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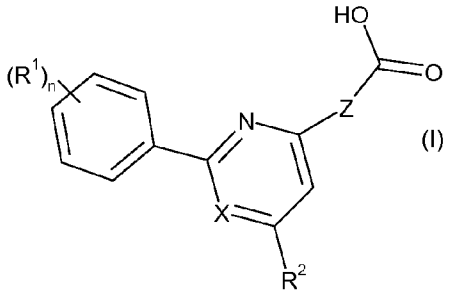
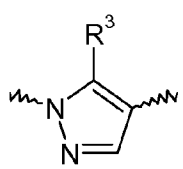
[Continued on next page]

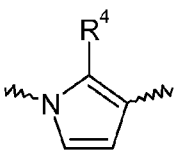
(54) Title: 2, 6-DISUBSTITUTED PYRIDINES AND 2, 4-DISUBSTITUTED PYRIMIDINES AS SOLUBLE GUANYLATE CYCLASE ACTIVATORS



(I)



(A)



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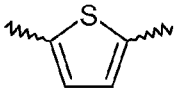

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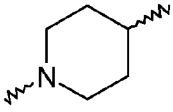

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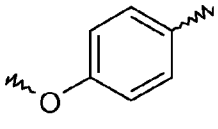

(E)

(57) Abstract: Disclosed are compounds of formula (I): wherein n represents 1 or 2; each R^1 independently represents halo or trifluoromethyl; wherein halo represents fluoro, chloro or bromo; R^2 represents hydrogen or C_{1-3}alkyl; X represents N or CH; wherein -Z- represents a group selected from: (A), (B) or (C), wherein R^3 represents trifluoromethyl or C_{1-3}alkyl; and R^4 represents hydrogen, trifluoromethyl or C_{1-3}alkyl; with the proviso that where Z represents a thiophene group and X represents N, R^2 cannot represent C_{1-3}alkyl; and when X represents CH, -Z- can additionally represent a group selected from: (D) or (E) or salts thereof which activate soluble guanylate cyclase (sGC) pharmaceutical compositions containing them, their use is medicine, and processes for their preparation.

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2,6-DISUBSTITUTED PYRIDINES AND 2,4-DISUBSTITUTED PYRIMIDINES AS SOLUBLE GUANYLATE CYCLASE ACTIVATORS

The present invention relates to novel compounds, pharmaceutical compositions containing them, to their use in medicine, and to processes for their preparation. In particular the present invention relates to compounds which, when administered to a patient, activate soluble guanylate cyclase (sGC) and to the use of such compounds for the activation of sGC in patients for a therapeutic effect.

sGC is a member of a family of related enzymes which share homologous catalytic domains but are activated in different ways. This family includes the adenylate cyclases, a class of membrane bound enzymes that convert ATP to cAMP, which are regulated by G proteins, and the membrane-bound guanylate cyclases that make cyclic guanosine monophosphate (cGMP) in response to hormone signals via an extracellular ligand binding domain.

Whilst not wishing to be bound by theory, it is considered that the active enzyme contains one heme unit in a heterodimer arrangement, composed of one alpha and one beta-subunit. Several subtypes of subunits have been described, which differ from each other with respect to sequence and tissue-specific distribution. The subtypes alpha-1 and beta-1 are thought to be mainly expressed in the brain and the lung but have also been shown to be expressed in heart, kidney, liver, skeletal muscle, placenta, colon, uterus, prostate, spleen, pancreas, platelets and isolated blood vessels. Alpha-2 subunits have been detected in the brain, placenta, uterus and pancreas, while beta-2 subunits seem to be expressed in the liver and kidney.

The enzyme is thought to be a principal receptor for the ubiquitous signalling molecule, nitric oxide (NO), forming a NO-sGC-cGMP signal transduction axis. It is believed that soluble guanylate cyclase is a heme sensor protein that selectively binds NO at the heme iron, which activates the enzyme to convert guanosine triphosphate (GTP) to cGMP. It is thought that cGMP subsequently mediates a number of important physiological processes, including smooth muscle relaxation and neurotransmission. It has been suggested that cGMP is a critical component involved in the regulation of various (patho)physiological processes, for example in cardiovascular, respiratory, gastrointestinal, urogenital, nervous and immune systems including, neuronal excitability and particularly smooth muscle tone, thereby controlling, among other things, blood pressure, gastro-intestinal motility and genital erection.

Due to its ubiquitous nature, activation of this enzyme is likely to have significant pathological implications. This is particularly true of the cardiovascular system in which dysfunction of NO-sGC-cGMP signalling is thought to be involved in diseases and conditions such as atherosclerosis, stroke and sepsis. Thus, novel drugs based on selective activation of the enzyme have the potential for therapeutic benefit.

For a review of NO-independent activation of sGC see Oleg V. Evgenov et al.; Nature Reviews, Vol. 5, September 2006, pp755-768. Reference is made therein to the compounds

BAY 58-2667 (see also WO01/19780) and HMR-1766 (see also WO00/02851) as sGC activators. The following more recent article discusses BAY 58-2667 in the context of treatment of congestive heart failure: Hypertension, 2007, 49, 1128-1133.

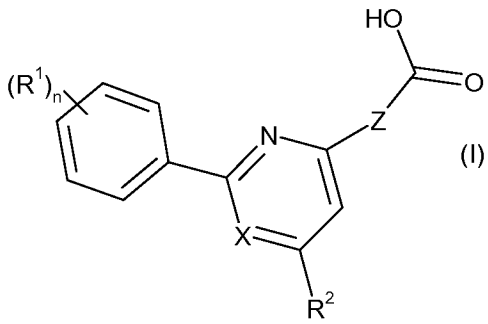
The novel compounds are activators of sGC and consequently may have application in the treatment of one or more diseases or conditions, which include: cardiovascular diseases and conditions, such as angina (including stable and unstable angina pectoris), low cardiac output, cerebral ischemia, cardiac ischemia, myocardial infarction, coronary reperfusion injury, arterial hypertension (including pulmonary arterial hypertension), congestive heart failure (for example due to systolic and/or diastolic cardiac dysfunction, low cardiac output or high systemic vascular resistance), heart failure with preserved ejection fraction, acute heart failure syndromes (AHFS), cardiac hypertrophy, acute coronary syndrome, thromboses (including arterial or venous thrombosis), atherosclerosis, peripheral vascular disease, glomerulonephritis, restenosis (for example following percutaneous vascular intervention, vascular angioplasty or stent placement), Raynaud's disease, vascular complications of diabetes or of obesity, stroke, hereditary cerebral haemorrhage, endothelial dysfunction, and other inflammatory cardiovascular disorders; erectile dysfunction; female sexual arousal disorder, respiratory failure, acute respiratory distress syndrome, gall bladder dysfunction, sickle cell disease, osteoporosis, inflammation, wound healing, chronic kidney insufficiency, renal fibrosis, renal failure, glomerulonephritis, chronic renal disease, cardiorenal syndrome, hepatorenal syndrome, liver cirrhosis, diabetes, metabolic syndrome, male pattern baldness; neuro-function disorders (including diseases or conditions displaying neuroinflammation pathology and neurodegenerative diseases, particularly chronic neurodegenerative conditions) such as Alzheimer's disease, dementia, age-related memory dysfunction, mild cognitive impairment, cognitive deficit, corticobasal degeneration, frontotemporal dementia, diffuse Lewis body type of Alzheimer's disease, and apoptotic insults caused by beta-amyloid treatment, epilepsy; pain of neuropathic origin including neuralgias, Parkinson's disease, subacute sclerosing panencephalitic Parkinsonism, postencephalitic Parkinsonism, guam Parkinsonism-dementia complex, progressive supranuclear palsy, pugilistic encephalitis, Pick's disease, Huntingdon's disease, AIDS-associated dementia; multiple sclerosis, amyotrophic lateral sclerosis; sleep disorders (including narcolepsy and sleep deficits associated with Parkinson's disease), and ALS (motor neuron disease).

Thus representative diseases and conditions for which the novel compounds may be useful include arterial hypertension (including pulmonary arterial hypertension), angina, cardiac ischemia, myocardial infarction, congestive heart failure (for example due to systolic and/or diastolic cardiac dysfunction, low cardiac output or high systemic vascular resistance), cardiac hypertrophy, acute coronary syndrome, atherosclerosis, peripheral vascular disease, cardiorenal syndrome, hepatorenal syndrome and restenosis (for example following percutaneous vascular intervention, vascular angioplasty or stent placement).

A particular disease or condition for which the novel compounds may be useful is congestive heart failure. Another particular disease or condition for which the novel compounds may be

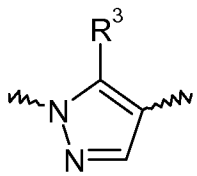
useful is peripheral vascular disease. Another particular disease or condition for which the novel compounds may be useful is arterial hypertension (also known as systemic hypertension). Another particular disease or condition for which the novel compounds may be useful is pulmonary arterial hypertension. Another particular disease or condition for which the novel compounds may be useful is angina.

