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(54) Title: FUSED THIOPHENE DERIVATIVES AS MEK INHIBITORS

(57) Abstract: A series of 7-oxo-4,5,6,7-tetrahydrothieno[2,3-c]pyridine derivatives, and analogues thereof, which are substituted in the 2-position by a substituted anilino moiety, being selective inhibitors of human MEK (MAPKK) enzymes, are accordingly of benefit in medicine, for example in the treatment of inflammatory, autoimmune, cardiovascular, proliferative (including oncological) and nociceptive conditions.

FUSED THIOPHENE DERIVATIVES AS MEK INHIBITORS

The present invention relates to a class of fused thiophene derivatives and to their use in therapy. More particularly, the invention is concerned with 7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine derivatives, and analogues thereof, which are substituted in the 2-position by a substituted anilino moiety. These compounds are selective inhibitors of MEK (MAPKK) enzymes, and are accordingly of benefit as pharmaceutical agents, especially in the treatment of adverse inflammatory, autoimmune, cardiovascular, proliferative (including oncological) and nociceptive conditions.

MEK enzymes are implicated in a variety of physiological and pathological functions that are believed to be operative in a range of human diseases. These functions are summarised in paragraphs [0004] and [0005] of US 2005/0049276 A1.

The compounds of use in the present invention, being potent and selective MEK inhibitors, are therefore beneficial in the treatment and/or prevention of various human ailments. These include autoimmune and inflammatory disorders such as rheumatoid arthritis, osteoarthritis, multiple sclerosis, asthma, inflammatory bowel disease, psoriasis and transplant rejection; cardiovascular disorders including thrombosis, cardiac hypertrophy, hypertension, and irregular contractility of the heart (e.g. during heart failure); proliferative disorders such as restenosis, and oncological conditions including leukaemia, glioblastoma, lymphoma, melanoma, and human cancers of the liver, bone, skin, brain, pancreas, lung, breast, stomach, colon, rectum, prostate, ovary and cervix; and pain and nociceptive disorders, including chronic pain and neuropathic pain.

In addition, the compounds of use in 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 use in this invention may be useful as radioligands in assays for detecting compounds capable of binding to human MEK enzymes.

WO 2005/023818 describes a broad-ranging class of compounds based on a fused heterobicyclic ring system, which generically encompasses 5,6-dihydro-1-benzothiophen-7(4*H*)-one and 5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one derivatives attached to a substituted anilino moiety but nowhere specifically discloses any actual compound of this type. Whilst no discrete pharmacological activity is ascribed to the compounds described

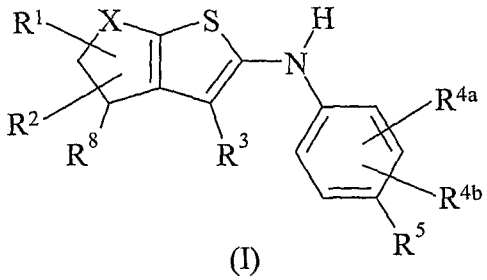
therein, they are nevertheless stated to be useful *inter alia* in the treatment of cell proliferative diseases such as cancer.

Copending international patent application no. PCT/GB2007/003114, published on 21 February 2008 as WO 2008/020206, describes a class of fused bicyclic thiophene derivatives which are selective inhibitors of MEK enzymes and are accordingly of benefit in medicine, for example in the treatment of adverse inflammatory, autoimmune, cardiovascular, proliferative (including oncological) and nociceptive conditions.

The compounds of the present invention are potent and selective MEK inhibitors having a binding affinity (IC_{50}) for the human MEK1 and/or MEK2 enzyme of 50 μM or less, generally of 20 μM or less, usually of 5 μM or less, typically of 1 μM or less, suitably of 500 nM or less, ideally of 100 nM or less, and preferably of 20 nM or less (the skilled person will appreciate that a *lower* IC_{50} figure denotes a *more active* compound). The compounds of the invention may possess at least a 10-fold selective affinity, typically at least a 20-fold selective affinity, suitably at least a 50-fold selective affinity, and ideally at least a 100-fold selective affinity, for the human MEK1 and/or MEK2 enzyme relative to other human kinases.

The compounds of the present invention possess interesting pharmacokinetic properties owing to their improved solubility and clearance.

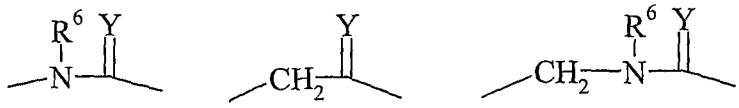
The present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof:



(I)

wherein

-X- represents a group of formula (a), (b) or (c):



(a) (b) (c)

Y represents oxygen, sulphur or N-R^7;

R^1 and R^2 independently represent hydrogen; or 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; or

R^1 and R^2, when both are attached to the same carbon atom, represent, when taken together with the carbon atom to which they are both attached, C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents; or

R^1 and R^2, when attached to adjacent carbon atoms, represent, when taken together with the carbon atoms to which they are attached, C_{5-7} cycloalkyl, phenyl or heteroaryl, any of which groups may be optionally benzo-fused and/or substituted by one or more substituents;

R^3 represents hydrogen, C_{1-6} alkyl, C_{3-7} heterocycloalkenyl (optionally substituted by one or two methyl groups), cyano, $-CO_2R^a$, $-COR^b$, $-CONR^bR^c$, $-SO_2NR^bR^c$, $-CON(OR^b)R^c$, $-CON(R^c)COR^b$, $-CON(R^c)SO_2R^b$, $-SO_2N(R^c)COR^b$, $-CON(R^d)NR^bR^c$, $-C(=NR^e)NR^bR^c$ or $-CON(R^d)C(=NR^e)NR^bR^c$; or

R^3 represents an optionally substituted five-membered heteroaromatic ring selected from furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl; or

R^3 represents an optionally substituted six-membered heteroaromatic ring selected from pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl and triazinyl;

R^{4a} and R^{4b} independently represent hydrogen, halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, C_{1-6} alkoxy, trifluoromethoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl or C_{1-6} alkylsulphonyl;

R^5 represents halogen, nitro, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxy(C_{1-6})alkyl or formyl;

R^6 represents hydrogen, C_{1-6} alkyl, formyl, C_{2-6} alkylcarbonyl, trifluoromethylcarbonyl or C_{1-6} alkylsulphonyl;

R^7 represents hydrogen or C_{1-6} alkyl;

R^8 represents halogen, $-OR^x$, $-S(O)_nR^x$ or $-NR^yR^z$;

n is zero, 1 or 2;

R^a represents hydrogen, C_{1-6} alkyl or C_{3-7} heterocycloalkyl(C_{1-6})alkyl;

R^b represents hydrogen or trifluoromethyl; or 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, C_{4-9} heterobicycloalkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; and

R^c represents hydrogen or C_{1-6} alkyl (optionally substituted by hydroxy); or

R^b and R^c, when taken together with the nitrogen atom to which they are both attached, represent azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, homopiperidinyl, homomorpholinyl or homopiperazinyl, any of which groups may be optionally substituted by one or more substituents; or

the moiety $-N(OR^b)R^c$ represents an optionally substituted heterocyclic ring wherein R^b and R^c are taken together and represent a C_{2-5} alkylene linkage;

R^d and R^e independently represent hydrogen or C_{1-6} alkyl; and

R^x, R^y and R^z independently represent hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Where a group 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 a group will be unsubstituted, or substituted by one or two substituents. Suitably, such a group will be unsubstituted or monosubstituted.

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 the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound of the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, e.g. carboxy, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g.

sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope solvates of the compounds of formula (I) above. Such solvates may be formed with common organic solvents, e.g. hydrocarbon solvents such as benzene or toluene; chlorinated solvents such as chloroform or dichloromethane; alcoholic solvents such as methanol, ethanol or isopropanol; ethereal solvents such as diethyl ether or tetrahydrofuran; or ester solvents such as ethyl acetate. Alternatively, the solvates of the compounds of formula (I) may be formed with water, in which case they will be hydrates.

Suitable alkyl groups which may be present on the compounds of the invention include straight-chained and branched C_{1-6} alkyl groups, for example C_{1-4} alkyl 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 and 2,2-dimethylpropyl. Derived expressions such as "C_{1-6} alkoxy", "C_{1-6} alkylthio", "C_{1-6} alkylsulphonyl" and "C_{1-6} alkylamino" are to be construed accordingly.

Specific C_{3-7} cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Suitable aryl groups include phenyl and naphthyl, preferably phenyl.

Suitable aryl(C_{1-6})alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups, which may comprise benzo-fused analogues thereof, include azetidinyl, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, indolinyl, thiazolidinyl, imidazolidinyl, tetrahydropyranyl, piperidinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, piperazinyl, 1,2,3,4-tetrahydroquinoxalinyl, morpholinyl, thiomorpholinyl, homopiperidinyl and homopiperazinyl.

A typical C_{3-7} heterocycloalkenyl group is dihydroimidazolyl (e.g. 4,5-dihydro-1*H*-imidazol-2-yl).

A typical C_{4-9} heterobicycloalkyl group is azabicyclo[2.2.2]octyl (e.g. quinuclidin-3-yl).

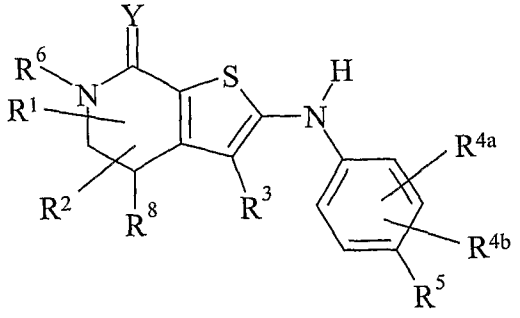
Suitable heteroaryl groups include furyl, benzofuryl, dibenzofuryl, thienyl, benzothienyl, pyrrolyl, indolyl, pyrrolo[2,3-*b*]pyridinyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, imidazo[1,2-*a*]pyridinyl, benzimidazolyl,

oxadiazolyl, thiadiazolyl, triazolyl, benzotriazolyl, tetrazolyl, pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl and pyrazinyl groups.

