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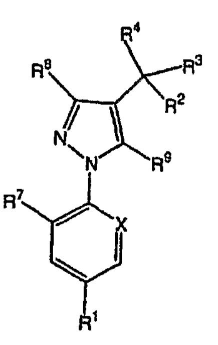
(54) Title: SUBSTITUTED ARYLPYRAZOLES



(I)

(57) Abstract: This invention relates to a range of C4 substituted aryl pyrazoles of Formula (I) including those 1-arylpyrazoles in which the 4-position is substituted with an acyclic substituent, a cycloalkyl ring structure or heterocyclic ring structure and which compounds are optionally further substituted at the position a to the pyrazole ring, and pharmaceutically acceptable salts and solvates thereof, to compositions comprising such compounds, processes to their synthesis and their use as parasiticides.

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SUBSTITUTED ARYLPYRAZOLES

This invention relates to pyrazole derivatives. The compounds of interest are C4 substituted aryl pyrazoles including, among others, those 1-arylpyrazoles in which the 4-position is substituted with an acyclic, cycloalkyl or heterocyclic ring structure and which compounds are optionally further substituted at the position α to the pyrazole ring. Such compounds are useful for having parasiticidal properties.

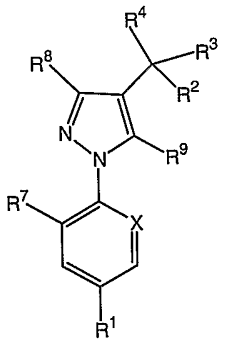
International Patent Application Publication No. (WO) 98/24767, European Patent Application Publication No. (EP) 933363, European Patent Application Publication No. (EP) 959071 and International Patent Application Publication No. (WO) 2005/060749 all describe arylpyrazoles having parasiticidal activity for the control of arthropods.

However, the prior art compounds do not always demonstrate good activity or a long duration of action against parasites. Similarly, some parasiticidal agents are useful only for a narrow spectrum of parasites. In some cases this may be attributed to the low bioavailability of the compounds in the treated animal and this can also lead to poor activity. It is an aim of the present invention to overcome various disadvantages of, or improve on, the properties of the prior art compounds. Thus it is an aim of the invention to provide an arylpyrazole which has the same or improved activity relative to prior art compounds against parasites. It is a further aim of the present invention to provide arylpyrazole compounds with improved bioavailability whilst maintaining or improving their activity. The compounds of the present invention have especially good ability to control a broad spectrum of arthropods as shown by the results of tests demonstrating their potency and efficacy. In particular, the compounds of the present invention are significantly more active against fleas than similar prior art compounds.

It is a further aim to provide compounds with a long duration of action. Surprisingly it has been found that improving the bioavailability of the compounds does not negatively impact their duration of action. The extended duration of action is generally attributed to an extended half life of the compound in vivo in the host mammal.

It is also desirable that the compounds of the present invention should have an improved pharmacokinetic profile, improved safety, improved persistence and improved solubility.

Thus, according to the present invention, there is provided a compound of formula (I):



(I)

wherein:

X is selected from CR^{10} or N;

R^1 is selected from halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, amino, C_{1-6} alkyl amino, di C_{1-6} alkyl amino, het, phenyl, SF_5 and $S(O)_nR^{11}$;

R^2 is selected from cyano, C(O)OH, $S(O)_nR^{11}$, $C(O)NR^aR^b$, and $C(S)NR^aR^b$;

or R^2 is selected from $C(O)OC_{1-6}$ alkyl, amino, C_{1-6} alkyl amino, and di C_{1-6} alkyl amino each of which may be optionally and independently further substituted by one or more substitutents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, $C(O)NR^cR^d$, $NR^cC(O)R^d$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, $-C(O)OC_{1-6}$ alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, $-C(O)OC_{1-6}$ haloalkyl, amino, NR^cR^d, het, phenyl and $S(O)_nR^{11}$;

R^a and R^b are independently selected from hydrogen, het, phenyl and $S(O)_nR^{11}$;

or either one or both of R^a and R^b are independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{1-6} alkanoyl, and $C(O)OC_{1-6}$ alkyl, each of which R^a and R^b may be optionally and independently further substituted by one or more substituents selected from, where chemcially possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, $C(O)NR^cR^d$, $NR^cC(O)R^d$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, $-C(O)OC_{1-6}$ alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, $-C(O)OC_{1-6}$ haloalkyl, amino, NR^cR^d, het, phenyl and $S(O)_nR^{11}$;

or R^a and R^b together with the N atom to which they are attached may form a three to seven – membered saturated, partially saturated, unsaturated or aromatic heterocyclic ring which may optionally contain one or more further N, O or S atoms and which may be optionally further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11};

or R^2 and R^e together with the N atom to which R^e is attached may form a six to seven – membered saturated, partially saturated, or unsaturated heterocyclic ring which may optionally contain one or more further N, O or S atoms and which may be optionally further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11};

R^3 and R^4 are independently selected from hydrogen, het, phenyl, S(O)$_n$R^{11}, and NR^{x}R^y;

or either one or more of R^3 and R^4 are independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{4-8} cycloalkyl, C_{1-6} alkoxy, and benzyl, which R^3 and R^4 may be optionally and independently further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11};

or R^3 and R^4 together with the carbon to which they are attached may form a four to seven – membered saturated, partially saturated, unsaturated or aromatic ring which may optionally contain one or more N, O or S atoms and which may be optionally further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11};

with the proviso that R^3 and R^4 are not both hydrogen;

R^x and R^y are independently selected from hydrogen, het, phenyl, benzyl and S(O)$_n$R^{11};

or either one or more of R^x and R^y are independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{1-6} alkanoyl, C(O)OC_{1-6} alkyl, each of which R^x and R^y may be optionally and independently further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11};

or R^x and R^y together with the N atom to which they are attached may form a three to seven – membered saturated, partially saturated, unsaturated or aromatic heterocyclic ring which may optionally contain one or more further N, O or S atoms and which may be optionally further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11};

R^7 is selected from halo, C_{1-6} alkyl and C_{1-6} alkoxy where, when R^7 is C_{1-6} alkyl or C_{1-6} alkoxy, R^7 may be optionally substituted with one or more halo substituents;

R^8 is selected from hydrogen, cyano, hydroxy, C(O)OH, nitro, halo, het, phenyl, and -S(O)$_n$R^{11};

or R^8 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, and C(O)OC_{1-6} alkyl, which R^8 may be optionally and independently further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11};

or R^8 is amino, which R^8 may be optionally and independently further substituted by one or more substituents selected from, where chemically possible, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, het, phenyl and S(O)$_n$R^{11};

R^9 is selected from hydrogen, cyano, halo, hydroxy, C(O)OH, nitro, het, phenyl and S(O)$_n$R^{11} and NR^{e}R^f;

or R^9 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C(O)OC_{1-6} alkyl, which R^9 may be optionally and independently further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11};

R^e and R^f are independently selected from hydrogen, het, phenyl and S(O)$_n$R^{11};

or either one or both of R^e and R^f are independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{1-6} alkanoyl, C(O)OC_{1-6} alkyl, -C(O)OC_{1-6} alkylC_{3-8} cycloalkyl, -C(O)OC_{3-8} cycloalkyl, each of which R^e or R^f may be optionally and independently further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11};

or R^e or R^f together with the N atom to which they are attached may form a three to seven – membered saturated, partially saturated, unsaturated or aromatic heterocyclic ring which may optionally contain one or more further N, O or S atoms and which may be optionally further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11};

or R^e and R^2 together with the atoms to which they are attached may form a six to seven – membered heterocyclic ring as previously described;

R^{10} is selected from halo, C_{1-6} alkyl and C_{1-6} alkoxy and where when R^{10} is C_{1-6} alkyl or C_{1-6} alkoxy it may optionally be substituted with one or more halo substituents;

each R^c and R^d are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkanoyl, C_{1-6} haloalkanoyl, C(O)OC_{1-6} alkyl, het, phenyl and S(O)$_n$R^{11};

or R^c and R^d together with the N atom to at least one of them is attached may form a three to seven – membered saturated, partially saturated, unsaturated or aromatic heterocyclic ring which may optionally contain one or more further N, O or S atoms;

each n is independently 0, 1 or 2;

each R^{11} is independently selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, amino, C_{1-6} alkyl amino and di C_{1-6} alkyl amino;

each phenyl may be optionally substituted by one or more further substitutents selected from the group consisting of halo, cyano, nitro, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkyl amino, di C_{1-6} alkyl amino, -NHS(O)$_nR^{11}$, and S(O)$_nR^{11}$;

and each het independently represents a four to seven membered heterocyclic group, which is aromatic or non-aromatic, unsaturated, partially saturated or satureated and which contains one or more heteroatoms selected from nitrogen, N-oxide, oxygen, sulphur and wherein said heterocyclic ring is optionally substituted, where the valence allows, with one or more substituents selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, OC(O) C_{1-6} alkyl, C_{1-6} alkanoyl, C(O)O C_{1-6} alkyl and NR^gR^h, where R^g and R^h are independently selected from hydrogen, C_{1-6} alkyl and C_{2-6} alkenyl, and where each of the above groups may include one or more optional substituents where chemically possible independently selected from cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^cR^d, NR^cC(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, C_{1-6} alkyl amino, di C_{1-6} alkyl amino, phenyl and S(O)$_nR^{11}$;

or a pharmaceutically acceptable salt or a prodrug thereof.

Preferably, R^1 is selected from: C_{1-6} haloalkyl, for example, trifluoromethyl; C_{1-6} haloalkoxy, for example, difluoromethoxy or trifluoromethoxy; SF_5; and S(O)$_nR^{11}$ where, for example, R^{11} is C_{1-6} haloalkyl to form, for example, trifluoromethylthio, (trifluoromethyl)sulphinyl or (trifluoromethyl)sulphonyl. More preferably R^1 is selected from: C_{1-6} haloalkyl for example trifluoromethyl; C_{1-6} haloalkoxy for example difluoromethoxy or trifluoromethoxy; and SF_5. Even more preferably R^1 is selected from CF_3, OCF_3, or SF_5. Most preferably R^1 is SF_5.

Suitably, R^2 is selected from: cyano and C(O)OH.

Equally suitably R^2 is C(O)NR^aR^b or C(S)NR^aR^b, preferably C(O)NR^aR^b, where R^a and R^b are independently selected from: hydrogen; C_{1-6} alkyl, eg methyl, ethyl, isopropyl or isobutyl to form, for example, (methylamino)carbonyl, (dimethylamino)carbonyl or (isopropylamino)carbonyl, which C_{1-6} alkyl may in turn be substituted with one or more groups selected from fluoro to form, for example, (trifluromethylamino)carbonyl, or C_{3-8} cycloalkyl, eg cyclopropyl to form, for example, [(cyclopropylmethyl)amino]carbonyl; C_{3-8} cycloalkyl eg cyclopropyl to form (cyclopropylamino)carbonyl; het, eg pyridinyl to form for example (pyridinylamino)carbonyl; and $S(O)_nR^{11}$ where, for example, R^{11} is C_{1-6} alkyl, eg methyl to form, for example, [(methylsulphonyl)amino]carbonyl. Where optionally R^a and R^b together with the N atom to which they are attached form a three to seven – membered heterocyclic ring optionally containing one or more further N, O or S atoms, the ring is suitably a pyrrolidinyl ring.

Where R^2 and R^e together with the N atom to which R^e is attached form a six to seven – membered saturated, partially saturated, or unsaturated heterocyclic ring which may optionally contain one or more further N, O or S atoms it is preferred that R^2 is selected from $C(O)NR^aR^b$, $C(S)NR^aR^b$ wherein it is then R^a and R^e together with the N atoms to which they are attached form a six to seven – membered saturated, partially saturated, or unsaturated heterocyclic ring which may optionally contain one or more further N, O or S atoms. Suitably the ring is a partially unsaturated 1, 3-diazepanyl which may be further substituted by C_{1-6} alkyl, eg methyl to form, for example, a 7'-methyl-5'-oxo-5',6',7',8'-tetrahydro-pyrazolo[3,4-d][1,3]diazepine.

Equally suitable compounds include those where R^2 is amino or C_{1-6} alkyl amino, eg methylamino, ethylamino or isopropylamino, which C_{1-6} alkyl amino is optionally further substituted with $S(O)_nR^{11}$ where, for example, R^{11} is methyl to form, for example, (methyl)(methylsulphonyl)amino.

Still further equally suitable compounds include those where R^2 is $S(O)_nR^{11}$ and R^{11} is selected from: C_{1-6} alkyl, eg methyl, ethyl or isopropyl to form, for example, methylthio, methylsulphinyl, methylsulphonyl or 2-isopropylthio; amino to form, for example, aminosulphonyl; and di C_{1-6} alkyl amino, eg dimethylamino to form, for example, (dimethylamino)sulphonyl.

Preferably, R^2 is selected from: cyano; $C(O)NR^aR^b$, where R^a and R^b are independently selected from hydrogen, C_{1-6} alkyl and C_{3-8} cycloalkyl wherein each of the above R^a and R^b groups may in turn be substituted with one or more groups selected from fluoro; amino; C_{1-6} alkyl amino, which C_{1-6} alkyl amino may optionally be substituted with $S(O)_nR^{11}$ where, for example, R^{11} is C_{1-6} alkyl; and $S(O)_nR^{11}$ where R^{11} is C_{1-6} alkyl. More preferably, R^2 is $C(O)NR^aR^b$ where R^a is hydrogen and R^b is selected from hydrogen, C_{1-6} alkyl, and C_{3-8} cycloalkyl wherein each of the above R^a and R^b groups may in turn be substituted with one or more groups selected from fluoro. Most preferably, R^2 is $C(O)NR^aR^b$ where both R^a and R^b are hydrogen.

Suitable compounds include those where R^4 is hydrogen and R^3 is C_{1-6} alkyl, eg methyl, ethyl, n-propyl, or isopropyl which C_{1-6} alkyl may optionally be substituted with one or more substituents independently selected from: hydroxy; halo, eg fluoro or chloro to form, for example, trifluoromethyl; C_{1-6} alkyl, eg methyl, ethyl, n-propyl, or isopropyl; C_{1-6} haloalkyl, eg trifluoromethyl or trifluoroethyl; C_{3-8} cycloalkyl, eg cyclopropyl; C_{3-8} cycloalkylC_{1-6} alkyl, eg cyclopropylmethyl or cyclopropylethyl which C_{3-8} cycloalkylC_{1-6} alkyl may be optionally substituted with one or more groups selected from halo eg fluoro or chloro, to form, for example, (1-fluorocyclopropyl)methyl, C_{1-4} alkyl, eg methyl or ethyl to form, for example, (1-methylcyclopropyl)methyl or (1-ethylcyclopropyl)methyl, or C_{1-4} haloalkyl to form, for example, [(1-trifluoromethyl)cyclopropyl]methyl; C_{1-6} alkoxy, eg methoxy or ethoxy; C_{1-6} haloalkoxy, eg trifluoromethoxy or trifluoroethoxy; C_{1-6} alkanoyl, eg acetyl or propanoyl; het, eg pyrazinyl, pyridinyl, pyrimidinyl, imidazolyl, 1-oxa-3, 4-diazolyl, 1, 3, 4-triazolyl; phenyl or benzyl which phenyl or benzyl may in turn be optionally substituted by one or more substituents selected from halo, eg chloro or fluoro to form, for example, 4-fluorophenyl, 3, 4-difluorophenyl, C_{1-4} alkyl optionally substituted by one or more halo groups, eg chloro or fluoro to form, for example, 4-(trifluoromethyl)phenyl; amino; C_{1-6} alkyl amino, eg methylamino; and $S(O)_nR^{11}$, eg where R^{11} is methyl.

Suitable compounds also include those where both R^3 and R^4 are independently selected C_{1-6} alkyl, eg methyl, ethyl, n-propyl, or isopropyl which C_{1-6} alkyl may optionally be substituted with one or more substituents independently selected from: hydroxy; halo, eg fluoro or chloro to form, for example, trifluoromethyl; C_{1-6} alkyl, eg methyl, ethyl, n-propyl, or isopropyl; C_{1-6} haloalkyl, eg trifluoromethyl or trifluoroethyl; C_{3-8} cycloalkyl, eg cyclopropyl; C_{3-8} cycloalkylC_{1-6} alkyl, eg cyclopropylmethyl or cyclopropylethyl which C_{3-8} cycloalkylC_{1-6} alkyl may be optionally substituted with one or more groups selected from halo eg fluoro or chloro, to form, for example, (1-fluorocyclopropyl)methyl, C_{1-4} alkyl, eg methyl or ethyl to form, for example, (1-methylcyclopropyl) methyl or (1-ethylcyclopropyl)methyl, or C_{1-4} haloalkyl to form, for example, [(1-trifluoromethyl)cyclopropyl]methyl; C_{1-6} alkoxy, eg methoxy or ethoxy; C_{1-6} haloalkoxy, eg trifluoromethoxy or trifluoroethoxy; C_{1-6} alkanoyl, eg acetyl or propanoyl; het, eg pyrazinyl, pyridinyl, pyrimidinyl, imidazolyl, 1-oxa-3, 4-diazolyl, 1, 3, 4-triazolyl; phenyl or benzyl which phenyl or benzyl may in turn be optionally substituted by one or more substituents selected from halo, eg chloro or fluoro to form, for example, 4-fluorophenyl, 3, 4-difluorophenyl, C_{1-4} alkyl optionally substituted by one or more halo groups, eg chloro or fluoro to form, for example, 4-(trifluoromethyl)phenyl; amino; C_{1-6} alkyl amino, eg methylamino; and $S(O)_nR^{11}$, eg where R^{11} is methyl.

Equally suitable compounds include those where R^4 is hydrogen and R^3 is C_{1-6} alkoxy, eg methoxy or ethoxy which C_{1-6} alkoxy may optionally be substituted with one or more substituents independently selected from: hydroxy; halo, eg fluoro or chloro; C_{1-6} alkyl, eg methyl, ethyl, n-propyl, or isopropyl; C_{1-6} haloalkyl, eg trifluoromethyl or trifluoroethyl; C_{3-8} cycloalkyl, eg cyclopropyl; C_{3-8} cycloalkylC_{1-6} alkyl, eg cyclopropylmethyl or cyclopropylethyl which C_{3-8} cycloalkylC_{1-6} alkyl may be optionally substituted with one or more groups selected from halo eg fluoro or chloro, to form, for example, (1-fluorocyclopropyl)methyl, C_{1-4} alkyl, eg methyl or ethyl to form, for example, (1-methylcyclopropyl) methyl or (1-ethylcyclopropyl)methyl, or C_{1-4} haloalkyl to form, for example, [(1-trifluoromethyl)cyclopropyl]methyl; C_{1-6} alkoxy, eg methoxy or ethoxy; C_{1-6} haloalkoxy, eg trifluoromethoxy or trifluoroethoxy; C_{1-6} alkanoyl, eg acetyl or propanoyl; het, eg pyrazinyl, pyridinyl, pyrimidinyl, imidazolyl, 1-oxa-3, 4-diazolyl, 1, 3, 4-triazolyl; phenyl or benzyl which phenyl or benzyl may in turn be optionally substituted by one or more substituents selected from halo, eg chloro or fluoro to form, for example, 4-fluorophenyl, 3, 4-difluorophenyl, C_{1-4} alkyl optionally substituted by one or more halo groups, eg chloro or fluoro to form, for example, 4-(trifluoromethyl)phenyl; amino; C_{1-6} alkyl amino, eg methylamino; and $S(O)_nR^{11}$, eg where R^{11} is methyl.

Equally suitable compounds also include those where R^4 is hydrogen and R^3 is C_{3-8} cycloalkylC_{1-6} alkyl eg cyclopropylmethyl or cyclopropylethyl which C_{3-8} cycloalkylC_{1-6} alkyl may optionally be substituted with one or more substituents independently selected from: halo eg fluoro or chloro, to form, for example, (1-fluorocyclopropyl)methyl; C_{1-4} alkyl eg methyl or ethyl to form, for example, (1-methylcyclopropyl)methyl or (1-ethylcyclopropyl)methyl; and C_{1-4} haloalkyl to form, for example, [(1-trifluoromethyl)cyclopropyl]methyl. Further suitable compounds include those where the C_{3-8} cycloalkyl of the C_{3-8} cycloalkylC_{1-6} alkyl is optionally substituted with one or more substituents independently selected from: halo, eg chloro or fluoro; and C_{1-4} alkyl, eg methyl which C_{1-4} alkyl may be optionally further substituted by 1 to 5 halo groups independently selected from chloro or fluoro to form, for example, trifluoromethyl. Optionally a single carbon of the C_{3-8} cycloalkyl of the C_{3-8} cycloalkylC_{1-6} alkyl is di-substituted with the same substitutent selected from fluoro, chloro or methyl while the other carbon of the C_{3-8} cycloalkyl of the C_{3-8} cycloalkylC_{1-6} alkyl remains di-substituted with hydrogen.

Further suitable compounds also include those where R^4 is hydrogen and R^3 is $S(O)_nR^{11}$ eg where R^{11} is C_{1-6} alkyl, eg methyl, or C_{1-6} haloalkyl, eg trifluoromethyl.

Equally further suitable compounds also include those where R^4 is hydrogen and R^3 is NR^xR^y where each of R^x or R^y is independently selected from: hydrogen; C_{1-6} alkyl, eg methyl, ethyl, isopropyl or t-butyl, which C_{1-6} alkyl may in turn be substituted with one or more substituents independently selected from halo, eg fluoro or chloro to form, for example, trifluoromethyl or trifluoroethyl, C_{1-6} alkyl, eg t-butyl to form, for example, t-butylmethyl, C_{3-8} cycloalkyl, eg cyclopropyl, het, eg pyrazinyl, imidazolyl, 1, 3, 4-triazolyl, or pyridinyl, phenyl to form, for example, benzyl which phenyl may in turn be optionally substituted by one or more substituents selected from halo, eg chloro or fluoro to form, for example, 4-fluorobenzyl or 3, 4-difluorobenzyl, C_{1-4} alkyl optionally substituted by one or more halo groups, eg chloro or fluoro to form, for example, (trifluoromethyl)benzyl, or $S(O)_nR^{11}$, eg where R^{11} is methyl to form, for example, (4-methylsulphonyl)benzyl; C_{1-6} haloalkyl, eg trifluoromethyl, or trifluoroethyl; C_{3-8} cycloalkyl, eg cyclopropyl; C_{3-8} cycloalkylC_{1-6} alkyl eg cyclopropylmethyl or cyclopropylethyl which C_{3-8} cycloalkylC_{1-6} alkyl may be optionally substituted with one or more groups selected from halo eg fluoro or chloro, to form, for example, (1-fluorocyclopropyl)methyl, C_{1-4} alkyl eg methyl or ethyl to form, for example, (1-methylcyclopropyl)methyl or (1-ethylcyclopropyl)methyl, or C_{1-4} haloalkyl to form, for example, [(1-trifluoromethyl)cyclopropyl]methyl; C_{1-6} alkanoyl, eg acetyl or propanoyl; $C(O)OC_{1-6}$ alkyl, eg ethoxycarbonyl; and $S(O)_nR^{11}$, eg where R^{11} is methyl. Where R^x and

R^y together with the N atom to which they are attached form a three to seven – membered heterocyclic ring optionally containing one or more further N, O or S atoms, the ring is suitably a pyrrolidinyl ring.

Yet more equally suitable compounds also include those where R^4 is hydrogen and R^3 is het eg tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, pyrrolyl, furanyl, imidazolyl, oxazolyl, 1,3,4-triazolyl, 1-oxa-3,4-diazolyl, pyridinyl, pyrimidinyl or pyrazinyl, which het may optionally be substituted with one or more substituents independently selected from: hydroxy; halo, eg fluoro or chloro; C_{1-6} alkyl, eg methyl, ethyl, n-propyl, or isopropyl; C_{1-6} haloalkyl, eg trifluoromethyl or trifluoroethyl; C_{3-8} cycloalkyl, eg cyclopropyl; C_{3-8} cycloalkylC_{1-6} alkyl, eg cyclopropylmethyl or cyclopropylethyl which C_{3-8} cycloalkylC_{1-6} alkyl may be optionally substituted with one or more groups selected from halo eg fluoro or chloro, to form, for example, (1-fluorocyclopropyl)methyl, C_{1-4} alkyl, eg methyl or ethyl to form, for example, (1-methylcyclopropyl) methyl or (1-ethylcyclopropyl)methyl, or C_{1-4} haloalkyl to form, for example, [(1-trifluoromethyl)cyclopropyl]methyl; C_{1-6} alkoxy, eg methoxy or ethoxy; C_{1-6} haloalkoxy, eg trifluoromethoxy or trifluoroethoxy; C_{1-6} alkanoyl, eg acetyl or propanoyl; phenyl or benzyl which phenyl or benzyl may in turn be optionally substituted by one or more substituents selected from halo, eg chloro or fluoro to form, for example, 4-fluorophenyl, 3, 4-difluorophenyl, C_{1-4} alkyl optionally substituted by one or more halo groups, eg chloro or fluoro to form, for example, 4-(trifluoromethyl)phenyl; amino; C_{1-6} alkyl amino, eg methylamino; and $S(O)_nR^{11}$, eg where R^{11} is methyl.

