A and IL-17F
are expressed by the recently defined autoimmune related subset of T helper cells, Th17,
that also express IL-21 and IL-22 signature cytokines (Korn *et al.*, *Ann. Rev. Immunol.*,
2009, **27**, 485-517). IL-17A and IL-17F are expressed as homodimers, but may also be
expressed as the IL-17A/F heterodimer (Wright *et al.*, *J. Immunol.*, 2008, **181**, 2799-
20 2805). IL-17A and F signal through the receptors IL-17R, IL-17RC or an IL-17RA/RC
receptor complex (Gaffen, *Cytokine*, 2008, **43**, 402-407). Both IL-17A and IL-17F have
been associated with a number of autoimmune diseases.

The compounds in accordance with the present invention, being potent modulators
of human IL-17 activity, are therefore beneficial in the treatment and/or prevention of
25 various human ailments, including inflammatory and autoimmune disorders.

Furthermore, the compounds in accordance with the present invention may be
beneficial as pharmacological standards for use in the development of new biological tests
and in the search for new pharmacological agents. Thus, the compounds of this invention
may be useful as radioligands in assays for detecting pharmacologically active
30 compounds.

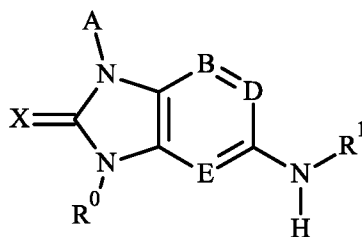
WO 2013/116682 and WO 2014/066726 relate to separate classes of chemical
compounds that are stated to modulate the activity of IL-17 and to be useful in the
treatment of medical conditions, including inflammatory diseases.

Co-pending international patent application PCT/EP2018/065558 (published on 20 December 2018 as WO 2018/229079) describes spirocyclic oxoindoline derivatives, and analogues thereof, that are potent modulators of human IL-17 activity, and are therefore beneficial in the treatment of human ailments, including inflammatory and autoimmune disorders.

Co-pending international patent application PCT/EP2019/050594 (published on 18 July 2019 as WO 2019/138017) describes substituted fused bicyclic imidazole derivatives, including benzimidazole derivatives and analogues thereof, that are potent modulators of human IL-17 activity, and are therefore beneficial in the treatment of human ailments, including inflammatory and autoimmune disorders.

None of the prior art available to date, however, discloses or suggests the precise structural class of benzimidazole derivatives, and analogues thereof, as provided by the present invention.

The present invention provides a compound of formula (I) or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof:



(I)

wherein

A represents C₃₋₉ cycloalkyl, C₃₋₇ heterocycloalkyl or C₄₋₉ heterobicycloalkyl, any of which groups may be optionally substituted by one or more substituents;

B represents C-R² or N;

D represents C-R³ or N;

E represents C-R⁴ or N;

X represents O or S;

R⁰ represents hydrogen or C₁₋₆ alkyl;

R¹ represents -COR^a or -SO₂R^b; or R¹ represents C₁₋₆ alkyl, C₃₋₉ cycloalkyl, C₃₋₉ cycloalkyl(C₁₋₆)alkyl, C₅₋₉ spirocycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ hetero-

cycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents;

R² represents hydrogen, halogen, cyano, C₁₋₆ alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkyl-
5 sulphinyl or C₁₋₆ alkylsulphonyl;

R³ represents hydrogen, halogen, cyano, C₁₋₆ alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkyl-
sulphinyl or C₁₋₆ alkylsulphonyl;

R⁴ represents hydrogen, halogen, cyano, C₁₋₆ alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkyl-
10 sulphinyl or C₁₋₆ alkylsulphonyl;

R^a represents hydrogen; or R^a represents C₁₋₆ alkyl, C₂₋₇ alkenyl, C₃₋₉ cycloalkyl, C₃₋₉ cycloalkyl(C₁₋₆)alkyl, C₃₋₉ cycloalkylidenyl(C₁₋₆)alkyl, C₄₋₉ bicycloalkyl(C₁₋₆)alkyl, C₄₋₉ bicycloalkylidenyl(C₁₋₆)alkyl, C₅₋₉ spirocycloalkyl(C₁₋₆)alkyl, C₉₋₁₁ tricycloalkyl-
15 (C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkylidenyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents; and

R^b represents C₁₋₆ alkyl, C₂₋₇ alkenyl, C₃₋₉ cycloalkyl, C₃₋₉ cycloalkyl(C₁₋₆)alkyl, C₃₋₉ cycloalkylidenyl(C₁₋₆)alkyl, C₄₋₉ bicycloalkyl(C₁₋₆)alkyl, C₄₋₉ bicycloalkylidenyl-
20 (C₁₋₆)alkyl, C₅₋₉ spirocycloalkyl(C₁₋₆)alkyl, C₉₋₁₁ tricycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkylidenyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents.

The present invention also provides a compound of formula (I) as defined above
25 or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof, for use in therapy.

The present invention also provides a compound of formula (I) as defined above or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of disorders for which the administration of a modulator of IL-17 function is indicated.

30 The present invention also provides the use of a compound of formula (I) as defined above or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment and/or prevention of disorders for which the administration of a modulator of IL-17 function is indicated.

The present invention also provides a method for the treatment and/or prevention of disorders for which the administration of a modulator of IL-17 function is indicated which comprises administering to a patient in need of such treatment an effective amount of a compound of formula (I) as defined above or an *N*-oxide thereof, or a
5 pharmaceutically acceptable salt thereof.

Where any of the groups in the compounds of formula (I) above is stated to be optionally substituted, this group may be unsubstituted, or substituted by one or more substituents. Typically, such groups will be unsubstituted, or substituted by one, two or three substituents. Suitably, such groups will be unsubstituted, or substituted by one or
10 two substituents.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of formula (I) or of their pharmaceutically acceptable salts. Standard principles underlying the selection and preparation of pharmaceutically acceptable salts
15 are described, for example, in *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, ed. P.H. Stahl & C.G. Wermuth, Wiley-VCH, 2002. Suitable pharmaceutically acceptable salts of the compounds of formula (I) include acid addition salts which may, for example, be formed by mixing a solution of a compound of formula (I) with a solution of a pharmaceutically acceptable acid.

20 The present invention also includes within its scope co-crystals of the compounds of formula (I) above. The technical term “co-crystal” is used to describe the situation where neutral molecular components are present within a crystalline compound in a definite stoichiometric ratio. The preparation of pharmaceutical co-crystals enables modifications to be made to the crystalline form of an active pharmaceutical ingredient,
25 which in turn can alter its physicochemical properties without compromising its intended biological activity (see *Pharmaceutical Salts and Co-crystals*, ed. J. Wouters & L. Quere, RSC Publishing, 2012).

Suitable alkyl groups which may be present on the compounds of use in the invention include straight-chained and branched C₁₋₆ alkyl groups, for example C₁₋₄ alkyl
30 groups. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, 2,2-dimethylpropyl and 3-

methylbutyl. Derived expressions such as “C₁₋₆ alkoxy”, “C₁₋₆ alkylthio”, “C₁₋₆ alkylsulphonyl” and “C₁₋₆ alkylamino” are to be construed accordingly.

Suitable alkenyl groups which may be present on the compounds of use in the invention include straight-chained and branched C₂₋₇ alkenyl groups, for example C₂₋₄ alkenyl groups. Typical examples include vinyl, allyl and buten-1-yl.

The term “C₃₋₉ cycloalkyl” as used herein refers to monovalent groups of 3 to 9 carbon atoms derived from a saturated monocyclic hydrocarbon, and may comprise benzo-fused analogues thereof. Suitable C₃₋₉ cycloalkyl groups include cyclopropyl, cyclobutyl, benzocyclobutenyl, cyclopentyl, indanyl, cyclohexyl, tetrahydronaphthalenyl, cycloheptyl, benzocycloheptenyl, cyclooctyl and cyclononanyl.

The term “C₃₋₉ cycloalkylidenyl” as used herein refers to monovalent groups of 3 to 9 carbon atoms derived from a saturated monocyclic hydrocarbon, optionally comprising benzo-fused analogues thereof, attached to the remainder of the molecule via a C=C double bond. Typically, such groups include cyclobutylidenyl, cyclopentylidenyl, cyclohexylidenyl, cycloheptylidenyl, cyclooctylidenyl and cyclononylidenyl.

The term “C₄₋₉ bicycloalkyl” as used herein refers to monovalent groups of 4 to 9 carbon atoms derived from a saturated bicyclic hydrocarbon. Typical bicycloalkyl groups include bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexanyl, bicyclo[4.1.0]heptanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[3.3.0]octanyl and bicyclo[3.2.1]octanyl.

The term “C₄₋₉ bicycloalkylidenyl” as used herein refers to monovalent groups of 4 to 9 carbon atoms derived from a saturated bicyclic hydrocarbon, attached to the remainder of the molecule via a C=C double bond. Typically, such groups include bicyclo[3.1.0]hexanylidenyl, bicyclo[2.2.1]heptanylidenyl and bicyclo[3.2.1]octanylidenyl.

The term “C₅₋₉ spirocycloalkyl” as used herein refers to saturated bicyclic ring systems containing 5 to 9 carbon atoms, in which the two rings are linked by a common atom. Suitable spirocycloalkyl groups include spiro[2.3]hexanyl, spiro[2.4]heptanyl, spiro[3.3]heptanyl, spiro[3.4]octanyl, spiro[3.5]nonanyl and spiro[4.4]nonanyl.

The term “C₉₋₁₁ tricycloalkyl” as used herein refers to monovalent groups of 9 to 11 carbon atoms derived from a saturated tricyclic hydrocarbon. Typical tricycloalkyl groups include adamantanyl.

The term “aryl” as used herein refers to monovalent carbocyclic aromatic groups derived from a single aromatic ring or multiple condensed aromatic rings. Suitable aryl groups include phenyl and naphthyl, preferably phenyl.

Suitable aryl(C₁₋₆)alkyl groups include benzyl, phenylethyl, phenylpropyl and
5 naphthylmethyl.

The term “C₃₋₇ heterocycloalkyl” as used herein refers to saturated monocyclic rings containing 3 to 7 carbon atoms and at least one heteroatom selected from oxygen, sulphur and nitrogen, and may comprise benzo-fused analogues thereof. Suitable heterocycloalkyl groups include oxetanyl, azetidiny, tetrahydrofuranyl, dihydrobenzo-
10 furanyl, dihydrobenzothienyl, pyrrolidiny, indoliny, isoindoliny, oxazolidiny, thiazolidiny, isothiazolidiny, imidazolidiny, tetrahydropyranyl, chromanyl, tetrahydrothiopyranyl, piperidiny, 1,2,3,4-tetrahydroquinoliny, 1,2,3,4-tetrahydroisoquinoliny, piperaziny, 1,2,3,4-tetrahydroquinoxaliny, hexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyraziny, homopiperaziny, morpholiny, benzoxaziny, thiomorpholiny, azepanyl, oxazepanyl,
15 diazepanyl, thiadiazepanyl and azocanyl.

The term “C₃₋₇ heterocycloalkylidenyl” as used herein refers to saturated monocyclic rings containing 3 to 7 carbon atoms and at least one heteroatom selected from oxygen, sulphur and nitrogen, attached to the remainder of the molecule via a C=C double bond. Typically, such groups include tetrahydropyranylideny and piperidinylideny.

20 The term “C₄₋₉ heterobicycloalkyl” as used herein corresponds to C₄₋₉ bicycloalkyl wherein one or more of the carbon atoms have been replaced by one or more heteroatoms selected from oxygen, sulphur and nitrogen. Typical heterobicycloalkyl groups include 6-oxabicyclo[3.1.0]hexanyl, 3-azabicyclo[3.1.0]hexanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 6-azabicyclo[3.2.0]heptanyl, 6-oxabicyclo[3.1.1]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 3-
25 azabicyclo[4.1.0]heptanyl, 2-oxabicyclo[2.2.2]octanyl, quinuclidiny, 2-oxa-5-azabicyclo[2.2.2]octanyl, 8-oxabicyclo[3.2.1]octanyl, 3-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 3,6-diazabicyclo[3.2.2]nonanyl, 3-oxa-7-azabicyclo[3.3.1]nonanyl, 3,7-dioxa-9-azabicyclo[3.3.1]nonanyl and 3,9-diazabicyclo[4.2.1]nonanyl.

30 The term “heteroaryl” as used herein refers to monovalent aromatic groups containing at least 5 atoms derived from a single ring or multiple condensed rings, wherein one or more carbon atoms have been replaced by one or more heteroatoms selected from oxygen, sulphur and nitrogen. Suitable heteroaryl groups include furyl, benzofuryl,

dibenzofuryl, thienyl, benzothienyl, thieno[2,3-*c*]pyrazolyl, thieno[3,4-*b*][1,4]dioxinyl, dibenzothienyl, pyrrolyl, indolyl, pyrrolo[2,3-*b*]pyridinyl, pyrrolo[3,2-*c*]pyridinyl, pyrrolo[3,4-*b*]pyridinyl, pyrazolyl, pyrazolo[1,5-*a*]pyridinyl, pyrazolo[3,4-*d*]pyrimidinyl, pyrazolo[1,5-*a*]pyrazinyl, indazolyl, 4,5,6,7-tetrahydroindazolyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, imidazo-
5 [2,1-*b*]thiazolyl, imidazo[1,2-*a*]pyridinyl, imidazo[4,5-*b*]pyridinyl, imidazo[1,2-*b*]-pyridazinyl, purinyl, imidazo[1,2-*a*]pyrimidinyl, imidazo[1,2-*a*]pyrazinyl, oxadiazolyl, thiadiazolyl, triazolyl, [1,2,4]triazolo[1,5-*a*]pyrimidinyl, benzotriazolyl, tetrazolyl, pyridinyl, quinolinyl, isoquinolinyl, naphthyridinyl, pyridazinyl, cinnolinyl, phthalazinyl, pyrimidinyl, quinazolinyl, pyrazinyl, quinoxalinyl, pteridinyl, triazinyl and chromenyl
10 groups.

The term “halogen” as used herein is intended to include fluorine, chlorine, bromine and iodine atoms, typically fluorine, chlorine or bromine.

Where the compounds of formula (I) have one or more asymmetric centres, they
15 may accordingly exist as enantiomers. Where the compounds in accordance with the invention possess two or more asymmetric centres, they may additionally exist as diastereomers. The invention is to be understood to extend to the use of all such enantiomers and diastereomers, and to mixtures thereof in any proportion, including racemates. Formula (I) and the formulae depicted hereinafter are intended to represent all
20 individual stereoisomers and all possible mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (I) may exist as tautomers, for example keto ($\text{CH}_2\text{C}=\text{O}$) $\leftrightarrow$ enol ($\text{CH}=\text{CHOH}$) tautomers or amide ($\text{NHC}=\text{O}$) $\leftrightarrow$ hydroxyimine ($\text{N}=\text{COH}$) tautomers. Formula (I) and the formulae depicted hereinafter are intended to represent all individual tautomers and all possible mixtures thereof, unless stated or shown
25 otherwise.

It is to be understood that each individual atom present in formula (I), or in the formulae depicted hereinafter, may in fact be present in the form of any of its naturally occurring isotopes, with the most abundant isotope(s) being preferred. Thus, by way of example, each individual hydrogen atom present in formula (I), or in the formulae depicted
30 hereinafter, may be present as a ^1H , ^2H (deuterium) or ^3H (tritium) atom, preferably ^1H . Similarly, by way of example, each individual carbon atom present in formula (I), or in the formulae depicted hereinafter, may be present as a ^{12}C , ^{13}C or ^{14}C atom, preferably ^{12}C .

In a first embodiment, integer A represents optionally substituted C₃₋₉ cycloalkyl. In one aspect of that embodiment, A represents optionally substituted C₄₋₇ cycloalkyl.

In a second embodiment, integer A represents optionally substituted C₃₋₇ heterocycloalkyl. In one aspect of that embodiment, A represents optionally substituted C₄₋₆ heterocycloalkyl.

In a third embodiment, integer A represents optionally substituted C₄₋₉ heterobicycloalkyl. In one aspect of that embodiment, A represents optionally substituted C₅₋₇ heterobicycloalkyl.

Typically, integer A represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, oxetanyl, azetidyl, tetrahydrofuryl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, isothiazolidinyl, imidazolidinyl, tetrahydropyran, tetrahydrothiopyran, piperidinyl, piperazinyl, homopiperazinyl, morpholinyl, thiomorpholinyl, azepanyl, oxazepanyl, diazepanyl, thiadiazepanyl, azocanyl, 6-oxabicyclo[3.1.0]hexanyl, 6-oxabicyclo[3.1.1]heptanyl or 8-oxabicyclo[3.2.1]octanyl, any of which groups may be optionally substituted by one or more substituents.

Appositely, integer A represents oxetanyl, pyrrolidinyl, tetrahydropyran, tetrahydrothiopyran or piperidinyl, any of which groups may be optionally substituted by one or more substituents.

Suitably, integer A represents oxetanyl or tetrahydropyran, either of which groups may be optionally substituted by one or more substituents.

Typical examples of optional substituents on integer A include one, two or three substituents independently selected from C₁₋₆ alkyl, halogen, cyano, trifluoromethyl, hydroxy, oxo, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonyl, C₂₋₆ alkylcarbonyl, amino, imino, C₁₋₆ alkylamino and di(C₁₋₆)alkylamino.

Suitable examples of optional substituents on integer A include one, two or three substituents independently selected from C₁₋₆ alkyl, oxo and imino.

Typical examples of particular substituents on integer A include one, two or three substituents independently selected from methyl, fluoro, chloro, bromo, cyano, trifluoromethyl, hydroxy, oxo, methoxy, methylthio, methylsulphinyl, methylsulphonyl, acetyl, amino, imino, methylamino and dimethylamino.

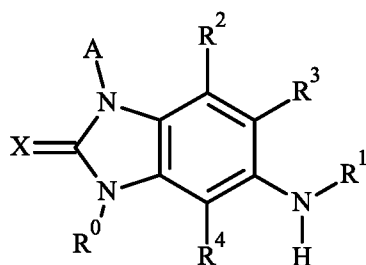
Suitable examples of particular substituents on integer A include one, two or three substituents independently selected from methyl, oxo and imino.

Typical values of integer A include oxetanyl, pyrrolidinyl, tetrahydropyranyl, (methyl)tetrahydropyranyl, tetrahydrothiopyranyl, (oxo)tetrahydrothiopyranyl, (dioxo)-tetrahydrothiopyranyl, (imino)(oxo)tetrahydrothiopyranyl and piperidinyl.