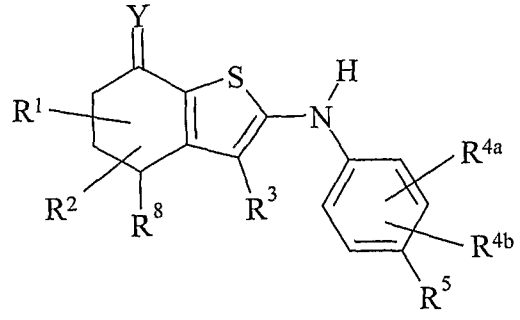
The term "halogen" as used herein is intended to include fluorine, chlorine, bromine and iodine atoms.

Where the compounds of formula (I) have one or more asymmetric centres, they may accordingly exist as enantiomers. Where the compounds of the invention possess two or more asymmetric centres, they may additionally exist as diastereomers. The invention is to be understood to extend to 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 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 ($CH_2C=O$)↔enol ($CH=CHOH$) tautomers or amide ($NHC=O$)↔hydroxyimine ($N=COH$) tautomers. Formula (I) and the formulae depicted hereinafter are intended to represent all individual tautomers and all possible mixtures thereof, unless stated or shown otherwise.

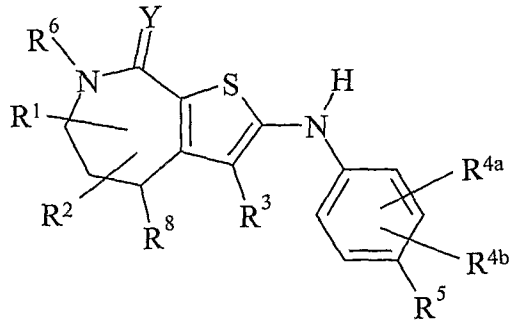
Specific sub-classes of compounds in accordance with the present invention are represented by the compounds of formula (IA), (IB) and (IC):



(IA)



(IB)



(IC)

wherein Y, R^1, R^2, R^3, R^{4a}, R^{4b}, R^5, R^6 and R^8 are as defined above.

In one embodiment, the compounds according to the present invention are represented by formula (IA) as depicted above. In another embodiment, the compounds according to the present invention are represented by formula (IB) as depicted above. In a further embodiment, the compounds according to the present invention are represented by formula (IC) as depicted above.

In one embodiment of the compounds of formula (I), -X- represents a group of formula (a) as depicted above. In another embodiment, -X- represents a group of formula (b) as depicted above. In a further embodiment, -X- represents a group of formula (c) as depicted above.

In one embodiment, Y is oxygen. In another embodiment, Y is sulphur. In a further embodiment, Y is N-R^7 in which R^7 is as defined above.

Suitably, R^1 represents hydrogen; or C_{1-6} alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

Suitably, R^2 represents hydrogen or optionally substituted C_{1-6} alkyl.

Examples of typical substituents on R^1 and/or R^2 include halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulphonylamino, formyl, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, aminocarbonyl, C_{1-6} alkylamino-carbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulphonyl, C_{1-6} alkylaminosulphonyl and di(C_{1-6})alkylaminosulphonyl; especially halogen, C_{1-6} alkoxy or C_{1-6} alkylthio.

Examples of particular substituents on R^1 and/or R^2 include fluoro, chloro, bromo, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoro-methoxy, phenoxy, methylthio, methylsulphonyl, amino, methylamino, dimethylamino, acetylamino, methoxycarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy,

methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl; especially chloro, methoxy or methylthio.

Typical values of R^1 include hydrogen, methyl, *n*-propyl, isopropyl, phenyl, chlorophenyl, methoxyphenyl, methylthiophenyl and furyl. In one embodiment, R^1 is hydrogen. In another embodiment, R^1 is C_{1-6} alkyl, especially methyl.

Typical values of R^2 include hydrogen and methyl. In one embodiment, R^2 is hydrogen. In another embodiment, R^2 is C_{1-6} alkyl, especially methyl.

Alternatively, R^1 and R^2, when both are attached to the same carbon atom, may together form an optionally substituted spiro linkage. Thus, R^1 and R^2, when both are attached to the same carbon atom, may represent, when taken together with the carbon atom to which they are both attached, C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be unsubstituted, or substituted by one or more, typically by one or two, substituents. In this context, R^1 and R^2, when taken together with the carbon atom to which they are both attached, may suitably represent an optionally substituted cyclopentyl, cyclohexyl, pyrrolidine or piperidine ring, especially cyclopentyl or cyclohexyl.

Alternatively, R^1 and R^2, when attached to adjacent carbon atoms, may together form an optionally benzo-fused and/or substituted cycloalkyl, phenyl or heteroaryl (e.g. pyridinyl) ring fused to the ring containing the variable X. Thus, R^1 and R^2, when attached to adjacent carbon atoms, may represent, when taken together with the carbon atoms to which they are attached, C_{5-7} cycloalkyl, phenyl or heteroaryl (e.g. pyridinyl), any of which groups may be benzo-fused and/or unsubstituted, or substituted by one or more, typically by one or two, substituents. In this context, in one embodiment, R^1 and R^2, when taken together with the adjacent carbon atoms to which they are attached, suitably represent a phenyl ring fused to the ring containing the variable X. Also in this context, in another embodiment, R^1 and R^2, when taken together with the adjacent carbon atoms to which they are attached, suitably represent a benzo-fused cyclopentyl ring, i.e. an indanyl moiety fused to the ring containing the variable X.

Typically, R^a represents hydrogen or C_{1-6} alkyl. Suitably, R^a represents hydrogen, methyl or ethyl, especially hydrogen or ethyl. In one embodiment, R^a represents hydrogen. In another embodiment, R^a represents C_{1-6} alkyl. In one aspect of that embodiment, R^a represents methyl. In another aspect of that embodiment, R^a represents

ethyl. In a further embodiment, R^a represents C_{3-7} heterocycloalkyl(C_{1-6})alkyl, especially piperidinylmethyl.

Typically, R^b represents hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, C_{4-9} heterobicycloalkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Suitable values of R^b include hydrogen; or methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclohexylmethyl, benzyl, phenylethyl, azetidinyl, tetrahydrofuryl, tetrahydrothienyl, pyrrolidinyl, piperidinyl, homopiperidinyl, quinuclidinyl, azetidinylmethyl, tetrahydrofurylmethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, thiazolidinylmethyl, imidazolidinylethyl, piperidinylmethyl, piperidinylethyl, tetrahydroquinolinylmethyl, piperazinylpropyl, morpholinylethyl, morpholinylpropyl, pyridinyl, indolylethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, benzimidazolylmethyl, triazolylethyl, pyridinylmethyl and pyridinylethyl, any of which groups may be optionally substituted by one or more substituents.

Typical examples of suitable substituents on R^b, or on the heterocyclic moiety $-NR^bR^c$ or $-N(OR^b)R^c$, include C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino(C_{1-6})alkoxy, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, hydroxy, hydroxy(C_{1-6})alkyl, amino(C_{1-6})alkyl, nitro(C_{1-6})alkyl, cyano, trifluoromethyl, oxo, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, bis[hydroxy(C_{1-6})alkyl]amino, C_{1-6} alkylamino(C_{1-6})alkylamino, phenylamino, pyridinylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxycarbonylamino, [(C_{2-6})alkoxy-carbonyl][(C_{1-6})alkyl]amino, bis[(C_{2-6})alkoxycarbonyl(C_{1-6})alkyl]amino, C_{2-6} alkoxycarbonylamino(C_{1-6})alkyl, aminocarbonyl and guanidinyl.

Suitable examples of specific substituents on R^b, or on the heterocyclic moiety $-NR^bR^c$ or $-N(OR^b)R^c$, include methyl, ethyl, isopropyl, methoxy, isopropoxy, methylaminoethoxy, methoxymethyl, methylthio, ethylthio, methylsulphonyl, hydroxy, hydroxymethyl, hydroxyethyl, aminomethyl, nitromethyl, cyano, trifluoromethyl, oxo, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, amino, methylamino, ethylamino, dimethylamino, bis(hydroxyethyl)amino, ethylaminoethylamino, phenylamino, pyridinylamino, acetylamino, *tert*-

butoxycarbonylamino, (*tert*-butoxycarbonyl)(methyl)amino, bis(ethoxycarbonylmethyl)-amino, *tert*-butoxycarbonylaminomethyl, aminocarbonyl and guanidinyl.