Yet more equally suitable compounds also include those where R^4 is hydrogen and R^3 is phenyl which phenyl may optionally be substituted with one or more substituents independently selected from: hydroxy; halo, eg fluoro or chloro; C_{1-6} alkyl, eg methyl, ethyl, n-propyl, or isopropyl; C_{1-6} haloalkyl, eg trifluoromethyl, or trifluoroethyl; C_{1-6} alkoxy, eg methoxy or ethoxy; C_{1-6} haloalkoxy, eg trifluoromethoxy or trifluoroethoxy; C_{1-6} alkanoyl, eg acetyl or propanoyl; and $S(O)_nR^{11}$, eg where R^{11} is methyl.

Even further equally suitable compounds include those where where R^4 is hydrogen and R^3 is C_{4-8} cycloalkyl which C_{4-8} cycloalkyl may be optionally substituted with one or more substitutents independently selected from: hydroxy; halo, eg fluoro or chloro to form, for example, trifluoromethyl; C_{1-6} alkyl, eg methyl, ethyl, n-propyl, or isopropyl; C_{1-6} haloalkyl, eg trifluoromethyl or trifluoroethyl; C_{3-8} cycloalkyl, eg cyclopropyl; C_{3-8} cycloalkylC_{1-6} alkyl, eg cyclopropylmethyl or cyclopropylethyl which C_{3-8} cycloalkylC_{1-6} alkyl may be optionally substituted with one or more groups selected from halo eg fluoro or chloro, to form, for example, (1-fluorocyclopropyl)methyl, C_{1-4} alkyl, eg methyl or ethyl to form, for example, (1-methylcyclopropyl) methyl or (1-ethylcyclopropyl)methyl, or C_{1-4} haloalkyl to form, for example, [(1-trifluoromethyl)cyclopropyl]methyl; C_{1-6} alkoxy, eg methoxy or ethoxy; C_{1-6} haloalkoxy, eg trifluoromethoxy or trifluoroethoxy; C_{1-6} alkanoyl, eg acetyl or propanoyl;

het, eg pyrazinyl, pyridinyl, pyrimidinyl, imidazolyl, 1-oxa-3, 4-diazolyl, 1, 3, 4-triazolyl; phenyl or benzyl which phenyl or benzyl may in turn be optionally substituted by one or more substituents selected from halo, eg chloro or fluoro to form, for example, 4-fluorophenyl, 3, 4-difluorophenyl, C_{1-4} alkyl optionally substituted by one or more halo groups, eg chloro or fluoro to form, for example, 4-(trifluoromethyl)phenyl; amino; C_{1-6} alkyl amino, eg methylamino; and $S(O)_nR^{11}$, eg where R^{11} is methyl. Preferably the C_{4-8} cycloalkyl is substituted with one or more substituents selected from halo, eg chloro or fluoro or C_{1-4} alkyl, eg methyl which C_{1-4} alkyl is optionally substituted by 1 to 5 halo groups independently selected from chloro or fluoro to form, for example, trifluoromethyl. More preferably, a single carbon of the C_{4-8} cycloalkyl is di-substituted with the same substitutent selected from fluoro, chloro or methyl while the other carbons of the C_{4-8} cycloalkyl remain di-substituted with hydrogen.

Even further equally suitable compounds also include those where R^4 and R^3 together with the carbon to which they are attached form a four to seven – membered ring optionally containing one or more N, O or S heteroatoms to form, for example, a carbocyclic ring eg cyclobutyl, cyclopentyl, cyclohexyl, or het eg tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl or piperidinyl, which four to seven –membered ring may optionally be substituted with one or more substituents selected from: hydroxy; oxo; halo, eg fluoro or chloro; C_{1-6} alkyl, eg methyl, ethyl, n-propyl, or isopropyl; C_{1-6} haloalkyl, eg trifluoromethyl or trifluoroethyl; C_{3-8} cycloalkyl, eg cyclopropyl; C_{3-8} cycloalkylC_{1-6} alkyl, eg cyclopropylmethyl or cyclopropylethyl which C_{3-8} cycloalkylC_{1-6} alkyl may be optionally substituted with one or more groups selected from halo eg fluoro or chloro, to form, for example, (1-fluorocyclopropyl)methyl, C_{1-4} alkyl, eg methyl or ethyl to form, for example, (1-methylcyclopropyl) methyl or (1-ethylcyclopropyl)methyl, or C_{1-4} haloalkyl to form, for example, [(1-trifluoromethyl)cyclopropyl]methyl; C_{1-6} alkoxy, eg methoxy or ethoxy; C_{1-6} haloalkoxy, eg trifluoromethoxy or trifluoroethoxy; C_{1-6} alkanoyl, eg acetyl or propanoyl; phenyl or benzyl which phenyl or benzyl may in turn be optionally substituted by one or more substituents selected from halo, eg chloro or fluoro to form, for example, 4-fluorophenyl, 3, 4-difluorophenyl, C_{1-4} alkyl optionally substituted by one or more halo groups, eg chloro or fluoro to form, for example, 4-(trifluoromethyl)phenyl; amino; C_{1-6} alkyl amino, eg methylamino; and $S(O)_nR^{11}$, eg where R^{11} is methyl. Preferably the four to seven membered ring is a carbocyclic ring, which carbocyclic ring is optionally substituted with one or more substituents selected from halo, eg chloro or fluoro or C_{1-4} alkyl, eg methyl which C_{1-4} alkyl is optionally substituted by 1 to 5 halo groups independently selected from chloro or fluoro to form, for example, trifluoromethyl. More preferably, a single carbon of the carbocyclic ring is optionally di-substituted with the same substitutent selected from fluoro, chloro and methyl while the other carbon of the carbocyclic ring remains di-substituted with hydrogen.

Preferably R^4 is hydrogen and R^3 is independently selected from: C_{1-6} alkyl, eg methyl, ethyl, n-propyl, or isopropyl which C_{1-6} alkyl may optionally be substituted with one or more substituents selected from halo, eg fluoro or chloro to form, for example, trifluoromethyl, C_{1-6} haloalkyl, eg trifluoromethyl or trifluoroethyl to form, for example, (trifluoromethyl)methyl or (trifluoroethyl)methyl, C_{3-8} cycloalkyl, eg cyclopropyl to form, for example, cyclopropylmethyl, phenyl to form, for example, benzyl, which phenyl may in turn be optionally substituted by one or more substituents selected from halo, eg chloro or fluoro to form, for example, 4-fluorobenzyl, and $S(O)_nR^{11}$, eg where R^{11} is methyl to form, for example, (methylsulphonyl)methyl; C_{1-6} alkoxy, eg methoxy, ethoxy, which C_{1-6} alkoxy may optionally be substituted with one or more substituents selected from halo, eg fluoro or chloro, C_{1-6} haloalkyl, eg trifluoromethyl, or trifluoroethyl, C_{3-8} cycloalkyl, eg cyclopropyl, and $S(O)_nR^{11}$, eg where R^{11} is methyl; NR^xR^y where each of R^x or R^y is independently selected from hydrogen, C_{1-6} alkyl, eg methyl, which C_{1-6} alkyl is optionally substituted with one or more halo atoms, C_{1-6} alkanoyl eg acetyl, and $S(O)_nR^{11}$, eg where R^{11} is methyl; het eg tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, which het may be optionally substituted with one or more substituents selected from C_{1-6} alkyl or C_{1-6} haloalkyl; and phenyl which phenyl may optionally be substituted with one or more substituents selected from halo eg chloro or fluoro, C_{1-6} alkyl eg methyl, C_{1-6} haloalkyl eg trifluoromethyl, and $S(O)_nR^{11}$, eg where R^{11} is methyl. Further preferred compounds also include those where both R^3 and R^4 are independently selected from C_{1-6} alkyl, eg methyl, ethyl, n-propyl, or isopropyl which C_{1-6} alkyl may optionally be substituted with one or more substituents selected from halo, eg fluoro or chloro to form, for example, trifluoromethyl, C_{1-6} haloalkyl, eg trifluoromethyl, or trifluoroethyl, C_{3-8} cycloalkyl, eg cyclopropyl, and $S(O)_nR^{11}$, eg where R^{11} is methyl. Even further preferred compounds include those where R^3 and R^4 together with the carbon to which they are attached form a four to seven – membered carbocyclic ring which is optionally further substituted with one or more substituents selected from halo eg chloro or fluoro, C_{1-6} alkyl eg methyl, C_{1-6} haloalkyl eg trifluoromethyl, and $S(O)_nR^{11}$, eg where R^{11} is methyl.

More preferably R^4 is hydrogen and R^3 is C_{1-6} alkyl, eg methyl, ethyl, n-propyl, or isopropyl which C_{1-6} alkyl may optionally be substituted with halo, eg fluoro or chloro to form, for example, trifluoromethyl, or phenyl to form, for example, benzyl, which phenyl may in turn be optionally substituted by one or more substituents selected from halo, eg chloro or fluoro to form, for example, 4-fluorobenzyl, or R^3 and R^4 are both independently selected from C_{1-6} alkyl, eg methyl, ethyl, n-propyl, or isopropyl which may optionally be substituted with halo, eg fluoro or chloro to form, for example, trifluoromethyl; or R^3 and R^4 together with the carbon to which they are attached form a four to seven – membered carbocyclic ring eg cyclobutyl.

Even more preferably R^4 is hydrogen and R^3 is C_{1-6} alkyl, eg methyl or ethyl; or C_{1-6} alkyl which C_{1-6} alkyl is substituted with halo to form trifluoromethyl; or C_{1-6} alkyl which C_{1-6} alkyl is substituted with phenyl to form benzyl and which phenyl is in turn substituted by fluoro to form 4-fluorobenzyl; or R^3 and R^4 are both C_{1-6} alkyl, eg methyl or ethyl; or R^3 and R^4 are both C_{1-6} alkyl which C_{1-6} alkyl is substituted with halo to form trifluoromethyl; or R^3 and R^4 together with the carbon to which they are attached form a 4-membered carbocyclic ring.

Most preferably R^4 is hydrogen and R^3 methyl; or R^4 is hydrogen and R^3 ethyl; or R^4 is hydrogen and R^3 is trifluoromethyl; or R^4 is hydrogen and R^3 is 4-fluorobenzyl; or R^3 and R^4 are both methyl; or R^3 and R^4 are both trifluoromethyl.

Most preferably R^3 and R^4 together with the carbon to which they are attached form a cyclobutyl ring.

Suitable compounds include those where, when R^7 is halo, preferred halo substituents are fluoro, chloro or bromo. Further suitable compounds include those where, when R^7 is selected from C_{1-6} alkyl or C_{1-6} alkoxy where the C_{1-6} alkyl or C_{1-6} alkoxy are optionally substituted with one or more halo substituents, preferred halo substituents are fluoro, chloro or bromo. Preferably R^7 is selected from chloro, or fluoro. Most preferably R^7 is chloro.

Suitably, R^8 is selected from: cyano; halo, eg chloro or fluoro; C_{1-6} alkyl, eg methyl or ethyl which C_{1-6} alkyl may optionally be substituted with one or more fluoro groups to form, for example, trifluoromethyl; and C_{1-6} alkanoyl, eg acetyl or propanoyl which C_{1-6} alkanoyl may optionally be substituted by one or more groups independently selected from $-S(O)_nR^{11}$ eg where R^{11} is methyl, to form, for example, (methylthio)acetyl, halo eg chloro or fluoro, to form, for example, trifluoroacetyl or C_{1-4} alkoxy to form, for example, 2-ethoxy-2-oxoethyl. Preferably, R^8 is cyano, trifluoromethyl or methylthioacetyl. Most preferably, R^8 is cyano.

Suitably R^9 is selected from: hydrogen; cyano; hydroxy; and halo, eg chloro or fluoro.

Equally suitably R^9 is C_{1-6} alkyl, eg methyl, ethyl, isopropyl, or t-butyl which C_{1-6} alkyl may in turn optionally be substituted by one or more substituents selected from: halo, eg fluoro or chloro to form, for example, difluoromethyl, trifluoromethyl or trifluoroethyl; C_{1-6} alkyl, eg t-butyl to form, for example, t-butylmethyl; C_{3-8} cycloalkyl, eg cyclopropyl, cyclopentyl or cyclohexyl to form, for example, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl or cyclopropylethyl; C_{1-6} alkoxy, eg methoxy or ethoxy to form, for example, methoxymethyl, methoxyethyl, ethoxymethyl or ethoxyethyl; het, eg pyrazinyl to form, for example, pyrazinylmethyl or pyrazinylethyl, imidazolyl to form, for example, (1H-imidazolyl)methyl or (1H-imidazolyl)ethyl, 1, 3, 4-triazolyl to form, for example, (1, 3, 4-triazolyl)methyl or (1, 3, 4-triazolyl)ethyl, or pyridinyl to form, for example, (pyridin-2-yl)methyl, (pyridin-2-yl)ethyl, (pyridin-4-yl)methyl or (pyridine-2-yl)ethyl, where suitably the pyridinyl may be further substituted with, eg oxy to form, for example, (1-hydroxy-pyridinyl)methyl or (1-hydroxy-pyridinyl)ethyl; phenyl to form, for example, benzyl or phenylethyl which phenyl may in turn be optionally substituted by one or more substituents selected from halo, eg chloro or fluoro to form, for example, 4-fluorobenzyl, (4-fluorophenyl)ethyl, 3, 4-difluorobenzyl or (3, 4-difluorophenyl)ethyl, C_{1-4} alkyl optionally further substituted by one or more halo groups, eg chloro or fluoro to form, for example, (trifluoromethyl)benzyl or [(trifluoromethyl)phenyl]ethyl, or $S(O)_nR^{11}$, eg where R^{11} is methyl to form, for example, (4-methylsulphonyl)benzyl or [(4-methylsulphonyl)phenyl]ethyl; -C(O)OC$_{1-6}$ alkyl eg ethoxycarbonyl to form, for example, 2-ethoxy-2-oxoethyl; amino to form, for example, aminomethyl or aminoethyl; C$_{1-6}$ alkyl amino, eg methylamino to form, for example, (methylamino)methyl, (methylamino)ethyl, (ethylamino)methyl or (ethylamino)ethyl; and S(O)$_n$R^{11}, eg where R^{11} is methyl to form, for example, (methylthio)methyl, (methylthio)ethyl, (methylsulphinyl)methyl, (methylsulphinyl)ethyl, (methylsulphonyl)methyl, or (methylsulphonyl)ethyl.

Equally suitably R^9 is C$_{3-8}$ cycloalkyl, eg cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl which C$_{3-8}$ cycloalkyl may be optionally substituted with one or more groups selected from halo, eg fluoro or chloro to form, for example, 1-fluorocyclopropyl, cyano to form, for example, 1-cyanocyclopropyl, and hydroxy to form, for example, 1-hydroxycyclopropyl.

Equally suitably R^9 is C$_{3-8}$ cycloalkylC$_{1-6}$ alkyl eg cyclopropylmethyl or cyclopropylethyl which C$_{3-8}$ cycloalkylC$_{1-6}$ alkyl may be optionally substituted with one or more groups selected from: halo eg fluoro or chloro, to form, for example, (1-fluorocyclopropyl)methyl; C$_{1-4}$ alkyl eg methyl or ethyl to form, for example, (1-methylcyclopropyl)methyl or (1-ethylcyclopropyl)methyl; and C$_{1-4}$ haloalkyl eg trifluoromethyl to form, for example, [(1-trifluoromethyl)cyclopropyl]methyl.

Further equally suitable compounds include those where R^9 is C$_{1-6}$ alkoxy, eg methoxy, ethoxy, isopropoxy or t-butoxy which C$_{1-6}$ alkoxy may in turn optionally be substituted by one or more substituents selected from: halo, eg fluoro or chloro to form, for example, trifluoromethoxy or trifluoroethoxy; C$_{1-6}$ alkyl, eg t-butyl to form, for example, t-butylmethoxy; C$_{3-8}$ cycloalkyl, eg cyclopropyl, cyclopentyl or cyclohexyl to form, for example, cyclopropylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy or cyclopropylethoxy; het, eg pyrazinyl to form, for example, pyrazinylmethoxy, imidazolyl to form, for example, (1H-imidazolyl)methoxy, 1, 3, 4-triazolyl to form, for example, (1, 3, 4-triazolyl)methoxy or (1, 3, 4-triazolyl)ethoxy, or pyridinyl to form, for example, pyridin-2-ylmethoxy or pyridin-4-ylmethoxy, where suitably the pyridinyl may be further substituted with, eg oxy to form, for example, (1-hydroxypyridinyl)methoxy; phenyl to form, for example, benzyloxy which phenyl may in turn be optionally substituted by one or more substituents selected from halo, eg chloro or fluoro to form, for example, (4-fluorobenzyl)oxy or (3, 4-difluorobenzyl)oxy, C$_{1-4}$ alkyl optionally further substituted by one or more halo groups, eg chloro or fluoro to form, for example, [(trifluoromethyl)benzyl]oxy, or S(O)$_n$R^{11}, eg where R^{11} is methyl to form, for example, [(4-methylsulphonyl)benzyl]oxy; and C(O)OC$_{1-6}$ alkyl, eg ethoxycarbonyl to form, for example, 2-ethoxy-2-oxoethoxy.

Further equally suitable compounds include those where R^9 is C$_{3-8}$ cycloalkylC$_{1-6}$ alkoxy eg cyclopropylmethoxy or cyclopropylethoxy which C$_{3-8}$ cycloalkylC$_{1-6}$ alkoxy may be optionally substituted with one or more groups selected from: halo eg fluoro or chloro, to form, for example, (1-fluorocyclopropyl)methoxy; C$_{1-4}$ alkyl eg methyl or ethyl to form, for example, (1-

methylcyclopropyl)methoxy or (1-ethylcyclopropyl)methoxy; and C_{1-4} haloalkyl to form, for example, [(1-trifluoromethyl)cyclopropyl]methoxy.

Still further equally suitable compounds include those where R^9 is C_{2-6} alkenyl, eg ethenyl which C_{2-6} alkenyl may be substituted with one or more substituents selected from: het eg pyrazinyl, 1, 3, 4-triazolyl, imidazolyl, or pyridinyl; and phenyl, which phenyl may be further substituted by for example halo, eg chloro or fluoro to form, for example, 4-fluorophenyl or 3, 4-difluorophenyl, C_{1-4} alkyl optionally substituted by one or more halo groups, eg chloro or fluoro to form, for example, (trifluoromethyl)phenyl, or $S(O)_nR^{11}$, eg where R^{11} is methyl to form, for example, (4-methylsulphonyl)phenyl.

Still further equally suitable compounds include those where R^9 is het, eg pyrazinyl, imidazolyl, or pyridinyl to form, for example, pyridin-2-yl or pyridin-4-yl, where suitably the pyridinyl may be further substituted with oxy to form, for example, 1-hydroxypyridinyl.

Yet further equally suitable compounds also include those where R^9 is phenyl which phenyl may in turn be optionally substituted by one or more substituents selected from: halo, eg chloro or fluoro to form, for example, 4-fluorophenyl or 3, 4-difluorophenyl; and $S(O)_nR^{11}$, eg where R^{11} is methyl to form, for example, (4-methylsulphonyl)phenyl.

Yet further equally suitable compounds also include those where R^9 is $S(O)_nR^{11}$, eg where R^{11} is methyl to form, for example, methylsulphonyl.

Even further equally suitable compounds include those where R^9 is NR^eR^f where each of R^e or R^f is independently selected from: hydrogen; C_{1-6} alkyl, eg methyl, ethyl, isopropyl or t-butyl to form, for example, methylamino, isopropylamino or isobutylamino, which C_{1-6} alkyl may in turn be substituted with one or more substituents selected from halo, eg fluoro or chloro to form, for example, trifluoromethylamino or trifluoroethylamino, C_{1-6} alkyl, eg t-butyl to form, for example, (t-butylmethyl)amino, C_{3-8} cycloalkyl, eg cyclopropyl, cyclopentyl or cyclohexyl to form, for example, (cyclopropylmethyl)amino, (cyclopentylmethyl)amino, (cyclohexylmethyl)amino or (cyclopropylethyl)amino, het, eg pyrazinyl to form, for example, (pyrazinylmethyl)amino, imidazolyl to form, for example, [(1H-imidazolyl)methyl]amino, 1, 3, 4-triazolyl to form, for example, [(1, 3, 4-triazolyl)methyl]amino or [(1, 3, 4-triazolyl)ethyl]amino, or pyridinyl to form, for example, (pyridin-2-ylmethyl)amino or (pyridin-4-ylmethyl)amino, where suitably the pyridinyl may be further substituted with oxy to form, for example, [(1-hydroxy-pyridin-4-yl)methyl]amino, phenyl to form, for example, benzylamino which phenyl may in turn be optionally substituted by one or more substituents selected from halo, eg chloro or fluoro to form, for example, (4-fluorobenzyl)amino or (3, 4-difluorobenzyl)amino, C_{1-4} alkyl optionally substituted by one or more halo groups, eg chloro or fluoro to form, for example, [(trifluoromethyl)benzyl]amino, or $S(O)_nR^{11}$, eg where R^{11} is methyl to form, for example, [(4-methylsulphonyl)benzyl]amino. R^e or R^f may also be independently selected from: C_{3-8} cycloalkyl, eg cyclopropyl to form, for example, cyclopropylamino; C_{3-8} cycloalkylC_{1-6} alkyl eg cyclopropylmethyl or cyclopropylethyl to form for example (cyclopropylmethyl)amino or (cyclopropylethyl)amino, which C_{3-8} cycloalkylC_{1-6} alkyl may be optionally substituted with one or more groups selected from halo eg fluoro or chloro, to form, for example, [(1-fluorocyclopropyl)methyl]amino, C_{1-4} alkyl eg methyl or ethyl to form, for example, [(1-methylcyclopropyl)methyl]amino or [(1-ethylcyclopropyl)methyl]amino, or C_{1-4} haloalkyl to form, for example, {[1-(trifluoromethyl)cyclopropyl]methyl}amino; and -C(O)OC_{1-6} alkyl, eg ethoxycarbonyl to form, for example, ethoxycarbonylamino.

Preferably, R^9 is selected from: hydrogen; hydroxy; halo, eg chloro or fluoro; C_{1-6}alkyl eg methyl, which C_{1-6}alkyl may optionally be substituted by halo eg fluoro, to form, for example, difluoromethyl, C_{3-8}cycloalkyl eg cyclopropyl to form, for example, cyclopropylmethyl, or -C(O)OC_{1-6} alkyl eg ethoxycarbonyl to form, for example, 2-ethoxy-2-oxoethyl; C_{3-8}cycloalkylC_{1-6}alkyl eg cyclopropylmethyl, which C_{3-8} cycloalkylC_{1-6} alkyl may optionally be substituted by C_{1-4}alkyl eg methyl to form, for example, (1-methylcyclopropyl)methyl; C_{1-6}alkoxy, eg methoxy which methoxy may optionally be substituted by halo eg fluoro, to form, for example, trifluoromethoxy, or -C(O)OC_{1-6} alkyl eg ethoxycarbonyl to form, for example, 2-ethoxy-2-oxoethoxy; C_{3-8}cycloalkylC_{1-6}alkoxy, eg cyclopropylmethoxy which C_{3-8}cycloalkylC_{1-6}alkoxy may optionally be substituted by C_{1-6} alkyl eg methyl to form, for example, (1-methylcyclopropyl)methoxy; and NR^eR^f where each of R^e or R^f is independently selected from: hydrogen to form, for example, amino; C_{1-6} alkyl eg methyl to form, for example, methylamino, ethyl to form, for example, ethylamino or isopropyl to form, for example isopropylamino, which C_{1-6} alkyl may in turn be optionally further substituted by halo eg fluoro to form, for example, (trifluoromethyl)amino or (trifluoroethyl)amino, C_{3-8}cycloalkyl eg cyclopropyl to form, for example, (cyclopropylmethyl)amino, het eg 1, 3, 4-triazolyl to form, for example, [(1, 3, 4-triazolyl)methyl]amino or pyridinyl to form for example (pyridin-4-ylmethyl)amino; -C(O)OC_{1-6} alkyl eg ethoxycarbonyl to form, for example, ethoxycarbonylamino; and C_{3-8} cycloalkylC_{1-6} alkyl, eg cyclopropylmethyl to form (cyclopropylmethyl)amino which cyclopropylmethyl may optionally be further substituted with C_{1-6} alkyl eg methyl to form, for example, [(1-methylcyclopropyl)methyl]amino.