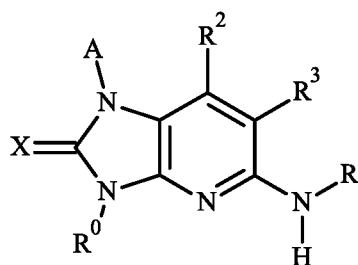
Particular values of integer A include oxetanyl and tetrahydropyranyl.

5 In one embodiment, B represents C-R². In another embodiment, B represents N.
In one embodiment, D represents C-R³. In another embodiment, D represents N.
In one embodiment, E represents C-R⁴. In another embodiment, E represents N.
In a first embodiment, B represents C-R², D represents C-R³ and E represents C-R⁴.

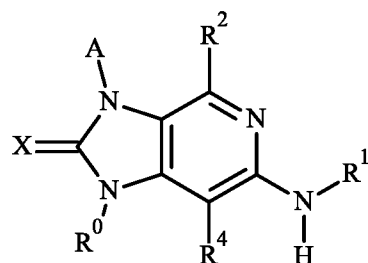
10 In a second embodiment, B represents C-R², D represents C-R³ and E represents N.
In a third embodiment, B represents C-R², D represents N and E represents C-R⁴.
In a fourth embodiment, B represents C-R², D represents N and E represents N.
In a fifth embodiment, B represents N, D represents C-R³ and E represents C-R⁴.
In a sixth embodiment, B represents N, D represents C-R³ and E represents N.
15 In a seventh embodiment, B represents N, D represents N and E represents C-R⁴.
In an eighth embodiment, B represents N, D represents N and E represents N.
Suitably, the present invention provides a compound of formula (I-1), (I-2), (I-3), (I-4) or (I-5) or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof:



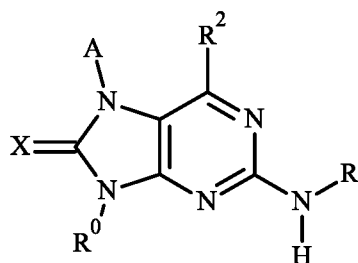
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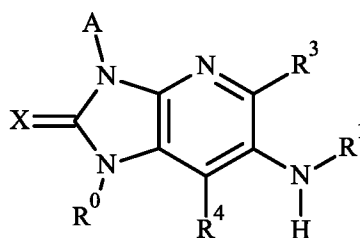
(I-2)



(I-3)



(I-4)



(I-5)

5 wherein A, X, R⁰, R¹, R², R³ and R⁴ are as defined above.

Appositely, the present invention provides a compound of formula (I-1) as defined above, or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof:

In a first embodiment, X represents O. In a second embodiment, X represents S.

In a first embodiment, R⁰ represents hydrogen. In a second embodiment, R⁰
10 represents C₁₋₆ alkyl, especially methyl.

Suitably, R⁰ represents hydrogen or methyl.

Typical examples of optional substituents on R¹ include one, two or three substituents independently selected from C₁₋₆ alkyl, halogen, cyano, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonyl, C₂₋₆
15 alkylcarbonyl, amino, C₁₋₆ alkylamino and di(C₁₋₆)alkylamino.

Typical examples of particular substituents on R¹ include one, two or three substituents independently selected from methyl, fluoro, chloro, bromo, cyano, trifluoromethyl, hydroxy, oxo, methoxy, methylthio, methylsulphinyl, methylsulphonyl, acetyl, amino, methylamino and dimethylamino.

20 Suitably, R¹ represents -COR^a.

Typically, R² represents hydrogen or halogen.

In a first embodiment, R^2 represents hydrogen. In a second embodiment, R^2 represents halogen. In a first aspect of that embodiment, R^2 represents fluoro. In a second aspect of that embodiment, R^2 represents chloro. In a third embodiment, R^2 represents cyano. In a fourth embodiment, R^2 represents C_{1-6} alkyl, especially methyl. In a fifth embodiment, R^2 represents fluoromethyl. In a sixth embodiment, R^2 represents difluoromethyl. In a seventh embodiment, R^2 represents trifluoromethyl. In an eighth embodiment, R^2 represents hydroxy. In a ninth embodiment, R^2 represents C_{1-6} alkoxy, especially methoxy. In a tenth embodiment, R^2 represents difluoromethoxy. In an eleventh embodiment, R^2 represents trifluoromethoxy. In a twelfth embodiment, R^2 represents C_{1-6} alkylsulphinyl, especially methylsulphinyl. In a thirteenth embodiment, R^2 represents C_{1-6} alkylsulphonyl, especially methylsulphonyl.

Suitably, R^2 represents hydrogen or fluoro.

Typically, R^3 represents hydrogen or halogen.

In a first embodiment, R^3 represents hydrogen. In a second embodiment, R^3 represents halogen. In a first aspect of that embodiment, R^3 represents fluoro. In a second aspect of that embodiment, R^3 represents chloro. In a third embodiment, R^3 represents cyano. In a fourth embodiment, R^3 represents C_{1-6} alkyl, especially methyl. In a fifth embodiment, R^3 represents fluoromethyl. In a sixth embodiment, R^3 represents difluoromethyl. In a seventh embodiment, R^3 represents trifluoromethyl. In an eighth embodiment, R^3 represents hydroxy. In a ninth embodiment, R^3 represents C_{1-6} alkoxy, especially methoxy. In a tenth embodiment, R^3 represents difluoromethoxy. In an eleventh embodiment, R^3 represents trifluoromethoxy. In a twelfth embodiment, R^3 represents C_{1-6} alkylsulphinyl, especially methylsulphinyl. In a thirteenth embodiment, R^3 represents C_{1-6} alkylsulphonyl, especially methylsulphonyl.

Appositely, R^3 represents hydrogen, fluoro or chloro.

Suitably, R^3 represents hydrogen or fluoro.

In a first embodiment, R^4 represents hydrogen. In a second embodiment, R^4 represents halogen. In a first aspect of that embodiment, R^4 represents fluoro. In a second aspect of that embodiment, R^4 represents chloro. In a third embodiment, R^4 represents cyano. In a fourth embodiment, R^4 represents C_{1-6} alkyl, especially methyl. In a fifth embodiment, R^4 represents fluoromethyl. In a sixth embodiment, R^4 represents difluoromethyl. In a seventh embodiment, R^4 represents trifluoromethyl. In an eighth embodiment, R^4 represents hydroxy. In a ninth embodiment, R^4 represents C_{1-6} alkoxy,

especially methoxy. In a tenth embodiment, R⁴ represents difluoromethoxy. In an eleventh embodiment, R⁴ represents trifluoromethoxy. In a twelfth embodiment, R⁴ represents C₁₋₆ alkylsulphinyl, especially methylsulphinyl. In a thirteenth embodiment, R⁴ represents C₁₋₆ alkylsulphonyl, especially methylsulphonyl.

5 In a particular embodiment, R^a is other than hydrogen.

Typically, R^a represents C₃₋₉ cycloalkyl(C₁₋₆)alkyl, which group may be optionally substituted by one or more substituents.

Typical values of R^a include cyclohexylmethyl and cyclooctylmethyl, either of which groups may be optionally substituted by one or more substituents.

10 Suitable values of R^a include cyclooctylmethyl, which group may be optionally substituted by one or more substituents.

Favoured examples of optional substituents on R^a include one, two or three substituents independently selected from halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl, phenyl, hydroxy, oxo, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxy carbonylamino, C₁₋₆ alkylsulfonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxy carbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulfonyl, C₁₋₆ alkylamino-sulfonyl, di(C₁₋₆)alkylaminosulfonyl, -R^{5a}, -NHCOR⁶, -NHS(O)₂R⁶, -R⁷, -NHR⁷ and
20 -CONHR⁷, wherein R^{5a}, R⁶ and R⁷ are as defined below.

Selected examples of optional substituents on R^a include one, two or three substituents independently selected from C₁₋₆ alkyl and -NHCOR⁶, wherein R⁶ is as defined below.

Favoured examples of specific substituents on R^a include one, two or three
25 substituents independently selected from fluoro, chloro, bromo, cyano, nitro, methyl, ethyl, isopropyl, *tert*-butyl, trifluoromethyl, trifluoroethyl, phenyl, hydroxy, oxo, methoxy, isopropoxy, *tert*-butoxy, difluoromethoxy, trifluoromethoxy, methylthio, methylsulfinyl, methylsulfonyl, amino, methylamino, *tert*-butylamino, dimethylamino, acetyl amino, methoxycarbonylamino, methylsulfonylamino, formyl, acetyl, carboxy,
30 methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl, dimethylaminosulfonyl, -R^{5a}, -NHCOR⁶, -NHS(O)₂R⁶, -R⁷, -NHR⁷ and -CONHR⁷, wherein R^{5a}, R⁶ and R⁷ are as defined below.

Selected examples of specific substituents on R^a include one, two or three substituents independently selected from methyl and -NHCOR⁶, wherein R⁶ is as defined below.

Typically, R^b represents C₃₋₉ cycloalkyl(C₁₋₆)alkyl or C₃₋₉ cycloalkylidenyl(C₁₋₆)alkyl, either of which groups may be optionally substituted by one or more substituents.

Suitable values of R^b include cyclohexylmethyl, cyclooctylmethyl and benzo-cyclobutylidenylmethyl, any of which groups may be optionally substituted by one or more substituents.

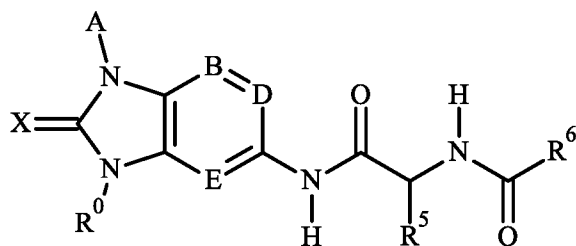
Favoured examples of optional substituents on R^b include one, two or three substituents independently selected from halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl, phenyl, hydroxy, oxo, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxycarbonylamino, C₁₋₆ alkylsulfonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆)alkylaminosulfonyl, -R^{5a}, -NHCOR⁶, -NHS(O)₂R⁶, -R⁷, -NHR⁷ and -CONHR⁷, wherein R^{5a}, R⁶ and R⁷ are as defined below.

Selected examples of optional substituents on R^b include one, two or three substituents independently selected from halogen, C₁₋₆ alkyl and -NHCOR⁶, wherein R⁶ is as defined below.

Favoured examples of specific substituents on R^b include one, two or three substituents independently selected from fluoro, chloro, bromo, cyano, nitro, methyl, ethyl, isopropyl, *tert*-butyl, trifluoromethyl, trifluoroethyl, phenyl, hydroxy, oxo, methoxy, isopropoxy, *tert*-butoxy, difluoromethoxy, trifluoromethoxy, methylthio, methylsulfinyl, methylsulfonyl, amino, methylamino, *tert*-butylamino, dimethylamino, acetylamino, methoxycarbonylamino, methylsulfonylamino, formyl, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl, dimethylaminosulfonyl, -R^{5a}, -NHCOR⁶, -NHS(O)₂R⁶, -R⁷, -NHR⁷ and -CONHR⁷, wherein R^{5a}, R⁶ and R⁷ are as defined below.

Selected examples of specific substituents on R^b include one, two or three substituents independently selected from chloro, methyl and -NHCOR⁶, wherein R⁶ is as defined below.

A particular sub-class of compounds according to the invention is represented by the compounds of formula (IA) and *N*-oxides thereof, and pharmaceutically acceptable salts thereof:



(IA)

5

wherein

A, B, D, E, X and R⁰ are as defined above;

R⁵ represents hydrogen; or R⁵ represents C₁₋₅ alkyl, C₃₋₉ cycloalkyl, C₃₋₉ cyclo-alkyl(C₁₋₅)alkyl, C₄₋₉ bicycloalkyl, C₄₋₉ bicycloalkyl(C₁₋₅)alkyl, C₅₋₉ spirocycloalkyl, C₅₋₉ spirocycloalkyl(C₁₋₅)alkyl, C₉₋₁₁ tricycloalkyl, C₉₋₁₁ tricycloalkyl(C₁₋₅)alkyl, aryl, aryl-(C₁₋₅)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₅)alkyl, heteroaryl or heteroaryl(C₁₋₅)alkyl, any of which groups may be optionally substituted by one or more substituents;

R⁶ represents -NR^{6a}R^{6b} or -OR^{6c}; or R⁶ represents C₁₋₉ alkyl, C₃₋₉ cycloalkyl, C₃₋₉ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl-(C₁₋₆)alkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl or spiro[(C₃₋₇)heterocycloalkyl][heteroaryl], any of which groups may be optionally substituted by one or more substituents;

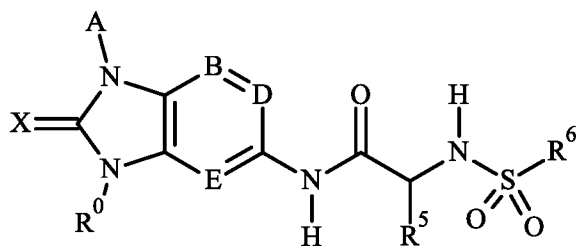
R^{6a} represents hydrogen; or R^{6a} represents C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cyclo-alkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)-alkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl or spiro[(C₃₋₇)heterocycloalkyl][heteroaryl], any of which groups may be optionally substituted by one or more substituents;

R^{6b} represents hydrogen or C₁₋₆ alkyl; and

R^{6c} represents C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents.

25

A second sub-class of compounds according to the invention is represented by the compounds of formula (IB) and *N*-oxides thereof, and pharmaceutically acceptable salts thereof:



(IB)

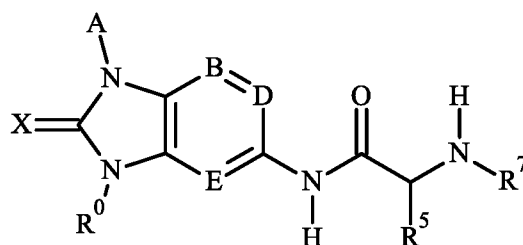
5

wherein

A, B, D, E, X, R⁰, R⁵ and R⁶ are as defined above.

A third sub-class of compounds according to the invention is represented by the compounds of formula (IC) and *N*-oxides thereof, and pharmaceutically acceptable salts thereof:

10



(IC)

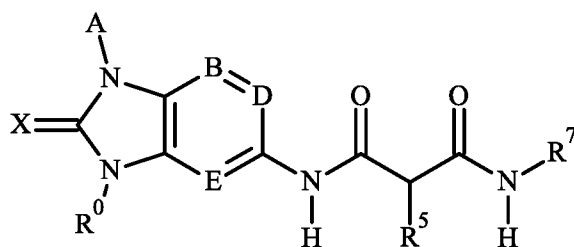
15 wherein

A, B, D, E, X, R⁰ and R⁵ are as defined above; and

R⁷ represents aryl, heteroaryl or spiro[(C₃₋₇)heterocycloalkyl][heteroaryl], any of which groups may be optionally substituted by one or more substituents.

A fourth sub-class of compounds according to the invention is represented by the compounds of formula (ID) and *N*-oxides thereof, and pharmaceutically acceptable salts thereof:

20

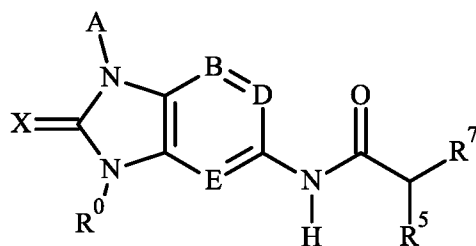


(ID)

wherein

A, B, D, E, X, R⁰, R⁵ and R⁷ are as defined above.

- 5 A fifth sub-class of compounds according to the invention is represented by the compounds of formula (IE) and *N*-oxides thereof, and pharmaceutically acceptable salts thereof:



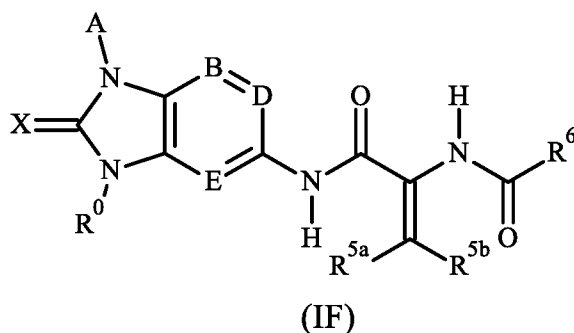
(IE)

10

wherein

A, B, D, E, X, R⁰, R⁵ and R⁷ are as defined above.

- A sixth sub-class of compounds according to the invention is represented by the compounds of formula (IF) and *N*-oxides thereof, and pharmaceutically acceptable salts thereof:
- 15



wherein

A, B, D, E, X, R^0 and R^6 are as defined above;

5 R^{5a} represents C₃₋₇ cycloalkyl, C₄₋₉ bicycloalkyl, aryl, C₃₋₇ heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents; and

R^{5b} represents hydrogen or C₁₋₆ alkyl; or

10 R^{5a} and R^{5b}, when taken together with the carbon atom to which they are both attached, represent C₃₋₇ cycloalkyl, C₄₋₉ bicycloalkyl or C₃₋₇ heterocycloalkyl, any of which groups may be optionally substituted by one or more substituents.

Typically, R⁵ represents hydrogen; or R⁵ represents C₁₋₅ alkyl, C₃₋₉ cycloalkyl, C₃₋₉ cycloalkyl(C₁₋₅)alkyl, C₄₋₉ bicycloalkyl, C₄₋₉ bicycloalkyl(C₁₋₅)alkyl, C₅₋₉ spiro-cycloalkyl, C₉₋₁₁ tricycloalkyl, C₉₋₁₁ tricycloalkyl(C₁₋₅)alkyl, aryl, aryl(C₁₋₅)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₅)alkyl or heteroaryl(C₁₋₅)alkyl, any of which groups may be optionally substituted by one or more substituents.

Suitably, R⁵ represents C₃₋₉ cycloalkyl, which group may be optionally substituted by one or more substituents.