According to one aspect the present invention provides a compound of formula (I)



(I)

or a salt thereof;
wherein
n represents 1 or 2;
each R^1 independently represents halo or trifluoromethyl; wherein halo represents fluoro, chloro or bromo;
R^2 represents hydrogen or C_{1-3}alkyl;
X represents N or CH;
wherein –Z– represents a group selected from:



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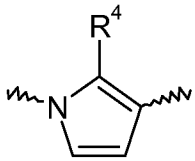
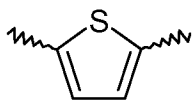


or

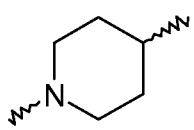


;

wherein R^3 represents trifluoromethyl or C_{1-3}alkyl; and R^4 represents hydrogen, trifluoromethyl or C_{1-3}alkyl;

with the proviso that where Z represents a thiophene group and X represents N, R^2 cannot represent C_{1-3}alkyl;

and when X represents CH, –Z– can additionally represent a group selected from:



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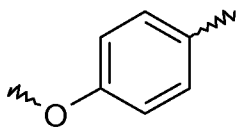

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As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C_{1-3}alkyl means a straight or branched alkyl containing at least 1, and at most 3, carbon atoms and examples include methyl, ethyl, n-propyl, and isopropyl.

In an embodiment there is provided a compound of formula (I) as defined above or a pharmaceutically acceptable salt thereof.

In an embodiment there is provided a compound of formula (I) as defined above.

In an embodiment there is provided a pharmaceutically acceptable salt of a compound of formula (I) as defined above.

As used herein, the term "pharmaceutically acceptable" means a compound which is suitable for pharmaceutical use.

In an embodiment each R^1 independently represents halo. In an embodiment n represents 2 and both R^1 groups independently represent halo. In an embodiment n represents 2 and both R^1 groups represent chloro.

In an embodiment each R^1 independently represents trifluoromethyl. In an embodiment n represents 2 and both R^1 groups represent trifluoromethyl. In an embodiment n represents 1 and the R^1 group represents trifluoromethyl.

In an embodiment the R^1 group(s) together with the phenyl ring to which they are attached represent 2,3-dichlorophenyl, 3,4-dichlorophenyl, or 3,5-dichlorophenyl.

In an embodiment the R^1 group(s) together with the phenyl ring to which they are attached represent 3,4-difluorophenyl, 3-chloro-4-fluorophenyl, or 4-bromo-3-fluorophenyl.

In an embodiment the R^1 group(s) together with the phenyl ring to which they are attached represent 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, or 3,5-bis(trifluoromethyl)phenyl.

In an embodiment the R^1 group(s) together with the phenyl ring to which they are attached represent 3,4-dichlorophenyl.

In an embodiment the R^1 group(s) together with the phenyl ring to which they are attached represent 3-trifluoromethylphenyl.

In an embodiment R^2 represents hydrogen or methyl.

In an embodiment X represents CH and R^2 represents hydrogen or methyl.

In an embodiment X represents N and R^2 represents hydrogen.

In an embodiment R^3 represents trifluoromethyl.

In an embodiment R^4 represents hydrogen or methyl.

In an embodiment Z represents the pyrazole group illustrated above. In an embodiment Z represents the pyrazole group illustrated above, X represents CH or N, R^2 represents hydrogen, R^3 represents trifluoromethyl and the R^1 group(s) together with the phenyl ring to which they are attached represent 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3,4-difluorophenyl, 3-chloro-4-fluorophenyl, 4-bromo-3-fluorophenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, or 3,5-bis(trifluoromethyl)phenyl.

In an embodiment Z represents the pyrrole group illustrated above. In an embodiment Z represents the pyrrole group illustrated above, X represents CH or N, R^2 represents hydrogen or methyl, R^4 represents hydrogen or methyl, and the R^1 group(s) together with the phenyl ring to which they are attached represent 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3,4-difluorophenyl, 3-chloro-4-fluorophenyl, 4-bromo-3-fluorophenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, or 3,5-bis(trifluoromethyl)phenyl; in an embodiment the R^1 group(s) together with the phenyl ring to which they are attached represent 3,4-dichlorophenyl.

In an embodiment Z represents the thiophene group illustrated above. In an embodiment Z represents the thiophene group illustrated above, X represents CH or N, R^2 represents hydrogen, and the R^1 group(s) together with the phenyl ring to which they are attached represent 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3,4-difluorophenyl, 3-chloro-4-fluorophenyl, 4-bromo-3-fluorophenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, or 3,5-bis(trifluoromethyl)phenyl; in an embodiment the R^1 group(s) together with the phenyl ring to which they are attached represent 3-trifluoromethylphenyl.

In an embodiment Z represents the piperidine group illustrated above. In an embodiment Z represents the piperidine group illustrated above, X represents CH, R^2 represents hydrogen, and the R^1 group(s) together with the phenyl ring to which they are attached represent 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3,4-difluorophenyl, 3-chloro-4-fluorophenyl, 4-bromo-3-fluorophenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, or 3,5-bis(trifluoromethyl)phenyl.

In an embodiment Z represents the phenoxy group illustrated above. In an embodiment Z represents the phenoxy group illustrated above, X represents CH, R^2 represents hydrogen, and the R^1 group(s) together with the phenyl ring to which they are attached represent 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3,4-difluorophenyl, 3-chloro-4-fluorophenyl, 4-bromo-3-fluorophenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, or 3,5-bis(trifluoromethyl)phenyl.

In an embodiment there is provided a compound of formula (I) as defined above selected from:
1-[6-(3,4-Dichlorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-{6-[4-(Trifluoromethyl)phenyl]-2-pyridinyl}-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-[6-(2,3-Dichlorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-{6-[3-(Trifluoromethyl)phenyl]-2-pyridinyl}-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-[6-(3,4-Difluorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-{6-[3,5-bis(Trifluoromethyl)phenyl]-2-pyridinyl}-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-[6-(3-Chloro-4-fluorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-[6-(4-Bromo-3-fluorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-[6-(3,5-Dichlorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-[6-(3,4-Dichlorophenyl)-4-methyl-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
or a salt thereof, in an embodiment a pharmaceutically acceptable salt thereof.

In an embodiment there is provided a compound of formula (I) as defined above selected from:
1-(6-(3,4-dichlorophenyl)-pyridin-2-yl)-pyrrole-3-carboxylic acid;
1-(6-(3,4-dichlorophenyl)-pyridin-2-yl)-2-methyl-pyrrole-3-carboxylic acid;
or a salt thereof, in an embodiment a pharmaceutically acceptable salt thereof.

In an embodiment there is provided a compound of formula (I) as defined above selected from:
1-(6-(3,4-dichlorophenyl)-pyridin-2-yl)-piperidine-4-carboxylic acid;
or a salt thereof, in an embodiment a pharmaceutically acceptable salt thereof.

In an embodiment there is provided a compound of formula (I) as defined above selected from:
4-(6-(3-trifluoromethylphenyl)-pyridin-2-yloxy)-benzoic acid;
or a salt thereof, in an embodiment a pharmaceutically acceptable salt thereof.

In an embodiment there is provided a compound of formula (I) as defined above selected from:
5-(6-(3-trifluoromethylphenyl)-pyridin-2-yl)-thiophene-2-carboxylic acid;
or a salt thereof, in an embodiment a pharmaceutically acceptable salt thereof.

In an embodiment there is provided a compound of formula (I) as defined above selected from:
5-(2-(3-trifluoromethylphenyl)-pyrimidin-4-yl)-thiophene-2-carboxylic acid;
1-[2-(3,4-dichlorophenyl)-4-pyrimidinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;

5-(trifluoromethyl)-1-{2-[3-(trifluoromethyl)phenyl]-4-pyrimidinyl}-1H-pyrazole-4-carboxylic acid;
or a salt thereof, in an embodiment a pharmaceutically acceptable salt thereof.

To the extent that certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms), the individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. Similarly the invention also extends to conformational isomers of compounds of formula (I) and any geometric (*cis* and/or *trans*) isomers of said compounds. Likewise, it is understood that if the compounds of formula (I) may exist in tautomeric forms other than that shown above, then these tautomers are also included within the scope of the present invention.

Salts of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion is pharmaceutically acceptable. However, salts having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts.

Solvates of the compounds of formula (I) and solvates of the salts of the compounds of formula (I) are included within the scope of the present invention. As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Those skilled in the art of organic chemistry will appreciate that many organic compounds can form such complexes with solvents in which they are reacted or from which they are precipitated or crystallized. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water. Where the solvent used is water such a solvate may then also be referred to as a hydrate.

Because of their potential use in medicine, in one embodiment the salts of the compounds of formula (I) will be pharmaceutically acceptable. Reference is made to Berge et al. J. Pharm. Sci., 1977, 66, 1-19, which is incorporated herein by reference. Also included within the scope of the invention are solvates (including hydrates) of salts of the compounds of formula (I). The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of formula (I).

Typically, a salt may be readily prepared by using a desired acid or base as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

Suitable pharmaceutically acceptable salts can include acid addition salts or base addition salts and will be apparent to those skilled in the art. A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic acid such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric or phosphoric acid; or with a suitable organic acid such as succinic, maleic, malic, mandelic, formic, acetic, propionic, hexanoic, fumaric, glutamic, lactic, citric, tartaric, benzoic, salicylic, aspartic, benzenesulfonic, p-toluenesulfonic, methanesulfonic, ethanesulfonic or naphthalenesulfonic acid. Other non-pharmaceutically acceptable salts such as oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. A pharmaceutically acceptable base addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic base, including salts of primary, secondary and tertiary amines, such as ammonia, isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexyl amine, N-methyl-D-glucamine triethylamine, triethanolamine, choline, arginine, lysine or histidine. Other suitable pharmaceutically acceptable salts include pharmaceutically acceptable metal salts, for example pharmaceutically acceptable alkali-metal or alkaline-earth-metal salts such as sodium, potassium, calcium or magnesium salts; in particular pharmaceutically acceptable metal salts of the carboxylic acid moiety that is present in the compound of formula (I). Since the compounds of formula (I) include a carboxylic acid moiety together with one or more basic nitrogen atom(s) they have the possibility to also form internal salts (including zwitterionic salts), which salts are also included within the scope of the present invention.