More preferably, R^9 is selected from: hydrogen; halo eg chloro; C_{1-6} haloalkyl eg difluoromethyl; C_{3-8} cycloalkylC_{1-6} alkoxy eg cyclopropylmethoxy; and NR^eR^f where R^e is hydrogen and R^f is independently selected from hydrogen, C_{1-6} alkyl for example methyl to form methylamino which methyl may in turn be optionally substituted by C_{3-8} cycloalkyl eg cyclopropyl to form, for example, cyclopropylmethyl)amino, or het eg pyridinyl to form, for example, (pyridin-4-ylmethyl)amino.

Even more preferably, R^9 is selected from hydrogen; halo eg chloro; C_{3-8} cycloalkylC_{1-6} alkoxy eg cyclopropylmethoxy; and NR^eR^f where R^e is hydrogen and R^f is independently selected from hydrogen to from amino, methyl to form methyl amino, or pyridin-4-ylmethyl to form (pyridin-4-

ylmethyl)amino.

Most preferably R^9 is amino.

Preferably X is CR^{10}. More preferably R^{10} is chloro. Other preferred compounds are those in which R^7 and R^{10} are the same. More preferably, both R^7 and R^{10} are Cl.

A further group of suitable compounds of the present invention are those of formula (I) where: R^1 – R^2, R^7 – R^9, X, R^c, R^d, n, R^{11} and het are all as defined for formula (I) above; R^4 is hydrogen and R^3 is C_{4-8} cycloalkyl, eg cyclobutyl or cyclopentyl, which C_{4-8} cycloalkyl may optionally be substituted with one or more substitutents selected from cyano, nitro, halo, oxo, hydroxy, C(O)OH, $C(O)NR^cR^d$, $NR^cC(O)R^d$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^cR^d, het, phenyl and $S(O)_nR^{11}$;

or a pharmaceutically acceptable salt or a prodrug thereof.

Preferably, in these compounds of formula (I): R^1 is CF_3, OCF_3 or SF_5, more preferably SF_5; R^2 is CN or $C(O)NR^aR^b$, where R^a is hydrogen and R^b is selected from hydrogen, C_{1-6} alkyl and C_{3-8} cycloalkyl, wherein each of the above groups may include one or more optional fluoro substituents, more preferably where both R^a and R^b are hydrogen; R^8 is cyano, trifluoromethyl or methylthiocarbonyl, more preferably cyano; R^9 is selected from hydrogen, chloro, methyl, difluoromethyl, cyclopropylmethoxy or NR^eR^f where R^e is hydrogen and R^f is independently selected from hydrogen, methyl, cyclopropylmethyl, (1-methylcyclopropyl)methyl, or pyridin-4-ylmethyl, more preferably R^9 is amino; X is CR^{10} and both R^7 and R^{10} are Cl.

A further group of suitable compounds of the present invention are those of formula (I) where: R^1 – R^2, R^7 – R^9, X, R^c, R^d, n, R^{11} are all as defined for formula (I) above; R^4 is hydrogen and R^3 is het eg tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, pyrrolyl, furanyl, imidazolyl, oxazolyl, 1, 3,4-triazolyl, 1-oxa-3, 4-diazolyl, pyridinyl, pyrimidinyl or pyrazinyl which het may optionally be substituted, where chemically possible, with one or more substitutents selected from cyano, nitro, halo, oxo, hydroxy, C(O)OH, $C(O)NR^cR^d$, $NR^cC(O)R^d$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^cR^d, het, phenyl and $S(O)_nR^{11}$;

or a pharmaceutically acceptable salt or a prodrug thereof.

Preferably, in these compounds of formula (I): R^1 is CF_3, OCF_3 or SF_5, more preferably SF_5; R^2 is CN or $C(O)NR^aR^b$, where R^a is hydrogen and R^b is selected from hydrogen, C_{1-6} alkyl and C_{3-8} cycloalkyl, wherein each of the above groups may include one or more optional fluoro substituents, more preferably where both R^a and R^b are hydrogen; R^8 is cyano, trifluoromethyl or methylthiocarbonyl, more preferably cyano; R^9 is selected from hydrogen, chloro, methyl, difluoromethyl, cyclopropylmethoxy or NR^eR^f where R^e is hydrogen and R^f is independently selected from hydrogen, methyl, cyclopropylmethyl, (1-methylcyclopropyl)methyl, or pyridin-4-ylmethyl, more preferably R^9 is amino; X is CR^{10} and both R^7 and R^{10} are Cl.

A further group of suitable compounds of the present invention are those of formula (I) where: R^1 – R^2, R^7 – R^9, X, R^c, R^d, n, R^{11} and het are all as defined for formula (I) above; R^4 is hydrogen and R^3 is phenyl which phenyl may be optionally substituted by one or more further substitutents selected from the group consisting of halo, cyano, nitro, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkyl amino, di C_{1-6} alkyl amino, $-NHS(O)_nR^{11}$, and $S(O)_nR^{11}$;
or a pharmaceutically acceptable salt or a prodrug thereof.
Preferably, in these compounds of formula (I): R^1 is CF_3, OCF_3 or SF_5, more preferably SF_5; R^2 is CN or $C(O)NR^aR^b$, where R^a is hydrogen and R^b is selected from hydrogen, C_{1-6} alkyl and C_{3-8} cycloalkyl, wherein each of the above groups may include one or more optional fluoro substituents, more preferably where both R^a and R^b are hydrogen; R^8 is cyano, trifluoromethyl or methylthiocarbonyl, more preferably cyano; R^9 is selected from hydrogen, chloro, methyl, difluoromethyl, cyclopropylmethoxy or NR^eR^f where R^e is hydrogen and R^f is independently selected from hydrogen, methyl, cyclopropylmethyl, (1-methylcyclopropyl)methyl, or pyridin-4-ylmethyl, more preferably R^9 is amino; X is CR^{10} and both R^7 and R^{10} are Cl.

A further group of suitable compounds of the present invention are those of formula (I) where: R^1 – R^2, R^7 – R^9, X, R^c, R^d, n, R^{11} and het are all as defined for formula (I) above; and R^4 and R^3 together with the carbon to which they are attached may form a four to seven – membered saturated, partially saturated, unsaturated or aromatic ring which may optionally contain one or more further N, O or S atoms and which may be optionally further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, $C(O)NR^cR^d$, $NR^cC(O)R^d$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, $-C(O)OC_{1-6}$ alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, $-C(O)OC_{1-6}$ haloalkyl, amino, NR^cR^d, het, phenyl and $S(O)_nR^{11}$;
or a pharmaceutically acceptable salt or a prodrug thereof.
Preferably, in these compounds of formula (I): R^1 is CF_3, OCF_3 or SF_5, more preferably SF_5; R^2 is CN or $C(O)NR^aR^b$, where R^a is hydrogen and R^b is selected from hydrogen, C_{1-6} alkyl and C_{3-8} cycloalkyl, wherein each of the above groups may include one or more optional fluoro substituents, more preferably where both R^a and R^b are hydrogen; R^8 is cyano, trifluoromethyl or methylthiocarbonyl, more preferably cyano; R^9 is selected from hydrogen, chloro, methyl, difluoromethyl, cyclopropylmethoxy or NR^eR^f where R^e is hydrogen and R^f is independently selected from hydrogen, methyl, cyclopropylmethyl, (1-methylcyclopropyl)methyl, or pyridin-4-ylmethyl, more preferably R^9 is amino; X is CR^{10} and both R^7 and R^{10} are Cl.

A further group of suitable compounds of the present invention are those of formula (I) where: $R^1 - R^2$, $R^7 - R^9$, X, R^c, R^d, n, R^{11} and het are all as defined for formula (I) above; and both R^3 and R^4 are independently selected C_{1-6} alkyl, eg methyl, ethyl, or isopropyl, which C_{1-6} alkyl may optionally be substituted with one or more substitutents selected from cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11};

or a pharmaceutically acceptable salt or a prodrug thereof.

Preferably, in these compounds of formula (I): R^1 is CF_3, OCF_3 or SF_5, more preferably SF_5; R^2 is CN or C(O)NR^{a}R^b, where R^a is hydrogen and R^b is selected from hydrogen, C_{1-6} alkyl and C_{3-8} cycloalkyl, wherein each of the above groups may include one or more optional fluoro substituents, more preferably where both R^a and R^b are hydrogen; R^8 is cyano, trifluoromethyl or methylthiocarbonyl, more preferably cyano; R^9 is selected from hydrogen, chloro, methyl, difluoromethyl, cyclopropylmethoxy or NR^{e}R^f where R^e is hydrogen and R^f is independently selected from hydrogen, methyl, cyclopropylmethyl, (1-methylcyclopropyl)methyl, or pyridin-4-ylmethyl, more preferably R^9 is amino; X is CR^{10} and both R^7 and R^{10} are Cl.

A further group of suitable compounds of the present invention are those of formula (I) where: R^1, $R^3 - R^9$, X, R^c, R^d, n, R^{11} and het are all as defined for formula (I) above; and R^2 is selected from cyano, C(O)OH, S(O)$_n$R^{11}, C(O)NR^{a}R^b, and C(S)NR^{a}R^b; or R^2 is selected from amino and C_{1-6} alkyl amino which amino or C_{1-6} alkyl amino may be optionally and independently further substituted by one or more substitutents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11}; where R^a and R^b are independently selected from hydrogen, het, phenyl and S(O)$_n$R^{11}, or either one or both of R^a and R^b are independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{1-6} alkanoyl, and C(O)OC_{1-6} alkyl, each of which R^a and R^b may be optionally and independently further substituted by one or more substituents selected from, where chemcially possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11}, or R^a and R^b together with the N atom to which they are attached may form a three to seven – membered saturated, partially saturated, unsaturated or aromatic heterocyclic ring which may optionally contain one or more further N, O or S atoms and which may be optionally further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11};

or a pharmaceutically acceptable salt or a prodrug thereof.

Preferably, in these compounds of formula (I): R^1 is CF_3, OCF_3 or SF_5, more preferably SF_5; R^4 is hydrogen and R^3 is C_{1-6} alkyl, eg methyl, ethyl, n-propyl, or isopropyl which C_{1-6} alkyl may optionally be substituted with halo, eg fluoro or chloro to form, for example, trifluoromethyl, or phenyl to form, for example, benzyl, which phenyl may in turn be optionally substituted by one or more substituents selected from halo, eg chloro or fluoro to form, for example, 4-fluorobenzyl, or R^3 and R^4 are both independently selected from C_{1-6} alkyl, eg methyl, ethyl, n-propyl, or isopropyl which may optionally be substituted with halo, eg fluoro or chloro to form, for example, trifluoromethyl; or R^3 and R^4 together with the carbon to which they are attached form a four to seven – membered carbocyclic ring eg cyclobutyl; R^8 is cyano, trifluoromethyl or methylthiocarbonyl, more preferably cyano; R^9 is selected from hydrogen, chloro, methyl, difluoromethyl, cyclopropylmethoxy or NR^{e}R^f where R^e is hydrogen and R^f is independently selected from hydrogen, methyl, cyclopropylmethyl, (1-methylcyclopropyl)methyl, or pyridin-4-ylmethyl, more preferably R^9 is amino; X is CR^{10} and both R^7 and R^{10} are Cl.

Preferred individual compounds of the invention are selected from:
1-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}cyclobutanecarboxamide;
2-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}propanamide;
2-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}-2-methylpropanamide;
1-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}cyclobutanecarboxamide;
1-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}cyclobutanecarboxamide;
1-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-(methylamino)-1H-pyrazol-4-yl}cyclobutanecarboxamide;
2-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propanamide;
2-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-3-(4-fluorophenyl)propanamide;
2-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}butanamide;
N-(1-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-2,2,2-trifluoroethyl)-N-methylmethanesulfonamide;
5-amino-1-[2,6-dichloro-4-pentafluorothiophenyl]-4-[1-(methylsulfonyl)ethyl]-1H-pyrazole-3-carbonitrile;
1-[2,6-dichloro-4-pentafluorothiophenyl]-4-[1-(methylsulfonyl)ethyl]-1H-pyrazole-3-carbonitrile;

2-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}propanamide;
2-{5-chloro-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}propanamide;
2-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-[(pyridin-4-ylmethyl)amino]-1H-pyrazol-4-yl}propanamide;
5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[2,2,2-trifluoro-1-(methylamino)-1-(trifluoromethyl)ethyl]-1H-pyrazole-3-carbonitrile;
5-amino-4-[1-amino-2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-3-carbonitrile;
5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[2,2,2-trifluoro-1-(isopropylthio)-1-(trifluoromethyl)ethyl]-1H-pyrazole-3-carbonitrile;
5-amino-4-[1-cyano-2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazole-3-carbonitrile;
2-{3-cyano-5-(cyclopropylmethoxy)-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}propanamide;
or a pharmaceutically acceptable salt or prodrug thereof.

In the compounds according to formula (I) the term 'halo' means a group selected from fluoro, chloro, bromo or iodo. Preferably the term "halo" means a group selected from fluoro, chloro or bromo..

Alkyl, alkenyl, alkynyl and alkoxy groups, containing the requisite number of carbon atoms, can be unbranched or branched. The term lower alkyl shall be taken to mean C_{1-6} alkyl. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy. Examples of alkenyl include methylene, 1,1-ethylene, 1,2-ethylene, 1,1-propylene, 1,2-propylene, 1,3-propylene and 2,2-propylene. The term cycloalkyl shall be taken to mean C_{3-8} cycloalkyl. Examples of include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

In the compounds according to formula (I) the term phenyl shall be taken to mean a six membered aromatic carbon ring, which phenyl can be substituted as described for compounds of formula (I).

In the compounds according to formula (I) the term "het" shall be taken to mean those substituents which fall into the definition as set out in Claim 1. Preferably the term "het" shall be taken to mean those substituents which represent a five to six membered heterocyclic group, which is aromatic or non-aromatic, unsaturated, partially saturated or saturated and which contains one or more heteroatoms selected from nitrogen, N-oxide, oxygen, and sulphur and wherein said heterocyclic ring is optionally substituted where the valence allows with one or more substituents selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, NR^gR^h, where R^g and R^h are independently selected from hydrogen, and C_{1-6} alkyl. More preferably the term "het" shall be taken to mean those substituents which represent a five to six membered heterocyclic ring, which is aromatic or non-aromatic, unsaturated, partially saturated or saturated and which contains at least one nitrogen or oxygen atom and optionally up to two further heterocyclic atoms selected from nitrogen, oxygen and sulphur and wherein said heterocyclic ring is optionally substituted where the valence allows with one or more substituents selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, NR^gR^h, where R^g and R^h are independently selected from hydrogen, and C_{1-6} alkyl.

In the case of substituents R^2, R^a, or R^b and further optional substituents thereof of compounds of formula (I), the term "het" shall most preferably be taken to mean those substituents which represent a five to six membered heterocyclic ring, which is aromatic, unsaturated, or partially saturated and which contains at least one nitrogen atom and optionally up to two further heteroatoms selected from nitrogen, oxygen or sulphur and wherein said heterocyclic ring is optionally substituted where the valence allows with one or more substituents selected from halo, and C_{1-6} alkyl. Suitable preferred examples of such rings include 1-oxa-3, 4-diazolyl, 5-methyl-1-3,4-oxadiazol-2-yl, pyridinyl, 1, 2, 4 triazolyl, or thiazolyl.

In the case of substituents R^9, R^e, or R^f and further optional substituents thereof of compounds of formula (I), the term "het" shall most preferably be taken to mean those substituents which represent a five to six membered heterocyclic ring, which is aromatic, unsaturated, partially saturated, or saturated and which contains at least one nitrogen atom or one oxygen atom and optionally up to two further heterocyclic atoms selected from nitrogen, oxygen or sulphur and wherein said heterocyclic ring is optionally substituted where the valence allows with one or more substituents selected from halo, and C_{1-6} alkyl. Suitable preferred examples of such rings include pyrazinyl, imidazolyl, pyridinyl, 1-hydroxy-pyridinyl, 1,2,4-triazolyl, 1,3,4-triazolyl, isoxaolyl, thiazolyl, 2-chloro-1,3-thiazol-4-yl, pyrazolyl, 1-methyl–1*H*-pyrazol-4-yl, 1-methyl-3-methyl-5-chloro-1*H*-pyrazol-4-yl, and tretrahydropyranyl. Most preferably in the case of substituents R^9, R^e, or R^f and further optional substituents thereof of compounds of formula (I) het is pyridinyl.

In the compounds according to formula (I) each phenyl group may be optionally and independently substituted as set out in Claim 1. More preferably each phenyl group may be optionally and independently substitueted with one or more further substitutents selected from the group consisting of halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-NHS(O)_nR^{11}$, and $S(O)_nR^{11}$. More preferably each phenyl group may be optionally substituted in the 4-position with a substituent selected from the group consisting of halo, C_{1-6} haloalkyl, $-NHS(O)_nR^{11}$, and $S(O)_nR^{11}$.

In the case of substituents R^9, R^e, or R^f and further optional substituents thereof of compounds of formula (I) it is preferred that each phenyl group may be optionally substituted in the 4-position a substituent selected from the group consisting of halo, C_{1-6} haloalkyl, $-NHS(O)_nR^{11}$, and $S(O)_nR^{11}$. Suitable examples of such phenyl groups include 4-fluorophenyl, 4-trifluoromethylphenyl, (4-methylsulphonyl)phenyl, 4-[(methylsulphonyl)amino]phenyl, and 4-[(methylamino)sulphonyl]phenyl.

It will be understood that compounds of formula (I) may exist as one or more geometric isomers. Thus included within the scope of the present invention are all such possible geometric isomer forms of the compounds of the present invention. Geometric isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

It will be understood that compounds of formula (I) may exist as one or more tautomeric isomers. Thus included within the scope of the present invention are all such possible tautomeric isomer forms of compounds of the present invention.

It is to be understood that compounds of formula (I) may contain one or more asymmetric carbon atoms, thus compounds of the invention can exist as two or more stereoisomers. Included within the scope of the present invention are all stereoisomers such as enantiomers and diasteromers. Also included are acid addition or base salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high performance liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, using conditions such as on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, "Stereochemistry of Organic Compounds" by E L Eliel (Wiley, New York, 1994).

Also included within the scope of the present invention are compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof.

For the avoidance of doubt, it will be understood that throughout the application all references to pharmaceutically acceptable compounds includes references to veterinarily acceptable compounds or agriculturally acceptable compounds. Furthermore it will be understood that throughout the application all references to pharmaceutical activity includes references to veterinary activity or agricultural activity.

Pharmaceutically acceptable salts of the compounds of formula (I) include the acid addition and base salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts. Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

The pharmaceutically, veterinarily and agriculturally acceptable acid addition salts of certain of the compounds of formula (I) may also be prepared in a conventional manner. For example, a solution of a free base may be treated with the appropriate acid, either neat or in a suitable solvent, and the resulting salt isolated either by filtration or by evaporation under reduced pressure of the reaction solvent. For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Hereinafter, and throughout the application, all references to compounds of formula (I) include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

The invention includes all polymorphs of the compounds of formula (I) as hereinbefore defined.

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water. Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, d_6-acetone, d_6-DMSO.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Within the scope of the invention are so-called 'prodrugs' of the compounds of formula (I). Thus certain derivatives of compounds of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985).

Some examples of prodrugs in accordance with the invention include:

(i) where the compound of formula (I) contains a carboxylic acid functionality (-COOH), an ester thereof, for example, replacement of the hydrogen with (C_1-C_8)alkyl;

(ii) where the compound of formula (I) contains an alcohol functionality (-OH), an ether thereof, for example, replacement of the hydrogen with (C_1-C_6)alkanoyloxymethyl; and

(iii) where the compound of formula (I) contains a primary or secondary amino functionality ($-NH_2$ or $-NHR$ where $R \neq H$), an amide thereof, for example, replacement of one or both hydrogens with (C_1-C_{10})alkanoyl.

Prodrugs in accordance with the invention can, for example, be produced by replacing the 5-amino substituent on the pyrazole ring in the compounds of formula (I) with certain moieties known to those skilled in the art as 'pro-drug moieties' as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985); "Design and application of prodrugs," Textbook of Drug Design and Discovery, (3rd Edition), 2002, 410-458, (Taylor and Francis Ltd., London); and references therein.

Suitable prodrugs may have an N-containing group at the 5-position of the pyrazole ring of formula (I) and are bound to the ring through N. The 5-N group can be substituted once or twice. Examples of substituents include: alkyl amines, aryl amines, amides, ureas, carbamates, cyclic carbamates, imines, enamines, imides, cyclic imides, sulfenamides, and sulfonamides. The hydrocarbon portion of these groups contain C_{1-6} alkyl, phenyl, heteroaryl such as pyridinyl, C_{2-6} alkenyl, and C_{3-8} cycloalkyl; wherein each of the above groups may include one or more optional substituents where chemically possible independently selected from: halo; hydroxy; C_{1-6} alkyl and C_{1-6} alkoxy.

Further examples of replacement groups in accordance with the foregoing example and examples of other prodrug types may be found in the aforementioned references.

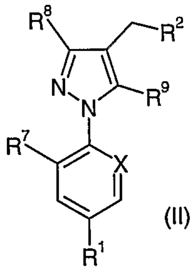
A prodrug according to the invention can be readily identified by administering it to a host animal and sampling a body fluid for a compound of formula (I). Finally, certain compounds of formula (I) may themselves act as prodrugs of other compounds of formula (I). Prodrugs may be cleaved to active drug by metabolism by the host or by the parasite targeting the host.

In a further aspect, the present invention provides processes for the preparation of a compound of formula (I), or a pharmaceutically, veterinarily or agriculturally acceptable salt thereof, or a pharmaceutically, veterinarily or agriculturally acceptable solvate (including hydrate) of either entity, as illustrated below.

It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of the invention. This may be achieved by conventional methods, for example as described in "Protective Groups in Organic Synthesis" by TW Greene and PGM Wuts, John Wiley & Sons Inc (1999), and references therein.

The following processes are illustrative of the general synthetic procedures which may be adopted in order to obtain the compounds of the invention.

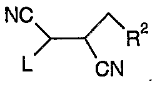
When one or more of R^1, R^2, R^3, R^4, R^7, R^8, R^9, R^{10} and R^{11} contain reactive functional groups then additional protection may be provided according to standard procedures during the synthesis of compounds of formula (I). In the processes described below, for all synthetic precursors used in the synthesis of compounds of formula (I), the definitions of R^1, R^2, R^3, R^4, R^7, R^8, R^9, R^{10} and R^{11}, wherein R^1, R^2, R^3, R^4, R^7, R^8, R^9, R^{10} and R^{11} are as defined for formula (I), are intended to optionally include suitably protected variants, P^1, P^2, P^3, P^4, P^7, P^8, P^9, P^{10} and P^{11}. Such suitable protecting groups for these functionalities are described in the references listed below and the use of these protecting groups where needed is specifically intended to fall within the scope of the processes described in the present invention for producing compounds of formula (I) and its precursors. When suitable protecting groups are used, then these will need to be removed to yield compounds of formula (I). Deprotection can be effected according to standard procedures including those described in the references listed below. For example, when R^9 in formula (I) is an unsubstituted amino group, certain precursors may require protection of the amino group in order to perform the necessary transformations, for example, by an imidoformamide group such as a compound of formula (I), where R^1-R^8 and R^{10} are as described for formula (I) and R^9 represents -N=C(H)-NR^{c}R^d, where R^c and R^d independently represent C_{1-6}alkyl, e.g. to form a N,N-dimethyl group. Such imidoformamides may be prepared by standard methods, typically by refluxing the unprotected amine in *N, N*-dimethylformamide dimethyl acetal for 2 – 16 hours, usually around 5 hours followed by stirring at room temperature for 5 – 24 hours, usually overnight. The imidoformamide protecting group may be removed using standard conditions, such as at elevated temperature, with a suitable acid such as hydrochloric acid or para-toluenesulfonic acid in a solvent such as methanol or dioxane.



(II)

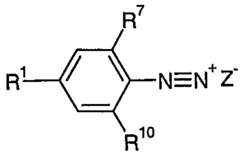
A compound of formula (II), wherein R^1, R^2, R^7, and R^8 are as defined for formula (I) is a key intermediate for the synthesis of compounds of formula (I) in which $R^9 = NH_2$. Compounds of formula (II) may be prepared by the Japp-Klingemann reaction. This reaction is described in Org. React., 1959, 10, 143-178. 3,4,5-Trisubstituted 1-arylpyrazoles may be produced directly in a reaction which involves coupling of an aryldiazonium species with an appropriately substituted precursor bearing a desired substituent. The desired substituent is introduced concomitantly at the C-4 position in a process, which does not involve any rearrangement. Furthermore, a very wide variety of 4-substituents may be introduced conveniently and directly.