Specific values of R^b include hydrogen, methyl, carboxymethyl, aminocarbonylmethyl, methoxyethyl (especially 2-methoxyethyl), methylaminoethoxyethyl (especially 2-[2-(methylamino)ethoxy]ethyl), ethylthioethyl (especially 2-(ethylthio)ethyl), methylsulphonylethyl (especially 2-(methylsulphonyl)ethyl), hydroxyethyl (especially 2-hydroxyethyl), cyanoethyl (especially 2-cyanoethyl), (hydroxy)(trifluoromethyl)ethyl (especially 2-hydroxy-3,3,3-trifluoropropyl), carboxyethyl (especially 2-carboxyethyl), ethoxycarbonylethyl (especially 2-(ethoxycarbonyl)ethyl), aminoethyl (especially 2-aminoethyl), (amino)(carboxy)ethyl (especially 2-amino-2-carboxyethyl), methylaminoethyl (especially 2-(methylamino)ethyl), dimethylaminoethyl (especially 2-(dimethylamino)ethyl), bis(hydroxyethyl)aminoethyl (especially 2-[bis(2-hydroxyethyl)amino]-ethyl), ethylaminoethylaminoethyl (especially 2-[2-(ethylamino)ethylamino]ethyl), phenylaminoethyl (especially 2-(phenylamino)ethyl), pyridinylaminoethyl (especially 2-(pyridin-2-ylamino)ethyl), acetylaminoethyl (especially 2-(acetylamino)ethyl), (*tert*-butoxycarbonylamino)(carboxy)ethyl (especially 2-(*tert*-butoxycarbonylamino)-2-carboxyethyl), (*tert*-butoxycarbonyl)(methyl)aminoethyl (especially 2-[*N*-(*tert*-butoxycarbonyl)-*N*-methylamino]ethyl), aminocarbonylethyl (especially 1-(aminocarbonyl)ethyl), propyl, methoxypropyl (especially 2-methoxy-1-methylethyl), isopropoxypropyl (especially 3-isopropoxypropyl), hydroxypropyl (especially 2-hydroxypropyl or 3-hydroxypropyl), dihydroxypropyl (especially 2,3-dihydroxypropyl), (carboxy)(methylthio)propyl (especially 1-carboxy-3-(methylthio)propyl), ethoxycarbonylpropyl (especially 2-ethoxycarbonyl-1-methylethyl), aminopropyl (especially 3-aminopropyl), (amino)(hydroxy)propyl (especially 3-amino-2-hydroxypropyl), methylaminopropyl (especially 3-(methylamino)propyl), ethylaminopropyl (especially 3-(ethylamino)propyl), dimethylaminopropyl (especially 3-(dimethylamino)propyl), *tert*-butyl, hydroxybutyl (especially 1,1-dimethyl-2-hydroxyethyl or 2-hydroxy-2-methylpropyl), dihydroxybutyl (especially 3,4-dihydroxybutyl), aminobutyl (especially 2-amino-2-methylpropyl or 4-aminobutyl), (carboxy)(guanidinyl)butyl (especially 1-carboxy-4-(guanidinyl)butyl), aminopentyl (especially 3-amino-2,2-dimethylpropyl), dimethylaminopentyl (especially 3-(dimethylamino)-2,2-dimethylpropyl), hydroxyhexyl (especially 1-(*tert*-butyl)-2-hydroxyethyl), hydroxycyclohexylmethyl, (aminomethyl)-cyclohexylmethyl, methoxybenzyl, (hydroxy)(phenyl)ethyl, (oxo)(phenyl)ethyl,

(carboxy)(hydroxyphenyl)ethyl, azetidinyl, (oxo)tetrahydrofuryl, (dioxo)tetrahydrothienyl, pyrrolidinyl, methylpyrrolidinyl, *tert*-butoxycarbonylpyrrolidinyl, piperidinyl, methylpiperidinyl, (oxo)homopiperidinyl, quinuclidinyl, azetidinylmethyl, hydroxyazetidinylmethyl, *tert*-butoxycarbonylazetidinylmethyl, (*tert*-butoxycarbonyl)(hydroxy)-azetidinylmethyl, tetrahydrofurylmethyl, pyrrolidinylmethyl, ethylpyrrolidinylmethyl, pyrrolidinylethyl, methylpyrrolidinylethyl, (carboxy)(isopropyl)(oxo)pyrrolidinylethyl, (oxo)pyrrolidinylpropyl, thiazolidinylmethyl, (oxo)imidazolidinylethyl, piperidinylmethyl, methylpiperidinylmethyl, *tert*-butoxycarbonylpiperidinylmethyl, piperidinylethyl, tetrahydroquinolinylmethyl, methylpiperazinylpropyl, morpholinylethyl, morpholinylpropyl, pyridinyl, aminopyridinyl, (carboxy)indolylethyl, dimethylpyrazolylethyl, methylimidazolylmethyl, imidazolylethyl, benzimidazolylmethyl, triazolylethyl, pyridinylmethyl and pyridinylethyl.

Suitably, R^c represents hydrogen or C_{1-6} alkyl. In one embodiment, R^c is hydrogen. In another embodiment, R^c represents C_{1-6} alkyl, especially methyl or ethyl, particularly methyl. In a further embodiment, R^c represents hydroxy-substituted C_{1-6} alkyl, e.g. hydroxyethyl (especially 2-hydroxyethyl).

Alternatively, the moiety $-NR^bR^c$ may suitably represent azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, homopiperidin-1-yl, homomorpholin-4-yl or homopiperazin-1-yl, any of which groups may be optionally substituted by one or more substituents. Favourably, the moiety $-NR^bR^c$ may suitably represent azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl or homopiperazin-1-yl, any of which groups may be optionally substituted by one or more substituents. Typically, the moiety $-NR^bR^c$ may suitably represent azetidin-1-yl, pyrrolidin-1-yl or piperazin-1-yl, any of which groups may be optionally substituted by one or more substituents.

Typical substituents on the heterocyclic moiety $-NR^bR^c$ include C_{1-6} alkyl, C_{1-6} alkoxy(C_{1-6})alkyl, hydroxy, hydroxy(C_{1-6})alkyl, amino(C_{1-6})alkyl, nitro(C_{1-6})alkyl, oxo, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, amino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxycarbonylamino, bis[(C_{2-6})alkoxycarbonyl(C_{1-6})alkyl]amino, C_{2-6} alkoxycarbonylamino(C_{1-6})alkyl and aminocarbonyl. Specific substituents include methyl, ethyl, methoxymethyl, hydroxy, hydroxymethyl, hydroxyethyl, aminomethyl, nitromethyl, oxo, acetyl, carboxy, methoxycarbonyl, *tert*-butoxycarbonyl, amino, acetylamino, *tert*-

butoxycarbonylamino, bis(ethoxycarbonylmethyl)amino, *tert*-butoxycarbonylamino-methyl and aminocarbonyl.

Definitive values of $-NR^bR^c$ include hydroxyazetidin-1-yl, (hydroxy)(nitro-methyl)azetidin-1-yl, aminoazetidin-1-yl, (aminomethyl)azetidin-1-yl, (aminomethyl)-(hydroxy)azetidin-1-yl, (*tert*-butoxycarbonylaminomethyl)azetidin-1-yl, pyrrolidin-1-yl, (methoxymethyl)pyrrolidin-1-yl, hydroxypyrrolidin-1-yl, (hydroxymethyl)pyrrolidin-1-yl, (aminomethyl)pyrrolidin-1-yl, carboxypyrrolidin-1-yl, (methoxycarbonyl)pyrrolidin-1-yl, aminopyrrolidin-1-yl, (acetylamino)pyrrolidin-1-yl, (*tert*-butoxycarbonylamino)-pyrrolidin-1-yl, [bis(ethoxycarbonylmethyl)amino]pyrrolidin-1-yl, (*tert*-butoxycarbonyl-aminomethyl)pyrrolidin-1-yl, hydroxypiperidin-1-yl, (hydroxymethyl)piperidin-1-yl, (hydroxyethyl)piperidin-1-yl, carboxypiperidin-1-yl, (aminocarbonyl) piperidin-1-yl, piperazin-1-yl, methylpiperazin-1-yl, ethylpiperazin-1-yl, (hydroxyethyl)piperazin-1-yl, oxopiperazin-1-yl, acetylpiperazin-1-yl, carboxypiperazin-1-yl, (*tert*-butoxycarbonyl)-(carboxy)piperazin-1-yl, morpholin-4-yl, dimethylmorpholin-4-yl, (hydroxymethyl)-morpholin-4-yl and homopiperazin-1-yl.

Where the moiety $-N(OR^b)R^c$ represents an optionally substituted heterocyclic ring wherein R^b and R^c are taken together and represent a C_{2-5} alkylene linkage, this is suitably a C_3 alkylene linkage whereby the moiety $-N(OR^b)R^c$ represents an optionally substituted isoxazolidin-2-yl ring. Typical examples of suitable substituents on this heterocylic ring are as described above. A particular substituent is hydroxy.

In one embodiment, R^d is hydrogen. In another embodiment, R^d represents C_{1-6} alkyl, especially methyl.

In one embodiment, R^e is hydrogen. In another embodiment, R^e represents C_{1-6} alkyl, especially methyl.

Where R^3 represents a five-membered heteroaromatic ring, this ring may be optionally substituted by one or, where possible, two substituents. As will be appreciated, where R^3 represents an oxadiazolyl, thiadiazolyl or tetrazolyl ring, only one substituent will be possible; otherwise, one or two optional substituents may be accommodated around the five-membered heteroaromatic ring R^3. Where R^3 represents a six-membered heteroaromatic ring, this ring may be optionally substituted by one or more substituents, typically by one or two substituents. Examples of suitable substituents on the five-membered or six-membered heteroaromatic ring as specified for R^3 include C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})-

alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, halogen, cyano and trifluoromethyl.

Favourably, R^3 represents hydrogen, C_{1-6} alkyl, C_{3-7} heterocycloalkenyl (optionally substituted by one or two methyl groups), cyano, $-CO_2R^a$, $-CONR^bR^c$, $-CON(OR^b)R^c$, $-CON(R^d)NR^bR^c$, $-C(=NR^e)NR^bR^c$ or $-CON(R^d)C(=NR^e)NR^bR^c$, in which R^a, R^b, R^c, R^d and R^e are as defined above.