It will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula (I), which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form a compounds of formula (I) which is pharmacologically active. Such derivatives may therefore be described as “prodrugs”. All such prodrugs of compounds of formula (I) are included within the scope of the invention. Examples of pro-drug functionality suitable for the compounds of the present invention are described in Drugs of Today, Volume 19, Number 9, 1983, pp 499 – 538 and in Topics in Chemistry, Chapter 31, pp 306 – 316 and in “Design of Prodrugs” by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference). In particular the carboxylic acid function attached to the group Y may be a suitable candidate for pro-drug functionality, for example by formation of appropriate esters or amides. It will further be appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as “pro-moieties”, for example as described by H. Bundgaard in “Design of Prodrugs” (the disclosure in which document is incorporated herein by reference) may be placed on appropriate functionalities when such functionalities are present within compounds of formula (I).

Hereinafter, a compound of formula (I) (whether in solvated or unsolvated form) or a pharmaceutically acceptable salt thereof (whether in solvated or unsolvated form) defined in

any aspect of the invention (except intermediate compounds in chemical processes) are referred to as "a compound of the invention".

Also included within the scope of the invention are alternative crystalline or non-crystalline forms, including polymorphic forms, of a compound of formula (I) or a salt thereof.

The invention also includes all suitable isotopic variations of a compound of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine and chlorine such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Certain isotopic variations of the invention, for example, those in which a radioactive isotope such as ^{3}H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e., ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the compounds of the invention can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Examples hereafter using appropriate isotopic variations of suitable reagents.

As discussed above, it is believed that a compound of the invention, as an activator of sGC, may be useful in the treatment of a disease or condition which is mediated by sGC activity.

According to a further aspect, the invention provides a pharmaceutical composition comprising a compound of the invention, together with one or more pharmaceutically acceptable carrier(s), diluents(s) and/or excipient(s). The carrier(s), diluent(s) and/or excipient(s) must each be “acceptable” in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

According to a further aspect there is provided a pharmaceutical composition comprising a) 0.1 mg to 1000 mg of a compound of the invention and b) 0.1g to 2g of one or more pharmaceutically acceptable carrier(s), diluents(s) and/or excipient(s).

According to a further aspect the invention provides a compound of the invention as defined above for use in therapy; in an embodiment the therapy is human therapy.

According to a further aspect, the invention provides a pharmaceutical composition as defined above for use in therapy; in an embodiment the therapy is human therapy.

According to a further aspect the invention provides a compound of the invention or a pharmaceutical composition as defined above for use in the treatment of a disease or condition mediated by sGC activity.

According to a further aspect the invention provides a compound of the invention or a pharmaceutical composition comprising a compound of the invention for use in the treatment of arterial hypertension, pulmonary arterial hypertension, angina, cardiac ischemia, myocardial infarction, congestive heart failure, cardiac hypertrophy, acute coronary syndrome, atherosclerosis, peripheral vascular disease, cardiorenal syndrome, hepatorenal syndrome or restenosis.

According to a further aspect the invention provides a compound of the invention or a pharmaceutical composition as defined above for use in the treatment of arterial hypertension, pulmonary arterial hypertension, angina, congestive heart failure or peripheral vascular disease.

According to a further aspect the invention provides the use of a compound of the invention for the preparation of a medicament for treating a disease or condition mediated by sGC activity.

According to a further aspect the invention provides the use of a compound of the invention for the preparation of a medicament for the treatment of arterial hypertension, pulmonary arterial hypertension, angina, cardiac ischemia, myocardial infarction, congestive heart failure, cardiac hypertrophy, acute coronary syndrome, atherosclerosis, peripheral vascular disease, cardiorenal syndrome, hepatorenal syndrome or restenosis.

According to a further aspect the invention provides the use of a compound of the invention for the preparation of a medicament for the treatment of arterial hypertension, pulmonary arterial hypertension, angina, congestive heart failure or peripheral vascular disease.

According to a further aspect the invention provides a method of treatment of a disease or condition which is mediated by the activity of sGC, in an embodiment arterial hypertension, pulmonary arterial hypertension, angina, cardiac ischemia, myocardial infarction, congestive heart failure, cardiac hypertrophy, acute coronary syndrome, atherosclerosis, peripheral vascular disease, cardiorenal syndrome, hepatorenal syndrome or restenosis, comprising administration to a human subject in need of such treatment of a therapeutically effective amount of a compound of the invention, or of a pharmaceutical composition as defined above.

According to a further aspect the invention provides a method of treatment of arterial hypertension, pulmonary arterial hypertension, angina, congestive heart failure or peripheral vascular disease comprising administration to a human subject in need of such treatment of

a therapeutically effective amount of a compound of the invention, or of a pharmaceutical composition comprising a compound of the invention.

A compound of the invention may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of the invention or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent.

When a compound of the invention or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone.

The compounds of the present invention may for example be used in combination with antihypertensive drugs such as diuretics (for example epitizide, bendroflumethiazide, chlortalidone, chlorthiazide, hydrochlorthiazide, indapamide, metolazone), ACE inhibitors (such as benzapril, captopril, enalapril, fosinopril, lisinopril, preindopril, quinapril, ramipril, trandopril), angiotensin receptor blockers (such as candesartan, irbesartan, losartan, telmisartan, valsartan), calcium channel inhibitors (such as amlodipine, felodipine, isradapine, nifedipine, niimodipine, nitrendipine, diltiazem, verapamil), α-adrenergic receptor antagonists (such as doxazosin, prazosin, terazosin, phentolamine, indoramin, phenoxybenzamine, tolazoline), β-adrenergic receptor antagonists (such as atenolol, metoprolol, nadolol, oxprenolol, pindolol, propanolol, timolol), mixed α/β-adrenergic receptor antagonists (such as bucindalol, carvedilol, labetolol) or may be used in combination with PDE5 inhibitors (such as sildenafil, tadalafil, vardenafil), or may be used in combination with cholesterol-lowering or lipid-lowering drugs, for example statins (such as atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin), fibrates (such as bezafibrate, ciprofibrate, gemfibrozil, fenofibrate), or nicotinic acid.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations by any convenient route.

When administration is sequential, either the compound of the invention or the second therapeutic agent may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition.

When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation.

When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

It will be appreciated that references herein to "treat", "treating" or "treatment" extend to prevention of recurrence of symptoms (whether mild, moderate or severe) and to suppression or amelioration of symptoms (whether mild, moderate or severe) as well as the treatment of established conditions.

The compound of the invention may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

The compound of the invention may be administered in conventional dosage forms prepared by combining a compound of the invention with one or more standard pharmaceutical excipients, carriers or diluents, according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate for the desired preparation.

The pharmaceutical compositions of the invention may be formulated for administration by any route, and include those in a form adapted for oral, topical or parenteral administration to mammals including humans.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatine, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other

suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatine, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories typically contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilising the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter-sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilised powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The pharmaceutical compositions of the invention may be formulated, for administration to mammals including humans, by any route, and include those in a form adapted for oral, topical or parenteral administration. The compositions may, for example, be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

Thus in one aspect the invention provides a pharmaceutical composition for oral administration such as an oral suspension or liquid, for example an aqueous based fluid formulation, or a solid dosage formulation such as a tablet or capsule.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

It will be recognised by one of skill in the art that the optimal quantity and spacing of individual doses of a compound of the invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e. the number of doses of a compound of the invention given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

Each dosage unit for oral administration typically contains for example from 0.5 to 250 mg (and for parenteral administration contains for example from 0.05 to 25 mg) of a compound of the invention calculated as the compound of formula (I).

A compound of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 1000 mg, for example between 1 mg and 500 mg, e.g. between 5 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, for example between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of formula (I) or a salt thereof calculated as the compound of formula (I), the compound of the invention being administered 1 to 4 times per day, for example 1 to 2 times a day. In one embodiment, a compound of the invention may be administered once a day.

Suitably a compound of the invention will be administered for a period of continuous therapy, for example for a week or more.

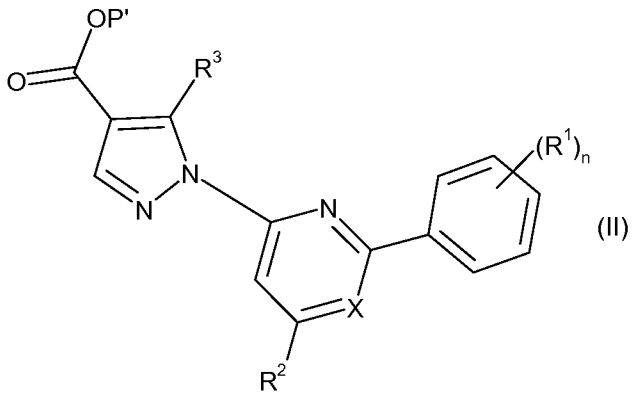
Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each suitably provided in substantially pure form, for example at least 60% pure, for example at least 75% pure, for example at least 85%, for example at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds typically contain at least 1%, for example at least 5%, for example from 10 to 59% of a compound of the invention.

Compounds of the invention may be prepared in a variety of ways. These processes form further aspects of the present invention.

Throughout the specification, general formulae are designated by Roman numerals (I), (II), (III), (IV) etc.