Thus, a compound of formula (II) can be prepared by reacting a compound of formula (III)



(III)

with a compound of formula (IV)



(IV)

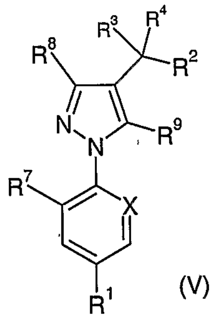
optionally in the presence of an acid, wherein: R^1 to R^{10} are as defined above in relation to the compounds of formula (I); L is an activating group; and Z is a compatible counter ion, followed by removal of group L. The counter ion Z^- may be any suitable counter ion normally found in diazonium reactions. Preferably, Z^- is halogen, HSO_4^-, or tetrafluoroborate and most preferably is tetrafluoroborate.

The group L is an electron withdrawing group which stabilises the anion intermediate in the process. Thus, preferably, L is a group which is capable of stabilising a negative charge on an adjacent carbon atom. The group L must also be removable. L can be removed under basic conditions, for example by base hydrolysis or can be removed by reduction and/or elimination. The group L is important as it serves to direct the reaction of the diazonium species with the compound of formula (IX) but then is removed in the subsequent stages of the reaction. Preferably L is an ester group or a group COR^{15}. More preferably, L is a group selected from: – $S(O)_pR^{16}$ where p is 1 or 2, $(R^{16}O)_2PO$, $COOR^{16}$ and $-COR^{15}$, wherein R^{15} is selected from: hydrogen, C_{1-8} alkyl, di-C_{1-8} alkylamino, C_{1-8} alkylthio, C_{3-8} cycloalkyl, $(CH_2)_nPh$ and $(CH_2)_n$ heteroaryl wherein n = 0, 1 or 2, each of which groups may be optionally substituted on any carbon atom by one or more groups selected independently from: halogen, hydroxy, cyano, nitro, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkanoyl, C_{1-4} haloalkanoyl, C_{1-4} alkylsulphinyl, C_{1-4} haloalkylsulphinyl, C_{1-4} alkylsulphonyl, C_{1-4} haloalkylsulphonyl, C_{3-8} cycloalkyl and C_{3-8} halocycloalkyl; and wherein R^{16} is selected from: C_{1-8} alkyl, C_{3-8} cycloalkyl, $(CH_2)_nPh$ and $(CH_2)_n$ heteroaryl wherein n = 0, 1 or 2, each of which groups may be optionally substituted on any carbon atom by one or more groups selected independently from: halogen, hydroxy, cyano, nitro, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkanoyl, C_{1-4} haloalkanoyl, C_{1-4} alkylsulphinyl, C_{1-4} haloalkylsulphinyl, C_{1-4} alkylsulphonyl, C_{1-4} haloalkylsulphonyl, C_{3-8} cycloalkyl and C_{3-8} halocycloalkyl. Preferably L is a selected from COR^{15} and $COOR^{16}$. Most preferably L is –COOMe or –COOEt.

In certain cases, the nature of the leaving group L means that the resulting intermediate is in the wrong oxidation state. Thus, where necessary, one or more reaction steps may be added to ensure the correct oxidation state is reached prior to cyclising to form the aryl pyrazole.

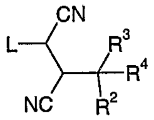
Ideally, for the coupling reaction to form the compound of formula (II), the solvent should be a polar solvent which does not react with either the diazonium salt or cation, or with the compound of formula (III). The reaction may optionally be carried out under mildly acidic conditions.

The diazonium salt of formula (IV) can be produced by conventional means and may be prepared *in situ* for further reaction or can be isolated and used in a subsequent reaction step. For example, by the dropwise addition of a solution of the corresponding aminobenzenes in glacial acetic acid to a solution of sodium nitrite in concentrated sulphuric/glacial acetic acid mixtures at reduced temperature, typically 10°C, followed by heating at 50°C for several hours, typically 1 hour and allowing to cool to room temperature. This solution of the diazonium salt is then added dropwise to a solution of a compound of formula (III) in a suitable solvent, such as acetic acid followed by stirring at room temperature for up to 1 hour. The reaction mixture is poured into water and extracted with a water immiscible organic solvent such as dichloromethane. Aqueous ammonium hydroxide is added to the organic extract and stirred overnight to give compounds of formula (II).

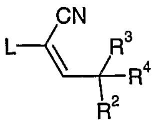

(V)

Compounds of formula (II) may be used to prepare compounds of formula (V), wherein R^1, R^3, R^4, R^7, R^8 ,R^9 and X are as defined for formula (I), provided R^2 is an electron withdrawing group capable of stabilising an α-anion, by alkylation with R^3Y and R^4Y, wherein Y is any suitable leaving group such as Cl, I, Br, OTos, OMes, in a suitable solvent, such as tetrahydrofuran, in the presence of base, such as potassium bis(trimethylsilyl)amide. Those skilled in the art will recognise that using appropriate reagents and reaction conditions either monoalkylation or bisalkylation may be achieved. By reaction with a bidentate electrophile, compounds of formula (II) may be converted to compounds of formula (V), wherein R^3 and R^4, together with the carbon atom to which they are both attached, are joined to form an optionally substituted carbocyclic or heterocyclic ring as defined in formula (I).

Alternatively, compounds of formula (V) may be prepared, using the Jappe-Klingemann reaction as described above, from intermediates of formula (VI) wherein R^2, R^3 and R^4 are as defined for compounds formula (I), L is a leaving group as defined for compounds of formula (III) and $R^9 = NH_2$.

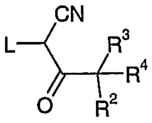

(VI)

Compounds of formula (VI) can be obtained from compounds of formula (VII) wherein R^3, R^4 and L are as defined for formula (VI), for example, by treating a compound of formula (VII) with a source of cyanide ions.



(VII)

Compounds of formula (VII) can be obtained by reducing and then dehydrating a compound of formula (VIII).



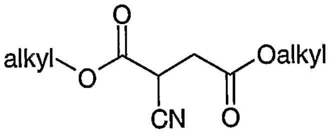
(VIII)

Compounds of formula (VIII) can, for example, be made by condensation of an alkyl cyanoalkanoate e.g. methyl cyanoacetate with an acid chloride in an aprotic solvent such as dichloromethane in the presence of a Lewis acid, such as magnesium chloride and a mild base, such as triethylamine, at reduced temperature.

Alternatively, compounds of formula (VII) can be accessed by Knoevenagel condensation of a suitable aldehyde or ketone with an alkyl alkanoate such as methyl cyanoacetate.

The above reactions are particularly successful where in compounds of formula (II), (III), (IV), (V), (VI), (VII) and (VIII) R^2 is $C(O)OC_{1-6}$ alkyl.

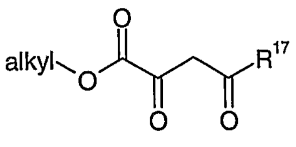
In addition, variations to the Japp-Klingemann reaction, utilising standard conditions well-known to those skilled in the art, for producing compounds of formula (I) and its precursors, are also intended to fall within the scope described in the present invention. For example, coupling of an aryldiazonium species with precursors of formula (IX):



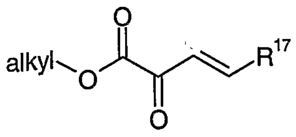
(IX)

in the presence of a suitable base, may be useful in accessing compounds in which R^9 is OH. These compounds may then undergo standard alkylation, acylation, carbamoylation, sulphonation and other standard well known procedures to produce, for example, the corresponding alkoxy derivatives.

Alternatively, arylpyrazoles may be prepared by the reaction of optionally substituted phenylhydrazine derivatives with compounds of formula (X) or (XI):



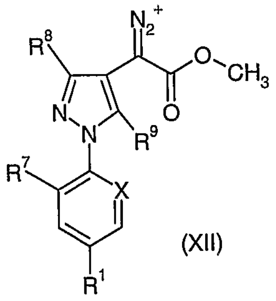
(X)



(XI)

in which R^{17} is C_{1-4}alkyl or C_{3-8}cycloalkyl.

A compound of formula (II) may be converted to the diazonium salt of formula (XII):



(XII)

wherein R^1, R^7, R^8, R^9 and X are as previously defined for formula (I), by reaction with an aryl sulphonylazide, in the presence of a suitable base, for example DBU. Diazonium salts of formula (XII) are versatile intermediates.

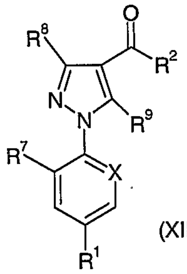
Compounds of formula (XII) may react with a wide range of nucleophiles, in a suitable solvent, typically dichloromethane, in the presence of a suitable metal catalyst, such as rhodium tetraacetate, to give compounds of formula (V) wherein R^3 is for example, without limitation, -Salkyl, -Oalkyl, -Ocycloalkyl, -Oaryl, -Oheteroaryl wherein these substituents are as defined in compounds of formula (I) and, furthermore, may be optionally substituted as defined in compounds of formula (I). Compounds of formula (XII) will undergo carbenoid addition reactions using standard literature procedures well known to those skilled in the art, for example C-H insertion reactions and cyclopropanation procedures.

Compounds of formula (II) may undergo α-bromination by reaction with typical brominating agents e.g. N-bromosuccinimide in the presence of light or a catalytic quantity of a radical initiator to give compounds of formula (V) wherein R^3 = Br. These bromo compounds of formula (V) undergo standard nucleophilic substitiution reactions as described in organic textbooks or literature precedent.

Alternatively, compounds of formula (II) may be α-hydroxylated by a variety of standard literature procedures. For example, reaction with TMS chloride in the presence of a suitable base, to give the enolate salt followed by reaction with a peracid, such as *m*-chloroperbenzoic acid, and subsequent removal of TMS can be used to prepare compounds of formula (V) wherein R^3 is OH. These hydroxy compounds of formula (V) wherein R^3 is OH may be alkylated, acylated and sulphonylated using literature procedures well known to those skilled in the art. Similarly, compounds of formula (V) wherein R^3 is –Oacetyl may be prepared from compounds of formula (II) using manganese triacetate in a suitable solvent, typically acetic acid, optionally with an added inorganic salt, such as lithium chloride.

Compounds of formula (V), wherein R^3 is Cl may be prepared from compounds of formula (V) wherein R^3 is -OH by reaction with thionyl chloride. These chloro compounds undergo nucleophilic substitiution reactions as described in organic textbooks or literature precedent; such nucleophiles include, without limitation, substituted thiols, mono and di-substituted amines, cyanide, and cyclic amines such as pyrrolidine,

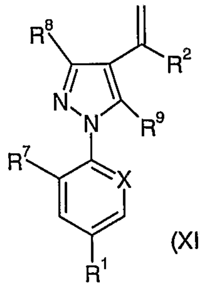
Compounds of formula (V), wherein R^3 is -OH, may be prepared by the reduction of compounds of formula (XIII) using standard literature reduction procedures, typically sodium borohydride in a suitable solvent.



(XIII)

Compounds of formula (XIII) undergo organometallic additions using standard literature procedures. For example, a compound of formula (XIII), wherein $R^2 = CF_3$ is stirred with trimethylamine N-oxide and molecular sieves in tetrahydrofuran under nitrogen for 30 minutes. (Trifluoromethyl)trimethylsilane can be added dropwise over an hour followed by stirring at room temperature for several days, typically 3 days yielding compounds of formula (I) wherein $R^2 = CF_3$, $R^3 = CF_3$ and $R^4 = OH$. The α-hydroxyester products may be deoxygenated using literature procedures to give compounds of formula (V) wherein R^3 can be alkyl, cycloalkyl, aryl and heteroaryl as defined for formula (I). The α-hydroxyester products may also be alkylated to give compounds of formula (V) wherein R^3 can be alkyl, cycloalkyl, aryl and heteroaryl as defined for formula (I) and R^4 is an O-linked substituent as defined in formula (I).

Compounds of formula (XIII) may be prepared from compounds of formula (XIV) by sequential reaction with osmium tetroxide and sodium periodate in a suitable solvent, typically acetone.



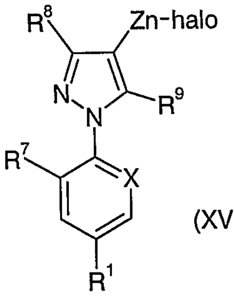
(XIV)

Compounds of formula (XIV) undergo a wide range of reactions described in organic textbooks or literature precedent. Nucleophilic addition to the α, β-unsaturated ester may be achieved using organometallic reagents such as organocuprates and Grignard reagents, cyanide ions, mono- and disubstituted amines, substituted thiolate anions, substituted alcoholate anions and heterocyclic anions. Literature Heck coupling procedures lead to the expected products which can be reduced or cyclopropanated using procedures well known to those skilled in the art. Epoxidation of the α, β-unsaturated ester may be achieved using a range of oxidising agents, typically a peracid such as *m*-chloroperbenzoic acid. These epoxides undergo standard literature nucleophilic epoxide ring-opening reactions. Reduction of the alkene to give compounds of formula (I), wherein R^3 = CH_3 can be achieved using standard literature reagents, such as sodium borohydride in a suitable solvent, such as ethanol.

Furthermore, compounds of formula (XIV) may be carbonylated using standard techniques to give compounds of formula (V) wherein R^3 is $-CH_2COOH$ and R^4 is -H; this acid functionality may be converted to –CN, substituted amides or heterocycles using reactions described in organic textbooks or literature precedent. Reduction, for example with sodium borohydride, gives compounds of formula (V) wherein R^3 is $-CH_2CH_2OH$ which may be tosylated and then reacted with a wide range of nucleophiles to give compounds of formula (I)

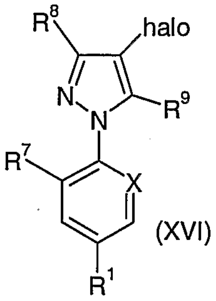
An alternative product of the carbonylation of compounds of formula (XIV) is a compound of formula (V), wherein R^3 is -CHO and R^4 is $-CH_3$. This aldehyde may be reacted with diethylamino sulphur tetrafluoride to give a compound of formula (V) wherein R^3 is $-CHF_2$ and R^4 is $-CH_3$. This aldehyde also undergoes functional group interconversions as described in organic textbooks or literature precedent.

Compounds of formula (XIV) can be synthesized using an organozinc reagent of formula (XV):



(XV)

wherein R^1, R^7, R^8, R^9 and X are as previously defined for formula (I). The organozinc reagent formula (XV) may be obtained by treatment of (XVI), wherein halo is preferably bromo or iodo, with activated zinc (Rieke zinc) in an aprotic solvent such as tetrahydrofuran, for several hours. The organozincate can then be cross coupled to a haloalkene in the presence of a palladium (II) species such as dichlorobis(triphenylphosphine) palladium (II) and a reducing agent such as diisobutylaluminium hydride in an aprotic solvent such as tetrahydrofuran, at elevated temperatures, normally at reflux.

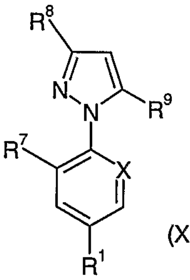


(XVI)

Alternatively, a compound of formula (XIV) may be obtained directly by the reaction of a compound of formula (XVI) with an organostannane in the presence of a metal catalyst such as tetrakis(triphenylphosphine)palladium(0) at an elevated temperature for several hours.

Alternatively, compounds of formula (XIV) may be prepared by dehydration of compounds of formula (I), wherein R^3 = OH and R^4 = CH_3 by converting the hydroxyl into a leaving group, for example by reaction with methane sulphonyl chloride, followed by by base catalysed elimination. A typical base being triethylamine in a suitable solvent such as dichloromethane.

A compound of formula (XVI) may be obtained from a compound of formula (XVIIA):

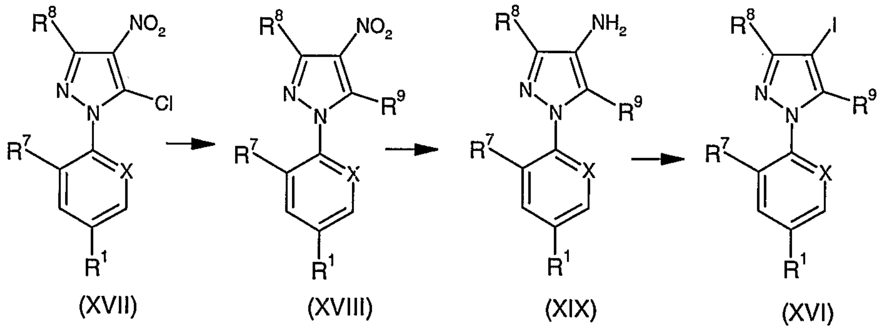


(XVIIA)

wherein R^1, R^7, R^8 and R^9 are as previously defined for formula (I), by conventional bromination or iodination procedures. For example, when halo is iodo, (XVIIA) is treated with N-iodosuccinimide in a suitable solvent such as acetonitrile at from about room temperature to about 85 °C.

Alternatively, a compound of formula (XVI) may be prepared as shown in Scheme 1 below:

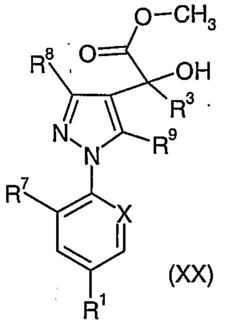
Scheme 1



wherein R^1, R^7, R^8 and X are as previously defined for formula (I) and R^9 is SR^r, NR^rR^s or OR^r

wherein R^r and R^s are each independently H, alkyl, cycloalkyl, aryl, heteroaryl, cycloalkylalkyl, arylalkyl, heteroarylalkyl in accordance with the definition of R^9 informula (I), wherein each alkyl, cycloalkyl, aryl, heteroaryl, cycloalkylalkyl, arylalkyl, heteroarylalkyl may be optionally substituted. Compounds of formula (XVIII) can be prepared from compounds of formula (XVII) via standard nucleophilic substitution procedures. The amine (XIX) may then be obtained by reduction using a suitable reducing agent, optionally in the presence of a catalyst, typically $SnCl_2/HCl$ or $Fe/CaCl_2$. Compounds of formula (XVI) may be prepared from (XIX) by conventional Sandmeyer procedures.

Alternatively, a compound of formula (XX), wherein R^1, R^3, R^7, R^8, R^9 and X are as previously defined for formula (I), may be obtained by the reaction of a compound of formula (XVI) with a suitable Grignard reagent, such as isopropylmagnesium chloride, followed by the addition of a substituted pyruvate ester in a suitable solvent such as tetrahydrofuran.



(XX)

Compounds of formula (XX) may be deoxygenated to give compounds of formula (V), wherein $R^2 = -COOCH_3$ and $R^4 = H$, using a range of literature procedures well known to those skilled in the art.

Compounds of formula (I), wherein $R^2 = C(O)OC_{1-6}$ alkyl and both R^3 and $R^4 = H$ can be prepared by de-trifluoromethylation of a compound of formula (I) in which $R^2 = C(O)OC_{1-6}$ alkyl, $R^3 = H$, $R^4 = CF_3$ by stirring with potassium carbonate in acetonitrile with a few added drops of water for several hours, typically overnight. The compound of formula (I) in which $R^2 = C(O)OC_{1-6}$ alkyl $R^3 = H$, $R^4 = CF_3$ can be prepared by the reduction of a compound of formula (I) in which R^2 $C(O)OC_{1-6}$ alkyl, $R^3 = Cl$, $R^4 = CF_3$. A particularly useful reducing agent is zinc in an aprotic solvent such as diethyl ether.

In another aspect, the invention provides processes for the preparation of compounds of formula (I) from alternative compounds of formula (I) through functional group interconversion. For example, saponification of a compound of (I) in which R^2 is a methyl ester to give the acid, may be achieved using standard ester hydrolysis conditions, such as adding tetrahydrofuran, water and lithium hydroxide and stirring at room temperature for from 1 to 60 h or by the addition of pyridine and lithium iodide and heating at elevated temperatures for an extended period of time. This acid can be further reacted with secondary, tertiary or cyclic amine compounds or ammonia or ammonium hydroxide in the presence of a suitable base such as triethylamine and an activating agent, such as ethyl chloroformate, in a suitable solvent such as tetrahydrofuran to give the amide derivative. For example, to a compound of formula (I) in which R^2 is CO_2H in tetrahydrofuran and triethylamine, cooled to 0°C can be added ethyl chloroformate, cyclopropylmethylamine and in tetrahydrofuran and allowed to warm to room temperature to give a compound of formula (I) in which R^2 is cyclopropanecarboxamide.

Compounds of formula (I), in which R^2 is a carboxylic acid, can be reduced by standard literature procedures, such as sodium borohydride, to give the corresponding alcohol.

Furthermore, compounds of formula (I), in which R^2 is a carboxylic acid, can rearrange under standard Curtius conditions to carbamates which after deprotection gave compounds of formula (I) wherein R^2 is NH_2. Compounds of formula (I), wherein R^2 is NH_2 may also be prepared from compounds of formula (I) wherein R^2 is halo. For example, ammonia is added to a solution of a compound of formula (I), wherein R^2 is chloro, in a suitable solvent, typically acetonitrile, followed by stirring at room temperature for several hours, typically 1 hour. Compounds of formula (I), in which R^2 is NH_2 may be alkylated, acylated and sulphonylated using standard literature procedures. Sulphonylation can be achieved by a room temperature reaction with a sulphonyl chloride in a suitable solvent, typically dichloromethane, in the presence of a suitable base, such as triethylamine. Both monosulphonamides and bis-sulphonamides may be obtained. Monosulphonamides may be further N-alkylated; for example by reaction with an alkyl halide, such as methyl iodide, in a suitable solvent, typically acetone, in the presence of a base, such as potassium carbonate. Generally, reactants are mixed at 0°C followed by refluxing for several hours.

Using standard reaction conditions, compounds of formula (I), wherein R^2 is an alkyl ester may be converted to amides, wherein R^2 is $CONH_2$. For example, trimethyl aluminium in hexane is added to ammonium chloride in a suitable solvent, typically toluene, at 0°C, optionally under nitrogen. After stirring for 1-2 hours at room temperature, a solution of a compound of formula (I), wherein R^2 is COOalkyl, in a suitable solvent is added. Conversion to the amide is achieved by stirring at elevated temperature, typically 50°C for 15 – 80 hours. Similarly, transesterifications may be achieved by reaction with a substituted alcohol and hydroxylamides (R^2 is CONHOH) prepared by reaction with hydroxylamine. Acylhydrazones and bis-acylhydrazones may be similarly prepared using literature conditions. These bis-acylhydrazones may be converted to 1,2,4-oxadiazoles by reaction with phosphorus oxychloride in a suitable solvent.

Compounds of formula (I) in which R^2 is an amide may undergo standard alkylation reactions with compounds of formula R^a-Y and R^b-Y, in which Y is a suitable leaving group and R^a and R^b are as defined for formula (I), to give the substituted amide. Persons skilled in the art will recognise that by choosing the appropriate reagents and conditions either monosubstituted or disubstituted amides may be formed. Compounds of formula (I) in which R^2 is an amide may undergo a functional group interconversion by refluxing with Lawesson's reagent for several hours in a suitable solvent, typically tetrahydrofuran, to produce the thioamide or be dehydrated by reaction with trifluoroacetic anhydride and 1,4-dioxane in pyridine at 0°C for several hours to give the nitrile, wherein R^2 is CN.

Compounds of formula (I) in which R^2 is aminomethyl may be obtained via formation of the thioalkylated intermediate formed by treatment of (I) in which R^2 is a thioamide, with an alkylating agent such as triethyloxonium tetrafluoroborate, in a suitable solvent, typically dichloromethane, at 0°C and then by stirring at room temperature for an extended period of time, followed by reduction with sodium borohydride at 0°C.

Compounds of formula (I) in which R^2 is thioamide may be reacted with haloketones or haloaldehydes to give (I) in which R^2 is substituted thiazole. Similarly, reaction with acylhydrazides to give compounds of formula (I) in which R^2 is substituted triazole.

Compounds of formula (I) in which R^2 is aminomethyl can be further treated with an acid anhydride, in a suitable solvent, typically dichloromethane and a mild base such as triethylamine and stirring at room temperature for an extended period of time, typically 60 hours, to give the corresponding amide.

Furthermore compounds of formula (I) in which R^2 is aminomethyl can be monosulphonated or disulphonated with alkyl or aryl sulphonyl halides under standard conditions well-known to those skilled in the art.