In a first embodiment, R⁵ represents hydrogen. In a second embodiment, R⁵ represents optionally substituted C₁₋₅ alkyl. In a third embodiment, R⁵ represents optionally substituted C₃₋₉ cycloalkyl. In a fourth embodiment, R⁵ represents optionally substituted C₃₋₉ cycloalkyl(C₁₋₅)alkyl. In a fifth embodiment, R⁵ represents optionally substituted C₄₋₉ bicycloalkyl. In a sixth embodiment, R⁵ represents optionally substituted C₄₋₉ bicycloalkyl(C₁₋₅)alkyl. In a seventh embodiment, R⁵ represents optionally substituted C₅₋₉ spirocycloalkyl. In an eighth embodiment, R⁵ represents optionally substituted C₅₋₉ spirocycloalkyl(C₁₋₅)alkyl. In a ninth embodiment, R⁵ represents optionally substituted C₉₋₁₁ tricycloalkyl. In a tenth embodiment, R⁵ represents optionally substituted C₉₋₁₁ tricycloalkyl(C₁₋₅)alkyl. In an eleventh embodiment, R⁵ represents

optionally substituted aryl. In a twelfth embodiment, R⁵ represents optionally substituted aryl(C₁₋₅)alkyl. In a thirteenth embodiment, R⁵ represents optionally substituted C₃₋₇ heterocycloalkyl. In a fourteenth embodiment, R⁵ represents optionally substituted C₃₋₇ heterocycloalkyl(C₁₋₅)alkyl. In a fifteenth embodiment, R⁵ represents optionally substituted heteroaryl. In a sixteenth embodiment, R⁵ represents optionally substituted heteroaryl(C₁₋₅)alkyl.

In a particular embodiment, R⁵ is other than hydrogen.

Typical values of R⁵ include methyl, cyclobutyl, benzocyclobutenyl, cyclopentyl, indanyl, cyclohexyl, tetrahydronaphthalenyl, cycloheptyl, benzocycloheptenyl, cyclooctyl, cyclononanyl, cyclobutylmethyl, cyclobutylethyl, bicyclo[3.1.0]hexanyl, bicyclo[2.2.1]-heptanyl, bicyclo[3.3.0]octanyl, bicyclo[3.2.1]octanyl, bicyclo[1.1.1]pentanylmethyl, spiro[3.3]heptanyl, adamantanyl, adamantanylmethyl, phenyl, benzyl, phenylethyl, phenylpropyl, tetrahydropyranyl, azocanyl, dihydrobenzofuranylmethyl and pyrrolylethyl, any of which groups may be optionally substituted by one or more substituents.

Suitable values of R⁵ include cyclohexyl and cyclooctyl, either of which groups may be optionally substituted by one or more substituents.

Apposite values of R⁵ include cyclooctyl, which group may be optionally substituted by one or more substituents.

Typical examples of optional substituents on R⁵ include one, two or three substituents independently selected from halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl, phenyl, hydroxy, oxo, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxy carbonylamino, C₁₋₆ alkylsulfonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxy carbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulfonyl, C₁₋₆ alkylamino-sulfonyl and di(C₁₋₆)alkylaminosulfonyl.

Suitable examples of optional substituents on R⁵ include one, two or three substituents independently selected from halogen, cyano, C₁₋₆ alkyl, trifluoromethyl, phenyl, hydroxy, C₁₋₆ alkoxy and aminocarbonyl, especially C₁₋₆ alkyl.

Typical examples of specific substituents on R⁵ include one, two or three substituents independently selected from fluoro, chloro, bromo, cyano, nitro, methyl, ethyl, isopropyl, *tert*-butyl, trifluoromethyl, trifluoroethyl, phenyl, hydroxy, oxo, methoxy, isopropoxy, *tert*-butoxy, difluoromethoxy, trifluoromethoxy, methylthio,

methysulfinyl, methysulfonyl, amino, methylamino, *tert*-butylamino, dimethylamino, acetilamino, methoxycarbonylamino, methysulfonylamino, formyl, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, aminocarbonyl, methylamino-carbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl and dimethyl-
5 aminosulfonyl.

Suitable examples of specific substituents on R⁵ include one, two or three substituents independently selected from fluoro, chloro, bromo, cyano, methyl, trifluoro-methyl, phenyl, hydroxy, methoxy, isopropoxy, *tert*-butoxy and aminocarbonyl, especially methyl.

10 Apposite values of R⁵ include hydrogen, *tert*-butoxymethylcyclobutyl, methylcyclobutyl, dimethylcyclobutyl, phenylcyclobutyl, benzocyclobutenyl, cyclopentyl, methylcyclopentyl, indanyl, cyclohexyl, difluorocyclohexyl, methylcyclohexyl, dimethylcyclohexyl, trifluoromethylcyclohexyl, tetrahydronaphthalenyl, cycloheptyl, benzocycloheptenyl, cyclooctyl, cyclononanyl, cyclobutylmethyl, difluorocyclobutyl-
15 methyl, dimethylcyclobutylmethyl, cyclobutylethyl, bicyclo[3.1.0]hexanyl, bicyclo[2.2.1]-heptanyl, bicyclo[3.3.0]octanyl, bicyclo[3.2.1]octanyl, bicyclo[1.1.1]pentanylmethyl, spiro[3.3]heptanyl, adamantanyl, adamantanylmethyl, (chloro)(fluoro)phenyl, (fluoro)-(methyl)phenyl, fluorobenzyl, chlorobenzyl, (chloro)(fluoro)benzyl, (bromo)(chloro)-benzyl, (chloro)(isopropoxy)benzyl, phenylethyl, chlorophenylethyl, phenylpropyl,
20 tetrahydropyranyl, tetramethyltetrahydropyranyl, azocanyl, dihydrobenzofuranylmethyl and methylpyrrolylethyl.

Favoured values of R⁵ include 4-methylcyclohexyl and cyclooctyl. In a first embodiment, R⁵ represents 4-methylcyclohexyl. In a second embodiment, R⁵ represents cyclooctyl.

25 In a first embodiment, R^{5a} represents optionally substituted C₃₋₇ cycloalkyl. In a second embodiment, R^{5a} represents optionally substituted C₄₋₉ bicycloalkyl. In a third embodiment, R^{5a} represents optionally substituted aryl. In a fourth embodiment, R^{5a} represents optionally substituted C₃₋₇ heterocycloalkyl. In a fifth embodiment, R^{5a} represents optionally substituted heteroaryl.

30 Typical values of R^{5a} include cyclobutyl, cyclopentyl, bicyclo[1.1.1]pentanyl, phenyl, dihydrobenzofuranyl and pyrrolyl, any of which groups may be optionally substituted by one or more substituents.

Typical examples of optional substituents on R^{5a} include C₁₋₆ alkyl, halogen, cyano, trifluoromethyl, trifluoroethyl, phenyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, C₂₋₆ alkylcarbonyl, amino, C₁₋₆ alkylamino and di(C₁₋₆)alkylamino.

5 Suitable examples of optional substituents on R^{5a} include C₁₋₆ alkyl and halogen.

Typical examples of particular substituents on R^{5a} include methyl, fluoro, chloro, bromo, cyano, trifluoromethyl, trifluoroethyl, phenyl, hydroxy, methoxy, methylthio, methylsulfinyl, methylsulfonyl, acetyl, amino, methylamino and dimethylamino.

Suitable examples of particular substituents on R^{5a} include methyl and chloro.

10 Suitable values of R^{5a} include cyclobutyl, cyclopentyl, bicyclo[1.1.1]pentanyl, phenyl, chlorophenyl, dihydrobenzofuranyl and methylpyrrolyl.

Suitably, R^{5b} represents hydrogen, methyl or ethyl.

In a first embodiment, R^{5b} represents hydrogen. In a second embodiment, R^{5b} represents C₁₋₆ alkyl, especially methyl or ethyl.

15 Alternatively, R^{5a} and R^{5b}, when taken together with the carbon atom to which they are both attached, may represent C₃₋₇ cycloalkyl, C₄₋₉ bicycloalkyl or C₃₋₇ heterocycloalkyl, any of which groups may be unsubstituted, or substituted by one or more substituents, typically by one or two substituents.

20 In a first embodiment, R^{5a} and R^{5b}, when taken together with the carbon atom to which they are both attached, may suitably represent optionally substituted C₃₋₇ cycloalkyl. Examples include cyclobutyl, benzocyclobutenyl, cyclopentyl, indanyl, cyclohexyl, tetrahydronaphthalenyl, cycloheptanyl, benzocycloheptenyl, cyclooctanyl and cyclononanyl, any of which groups may be optionally substituted by one or more substituents.

25 In a second embodiment, R^{5a} and R^{5b}, when taken together with the carbon atom to which they are both attached, may suitably represent optionally substituted C₄₋₉ bicycloalkyl. Examples include bicyclo[3.1.0]hexanyl, bicyclo[2.2.1]heptanyl and bicyclo[3.2.1]octanyl, any of which groups may be optionally substituted by one or more substituents.

30 In a third embodiment, R^{5a} and R^{5b}, when taken together with the carbon atom to which they are both attached, may suitably represent optionally substituted C₃₋₇ heterocycloalkyl. Examples include tetrahydropyranyl and piperidinyl, either of which groups may be optionally substituted by one or more substituents.

Typical examples of optional substituents on such groups include C₁₋₆ alkyl, halogen, cyano, trifluoromethyl, trifluoroethyl, phenyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, C₂₋₆ alkylcarbonyl, amino, C₁₋₆ alkylamino and di(C₁₋₆)alkylamino.

5 Suitable examples of optional substituents on such groups include C₁₋₆ alkyl, halogen, trifluoromethyl, trifluoroethyl, phenyl and C₁₋₆ alkoxy, especially halogen.

Typical examples of particular substituents on such groups include methyl, fluoro, chloro, bromo, cyano, trifluoromethyl, trifluoroethyl, phenyl, hydroxy, methoxy, methylthio, methylsulfinyl, methylsulfonyl, acetyl, amino, methylamino and
10 dimethylamino.

Suitable examples of particular substituents on such groups include methyl, chloro, trifluoromethyl, trifluoroethyl, phenyl and methoxy, especially chloro.

Typical values of R^{5a} and R^{5b}, when taken together with the carbon atom to which they are both attached, include methylcyclobutyl, dimethylcyclobutyl, phenylcyclobutyl,
15 benzocyclobutenyl, methylbenzocyclobutenyl, chlorobenzocyclobutenyl, methoxybenzocyclobutenyl, cyclopentyl, methylcyclopentyl, indanyl, chloroindanyl, cyclohexyl, methylcyclohexyl, dimethylcyclohexyl, trifluoromethylcyclohexyl, tetrahydronaphthalenyl, cycloheptanyl, benzocycloheptenyl, cyclooctanyl, cyclononanyl, bicyclo[3.1.0]hexanyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl, tetramethyl-
20 tetrahydropyranyl and trifluoroethylpiperidinyl.

Suitable values of R^{5a} and R^{5b}, when taken together with the carbon atom to which they are both attached, include chlorobenzocyclobutenyl.

Typically, R⁶ represents -NR^{6a}R^{6b} or -OR^{6c}; or R⁶ represents C₁₋₉ alkyl, aryl, C₃₋₇ heterocycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl or spiro[(C₃₋₇)heterocycloalkyl]-
25 [heteroaryl], any of which groups may be optionally substituted by one or more substituents.

Appositely, R⁶ represents aryl or heteroaryl, either of which groups may be optionally substituted by one or more substituents.

Suitably, R⁶ represents heteroaryl, which group may be optionally substituted by
30 one or more substituents.

In a first embodiment, R⁶ represents optionally substituted C₁₋₆ alkyl. In a second embodiment, R⁶ represents optionally substituted C₃₋₉ cycloalkyl. In a third embodiment, R⁶ represents optionally substituted C₃₋₉ cycloalkyl(C₁₋₆)alkyl. In a fourth embodiment,

R^6 represents optionally substituted aryl. In a fifth embodiment, R^6 represents optionally substituted aryl(C_{1-6})alkyl. In a sixth embodiment, R^6 represents optionally substituted C_{3-7} heterocycloalkyl. In a seventh embodiment, R^6 represents optionally substituted C_{3-7} heterocycloalkyl(C_{1-6})alkyl. In an eighth embodiment, R^6 represents optionally substituted heteroaryl. In a ninth embodiment, R^6 represents optionally substituted heteroaryl(C_{1-6})alkyl. In a tenth embodiment, R^6 represents optionally substituted spiro[(C_{3-7})heterocycloalkyl][heteroaryl]. In an eleventh embodiment, R^6 represents $-NR^{6a}R^{6b}$. In a twelfth embodiment, R^6 represents $-OR^{6c}$.

Typical values of R^6 include $-NR^{6a}R^{6b}$ and $-OR^{6c}$; and methyl, *tert*-butyl, heptanyl, phenyl, pyrrolidinyl, indolyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolyl, pyrazolyl, pyrazolo[1,5-*a*]pyridinyl, 4,5,6,7-tetrahydropyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyridinylmethyl or spiro[tetrahydrofuran]-[indole], any of which groups may be optionally substituted by one or more substituents.

Apposite values of R^6 include pyrazolyl and isoxazolyl, either of which groups may be optionally substituted by one or more substituents.

Suitable values of R^6 include isoxazolyl, which group may be optionally substituted by one or more substituents.

Typical examples of optional substituents on R^6 include one, two or three substituents independently selected from halogen, cyano, nitro, C_{1-6} alkyl, difluoromethyl, trifluoromethyl, difluoroethyl, trifluoroethyl, trifluoropropyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, phenyl, fluorophenyl, hydroxy, hydroxy(C_{1-6})alkyl, oxo, C_{1-6} alkoxy, C_{1-6} alkoxy(C_{1-6})alkyl, difluoromethoxy, trifluoromethoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, (C_{1-6})alkylsulfonyl(C_{1-6})alkyl, C_{1-6} alkylsulfonyloxy, amino, amino(C_{1-6})alkyl, C_{1-6} alkylamino, di(C_{1-6})alkylamino, di(C_{1-6})alkylamino(C_{1-6})alkyl, pyrrolidinyl, dioxoisothiazolidinyl, tetrahydropyranyl, morpholinyl, piperazinyl, C_{2-6} alkylcarbonylamino, C_{2-6} alkylcarbonylamino(C_{1-6})alkyl, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulfonylamino, formyl, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, amino-carbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6})alkylaminosulfonyl and di(C_{1-6})alkylsulfoximinyl.

Suitable examples of optional substituents on R^6 include one, two or three substituents independently selected from C_{1-6} alkyl.

Typical examples of specific substituents on R⁶ include one, two or three substituents independently selected from fluoro, chloro, bromo, cyano, nitro, methyl, ethyl, *n*-propyl, isopropyl, 2-methylpropyl, butan-2-yl, *tert*-butyl, difluoromethyl, trifluoromethyl, difluoroethyl, trifluoroethyl, trifluoropropyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, phenyl, fluorophenyl, hydroxy, hydroxymethyl, hydroxyethyl, oxo, methoxy, *tert*-butoxy, methoxymethyl, methoxyethyl, difluoromethoxy, trifluoromethoxy, methylthio, methylsulfinyl, methylsulfonyl, methylsulfonylmethyl, methylsulfonyloxy, amino, aminomethyl, aminoethyl, aminoisopropyl, methylamino, *tert*-butylamino, dimethylamino, dimethylaminoethyl, pyrrolidiny, dioxoisothiazolidiny, tetrahydro-
 5 pyran, morpholinyl, piperazinyl, acetyl amino, acetyl aminoethyl, methoxycarbonyl amino, methylsulfonylamino, formyl, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl, dimethylaminosulfonyl and dimethylsulfoximinyl.

Suitable examples of specific substituents on R⁶ include one, two or three substituents independently selected from methyl and ethyl, especially methyl.

Illustrative values of R⁶ include -NR^{6a}R^{6b}, -OR^{6c}, methyl, *tert*-butyl, hydroxyheptanyl, phenyl, fluorophenyl, methylsulfonylphenyl, methylsulfonylmethylphenyl, dioxoisothiazolidinylphenyl, methylsulfonylaminophenyl, dimethylsulfoximinylphenyl, pyrrolidiny, methylpyrrolidiny, indoliny, piperidiny, morpholinyl, dioxo-
 20 thiomorpholinyl, methylpiperazinyl, methylpyrrol, methylpyrazolyl, dimethylpyrazolyl, ethylpyrazolyl, (ethyl)(fluoro)pyrazolyl, (ethyl)(methyl)pyrazolyl, *n*-propylpyrazolyl, isopropylpyrazolyl, 2-methylpropylpyrazolyl, butan-2-ylpyrazolyl, difluoromethylpyrazolyl, (difluoromethyl)(methyl)pyrazolyl, difluoroethylpyrazolyl, trifluoroethylpyrazolyl, trifluoropropylpyrazolyl, cyclopropylpyrazolyl, cyclobutylpyrazolyl, cyclopropylmethylpyrazolyl, hydroxyethylpyrazolyl, methoxyethylpyrazolyl, dimethyl-
 25 aminoethylpyrazolyl, tetrahydropyranylpyrazolyl, (methyl)(tetrahydropyranyl)pyrazolyl, pyrazolo[1,5-*a*]pyridiny, methyl-4,5,6,7-tetrahydropyrazolyl, oxazolyl, methyloxazolyl, ethyloxazolyl, isoxazolyl, methylisoxazolyl, dimethylisoxazolyl, ethylisoxazolyl, isopropylisoxazolyl, *tert*-butylisoxazolyl, trifluoromethylisoxazolyl, cyclopropylisoxazolyl, cyclobutylisoxazolyl, methoxymethylisoxazolyl, aminomethylisoxazolyl, aminoisopropylisoxazolyl, thiazolyl, methylthiazolyl, dimethylthiazolyl, isothiazolyl, methylisothiazolyl, methylimidazolyl, methyloxadiazolyl, ethyloxadiazolyl, methylthiadiazolyl, methyltriazolyl, dimethyltriazolyl, ethyltriazolyl, methyltetrazolyl, pyridiny,

methylpyridinyl, pyridazinyl, pyrimidinyl, methylpyrimidinyl, pyridinylmethyl, amino-pyridinylmethyl and spiro[tetrahydrofuran][oxoindole].

Apposite values of R⁶ include methylpyrazolyl, ethylpyrazolyl, methylisoxazolyl and ethylisoxazolyl.

5 Representative values of R⁶ include methylisoxazolyl.

Typically, R^{6a} represents C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl or spiro[(C₃₋₇)heterocycloalkyl][heteroaryl], any of which groups may be optionally substituted by one or more substituents.