It will be appreciated that all novel intermediates used to prepare a compound of the invention form yet a further aspect of the present invention.

Compounds of formula (IA) wherein Z represents the pyrazole group as defined above can be prepared by deprotection of a compound of formula (II)



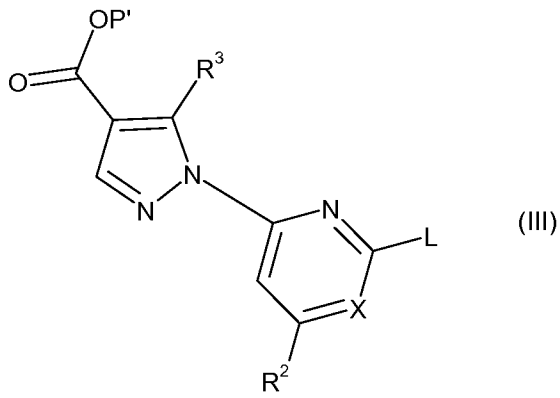
(II)

wherein

R^1, R^2, R^3, X, and n are as defined above and P' represents a carboxylic acid protecting group, for example C_{1-6} alkyl or benzyl, such that together with the carboxylic acid residue an ester is formed.

Suitable protecting groups and deprotection methods are, for example given in T. W. Greene, 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Alkyl ester carboxylic acid protection can be removed, for example, by treatment with mineral base such a potassium hydroxide at an elevated temperature such as reflux in a suitable solvent, for example an alcohol such as ethanol.

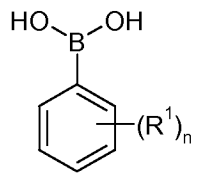
Compounds of formula (II) may be prepared by reaction of a compound of formula (III)



(III)

wherein

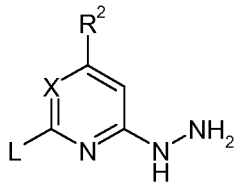
R^2, R^3, X and P' are as defined above and L is halo, such as chlorine or bromine, with a compound of formula (IV)


(IV)

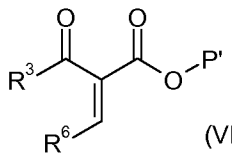
wherein R^1 and n are as defined above.

The reaction is typically carried out under nitrogen in a suitable solvent, such as dioxan and water, in the presence of a base, such as sodium carbonate, and a suitable catalyst, such as tetrakis(triphenylphosphine)palladium(0) or trans dichloro(tricyclohexylphosphine)palladium(II) at elevated temperature, suitably 100°C.

Compounds of formula (III) may be prepared by reaction of a compound of formula (V),


(V)

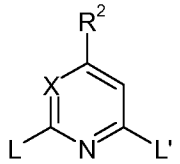
wherein R^2, X and L are as defined above, with a compound of formula (VI)


(VI)

wherein
R^3 and P' are as defined above and R^6 is C_{1-6} alkyl.

The reaction is typically carried out by adding a solution of compound (VI) in a suitable solvent (for example anhydrous tetrahydrofuran; adding dropwise under nitrogen at -15°C) to a solution of compound (V) in a suitable solvent (for example anhydrous tetrahydrofuran) followed by stirring at room temperature, suitably for between 4 to 24 hours.

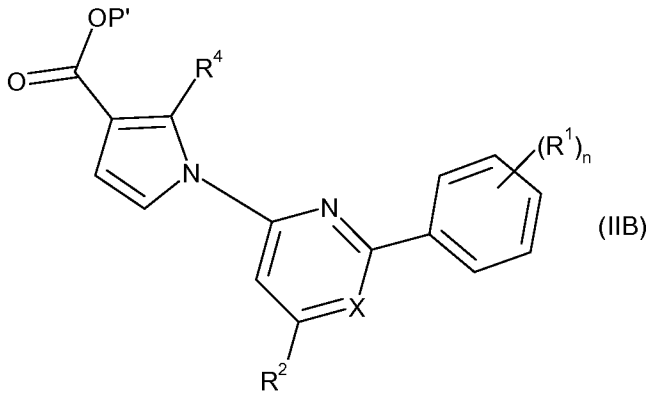
Compounds of formula (V) are either commercially available or are prepared from compounds of formula (VII)


(VII)

wherein R^2, X and L are as defined above and L' is a halogen atom, such as chlorine or bromine.

Compounds of formula (IV), formula (VII) and formula (VI) are either commercially available or can be readily prepared using known methodology.

Compounds of formula (IB) wherein Z represents the pyrrole group as defined above can be prepared by deprotection of a compound of formula (IIB) (similarly to that described previously for the compound of formula (II)):

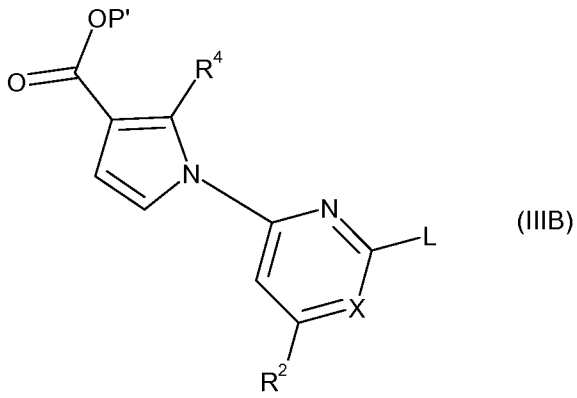


(IIB)

wherein

R^1, R^2, R^4, X, and n are as defined above and P' represents a carboxylic acid protecting group, for example C_{1-6} alkyl or benzyl, such that together with the carboxylic acid residue an ester is formed.

Compounds of formula (IIB) may be prepared by reaction of a compound of formula (IIIB)



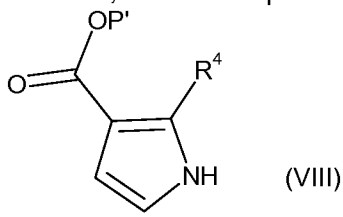
(IIIB)

wherein

R^2, R^4, X and P' are as defined above and L is halo, such as chlorine or bromine, with a compound of formula (VIII) wherein R^4 is defined above.

The reaction is typically carried out under nitrogen in a suitable solvent, such as dioxane and water, in the presence of a base, such as tripotasium phosphate or sodium carbonate, and a suitable catalyst, such as [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) or tetrakis(triphenylphosphine)palladium(0) at elevated temperature, suitably 100°C up to 150°C.

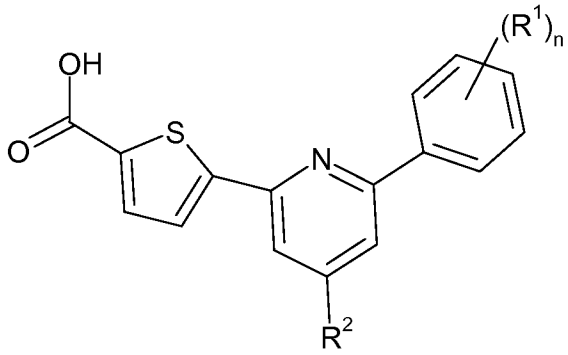
Compounds of formula (IIIB) may be prepared by reaction of a compound of formula (VII), wherein R^2, X and L are as defined above and L' is a halogen atom, such as chlorine or bromine, with a compound of formula (VIII) wherein R^4 and P' are as defined above.



(VIII)

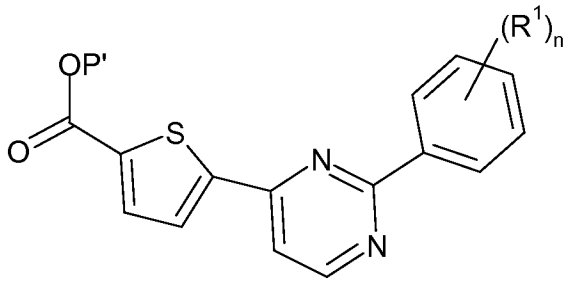
The reaction is typically carried out in a suitable solvent, such as DMF, in the presence of a base, such as sodium carbonate or cesium carbonate, at elevated temperature, suitably 100°C up to 130°C.

Compounds of formula (IC) wherein Z represents the thiophene group and X represents CH as defined above can be prepared by reaction of 5-carboxy-thiophene-2-boronic acid with a compound of formula (IIIC). The reaction is typically carried out under nitrogen in a suitable solvent, such as dimethoxyethane and water, in the presence of a base, such as sodium carbonate and a suitable catalyst, such as tetrakis(triphenylphosphine) palladium(0) at elevated temperature, suitably 100°C.



(IC)

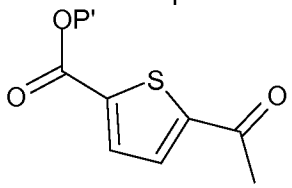
Compounds of formula (ID) wherein Z represents the thiophene group, X is N and R^2 is H can be prepared by deprotection of a compound of formula (IID)



(IID)

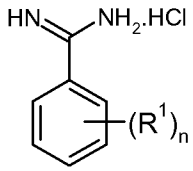
wherein R^1 and n are as defined above and P' represents a carboxylic acid protecting group, for example C_{1-6} alkyl, such that together with the carboxylic acid residue an ester is formed.