Compounds of formula (I), wherein R^2 is Cl may be prepared from compounds of formula (I) wherein R^2 is -OH by reaction with thionyl chloride in a suitable solvent, such as dichloroethane. Reagent is added dropwise at room temperature, followed by heating at elevated temperature, typically 60°C, for 5 – 25 hours, typically overnight. These chloro compounds undergo nucleophilic substitiution reactions as described in organic textbooks or literature precedent; such nucleophiles include, without limitation, substituted thiols, mono and di-substituted amines, cyanide,. and cyclic amines such as pyrrolidine,

Compounds of formula (I), wherein R^2 is OH may be prepared by the reduction of ketones of formula (I), in which R^2 and R^3 are oxo using standard reducing agents, such as sodium borohydride, or those described in "Handbook of Reagents for Organic Synthesis –Oxidising and Reducing Agents" edited by S.D.Burke and R.L.Danheiser

Compounds of formula (I) in which R^2 is halo can undergo standard nucleophilic substitution reactions by refluxing with a suitable acid catalyst such as p-toluenesulphonic acid and an alkylthiol or alcohol for an extended period of time, typically from 18 hours to several days, to produce the corresponding ether or thioether respectively. Compounds of formula (I) in which R^2 is halo can also undergo base catalysed standard nucleophilic substitution reactions with nucleophiles such as cyanide ion, alkylthiols and primary or secondary amines in a suitable solvent, such as acetonitrile. Reactions are stirred at room temperature for 2 – 24 hours and a typical base is potassium carbonate. Compounds of formula (I) in which R^2 is -Salkyl can be oxidised to the corresponding sulphines or sulphones using standard oxidizing agents, such as m-chloroperoxybenzoic acid or those described in "Handbook of Reagents for Organic Synthesis –Oxidising and Reducing Agents" edited by S.D.Burke and R.L.Danheiser

Compounds of formula (I) in which R^2 contains a secondary alcohol can be oxidized, for example by stirring with Dess Martin Periodinane at room temperature for 30 minutes in a suitable solvent, typically dichloromethane, to produce the corresponding ketone

Compounds of formula (I) in which R^9 is NH_2 may be used to synthesis imines by reacting the amino functionality of formula (I) with aldehydes and an appropriate acid catalyst, typically p-toluenesulphonic acid at room temperature, for an extended period of time, typically 16 hours or with aldehydes in the presence of a mild reducing agent such as sodium triacetoxyborohydride and a mild base to form secondary amines. For example, a compound of formula (I) in which R^9 is NH_2 undergoes reaction with isonicotinaldehyde and a mild base to give the corresponding imine functionality which can be further reduced by reaction with a suitable reducing agent such as sodium hydride to give the secondary amine. This can be further oxidized using standard procedures to give the N-oxide. Similarly, compounds of formula (I) in which R^9 is NH_2 may be reacted with optionally substituted ketones.

Compounds of formula (I) in which R^9 is NH_2, can undergo reaction with triethyl orthoformate in acidic conditions, by heating at elevated temperatures, typically 60°C, for several, typically from 2 to 4 hours, to give (I) in which R^9 is $-N=CHOC_2H_5$. This can, in turn, be further reduced by a suitable reducing agent, such as sodium borohydride, to give a compound of formula (I) in which R^5 is $-NHCH_3$. Compounds of formula (I) in which R^9 is NH_2 may be functionalised in a similar manner

A compound of formula (I) in which R^9 is H, may be prepared by the diazotisation of a compound of formula (I) in which R^9 is NH_2 by a variety of standard diazotisation procedures. For example, the reaction of a compound of formula (I), wherein R^9 is NH_2, with isoamyl nitrite in a suitable aprotic solvent, such as acetonitrile, at room temperature for 5 – 30 hours, typically 18 hours.

In a similar manner, compounds of formula (I) in which R^9 is -Salkyl, may be formed by coupling the diazonium species formed from a compound of formula (I) in which R^9 is NH_2 and an appropriate nucleophile such as $(alkylS)_2$. Furthermore, compounds of formula (I) in which R^9 is S-alkyl may be oxidised, using standard oxidising agents, such as hydrogen peroxide, to give the corresponding sulphines and sulphones.

Compounds of formula (I) in which R^9 is NH_2, can be converted to give a compound of formula (I) wherein R^9 is halo, utilising standard Sandmeyer reaction conditions. For example, the reaction of a compound of formula (I), wherein R^9 is NH_2, with isoamyl nitrite in a suitable aprotic solvent, such as acetonitrile, in the presence of cuprous chloride yields compounds of formula (I), wherein R^9 is Cl. These halo compounds may be used in standard organometallic coupling procedures, for example in the preparation of a compound of formula (I) in which R^9 = $-CF_3$.

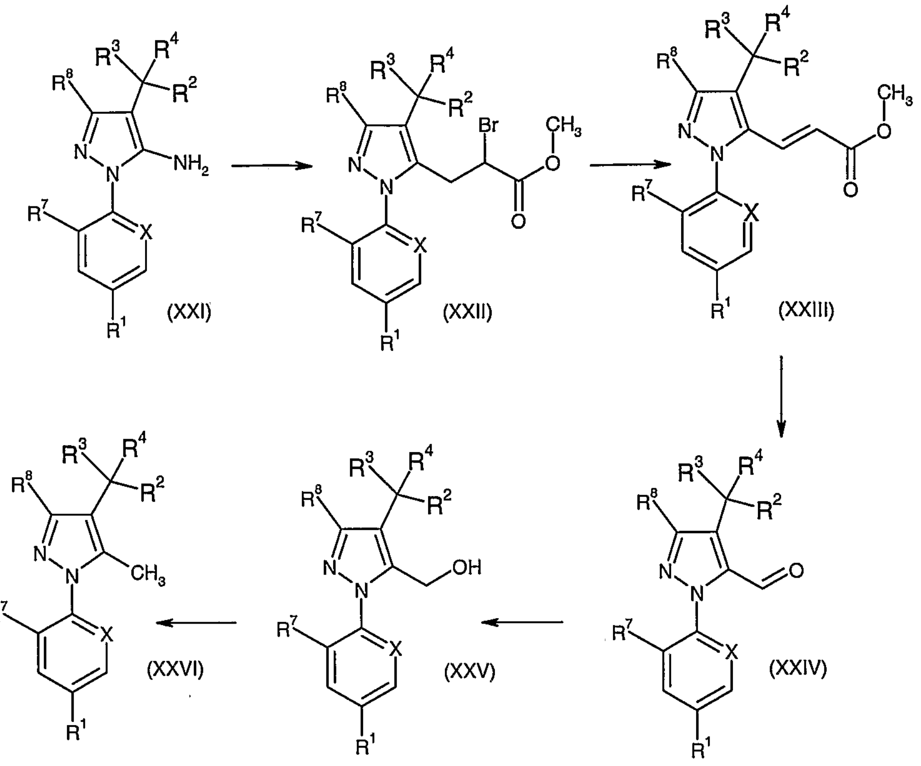
Compounds of formula (I), wherein R^9 = OH can be alkylated using standard literature procedures. For example by reaction with an alkyl halide in a suitable solvent, such as acetonitrile, in the presence of a suitable base, typically potassium carbonate at elevated temperatures, 45 – 60°C, for several hours, typically 3 hours.

Compounds of formula (I) in which R^9 is CH_2Y, in which Y is a suitable leaving group such as halo, may, in the presence of a suitable base, undergo a wide range of nucleophilic substitution reactions well known to those skilled in the art.

Furthermore, compounds of formula (I) in which R^9 is $-NH_2$ or aminoalkyl can be monosulphonated or disulphonated with alkyl or aryl sulphonyl halides under standard conditions well-known to those skilled in the art, to give the corresponding sulphonamides.

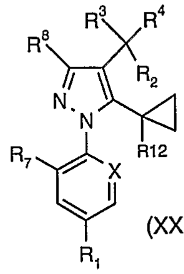
Compounds of formula (I) in which R^9 is $-NH_2$, may also be converted to compounds of formula (I) in which R^9 is $-CH_3$ or $-CHF_2$ as shown in Scheme 2 below. Firstly, compounds (XXI) may be converted to (XXII) by the radical arylation of methyl acrylate with the corresponding diazonium salts. Compounds of formula (XXII) can be dehydrobrominated using standard conditions by stirring with base, such as DBU, for several hours, to give enones, (XXIII). Conversion of (XXIII) to (XXIV) can be achieved via diol formation, utilising OsO_4, followed by oxidative cleavage, using an oxidising agent such as sodium periodate, to generate the aldehyde. Aldehydes of formula (XXIV) may be reduced to give alcohols of formula (XXV) by stirring with a reducing agent, typically sodium borohydride or reacted further with a halogenating reagent such as diethylaminosulfur trifluoride to obtain a compound of formula (I) in which R^9 is difluoromethyl. Reaction of (XXV) with thionyl chloride and heating at reflux for several hours gives the intermediate chloro derivative from compounds of formula (XXVI) may then be obtained by reduction, for example using Rieke zinc.

Scheme 2



Compounds of formula (XXIV) and (XXV) may be used to prepare compounds of formula (I) in which R^9 encompasses a wide variety of carbon linked substituents. For example, (XXV) may be alkylated and acylated using standard literature procedures. Also, in (XXV), activation of the hydroxyl, such as by mesylation or tosylation, gives an intermediate that undergoes a wide range of nucleophilic substitution reactions. The aldehyde, (XXIV) may be readily converted to the acid, nitrile, esters, amides and thioamides under standard conditions well-known to those skilled in the art. Standard Wittig olefination of the aldehyde (XXIV) may be followed by routine cyclopropanation procedures to give compounds in which R^9 is substituted cyclopropyl. For example, methylenation may be achieved using the Wittig reaction, using a Peterson reagent, using a Tebbe reagent or using the Lombardt procedure. Organometallic addition to the aldehyde, (XXIV), followed by oxidation of the secondary alcohol, then Wittig olefination and cyclopropanation may be used to prepare compounds of formula (XXVII), for example wherein R^{12} = $-CF_3$.

Such cyclopropanation methods may include treatment with a reactive species such as trimethylsilyl difluoro(fluorosulfonyl)acetate (TFDA) at reflux in the presence of sodium fluoride, as described by Dolbier et al., in J. Fluor Chem., 2004, 125, 459. Other methods for *in situ* carbenoid generation include treatment of chloroform or bromoform with base, preferably under phase transfer catalysis conditions, thermolysis of a suitable organometallic precursor such as an aryl trifluoromethyl, trichloromethyl, tribromomethyl or phenyl(trifluoromethyl) mercury derivative or treatment with a diazoalkane in the presence of a transition metal catalyst and treatment with a diazoalkane in the absence of a transition metal catalyst followed by thermolysis of the intermediate pyrazoline, or generation from a sulphur ylid.



(XXVII)

Alternatively, organometallic addition to the aldehyde, (XXIV), followed by elimination of the hydroxyl group using standard procedures such as reaction with $SOCl_2$ in the presence of a zinc catalyst, may be a means to generate compounds of formula (I) in which R^9 is optionally substituted alkyl, optionally substituted aryl or arylalkyl and optionally substituted heteroaryl or heteroarylalkyl in accordanced with the definition of R^9 for formula (I). Compounds of formula (XXIV) may also undergo standard Knovenagel type reactions, followed by reduction and partial hydrolysis and heating at elevated temperature to give the corresponding ester derivative which may be further derivatised. Alternatively, methylenation of compounds of formula (XXIV) may be readily achieved utilising standard known reactions such as the Wittig or the Horner-Wadsworth-Emmons reaction. The resulting compounds of formula (I) in which R^9 is vinyl, may be hydroxylated using standard conditions such as by reaction with hydrogen peroxide and a suitable base to give compounds in which R^9 is $-CH_2CH_2OH$. These compounds can, in turn, be further oxidised to give the corresponding aldehydes and acids, i.e. where R^9 is $-CH_2CHO$ or $-CH_2COOH$. These aldehydes undergo reactions well known to those skilled in the art, such as Wittig olefination reductive amination. The acids undergo the Curtius rearrangement o give compounds of formula (I), in which R^9 is $-CH_2NH_2$, which may be alkylated, acylated, sulphonylated and other electrophiles. Furthermore, compounds in which R^9 is $-CH_2CH_2OH$ may be activated for example by the addition of $SOCl_2$ or TsCl and further reacted with a wide range of nucleophiles such as ^-CN, ^-SR or ^-OR to achieve the corresponding alkylated derivative.

Alternatively, standard known catalysed cross coupling reactions, such as the Heck reaction, may be employed to generate compounds of formula (I) in which R^9 is substituted vinyl from the vinyl derivative.

Oxidation of compounds of formula (XXIV) using standard reaction conditions followed by further derivatisation of the acid formed may be a means of accessing compounds of formula (I) in whch R^9 is a heterocyclic moiety. For example, the oxidised product may undergo reaction with substituted acyl hydrazides to give oxadiazoles. Those skilled in the art will recognise that a wide variety of optionally substituted heterocycles may be synthesised from the aldehydes (XXIV) or the corresponding acids. These acids may also be derivatised using standard literature procedures.

A compound of formula (I) in which R^8 is $-C(O)SCH_3$ may be prepared from (I) $R^8 = -CN$ by the acid catalysed addition of methanethiol by heating under pressure at elevated temperatures, typically

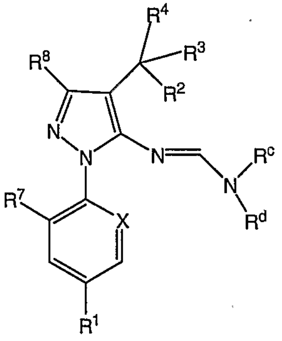
80°C for several hours, typically 16 hours. Compounds of formula (I) in which R^8 is –CN may undergo reactions of nitriles as recorded in organic chemistry textbooks and literature precedent.

It will also be appreciated by persons skilled in the art that, within certain of the processes described, the order of the synthetic steps employed may be varied and will depend *inter alia* on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates, and the protecting group strategy (if any) to be adopted. Clearly, such factors will also influence the choice of reagent for use in the said synthetic steps.

The skilled person will appreciate that the compounds of the invention could be made by methods other than those herein described, by adaptation of the methods herein described and/or adaptation of methods known in the art, for example the art described herein, or using standard textbooks such as "Comprehensive Organic Transformations - A Guide to Functional Group Transformations", RC Larock, Wiley-VCH (1999 or later editions).

It is to be understood that the synthetic transformation methods mentioned herein are exemplary only and they may be carried out in various different sequences in order that the desired compounds can be efficiently assembled. The skilled chemist will exercise his judgement and skill as to the most efficient sequence of reactions for synthesis of a given target compound.

The present invention also relates to intermediates of formula (XXX) below:

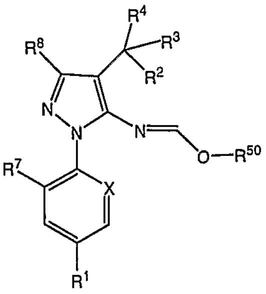


(XXX)

where:

R^1 – R^8, X, R^c, R^d, n, R^{11} and het are all as defined for formula (I) above; or a pharmaceutical salt or a prodrug thereof. With reference to formula XXX), suitably R^c = R^d = methyl.

The present invention also relates to further intermediates of formula (XXXI) below:



(XXXI)

where:

$R^1 - R^8$, X, n, R^{11} and het are all as defined for formula (I) above; where R^{50} is independently selected from hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkanoyl, C(O)OC_{1-6} alkyl, het, phenyl and $S(O)_nR^{11}$; or a pharmaceutical salt or a prodrug thereof. With reference to formula (XXXI), suitably R^{50} is methyl.

It will be understood that throughout the application all references to formula (I) apply equally to compounds of the formulas (XXX) and (XXXI). Furthermore, it will be understood that all the suitable groups and preferences applied to $R^1 - R^8$, X, R^c, R^d, n, R^{11} and het above for formula (I) apply equally to compounds of the formulas (XXX) and (XXXI).

This invention also relates to a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, together with a pharmaceutically acceptable diluent or carrier, which may be adapted for oral, parenteral or topical administration.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995).

The compounds may be administered alone or in a formulation appropriate to the specific use envisaged, the particular species of host mammal being treated and the parasite involved or as appropriate for the agricultural pest being treated and the crop designated for treatment. Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products, for example, spray-dried dispersions or as produced by melt-extrusion or nanomilling. They may be obtained, for example, as solid plugs, powders, or films (for example, rapid dissolving or mucoadhesive films) by methods such as precipitation, crystallization, freeze drying, or spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

The methods by which the compounds may be administered include oral administration by capsule, bolus, tablet, powders, lozenges, chews, multi and nanoparticulates, gels, solid solution, films, sprays, or liquid formulation. Liquid forms include suspensions, solutions, syrups, drenches and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet. Oral drenches are commonly prepared by dissolving or suspending the active ingredient in a suitable medium.

Thus compositions useful for oral administration may be prepared by mixing the active ingredient with a suitable finely divided diluent and/or disintegrating agent and/or binder, and/or lubricant etc. Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

For oral dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. Examples of suitable disintegrants for use herein include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Examples of suitable binders for use herein include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Examples of diluents include lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Oral formulations may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 wt% to 5 wt% of the tablet, and glidants may comprise from 0.2 wt% to 1 wt% of the tablet.

Lubricants include magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

Exemplary tablets contain up to about 80% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X).

The compounds may be administered topically to the skin, that is dermally or transdermally. The compounds may also be administered via the mucosa or mucous membranes. Typical formulations for this purpose include pour-on, spot-on, dip, spray, mousse, shampoo, powder formulation, gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999). Pour-on or spot-on formulations may be prepared by dissolving the active ingredient in an acceptable liquid carrier vehicle such as butyl digol, liquid paraffin or a non-volatile ester, optionally with the addition of a volatile component such as propan-2-ol. Alternatively, pour-on, spot-on or spray formulations can be prepared by encapsulation, to leave a residue of active agent on the surface of the animal.

Injectable formulations may be prepared in the form of a sterile solution which may contain other substances, for example enough salts or glucose to make the solution isotonic with blood. Acceptable liquid carriers include vegetable oils such as sesame oil, glycerides such as triacetin, esters such as benzyl benzoate, isopropyl myristate and fatty acid derivatives of propylene glycol, as well as organic solvents such as pyrrolidin-2-one and glycerol formal. The formulations are prepared by dissolving or suspending the active ingredient in the liquid carrier such that the final formulation contains from 0.01 to 10% by weight of the active ingredient. These formulations may be self-preserving, self-sterilising or may be non-sterile to which preservatives may be optionally added.

Equally suitably the compounds can be administered parenterally, or by injection directly into the blood stream, muscle or into an internal organ. Suitable routes for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques. Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as powdered a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water. The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art. The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Such formulations are prepared in a conventional manner in accordance with standard medicinal or veterinary practice.

These formulations will vary with regard to the weight of active compound contained therein, depending on the species of host animal to be treated, the severity and type of infection and the body weight of the host. For parenteral, topical and oral administration, typical dose ranges of the active ingredient are 0.01 to 100 mg per kg of body weight of the animal. Preferably the range is 0.1 to 10mg per kg.

Formulations may be immediate or be designed to have a controlled or modified release profile. Modified release formulations include those formulations which have a delayed-, sustained-, pulsed-, targeted, or programmed release. Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma et al, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298. Alternatively, compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

As an alternative the compounds may be administered to a non-human animal with the feedstuff and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed.

All aqueous dispersions, emulsions or spraying mixtures of the present invention can be applied, for example, to crops by any suitable means, chiefly by spraying, at rates which are generally of the order of about 100 to about 1,200 liters of spraying mixture per hectare, but may be higher or lower (eg. low or ultra-low volume) depending upon the need or application technique. The compounds or compositions according to the invention are conveniently applied to vegetation and in particular to roots or leaves having pests to be eliminated. Another method of application of the compounds or compositions according to the invention is by chemigation, that is to say, the addition of a formulation containing the active ingredient to irrigation water. This irrigation may be sprinkler irrigation for foliar pesticides or it can be ground irrigation or underground irrigation for soil or for systemic pesticides.

Concentrated suspensions, which can be applied by spraying, are prepared so as to produce a stable fluid product which does not settle (fine grinding) and usually contain from about 10 to about 75% by weight of active ingredient, from about 0.5 to about 30% of surface-active agents, from about 0.1 to about 10% of thixotropic agents, from about 0 to about 30% of suitable additives, such as anti-foaming agents, corrosion inhibitors, stabilizers, penetrating agents, adhesives and, as the carrier, water or an organic liquid in which the active ingredient is poorly soluble or insoluble Some organic solids or inorganic salts may be dissolved in the carrier to help prevent settling or as antifreezes for water.

Wettable powers (or powder for spraying) are usually prepared so that they contain from about 10 to about 80% by weight of active ingredient, from about 20 to about 90% of a solid carrier, from about 0 to about 5% of a wetting agent, from about 3 to about 10% of a dispersing agent and, when necessary, from about 0 to about 80% of one or more stabilizers and/or other additives, such as penetrating agents, adhesives, anti-caking agents, colorants, or the like. To obtain these wettable powders, the active ingredient(s) is (are) thoroughly mixed in a suitable blender with additional substances which may be impregnated on the porous filler and is(are) ground using a mill or other suitable grinder. This produces wettable powders, the wettability and the suspendability of which are advantageous. They may be suspended in water to give any desired concentration and this suspension can be employed very advantageously in particular for application to plant foliage.

"Water dispersible granules (WG)" (granules which are readily dispersible in water) have compositions which are substantially close to that of the wettable powders. They may be prepared by granulation of formulations described for the wettable powders, either by a wet route (contacting finely divided active ingredient with the inert filler and a little water, e.g. 1 to 20% by weight, or with an aqueous solution of a dispersing agent or binder, followed by drying and screening), or by a dry route (compacting followed by grinding and screening).

The rates and concentrations of the formulated compositions may vary according to the method of application or the nature of the compositions or use thereof. Generally speaking, the compositions for application to control arthropod, plant nematode, helminth or protozoan pests usually contain from about 0.00001 % to about 95%, more particularly from about 0.0005% to about 50% by weight of one or more compounds of formula (I), or pesticidally acceptable salts thereof, or of total active ingredients (that is to say the compound of formula (I), or a pesticidally acceptable salt thereof, together with: other substances toxic to arthropods or plant nematodes, anthelmintics, anticoccidials, synergists, trace elements or stabilizers). The actual compositions employed and their rate of application will be selected to achieve the desired effect(s) by the farmer, livestock producer, medical or veterinary practitioner, pest control operator or other person skilled in the art.

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

Compounds of the present invention may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). For example, compounds of the invention can also be mixed with one or more biologically active compounds or agents including insecticides, acaricides, anthelmintics, fungicides, nematocides, antiprotozoals, bactericides, growth regulators, vaccines (including live, attenuated or killed vaccines), entomopathogenic bacteria, viruses or fungi to form a multi-component pesticide giving an even broader spectrum of pharmaceutical, veterinary or agricultural utility. Thus, the present invention also pertains to a composition comprising a biologically effective amount of compounds of the invention and an effective amount of at least one additional biologically active compound or agent and can further comprise one or more of surfactant, a solid diluent or a liquid diluent. Specific further active compounds include those described in International Patent Application No WO 2005/090313, at pages 39 to 44.

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

Thus this invention also relates to a kit comprising two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I) in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

The compounds of the invention, i.e. those of formula (I), possess parasiticidal activity in humans, animals, insects and plants. They are particularly useful in the treatment of ectoparasites.

This invention also relates to a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, or a pharmaceutical composition containing any of the foregoing, for use as a medicament.

A further aspect of this invention relates to the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, for the manufacture of a medicament for the treatment of a parasitic infestation.

As used herein the term "long duration of action" shall be taken to mean compounds which have a duration of action of 14 days or greater, more preferably of 21 days or greater and most preferably of 28 days or greater.

In one embodiment this invention is useful for the manufacture of a medicament for the treatment of a parasitic infestation in humans.

In one embodiment this invention is useful for the manufacture of a medicament for the treatment of a parasitic infestation in animals.

An even further aspect of this invention relates to a method of treating a parasitic infestation in a which comprises treating said animal with an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, or a pharmaceutical composition containing any of the foregoing.

A yet further aspect of this invention relates to a method of preventing a parasitic infestation in a animal which comprises treating said animal with an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, or a pharmaceutical composition containing any of the foregoing.

In a still further embodiment this invention also relates to a method of controlling disease transmission in an animal which comprises treating said animal with an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, or a pharmaceutical composition containing any of the foregoing.

In one embodiment this invention is useful for the manufacture of a medicament for the treatment of a parasitic infestation in plants.