In a first embodiment, R^{6a} represents hydrogen. In a second embodiment, R^{6a}
 10 represents optionally substituted C₁₋₆ alkyl. In a first aspect of that embodiment, R^{6a} represents represents unsubstituted C₁₋₆ alkyl, especially methyl. In a second aspect of that embodiment, R^{6a} represents represents monosubstituted, disubstituted or trisubstituted C₁₋₆ alkyl. In a third embodiment, R^{6a} represents optionally substituted C₃₋₇ cycloalkyl. In a fourth embodiment, R^{6a} represents optionally substituted C₃₋₇ cycloalkyl(C₁₋₆)alkyl. In a
 15 fifth embodiment, R^{6a} represents optionally substituted aryl. In a sixth embodiment, R^{6a} represents optionally substituted aryl(C₁₋₆)alkyl. In a seventh embodiment, R^{6a} represents optionally substituted C₃₋₇ heterocycloalkyl. In an eighth embodiment, R^{6a} represents optionally substituted C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl. In a ninth embodiment, R^{6a} represents optionally substituted heteroaryl. In a tenth embodiment, R^{6a} represents
 20 optionally substituted heteroaryl(C₁₋₆)alkyl. In an eleventh embodiment, R^{6a} represents optionally substituted spiro[(C₃₋₇)heterocycloalkyl][heteroaryl].

Typical values of R^{6a} include methyl, ethyl, *n*-propyl, isopropyl, 2,2-dimethyl-propyl, cyclohexyl, benzyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl and spiro[tetrahydrofuran][indole], any of which groups may be optionally substituted by
 25 one or more substituents.

Typical examples of optional substituents on R^{6a} include one, two or three substituents independently selected from halogen, cyano, nitro, C₁₋₆ alkyl, trifluoro-methyl, phenyl, fluorophenyl, hydroxy, hydroxy(C₁₋₆)alkyl, oxo, C₁₋₆ alkoxy, difluoro-methoxy, trifluoromethoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, amino,
 30 amino(C₁₋₆)alkyl, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, pyrrolidinyl, morpholinyl, piperazinyl, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkylcarbonylamino(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonylamino, C₁₋₆ alkylsulfonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆

alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl and di(C₁₋₆)alkylaminosulfonyl.

Selected examples of optional substituents on R^{6a} include one, two or three substituents independently selected from trifluoromethyl, oxo and C₁₋₆ alkoxy.

5 Typical examples of specific substituents on R^{6a} include one, two or three substituents independently selected from fluoro, chloro, bromo, cyano, nitro, methyl, ethyl, isopropyl, *tert*-butyl, trifluoromethyl, phenyl, fluorophenyl, hydroxy, hydroxymethyl, oxo, methoxy, *tert*-butoxy, difluoromethoxy, trifluoromethoxy, methylthio, methylsulfinyl, methylsulfonyl, amino, aminomethyl, aminoethyl, methyl-
10 amino, *tert*-butylamino, dimethylamino, pyrrolidinyl, morpholinyl, piperazinyl, acetyl- amino, acetylaminoethyl, methoxycarbonylamino, methylsulfonylamino, formyl, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, aminocarbonyl, methyl- aminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl and dimethylaminosulfonyl.

15 Selected examples of specific substituents on R^{6a} include one, two or three substituents independently selected from trifluoromethyl, oxo and methoxy.

Selected values of R^{6a} include methyl, ethyl, trifluoroethyl, methoxyethyl, *n*-propyl, isopropyl, 2,2-dimethylpropyl, cyclohexyl, benzyl, tetrahydrofuranyl, tetrahydropyranyl, oxotetrahydrothiopyranyl and spiro[tetrahydrofuran][oxoindole].

20 Suitably, R^{6b} represents hydrogen, methyl, ethyl, *n*-propyl or isopropyl.

Typically, R^{6b} represents hydrogen or methyl.

In a first embodiment, R^{6b} represents hydrogen. In a second embodiment, R^{6b} represents C₁₋₆ alkyl. In a particular aspect of that embodiment, R^{6b} represents methyl, ethyl, *n*-propyl or isopropyl, especially methyl.

25 Typically, R^{6c} represents C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents.

In a first embodiment, R^{6c} represents optionally substituted C₁₋₆ alkyl. In a second embodiment, R^{6c} represents optionally substituted C₃₋₇ cycloalkyl. In a third embodiment,
30 R^{6c} represents optionally substituted C₃₋₇ cycloalkyl(C₁₋₆)alkyl. In a fourth embodiment, R^{6c} represents optionally substituted aryl. In a fifth embodiment, R^{6c} represents optionally substituted aryl(C₁₋₆)alkyl. In a sixth embodiment, R^{6c} represents optionally substituted C₃₋₇ heterocycloalkyl. In a seventh embodiment, R^{6c} represents optionally substituted C₃₋₇

heterocycloalkyl(C₁₋₆)alkyl. In an eighth embodiment, R^{6c} represents optionally substituted heteroaryl. In a ninth embodiment, R^{6c} represents optionally substituted heteroaryl(C₁₋₆)alkyl.

Typical values of R^{6c} include methyl, ethyl, isopropyl, 2-methylpropyl, *tert*-butyl, 2,2-dimethylpropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclohexylmethyl, oxetanyl, azetidiny, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyranylmethyl, pyrazolymethyl, oxazolymethyl, isoxazolymethyl, imidazolymethyl and pyrazinylmethyl, any of which groups may be optionally substituted by one or more substituents.

Typical examples of optional substituents on R^{6c} include one, two or three substituents independently selected from halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, phenyl, fluorophenyl, hydroxy, hydroxy(C₁₋₆)alkyl, oxo, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, amino, amino(C₁₋₆)alkyl, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, pyrrolidinyl, morpholinyl, piperazinyl, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkylcarbonylamino(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonylamino, C₁₋₆ alkylsulfonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxy carbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl and di(C₁₋₆)alkylaminosulfonyl.

Suitable examples of optional substituents on R^{6c} include one, two or three substituents independently selected from C₁₋₆ alkyl, trifluoromethyl, C₁₋₆ alkoxy and C₂₋₆ alkoxy carbonyl.

Typical examples of specific substituents on R^{6c} include one, two or three substituents independently selected from fluoro, chloro, bromo, cyano, nitro, methyl, ethyl, isopropyl, *tert*-butyl, trifluoromethyl, phenyl, fluorophenyl, hydroxy, hydroxymethyl, oxo, methoxy, *tert*-butoxy, difluoromethoxy, trifluoromethoxy, methylthio, methylsulfinyl, methylsulfonyl, amino, aminomethyl, aminoethyl, methylamino, *tert*-butylamino, dimethylamino, pyrrolidinyl, morpholinyl, piperazinyl, acetylamino, acetylaminoethyl, methoxycarbonylamino, methylsulfonylamino, formyl, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl and dimethylaminosulfonyl.

Suitable examples of specific substituents on R^{6c} include one, two or three substituents independently selected from methyl, trifluoromethyl, methoxy and *tert*-butoxycarbonyl.

Typical values of R^{6c} include methyl, trifluoroethyl, methoxyethyl, isopropyl, 2-methylpropyl, *tert*-butyl, 2,2-dimethylpropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclohexylmethyl, oxetanyl, methyloxetanyl, azetidiny, *tert*-butoxycarbonylazetidiny, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyranylmethyl, methylpyrazolylmethyl, oxazolylmethyl, isoxazolylmethyl, methylimidazolylmethyl and pyrazinylmethyl.

10 In a first embodiment, R⁷ represents aryl, which group may be optionally substituted by one or more substituents. In a second embodiment, R⁷ represents heteroaryl, which group may be optionally substituted by one or more substituents. In a third embodiment, R⁷ represents spiro[(C₃₋₇)heterocycloalkyl][heteroaryl], which group may be optionally substituted by one or more substituents.

15 Typical values of R⁷ include phenyl, pyrazolo[1,5-*a*]pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, imidazo[1,2-*b*]pyridazinyl, purinyl, pyridinyl, pyridazinyl, cinnolinyl, pyrimidinyl, pyrazinyl and spiro[tetrahydropyranyl][indole], any of which groups may be optionally substituted by one or more substituents.

Typical examples of optional substituents on R⁷ include one, two or three substituents independently selected from halogen, cyano, nitro, C₁₋₆ alkyl, difluoromethyl, trifluoromethyl, phenyl, fluorophenyl, hydroxy, hydroxy(C₁₋₆)alkyl, oxo, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, amino, amino(C₁₋₆)alkyl, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, pyrrolidinyl, morpholinyl, piperazinyl, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkylcarbonylamino(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonylamino, C₁₋₆ alkylsulfonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxy carbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl and di(C₁₋₆)alkylaminosulfonyl.

Suitable examples of optional substituents on R⁷ include one, two or three substituents independently selected from halogen, cyano, C₁₋₆ alkyl, difluoromethyl, trifluoromethyl, oxo, C₁₋₆ alkoxy, difluoromethoxy and di(C₁₋₆)alkylamino.

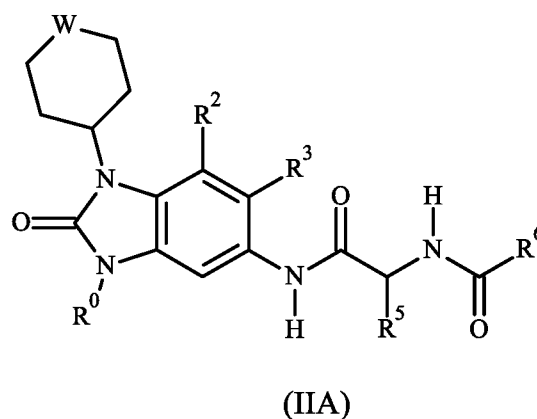
Typical examples of specific substituents on R⁷ include one, two or three substituents independently selected from fluoro, chloro, bromo, cyano, nitro, methyl, ethyl, isopropyl, *tert*-butyl, difluoromethyl, trifluoromethyl, phenyl, fluorophenyl,

hydroxy, hydroxymethyl, oxo, methoxy, isopropoxy, *tert*-butoxy, difluoromethoxy, trifluoromethoxy, methylthio, methylsulfinyl, methylsulfonyl, amino, aminomethyl, aminoethyl, methylamino, *tert*-butylamino, dimethylamino, pyrrolidinyl, morpholinyl, piperazinyl, acetylamino, acetylaminoethyl, methoxycarbonylamino, methylsulfonyl-
 5 amino, formyl, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl and dimethylaminosulfonyl.

Suitable examples of specific substituents on R⁷ include one, two or three substituents independently selected from fluoro, chloro, cyano, methyl, ethyl, isopropyl,
 10 difluoromethyl, trifluoromethyl, oxo, methoxy, isopropoxy, difluoromethoxy and dimethylamino.

Selected values of R⁷ include phenyl, pyrazolo[1,5-*a*]pyrazinyl, benzoxazolyl, fluorobenzoxazolyl, methylbenzoxazolyl, benzothiazolyl, benzimidazolyl, fluoro-benzimidazolyl, imidazo[1,2-*b*]pyridazinyl, purinyl, pyridinyl, cyanopyridinyl, methyl-
 15 pyridinyl, methoxypyridinyl, pyridazinyl, chloropyridazinyl, cyanopyridazinyl, methylpyridazinyl, ethylpyridazinyl, isopropylpyridazinyl, difluoromethylpyridazinyl, trifluoromethylpyridazinyl, methoxypyridazinyl, isopropoxypyridazinyl, difluoromethoxy-pyridazinyl, dimethylaminopyridazinyl, cinnolinyl, pyrimidinyl, pyrazinyl, methylpyrazinyl and spiro[tetrahydropyranyl][oxoindole].

20 One sub-class of the compounds of formula (IA) above is represented by the compounds of formula (IIA), and pharmaceutically acceptable salts thereof:



25 wherein

W represents O, S, S(O), S(O)₂, S(O)(NH) or N-R¹⁷;

R^{17} represents hydrogen or C_{1-6} alkyl; and

R^0 , R^2 , R^3 , R^5 and R^6 are as defined above.

Typically, W represents O, S, S(O), S(O)₂ or N- R^{17} .

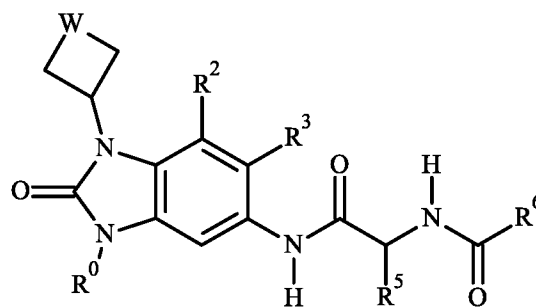
Suitably, W represents O, S or N- R^{17} .

- 5 In a first embodiment, W represents O. In a second embodiment, W represents S. In a third embodiment, W represents S(O). In a fourth embodiment, W represents S(O)₂. In a fifth embodiment, W represents S(O)(NH). In a sixth embodiment, W represents N- R^{17} .

Suitably, R^{17} represents hydrogen or methyl.

- 10 In a first embodiment, R^{17} represents hydrogen. In a second embodiment, R^{17} represents C_{1-6} alkyl. In a first aspect of that embodiment, R^{17} represents methyl.

Another sub-class of the compounds of formula (IA) above is represented by the compounds of formula (IIB), and pharmaceutically acceptable salts thereof:



(IIB)

15

wherein W, R^0 , R^2 , R^3 , R^5 and R^6 are as defined above.

- Specific novel compounds in accordance with the present invention include each of the compounds whose preparation is described in the accompanying Examples, and
20 pharmaceutically acceptable salts and solvates thereof.

The compounds in accordance with the present invention are beneficial in the treatment and/or prevention of various human ailments, including inflammatory and autoimmune disorders.

- 25 The compounds according to the present invention are useful in the treatment and/or prophylaxis of a pathological disorder that is mediated by a pro-inflammatory IL-17 cytokine or is associated with an increased level of a pro-inflammatory IL-17 cytokine. Generally, the pathological condition is selected from the group consisting of

infections (viral, bacterial, fungal and parasitic), endotoxic shock associated with infection, arthritis, rheumatoid arthritis, psoriatic arthritis, systemic onset juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), asthma, chronic obstructive airways disease (COAD), chronic obstructive pulmonary disease (COPD),
5 acute lung injury, pelvic inflammatory disease, Alzheimer's Disease, Crohn's disease, inflammatory bowel disease, irritable bowel syndrome, ulcerative colitis, Castleman's disease, ankylosing spondylitis and other spondyloarthropathies, dermatomyositis, myocarditis, uveitis, exophthalmos, autoimmune thyroiditis, Peyronie's Disease, coeliac disease, gall bladder disease, Pilonidal disease, peritonitis, psoriasis, atopic dermatitis,
10 vasculitis, surgical adhesions, stroke, autoimmune diabetes, Type I Diabetes, lyme arthritis, meningoencephalitis, immune mediated inflammatory disorders of the central and peripheral nervous system such as multiple sclerosis and Guillain-Barr syndrome, other autoimmune disorders, pancreatitis, trauma (surgery), graft-versus-host disease, transplant rejection, fibrosing disorders including pulmonary fibrosis, liver fibrosis, renal
15 fibrosis, scleroderma or systemic sclerosis, cancer (both solid tumours such as melanomas, hepatoblastomas, sarcomas, squamous cell carcinomas, transitional cell cancers, ovarian cancers and hematologic malignancies and in particular acute myelogenous leukaemia, chronic myelogenous leukemia, chronic lymphatic leukemia, gastric cancer and colon cancer), heart disease including ischaemic diseases such as
20 myocardial infarction as well as atherosclerosis, intravascular coagulation, bone resorption, osteoporosis, periodontitis, hypochlorhydria and pain (particularly pain associated with inflammation).

WO 2009/089036 reveals that modulators of IL-17 activity may be administered to inhibit or reduce the severity of ocular inflammatory disorders, in particular ocular
25 surface inflammatory disorders including Dry Eye Syndrome (DES). Consequently, the compounds in accordance with the present invention are useful in the treatment and/or prevention of an IL-17-mediated ocular inflammatory disorder, in particular an IL-17-mediated ocular surface inflammatory disorder including Dry Eye Syndrome. Ocular surface inflammatory disorders include Dry Eye Syndrome, penetrating keratoplasty,
30 corneal transplantation, lamellar or partial thickness transplantation, selective endothelial transplantation, corneal neovascularization, keratoprosthesis surgery, corneal ocular surface inflammatory conditions, conjunctival scarring disorders, ocular autoimmune conditions, Pemphigoid syndrome, Stevens-Johnson syndrome, ocular allergy, severe

allergic (atopic) eye disease, conjunctivitis and microbial keratitis. Particular categories of Dry Eye Syndrome include keratoconjunctivitis sicca (KCS), Sjögren syndrome, Sjögren syndrome-associated keratoconjunctivitis sicca, non-Sjögren syndrome-associated keratoconjunctivitis sicca, keratitis sicca, sicca syndrome, xerophthalmia, tear
5 film disorder, decreased tear production, aqueous tear deficiency (ATD), meibomian gland dysfunction and evaporative loss.

Illustratively, the compounds of the present invention may be useful in the treatment and/or prophylaxis of a pathological disorder selected from the group consisting of arthritis, rheumatoid arthritis, psoriasis, psoriatic arthritis, systemic onset juvenile
10 idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), asthma, chronic obstructive airway disease, chronic obstructive pulmonary disease, atopic dermatitis, scleroderma, systemic sclerosis, lung fibrosis, inflammatory bowel diseases (including Crohn's disease and ulcerative colitis), ankylosing spondylitis and other spondyloarthropathies, cancer and pain (particularly pain associated with inflammation).

15 Suitably, the compounds of the present invention are useful in the treatment and/or prophylaxis of psoriasis, psoriatic arthritis or ankylosing spondylitis.

The present invention also provides a pharmaceutical composition which comprises a compound in accordance with the invention as described above, or a pharmaceutically acceptable salt thereof, in association with one or more pharmaceutically
20 acceptable carriers.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, ophthalmic or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for
25 example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methyl cellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogenphosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting
30 agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared

by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles or preservatives. The preparations may also contain buffer salts, flavouring agents, colouring agents or sweetening agents, as appropriate.

- 5 Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

- 10 The compounds according to the present invention may be formulated for parenteral administration by injection, e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoules or multi-dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents.
- 15 Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds according to the present invention may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation or by intramuscular injection.

- 20 For nasal administration or administration by inhalation, the compounds according to the present invention may be conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, fluorotrichloromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

- 25 The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

- For topical administration the compounds according to the present invention may be conveniently formulated in a suitable ointment containing the active component
- 30 suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively, the compounds according to the present invention may be formulated in a suitable lotion

containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

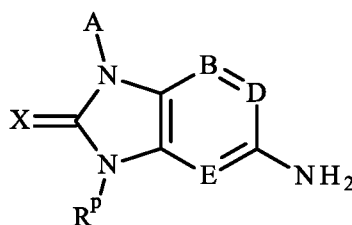
5 For ophthalmic administration the compounds according to the present invention may be conveniently formulated as micronized suspensions in isotonic, pH-adjusted sterile saline, either with or without a preservative such as a bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively, for ophthalmic administration the compounds according to the present
10 invention may be formulated in an ointment such as petrolatum.