Compounds of formula (IID) may be prepared by reaction of compounds of formula (IX), wherein P' represents a carboxylic acid protecting group, for example C_{1-6} alkyl,



(IX)

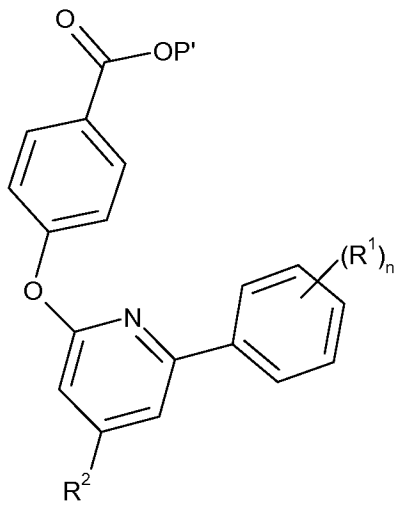
with a compound of formula (X), wherein R^1 and n are as defined above.



(X)

Compounds of formula (IX) are first treated with dimethylformamide dimethylacetal at 100°C, the resulting enaminone was then reacted with compounds of formula (X) in a suitable solvent, such as ethanol, in the presence of sodium ethylate at elevated temperature, suitably 80°C.

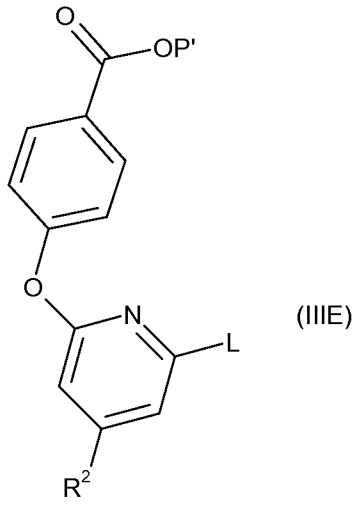
Compounds of formula (IE) wherein Z represents the phenoxy group as defined above can be prepared by deprotection of a compound of formula (IIE) (similarly to that described previously for the compound of formula (II)):



(IIE)

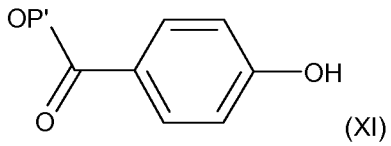
wherein R^1, R^2, X, and n are as defined above and P' represents a carboxylic acid protecting group, for example C_{1-6} alkyl or benzyl, such that together with the carboxylic acid residue an ester is formed.

Compounds of formula (IIE) may be prepared by reaction of a compound of formula (IIIE), wherein R^2, X and L are as defined above and L is a halogen atom, such as chlorine or bromine, with a compound of formula (IV) wherein R^1 and n are as defined above.



(IIIE)

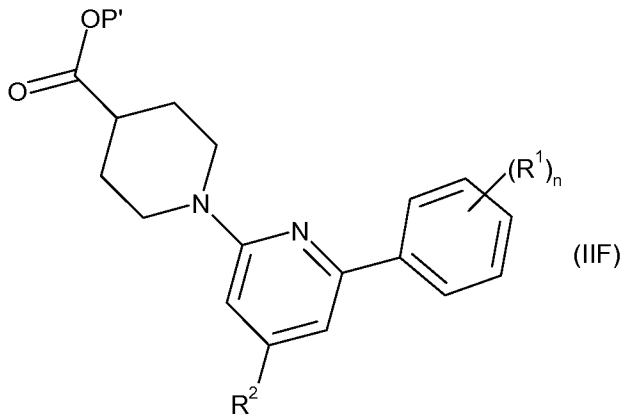
Compounds of formula (IIIE) may be prepared by reaction of a compound of formula (XI), wherein P' is defined above, with a compound of formula (VII) wherein R^2, X and L are as defined above and L' is a halogen atom, such as chlorine or bromine.



(XI)

The reaction is typically carried out in a suitable solvent, such as dimethylformamide, in the presence of a base, such as cesium carbonate, at elevated temperature, suitably 120°C.

Compounds of formula (IF) wherein X represents CH and Z represents the piperidinyl group as defined above can be prepared by deprotection of a compound of formula (IIF) (similarly to that described previously for the compound of formula (II)):

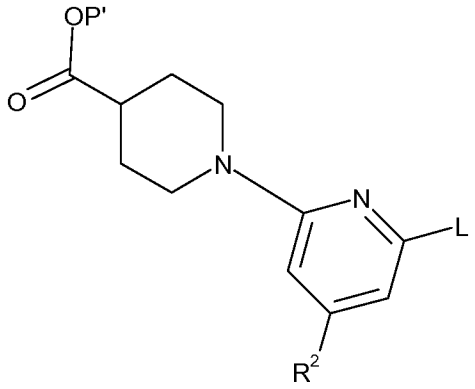


(IIF)

wherein

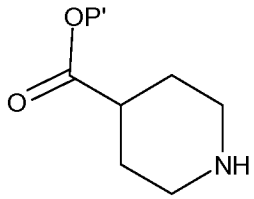
R^1, R^2 and n are as defined above, and P' represents a carboxylic acid protecting group, for example C_{1-6} alkyl or benzyl, such that together with the carboxylic acid residue an ester is formed.

Compounds of formula (IIF) can be prepared by reaction of compounds of formula (IIIF) wherein R^2, L and P' are defined above, with a compound of formula (IV) wherein R^1 and n are as defined above.



(IIIF)

Compounds of formula (IIIF) may be prepared by reaction of a compound of formula (XIII), wherein P' is defined above, with a compound of formula (VII) wherein X represents CH, and wherein R^2 and L are as defined above and L' is a halogen atom, such as chlorine or bromine.



(XIII)

The reaction is typically carried out in a suitable solvent, such as DMF, in the presence of a base, such as sodium carbonate or cesium carbonate, at elevated temperature, suitably 100°C up to 130°C.

Supporting Examples and Descriptions

The invention is illustrated by the Examples described below.

In the procedures that follow, after each starting material, reference to a Description by number is typically provided. This is provided merely for assistance to the skilled chemist. The starting material may not necessarily have been prepared from the batch referred to.

Where reference is made to the use of a "similar" procedure, as will be appreciated by those skilled in the art, such a procedure may involve variations known to those skilled in the art, for example reaction temperature, reagent/solvent amount, reaction time, work-up conditions or chromatographic purification conditions.

Compounds are named using ACD/Name PRO 6.02 chemical naming software (Advanced Chemistry Development Inc., Toronto, Ontario, M5H2L3, Canada).

LCMS (Liquid Chromatography Mass Spectroscopy)

Method A: LCMS was conducted using a Waters ZQ mass spectrometer operating in positive ion or negative ion electrospray mode, mass range 100-1000 amu. UV wavelength: 215-330nm; column: 3.3cm x 4.6mm ID, 3μm ABZ+PLUS; flow rate: 3ml/min; injection volume: 5μl. Solvent A: 95% acetonitrile + 5% of a 1% v/v solution of formic acid in water. Solvent B: 0.1% v/v solution of formic acid in 10mM aqueous ammonium acetate. Gradient: mixtures of Solvent A and Solvent B are used according to the following gradient profiles (expressed as % Solvent A in the mixture): 0% A/0.7min, 0-100% A/3.5min, 100% A/1.1min, 100-0% A/0.2min.

For mass directed automated preparation, the preparative column used was typically a Supelcosil ABZplus (10cm x 2.12cm internal diameter; particle size 5μm); UV detection wavelength: 200-320nm; flow rate: 20ml/min; injection volume: 0.5ml. Solvent A: 0.1% v/v solution of formic acid in water. Solvent B: 95% acetonitrile + 5% of a 1% v/v solution of formic acid in water

Method B : the mass spectra (MS) were recorded on a micromass ZQ-LC mass spectrometer using electrospray positive ionisation [ES+ve to give MH^+ molecular ion] or electrospray negative ionisation [ES-ve to give $(M-H)^-$ molecular ion] modes.
Analytical HPLC was conducted on a X-terra MS C18 column (3 x 30 mm internal diameter, particule size 2,5 μm), eluting with 0,01M ammonium acetate in water (solvent A) and 100% acetonitrile using the following elution gradient: 0-4 minutes, 5 to 100% B; 4-5 minutes, 100%B at a flow rate of 1,1 mL/min at 40°C.

LC-HRMS (Liquid Chromatography - High-resolution mass spectroscopy)
Analytical HPLC was conducted on a LUNA 3u C18 column (30 x 3 mm internal diameter, particule size 2,5 μm). eluting with 0,01M ammonium acetate in water (solvent A) and 100% acetonitrile (solvent B) using the following elution gradient: 0-0,5 minutes, 5%B; 0,5-3,5 minutes, 5 to 100%B; 3,5-4 minutes, 100%B; 4-4,5 minutes, 100 to 5%B; 4,5-5,5 minutes, 5%B at a flowrate of 1,3 mL/min with a temperature of 40°C.

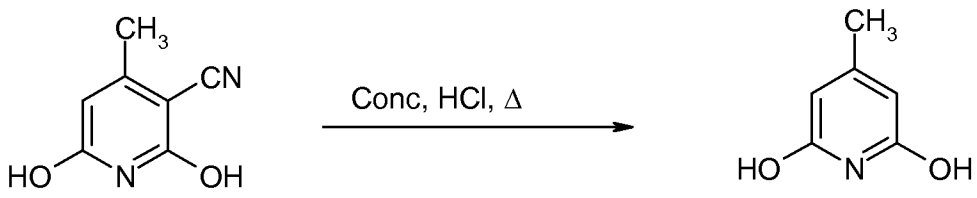
The mass spectra (MS) were recorded on a micromass LCT, mass spectrometer using electrospray positive ionisation [ES+ve to give MH^+ molecular ion] or electrospray negative ionisation [ES-ve to give $(M-H)^-$ molecular ion] modes.