According to another aspect of the present invention, there is provided a method for the control of arthropod, plant nematode or helminth pests at a locus which comprises the treatment of the locus (e.g. by application or administration) with an effective amount of a compound of general formula (I), or a pesticidally acceptable salt thereof.

According to a yet further aspect of the present invention, there is provided a method for the control or eradication of a parasitic infestation from the environment, for example the living or accommodation areas of an animal, particularly a companion animal, which comprises treating said animal with an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, or a pharmaceutical composition containing any of the foregoing.

For the avoidance of doubt, references herein to “treatment” as used herein includes references to curative, palliative and prophylactic treatment, references to “control” (of parasites and / or pests etc.) include kill, repel, expel, incapacitate, deter, eliminate, alleviate, minimise, eradicate.

The compounds of the invention have utility in the control of arthropod pests. They may have activity against resistant strains where control is not achievable by known parasiticides or combinations thereof. They may, in particular, be used in the fields of veterinary medicine, livestock husbandry and the maintenance of public health: against arthropods which are parasitic internally or externally upon humans and animals, including mammals, poultry and fish. Examples of mammals include domestic animals such as dogs, cats, cattle, sheep, goats, equines, swine. Examples of arthropods include Acarina, including ticks (e.g. Ixodes spp., Boophilus spp. e.g. Boophilus microplus, Amblyomma spp., Hyalomma spp., Rhipicephalus spp. e.g. Rhipicephalus appendiculatus, Haemaphysalis spp., Dermacentor spp., Ornithodorus spp. (e.g. Omithodorus moubata), mites (e.g. Damalinia spp., Dermanyssus gallinae, Sarcoptes spp. e.g. Sarcoptes scabiei, Psoroptes spp., Chorioptes spp., Demodex spp., Eutrombicula spp.); Diptera (e.g. Aedes spp., Anopheles spp., Muscidae spp. e.g. Stomoxys calcitrans and Haematobia irritans, Hypoderma spp., Gastrophilus spp., Simulium spp.); Hemiptera (e.g. Triatoma spp.); Phthiraptera (e.g. Damalinia spp., Linognathus spp.); Siphonaptera (e.g. Ctenocephalides spp.); Dictyoptera (e.g. Periplaneta spp., Blatella spp.) and Hymenoptera (e.g. Monomorium pharaonis). The compounds of the present invention also have utility in the field of control of plant pests, soil inhabiting pests and other environmental pests. Specific further arthropod pests include those described in International Patent Application No WO

The present invention is particularly useful in the control of arthropod pests in humans and animals, particularly mammals. Preferably this invention is useful in the control of arthropod pests in animals which includes livestock such as cattle, sheep, goats, equines, swine and companion animals such as dogs and cats.

The compounds of the invention are of particular value in the control of arthropods which are injurious to, or spread or act as vectors of diseases in, man and domestic animals, for example those hereinbefore mentioned, and more especially in the control of ticks, mites, lice, fleas, midges and biting, nuisance and myiasis flies. They are particularly useful in controlling arthropods which are present inside domestic host animals or which feed in or on the skin or suck the blood of the animal, for which purpose they may be administered orally, parenterally, percutaneously or topically.

The compounds of the invention are of value for the treatment and control of the various lifecycle stages of parasites including egg, nymph, larvae, juvenile and adult stages.

According to another aspect of the present invention, there is provided a method for the control of arthropod pests of insects which comprises treatment of the insect with an effective amount of a compound of general formula (I), or a pesticidally acceptable salt thereof. Compounds of the present invention may also be used for the treatment of infections caused by mites, and in particular varoaa mites. In particular compounds of the present invention may also be used for the treatment of varoaa mite infection in bees.

According to another aspect of the present invention, there is provided a method for the control of arthropod pests of plants which comprises treatment of the plant with an effective amount of a compound of general formula (I), or a pesticidally acceptable salt thereof. The compounds of the invention also have utility in the control of arthropod pests of plants. The active compound is generally applied to the locus at which the arthropod infestation is to be controlled at a rate of about 0.005 kg to about 25 kg of active compound per hectare (ha) of locus treated, preferably 0.02 to 2 kg/ha. Under ideal conditions, depending on the pest to be controlled, the lower rate may offer adequate protection. On the other hand, adverse weather conditions and other factors may require that the active ingredient be used in higher proportions. For foliar application, a rate of 0.01 to 1 kg/ha may be used. Preferably, the locus is the plant surface, or the soil around the plant to be treated.

According to another aspect of the present invention, there is provided a method for the protection of timber which comprises treatment of the timber with an effective amount of a compound of general formula (I), or a pesticidally acceptable salt thereof. Compounds of the present invention are also valuable in the protection of timber (standing, felled, converted, stored or structural) from attack by sawflies or beetles or termites. They have applications in the protection of stored products such as grains, fruits, nuts, spices and tobacco, whether whole, milled or compounded into products, from moth, beetle and mite attack. Also protected are stored animal products such as skins, hair, wool and feathers in natural or converted form (e.g. as carpets or textiles) from moth and beetle attack; also stored meat and fish from beetle, mite and fly attack. Solid or liquid compositions for application topically to timber, stored products or household goods usually contain from about 0.00005% to about 90%, more particularly from about 0.001 % to about 10%, by weight of one or more compounds of formula (I) or pesticidally acceptable salts thereof.

The liquid compositions of this invention may, in addition to normal agricultural use applications be used for example to treat substrates or sites infested or liable to infestation by arthropods (or other pests controlled by compounds of this invention) including premises, outdoor or indoor storage or processing areas, containers or equipment or standing or running water.

The present invention also relates to a method of cleaning animals in good health comprising the application to the animal of compound of formula (I) or a veterinarily acceptable salt. The purpose of such cleaning is to reduce or eliminate the infestation of humans with parasites carried by the animal and to improve the environment in which humans inhabit.

The flea membrane feed test is used to measure the biological activities of the compounds claimed. The assay involves *in vitro* testing against Ctenocephalides felis conducted according to the following general procedure.

Fleas are cultured in vitro using dog blood. 25-30 adult Ctenocephalides felis (cat flea) were collected and placed in a test chamber (50ml polystyrene tube with fine nylon mesh sealing the end). Citrated dog blood was prepared by adding aqueous sodium citrate solution (10 ml, 20% w/v, 20g sodium citrate in 100 ml water) to dog blood (250 ml). Test compounds were dissolved in dimethylsulfoxide to give a working stock solution of 4 mg/ml. The stock solution (12.5 µl) was added to citrated dog blood (5 ml) to give an initial test concentration of 10 µg/ml. For testing at 30µg/ml, working stock solutions of 12mg/ml were prepared.

Citrated dog blood containing the test compound (5 ml, 100µg/ml) was placed into a plastic Petri dish lid, which was kept at 37°C on a heated pad. Parafilm was stretched over the open top to form a tight membrane for the fleas to feed through. The test chamber containing the fleas was placed carefully onto the parafilm membrane and the fleas commenced feeding.

The fleas were allowed to feed for 2 hours and the test chambers were then removed and stored overnight at room temperature.

The fleas were observed and the percentage of fleas killed recorded. Compounds were initially tested at 100μg/ml, wherefrom relevant dose responses (100, 30, 10, 3, 1, 0.3, 0.1μg/ml) were conducted and repeated n=5. Data was plotted to generate ED80, ED90 & ED95 values.

The compounds of the present invention have significantly better activity than the prior art compounds. All the Examples of the present invention have flea ED80 values of less than 100μg/ml. Results for some of the compounds are presented below.

Example	Flea feed ED80 results μg/ml
1	≤ 1
2	≤ 1
4	≤ 1
9	≤ 1
11	≤ 1
15	≤ 1

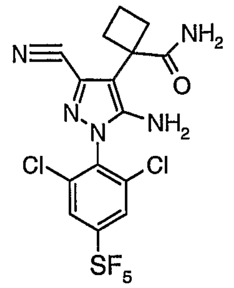
EXAMPLES

The following Examples illustrate the preparation of compounds of the formula (I).

In the following experimental details, nuclear magnetic resonance spectral data were obtained using Varian Inova 300, Varian Inova 400, Varian Mercury 400, Varian Unityplus 400, Bruker AC 300MHz, Bruker AM 250MHz or Varian T60 MHz spectrometers, the observed chemical shifts being consistent with the proposed structures. Mass spectral data were obtained on a Finnigan Masslab Navigator, a Fisons Instrument Trio 1000, or a Hewlett Packard GCMS System Model 5971 spectrometer. The calculated and observed ions quoted refer to the isotopic composition of lowest mass. HPLC means high performance liquid chromatography. Room temperature means 20 to 25°C.

Example 1

1-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}cyclobutanecarboxamide



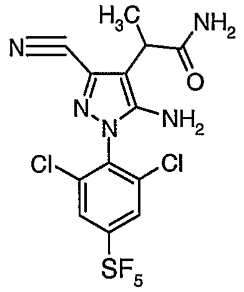
To a solution of Preparation 23 (500 mg, 1.05 mmol) in tetrahydrofuran (12.5 ml), under nitrogen, was added triethylamine (0.29 ml, 2.10 mmol), followed by ethyl chloroformate (0.11 ml, 1.12 mmol) in tetrahydrofuran (0.5 ml), added dropwise. After stirring for 10 min, aqueous ammonium hydroxide solution (29.7 wt%, 0.62 g, 5.25 mmol) was added and the reaction mixture was stirred under nitrogen for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (25 ml) and ethyl acetate (35 ml). The two layers were separated and the aqueous layer was extracted with ethyl acetate (35 ml). The combined organic phases were washed with brine (25 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in acetonitrile/dimethyl sulphoxide (2.5 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 50 mm Sunfire LUNA C18 10μm column) using an acetonitrile : water [50:50 to 98:2] gradient. The appropriate fractions were combined and concentrated to give the titled compound (153 mg).

Experimental MH^+ 475.9; expected 476.0

^{1}H-NMR (d_6-DMSO): 1.80 - 1.93 (2H), 2.41 - 2.48 (2H), 2.62 - 2.70 (2H), 5.74 - 5.79 (2H), 7.13 - 7.19 (1H), 7.27 - 7.33 (1H), 8.41 - 8.44 (2H)

Example 2

2-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}propanamide



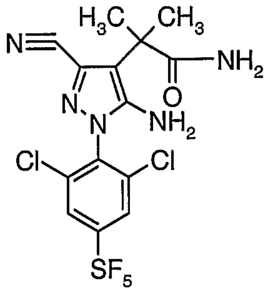
To a mixture of Preparation 18 (1.91 g, 4.24 mmol) and triethylamine (0.65 ml, 4.66 mmol) in tetrahydrofuran (20 ml), at -10°C, was added ethyl chloroformate (0.45 ml, 4.66 mmol). After stirring for 1 h at 0°C, aqueous ammonium hydroxide solution (35%, 0.35 μl, 6.36 mmol) in tetrahydrofuran (3 ml) was added and the reaction mixture was stirred at room temperature for 18 h. To the reaction mixture was added saturated brine solution (60 ml) and the mixture was extracted with ethyl acetate (3 x 25 ml). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in acetonitrile/water (4 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm LUNA C18(2) 10μm column) using an acetonitrile : water gradient [45:55 to 98:2]. The appropriate fractions were concentrated *in vacuo* to give the titled compound 1.87g.

Experimental MH$^+$ 449.9; expected 450.0

^{1}H-NMR (d_6-DMSO): 1.25 – 1.30 (3H), 3.50 – 3.56 (1H), 6.00 – 6.07 (2H), 7.00 – 7.03 (1H), 7.40 – 7.44 (1H), 8.40 – 8.42 (2H)

Example 3

2-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}-2-methylpropanamide

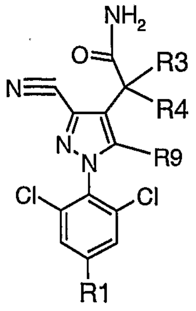


To a solution of Preparation 20 (280 mg, 0.60 mmol) in tetrahydrofuran (10 ml), at -10°C and under nitrogen, was added triethylamine (167 μl, 1.20 mmol), followed by ethyl chloroformate (115 μl, 1.20 mmol). After stirring for 3 h at 0°C, aqueous ammonium hydroxide solution (702 μl, 1.20 mmol) was added and the reaction mixture was stirred for a further 3 h at room temperature. To the reaction mixture was added brine (10 ml) and the mixture was extracted with ethyl acetate (3 x 10 ml). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in acetonitrile (3 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18 10μm column) using an acetonitrile : water [45:55 to 95:5] gradient. The appropriate fractions were combined and concentrated to give the titled compound (84 mg).

Experimental MH$^+$ 463.9; expected 464.0

^{1}H-NMR ($CDCl_3$): 1.73 - 1.78 (6H), 4.44 – 4.57 (2H), 5.36 – 5.44 (1H), 5.79 – 5.89 (1H), 7.88 – 7.91 (2H)

Similarly prepared were:



Example	R1	R3	R4	R9	From

Example 4	CF_3O	cyclobutyl		NH_2	Preparation 24
Example 5	CF_3	cyclobutyl		NH_2	Preparation 25
Example 6	SF_5	cyclobutyl		$NHCH_3$	Preparation 26
Example 7	CF_3	CH_3	H	NH_2	Preparation 19
Example 8	CF_3	4-fluorobenzyl	H	NH_2	Preparation 21
Example 9	CF_3	C_2H_5	H	NH_2	Preparation 22

Example 4

1-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}cyclobutanecarboxamide

Experimental MH^+ 434.0; expected 434.0

^{1}H-NMR (d_6-DMSO): 1.79 - 1.92 (2H), 2.41 - 2.48 (2H), 2.61 - 2.70 (2H), 5.65 - 5.72 (2H), 7.12 - 7.19 (1H), 7.26 - 7.33 (1H), 7.90 - 7.93 (2H)

Example 5

1-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}cyclobutanecarboxamide

Experimental MH^+ 418.1; expected 418.0

^{1}H-NMR (d_6-DMSO): 1.80 - 1.92 (2H), 2.41 - 2.48 (2H), 2.62 - 2.71 (2H), 5.68 - 5.75 (2H), 7.13 - 7.20 (1H), 7.28 - 7.35 (1H), 8.21 - 8.24 (2H)

Example 6

1-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-(methylamino)-1H-pyrazol-4-yl}cyclobutanecarboxamide

Experimental MH^+ 490.0; expected 490.0

^{1}H-NMR ($CDCl_3$): 2.00 – 2.20 (2H), 2.45 – 2.50 (3H), 2.65 – 2.80 (4H), 5.40 – 5.50 (1H), 5.80 – 5.90 (1H), 7.90 – 7.95 (2H)

Example 7

2-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propanamide

Experimental MH^+ 392.0; expected 392.0

^{1}H-NMR ($CDCl_3$): 1.50 – 1.54 (3H), 3.61 – 3.64 (1H), 5.38 – 5.42 (1H), 5.80 – 5.90 (1H), 7.70 – 7.74 (2H)

Example 8

2-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-3-(4-fluorophenyl)propanamide

Experimental MH^+ 486.0; expected 486.1

^{1}H-NMR (d_6-DMSO): 2.90 – 3.00 (1H), 3.10 – 3.20 (1H), 3.65 – 3.70 (1H), 6.05 – 6.15 (2H), 7.00 – 7.10 (4H), 7.19 – 7.21 (1H), 7.70 – 7.80 (1H), 8.18 – 8.24 (2H)

Example 9

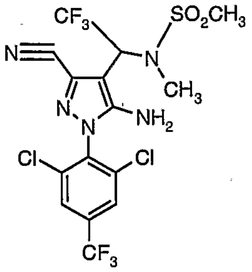
2-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}butanamide

Experimental MH^+ 406.0; expected 406.0

^{1}H-NMR ($CDCl_3$): 0.94 - 1.01 (3H), 1.84 – 1.95 (1H), 1.98 - 2.10 (3H), 3.37 – 3.43 (1H), 5.40 – 5.51 (1H), 5.84 – 5.94 (1H), 7.74 – 7.79 (2H)

Example 10

N-(1-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-2,2,2-trifluoroethyl)-N-methylmethanesulfonamide



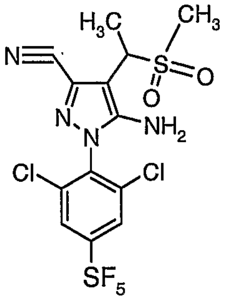
To a solution of Preparation 1 (70 mg, 0.14 mmol) in acetone (2 ml), at 0°C, was added potassium carbonate (20 mg, 0.14 mmol), followed by methyl iodide (9 µl, 0.17 mmol). The reaction mixture was heated at reflux for 2 h and then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water and the two layers were separated. The aqueous layer was extracted with ethyl acetate (x 2) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in methanol (1 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm LUNA C18(2) 10µm column) using an acetonitrile : water gradient [45:55 to 95:5]. The appropriate fractions were concentrated *in vacuo* to give the titled compound (17 mg).

Experimental MH$^+$ 509.9; expected 510.0

^{1}H-NMR ($CDCl_3$): 2.90 – 2.95 (3H), 2.95 – 2.98 (3H), 4.35 – 4.45 (3H), 5.50 – 5.60 (1H), 7.77 – 7.81 (2H)

Example 11

5-amino-1-[2,6-dichloro-4-pentafluorothiophenyl]-4-[1-(methylsulfonyl)ethyl]-1H-pyrazole-3-carbonitrile



A mixture of Preparation 9 (363 mg, 0.67 mmol), methanol (1 ml), dioxane (8 ml) and hydrochloric acid (1N, 1 ml) was heated at 80°C for 5 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in methanol (2 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 4.6 mm LUNA C18(2) 5µm column) using an acetonitrile

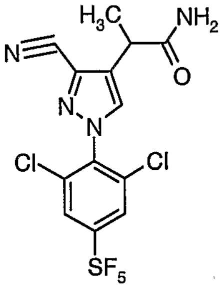
: water gradient [50:50 to 98:2]. The appropriate fractions were concentrated *in vacuo* to give the titled compound (77 mg).

Experimental MH^+ 485.0; expected 485.0

^{1}H-NMR ($CDCl_3$): 1.80 – 1.84 (3H), 2.85 – 2.88 (3H), 4.21 – 4.25 (1H), 4.40 – 4.50 (2H), 7.90 – 7.92 (2H)

Example 12

2-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}propanamide



To a solution of Example 2 (100 mg, 0.22 mmol) and copper (II) chloride (45 mg, 0.33 mmol) in acetonitrile (3 ml) was added *tert*-butylnitrite (30 µl, 0.27 mmol) in acetonitrile. The reaction mixture was stirred at room temperature for 18 h and then partitioned between ethyl acetate and water. The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in acetonitrile : water (1:1, 0.75 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm LUNA C18(2) 10µm column) using an acetonitrile : water gradient [50:20 to 98:2]. The appropriate fractions were concentrated *in vacuo* to give the titled compound (21mg) together with the 5-chloro derivative.

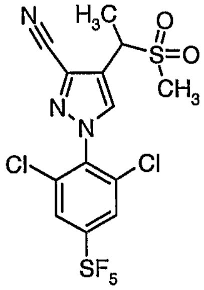
Experimental MH^+ (acetonitrile adduct) 476.1; expected 476.0

^{1}H-NMR (d_6-DMSO): 1.38 – 1.42 (3H), 3.70 – 3.80 (1H), 7.00 – 7.05 (1H), 7.58 – 7.61 (1H), 8.25 – 8.30 (1H), 8.45 – 8.50 (2H)

Similarly prepared was:

Example 13

1-[2,6-dichloro-4-pentafluorothiophenyl]-4-[1-(methylsulfonyl)ethyl]-1H-pyrazole-3-carbonitrile from Example 11



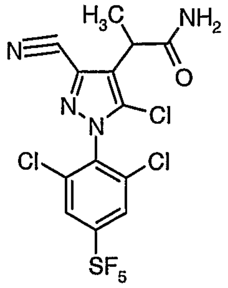
Experimental MH^+ 470.0; expected 470.0

^{1}H-NMR ($CDCl_3$): 1.79 – 1.82 (3H), 2.80 – 2.82 (3H), 4.30 – 4.39 (1H), 7.81 – 7.83 (1H), 7.88 – 6.92

(2H)

Example 14

2-{5-chloro-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}propanamide



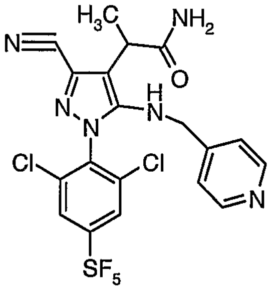
To a solution of Example 2 (100 mg, 0.22 mmol) and copper (II) chloride (45 mg, 0.33 mmol) in acetonitrile (3 ml) was added *tert*-butylnitrite (30 μl, 0.27 mmol) in acetonitrile. The reaction mixture was stirred at room temperature for 18 h and then partitioned between ethyl acetate and water. The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in acetonitrile : water (1:1, 0.75 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm LUNA C18(2) 10μm column) using an acetonitrile : water gradient [50:50 to 98:2]. The appropriate fractions were concentrated *in vacuo* to give the titled compound (35 mg) together with the 5-hydrido derivative.

Experimental MH^+ (acetonitrile adduct) 510.1; expected 510.0

^{1}H-NMR (d_6-DMSO): 1.45 – 1.55 (3H), 3.70 – 3.80 (1H), 7.10 – 7.20 (1H), 7.60 – 7.70 (1H), 8.60 – 8.65 (2H)

Example 15

2-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-[(pyridin-4-ylmethyl)amino]-1H-pyrazol-4-yl}propanamide



To a solution of Preparation 41 (240 mg, 0.44 mmol) in methanol (10 ml), at 0°C, was added sodium borohydride (40 mg, 1.06 mmol). The reaction mixture was stirred at room temperature for 18 h and then quenched with water. The mixture was adjusted to pH 2 by addition of hydrochloric acid (4N) and the two layers were separated. The aqueous layer was extracted with ethyl acetate (x 3) and the combined organic phases were washed with brine and aqueous sodium hydrogen carbonate solution, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in acetonitrile (2 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.4 mm

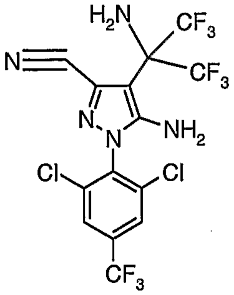
LUNA C18(2) 5µm column) using an acetonitrile : 0.1% trifluoroacetic acid gradient [45:55 to 95:5]. The appropriate fractions were concentrated *in vacuo* to give the titled compound (6 mg).

Experimental MH$^+$ 541.0; expected 541.0

^{1}H-NMR ($CDCl_3$): 1.60 – 1.70 (3H), 3.70 – 3.80 (1H), 4.10 – 4.20 (1H), 4.35 – 4.45 (1H), 5.80 – 5.90 (1H), 6.20 – 6.30 (2H), 7.50 – 7.70 (4H, 8.60 – 8.70 (2H)

Example 16

5-amino-4-[1-amino-2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-3-carbonitrile

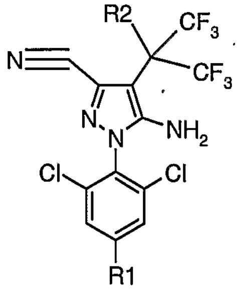


To a slurry of potassium carbonate (100 mg, 0.70 mmol) in acetonitrile (0.5 ml) was added ammonia (35% in water, 50 µl, 1.00 mmol), followed by Preparation 29 (50 mg, 0.1 mmol). The reaction mixture was stirred at room temperature for 18 h and then partitioned between dichloromethane and water. The mixture was filtered through a hydrophobic frit and the filtrate was concentrated under a stream of nitrogen. The residue was dissolved in acetonitrile/water/dimethyl sulphoxide (1 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm LUNA C18(2) 10µm column) using an acetonitrile : water gradient [60:40 to 95:5]. The appropriate fractions were concentrated *in vacuo* to give the titled compound (18 mg).