In one embodiment, R^3 represents hydrogen. In another embodiment, R^3 represents C_{1-6} alkyl, especially methyl. In another embodiment, R^3 represents C_{3-7} heterocycloalkenyl (optionally substituted by one or two methyl groups), e.g. 4,4-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl. In another embodiment, R^3 represents cyano. In another embodiment, R^3 represents $-CO_2R^a$, in which R^a is as defined above. In a further embodiment, R^3 represents $-CONR^bR^c$, in which R^b and R^c are as defined above. In a still further embodiment, R^3 represents $-CON(OR^b)R^c$, in which R^b and R^c are as defined above. In an additional embodiment, R^3 represents $-CONHNR^bR^c$, in which R^b and R^c are as defined above. In another additional embodiment, R^3 represents $-C(=NH)NR^bR^c$, in which R^b and R^c are as defined above. In a further additional embodiment, R^3 represents $-CONHC(=NH)NR^bR^c$, in which R^b and R^c are as defined above.

Suitable values of R^{4a} and/or R^{4b} include hydrogen, halogen (especially fluoro or chloro) and C_{1-6} alkyl (especially methyl).

Preferably, R^{4a} is attached at the 2-position relative to the anilino nitrogen atom.

Suitably, R^{4a} represents halogen. In one embodiment, R^{4a} is fluoro. In another embodiment, R^{4a} is chloro.

Typically, R^{4b} may be attached at the 6-position relative to the anilino nitrogen atom.

Suitably, R^{4b} is hydrogen.

Suitably, R^5 represents halogen, nitro, cyano, C_{2-6} alkynyl, hydroxy(C_{1-6})alkyl or formyl. Typically, R^5 represents halogen, nitro, hydroxy(C_{1-6})alkyl or formyl.

In one embodiment, R^5 represents halogen, especially bromo or iodo, particularly iodo. In another embodiment, R^5 represents nitro. In another embodiment, R^5 represents cyano. In another embodiment, R^5 represents C_{1-6} alkyl, especially methyl. In another embodiment, R^5 represents C_{2-6} alkynyl, especially ethynyl. In a further embodiment, R^5 represents hydroxy(C_{1-6})alkyl, especially hydroxymethyl. In an additional embodiment, R^5 represents formyl.

Suitably, R^6 represents hydrogen or C_{1-6} alkyl. In one embodiment, R^6 represents hydrogen. In another embodiment, R^6 represents C_{1-6} alkyl, especially methyl.

In one embodiment, R^7 represents hydrogen. In another embodiment, R^7 represents C_{1-6} alkyl, especially methyl.

In one embodiment, n is zero. In another embodiment, n is 1. In a further embodiment, n is 2.

Suitably, R^x represents hydrogen or C_{1-6} alkyl. In one embodiment, R^x represents hydrogen. In another embodiment, R^x represents C_{1-6} alkyl, especially methyl.

Suitably, R^y represents hydrogen or C_{1-6} alkyl. In one embodiment, R^y represents hydrogen. In another embodiment, R^y represents C_{1-6} alkyl, especially methyl.

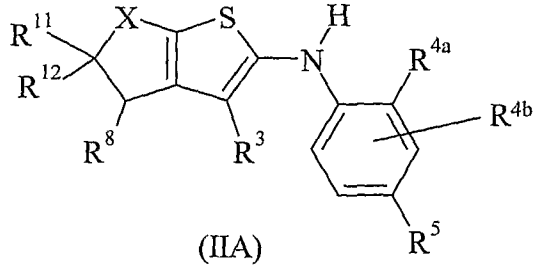
Suitably, R^z represents hydrogen or C_{1-6} alkyl. In one embodiment, R^z represents hydrogen. In another embodiment, R^z represents C_{1-6} alkyl, especially methyl.

In one embodiment, R^8 represents halogen, especially chloro. In another embodiment, R^8 represents $-OR^x$, especially methoxy. In a further embodiment, R^8 represents $-S(O)_nR^x$. In another embodiment, R^8 represents $-NR^yR^z$, especially amino.

Typically, R^8 represents halogen, $-OR^x$ or $-NR^yR^z$, wherein R^x, R^y and R^z are as defined above.

Suitable values of R^8 include chloro, methoxy and amino.

One sub-class of compounds according to the invention is represented by the compounds of formula (IIA), and pharmaceutically acceptable salts and solvates thereof:



(IIA)

wherein

-X-, R^3, R^{4a}, R^{4b}, R^5 and R^8 are as defined above;

R^{11} represents hydrogen or optionally substituted C_{1-6} alkyl; and

R^{12} represents hydrogen; or 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; or

R^{11} and R^{12}, when taken together with the carbon atom to which they are both attached, represent C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents.

Where R^{11} and/or R^{12} in the compounds of formula (IIA) above is stated to be optionally substituted, this group may be unsubstituted, or substituted by one or more substituents. Typically, R^{11} and/or R^{12} will be unsubstituted, or substituted by one or two substituents. Suitably, R^{11} and/or R^{12} will be unsubstituted or monosubstituted.

Suitably, R^{11} represents hydrogen or unsubstituted C_{1-6} alkyl.

Suitably, R^{12} represents hydrogen; or C_{1-6} alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents. Particular values of R^{12} include hydrogen and unsubstituted C_{1-6} alkyl.

Examples of typical substituents on R^{11} and/or R^{12} include halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, aryloxy, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulphonylamino, formyl, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, aminocarbonyl, C_{1-6} alkylamino-carbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulphonyl, C_{1-6} alkylaminosulphonyl and di(C_{1-6})alkylaminosulphonyl; especially halogen, C_{1-6} alkoxy or C_{1-6} alkylthio.

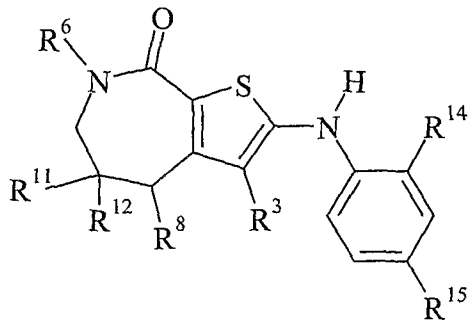
Examples of particular substituents on R^{11} and/or R^{12} include fluoro, chloro, bromo, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, phenoxy, methylthio, methylsulphonyl, amino, methylamino, dimethylamino, acetylamino, methoxycarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl; especially chloro, methoxy or methylthio.

Typical values of R^{11} include hydrogen and methyl. In one embodiment, R^{11} is hydrogen. In another embodiment, R^{11} is C_{1-6} alkyl, especially methyl.

Typical values of R^{12} include hydrogen, methyl, *n*-propyl, isopropyl, phenyl, chlorophenyl, methoxyphenyl, methylthiophenyl and furyl, especially hydrogen or methyl. In one embodiment, R^{12} is hydrogen. In another embodiment, R^{12} is C_{1-6} alkyl, especially methyl.

Alternatively, R^{11} and R^{12} may together form an optionally substituted spiro linkage. Thus, R^{11} and R^{12}, when taken together with the carbon atom to which they are both attached, may represent C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be unsubstituted, or substituted by one or more, typically by one or two, substituents. In this context, R^{11} and R^{12}, when taken together with the carbon atom to which they are both attached, may suitably represent an optionally substituted cyclopentyl, cyclohexyl, pyrrolidine or piperidine ring, especially cyclopentyl or cyclohexyl.

One particular sub-group of the compounds of formula (IIA) is represented by the compounds of formula (IIB), and pharmaceutically acceptable salts and solvates thereof:



(IIB)

wherein

R^3, R^6, R^8, R^{11} and R^{12} are as defined above;

R^{14} represents halogen; and

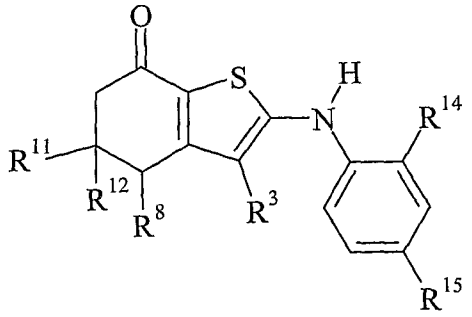
R^{15} represents halogen, nitro, cyano, C_{2-6} alkynyl, hydroxy(C_{1-6})alkyl or formyl.

In one specific embodiment, R^{14} is fluoro. In another specific embodiment, R^{14} is chloro.

Typically, R^{15} represents halogen, nitro, hydroxy(C_{1-6})alkyl or formyl.

In one embodiment, R^{15} represents halogen, especially iodo. In another embodiment, R^{15} represents nitro. In another embodiment, R^{15} represents cyano. In another embodiment, R^{15} represents C_{2-6} alkynyl, especially ethynyl. In a further embodiment, R^{15} represents hydroxy(C_{1-6})alkyl, especially hydroxymethyl. In an additional embodiment, R^{15} represents formyl.

Another sub-group of the compounds of formula (IIA) is represented by the compounds of formula (IIC), and pharmaceutically acceptable salts and solvates thereof:

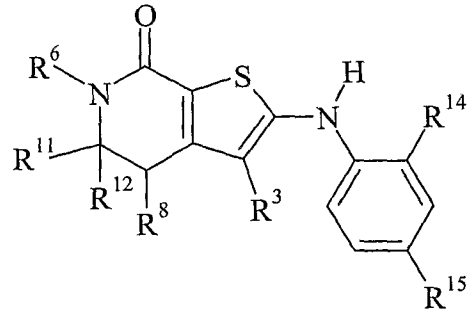


(IIC)

wherein

R^3, R^8, R^{11}, R^{12}, R^{14} and R^{15} are as defined above.

A further sub-group of the compounds of formula (IIA) is represented by the compounds of formula (IID), and pharmaceutically acceptable salts and solvates thereof:



(IID)

wherein

R^3, R^6, R^8, R^{11}, R^{12}, R^{14} and R^{15} 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 pharmaceutically acceptable salts and solvates thereof.