Proton Magnetic Resonance (^1H NMR) spectra were recorded using a Brucker DPX 400MHz spectrometer. Chemical shifts are reported in ppm (δ) using tetramethylsilane as the internal standard. Splitting patterns are designed as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

The following table lists the used abbreviations:

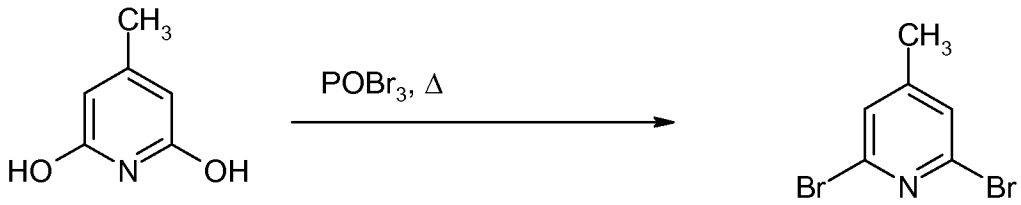
Abbreviation	Meaning
LCMS	Liquid chromatography mass spectroscopy
Rt	Retention time
$CDCl_3$	Deuterated chloroform
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
Cs_2CO_3	Cesium carbonate
DME	1,2-dimethoxyethane
DMF	Dimethylformamide
DMF.DMA	N,N-dimethylformamide dimethylacetal
DMSO d6	Deuterated dimethylsulfoxide
DIPEA	N,N'-Diisopropylethylamine
EDTA	Ethylenediaminetetraacetic acid
EtOH	Ethanol
EtOAc	Ethyl acetate
EtONa	Sodium ethylate
c-Hex	cyclohexane
i-PrO2	diisopropylether
$MgSO_4$	Magnesium sulfate
Na_2CO_3	sodium carbonate
Na_2SO_4	Sodium sulfate
NaOH	sodium hydroxide
$Pd(PPh_3)_4$	Palladium tetrakis(triphenylphosphine)
$PdCl_2(dppf)$	[1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium (II)

Description 1: 6-Hydroxy-4-methyl-2(1*H*)-pyridinone hydrochloride (D1)



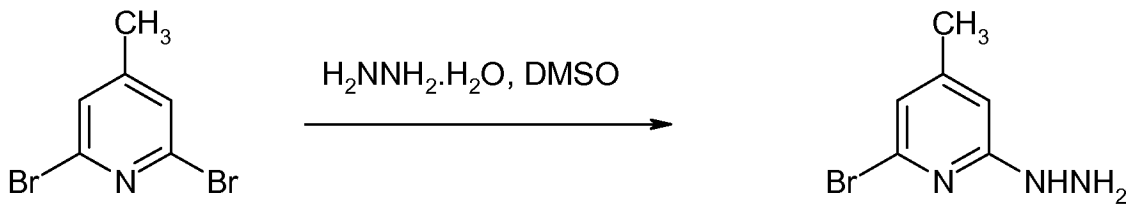
6-Hydroxy-4-methyl-2-oxo-1,2-dihydro-3-pyridinecarbonitrile (Aldrich, 5g, 33.31mmol) was stirred and heated under reflux in concentrated hydrochloric acid (60ml) for 5 days. A further quantity (150ml) of acid was added and heating was continued for a further 7 days. The mixture was evaporated to give the title compound (8.287g) as a pale brown solid. LCMS (method A): single peak, Rt = 0.75mins; MH^+ 126 (free base).

Description 2: 2, 6-Dibromo-4-methylpyridine (D2)



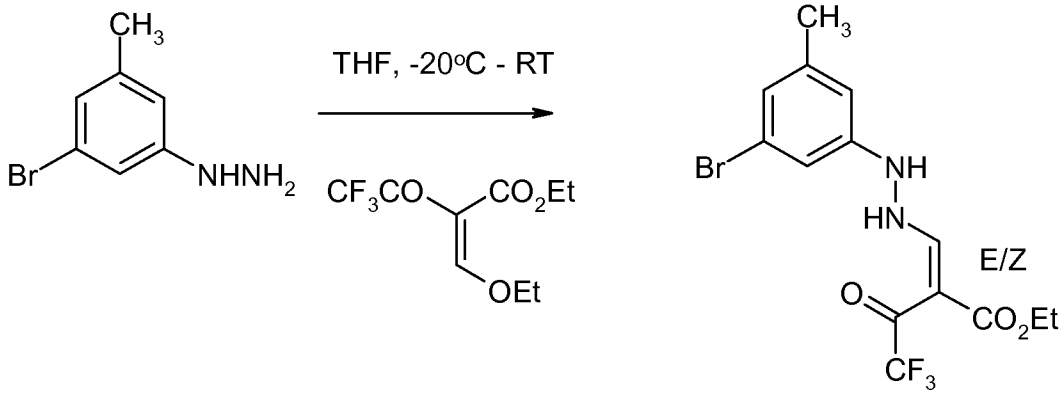
6-Hydroxy-4-methyl-2-oxo-1,2-dihydro-3-pyridinecarbonitrile hydrochloride (D1, 5g, 30.94mmol) and phosphorus oxybromide (25g, 87.2mmol) were heated together at 130°C for 6 hours. The mixture was cooled in ice and water was added cautiously and the mixture was then basified with 2M sodium hydroxide solution and extracted with dichloromethane. The organic phase was separated and evaporated to give a pale brown solid. This was purified by silica gel chromatography (CombiFlash Companion, Redisep 80g silica gel column) eluting with cyclohexane-dichloromethane mixtures (100%-70% cyclohexane). Fractions which contained the major component were combined and evaporated to give the title compound (1.279g, 16%) as a colourless solid. LCMS (method A): single peak, Rt = 3.09mins; MH^+ 250, 252, 254.

Description 3: 2-Bromo-6-hydrazino-4-methylpyridine (D3)



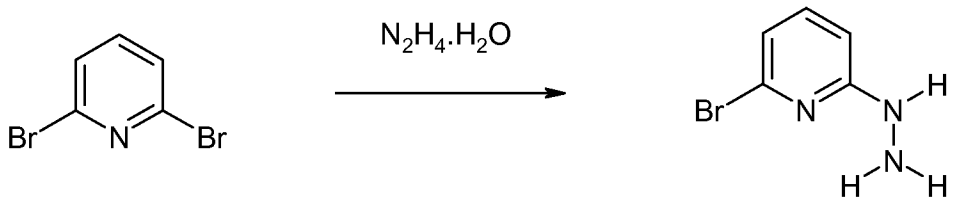
2,6-Dibromo-4-methylpyridine (D2, 1.279g, 5.098mmol) was dissolved in anhydrous dimethylsulfoxide (12ml) and stirred at room temperature. Hydrazine monohydrate (0.99ml, 20.39mmol, 4eq.) was added slowly and the mixture was then stirred at room temperature for 3 hours and then at 120°C for 18 hours. The mixture was cooled to room temperature and poured into water and the resulting precipitate was collected by filtration, washed with water and dried to give the title compound (881mg, 85%) as a beige coloured solid. LCMS (method A): major peak, Rt = 1.60mins; MH^+ 202, 204.

Description 4: Ethyl (2*E/Z*)-3-[2-(6-bromo-4-methyl-2-pyridinyl)hydrazino]-2-(trifluoroacetyl)-2-propenoate (D4)



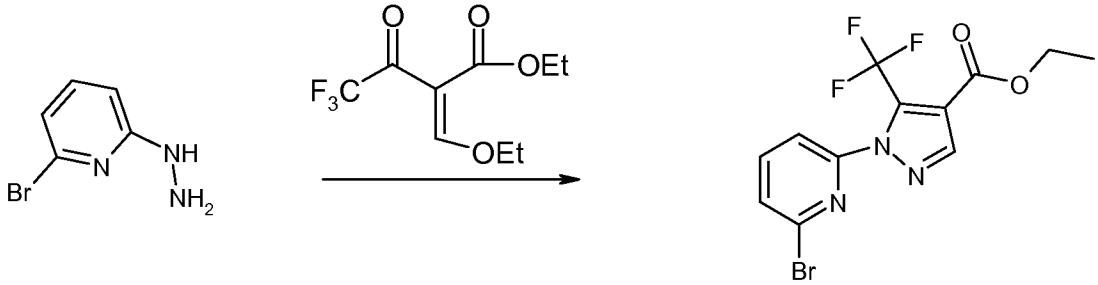
A solution of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutyrate (Aldrich, 1.047g, 4.36mmol, 0.85ml) in anhydrous tetrahydrofuran (11ml) was added dropwise, under nitrogen, to a stirred solution of 6-bromo-4-methyl-2(1H)-pyridinone hydrazone (D3, 881mg, 4.36mmol) at -15°C. When the addition was complete the solution was allowed to attain room temperature and stirred for 4 hours. The mixture was evaporated under reduced pressure to give the title compound as an orange-brown oil. LCMS (method A): 2 peaks, Rt = 3.51mins and 3.54mins; MH^+ 396, 398 (1st peak), MH^+ 396, 398 (2nd peak).