Experimental MH$^+$ 485.9; expected 486.0

^{1}H-NMR (d_6-DMSO): 3.60 – 3.70 (2H), 6.30 - 6.45 (2H), 8.21 – 8.27 (2H)

Similarly prepared, using the appropriate nucleophile, were:



Example	R1	R2	From
Example 17	CF_3	$NHCH_3$	Preparation 29
Example 18	CF_3	i-Prs	Preparation 29
Example 19	SF_5	CN	Preparation 6

Example 17

5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[2,2,2-trifluoro-1-(methylamino)-1-(trifluoromethyl)ethyl]-1H-pyrazole-3-carbonitrile

Experimental MH^+ 500.0; expected 500.0

^{1}H-NMR (CD_3OD): 2.40 – 2.45 (3H), 8.00 – 8.05 (2H)

Example 18

5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[2,2,2-trifluoro-1-(isopropylthio)-1-(trifluoromethyl)ethyl]-1H-pyrazole-3-carbonitrile

Experimental MH^+ 544.8; expected 545.0

^{1}H-NMR (CD_3OD): 1.35 – 1.40 (6H), 3.10 – 3.20 (1H), 8.05 – 8.08 (2H)

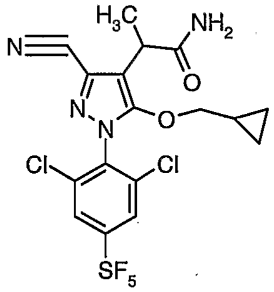
Example 19

5-amino-4-[1-cyano-2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazole-3-carbonitrile

^{1}H-NMR ($CDCl_3$): 6.35 – 6.40 (2H), 7.95 – 8.00 (2H)

Example 20

2-{3-cyano-5-(cyclopropylmethoxy)-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}propanamide



To Preparation 46 (65 mg, 0.13 mmol) in tetrahydrofuran : water (4:1, 3 ml) was added lithium hydroxide monohydrate (55 mg, 1.30 mmol) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was acidified with hydrochloric acid (1M) and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. To a solution of the residue in tetrahydrofuran (3 ml), at 0°C, was added triethylamine (46 μl, 0.33 mmol) and ethyl chloroformate (15 μl, 0.16 mmol). After stirring for 30 min, aqueous ammonium hydroxide solution (0.5 ml) was added and the reaction mixture was warmed to room temperature. The reaction mixture was adjusted to pH 1 by addition of hydrochloric acid (1M) and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in acetonitrile (0.6 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm LUNA C18(2) 10μm column) using an acetonitrile : water gradient [20:80 to 98:2]. The appropriate fractions were concentrated *in vacuo* to give the titled compound (10 mg).

Experimental MH^+ 505.0; expected 505.0

^{1}H-NMR (CD_3OD): 0.10 – 0.20 (2H), 0.45 – 0.50 (2H), 0.95 – 1.05 (1H), 1.61 – 1.66 (3H), 3.80 – 3.89 (3H), 8.22 – 8.27 (2H)

The following Preparations illustrate the synthesis of certain intermediates used in the preparation of the preceding Examples.

Preparation 1

N-(1-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-2,2,2-trifluoroethyl)-methanesulfonamide

To a solution of Preparation 2 (100 mg, 0.24 mmol) in dichloromethane (2 ml), at 0°C, was added triethylamine (53 μl, 0.38 mmol) and methanesulphonyl chloride (28 μl, 0.36 mmol). The reaction mixture was stirred at room temperature for 1 h, before addition of ethyl acetate. The mixture was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the titled compound (70 mg).

Experimental MH^+ 495.9; expected 496.0

Preparation 2

5-amino-4-(1-amino-2,2,2-trifluoroethyl)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-3-carbonitrile

To a solution of Preparation 3 (100 mg, 0.23 mmol) in acetonitrile (1.5 ml) was added ammonia (35% in water, 80 μl) and the reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and water. The two layers were separated and the organic layer was washed with saturated brine solution (x 2), dried ($MgSO_4$) and concentrated *in vacuo* to give the titled compound (100 mg). The compound was used directly in the synthesis of Preparation 1.

Preparation 3

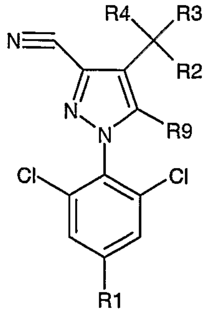
5-amino-4-(1-chloro-2,2,2-trifluoroethyl)-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-3-carbonitrile

To a solution of Preparation 8 (1.0 g, 2.39 mmol) in dichloroethane (10 ml) was added dropwise thionyl chloride (261 μl, 3.59 mmol). The reaction mixture was then stirred at 60°C overnight.

The reaction mixture was concentrated *in vacuo* and to the residue was added dichloromethane. This solution was washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to give the titled compound (900 mg) as a white solid.

1H-NMR ($CDCl_3$): 4.10 – 4.30 (2H), 5.21 – 5.24 (1H), 7.76 – 7.80 (2H)

Similarly prepared were:



Preparation	R1	R2	R3	R4	R9	From
Preparation 4	CF_3	$COOCH_3$	CF_3	Cl	$-N{=}CH{-}N(CH_3)_2$	Preparation 38
Preparation 5	CF_3	CF_3	CF_3	Cl	$-N{=}CH{-}N(CH_3)_2$	Preparation 47
Preparation 6	SF_5	CF_3	CF_3	Cl	NH_2	Preparation 32
Preparation 7	SF_5	$COOCH_3$	CH_3	Cl	cyclopropylmethoxy	Preparation 39

Preparation 4

methyl 2-chloro-2-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[-(dimethylamino)methylene]amino}-1H-pyrazol-4-yl)-3,3,3-trifluoropropanoate

Experimental MH^+ 550.1; expected 550.0

Preparation 5

N'-{4-[1-chloro-2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-5-yl}-N,N-dimethylimidoformamide

Experimental MH^+ 560.0; expected 560.0

Preparation 6

5-amino-4-[1-chloro-2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazole-3-carbonitrile

Experimental MH^+ 562.8; expected 562.9

Preparation 7

methyl 2-chloro-2-{3-cyano-5-(cyclopropylmethoxy)-1-[2,6-dichloro-4 pentafluorothiophenyl]-1H-pyrazol-4-yl}propanoate

Experimental MH^+ 554.0; expected 554.0

Preparation 8

5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(2,2,2-trifluoro-1-hydroxyethyl)-1H-pyrazole-3-carbonitrile

To a stirred solution of Preparation 61 (214 mg, 0.51 mmol) in ethanol (4 ml) was added sodium borohydride (20 mg, 0.51 mmol). The reaction mixture was then stirred at room temperature for 20 min. To the reaction mixture was added acetic acid (0.5 ml) and the mixture was concentrated *in vacuo*. To the residue was added dichloromethane and the solution was washed with water, followed by saturated aqueous sodium bicarbonate solution and brine. The organic phase was then dried ($MgSO_4$) and concentrated *in vacuo* to give the titled compound (178 mg, 83%) as a white solid.

Experimental MH^+ 419.3; expected 419.0

Preparation 9

N'-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-4-[1-(methylsulfonyl)ethyl]-1H-pyrazol-5-yl}-N,N-dimethylimidoformamide

To a suspension of Preparation 12 (520 mg, 0.96 mmol) in ethanol (30 ml) was added sodium borohydride (160 mg, 4.20 mmol) and the reaction mixture was stirred at room temperature for 18 h. To the reaction mixture was added hydrochloric acid (1N, 7 ml) and the solution was concentrated *in vacuo*. The residue was partitioned between dichloromethane (25 ml) and water (25 ml) and the two layers were separated. The aqueous layer was extracted with dichloromethane (2 x 25 ml) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give the titled compound (430 mg).

Experimental MH^+ 539.9; expected 540.0

Similarly prepared were:

Preparation 10

methyl 2-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[-(dimethylamino)methylene]amino}-1H-pyrazol-4-yl)propanoate from Preparation 34.

Experimental MH^+ 462.0; expected 462.1

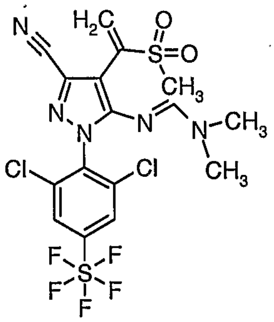
Preparation 11

methyl 2-(3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-{[-(dimethylamino)methylene]amino}-1H-pyrazol-4-yl)propanoate from Preparation 35.

Experimental MH^+ 520.1; expected 520.0

Preparation 12

N'-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-4-[1-(methylsulfonyl)vinyl]-1H-pyrazol-5-yl}-N,N-dimethylimidoformamide



To a solution of Preparation 70 (5.50 g, 29.70 mmol) in tetrahydrofuran (75 ml) was added Rieke® Zinc (0.76M in tetrahydrofuran, 100 ml, 76.00 mmol) and the mixture was stirred at room temperature for 4 h. To a solution of tetrakis(triphenylphosphine)palladium(0) (560 mg) and Preparation 13 (5.55 g, 9.90 mmol) in tetrahydrofuran (75 ml) was added a solution of the zinc reagent in tetrahydrofuran (approximately 14.90 mmol), via syringe. The reaction mixture was then heated at reflux for 24 h. The reaction mixture was passed through a silica plug, eluting with ethyl acetate, and the filtrate was concentrated *in vacuo.* The residue was purified by column chromatography (silica) eluting with ethyl acetate/cyclohexane [35:65]. The appropriate fractions were combined and concentrated to give the titled compound (1.40 g).

Experimental MH$^+$ 538.0; expected 538.0

Preparation 13

N'-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-4-iodo-1H-pyrazol-5-yl}-N,N-dimethylimidoformamide

A solution of Preparation 16 (52.00 g, 103.00 mmol) in N,N-dimethylformamide dimethyl acetal (300 ml) was heated at reflux for 5 h, cooled to room temperature and stirred for 18 h.

The reaction mixture was purified by column chromatography (silica, 1 kg) with gradient elution, hexane : ethyl acetate [6:1 to 4:1]. The appropriate fractions were combined and concentrated to give the titled compound (45.00 g).

The reaction mixture was purified by column chromatography (silica, 1 kg) with gradient elution, hexane : ethyl acetate [6 : 1 to 4 : 1]. The appropriate fractions were combined and concentrated to give the titled compound (45 g) as a light brown solid.

^{1}H-NMR (CDCl3): 2.77 - 2.81 (3H), 3.02 - 3.05 (3H), 7.78 - 7.81 (2H), 8.21 - 8.24 (1H)

Similarly prepared were

Preparation 14

N'-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-iodo-1H-pyrazol-5-yl}-N,N-dimethylimidoformamide from Preparation 63.

Experimental MH$^+$ 502.1; expected 502.9

Preparation 15

N'-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(trifluoroacetyl)-1H-pyrazol-5-yl}-N,N-dimethylimidoformamide from Preparation 61.

Experimental MH$^+$ 472.0; expected 472.0

Preparation 16

5-amino-1-[2,6-dichloro-4-pentafluorothiophenyl]-4-iodo-1H-pyrazole-3-carbonitrile

To a solution of Preparation 62 (40.00 g, 106.00 mmol) in acetonitrile (400 ml) was added N-iodosuccinimide (26.40 g, 117.00 mmol) and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with ethyl acetate (1 l) and washed with aqueous sodium thiosulphate solution (10%, 3 x 500 ml) and brine (500 ml). The organic phase was dried (MgSO4) and concentrated in vacuo to give the titled compound (53.00 g).

^{1}H-NMR (CDCl3): 3.87 - 3.94 (2H), 7.88 - 7.90 (2H)

Preparation 17

5-(cyclopropylmethoxy)-1-[2,6-dichloro-4-pentafluorothiophenyl]-4-iodo-1H-pyrazole-3-carbonitrile

To a solution of Preparation 59 (2.97 g, 6.84 mmol) in ethanol (68 ml) was added silver sulphate (4.30 g, 13.70 mmol), followed by iodine (3.50 g, 13.70 mmol). After stirring for 3 h, the solution was filtered and the precipitate partitioned between aqueous sodium hydroxide solution (1M) and dichloromethane. The two layers were separated and the organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was filtered through silica, washing through with ethyl acetate, and the filtrate was concentrated *in vacuo* to give the titled compound (3.53 g).

Experimental MH^+ (acetonitrile adduct) 600.8; expected 600.9

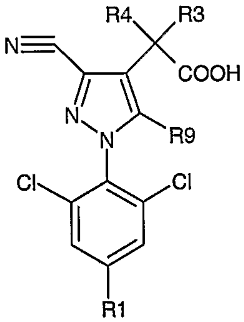
Preparation 18

2-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}propanoic acid

A mixture of Preparation 30 (2.00 g, 3.84 mmol) and lithium hydroxide monohydrate (323 mg, 7.69 mmol) in tetrahydrofuran (20 ml) and water (4 ml) was stirred at room temperature for 60 h. The reaction mixture was acidified and then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water and the organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo* to give the titled compound (1.91 g).

Experimental MH^+ 451.0; expected 451.0

Similarly prepared were:



Preparation	R1	R3	R4	R9	Experimental MH^+	Expected MH^+	From
Preparation 19	CF_3	CH_3	H	NH_2	392.9	393.0	Preparation 28
Preparation 20	SF_5	CH_3	CH_3	NH_2	465.0	465.0	Preparation 27
Preparation 21	CF_3	4-fluorobenzyl	H	NH_2	486.9	487.0	Preparation 31
Preparation 22	CF_3	ethyl	H	NH_2	407.0	407.0	Preparation 33

Preparation 23	SF_5	cyclobutyl	NH_2	476.9	477.0	Preparation 50
Preparation 24	CF_3O	cyclobutyl	NH_2	435.0	435.0	Preparation 51
Preparation 25	CF_3	cyclobutyl	NH_2	419.0	419.0	Preparation 52
Preparation 26	SF_5	cyclobutyl	$NHCH_3$	491.0	491.0	Preparation 57

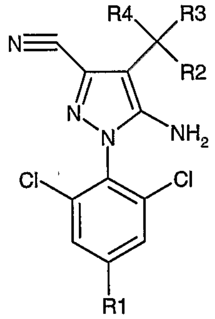
Preparation 27

methyl 2-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}-2-methylpropanoate

A mixture of Preparation 42 (540 mg, 1.00 mmol) and hydrochloric acid (5M, 0.5 ml) in methanol (4 ml) and 1,4-dioxane (4 ml) was heated at 90°C, under nitrogen, for 5 h. The reaction mixture was concentrated *in vacuo* and to the residue was added water (5 ml). The mixture was extracted with ethyl acetate (3 x 5 ml) and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the titled compound (581 mg).

Experimental MH^+ 479.0; expected 479.0

Similarly prepared were:



Preparation	R1	R2	R3	R4	Experimental MH^+	Expected MH^+	From
Preparation 28	CF_3	$COOCH_3$	CH_3	H	407.0	407.0	Preparation 10
Preparation 29	CF_3	OH	CF_3	CF_3	505.0	504.9	Preparation 5
Preparation 30	SF_5	$COOCH_3$	CH_3	H	465.0	465.0	Preparation 11
Preparation 31	CF_3	$COOCH_3$	4-fluorobenzyl	H	500.9	501.1	Preparation 43
	SF_5	OH	CF_3	CF_3	545.0	544.9	

Preparation 32							Preparation 48
Preparation 33	CF_3	$COOCH_3$	ethyl	H	420.9	421.0	Preparation 49

Preparation 34

methyl 2-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[-(dimethylamino)methylene]amino}-1H-pyrazol-4-yl)acrylate

To a solution of Preparation 36 (7.2 g, 15.1 mmol) in dichloromethane (600 ml), at 0°C, was added triethylamine (5.3 ml, 37.8 mmol), followed by methanesulphonyl chloride (1.5 ml, 19.6 mmol). The reaction mixture was then allowed to warm to room temperature over 2 h.

The reaction mixture was poured into ice/hydrochloric acid (0.5M) and the mixture was extracted with dichloromethane (3 x 150 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*.

The residue was purified by column chromatography (silica) with gradient elution, hexane : ethyl acetate [2 : 1 to 1 : 1]. The appropriate fractions were combined and concentrated to give the titled compound (6.2 g).

Experimental MH^+ 460.07; expected 461.3

Similarly prepared was

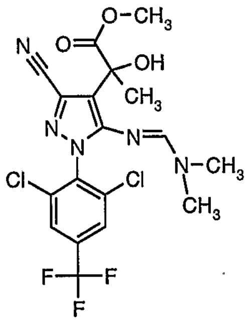
Preparation 35

methyl 2-(3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-{[(dimethylamino)methylene]amino}-1H-pyrazol-4-yl)acrylate from Preparation 37.

Experimental MH^+ 518.0; expected 518.0

Preparation 36

methyl 2-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[-(dimethylamino)methylene]amino}-1H-pyrazol-4-yl)-2-hydroxypropanoate



To a solution of Preparation 14 (6.3 g, 12.5 mmol) in tetrahydrofuran (50 ml), at -78°C, was added isopropylmagnesium chloride (2M in tetrahydrofuran, 6.9 ml, 13.8 mmol), using a syringe. After stirring at -78°C for 30 min, the solution was warmed to -30°C and methyl pyruvate (1.73 ml, 18.9 mmol) in tetrahydrofuran (30 ml) was added via syringe. The reaction mixture was then allowed to warm to room temperature over 2 h. The reaction mixture was added to an ice/hydrochloric acid (2M) mixture (300 ml) and extracted with ethyl acetate (3 x 150 ml). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo.*

The residue was purified by column chromatography (silica) with gradient elution, hexane : ethyl acetate [1 : 1 to 1 : 2]. The appropriate fractions were combined and concentrated to give the titled compound (8.7 g).

Experimental MH^+ 480.0; expected 479.3

Similarly prepared were:

Preparation 37

methyl 2-(3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-{[-(dimethylamino)methylene]amino}-1H-pyrazol-4-yl)-2-hydroxypropanoate from Preparation 64.

Experimental MH^+ 536.0; expected 536.0

Preparation 38

methyl 2-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[-(dimethylamino)methylene]amino}-1H-pyrazol-4-yl)-3,3,3-trifluoro-2-hydroxypropanoate from Preparation 14.

Experimental MH^+ 532.2; expected 532.0

Preparation 39

methyl 2-{3-cyano-5-(cyclopropylmethoxy)-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}-2-hydroxypropanoate from Preparation 17.

Experimental MH^+ 536.1; expected 536.0

Preparation 40

N'-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-4-(trifluoroacetyl)-1H-pyrazol-5-yl}-N,N-dimethylimidoformamide from Preparation 64.

Experimental MH^+ 530.0; expected 530.0

Preparation 41

2-(3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-{[1-pyridin-4-ylmethylene]amino}-1H-pyrazol-4-yl)propanamide

To a solution of Example 2 (200 mg, 0.44 mmol) in toluene (4 ml) was added 4A molecular sieves (175 mg), 4-pyridinecarboxaldehyde (0.13 ml, 1.33 mmol) and *p*-toluenesulphonic acid (8 mg). The reaction mixture was heated at 115°C, under nitrogen, for 18 h and then cooled to room temperature. The reaction mixture was concentrated *in vacuo* to give the titled compound (240 mg).

Experimental MH^+ 539.0; expected 539.0

Preparation 42

methyl 2-(3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-{[-(dimethylamino)methylene]amino}-1H-pyrazol-4-yl)-2-methylpropanoate

To a solution of Preparation 11 (1.10 g, 2.10 mmol) in tetrahydrofuran (20 ml), at -78°C and under nitrogen, was added potassium bis(trimethylsilyl)amide (0.5M in toluene, 5.08 ml, 2.50 mmol). After stirring at -78°C for 20 min, methyl iodide (0.26 ml, 4.20 mmol) was added and the reaction mixture was allowed to warm to room temperature over 3 h.

To the reaction mixture was added saturated aqueous ammonium chloride solution (15 ml) and the mixture was extracted with ethyl acetate (3 x 15 ml). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the titled compound (540 mg).

Experimental MH^+ 534.1; expected 534.1

Similarly prepared was:

Preparation 43

methyl 2-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[-(dimethylamino)methylene]amino}-1H-pyrazol-4-yl)-3-(4-fluorophenyl)propanoate from Preparation 44.

Experimental MH^+ 556.1; expected 556.1

Preparation 44

methyl (3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[-(dimethylamino)methylene]amino}-1H-pyrazol-4-yl)acetate

To a solution of Preparation 45 (201 mg, 0.39 mmol) in acetonitrile (10 ml) was added potassium carbonate (539 mg, 3.90 mmol), followed by water (few drops). The reaction mixture was stirred at room temperature for 18 h and then quenched with hydrochloric acid (2N). The mixture was concentrated *in vacuo* and the residue was partitioned between water (15 ml) and ethyl acetate (15 ml). The two layers were separated and the organic layer was washed with brine (15 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the titled compound (100 mg).

Experimental MH^+ 448.1; expected 448.1

Preparation 45

methyl 2-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[-(dimethylamino)methylene]amino}-1H-pyrazol-4-yl)-3,3,3-trifluoropropanoate

To a solution of Preparation 4 (112 mg, 0.20 mmol) in acetic acid (5 ml) and diethyl ether (5 ml) was added zinc powder (78 mg, 1.20 mmol). The reaction mixture was stirred at room temperature for 18 h and then quenched with saturated ammonium chloride solution (10 ml). The mixture was extracted with diethyl ether (2 x 10 ml) and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the titled compound (200 mg).

Experimental MH^+ 516.1; expected 516.0

Similarly prepared was:

Preparation 46

methyl 2-{3-cyano-5-(cyclopropylmethoxy)-1-[2,6-dichloro-4-(pentafluoro-lambda~6~-sulfanyl)phenyl]-1H-pyrazol-4-yl}propanoate from Preparation 7

Experimental MH^+ 490.8; expected 491.0

Preparation 47

N'-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]-1H-pyrazol-5-yl}-N,N-dimethylimidoformamide

A mixture of Preparation 15 (5.42 g, 11.50 mmol), trimethylamine *N*-oxide (860 mg, 11.40 mmol) and molecular sieves in tetrahydrofuran (50 ml) was stirred under nitrogen for 30 min. To the solution was added (trifluoromethyl)trimethylsilane (9.4 ml, 63.20 mmol), via syringe over 1 h, and the reaction mixture was stirred at room temperature for 3 days. To the mixture was added tetrabutylammonium fluoride (1M in tetrahydrofuran, 10 ml), with cooling, and the mixture was stirred for 30 min. Water (100 ml) was added and the two layers were separated. The aqueous layer was extracted with diethyl ether (2 x 100 ml) and the combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in dichloromethane and filtered through silica, washing through with dichloromethane. The filtrate was concentrated *in vacuo* to give the titled compound (4.38 g).

Experimental MH^+ 542.1; expected 542.0

Similarly prepared was:

Preparation 48

N'-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]-1H-pyrazol-5-yl}-N,N-dimethylimidoformamide from Preparation 40.

Experimental MH^+ 600.0; expected 600.0

Preparation 49

methyl 2-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[-(dimethylamino)methylene]amino}-1H-pyrazol-4-yl)butanoate

To a solution of Preparation 44 (200 mg, 0.44 mmol) in tetrahydrofuran (6 ml), at -78°C and under nitrogen, was added potassium hexamethyldisilazide (0.5M, 0.94 ml, 0.46 mmol), followed by iodoethane (0.14 ml, 1.76 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. To the reaction mixture was added ammonium chloride solution (10 ml) and the mixture was extracted with ethyl acetate (3 x 10 ml). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the titled compound (221 mg).

Experimental MH^+ 475.9; expected 476.1

Preparation 50

methyl 1-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}cyclobutanecarboxylate

To a solution of Preparation 71 (534 mg, 1.85 mmol) in ethanol (15 ml), at -2°C and under nitrogen, was added aqueous tetrafluoroboric acid solution (48 wt%, 0.48 ml, 3.70 mmol). The reaction mixture was cooled to -4°C and isoamyl nitrite (239 mg, 2.04 mmol) was added. After stirring at -2°C for 1 h, Preparation 53 (511 mg, 2.04 mmol) was added and the reaction mixture was stirred at -2°C for 1 h and then at room temperature for 24 h. To the reaction mixture was added dropwise aqueous ammonium hydroxide solution (29.7 wt%, 0.65 g, 5.55 mmol) and the solution was stirred for 80 min. The reaction mixture was partitioned between water (100 ml) and diethyl ether (100 ml) and the two layers were separated. The aqueous layer was extracted with diethyl ether (50 ml) and the combined organic phases were washed with brine (50 ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the titled compound (660 mg).

Experimental MH^+ 490.8; expected 491.0

Similarly prepared were:

Preparation 51

methyl 1-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}cyclobutanecarboxylate from Preparation 68.

Experimental MH^+ 449.0; expected 449.0

Preparation 52

methyl 1-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}cyclobutanecarboxylate from Preparation 69.

Experimental MH^+ 433.0; expected 433.0

Preparation 53

methyl 1-(1,2-dicyano-3-methoxy-3-oxopropyl)cyclobutanecarboxylate

To a solution of Preparation 54 (730 mg, 2.70 mmol) in methanol (15 ml), at 0°C and under nitrogen, was added potassium cyanide (210 mg, 3.20 mmol). The reaction mixture was stirred in an ice bath for 18 h, before addition of silica (10 g) and glacial acetic acid (324 mg, 5.40 mmol). The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (silica), eluting with diethyl ether/pentane [55:45]. The appropriate fractions were combined and concentrated to give the titled compound (676 mg).