 For rectal administration the compounds according to the present invention may be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and so will melt in the rectum to release the active component.
15 Such materials include, for example, cocoa butter, beeswax and polyethylene glycols.

 The quantity of a compound according to the present invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen and the condition of the patient to be treated. In general, however, daily dosages may range from around 10 ng/kg to 1000 mg/kg, typically from 100 ng/kg to 100 mg/kg,
20 e.g. around 0.01 mg/kg to 40 mg/kg body weight, for oral or buccal administration, from around 10 ng/kg to 50 mg/kg body weight for parenteral administration, and from around 0.05 mg to around 1000 mg, e.g. from around 0.5 mg to around 1000 mg, for nasal administration or administration by inhalation or insufflation.

 If desired, a compound in accordance with the present invention may be co-
25 administered with another pharmaceutically active agent, e.g. an anti-inflammatory molecule.

 The compounds of formula (I) above wherein R^1 represents $-COR^a$ may be prepared by a process which comprises reacting a carboxylic acid of formula R^aCO_2H , or a salt thereof, e.g. a lithium salt thereof, with a compound of formula (III):



(III)

wherein A, B, D, E, X and R^a are as defined above, and R^P corresponds to the group R⁰ as defined above, or R^P represents a *N*-protecting group; followed, as necessary, by removal
 5 of the *N*-protecting group R^P.

The *N*-protecting group R^P will suitably be *tert*-butoxycarbonyl (BOC), benzyl, or 2-(trimethylsilyl)ethoxymethyl (SEM).

The reaction is conveniently accomplished in the presence of a coupling agent. Suitable coupling agents may comprise the following:

- 10
- 2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU);
 - 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide (propylphosphonic anhydride); or
 - a mixture of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride and 1-
 15 hydroxybenzotriazole.

Where compound (III) is reacted with a carboxylic acid of formula R^aCO₂H, the reaction is generally carried out in the presence of a base. Suitable bases include organic amines, e.g. a trialkylamine such as *N,N*-diisopropylethylamine or triethylamine. The reaction is conveniently performed at ambient temperature in a suitable solvent, e.g. a
 20 cyclic ether such as tetrahydrofuran, or a dipolar aprotic solvent such as *N,N*-dimethylformamide, or a chlorinated solvent such as dichloromethane.

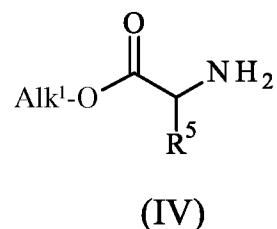
Where compound (III) is reacted with the lithium salt of a carboxylic acid of formula R^aCO₂H, the reaction is generally carried out at ambient temperature in a suitable solvent, e.g. a dipolar aprotic solvent such as *N,N*-dimethylformamide, or a chlorinated
 25 solvent such as dichloromethane.

Where the *N*-protecting group R^P is BOC, the subsequent removal thereof may conveniently be effected by treatment with an acid, e.g. a mineral acid such as hydrochloric acid, or an organic acid such as trifluoroacetic acid.

Where the *N*-protecting group R^P is benzyl, the subsequent removal thereof may conveniently be effected by catalytic hydrogenation, typically by treatment with gaseous hydrogen in the presence of a hydrogenation catalyst, e.g. palladium on charcoal.

Where the *N*-protecting group R^P is SEM, the subsequent removal thereof may conveniently be effected by treatment with a fluoride salt, e.g. tetra-*n*-butylammonium fluoride; or by treatment with an acid, e.g. a mineral acid such as hydrochloric acid, or an organic acid such as trifluoroacetic acid.

Where R^a represents -CH(R⁵)N(H)C(O)R⁶, the intermediates of formula R^aCO₂H may be prepared by a two-step procedure which comprises: (i) reacting a carboxylic acid of formula R⁶-CO₂H with a compound of formula (IV):



wherein Alk¹ represents C₁₋₄ alkyl, e.g. methyl, and R⁵ and R⁶ are as defined above; under conditions analogous to those described above for the reaction between compound (III) and a carboxylic acid of formula R^aCO₂H; and (ii) saponification of the resulting material by treatment with a base.

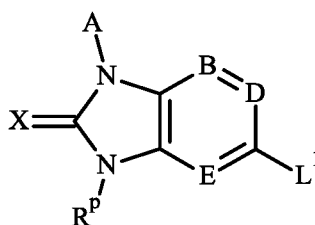
The saponification reaction in step (ii) will generally be effected by treatment with a base. Suitable bases include inorganic hydroxides, e.g. an alkali metal hydroxide such as lithium hydroxide. Where lithium hydroxide is employed in step (ii) of the above procedure, the product may be the lithium salt of the carboxylic acid of formula R^aCO₂H.

Step (ii) is conveniently effected at ambient temperature in water and a suitable organic solvent, e.g. a cyclic ether such as tetrahydrofuran, optionally in admixture with a C₁₋₄ alkanol such as methanol.

In another procedure, the compounds of formula (I) above wherein R¹ represents -SO₂R^b may be prepared by a process which comprises reacting a compound of formula R^bSO₂Cl with a compound of formula (III) as defined above.

The reaction is conveniently accomplished at ambient temperature in the presence of a base, e.g. an organic base such as triethylamine, in a suitable solvent, e.g. a chlorinated hydrocarbon solvent such as dichloromethane.

In another procedure, the compounds of formula (I) above wherein R¹ represents
5 -COR^a may be prepared by a process which comprises reacting an amide of formula R^aCONH₂ with a compound of formula (V):



(V)

10 wherein A, B, D, E, X, R^a and R^p are as defined above, and L¹ represents a suitable leaving group; in the presence of a transition metal catalyst; followed, as necessary, by removal of the *N*-protecting group R^p.

The leaving group L¹ is suitably a halogen atom, e.g. chloro or bromo.

The transition metal catalyst is suitably [(2-di-*tert*-butylphosphino-3,6-dimethoxy-
15 2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methane-sulfonate (tBuBrettPhos Pd G3), in which case the reaction will generally be performed in the presence of 2-(di-*tert*-butylphosphino)-2',4',6'-triisopropyl-3,6-dimethoxy-1,1'-biphenyl (tBuBrettPhos). The reaction is conveniently carried out at an elevated temperature in the presence of a base, e.g. an inorganic base such as potassium carbonate,
20 in a suitable solvent, e.g. a lower alkanol such as *tert*-butanol.

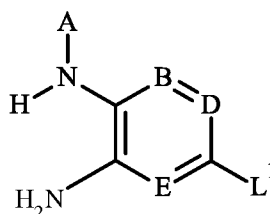
Alternatively, the transition metal catalyst may suitably be tris(dibenzylidene-acetone)dipalladium(0), in which case the reaction will generally be performed in the presence of 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos) or 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos). The reaction is conveniently
25 carried out at an elevated temperature in the presence of a base, e.g. a carbonate salt such as potassium carbonate or cesium carbonate, in a suitable solvent, e.g. a cyclic ether such as 1,4-dioxane, or a C₁₋₆ alkanol such as *tert*-butanol.

In another procedure, the compounds of formula (I) above wherein R¹ is an aryl or heteroaryl moiety may be prepared by a process which comprises reacting a compound of formula R¹-NH₂ with a compound of formula (V) as defined above in the presence of a transition metal catalyst; followed, as necessary, by removal of the *N*-protecting group R^P.

5 The transition metal catalyst is suitably tris(dibenzylideneacetone)dipalladium(0), in which case the reaction will generally be performed in the presence of 2-(di-*tert*-butyl)-phosphino-2',4',6'-triisopropylbiphenyl (*tert*-BuXPhos). The reaction is conveniently carried out at an elevated temperature in the presence of a base, e.g. a *tert*-butoxide salt such as sodium *tert*-butoxide, in a suitable solvent, e.g. a cyclic ether such as 1,4-dioxane.

10 The intermediates of formula (III) above may be prepared by reacting the corresponding compound of formula (V) above with sodium azide. The reaction will generally be accomplished in the presence of copper(I) iodide, L-proline and a base, e.g. an inorganic base such as potassium carbonate. The reaction is conveniently performed at an elevated temperature in a suitable solvent, e.g. an organic sulfoxide such as dimethyl
15 sulfoxide.

The intermediates of formula (V) above wherein X is O may be prepared by reacting a compound of formula (VI):



(VI)

20

wherein A, B, D, E and L¹ are as defined above; with 1,1'-carbonyldiimidazole; followed, as necessary, by attachment of the *N*-protecting group R^P.

The reaction will conveniently be carried out at ambient temperature in a suitable solvent, e.g. a cyclic ether such as tetrahydrofuran.

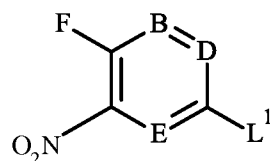
25

Where the *N*-protecting group R^P is SEM, attachment thereof will suitably be effected by treatment with 2-(trimethylsilyl)ethoxymethyl chloride. The reaction is generally performed in the presence of a base, e.g. an inorganic base such as sodium

hydride. The reaction will conveniently be carried out at ambient temperature in a suitable solvent, e.g. a dipolar aprotic solvent such as *N,N*-dimethylformamide.

The intermediates of formula (VI) above may be prepared by a two-step procedure from a compound of formula (VII):

5



(VII)

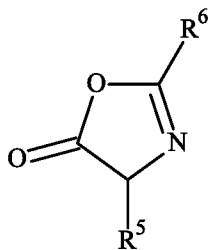
wherein B, D, E and L^1 are as defined above; which procedure comprises the following steps:

- 10 (i) reaction of compound (VII) with a compound of formula $A-NH_2$; and
 (ii) treatment of the material thereby obtained with a reducing agent.

Step (i) is typically effected in the presence of a base, e.g. an inorganic base such as potassium carbonate. The reaction is conveniently carried out at an elevated temperature in a suitable solvent, e.g. a cyclic ether such as tetrahydrofuran.

- 15 The reducing agent of use in step (ii) suitably comprises a mixture of metallic zinc and ammonium formate. The reaction is conveniently carried out at ambient temperature in a suitable solvent, e.g. a lower alkanol such as methanol.

- In another procedure, the compounds of formula (IA) above may be prepared by a process which comprises reacting a compound of formula (III) as defined above with a
 20 compound of formula (VIII):

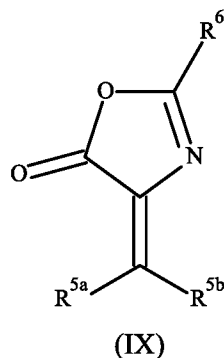


(VIII)

wherein R^5 and R^6 are as defined above; followed, as necessary, by removal of the *N*-protecting group R^P .

The reaction between compounds (III) and (VIII) will generally be performed in the presence of acetic acid. The reaction is conveniently carried out at an elevated
5 temperature in a suitable solvent, e.g. a cyclic ether such as tetrahydrofuran.

Similarly, the compounds of formula (IF) above may be prepared by a process which comprises reacting a compound of formula (III) as defined above with a compound of formula (IX):



10

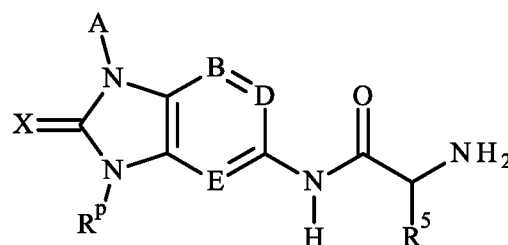
wherein R^{5a} , R^{5b} and R^6 are as defined above; under conditions analogous to those described above for the reaction between compounds (III) and (VIII); followed, as necessary, by removal of the *N*-protecting group R^P .

15 Where the respective values of R^5 , R^{5a} and R^{5b} permit, an intermediate of formula (VIII) may be obtained from the corresponding intermediate of formula (IX) by conventional catalytic hydrogenation.

The intermediates of formula (IX) above may be prepared by reacting a compound of formula $R^{5a}C(O)R^{5b}$ with a compound of formula (VIII) as defined above wherein R^5
20 represents hydrogen.

The reaction is conveniently effected by treating the reagents with titanium tetrachloride; followed by treatment of the resulting material with pyridine.

In another procedure, the compounds of formula (IA) above may be prepared by a process which comprises reacting a carboxylic acid of formula R^6-CO_2H with a compound
25 of formula (X):



(X)

wherein A, B, D, E, X, R^P, R⁵ and R⁶ are as defined above; under conditions analogous to those described above for the reaction between compound (III) and a carboxylic acid of
 5 formula R^aCO₂H; followed, as necessary, by removal of the *N*-protecting group R^P.

Similarly, the compounds of formula (IA) above wherein R⁶ represents -NR^{6a}R^{6b} may be prepared by a process which comprises reacting a carbamate derivative of formula L²-C(O)NR^{6a}R^{6b}, wherein L² represents a suitable leaving group, with a compound of formula (X) as defined above; followed, as necessary, by removal of the *N*-protecting
 10 group R^P.

The leaving group L² is suitably a halogen atom, e.g. chloro; or L² is suitably phenoxy.

Where L² is a halogen atom, the reaction is conveniently carried out at ambient temperature in the presence of a base, e.g. an organic amine such as triethylamine, in a
 15 suitable solvent, e.g. a chlorinated solvent such as dichloromethane.

Where L² is phenoxy, the reaction is conveniently carried out at an elevated temperature in the presence of 4-(dimethylamino)pyridine, in a suitable solvent, e.g. a nitrile solvent such as acetonitrile.

Similarly, the compounds of formula (IA) above wherein R⁶ represents -OR^{6c} may
 20 be prepared by a process which comprises reacting a compound of formula L³-C(O)OR^{6c}, wherein L³ represents a suitable leaving group, with a compound of formula (X) as defined above; followed, as necessary, by removal of the *N*-protecting group R^P.

The leaving group L³ is suitably a halogen atom, e.g. chloro.

The reaction is conveniently carried out at ambient temperature in the presence of a
 25 base, e.g. an organic amine such as triethylamine, typically in admixture with pyridine, in a suitable solvent, e.g. a cyclic ether such as tetrahydrofuran.

In another procedure, the compounds of formula (IB) above may be prepared by a process which comprises reacting a compound of formula (X) as defined above with a

compound of formula $L^4-S(O)_2R^6$, wherein R^6 is as defined above, and L^4 represents a suitable leaving group; followed, as necessary, by removal of the *N*-protecting group R^P .

The leaving group L^4 is suitably a halogen atom, e.g. chloro.

The reaction is conveniently carried out at ambient temperature in the presence of a
5 base, e.g. an organic amine such as *N,N*-diisopropylethylamine, in a suitable solvent, e.g. a chlorinated solvent such as dichloromethane.

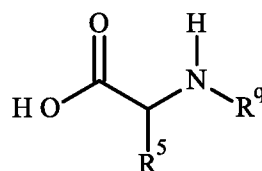
In another procedure, the compounds of formula (IC) above may be prepared by a process which comprises reacting a compound of formula (X) as defined above with a compound of formula L^5-R^7 , wherein R^7 is as defined above, and L^5 represents a suitable
10 leaving group; followed, as necessary, by removal of the *N*-protecting group R^P .

The leaving group L^5 is suitably a halogen atom, e.g. chloro or bromo.

The reaction is conveniently carried out in the presence of a base. Suitable bases include organic amines, e.g. a trialkylamine such as *N,N*-diisopropylethylamine. The reaction is typically performed at an elevated temperature in a suitable solvent, e.g. a
15 cyclic ether such as 1,4-dioxane.

Alternatively, the reaction may be performed in the presence of a transition metal catalyst. Suitable transition metal catalysts of use in this procedure include [(2-di-*tert*-butylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (tBuBrettPhos Pd G3). The reaction is
20 conveniently carried out at an elevated temperature in the presence of a base, e.g. an inorganic base such as potassium *tert*-butoxide, in a suitable solvent or solvent mixture. The solvent or solvents may suitably be selected from a cyclic ether such as 1,4-dioxane, and a sulfoxide solvent such as dimethyl sulfoxide.

The intermediates of formula (X) above may be prepared by reacting a compound
25 of formula (III) as defined above with a compound of formula (XI), or a salt thereof, e.g. a lithium salt thereof:



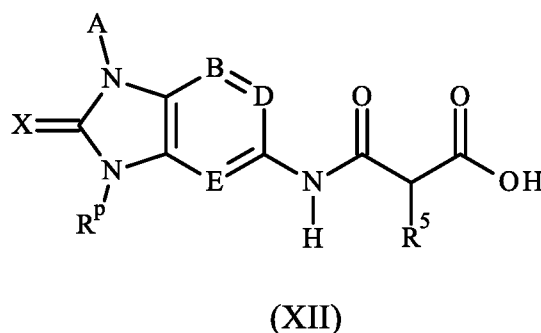
(XI)

wherein R^5 is as defined above, and R^q represents hydrogen or an *N*-protecting group; under conditions analogous to those described above for the reaction between compound (III) and a carboxylic acid of formula R^aCO_2H ; followed, as necessary, by removal of the *N*-protecting group R^q .

5 The *N*-protecting group R^q will suitably be *tert*-butoxycarbonyl (BOC).

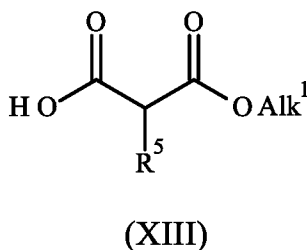
Where the *N*-protecting group R^q is BOC, the subsequent removal thereof may conveniently be effected by treatment with an acid, e.g. a mineral acid such as hydrochloric acid, or an organic acid such as trifluoroacetic acid.

10 In another procedure, the compounds of formula (ID) above may be prepared by a process which comprises reacting a compound of formula R^7-NH_2 with a compound of formula (XII):



15 wherein A, B, D, E, X, R^p , R^5 and R^7 are as defined above; under conditions analogous to those described above for the reaction between compound (III) and a carboxylic acid of formula R^aCO_2H ; followed, as necessary, by removal of the *N*-protecting group R^p .

The intermediates of formula (XII) above may be prepared by a two-step procedure which comprises: (i) reacting a compound of formula (III) as defined above with a
20 compound of formula (XIII), or a salt thereof, e.g. a lithium salt thereof:



wherein R^5 and Alk^1 are as defined above; under conditions analogous to those described above for the reaction between compound (III) and a carboxylic acid of formula R^aCO_2H ; and (ii) saponification of the resulting material by treatment with a base.