Description 5: 2-Bromo-6-hydrazinopyridine (D5)



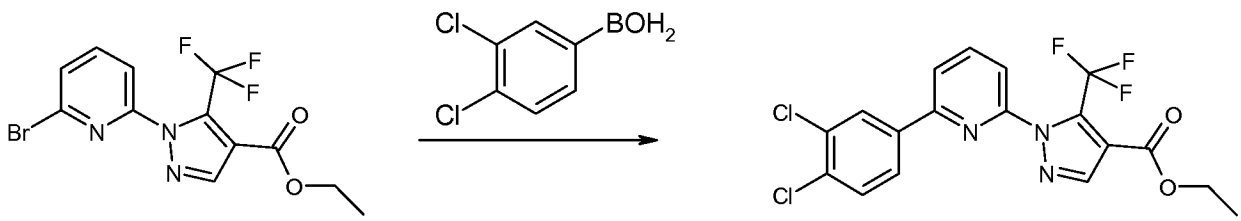
A mixture of 2,6-dibromopyridine (Aldrich; 2.37g, 0.01 mol) and hydrazine hydrate (0.53 ml) in ethanol (50 ml) was heated at 80°C for 2 hours. A further portion of hydrazine hydrate (2.65 ml) was added and the mixture was heated under reflux for 4 days. The reaction was evaporated to give a cream solid. This was purified by chromatography on silica (isolute 50g) using dichloromethane-ethanol-ammonia (300:8:1) as eluant. Appropriate eluates were collected and evaporated to a pale cream solid. Crystallisation from ethyl acetate-cyclohexane gave the title compound as a white fluffy solid (1.5g, 80%). LCMS (method A): Rt = 0.68 mins; MH^+ 188, 190

Description 6: Ethyl 1-(6-bromo-2-pyridinyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (D6)



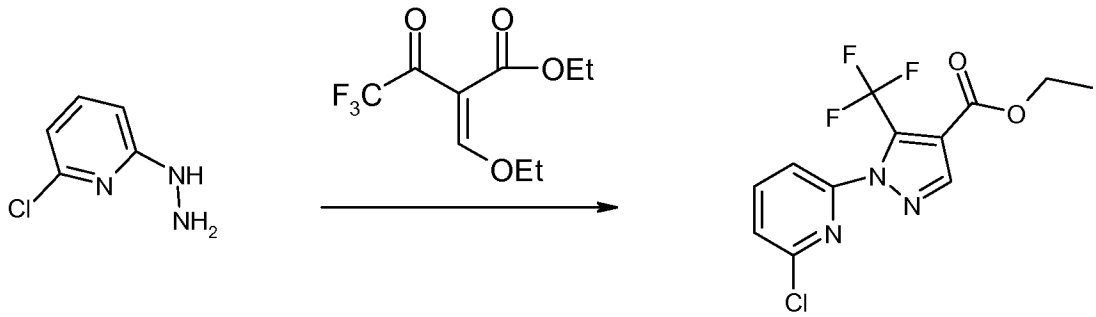
Ethyl (2Z)-3-(ethyloxy)-2-(trifluoroacetyl)-2-propenoate (Aldrich, 1.32g, 0.0055 mol) was added in a solution of ethanol (25 ml) to a solution of 2-bromo-6-hydrazinopyridine (D5, 0.94g, 0.005 mol) in ethanol (25 ml) containing diisopropylethylamine (0.92 ml, 0.0055 mol) at -20°C over a 30 minute period. The solution was allowed to slowly warm to room temperature and stirred for a further 2 hours. The orange solution was evaporated to an orange-red gum. This was purified by chromatography on silica (50g; Isolute cartridge) using dichloromethane-ethanol-ammonia (1000:8:1) as eluant. Appropriate eluates were collected and evaporated to yield the product as a pale yellow oil (1.35g, 74%). This solidified on standing. LCMS (method A): single Peak, Rt = 3.41 mins; MH^+ 364, 366.

Description 7: Ethyl 1-[6-(3,4-dichlorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (D7)



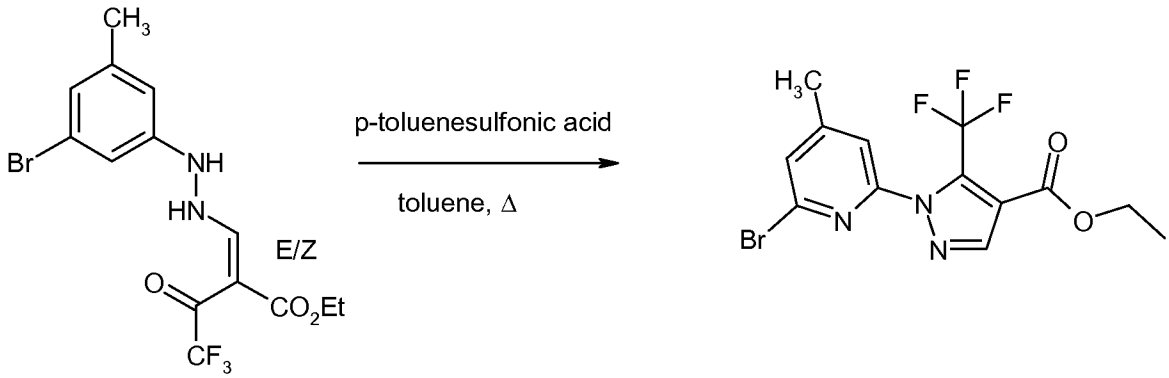
A mixture of ethyl 1-(6-bromo-2-pyridinyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (D6, 0.364g, 0.001 mol), 3,4-dichlorophenyl boronic acid (0.209g, 0.0011 mol), sodium carbonate (0.106g, 0.001 mol) and tetrakis triphenylphosphine palladium (0.057g, 0.00005 mol) in degassed dioxan (10 ml) and water (10 ml) was heated at 100°C for 2 hrs. The dark mixture was poured into ethyl acetate (50 ml) and brine (50 ml). The organic phase was dried (Na_2SO_4) and evaporated to a yellow-brown gum. This was purified on silica (50g; Isolute cartridge) using dichloromethane-ethanol-ammonia (1000:8:1) as eluant. Appropriate eluates were collected and evaporated to yield the title compound as a white solid (0.42g, 97%). LCMS (method A): Rt= 4.13 mins; MH^+ 430, 432, 434.

Description 8: Ethyl 1-(6-chloro-2-pyridinyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (D8)



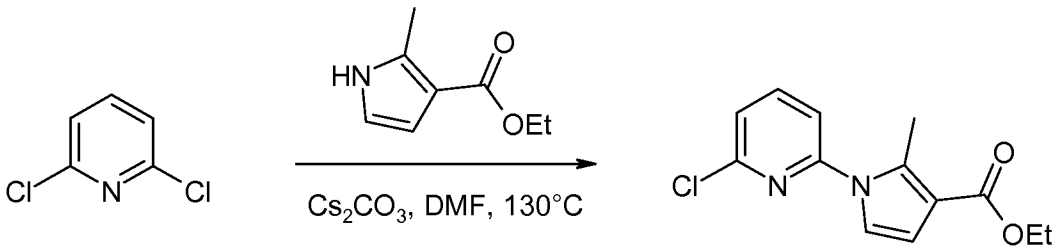
A solution of Ethyl (2*Z*)-3-(ethyloxy)-2-(trifluoroacetyl)-2-propenoate (Aldrich,1.2g, 0.005 mol) in dry tetrahydrofuran (10ml) was added to a solution of 2-chloro-6-hydrazinopyridine (Bionet Research Intermediates, 0.715g, 0.005 mol) in dry tetrahydrofuran (10ml) at -20°C over 15 minutes. When the addition was complete, the solution was allowed to slowly warm to room temperature. After 2 hours, the solution was evaporated and the residue was purified by chromatography on silica (50g; Isolute cartridge) using dichloromethane-ethanol-ammonia (1000:8:1) as eluant. Appropriate eluates were collected and evaporated to give a pale-yellow oil (1.35g, 85%). Crystallisation from 40-60 petrol gave the title compound as a white powder (1.1g). LCMS (method A): single peak, Rt = 3.38 mins; MH^+ 320, 322.

Description 9: Ethyl 1-(6-bromo-4-methyl-2-pyridinyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (D9)



Ethyl (2*E/Z*)-3-[2-(6-bromo-4-methyl-2-pyridinyl)hydrazino]-2-(trifluoroacetyl)-2-propenoate (D4, 1.611g, 4.066mmol) and p-tolenesulfonic acid monohydrate (30mg) were stirred and heated under reflux in anhydrous toluene (20ml) for 18 hours. The mixture was diluted with toluene and poured into saturated sodium hydrogen carbonate solution and the mixture stirred. The organic phase was separated, dried ($MgSO_4$) and evaporated to give the title compound (1.225g) as a brown oil. LCMS (method A): single peak, Rt = 3.49 mins; MH^+ 378, 380.

Description 10: Ethyl 1-(6-chloropyridin-2-yl)-2-methyl-pyrrole-3-carboxylate (D10)

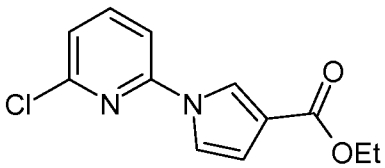


To a solution of 2,6-dichloropyridine (Aldrich, 1.257g, 8.5 mmol) in DMF (50ml) was added cesium carbonate (2.34g, 7.18 mmol) and then ethyl 2-methyl-pyrrole-3-carboxylate (1g, 6.53 mmol). The mixture was heated at 130°C for 24 hours , then cooled and poured into water. After extraction with CH_2Cl_2, the organic phase was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/cHex, 3/2 then 4/1) to give the titled compound as a colorless oil which crystallised (0.55g, 31.8%); LC/MS (method B): Rt= 3.30 min; MH+ 265.1.