The present invention also provides a pharmaceutical composition which comprises a compound of formula (I) as defined above, or a pharmaceutically acceptable salt or solvate thereof, in association with one or more pharmaceutically 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 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 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.

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.

The compounds of formula (I) 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. 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 of formula (I) may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation or by intramuscular injection.

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.

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 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.

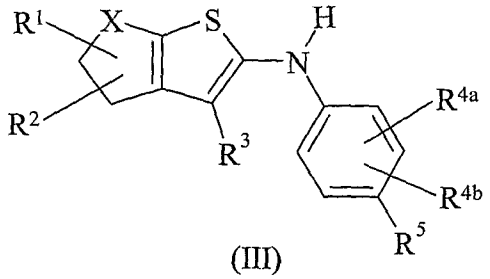
For ophthalmic administration the compounds according to the present invention may be conveniently formulated as microionized suspensions in isotonic, pH-adjusted sterile saline, either with or without a preservative such as a bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively, for ophthalmic administration compounds 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. Such materials include, for example, cocoa butter, beeswax and polyethylene glycols.

The quantity of a compound of the 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, 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.

The compounds of formula (I) above wherein R^8 represents halogen may be prepared by a process which comprises reacting a compound of formula (III):

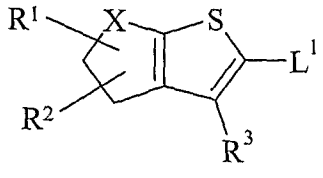


(III)

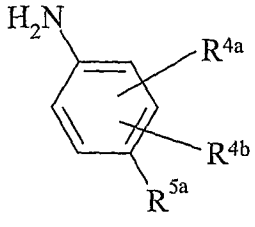
wherein -X-, R^1, R^2, R^3, R^{4a}, R^{4b} and R^5 are as defined above; with a halogenating agent.

The halogenating agent of use in the reaction with compound (III) is suitably an *N*-halosuccinimide, e.g. *N*-chlorosuccinimide, in which case the reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. a cyclic ether such as tetrahydrofuran. Alternatively, the halogenating agent may be iodine monochloride, in which case the reaction is conveniently effected in an inert organic solvent such as dichloromethane.

The intermediates of formula (III) above may be prepared by reacting a compound of formula (IV) with a compound of formula (V):



(IV)



(V)

wherein -X-, R^1, R^2, R^3, R^{4a} and R^{4b} are as defined above, R^{5a} corresponds to the group R^5 or represents a precursor group thereto, and L^1 represents a suitable leaving group;

followed, where necessary, by conversion of the precursor group R^{5a} into the desired group R^5.

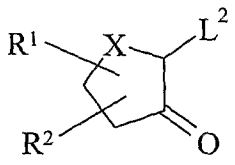
A suitable precursor group R^{5a} is trimethylsilyl (TMS).

The leaving group L^1 is typically a halogen atom, e.g. bromo.

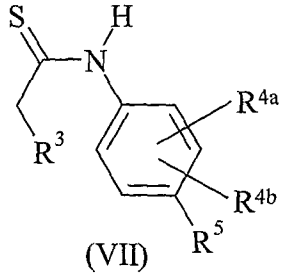
The reaction is conveniently effected at an elevated temperature in the presence of a transition metal catalyst. A suitable catalyst is bis(dibenzylideneacetone)palladium, in which case the reaction will typically be performed in the presence of 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), generally under basic conditions, e.g. in the presence of an inorganic base such as caesium carbonate.

Where R^{5a} represents TMS, this group may be converted into the desired group R^5 wherein R^5 represents iodo by treatment with iodine monochloride.

In an alternative procedure, the intermediates of formula (III) above may be prepared by reacting a compound of formula (VI) with a compound of formula (VII):



(VI)



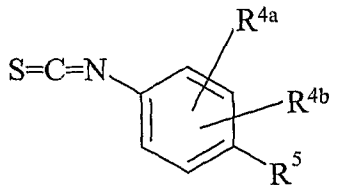
(VII)

wherein -X-, R^1, R^2, R^3, R^{4a}, R^{4b} and R^5 are as defined above, and L^2 represents a suitable leaving group.

The leaving group L^2 is typically a halogen atom, e.g. bromo.

The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. *N*,*N*-dimethylformamide, typically under basic conditions, e.g. in the presence of a base such as cesium carbonate.

By way of example, the intermediates of formula (VII) above wherein R^3 is ethoxycarbonyl may be prepared by a process which comprises reacting the product formed by reacting ethyl acetoacetate and sodium ethoxide with a compound of formula (VIII):



(VIII)

wherein R^{4a}, R^{4b} and R^5 are as defined above.

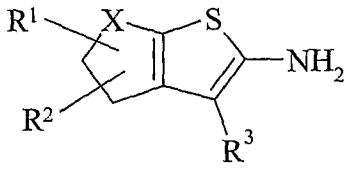
The reaction is conveniently effected by stirring the reactants in a suitable solvent, e.g. a lower alkanol such as ethanol.

Similarly, the intermediates of formula (VII) above wherein R^3 is cyano may be prepared by a process which comprises reacting compound (VIII) with acetonitrile, typically in the presence of a strong base such as sodium hexamethyldisilazide.

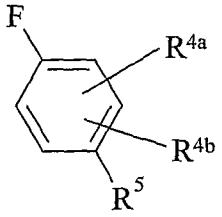
The intermediates of formula (VIII) above may be prepared by reacting a compound of formula (V) as defined above with thiophosgene.

The reaction is conveniently effected in a suitable solvent, typically a mixture of chloroform and water.

In another procedure, the compounds of formula (III) above may be prepared by reacting a compound of formula (IX) with a compound of formula (X):



(IX)

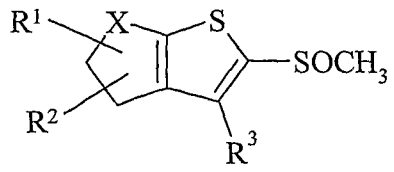


(X)

wherein -X-, R^1, R^2, R^3, R^{4a}, R^{4b} and R^5 are as defined above.

The reaction is conveniently effected, at an elevated temperature if required, in a suitable solvent, e.g. *N,N*-dimethylformamide, typically under basic conditions, e.g. in the presence of a base such as cesium carbonate.

In a further procedure, the compounds of formula (III) above may be prepared by reacting a compound of formula (V) as defined above with a compound of formula (XI):



(XI)

wherein -X-, R^1, R^2 and R^3 are as defined above.

The reaction is conveniently effected in the presence of a strong base such as sodium hexamethyldisilazide.

The intermediates of formula (XI) above may be prepared from the precursors of formula (IV) above wherein L^1 represents bromo by treatment with dimethyl disulphide, typically in the presence of a strong base such as *tert*-butyllithium; followed by oxidation of the methylthio derivative thereby obtained, typically with an oxidising agent such as 3-chloroperoxybenzoic acid, to afford the desired compound of formula (XI).

The intermediates of formula (IV) and (IX) above may be prepared by the procedures described in WO 2007/141504.

Where they are not commercially available, the starting materials of formula (V), (VI) and (X) 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 compound of formula (I) by techniques known from the art. By way of example, a compound of formula (I) wherein R^8 represents halogen, e.g. chloro, can be converted into the corresponding compound wherein R^8 represents $-OR^x$, e.g. methoxy, by treatment with the appropriate substance of formula $H-OR^x$, e.g. methanol. Similarly, a compound of formula (I) wherein R^8 represents halogen, e.g. chloro, can be converted into the corresponding compound wherein R^8 represents $-NR^yR^z$, e.g. amino, by treatment with the appropriate substance of formula $H-NR^yR^z$, e.g. ammonia.

A compound of formula (IA), (IB) or (IC) wherein Y is oxygen may be converted into the corresponding compound wherein Y is sulphur by treatment with Lawesson's Reagent (i.e. 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide). A compound of formula (IB) wherein Y is oxygen and R^1 is hydrogen may be converted into the corresponding compound wherein R^1 is methyl by treatment with a methyl halide,

e.g. iodomethane, in the presence of a strong base, e.g. lithium diisopropylamide. A compound of formula (IC) wherein Y is sulphur may be converted into the corresponding compound wherein Y is NH by treatment with dimethyl sulphate or iodomethane, followed by treatment of the methylthio-substituted cyclic imine thereby obtained with ammonia, typically at elevated temperature and pressure, or with ammonium acetate, typically at elevated temperature.

A compound of formula (IC) wherein R^6 represents hydrogen may be converted into the corresponding compound wherein R^6 represents C_{1-6} alkyl by treatment with a trialkylsilyl halide, e.g. trimethylsilyl chloride or *tert*-butyldimethylsilyl chloride, in the presence of a base, e.g. sodium hydride, followed by treatment with a C_{1-6} alkyl halide, e.g. iodomethane, in the presence of a base, e.g. sodium hydride.