The saponification reaction in step (ii) will generally be effected by treatment with
5 a base. Suitable bases include inorganic hydroxides, e.g. an alkali metal hydroxide such as lithium hydroxide. Where lithium hydroxide is employed in step (ii) of the above procedure, the product may be the lithium salt of the carboxylic acid of formula (XII).

Step (ii) is conveniently effected at ambient temperature in water and a suitable organic solvent, e.g. a C_{1-4} alkanol such as ethanol.

10 Where they are not commercially available, the starting materials of formula (IV), (VII), (XI) and (XIII) may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be understood that any compound of formula (I) initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further
15 compound of formula (I) by techniques known from the art. By way of example, a compound of formula (I) comprising a N-BOC moiety (wherein BOC is an abbreviation for *tert*-butoxycarbonyl) may be converted into the corresponding compound comprising a N-H moiety by treatment with an acid, e.g. a mineral acid such as hydrochloric acid, or an organic acid such as trifluoroacetic acid.

20 A compound of formula (I) wherein X is O may be converted into the corresponding compound wherein X is S by treatment with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson reagent).

A compound of formula (I) comprising an amino ($-NH_2$) moiety may be acylated, e.g. acetylated, by treatment with a suitable acyl halide, e.g. acetyl chloride, typically in
25 the presence of a base, e.g. an organic base such as *N,N*-diisopropylethylamine.

A compound which contains an N-H moiety may be alkylated, e.g. methylated, by treatment with the appropriate alkyl halide, e.g. iodomethane, typically at ambient temperature in the presence of a base, e.g. sodium hydride, in a suitable solvent, e.g. a dipolar aprotic solvent such as *N,N*-dimethylformamide.

30 A compound of formula (I) wherein R^2 or R^3 or R^4 is hydrogen may be converted into the corresponding compound wherein R^2 or R^3 or R^4 is fluoro by treatment with SelectfluorTM.

A compound of formula (I) wherein R^2 or R^3 or R^4 is hydrogen may be converted into the corresponding compound wherein R^2 or R^3 or R^4 is chloro by treatment with *N*-chlorosuccinimide, typically in the presence of acetic acid.

Where the respective values of R^5 , R^{5a} and R^{5b} permit, a compound of formula (IA) may be obtained from the corresponding compound of formula (IF) by conventional catalytic hydrogenation, e.g. by treatment with gaseous hydrogen in the presence of a hydrogenation catalyst such as palladium on charcoal.

A compound containing the moiety -S- may be converted into the corresponding compound containing the moiety -S(O)- by treatment with 3-chloroperoxybenzoic acid. Likewise, a compound containing the moiety -S- or -S(O)- may be converted into the corresponding compound containing the moiety -S(O)₂- by treatment with 3-chloroperoxybenzoic acid.

A compound containing the moiety -S- may be converted into the corresponding compound containing the moiety -S(O)(NH)- by treatment with ammonium carbamate and (diacetoxyiodo)benzene.

Where a mixture of products is obtained from any of the processes described above for the preparation of compounds according to the invention, the desired product can be separated therefrom at an appropriate stage by conventional methods such as preparative HPLC; or column chromatography utilising, for example, silica and/or alumina in conjunction with an appropriate solvent system.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques. In particular, where it is desired to obtain a particular enantiomer of a compound of formula (I) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers. Thus, for example, diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (I), e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation, and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt. In another resolution process a racemate of formula (I) may be separated using chiral HPLC. Moreover, if desired, a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above. Alternatively, a

particular enantiomer may be obtained by performing an enantiomer-specific enzymatic biotransformation, e.g. an ester hydrolysis using an esterase, and then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode.

Chromatography, recrystallisation and other conventional separation procedures may also
5 be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Greene's*
10 *Protective Groups in Organic Synthesis*, ed. P.G.M. Wuts, John Wiley & Sons, 5th edition, 2014. The protecting groups may be removed at any convenient subsequent stage utilising methods known from the art.

The compounds in accordance with this invention potentially inhibit the ability of IL-17A to bind to IL-17RA. When tested in the IL-17 FRET assay described below,
15 compounds of the present invention exhibit an IC₅₀ value of 10 µM or less, generally of 5 µM or less, usually of 1 µM or less, typically of 500 nM or less, suitably of 100 nM or less, ideally of 50 nM or less, and preferably of 25 nM or less (the skilled person will appreciate that a *lower* IC₅₀ figure denotes a *more active* compound).

Moreover, certain compounds in accordance with this invention potentially inhibit
20 IL-17 induced IL-6 release from human dermal fibroblasts. Indeed, when tested in the HDF cell line assay described below, compounds of the present invention exhibit an IC₅₀ value of 10 µM or less, generally of 5 µM or less, usually of 1 µM or less, typically of 500 nM or less, suitably of 100 nM or less, ideally of 50 nM or less, and preferably of 25 nM or less (as before, the skilled person will appreciate that a *lower* IC₅₀ figure denotes a *more*
25 *active* compound).

IL-17 FRET Assay

The purpose of this assay is to test the ability of compounds to disrupt the interaction between IL-17A and soluble IL-17 Receptor A (IL-17RA). The ability of a
30 compound to inhibit IL-17A binding to IL-17RA is measured in this assay.

An IL-17AA-TEV-Human Fc construct was expressed in a CHO SXE cell system and purified by protein A chromatography and size exclusion. The protein was labelled

with an amine reactive AlexaFluor 647 dye (Thermo Fisher #A20006), as per manufacturer's instruction.

Soluble IL-17RA (33-317)-HKH-TEV-Fc was expressed in an Expi HEK293 cell system and purified by protein A chromatography and size exclusion. The Fc tag was
5 cleaved by TEV, producing IL-17RA (33-317)-HKH, and the protein was labelled with amine reactive terbium (Thermo Fisher #PV3581).

In assay buffer [Dulbecco's PBS (Sigma #14190-094), 0.05% P20 (Thermo Scientific #28320), 1 mg/mL BSA (Sigma #A2153-500G)] the following solutions were prepared:

10 For IL-17A assay

- IL-17A-Fc-AF647 at 5 nM
- IL-17RA-HKH-Tb at 5 nM

Compounds were serially diluted in DMSO before receiving an aqueous dilution into a 384 well dilution plate (Greiner #781281), to give a 25% DMSO solution.

15 IL-17A (10 μ L) was added to a black low volume assay plate (Costar #4511) and diluted compound (5 μ L) was transferred from the aqueous dilution plate. The cytokine and compound were allowed to incubate for 1 h, then IL-17RA (10 μ L) was added. The plates were wrapped in foil and incubated at room temperature for 18-20 h with gentle shaking (<400 rpm) before being read on a Perkin Elmer Envision plate reader
20 (Excitation: 330 nm; Emission 615/645 nm).

The final assay concentrations were IL-17A-AF647 2 nM and IL-17RA-Tb 2 nM, 5% DMSO.

When tested in the IL-17 FRET assay, the compounds of the accompanying Examples were all found to exhibit IC₅₀ values of 10 μ M or better.

25 When tested in the IL-17 FRET assay, compounds of the accompanying Examples exhibit IC₅₀ values generally in the range of about 0.01 nM to about 10 μ M, usually in the range of about 0.01 nM to about 5 μ M, typically in the range of about 0.01 nM to about 1 μ M, suitably in the range of about 0.01 nM to about 500 nM, appositely in the range of about 0.01 nM to about 100 nM, ideally in the range of about 0.01 nM to about 50 nM, and
30 preferably in the range of about 0.01 nM to about 25 nM.

Inhibition of IL-17A induced IL-6 release from Dermal Fibroblast Cell Line

The purpose of this assay is to test the neutralising ability to IL-17 proteins, in a human primary cell system. Stimulation of normal human dermal fibroblasts (HDF) with IL-17 alone produces only a very weak signal but in combination with certain other
5 cytokines, such as TNF α , a synergistic effect can be seen in the production of inflammatory cytokines, i.e. IL-6.

HDFs were stimulated with IL-17A (50 pM) in combination with TNF- α (25 pM). The resultant IL-6 response was then measured using a homogenous time-resolved FRET kit from Cisbio. The kit utilises two monoclonal antibodies, one labelled with Eu-
10 Cryptate (Donor) and the second with d2 or XL665 (Acceptor). The intensity of the signal is proportional to the concentration of IL-6 present in the sample (Ratio is calculated by $665/620 \times 104$).

The ability of a compound to inhibit IL-17 induced IL-6 release from human dermal fibroblasts is measured in this assay.

15 HDF cells (Sigma #106-05n) were cultured in complete media (DMEM + 10% FCS + 2 mM L-glutamine) and maintained in a tissue culture flask using standard techniques. Cells were harvested from the tissue culture flask on the morning of the assay using TrypLE (Invitrogen #12605036). The TrypLE was neutralised using complete medium (45 mL) and the cells were centrifuged at $300 \times g$ for 3 minutes. The cells were
20 re-suspended in complete media (5 mL) counted and adjusted to a concentration of 3.125×10^4 cells/mL before being added to the 384 well assay plate (Corning #3701) at 40 μ L per well. The cells were left for a minimum of three hours, at 37°C/5% CO₂, to adhere to the plate.

Compounds were serially diluted in DMSO before receiving an aqueous dilution
25 into a 384 well dilution plate (Greiner #781281), where 5 μ L from the titration plate was transferred to 45 μ L of complete media and mixed to give a solution containing 10% DMSO.

Mixtures of TNF α and IL-17 cytokine were prepared in complete media to final concentrations of TNF α 25 pM/IL-17A 50 pM, then 30 μ L of the solution was added to a
30 384 well reagent plate (Greiner #781281).

10 μ L from the aqueous dilution plate was transferred to the reagent plate containing 30 μ L of the diluted cytokines, to give a 2.5% DMSO solution. The compounds were incubated with the cytokine mixtures for one hour at 37°C. After the

incubation, 10 μ L was transferred to the assay plate, to give a 0.5% DMSO solution, then incubated for 18-20 h at 37°C/5% CO₂.

From the Cisbio IL-6 FRET kit (Cisbio #62IL6PEB) europium cryptate and Alexa 665 were diluted in reconstitution buffer and mixed 1:1, as per kit insert. To a white low
5 volume 384 well plate (Greiner #784075) were added FRET reagents (10 μ L), then supernatant (10 μ L) was transferred from the assay plate to Greiner reagent plate. The mixture was incubated at room temperature for 3 h with gentle shaking (<400 rpm) before being read on a Synergy Neo 2 plate reader (Excitation: 330 nm; Emission: 615/645 nm).

When tested in the above assay, compounds of the accompanying Examples were
10 found to exhibit IC₅₀ values of 10 μ M or better.

When tested in the above assay, compounds of the accompanying Examples exhibit IC₅₀ values generally in the range of about 0.01 nM to about 10 μ M, usually in the range of about 0.01 nM to about 5 μ M, typically in the range of about 0.01 nM to about 1 μ M, suitably in the range of about 0.01 nM to about 500 nM, appositely in the range of about
15 0.01 nM to about 100 nM, ideally in the range of about 0.01 nM to about 50 nM, and preferably in the range of about 0.01 nM to about 25 nM.

The following Examples illustrate the preparation of compounds according to the invention.

20

EXAMPLES

Abbreviations

DCM: dichloromethane	DMF: <i>N,N</i> -dimethylformamide
25 MeOH: methanol	THF: tetrahydrofuran
DMSO: dimethyl sulfoxide	DIPEA: <i>N,N</i> -diisopropylethylamine
EtOAc: ethyl acetate	HOBt: 1-hydroxybenzotriazole
TFA: trifluoroacetic acid	
EDC.HCl: <i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride	
30 SEM-Cl: 2-(trimethylsilyl)ethoxymethyl chloride	
h: hour	r.t.: room temperature
M: mass	RT: retention time
HPLC: High Performance Liquid Chromatography	

LCMS: Liquid Chromatography Mass Spectrometry

ES+: Electrospray Positive Ionisation

Analytical Conditions

5 Compounds were named with the aid of ACD/Name Batch (Network) version 11.01, and/or Accelrys Draw 4.2, and/or Elemental, Dotmatics, and/or Chemaxon.

 All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen atmosphere using dried solvents and glassware.

 NMR spectra were recorded on a Bruker Avance III HD 500 MHz, 400 MHz, 300
10 MHz or 250 MHz spectrometer.

HPLC-MS

1. Performed on an Agilent 1200-6120 LC-MS system coupled to Detection (230 to 400
nm and 215 nm) and Mass Spec Detection Agilent 6120 Mass Spectrometer (ES) *m/z*
15 120 to 800.

Method 1

Waters X-Bridge C18 (2.1 x 20 mm, 2.5 µm) column

Mobile Phase A: 10 mM ammonium formate in water + 0.1% formic acid

20 Mobile Phase B: acetonitrile + 5% water + 0.1% formic acid

Gradient program: Flow rate 1 mL/minute

	Time	A%	B%
	0.00	94.00	6.00
25	1.50	5.00	95.00
	2.25	5.00	95.00
	2.50	94.00	6.00

2. Performed on a Shimadzu LCMS-2010EV system coupled to SPD-M20A PDA and
30 PL 2100 detectors.

Method 2

Waters Atlantis dC18 (2.1 x 100 mm, 3 µm) column

Mobile Phase A: 0.1% formic acid in water
Mobile Phase B: 0.1% formic acid in acetonitrile
Gradient program: Flow rate 0.6 mL/minute; column temperature 40°C

5 Time A% B%
 0.00 95.00 5.00
 5.00 0.00 100.0
 5.40 0.00 100.0
 5.42 95.00 5.00

10

Method 3

Phenomenex Kinetex Core-Shell C8 (2.1 x 50 mm, 5 µm) column

Mobile Phase A: 0.1% formic acid in water
Mobile Phase B: 0.1% formic acid in acetonitrile
15 Gradient program: Flow rate 1.2 mL/minute; column temperature 40°C

 Time A% B%
 0.00 95.00 5.00
 1.20 0.00 100.0
20 1.30 0.00 100.0
 1.31 95.00 5.00

3. Performed on a Waters ZQ system coupled to Waters 2996 PDA and Waters 2420 detectors.

25

Method 4

Waters Atlantis dC18 (4.6 x 50 mm, 3µm) column

Mobile Phase A: 0.1% formic acid in water
Mobile Phase B: 0.1% formic acid in acetonitrile
30 Gradient program: Flow rate 0.8 mL/minute; column temperature 40°C

 Time A% B%
 0.00 30.00 70.00

3.00	90.00	10.0
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6.00	90.00	10.0
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Method 5

5 Waters Atlantis dC18 (4.6 x 50 mm, 3 µm) column

Mobile Phase A: 0.1% formic acid in water

Mobile Phase B: 0.1% formic acid in acetonitrile

Gradient program: Flow rate 0.6 mL/minute; column temperature 40°C

10	Time	A%	B%
	0.00	50.00	50.00
	3.00	95.00	5.00
	6.00	95.00	5.00

15 4. Performed on a Shimadzu LCMS-2010EV system coupled to SPD-M20A PDA and Softa Model 400 ELS detectors

Method 6

Waters X-Bridge C18 (2.1 x 30 mm, 2.5 µm) column

20 Mobile Phase A: 5 mM ammonium formate in water + 0.1% ammonia solution

Mobile Phase B: acetonitrile + 5% 5 mM ammonium formate in water + 0.1% ammonia solution

Gradient program: Flow rate 1 mL/minute

25	Time	A%	B%
	0.00	95.00	5.00
	4.00	5.00	95.00
	5.00	5.00	95.00
	5.10	95.00	5.00
30	6.50	95.00	5.00

INTERMEDIATE 1

Methyl 2-cyclooctylidene-2-formamidoacetate

A solution of potassium *tert*-butoxide in THF (1M, 48 mL, 48 mmol) was added dropwise to a solution of methyl isocyanoacetate (4.0 mL, 41.8 mmol) in anhydrous THF (40 mL) at -65°C under nitrogen. After 5 minutes, a solution of cyclooctanone (5 g, 39.62 mmol) in anhydrous THF (20 mL) was added slowly at -70°C. The reaction mixture was stirred at -70°C for 30 minutes, then allowed to warm to r.t. After 60 h, the reaction mixture was quenched with water (100 mL) and stirred at r.t. for 1 h. The residue was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (50 mL) and dried over magnesium sulfate, then filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography, using a gradient of ethyl acetate in heptane (0-90%), to afford the *title compound* (5.37 g, 58%) as a viscous orange oil, which solidified upon standing. δ_{H} (500 MHz, DMSO- d_6) 9.31 (s, 1H), 8.01 (d, *J* 1.5 Hz, 1H), 3.60 (s, 3H), 2.52-2.47 (m, 2H), 2.31-2.23 (m, 2H), 1.74-1.60 (m, 4H), 1.50-1.31 (m, 6H). HPLC-MS (method 1): MNa+ *m/z* 248, RT 1.63 minutes.

INTERMEDIATE 2

Methyl 2-cyclooctyl-2-formamidoacetate

Magnesium turnings (3.15 g, 130 mmol) were added to a stirred solution of *Intermediate 1* (3.04 g, 13.00 mmol) in anhydrous MeOH (65 mL) at 0°C. The suspension was stirred at 0°C for 1 h, then allowed to warm to r.t. After 16 h, an additional portion of magnesium turnings (1.00 g, 41.1 mmol) was added, and the suspension was stirred at r.t. for 3.5 h. The mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (100 mL) and water (200 mL), then cooled to 0°C. Concentrated HCl was cautiously added to aid dissolution of the solids (pH 4). The organic layer was removed, then the aqueous suspension was treated with further concentrated HCl (pH 1) and the material was extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine (50 mL) and dried over magnesium sulfate, then filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography, using a gradient of EtOAc in heptane (0-80%), to afford the *title compound* (1.53 g, 52%) as a viscous orange oil. δ_{H} (500 MHz, DMSO- d_6) 8.46 (d, *J* 8.5

Hz, 1H), 8.06 (s, 1H), 4.29 (dd, *J* 8.6, 6.1 Hz, 1H), 3.64 (s, 3H), 2.04-1.93 (m, 1H), 1.73-1.19 (m, 14H). HPLC-MS (method 2): MH+ *m/z* 228, RT 3.94 minutes.