Experimental MH^+ 251.2; expected 251.1

Preparation 54

methyl 1-[-2-cyano-3-methoxy-3-oxoprop-1-en-1-yl]cyclobutanecarboxylate

A mixture of Preparation 55 (390 mg, 2.70 mmol), methyl cyanoacetate (0.24 ml, 2.70 mmol) and piperidine (54 µl, 0.54 mmol) in glacial acetic acid (2 ml) was heated at 65°C, under nitrogen, for 18 h. The reaction mixture was poured into water (65 ml) and extracted with dichloromethane (2 x 20 ml). The combined extracts were washed with saturated aqueous sodium hydrogencarbonate solution (35 ml) and brine (35 ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the titled compound (1.02 g).

^{1}H-NMR ($CDCl_3$): 1.94 - 2.06 (2H), 2.47 - 2.58 (4H), 3.78 - 3.79 (3H), 3.88 - 3.89 (3H), 7.78 - 7.80 (1H)

Preparation 55

methyl 1-formylcyclobutanecarboxylate

To a solution of oxalyl chloride (0.61 ml, 7.00 mmol) in dichloromethane (35 ml), at -78°C and under nitrogen, was added dropwise dimethyl sulphoxide (1.01 ml, 14.20 mmol), followed by a solution of Preparation 56 (0.84 g, 5.80 mmol) in dichloromethane (17.5 ml) and triethylamine (4.04 ml, 29.00 mmol). The reaction mixture was stirred at -78°C for 45 min and then at room temperature for 20 h. The reaction mixture was partitioned between hydrochloric acid (1M, 50 ml) and dichloromethane (100 ml) and the two layers were separated. The organic phase was washed with hydrochloric acid (1M, 50 ml), water (50 ml), saturated aqueous sodium hydrogencarbonate solution (50 ml) and brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica), eluting with diethyl ether/pentane [5:95]. The appropriate fractions were combined and concentrated to give the titled compound (390 mg).

^{1}H-NMR ($CDCl_3$): 1.90 - 2.06 (2H), 2.45 - 2.51 (4H), 3.78 - 3.80 (3H), 9.77 - 9.79 (1H)

Preparation 56

methyl 1-(hydroxymethyl)cyclobutanecarboxylate

To a solution of dimethyl 1,1-cyclobutanedicarboxylate Preparation 65 (4.29 g, 24.90 mmol) in dry tetrahydrofuran (140 ml), under nitrogen, was added lithium tri-*tert*-butoxyaluminohydride (1M in tetrahydrofuran, 54.8 ml, 54.80 mmol). The reaction mixture was heated at reflux, under nitrogen, for 18 h, and then stirred at room temperature for a further 18 h.

The reaction mixture was poured into a mixture of aqueous ammonium chloride solution (10 wt%, 450 ml) and brine (100 ml) and extracted with ethyl acetate (250 ml). The combined extracts were washed with brine (200 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the titled compound (6.50 g).

^{1}H-NMR ($CDCl_3$): 1.93 - 2.00 (4H), 2.38 - 2.47 (2H), 3.74 - 3.75 (3H), 3.82 - 3.83 (2H)

Preparation 57

methyl 1-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-(methylamino)-1H-pyrazol-4-yl}cyclobutanecarboxylate

To a solution of Preparation 58 (578 mg, 1.06 mmol) in acetic acid (11 ml), under nitrogen, was added sodium cyanoborohydride (133 mg, 2.12 mmol). After stirring for 1.5 h, the reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (50 ml), water (50 ml) and brine (5 ml). The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo* to give the titled compound (768 mg).

Experimental MH^+ 505.0; expected 505.0

Preparation 58

methyl 1-(3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-{[(1E)-ethoxymethylene]amino}-1Hpyrazol-4-yl)cyclobutanecarboxylate

To a suspension of Preparation 50 (1.02 g, 2.10 mmol) in triethyl orthoformate (50 ml) was added concentrated hydrochloric acid (4 drops). The reaction mixture was then stirred at 50°C, under nitrogen, for 1.5 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in toluene (50 ml) and re-concentrated (x 3). The residue was then dissolved in ethyl acetate (50 ml), washed with saturated aqueous sodium hydrogen carbonate solution (50 ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the titled compound (1.09 g).

Experimental MH^+ 547.0; expected 547.0

Preparation 59

5-(cyclopropylmethoxy)-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazole-3-carbonitrile

To a mixture of Preparation 60 (6.37 g, 16.80 mmol) and potassium carbonate (7.00 g, 50.40 mmol) in acetonitrile (75 ml) was added (bromomethyl)cyclopropane (6.5 ml, 67.20 mmol). The reaction mixture was stirred at room temperature for 1 h and then heated at 50°C for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between hydrochloric acid (1M) and ethyl acetate. The two layers were separated and the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography with gradient elution, ethyl acetate : cyclohexane [2:98 to 20:80]. The appropriate fractions were combined and concentrated to give the titled compound (2.97 g).

Experimental MH^+ 433.9; expected 434.0

Preparation 60

1-[2,6-dichloro-4-pentafluorothiophenyl]-5-hydroxy-1*H*-pyrazole-3-carbonitrile

Sodium nitrite (1.32 g, 19.1 mmol) was added carefully to sulphuric acid (concentrated, 6.8 ml), whilst cooling the solution to 0°C. The solution was heated to 60°C for 30 min, allowed to cool and then diluted with acetic acid (12 ml). To the solution was added Preparation 67 (5.0 mg, 17.4 mmol) in acetic acid (11 ml) and the reaction mixture was heated at 55°C for 1 h.

To a solution of Preparation 66 (3.09 g, 18.1 mmol) in acetic acid (24 ml) and water (36 ml) was added dropwise the solution of the diazonium salt, followed by sodium acetate (24.2 g) in water (42 ml). The reaction mixture was then stirred at room temperature for 30 min.

The reaction mixture was poured into ice/water (200 ml) and the mixture was extracted with dichloromethane (4 x 60 ml). The combined extracts were then washed with ammonium hydroxide (48 ml), dried and concentrated *in vacuo*.

To a solution of sodium methoxide (25 wt.%, 11.5 ml, 50.1 mmol) in methanol (450 ml) was added dropwise a solution of the residue in methanol (100 ml). The reaction mixture was then stirred at room temperature for 2 h.

The reaction mixture was concentrated *in vacuo* and to the residue was added water. This solution was adjusted to pH 1 by addition of hydrochloric acid (4N) and the mixture was extracted with dichloromethane (3 x 100 ml). The combined extracts were dried ($MgSO_4$) and concentrated *in* *vacuo.*

The residue was purified by column chromatography, eluting with hexane/ethyl acetate [3 : 1]. The appropriate fractions were combined and concentrated to give the titled compound (4.5 g).

Experimental MH^+ 380.0; expected 380.0

Preparation 61

5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(trifluoroacetyl)-1H-pyrazole-3-carbonitrile

Reference: WO 98/04530 A1, EP 918756 A1, JP 08311036 A2

Preparation 62

5-amino-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazole-3-carbonitrile

Reference: WO 93/06089 A1, EP 605469 A1

Preparation 63

5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-iodo-1H-pyrazole-3-carbonitrile

Reference: US 6069157 A, EP 933363 A1, WO 98/28278 A1

Preparation 64

N'-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-4-iodo-1H-pyrazol-5-yl}-N,N-dimethylimidoformamide

Reference: WO 2005/060749

Preparation 65

dimethyl cyclobutane-1,1-dicarboxylate

Commercially available from Lancaster Synthesis Ltd. Newgate, White Lund Morecambe Lancashire LA3 3BN UK

Preparation 66

dimethyl 2-cyanosuccinate

Reference: EP 28430 A1, JP 56075584 A2, Hall, H. K., Jr.; Ykman, P., J. Am. Chem. Soc. (1975), 97(4), 800-807, US 4028201 A

Preparation 67

2,6-dichloro-4-pentafluorothioaniline

Reference: WO 94/21606 A1, WO 93/06089 A1

Preparation 68

2,6-dichloro-4-(trifluoromethoxy)benzenediazonium tetrafluoroborate

To a solution of 2,6-dichloro-4-(trifluoromethoxy)aniline (1.00 g, 4.10 mmol) in ethanol (1.2 ml), at -

5°C and under nitrogen, was added dropwise tetrafluoroboric acid (48 wt%, 0.54 ml, 8.50 mmol), followed by isoamyl nitrite (0.60 ml, 4.50 mmol). The reaction mixture was stirred at room temperature for 1 h and the resulting precipitate was collected by filtration, washed with ethanol and diethyl ether and dried under nitrogen to give the titled compound (126 mg) which was used directly.

Preparation 69

2,6-dichloro-4-(trifluoromethyl)benzenediazonium tetrafluoroborate

Reference: WO 2005/023773 A1

Preparation 70

1-bromo-1-(methylsulfonyl)ethylene

Reference: JACS (1972), 94 (3), 1012-13

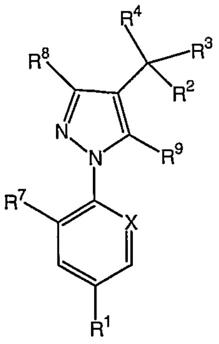
Preparation 71

2,6-dichloro-4-pentafluorothioaniline

Reference: WO94/21606A1

Claims

1. A compound of formula (I):



(I)

wherein:

X is selected from CR^{10} or N;

R^1 is selected from halo, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, amino, C_{1-6} alkyl amino, di C_{1-6} alkyl amino, het, phenyl, SF_5 and $S(O)_nR^{11}$;

R^2 is selected from cyano, C(O)OH, $S(O)_nR^{11}$, $C(O)NR^aR^b$, and $C(S)NR^aR^b$;

or R^2 is selected from $C(O)OC_{1-6}$ alkyl, amino, C_{1-6} alkyl amino, and di C_{1-6} alkyl amino each of which may be optionally and independently further substituted by one or more substitutents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, $C(O)NR^cR^d$, $NR^cC(O)R^d$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, $-C(O)OC_{1-6}$ alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, $-C(O)OC_{1-6}$ haloalkyl, amino, NR^cR^d, het, phenyl and $S(O)_nR^{11}$;

R^a and R^b are independently selected from hydrogen, het, phenyl and $S(O)_nR^{11}$;

or either one or both of R^a and R^b are independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{1-6} alkanoyl, and $C(O)OC_{1-6}$ alkyl, each of which R^a and R^b may be optionally and independently further substituted by one or more substituents selected from, where chemcially possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, $C(O)NR^cR^d$, $NR^cC(O)R^d$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, $-C(O)OC_{1-6}$ alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, $-C(O)OC_{1-6}$ haloalkyl, amino, NR^cR^d, het, phenyl and $S(O)_nR^{11}$;

or R^a and R^b together with the N atom to which they are attached may form a three to seven –

membered saturated, partially saturated, unsaturated or aromatic heterocyclic ring which may optionally contain one or more further N, O or S atoms and which may be optionally further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11};

or R^2 and R^e together with the N atom to which R^e is attached may form a six to seven – membered saturated, partially saturated, or unsaturated heterocyclic ring which may optionally contain one or more further N, O or S atoms and which may be optionally further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11};

R^3 and R^4 are independently selected from hydrogen, het, phenyl, S(O)$_n$R^{11}, and NR^{x}R^y;

or either one or more of R^3 and R^4 are independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{4-8} cycloalkyl, C_{1-6} alkoxy, and benzyl, which R^3 and R^4 may be optionally and independently further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11};

or R^3 and R^4 together with the carbon to which they are attached may form a four to seven – membered saturated, partially saturated, unsaturated or aromatic ring which may optionally contain one or more N, O or S atoms and which may be optionally further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^{c}R^d, het, phenyl and S(O)$_n$R^{11};

with the proviso that R^3 and R^4 are not both hydrogen;

R^x and R^y are independently selected from hydrogen, het, phenyl, benzyl and S(O)$_n$R^{11};

or either one or more of R^x and R^y are independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{1-6} alkanoyl, C(O)OC_{1-6} alkyl, each of which R^x and R^y may be optionally and independently further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^cR^d, NR^cC(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^cR^d, het, phenyl and S(O)$_nR^{11}$;

or R^x and R^y together with the N atom to which they are attached may form a three to seven – membered saturated, partially saturated, unsaturated or aromatic heterocyclic ring which may optionally contain one or more further N, O or S atoms and which may be optionally further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^cR^d, NR^cC(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^cR^d, het, phenyl and S(O)$_nR^{11}$;

R^7 is selected from halo, C_{1-6} alkyl and C_{1-6} alkoxy where, when R^7 is C_{1-6} alkyl or C_{1-6} alkoxy, R^7 may be optionally substituted with one or more halo substituents;

R^8 is selected from hydrogen, cyano, hydroxy, C(O)OH, nitro, halo, het, phenyl, and -S(O)$_nR^{11}$;

or R^8 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, and C(O)OC_{1-6} alkyl, which R^8 may be optionally and independently further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^cR^d, NR^cC(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, NR^cR^d, het, phenyl and S(O)$_nR^{11}$;

or R^8 is amino, which R^8 may be optionally and independently further substituted by one or more substituents selected from, where chemically possible, C(O)OH, C(O)NR^cR^d, NR^cC(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, het, phenyl and S(O)$_nR^{11}$;

R^9 is selected from hydrogen, cyano, halo, hydroxy, C(O)OH, nitro, het, phenyl and S(O)$_nR^{11}$ and NR^eR^f;

or R^9 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, $C(O)OC_{1-6}$ alkyl, which R^9 may be optionally and independently further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, $C(O)NR^cR^d$, $NR^cC(O)R^d$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -$C(O)OC_{1-6}$ alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -$C(O)OC_{1-6}$ haloalkyl, amino, NR^cR^d, het, phenyl and $S(O)_nR^{11}$;

R^e and R^f are independently selected from hydrogen, het, phenyl and $S(O)_nR^{11}$;

or either one or both of R^e and R^f are independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{1-6} alkanoyl, $C(O)OC_{1-6}$ alkyl, -$C(O)OC_{1-6}$ alkylC_{3-8} cycloalkyl, -$C(O)OC_{3-8}$ cycloalkyl, each of which R^e or R^f may be optionally and independently further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, $C(O)NR^cR^d$, $NR^cC(O)R^d$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -$C(O)OC_{1-6}$ alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -$C(O)OC_{1-6}$ haloalkyl, amino, NR^cR^d, het, phenyl and $S(O)_nR^{11}$;

or R^e or R^f together with the N atom to which they are attached may form a three to seven – membered saturated, partially saturated, unsaturated or aromatic heterocyclic ring which may optionally contain one or more further N, O or S atoms and which may be optionally further substituted by one or more substituents selected from, where chemically possible, cyano, nitro, halo, oxo, hydroxy, C(O)OH, $C(O)NR^cR^d$, $NR^cC(O)R^d$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -$C(O)OC_{1-6}$ alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -$C(O)OC_{1-6}$ haloalkyl, amino, NR^cR^d, het, phenyl and $S(O)_nR^{11}$;

or R^e and R^2 together with the atoms to which they are attached may form a six to seven – membered heterocyclic ring as previously described;

R^{10} is selected from halo, C_{1-6} alkyl and C_{1-6} alkoxy and where when R^{10} is C_{1-6} alkyl or C_{1-6} alkoxy it may optionally be substituted with one or more halo substituents;

each R^c and R^d are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkanoyl, C_{1-6} haloalkanoyl, $C(O)OC_{1-6}$ alkyl, het, phenyl and $S(O)_nR^{11}$;

or R^c and R^d together with the N atom to at least one of them is attached may form a three to seven – membered saturated, partially saturated, unsaturated or aromatic heterocyclic ring which may optionally contain one or more further N, O or S atoms;

each n is independently 0, 1 or 2;

each R^{11} is independently selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, amino, C_{1-6} alkyl amino and di C_{1-6} alkyl amino;

each phenyl may be optionally substituted by one or more further substitutents selected from the group consisting of halo, cyano, nitro, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkyl amino, di C_{1-6} alkyl amino, -NHS(O)$_n$R^{11}, and S(O)$_n$R^{11};

and each het independently represents a four to seven membered heterocyclic group, which is aromatic or non-aromatic, unsaturated, partially saturated or satureated and which contains one or more heteroatoms selected from nitrogen, N-oxide, oxygen, sulphur and wherein said heterocyclic ring is optionally substituted, where the valence allows, with one or more substituents selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, OC(O) C_{1-6} alkyl, C_{1-6} alkanoyl, C(O)O C_{1-6} alkyl and NR^{g}R^h, where R^g and R^h are independently selected from hydrogen, C_{1-6} alkyl and C_{2-6} alkenyl, and where each of the above groups may include one or more optional substituents where chemically possible independently selected from cyano, nitro, halo, oxo, hydroxy, C(O)OH, C(O)NR^{c}R^d, NR^{c}C(O)R^d, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylC_{1-6} alkyl, C_{3-8} cycloalkylC_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, -C(O)OC_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} haloalkoxy, C_{1-6} haloalkanoyl, -C(O)OC_{1-6} haloalkyl, amino, C_{1-6} alkyl amino, di C_{1-6} alkyl amino, phenyl and S(O)$_n$R^{11};

or a pharmaceutically acceptable salt or a prodrug thereof.

2. A compound as claimed in Claim 1 wherein R^1 is CF_3, OCF_3, or SF_5.

3. A compound as claimed in Claim 1 or Claim 2 wherein R^2 is cyano; C(O)NR^{a}R^b, where R^a and R^b are independently selected from hydrogen, C_{1-6} alkyl and C_{3-8} cycloalkyl; amino; C_{1-6} alkyl amino, which C_{1-6} alkyl amino is optionally substituted with S(O)$_n$R^{11}; or S(O)$_n$R^{11}.

4. A compound as claimed in Claim 3 wherein R^2 is C(O)NR^{a}R^b and where both of R^a and R^b are hydrogen.

5. A compound as claimed in any of Claims 1 to 4 wherein R^4 is hydrogen and R^3 is C_{1-6} alkyl, which C_{1-6} alkyl may optionally be substituted with halo or phenyl which phenyl may in turn be

optionally substituted with halo.

6. A compound as claimed in Claim 5 wherein R^4 is hydrogen and R^3 is methyl, ethyl, trifluoromethyl or 4-fluorobenzyl.

7. A compound as claimed in any of Claims 1 to 4 wherein R^3 and R^4 are both independently selected from C_{1-6} alkyl which may optionally be substituted with halo.

8. A compound as claimed in Claim 7 wherein R^3 and R^4 are both independently selected from methyl or trifluoromethyl.

9. A compound as claimed in any one of Claims 1 to 4 wherein R^3 and R^4 together with the carbon to which they are attached form a four to seven – membered carbocyclic ring.

10. A compound as claimed in Claim 9 wherein R^3 and R^4 together with the carbon to which they are attached form a cyclobutyl ring.

11. A compound as claimed in any of Claims 1 to 10 wherein R^8 is cyano.

12. A compound as claimed in any of Claims 1 to 11 wherein R^9 is selected from the group consisting of hydrogen; halo; C_{3-8} cycloalkylC_{1-6} alkoxy; and NR^eR^f where R^e is hydrogen and R^f is independently selected from hydrogen, methyl or 4-pyridinyl methyl.

13. A compound as claimed in Claim 12 wherein R^9 is amino.

14. A compound as claimed in any of Claims 1 to 13 wherein X is CR^{10} and R^{10} is chloro.

15. A compound as claimed in Claim 14 wherein both R^7 and R^{10} are Cl.

16. A compound selected from:
1-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}cyclobutanecarboxamide;
2-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}propanamide;
2-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}-2-methylpropanamide;
1-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethoxy)phenyl]-1H-pyrazol-4-yl}cyclobutanecarboxamide;
1-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}cyclobutanecarboxamide;
1-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-(methylamino)-1H-pyrazol-4-

yl}cyclobutanecarboxamide;
2-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}propanamide;
2-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-3-(4-fluorophenyl)propanamide;
2-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}butanamide;
N-(1-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl}-2,2,2-trifluoroethyl)-N-methylmethanesulfonamide;
5-amino-1-[2,6-dichloro-4-pentafluorothiophenyl]-4-[1-(methylsulfonyl)ethyl]-1H-pyrazole-3-carbonitrile;
1-[2,6-dichloro-4-pentafluorothiophenyl]-4-[1-(methylsulfonyl)ethyl]-1H-pyrazole-3-carbonitrile;
2-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}propanamide;
2-{5-chloro-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}propanamide;
2-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-[(pyridin-4-ylmethyl)amino]-1H-pyrazol-4-yl}propanamide;
5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[2,2,2-trifluoro-1-(methylamino)-1-(trifluoromethyl)ethyl]-1H-pyrazole-3-carbonitrile;
5-amino-4-[1-amino-2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1H-pyrazole-3-carbonitrile;
5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[2,2,2-trifluoro-1-(isopropylthio)-1-(trifluoromethyl)ethyl]-1H-pyrazole-3-carbonitrile;
5-amino-4-[1-cyano-2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazole-3-carbonitrile;
2-{3-cyano-5-(cyclopropylmethoxy)-1-[2,6-dichloro-4-pentafluorothiophenyl]-1H-pyrazol-4-yl}propanamide;
or a pharmaceutically acceptable salt or prodrug thereof.

17. A pharmaceutical composition comprising a compound as claimed in any of Claims 1 to 16 and a pharmaceutically acceptable carrier.

18. A compound as claimed in any of Claims 1 to 16 for use as a medicament.

19. The use of a compound as claimed in any of Claims 1 to 16 for the manufacture of a medicament for the treatment of a parasitic infection.

20. A method of treating a parasitic infection comprising treating an animal with an effective amount of a compound according to Claims 1 to 16.

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D231/38 C07D231/14 C07D231/16 C07D401/12 C07D231/22
A61K31/415 A61K31/4439 A61P33/00

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, WPI Data, EMBASE, BIOSIS, BEILSTEIN Data, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1997, no. 03, 31 March 1997 (1997-03-31) -& JP 08 311036 A (TAKEDA CHEM IND LTD), 26 November 1996 (1996-11-26) Formula (I); examples 1-44 to 1-47, 1-49, 1-67 to 1-69, 1-72 tol-77, 1-79 to 1-82, 1-94, 1-101 to 1-102, 1-104, 1-106, 1-108, 1-112, 1-113, 1-38, 2-1 to 2-18, 3-1 to 3-4, 4-1 to 4-2 abstract -----	1-20
X	DE 195 18 054 A1 (HOECHST SCHERING AGREVO GMBH, 13509 BERLIN, DE) 12 September 1996 (1996-09-12) Claims 1-17; Formula (I); example 705-706 ----- -/--	1-20

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

☒ See patent family annex.

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Date of the actual completion of the international search 28 September 2006	Date of mailing of the international search report 24/10/2006
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Kirsch, Cécile

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MEEGALLA, SANATH K. ET AL: "Synthesis and GABA receptor potency of 3-thiomethyl-4-(hetero)aryl-5-amino-1-phenylpyrazoles" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS , 14(19), 4949-4953 CODEN: BMCLE8; ISSN: 0960-894X, 2004, XP002400751 compounds 4, 12, 15-54	1,2,9, 12-15, 17-20
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X	PAVLOV I V ET AL: "TRANSFORMATIONS OF 5-AMINO-4-(3,4-DIMETHOXYPHENYL)PYRAZOLES IN THE DIAZOTIZATION REACTION" CHEMISTRY OF HETEROCYCLIC COMPOUNDS (A TRANSLATION OF KHIMIYA GETEROTSIKLICHESKIKH SOEDINENII), PLENUM PRESS CO., NEW YORK, NY, US, vol. 40, no. 7, 2004, pages 964-965, XP008060598 ISSN: 0009-3122 compound 1	1,9,12, 13
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARKWALDER, JAY A. ET AL: "Synthesis and Biological Evaluation of 1-Aryl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-one Inhibitors of Cyclin-Dependent Kinases" JOURNAL OF MEDICINAL CHEMISTRY , 47(24), 5894-5911 CODEN: JMCMAR; ISSN: 0022-2623, 2004, XP002400752 compounds 1,4,4u-4x,4w,10,10a-10b,10d-10e,10g-10m, 10i, 11,12a-12c,16, 17, 17a-17d,17i,17l-17o,18,18a-18b,18e,21, -----	1,2,9, 11,14, 15,17,18
E	WO 2006/063700 A (BAYER CROPSCIENCE S.A; CHOU, DAVID, T; MAIER, MICHAEL; PETRY, FRIEDERI) 22 June 2006 (2006-06-22) Claims 1-34; Formula (I); compounds 1-61 to1-69, 1-74 to 1-78, 1-80 to 1-82, 2-61 to 2-65, 2-67 to 2-69, 2-74 to 2-82 -----	1-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/001566

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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