A compound of formula (I) wherein R^3 represents $-CO_2R^a$ in which R^a is other than hydrogen may be saponified to give the corresponding compound in which R^3 represents $-CO_2H$ by treatment with a base such as lithium hydroxide; more prolonged treatment with lithium hydroxide gives rise to the decarboxylated product in which R^3 represents hydrogen. A compound of formula (I) wherein R^3 represents $-CO_2R^a$ may be converted into the corresponding compound wherein R^3 represents $-CONH_2$ by treatment with ammonia, typically at elevated temperature and optionally also at elevated pressure. A compound of formula (I) wherein R^3 represents $-CO_2H$ may be converted into the corresponding compound wherein R^3 represents $-CONR^bR^c$, $-CON(OR^b)R^c$ or $-CON(R^d)C(=NR^e)NR^bR^c$ by treatment with the appropriate amine of formula $H-NR^bR^c$, $H-N(OR^b)R^c$ or $H-N(R^d)C(=NR^e)NR^bR^c$ respectively and a condensing agent such as 1,1'-carbonyldiimidazole (CDI) or 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC), typically in the presence of 4-methylmorpholine (NMM) and 1-hydroxybenzotriazole (HOBT). Alternatively, a compound of formula (I) wherein R^3 represents $-CO_2H$ may be converted into the corresponding compound wherein R^3 represents $-CONR^bR^c$, $-CON(OR^b)R^c$ or $-CON(R^d)NR^bR^c$ by a two-stage procedure which comprises (i) treatment with pentafluorophenol and a condensing agent such as EDC, typically in the presence of NMM and HOBT; and (ii) reaction of the pentafluorophenyl ester thereby obtained with the appropriate amine of formula $H-NR^bR^c$, $H-N(OR^b)R^c$ or $H-N(R^d)NR^bR^c$ respectively, typically in the presence of an organic base such as triethylamine.

A compound of formula (I) wherein R^3 represents $-CO_2H$ may be converted into the corresponding compound wherein R^3 represents $-CO_2R^a$ by a two-stage procedure

which comprises (i) treatment with pentafluorophenol and a condensing agent such as EDC, typically in the presence of NMM and HOBT; and (ii) reaction of the pentafluorophenyl ester thereby obtained with the appropriate alcohol of formula R^aOH, typically in the presence of an organic base such as triethylamine.

A compound of formula (I) wherein R^3 represents $-CO_2H$ may be converted into the corresponding compound wherein R^3 represents $-CONR^bR^c$ by a two-stage procedure which comprises (i) treatment with tetrafluorophenol resin and a condensing agent such as 1,3-diisopropylcarbodiimide, typically in the presence of 4-(dimethylamino)pyridine; and (ii) reaction of the tetrafluorophenyl ester functionalised resin thereby obtained with the appropriate amine of formula $H\text{-}NR^bR^c$.

A compound of formula (I) wherein R^3 represents $-CO_2R^a$ (e.g. ethoxycarbonyl) may be converted into the corresponding compound wherein R^3 represents methyl by treatment with a reducing agent such as diisobutylaluminium hydride.

A compound of formula (I) wherein R^3 represents $-CO_2R^a$ (e.g. ethoxycarbonyl) may be converted into the corresponding compound wherein R^3 represents $-CONR^bR^c$ by treatment with the appropriate amine of formula $H\text{-}NR^bR^c$ in the presence of trimethylaluminium. Similarly, a compound of formula (I) wherein R^3 represents cyano may be converted into the corresponding compound wherein R^3 represents $-C(=NH)NR^bR^c$ by treatment with the appropriate amine of formula $H\text{-}NR^bR^c$ in the presence of trimethylaluminium. A compound of formula (I) wherein R^3 represents cyano may be converted into the corresponding compound wherein R^3 represents 4,4-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl in a single step by treatment with 1,2-diamino-2-methylpropane in the presence of trimethylaluminium.

A compound of formula (I) wherein R^3 represents cyano may be converted into the corresponding compound wherein R^3 represents $-CONH_2$ by treatment with hydroxylamine.

A compound of formula (I) wherein R^3 contains a NH functionality may be converted into the corresponding compound wherein R^3 contains a N-methyl functionality by treatment with formaldehyde in the presence of a suitable reducing agent, e.g. sodium cyanoborohydride.

A compound of formula (I) wherein R^3 contains an amino moiety protected by a *tert*-butoxycarbonyl (BOC) group may be deprotected by treatment with an acid, e.g. an organic acid such as trifluoroacetic acid, or a mineral acid such as hydrochloric acid.

A compound of formula (I) wherein R^5 represents formyl may be converted into the corresponding compound wherein R^5 represents hydroxymethyl by treatment with a suitable reducing agent, e.g. sodium borohydride.

A compound of formula (I) wherein R^5 represents iodo may be converted into the corresponding compound wherein R^5 represents ethynyl by treatment at an elevated temperature with (trimethylsilyl)acetylene and a transition metal catalyst, e.g. bis(triphenylphosphine)palladium(II) dichloride, typically in the presence of copper(I) iodide and a base such as diisopropylamine.

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 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 *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3rd edition, 1999. The protecting groups may be removed at any convenient subsequent stage utilising methods known from the art.

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

The compounds in accordance with this invention potently inhibit the activity of human MEK enzyme.

In vitro MEK assay

MEK1 activity was measured in a cascade assay initiated by active Raf, via activation of MEK, Erk2 and subsequent phosphorylation of fluorescein-labelled Erk-tide substrate in an assay based on fluorescence polarisation (IMAP). The assay was carried out in 20m*M* Tris + 5m*M* $MgCl_2$ + 2m*M* DL-dithiothreitol + 0.01% Tween 20 pH 7.2, containing 1.5n*M* unactive MEK, 100n*M* unactive Erk and 200n*M* Erk-tide (all concentrations are final concentrations). Compounds, or DMSO controls, were tested at a final concentration of 2% DMSO, and the assay initiated in the presence of 5μ*M* ATP by addition of 1.25n*M* active Raf in assay buffer. After 20 min at r.t., stop solution was added followed by IMAP binding beads, the assay mixture was then incubated for 90 min at r.t. (with shaking) and then read on a Molecular Devices LJL HT reader.

When tested in the above assay, the compounds of the accompanying Examples were all found to inhibit human MEK enzyme with IC_{50} values of 10 μM or better.

EXAMPLES

Abbreviations

EtOAc - ethyl acetate
DCM - dichloromethane
THF - tetrahydrofuran
h - hour(s)
DMSO - dimethylsulphoxide
DMF - *N*,*N*-dimethylformamide
RT - retention time
r.t. - room temperature

BINAP - 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

All NMRs were obtained either at 300 MHz or 400 MHz.

Standard LCMS method

The LC-MS system used comprises a Waters Alliance 2795 HT quaternary HPLC, Waters 996 Photo Diode Array (PDA) detector and Waters ZQ 4000 single quadrupole mass spectrometer. The ZQ can acquire data simultaneously in positive and negative electrospray ionisation modes.

ZQ Mass Spectrometer

Capillary	3.5kV	Cone	50V
Extractor	2V	Source Temp	80°C
Desolvation Temp	200°C	Cone Gas	150 l/h
Desolvation Gas	250 l/h	Multiplier	650V

Data were acquired in a full scan from 100 to 1000 m/z.

Scan duration	0.80 s
Interscan delay	0.20 s

HPLC

The reverse phase separation was carried out on a Gemini C18 from Phenomenex 50 x 4.6 mm with 5 μm silica.

Injection Volume	5 μl
UV data	240 to 400 nm
Sample Temperature	20°C
Column Temperature	30°C
Flow Rate	0.9 ml/min
Split to ZQ	~0.40 ml/min

Solvent A: 90% 10m*M* NH_4HCO_2 in water / 0.1% formic acid / 10% CH_3CN

Solvent B: 90% CH_3CN / 0.1% formic acid / 10% 10m*M* NH_4HCO_2 in water

Gradient Program

Time (min)	A%	B%	Flow	Curve
0.00	95.0	5.0	0.900	1
2.00	5.0	95.0	0.900	6
4.00	5.0	95.0	0.900	6
5.00	95.0	5.0	0.900	6

The aqueous solvent was approximately pH 3.2.

INTERMEDIATE 1

2-Fluoro-4-(trimethylsilanyl)phenylamine

To a stirred solution of bis(dibenzylideneacetone)palladium chloroform adduct (190 mg, 0.2 mmol) and dicyclohexylphenylphosphine (430 mg, 1.2 mmol) in 1,4-dioxane (16 mL) was added hexamethyldisilane (5.0 mL, 24.4 mmol), 4-chloro-2-fluoroaniline (1.5 mL, 13.6 mmol), water (0.2 mL, 13.6 mmol) and KF (3.9 g, 68.0 mmol). The reaction mixture was heated in a sealed flask at 100°C for 18 h. DCM (200 mL) was added to the reaction mixture. The solids were filtered off, water was added and the mixture extracted with DCM. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by chromatography (silica, 100% hexane) to give the *title compound* as a yellow oil (2.3 g, 93%). δ_H (DMSO-d_6) 6.85 (1H, dd, *J* 11.9, 1.1 Hz), 6.80 (1H, dd, *J* 7.7, 1.3 Hz), 6.59 (1H, dd, *J* 8.9, 7.9 Hz), 5.01 (2H, s), 0.01 (9H, s).

INTERMEDIATE 2

2-[2-Fluoro-4-(trimethylsilanyl)phenylamino]-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid ethyl ester

To a stirred solution of bis(dibenzylideneacetone)palladium (140 mg, 0.2 mmol) and BINAP (190 mg, 0.3 mmol) in toluene (40 mL) was added ethyl 2-bromo-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate (Intermediate 17 of WO 2007/141504) (1.0 g, 3.0 mmol), Intermediate 1 (660 mg, 3.6 mmol) and Cs_2CO_3 (1.4 g, 4.2 mmol). The reaction mixture was heated in a sealed flask at 110°C for 18 h. Water was added and the mixture extracted with DCM (3 x 200 mL). The combined

organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by chromatography (silica, 0-30% EtOAc in DCM) to give the *title compound* as a cream solid (680 mg, 52%). δ_H (DMSO-d_6) 10.42 (1H, s), 7.66 (1H, t, *J* 8.0 Hz), 7.54 (1H, s), 7.48-7.42 (2H, m), 4.32 (2H, q, *J* 7.1 Hz), 2.99 (2H, s), 1.33 (3H, t, *J* 7.1 Hz), 1.27 (6H, s), 0.27 (9H, s). LCMS (ES^+) RT 3.83 minutes, 435 $(M+H)^+$.