INTERMEDIATE 3

5

Methyl 2-amino-2-cyclooctylacetate hydrochloride

Acetyl chloride (1.9 mL, 26.7 mmol) was added at 0°C to a stirred solution of *Intermediate 2* (1.69 g, 6.77 mmol) in MeOH (70 mL) under nitrogen. The mixture was heated at 50°C for 2 h, then cooled to r.t. and concentrated *in vacuo*. The resulting crude material was triturated with diethyl ether (40 mL) and the solids were collected by
10 filtration, washing with diethyl ether (2 x 20 mL). The solids were dried *in vacuo* at 50°C for 6 h to afford the *title compound* (1.43 g, 81%) as a tan powder. δ_{H} (500 MHz, DMSO- d_6) 8.61 (br s, 3H), 3.86 (d, *J* 4.4 Hz, 1H), 3.73 (s, 3H), 2.19-2.09 (m, 1H), 1.68-1.37 (m, 13H), 1.32-1.20 (m, 1H). HPLC-MS (method 3): MH+ *m/z* 200, RT 0.75 and 0.86
15 minutes.

INTERMEDIATE 4

Methyl 2-cyclooctyl-2-[(3-methylisoxazole-4-carbonyl)amino]acetate

To a solution of 3-methylisoxazole-4-carboxylic acid (12.9 g, 66.1 mmol) in dry DMF (100 mL) at 0°C were added DIPEA (54.9 g, 424.6 mmol), EDC.HCl (19.5 g, 101.9 mmol) and HOBt (13.8 g, 101.9 mmol). The reaction mixture was stirred for 15 minutes at 0°C, then *Intermediate 3* (20.0 g, 84.9 mmol) was added. The reaction mixture was stirred at r.t. for 48 h, then poured into ice-cold water (500 mL) and extracted with EtOAc
25 (2 x 400 mL). The organic layer was separated, washed with ice-cold water (2 x 100 mL) and 1N HCl (2 x 50 mL), then dried over anhydrous Na₂SO₄, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography, using a gradient of EtOAc in hexanes (0-15%), to afford the *title compound* (7.9 g, 41.3%) as a pale yellow viscous oil. LC-MS (method 4): MH+ *m/z* 309, RT 5.5 minutes.

30

INTERMEDIATE 5

Lithium 2-cyclooctyl-2-[(3-methylisoxazole-4-carbonyl)amino]acetate

To a solution of *Intermediate 4* (11.01 g, 35.7 mmol) in THF (90 mL) were added
5 water (30 mL) and lithium hydroxide monohydrate (2.25 g, 53.6 mmol). The reaction
mixture was stirred at r.t. for 16 h, then concentrated *in vacuo*. To the residue was added
diethyl ether (50 mL). The mixture was stirred for 10 minutes, then filtered. The
resultant solid was washed with diethyl ether (50 mL) and pentane (50 mL), then dried
under vacuum, to afford the *title compound* (9.51 g, 91%) as an off-white solid. δ_{H} (400
10 MHz, DMSO- d_6) 9.69 (s, 1H), 8.21 (s, 1H), 4.11 (dd, J 8.0, 4.0 Hz, 1H), 2.35 (s, 3H),
2.05 (br s, 1H), 1.65-1.35 (m, 14H). HPLC-MS (method 5): MH^+ m/z 295, RT 5.4
minutes.

INTERMEDIATE 6

15

N-(4-Bromo-2-nitrophenyl)oxetan-3-amine

To a stirred solution of 4-bromo-1-fluoro-2-nitrobenzene (2.00 g, 9.09 mmol) in
THF (50 mL) were added oxetan-3-amine (0.80 g, 10.9 mmol) and potassium carbonate
(1.26 g, 9.09 mmol) at 0°C. The reaction mixture was heated in a sealed tube at 60°C for
20 6 h, then diluted with EtOAc (500 mL) and washed with water (2 x 200 mL). The
organic layer was separated and dried over sodium sulfate, then filtered and concentrated
in vacuo. The residue was purified by recrystallisation from 5% EtOAc in hexanes (100
mL) to afford the *title compound* (2.20 g, 86%) as a yellow solid. δ_{H} (400 MHz, DMSO-
 d_6) 8.26 (d, J 3.9 Hz, 1H), 8.19 (d, J 2.0 Hz, 1H), 7.65 (dd, J 9.1, 2.2 Hz, 1H), 6.69 (d, J
25 9.3 Hz, 1H), 4.92-4.86 (m, 2H), 4.84-4.77 (m, 1H), 4.59-4.54 (m, 2H). HPLC-MS
(method 6): no ionisation, RT 1.97 minutes.

INTERMEDIATE 7

30 4-Bromo-*N*¹-(oxetan-3-yl)benzene-1,2-diamine

To a solution of *Intermediate 6* (2.20 g, 8.06 mmol) in MeOH (100 mL) were
added zinc (2.64 g, 40.3 mmol) and ammonium formate (2.54 g, 40.3 mmol) at 0°C. The
reaction mixture was allowed to warm to r.t. with stirring. After 1 h, the reaction mixture

was filtered through a pad of Celite[®], washing with MeOH (3 x 50 mL), and the filtrate was concentrated *in vacuo*. The residue was dissolved in DCM (500 mL), cooled to 0°C over 15 minutes, then decanted and washed with water (2 x 200 mL). The organic layer was separated and dried over sodium sulfate, then filtered and concentrated *in vacuo*. The residue was purified by recrystallisation from 5% EtOAc in hexanes (100 mL) to afford the *title compound* (1.60 g, 81%) as a brown solid. δ_{H} (400 MHz, DMSO-d₆) 6.69 (s, 1H), 6.54 (d, *J* 8.3 Hz, 1H), 6.02 (d, *J* 8.3 Hz, 1H), 5.27 (d, *J* 5.4 Hz, 1H), 4.92 (br s, 2H), 4.89-4.82 (m, 2H), 4.50-4.38 (m, 3H). HPLC-MS (method 6): MH⁺ *m/z* 243, RT 1.74 minutes.

10

INTERMEDIATE 8

6-Bromo-3-(oxetan-3-yl)-1H-benzimidazol-2-one

To a solution of *Intermediate 7* (1.60 g, 6.58 mmol) in THF (50 mL) was added 1,1'-carbonyldiimidazole (1.60 g, 9.87 mmol) at 0°C. The reaction mixture was stirred at r.t. for 6 h, then quenched with water (100 mL) and extracted with a 10% solution of MeOH in DCM (2 x 200 mL). The organic layer was separated and washed with brine (100 mL), then dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by recrystallisation from 20% EtOAc in hexanes (50 mL) to afford the *title compound* (1.40 g, 77%) as a light pink solid. δ_{H} (400 MHz, DMSO-d₆) 11.14 (br s, 1H), 7.38 (d, *J* 8.3 Hz, 1H), 7.24 (dd, *J* 8.6, 1.7 Hz, 1H), 7.16 (d, *J* 2.0 Hz, 1H), 5.49-5.41 (m, 1H), 5.04-5.00 (m, 2H), 4.97-4.90 (m, 2H). HPLC-MS (method 6): M⁺ *m/z* 269, RT 1.66 minutes.

25

INTERMEDIATE 9

5-Bromo-1-(oxetan-3-yl)-3-[2-(trimethylsilyl)ethoxymethyl]benzimidazol-2-one

To a stirred solution of *Intermediate 8* (1.40 g, 5.20 mmol) in DMF (30 mL) was added sodium hydride (0.19 g, 7.80 mmol) at 0°C. The reaction mixture was stirred at 0°C for 30 minutes. SEM-Cl (1.74 g, 10.4 mmol) was added at 0°C, and the reaction mixture was allowed to warm to r.t. After 3 h, the reaction mixture was quenched with water (50 mL) and extracted with EtOAc (2 x 200 mL). The organic layer was separated, washed with water (200 mL) and brine (100 mL), then dried over sodium sulfate, filtered

30

and concentrated *in vacuo*. The residue was purified by flash column chromatography, using a gradient of EtOAc in hexanes (20-30%), to afford the *title compound* (1.40 g, 66%) as a light pink solid. δ_{H} (400 MHz, DMSO- d_6) 7.51 (s, 1H), 7.45 (d, *J* 8.8 Hz, 1H), 7.34 (dd, *J* 8.3, 1.0 Hz, 1H), 5.51 (t, *J* 6.9 Hz, 1H), 5.26 (s, 2H), 5.06-5.01 (m, 2H), 4.98-4.92 (m, 2H), 3.55 (t, *J* 8.1 Hz, 2H), 0.89-0.83 (m, 2H), -0.07 (s, 9H). HPLC-MS (method 6): MH+ *m/z* 401, RT 2.20 minutes.

INTERMEDIATE 10

10 5-Amino-1-(oxetan-3-yl)-3-[2-(trimethylsilyl)ethoxymethyl]benzimidazol-2-one

To a solution of *Intermediate 9* (0.40 g, 1.00 mmol) in DMSO (20 mL) were added sodium azide (0.13 g, 2.00 mmol) and potassium carbonate (0.42 g, 3.00 mmol) at r.t. The reaction mixture was purged with argon for 30 minutes. Copper(I) iodide (0.02 g, 0.10 mmol) and L-proline (0.12 g, 1.00 mmol) were added, and the reaction mixture was again purged with nitrogen for 10 minutes. The reaction mixture was heated at 100°C for 16 h, then diluted with EtOAc (400 mL) and washed with water (2 x 100 mL) and brine (100 mL). The organic layer was separated and dried over sodium sulfate, then filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography, using a gradient of EtOAc in hexanes (50-60%), to afford the *title compound* (0.25 g, 57%) as a light yellow solid. δ_{H} (400 MHz, DMSO- d_6) 7.17 (d, *J* 8.3 Hz, 1H), 6.51 (d, *J* 2.0 Hz, 1H), 6.39 (dd, *J* 8.3, 2.0 Hz, 1H), 5.47-5.38 (m, 1H), 5.12 (s, 2H), 5.04-5.00 (m, 2H), 4.96-4.90 (m, 4H), 3.57-3.48 (m, 2H), 0.88-0.79 (m, 2H), -0.05 (s, 9H). HPLC-MS (method 6): MH+ *m/z* 336, RT 1.82 minutes.

25

INTERMEDIATE 11

N-[1-Cyclooctyl-2-({1-(oxetan-3-yl)-2-oxo-3-[2-(trimethylsilyl)ethoxymethyl]-benzimidazol-5-yl}amino)-2-oxoethyl]-3-methylisoxazole-4-carboxamide

To a solution of *Intermediate 10* (0.25 g, 0.75 mmol) and *Intermediate 5* (0.22 g, 0.75 mmol) in DCM (20 mL) was added propylphosphonic anhydride (50% solution in EtOAc, 1.42 g, 4.47 mmol) at 0°C. The reaction mixture was stirred at r.t. for 12 h, then diluted with DCM (200 mL) and washed with water (50 mL). The organic layer was separated and dried over sodium sulfate, then filtered and concentrated *in vacuo*. The

residue was purified by flash column chromatography, using a gradient of EtOAc in hexanes (50-60%), to afford the *title compound* (0.25 g, 49%) as an off-white solid. δ_{H} (400 MHz, DMSO- d_6) 10.28 (s, 1H), 9.44 (s, 1H), 8.47 (d, J 8.8 Hz, 1H), 7.77 (s, 1H), 7.45-7.42 (m, 1H), 7.37-7.31 (m, 1H), 5.53-5.46 (m, 1H), 5.20 (s, 2H), 5.07-5.01 (m, 2H), 4.98-4.91 (m, 2H), 4.51-4.46 (m, 1H), 3.53 (t, J 8.1 Hz, 2H), 2.37 (s, 3H), 2.09-2.07 (m, 1H), 1.73-1.37 (m, 14H), 0.84 (t, J 7.8 Hz, 2H), -0.08 (s, 9H). HPLC-MS (method 6): MH+ m/z 612, RT 2.29 minutes.

INTERMEDIATE 12

10

N-(4-Bromo-2-nitrophenyl)tetrahydropyran-4-amine

To a stirred solution of 4-bromo-1-fluoro-2-nitrobenzene (2.00 g, 9.09 mmol) in THF (50 mL) were added tetrahydropyran-4-amine (1.10 g, 10.9 mmol) and potassium carbonate (1.26 g, 9.09 mmol) at 0°C. The reaction mixture was heated in a sealed tube at 60°C for 6 h, then diluted with EtOAc (500 mL) and washed with water (2 x 200 mL). The organic layer was separated and dried over sodium sulfate, then filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography, using a gradient of EtOAc in hexanes (0-15%), to afford the *title compound* (2.70 g, 96%) as an off-white solid. δ_{H} (400 MHz, DMSO- d_6) 8.18 (d, J 2.5 Hz, 1H), 7.92 (d, J 7.4 Hz, 1H), 7.65 (dd, J 9.4, 2.5 Hz, 1H), 7.20 (d, J 9.4 Hz, 1H), 3.94-3.82 (m, 3H), 3.50-3.44 (m, 2H), 1.93 (d, J 12.8 Hz, 2H), 1.64-1.50 (m, 2H). HPLC-MS (method 6): no ionisation, RT 1.89 minutes.

20

INTERMEDIATE 13

25

4-Bromo-*N*¹-(tetrahydropyran-4-yl)benzene-1,2-diamine

To a solution of *Intermediate 12* (2.00 g, 6.64 mmol) in MeOH (35 mL) were added ammonium formate (2.09 g, 33.2 mmol) and zinc (2.17 g, 33.2 mmol) at 0°C. The reaction mixture was allowed to warm to r.t. with stirring. After 1 h, the reaction mixture was filtered through a pad of Celite[®], washing with MeOH (3 x 50 mL), and the filtrate was concentrated *in vacuo*. The residue was diluted with water (100 mL) and extracted with EtOAc (3 x 80 mL). The organic layer was separated and dried over sodium sulfate, the filtered and concentrated *in vacuo*, to afford the *title compound* (1.71 g, 95%) as a

30

pale brown solid, which was utilised without further purification. δ_{H} (400 MHz, DMSO- d_6) 6.67 (d, J 2.5 Hz, 1H), 6.56 (dd, J 8.3, 2.5 Hz, 1H), 6.41 (d, J 8.3 Hz, 1H), 4.85 (s, 2H), 4.33 (d, J 7.8 Hz, 1H), 3.90-3.83 (m, 2H), 3.45-3.36 (m, 3H), 1.88 (d, J 12.7 Hz, 2H), 1.44-1.33 (m, 2H). HPLC-MS (method 6): MH^+ m/z 273, RT 1.83 minutes.

5

INTERMEDIATE 14

6-Bromo-3-(tetrahydropyran-4-yl)-1H-benzimidazol-2-one

To a solution of *Intermediate 13* (1.70 g, 6.27 mmol) in THF (50 mL) was added
10 1,1'-carbonyldiimidazole (1.53 g, 9.40 mmol) at 0°C. The reaction mixture was stirred at
r.t. for 6 h, then quenched with water (100 mL) and extracted with EtOAc (3 x 100 mL).
The organic layer was separated and washed with brine (100 mL), then dried over sodium
sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column
chromatography, using a gradient of EtOAc in hexanes (80-90%), to afford the *title*
15 *compound* (1.71 g, 92%) as an off-white solid. δ_{H} (400 MHz, DMSO- d_6) 11.04 (s, 1H),
7.26-7.22 (m, 1H), 7.17-7.13 (m, 1H), 7.11 (d, J 2.0 Hz, 1H), 4.43-4.34 (m, 1H), 3.97 (dd,
 J 11.5, 4.2 Hz, 2H), 3.45 (t, J 11.5 Hz, 2H), 2.40-2.29 (m, 2H), 1.68-1.58 (m, 2H).
HPLC-MS (method 6): MH^+ m/z 299, RT 1.61 minutes.

20

INTERMEDIATE 15

5-Bromo-1-(tetrahydropyran-4-yl)-3-[2-(trimethylsilyl)ethoxymethyl]benzimidazol-2-one

To a stirred solution of *Intermediate 14* (1.70 g, 5.72 mmol) in DMF (20 mL) was
added sodium hydride (0.34 g, 8.58 mmol) at 0°C. The reaction mixture was stirred at
25 0°C for 30 minutes. SEM-Cl (1.33 mL, 11.4 mmol) was added at 0°C, and the reaction
mixture was allowed to warm to r.t. After 2 h, the reaction mixture was quenched with
ice water (150 mL) and filtered, then washed with water (50 mL) and dried *in vacuo*, to
afford the *title compound* (2.01 g crude) as an off-white solid, which was utilised without
further purification. δ_{H} (400 MHz, DMSO- d_6) 7.45 (d, J 1.5 Hz, 1H), 7.35-7.31 (m, 1H),
30 7.28-7.22 (m, 1H), 5.25 (s, 2H), 4.48-4.39 (m, 1H), 3.98 (dd, J 11.5, 4.2 Hz, 2H), 3.56-
3.42 (m, 4H), 2.37-2.33 (m, 2H), 1.67-1.60 (m, 2H), 0.83 (t, J 8.1 Hz, 2H), -0.09 (s, 9H).
HPLC-MS (method 6): no ionisation, RT 2.25 minutes.

INTERMEDIATE 16

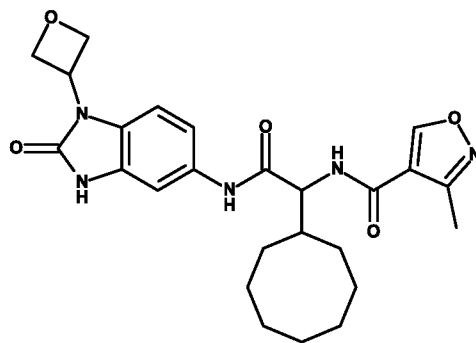
5-Amino-1-(tetrahydropyran-4-yl)-3-[2-(trimethylsilyl)ethoxymethyl]benzimidazol-2-one

To a solution of *Intermediate 15* (0.50 g, 1.17 mmol) in DMSO (10 mL) were
5 added sodium azide (0.23 g, 3.51 mmol) and potassium carbonate (0.65 g, 4.68 mmol) at
r.t. The reaction mixture was purged with argon for 30 minutes. Copper(I) iodide (0.22
g, 1.17 mmol) and L-proline (0.27 g, 2.34 mmol) were added. The reaction mixture was
heated at 120°C for 24 h, then diluted with water (80 mL) and extracted with EtOAc (3 x
50 mL). The organic layer was separated and washed with brine (50 mL), then dried over
10 sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash
column chromatography, using a gradient of EtOAc in hexanes (35-45%), to afford the
title compound (203 mg, 48%) as a pale brown semi-solid. δ_{H} (400 MHz, DMSO- d_6)
6.97 (d, J 8.3 Hz, 1H), 6.46 (d, J 1.5 Hz, 1H), 6.32 (dd, J 8.3, 2.0 Hz, 1H), 5.11 (s, 2H),
4.84 (br s, 2H), 4.30-4.36 (m, 1H), 3.93-4.00 (m, 2H), 3.40-3.54 (m, 4H), 2.27-2.37 (m,
15 2H), 1.57-1.61 (m, 2H), 0.82-0.88 (m, 2H), -0.02 (s, 9H). HPLC-MS (method 6): MH^+
 m/z 364, RT 1.92 minutes.