INTERMEDIATE 3

2-(2-Fluoro-4-iodophenylamino)-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylic acid ethyl ester

To a stirred solution of Intermediate 2 (300 mg, 0.7 mmol) in DCM (10 mL) at 0°C was added ICl (220 mg, 1.4 mmol). The reaction mixture was warmed to r.t. and stirred for 18 h. Sodium metabisulphite solution (20 mL) was added and the mixture extracted with DCM (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude products were purified by chromatography (silica, 0-30% EtOAc in DCM) to give the *title compound* as a cream solid (150 mg, 44%). δ_H (DMSO-d_6) 10.28 (1H, s), 7.81 (1H, dd, *J* 10.4, 1.9 Hz), 7.66 (1H, dd, *J* 8.5, 1.1 Hz), 7.54 (1H, s), 7.46 (1H, t, *J* 8.6 Hz), 4.31 (2H, q, *J* 7.1 Hz), 2.98 (2H, s), 1.32 (3H, t, *J* 7.1 Hz), 1.27 (6H, s). LCMS (ES^+) RT 3.43 minutes, 489 $(M+H)^+$.

INTERMEDIATE 4

2-(2-Chloro-4-iodophenylamino)-5,5-dimethyl-8-oxo-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*c*]azepine-3-carboxylic acid ethyl ester

Caesium carbonate (2.77 g, 8.51 mmol) and 2-chloro-4-iodo-1-fluorobenzene (2.18 g, 8.51 mmol) were added to a solution of 2-amino-5,5-dimethyl-8-oxo-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*c*]azepine-3-carboxylic acid ethyl ester (WO 2007/141504, Intermediate 20) (2.0 g, 7.09 mmol) in DMF (20 mL) and heated at 65°C for 18 h. Brine (100 mL) was added to the reaction and the mixture extracted with DCM (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residual DMF was azeotroped with heptane. The crude product was purified by chromatography (silica, 0-30% EtOAc in DCM) to give the *title compound* as a cream solid (916 mg, 25%). δ_H (DMSO-d6) 10.60 (1H, s), 8.01 (1H, t, *J* 5.0 Hz), 7.95 (1H, d, *J*

2.0 Hz), 7.78 (1H, dd, *J* 8.6, 2.0 Hz), 7.54 (1H, d, *J* 8.6 Hz), 4.32 (2H, q, *J* 7.1 Hz), 2.91 (2H, s), 2.85 (2H, d, *J* 5.2 Hz), 1.33 (3H, t, *J* 7.1 Hz), 0.99 (6H, s). LCMS (ES^+) RT 3.81 minutes, 519 $(M+H)^+$.

INTERMEDIATE 5

2-(2-Chloro-4-iodophenylamino)-5,5-dimethyl-8-oxo-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*c*]azepine-3-carboxylic acid

Lithium hydroxide monohydrate (49 mg, 1.16 mmol) was added to a solution of Intermediate 4 (300 mg, 0.58 mmol) in THF (20 mL) and water (5 mL) and heated to reflux for 18 h. The reaction mixture was concentrated *in vacuo* and 5% citric acid (10 mL) added. The resulting precipitate was filtered and dried *in vacuo* to give the *title compound* as a cream solid (225 mg, 79%). δ_H (DMSO-d_6) 13.90 (1H, br s), 7.79 (1H, d, *J* 2.0 Hz), 7.75-7.70 (1H, m), 7.67 (1H, dd, *J* 8.6, 2.0 Hz), 7.43 (1H, d, *J* 8.6 Hz), 3.13 (2H, s), 2.82 (2H, d, *J* 5.0 Hz), 0.96 (6H, s). LCMS (ES^+) RT 3.10 minutes, 491 $(M+H)^+$.

INTERMEDIATE 6

2-(2-Chloro-4-iodophenylamino)-5,5-dimethyl-8-oxo-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*c*]azepine-3-carboxylic acid pentafluorophenyl ester

From Intermediate 5 (6.0 g, 12.2 mmol) by treatment with pentafluorophenol, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide, 4-methylmorpholine and 1-hydroxybenzotriazole in DCM/DMF under standard conditions to yield the *title compound* (5.17 g, 65%). δ_H (DMSO-d_6) 10.02 (1H, s), 8.08 (1H, t, *J* 5.0 Hz), 8.03 (1H, d, *J* 1.9 Hz), 7.84 (1H, dd, *J* 8.4, 1.9 Hz), 7.53 (1H, d, *J* 8.4 Hz), 2.94 (2H, s), 2.90 (2H, d, *J* 5.0 Hz), 0.99 (6H, s). LCMS (ES^+) RT 4.14 minutes, 657/659 $(M+H)^+$.

INTERMEDIATE 7

2-(2-Chloro-4-iodophenylamino)-5,5-dimethyl-8-oxo-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*c*]azepine-3-carboxylic acid amide

Intermediate 6 (1 g, 1.52 mmol) was dissolved in 7M ammonia in methanol (10 mL) and stirred at r.t. overnight. The reaction mixture was concentrated *in vacuo* and

triturated with a 1:1 mixture of dichloromethane and diisopropyl ether to remove the pentafluorophenol, yielding the *title compound* (700mg) as a white solid. δ_H (DMSO-d_6) 9.89 (1H, s), 7.99-7.93 (1H, m), 7.83 (1H, d, *J* 1.9 Hz), 7.67 (1H, dd, *J* 8.5, 1.9 Hz), 7.54-7.41 (2H, m), 7.27 (1H, d, *J* 8.7 Hz), 2.90 (2H, d, *J* 5.1 Hz), 2.82 (2H, s), 0.98 (6H, s). LCMS pH 3 (ES^+) RT 2.71 minutes, 490 $(M+H)^+$.

EXAMPLE 1

4-Chloro-2-(2-fluoro-4-iodophenylamino)-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid ethyl ester

From chromatographic purification of the product of Intermediate 3 the *title compound* was also isolated as a cream solid (110 mg, 30%). δ_H (DMSO-d_6) 10.17 (1H, s), 8.00 (1H, s), 7.83 (1H, dd, *J* 10.3, 1.9 Hz), 7.69-7.65 (1H, m), 7.47 (1H, t, *J* 8.6 Hz), 5.47 (1H, d, *J* 1.2 Hz), 4.48-4.25 (2H, m), 1.45 (3H, s), 1.35 (3H, t, *J* 7.1 Hz), 1.30 (3H, s). LCMS (ES^+) RT 3.20 minutes, 523 $(M+H)^+$.

EXAMPLE 2

2-(2-Fluoro-4-iodophenylamino)-4-methoxy-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid ethyl ester

Example 1 (50 mg, 0.1 mmol) was suspended in 7N ammonia in methanol (2 mL). The reaction mixture was heated in a microwave at 60°C for 5 minutes. The reaction mixture was concentrated *in vacuo* and the crude products were purified by chromatography (silica, 0-100% EtOAc in DCM) to give the *title compound* as a white solid (5 mg, 10%). δ_H (DMSO-d_6) 10.26 (1H, d, *J* 0.6 Hz), 7.82 (1H, dd, *J* 10.4, 1.9 Hz), 7.67 (2H, d, *J* 9.3 Hz), 7.49 (1H, t, *J* 8.7 Hz), 4.53 (1H, d, *J* 0.6 Hz), 4.38 (2H, q, *J* 6.8 Hz), 3.34 (3H, s), 1.38-1.35 (6H, m), 1.12 (3H, s). LCMS (ES^+) RT 3.18 minutes, 519 $(M+H)^+$.

EXAMPLE 3

4-Amino-2-(2-fluoro-4-iodo-phenylamino)-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid ethyl ester

From chromatographic purification of the product of Example 2 the *title compound* was also isolated as a white solid (29 mg, 58%). δ_H (DMSO-d_6) 10.23 (1H, br s), 7.85 (2H, d, *J* 9.5 Hz), 7.69 (1H, d, *J* 8.3 Hz), 7.46 (1H, t, *J* 8.7 Hz), 4.36-4.32 (3H, m), 1.37-1.33 (6H, m), 1.23 (3H, s). LCMS (ES^+) RT 2.02 minutes, 504 $(M+H)^+$.

EXAMPLE 4

4-Chloro-2-(2-chloro-4-iodophenylamino)-5,5-dimethyl-8-oxo-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*c*]azepine-3-carboxylic acid amide

Intermediate 7 (700 mg, 1.5 mmol) and *N*-chlorosuccinimide (214 mg, 1.6 mmol) were suspended in THF (5 mL) and heated in a microwave at 100°C for 1 h. The reaction was concentrated *in vacuo*, then triturated with diisopropyl ether. The resultant solid was dissolved in DCM and washed with water to remove succinimide, dried over Na_2SO_4, and concentrated to yield the *title compound* (300 mg) as a waxy solid. LCMS pH 3 (ES^+) RT 2.83 minutes, 522 $(M-H)^-$.

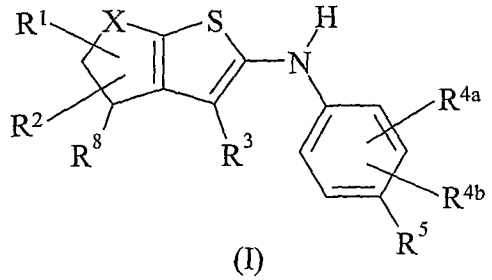
EXAMPLE 5

4-Amino-2-(2-chloro-4-iodophenylamino)-5,5-dimethyl-8-oxo-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*c*]azepine-3-carboxylic acid amide

Example 4 (300 mg, 0.57 mmol) in 7M ammonia in methanol (5 mL) were heated in a microwave at 100°C for 1 h. The reaction mixture was concentrated *in vacuo* and chromatographed on silica (1:1 DCM:EtOAc with 10% MeOH/DCM). Further chromatography by reverse-phase preparative HPLC yielded the *title compound* (8 mg) as a yellow powder. δ_H (DMSO-d_6) 8.19 (1H, s), 7.71 (1H, d, *J* 2.1 Hz), 7.60 (1H, d, *J* 6.0 Hz), 7.55 (1H, dd, *J* 8.7, 2.1 Hz), 7.17 (1H, d, *J* 8.5 Hz), 6.71-6.51 (1H, m), 4.19 (1H, br s), 3.50 (1H, d, *J* 14.3 Hz), 1.03 (3H, s), 0.90 (3H, s). LCMS pH 3 (ES^+) RT 1.66 minutes, 505 $(M+H)^+$.

Claims:

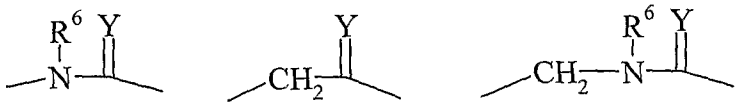
1. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof:



(I)

wherein

-X- represents a group of formula (a), (b) or (c):



(a) (b) (c)

Y represents oxygen, sulphur or N-R^7;

R^1 and R^2 independently represent hydrogen; or 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; or

R^1 and R^2, when both are attached to the same carbon atom, represent, when taken together with the carbon atom to which they are both attached, C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents; or

R^1 and R^2, when attached to adjacent carbon atoms, represent, when taken together with the carbon atoms to which they are attached, C_{5-7} cycloalkyl, phenyl or heteroaryl, any of which groups may be optionally benzo-fused and/or substituted by one or more substituents;

R^3 represents hydrogen, C_{1-6} alkyl, C_{3-7} heterocycloalkenyl (optionally substituted by one or two methyl groups), cyano, $-CO_2R^a$, $-COR^b$, $-CONR^bR^c$, $-SO_2NR^bR^c$, $-CON(OR^b)R^c$, $-CON(R^c)COR^b$, $-CON(R^c)SO_2R^b$, $-SO_2N(R^c)COR^b$, $-CON(R^d)NR^bR^c$, $-C(=NR^e)NR^bR^c$ or $-CON(R^d)C(=NR^e)NR^bR^c$; or

R^3 represents an optionally substituted five-membered heteroaromatic ring selected from furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl; or

R^3 represents an optionally substituted six-membered heteroaromatic ring selected from pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl and triazinyl;

R^{4a} and R^{4b} independently represent hydrogen, halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, C_{1-6} alkoxy, trifluoromethoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl or C_{1-6} alkylsulphonyl;

R^5 represents halogen, nitro, cyano, C_{1-6} alkyl, C_{2-6} alkynyl, hydroxy(C_{1-6})alkyl or formyl;

R^6 represents hydrogen, C_{1-6} alkyl, formyl, C_{2-6} alkylcarbonyl, trifluoromethylcarbonyl or C_{1-6} alkylsulphonyl;

R^7 represents hydrogen or C_{1-6} alkyl;

R^8 represents halogen, $-OR^x$, $-S(O)_nR^x$ or $-NR^yR^z$;

n is zero, 1 or 2;

R^a represents hydrogen, C_{1-6} alkyl or C_{3-7} heterocycloalkyl(C_{1-6})alkyl;

R^b represents hydrogen or trifluoromethyl; or 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, C_{4-9} heterobicycloalkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; and

R^c represents hydrogen or C_{1-6} alkyl (optionally substituted by hydroxy); or

R^b and R^c, when taken together with the nitrogen atom to which they are both attached, represent azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, homopiperidinyl, homomorpholinyl or homopiperazinyl, any of which groups may be optionally substituted by one or more substituents; or

the moiety $-N(OR^b)R^c$ represents an optionally substituted heterocyclic ring wherein R^b and R^c are taken together and represent a C_{2-5} alkylene linkage;

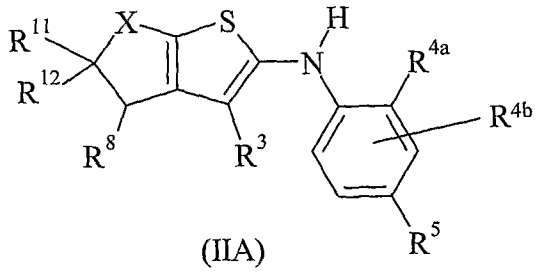
R^d and R^e independently represent hydrogen or C_{1-6} alkyl; and

R^x, R^y and R^z independently represent hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(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 wherein R^3 represents hydrogen, C_{1-6} alkyl, C_{3-7} heterocycloalkenyl (optionally substituted by one or two methyl groups), cyano, $-CO_2R^a$, $-CONR^bR^c$, $-CON(OR^b)R^c$, $-CON(R^d)NR^bR^c$, $-C(=NR^e)NR^bR^c$ or $-CON(R^d)C(=NR^e)NR^bR^c$, in which R^a, R^b, R^c, R^d and R^e are as defined in claim 1.

3. A compound as claimed in claim 1 or claim 2 wherein R^8 represents halogen, $-OR^x$ or $-NR^yR^z$, in which R^x, R^y and R^z are as defined in claim 1.

4. A compound as claimed in claim 1 represented by formula (IIA), and pharmaceutically acceptable salts and solvates thereof:



(IIA)

wherein

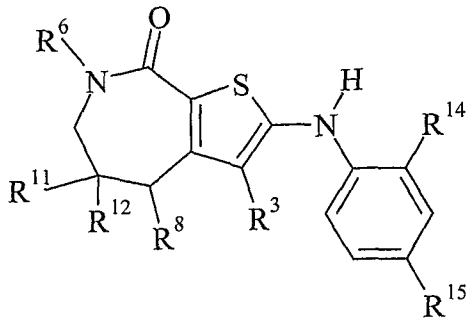
-X-, R^3, R^{4a}, R^{4b}, R^5 and R^8 are as defined in claim 1;

R^{11} represents hydrogen or optionally substituted C_{1-6} alkyl; and

R^{12} represents hydrogen; or 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; or

R^{11} and R^{12}, when taken together with the carbon atom to which they are both attached, represent C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl, either of which groups may be optionally substituted by one or more substituents.

5. A compound as claimed in claim 4 represented by formula (IIB), and pharmaceutically acceptable salts and solvates thereof:



(IIB)

wherein

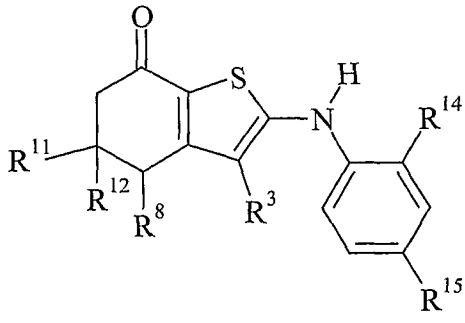
R^3, R^6 and R^8 are as defined in claim 1;

R^{11} and R^{12} are as defined in claim 4;

R^{14} represents halogen; and

R^{15} represents halogen, nitro, cyano, C_{2-6} alkynyl, hydroxy(C_{1-6})alkyl or formyl.

6. A compound as claimed in claim 4 represented by formula (IIC), and pharmaceutically acceptable salts and solvates thereof:



(IIC)

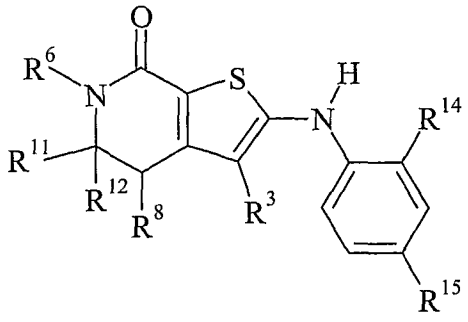
wherein

R^3 and R^8 are as defined in claim 1;

R^{11} and R^{12} are as defined in claim 4; and

R^{14} and R^{15} are as defined in claim 5.

7. A compound as claimed in claim 4 represented by formula (IID), and pharmaceutically acceptable salts and solvates thereof:



(IID)

wherein

R^3, R^6 and R^8 are as defined in claim 1;

R^{11} and R^{12} are as defined in claim 4; and

R^{14} and R^{15} are as defined in claim 5.

8. A compound as claimed in any one of claims 5 to 7 wherein R^{14} represents fluoro or chloro.

9. A compound as claimed in any one of claims 5 to 8 wherein R^{15} represents iodo.

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

11. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, in association with a pharmaceutically acceptable carrier.

12. A compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

13. A compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment and/or prevention of disorders for which the administration of a selective MEK inhibitor is indicated.

14. The use of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prevention of disorders for which the administration of a selective MEK inhibitor is indicated.

15. A method for the treatment and/or prevention of disorders for which the administration of a selective MEK inhibitor 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 a pharmaceutically acceptable salt or solvate thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/000151

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D495/04 A61K31/428 A61K31/429 A61P29/00 A61P35/00

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 A61K A61P

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 practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2008/020206 A (UCB PHARMA SA [BE]; LAING VICTORIA ELIZABETH [GB]; BROOKINGS DANIEL CH) 21 February 2008 (2008-02-21) claim 1	1-15
A	WO 2005/023818 A (AXXIMA PHARMACEUTICALS AG [DE]; KOUL ANIL [BE]; KLEBL BERT [DE]; MUELL) 17 March 2005 (2005-03-17) the whole document	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 April 2009	15/04/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bader, Karl Günther

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2009/000151

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008020206 A	21-02-2008	NONE	
WO 2005023818 A	17-03-2005	AU 2004270394 A1	17-03-2005
		CA 2572750 A1	17-03-2005
		EP 1670804 A2	21-06-2006
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