INTERMEDIATE 17

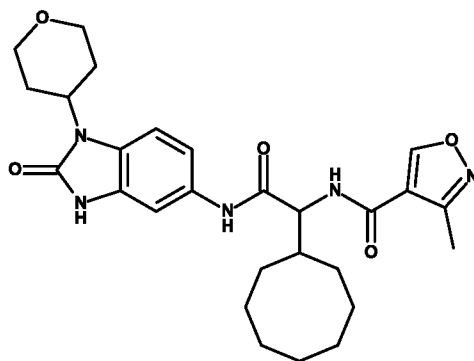
N-[1-Cyclooctyl-2-oxo-2-({2-oxo-1-(tetrahydropyran-4-yl)-3-[2-(trimethylsilyl)ethoxymethyl]benzimidazol-5-yl}amino)ethyl]-3-methylisoxazole-4-carboxamide

To a solution of *Intermediate 16* (0.20 g, 0.55 mmol) and *Intermediate 5* (0.16 g,
0.55 mmol) in DCM (20 mL) was added propylphosphonic anhydride (50% solution in
EtOAc, 1.05 g, 3.30 mmol) at 0°C. The reaction mixture was stirred at r.t. for 12 h, then
25 diluted with DCM (100 mL) and washed with water (50 mL). The organic layer was
separated and dried over sodium sulfate, then filtered and concentrated *in vacuo*. The
residue was purified by flash column chromatography, using a gradient of EtOAc in
hexanes (50-60%), to afford the *title compound* (0.23 g, 65%) as an off-white solid. δ_{H}
(400 MHz, DMSO- d_6) 10.20 (s, 1H), 9.44 (s, 1H), 8.44 (d, J 8.8 Hz, 1H), 7.68 (s, 1H),
30 7.28 (s, 2H), 5.19 (s, 2H), 4.49-4.41 (m, 2H), 4.04-3.93 (m, 3H), 3.54-3.43 (m, 4H), 2.37
(s, 3H), 2.09-2.06 (m, 2H), 1.73-1.36 (m, 16H), 0.87-0.79 (m, 2H), -0.10 (s, 9H). HPLC-
MS (method 6): M^+ m/z 639, RT 2.26 minutes.

EXAMPLE 1

N-(1-Cyclooctyl-2-[[1-(oxetan-3-yl)-2-oxo-3H-benzimidazol-5-yl]amino]-2-oxoethyl)-3-methylisoxazole-4-carboxamide

- 5 To a solution of *Intermediate 11* (0.16 g, 0.26 mmol) in DCM (20 mL) was added TFA (1.00 mL, 13.1 mmol) at 0°C. The reaction mixture was stirred at r.t. for 30 minutes, then concentrated *in vacuo*. The residue was diluted with acetonitrile (2 mL) and methanolic ammonia (3 mL) at 0°C and stirred at r.t. for 10 minutes, then concentrated *in vacuo*. The residue was purified by flash column chromatography, using
- 10 a gradient of MeOH in DCM (3-4%), to afford the *title compound* (35 mg, 27%) as a white solid. δ_{H} (400 MHz, DMSO- d_6) 10.92 (s, 1H), 10.18 (s, 1H), 9.43 (s, 1H), 8.47 (d, J 8.8 Hz, 1H), 7.59 (s, 1H), 7.36 (d, J 8.8 Hz, 1H), 7.19 (d, J 8.3 Hz, 1H), 5.43 (t, J 7.1 Hz, 1H), 5.04 (t, J 6.4 Hz, 2H), 4.96-4.91 (m, 2H), 4.46 (t, J 8.8 Hz, 1H), 2.37 (s, 3H), 2.09-2.07 (m, 1H), 1.65-1.36 (m, 14H). HPLC-MS (method 6): MH^+ m/z 482, RT 2.52
- 15 minutes.

EXAMPLE 2

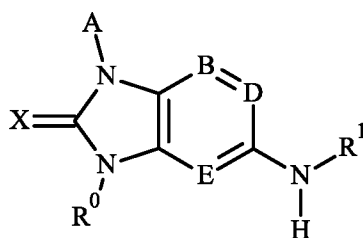
N-(1-Cyclooctyl-2-oxo-2-{[2-oxo-1-(tetrahydropyran-4-yl)-3*H*-benzimidazol-5-yl]-amino}ethyl)-3-methylisoxazole-4-carboxamide

- 5 To a solution of *Intermediate 17* (0.20 g, 0.31 mmol) in DCM (5 mL) was added TFA (0.96 mL, 12.5 mmol) at 0°C. The reaction mixture was stirred at r.t. for 3 h, then concentrated *in vacuo*. The residue was diluted with acetonitrile (1 mL) and methanolic ammonia (2 mL) at 0°C and stirred at r.t. for 1 h, then concentrated *in vacuo*. The residue was purified by flash column chromatography, using a gradient of MeOH in DCM (3-
10 4%), to afford the *title compound* (9 mg, 57%) as a white solid. δ_{H} (400 MHz, DMSO- d_6) 10.81 (s, 1H), 10.13 (s, 1H), 9.43 (s, 1H), 8.47 (d, J 8.8 Hz, 1H), 7.52 (s, 1H), 7.20-7.16 (m, 1H), 7.14-7.10 (m, 1H), 4.45 (t, J 8.8 Hz, 1H), 4.40-4.30 (m, 1H), 3.98 (dd, J 11.0, 3.7 Hz, 2H), 3.45 (t, J 11.5 Hz, 2H), 2.37 (s, 3H), 2.35-2.31 (m, 2H), 2.13-2.07 (m, 1H), 1.72-1.35 (m, 16H). HPLC-MS (method 6): MH^+ m/z 510, RT 2.60 minutes.

Claims:

1. A compound of formula (I) or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof:

5



(I)

wherein

A represents C₃₋₉ cycloalkyl, C₃₋₇ heterocycloalkyl or C₄₋₉ heterobicycloalkyl, any
10 of which groups may be optionally substituted by one or more substituents;

B represents C-R² or N;

D represents C-R³ or N;

E represents C-R⁴ or N;

X represents O or S;

15 R⁰ represents hydrogen or C₁₋₆ alkyl;

R¹ represents -COR^a or -SO₂R^b; or R¹ represents C₁₋₆ alkyl, C₃₋₉ cycloalkyl, C₃₋₉ cycloalkyl(C₁₋₆)alkyl, C₅₋₉ spirocycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents;

20 R² represents hydrogen, halogen, cyano, C₁₋₆ alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkylsulphinyl or C₁₋₆ alkylsulphonyl;

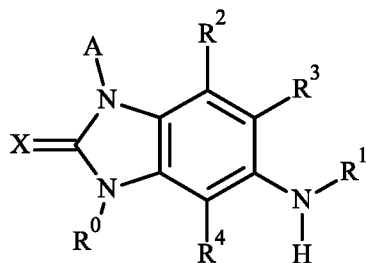
R³ represents hydrogen, halogen, cyano, C₁₋₆ alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkylsulphinyl or C₁₋₆ alkylsulphonyl;
25

R⁴ represents hydrogen, halogen, cyano, C₁₋₆ alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkylsulphinyl or C₁₋₆ alkylsulphonyl;

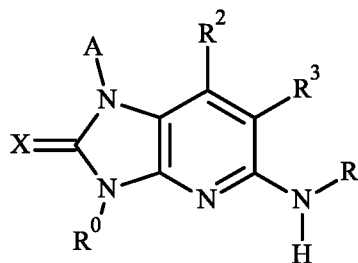
R^a represents hydrogen; or R^a represents C_{1-6} alkyl, C_{2-7} alkenyl, C_{3-9} cycloalkyl, C_{3-9} cycloalkyl(C_{1-6})alkyl, C_{3-9} cycloalkylidenyl(C_{1-6})alkyl, C_{4-9} bicycloalkyl(C_{1-6})alkyl, C_{4-9} bicycloalkylidenyl(C_{1-6})alkyl, C_{5-9} spirocycloalkyl(C_{1-6})alkyl, C_{9-11} tricycloalkyl-
 5 (C_{1-6}) alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkylidenyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; and

R^b represents C_{1-6} alkyl, C_{2-7} alkenyl, C_{3-9} cycloalkyl, C_{3-9} cycloalkyl(C_{1-6})alkyl, C_{3-9} cycloalkylidenyl(C_{1-6})alkyl, C_{4-9} bicycloalkyl(C_{1-6})alkyl, C_{4-9} bicycloalkylidenyl-
 10 (C_{1-6}) alkyl, C_{5-9} spirocycloalkyl(C_{1-6})alkyl, C_{9-11} tricycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkylidenyl-
 (C_{1-6}) alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

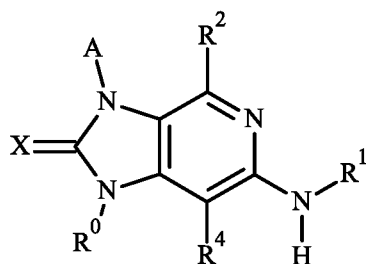
2. A compound as claimed in claim 1 represented by formula (I-1), (I-2), (I-3),
 15 (I-4) or (I-5) or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof:



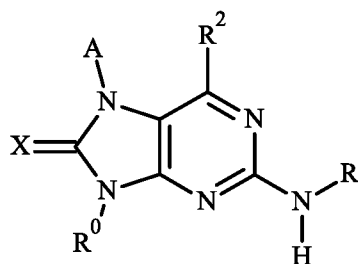
(I-1)



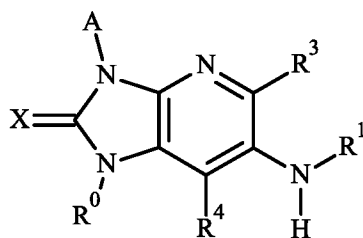
(I-2)



(I-3)



(I-4)



(I-5)

wherein A, X, R⁰, R¹, R², R³ and R⁴ are as defined in claim 1.

5 3. A compound as claimed in claim 1 or claim 2 wherein R¹ represents -COR^a, in which R^a is as defined in claim 1.

4. A compound as claimed in claim 3 wherein R^a represents -CH(R⁵)N(H)C(O)R⁶, -CH(R⁵)N(H)S(O)₂R⁶, -C(=CR^{5a}R^{5b})N(H)C(O)R⁶, -CH(R⁵)R⁷, -CH(R⁵)N(H)R⁷ or
10 -CH(R⁵)C(O)N(H)R⁷, in which

R⁵ represents hydrogen; or R⁵ represents C₁₋₅ alkyl, C₃₋₉ cycloalkyl, C₃₋₉ cycloalkyl(C₁₋₅)alkyl, C₄₋₉ bicycloalkyl, C₄₋₉ bicycloalkyl(C₁₋₅)alkyl, C₅₋₉ spirocycloalkyl, C₅₋₉ spirocycloalkyl(C₁₋₅)alkyl, C₉₋₁₁ tricycloalkyl, C₉₋₁₁ tricycloalkyl(C₁₋₅)alkyl, aryl, aryl-(C₁₋₅)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₅)alkyl, heteroaryl or
15 heteroaryl(C₁₋₅)alkyl, any of which groups may be optionally substituted by one or more substituents;

R^{5a} represents C₃₋₇ cycloalkyl, C₄₋₉ bicycloalkyl, aryl, C₃₋₇ heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents; and

20 R^{5b} represents hydrogen or C₁₋₆ alkyl; or

R^{5a} and R^{5b}, when taken together with the carbon atom to which they are both attached, represent C₃₋₇ cycloalkyl, C₄₋₉ bicycloalkyl or C₃₋₇ heterocycloalkyl, any of which groups may be optionally substituted by one or more substituents;

R⁶ represents -NR^{6a}R^{6b} or -OR^{6c}; or R⁶ represents C₁₋₉ alkyl, C₃₋₉ cycloalkyl, C₃₋₉ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl-(C₁₋₆)alkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl or spiro[(C₃₋₇)heterocycloalkyl][heteroaryl],
25 any of which groups may be optionally substituted by one or more substituents;

R^{6a} represents hydrogen; or R^{6a} represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl or spiro[(C_{3-7})heterocycloalkyl][heteroaryl], any of which groups may be optionally substituted by one or more substituents;

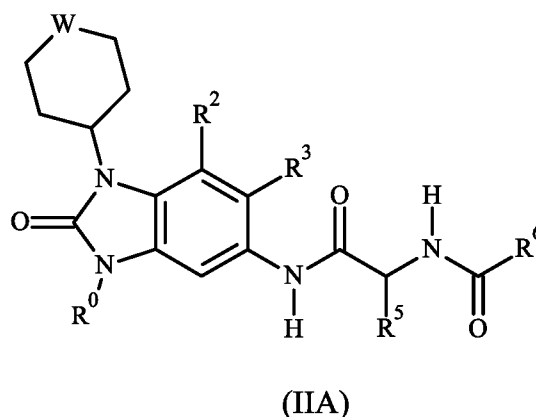
5 R^{6b} represents hydrogen or C_{1-6} alkyl;

R^{6c} represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; and

10 R^7 represents aryl, heteroaryl or spiro[(C_{3-7})heterocycloalkyl][heteroaryl], any of which groups may be optionally substituted by one or more substituents.

5. A compound as claimed in claim 4 represented by formula (IIA), or a pharmaceutically acceptable salt thereof:

15



wherein

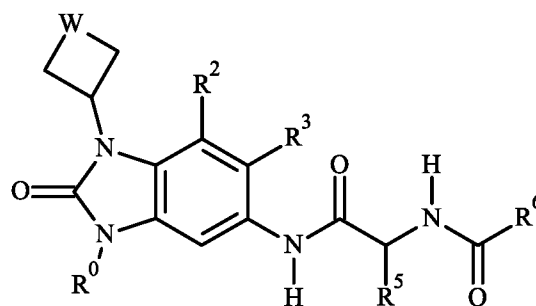
W represents O, S, S(O), S(O)₂, S(O)(NH) or N- R^{17} ;

20 R^{17} represents hydrogen or C_{1-6} alkyl;

R^0 , R^2 and R^3 are as defined in claim 1; and

R^5 and R^6 are as defined in claim 4.

6. A compound as claimed in claim 4 represented by formula (IIB), or a
25 pharmaceutically acceptable salt thereof:



(IIB)

wherein

R^0 , R^2 and R^3 are as defined in claim 1;

5 R^5 and R^6 are as defined in claim 4; and

W is as defined in claim 5.

7. A compound as claimed in any one of claims 4 to 6 wherein R^5 represents C_{1-5} alkyl, C_{3-9} cycloalkyl, C_{3-9} cycloalkyl(C_{1-5})alkyl, C_{4-9} bicycloalkyl, C_{4-9} bicycloalkyl(C_{1-5})alkyl, C_{5-9} spirocycloalkyl, C_{9-11} tricycloalkyl, C_{9-11} tricycloalkyl(C_{1-5})alkyl, aryl, aryl-
 10 (C_{1-5})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-5})alkyl or heteroaryl(C_{1-5})alkyl, any of which groups may be optionally substituted by one, two or three substituents independently selected from halogen, cyano, C_{1-6} alkyl, trifluoromethyl, phenyl, hydroxy, C_{1-6} alkoxy and aminocarbonyl.

15

8. A compound as claimed in any one of claims 4 to 7 wherein R^6 represents $-NR^{6a}R^{6b}$ or $-OR^{6c}$; or R^6 represents C_{1-9} alkyl, aryl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl or spiro[(C_{3-7})heterocycloalkyl][heteroaryl], any of which groups may be optionally substituted by one, two or three substituents independently selected
 20 from halogen, cyano, nitro, C_{1-6} alkyl, difluoromethyl, trifluoromethyl, difluoroethyl, trifluoroethyl, trifluoropropyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, phenyl, fluorophenyl, hydroxy, hydroxy(C_{1-6})alkyl, oxo, C_{1-6} alkoxy, C_{1-6} alkoxy(C_{1-6})alkyl, difluoromethoxy, trifluoromethoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, (C_{1-6})alkylsulfonyl(C_{1-6})alkyl, C_{1-6} alkylsulfonyloxy, amino, amino(C_{1-6})alkyl, C_{1-6}
 25 alkylamino, di(C_{1-6})alkylamino, di(C_{1-6})alkylamino(C_{1-6})alkyl, pyrrolidinyl, dioxo-isothiazolidinyl, tetrahydropyranyl, morpholinyl, piperazinyl, C_{2-6} alkylcarbonylamino, C_{2-6} alkylcarbonylamino(C_{1-6})alkyl, C_{2-6} alkoxy carbonylamino, C_{1-6} alkylsulfonylamino,

formyl, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxy carbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl, di(C₁₋₆)alkylaminosulfonyl and di(C₁₋₆)alkylsulfoximiny.

5 9. A compound as claimed in claim 1 as herein specifically disclosed in any one of the Examples.

10 10. A compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof, for use in therapy.

11. A compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of disorders for which the administration of a modulator of IL-17 function is indicated.

15 12. A compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of an inflammatory or autoimmune disorder.

20 13. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

25 14. A pharmaceutical composition as claimed in claim 13 further comprising an additional pharmaceutically active ingredient.

15. The use of a compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment and/or prevention of disorders for which the administration of a modulator of IL-17 function is indicated.

30 16. The use of a compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof, for the manufacture of a

medicament for the treatment and/or prevention of an inflammatory or autoimmune disorder.

5 17. A method for the treatment and/or prevention of disorders for which the administration of a modulator of IL-17 function is indicated which comprises administering to a patient in need of such treatment an effective amount of a compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof.

10 18. A method for the treatment and/or prevention of an inflammatory or autoimmune disorder, which comprises administering to a patient in need of such treatment an effective amount of a compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/082774

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/422 C07D413/14 A61P29/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 144 341 A (CLARK ROBERT L ET AL) 13 March 1979 (1979-03-13) see compounds of claim 1 as anti-inflammatory agents and definition of residue R4 -----	1-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

3 March 2020

Date of mailing of the international search report

23/03/2020

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Authorized officer

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2019/082774

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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			BE 842255 A 26-11-1976
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