H^1 NMR (300MHz, $CDCl_3$, ppm): 7.8 (t, 1H), 7.35 (d, 1H), 7.25 (d, 1H), 6.95 (d, 1H), 6.7 (d, 1H), 4.3 (q, 2H), 2.7 (s, 3H), 1.4 (t, 3H).

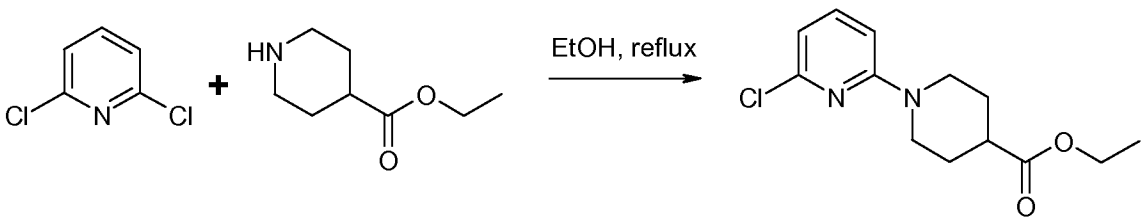
Using a similar procedure to that of Description 10, the following compound was prepared:

Description 11: Ethyl 1-(6-chloropyridin-2-yl)-pyrrole-3-carboxylate (D11)



H^1 NMR (300MHz, $CDCl_3$, ppm): 8.1 (s, 1H), 7.75 (t, 1H), 7.45 (d, 1H), 7.3 (d, 1H), 7.2 (d, 1H), 6.75 (d, 1H), 4.35 (q, 2H), 1.4 (t, 3H)

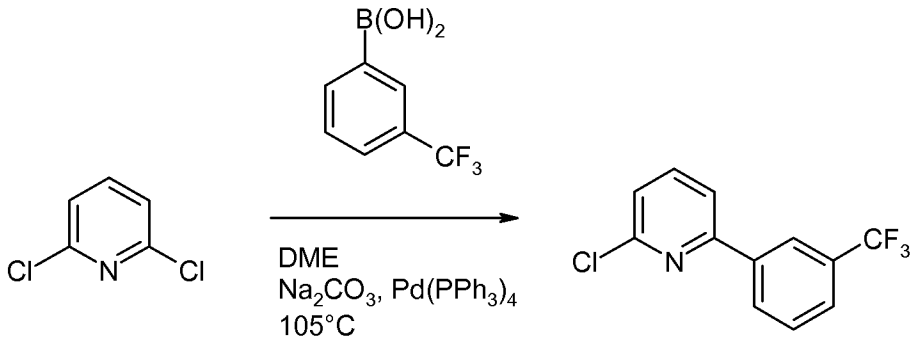
Description 12: Ethyl 1-(6-chloropyridin-2-yl)-piperidine-4-carboxylate (D12)



To a solution of 2,6-dichloropyridine (Aldrich, 4g, 27.03mmol) in EtOH (50ml) was added ethyl piperidine-4-carboxylate (Emka-Chemie, 10.41ml, 67.57 mmol) . The mixture was heated under reflux for 24 hours and then poured into water. . After extraction with CH_2Cl_2, the organic phase was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/cHex, 3/2 then 4/1) to give the titled compound as a colorless oil (3.93g, 54.15%). LC/MS (method B): Rt= 3.54 min; MH^+ 269.1;

H^1 NMR (300MHz, $CDCl_3$, ppm): 7.3 (t, 1H), 6.5 (d, 1H), 6.4 (d, 1H), 4.05 (m, 4H), 2.9 (m, 2H), 2.45 (m, 1H), 1.9 (m, 2H), 1.7 (m, 2H), 1.2 (t, 3H).

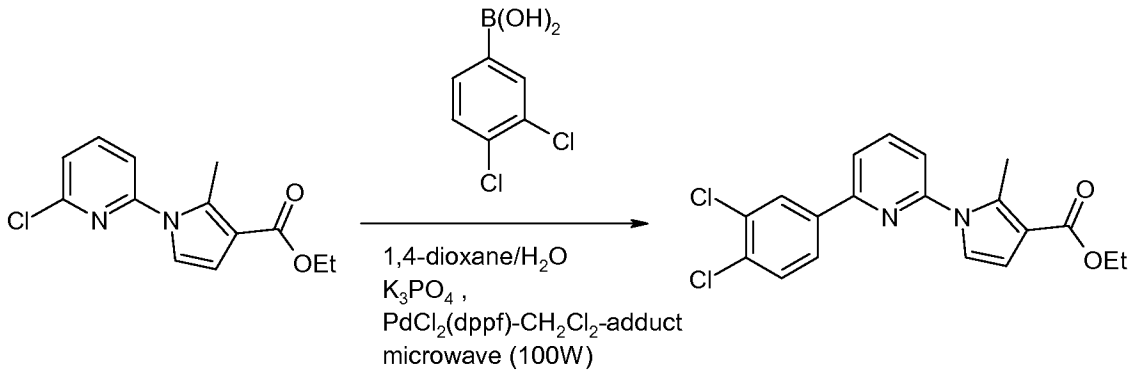
Description 13: 6-chloro-2-(3-trifluoromethylphenyl)-pyridine (D13)



To a solution of 2,6-dichloropyridine (Aldrich, 2g, 13.5mmol) in DME (30ml) were added $Pd(PPh_3)_4$ (1.56g, 1.35mmol), then 3-trifluoromethylphenylboronic acid (3.85g, 20.27mmol) and Na_2CO_3 (13.5ml of a solution 2M, 27mmol) and the mixture was heated at 105°C for 18 hours. After cooling, the mixture was poured into water. After extraction with CH_2Cl_2, the organic phase was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient CH_2Cl_2/cHex, 3/7 to CH_2Cl_2 100%) to give the titled compound as a colorless oil (1.31g, 37.7%).

LC/MS (method B): Rt= 3.68 min; MH^+ 258.16 .

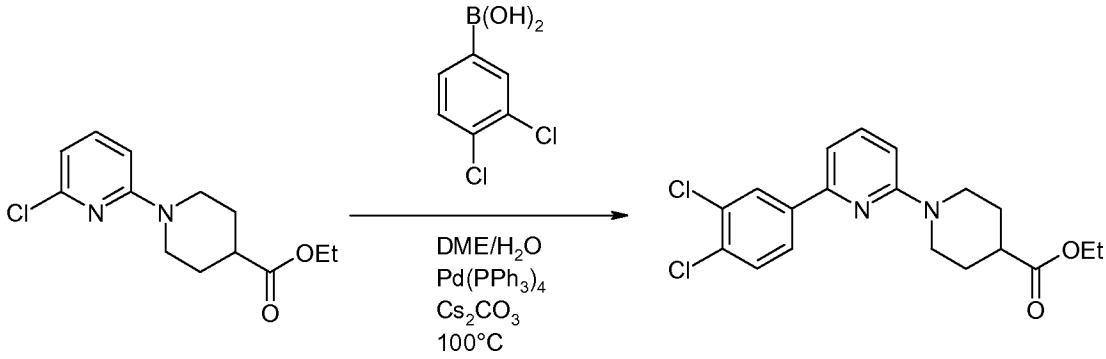
Description 14: Ethyl-1-(6-(3,4-dichlorophenyl)-pyridin-2-yl)-2-methyl-pyrrole-3-carboxylate (D14)



To a solution of intermediate ethyl 1-(6-chloropyridin-2-yl)-2-methyl-pyrrole-3-carboxylate (D10, 0.3g, 1.13mmol) in 1,4-dioxane (10ml), were added 3,4-dichlorophenylboronic acid (0.324g, 1.7mmol), potassium phosphate tribasic (0.481g, 2.267mmol) in water (2ml) and $PdCl_2(dppf)$-CH_2Cl_2-adduct (0.093g, 0.113mmol). The mixture was heated under microwave (100W) for 40 minutes. The mixture was then filtered over celite, and the filtrate was extracted with EtOAc/H_2O, the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silicagel (CH_2Cl_2). The title compound was obtained as white powder (0.195g, yield= 45.9%). H^1 NMR ($CDCl_3$,

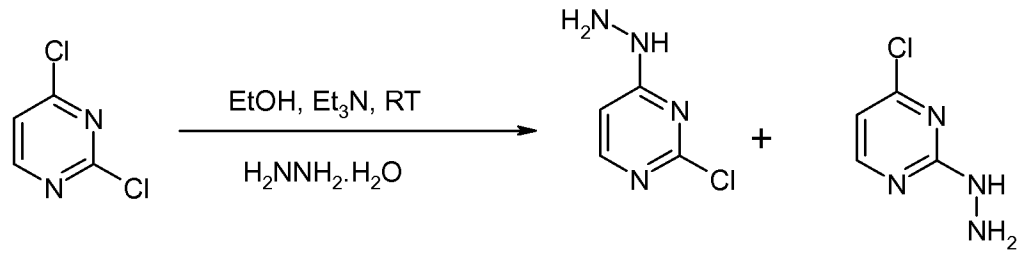
ppm): 8.1 (s, 1H), 7.85 (m, 2H), 7.65 (d, 1H), 7.45 (d, 1H), 7.2 (d, 1H), 6.9 (d, 1H), 6.65 (d, 1H), 4.25 (q, 2H), 2.7 (s, 3H), 1.3 (t, 3H)

Description 15: Ethyl-1-(6-(3,4-dichlorophenyl)-pyridin-2-yl)-piperidine-4-carboxylate (D15)



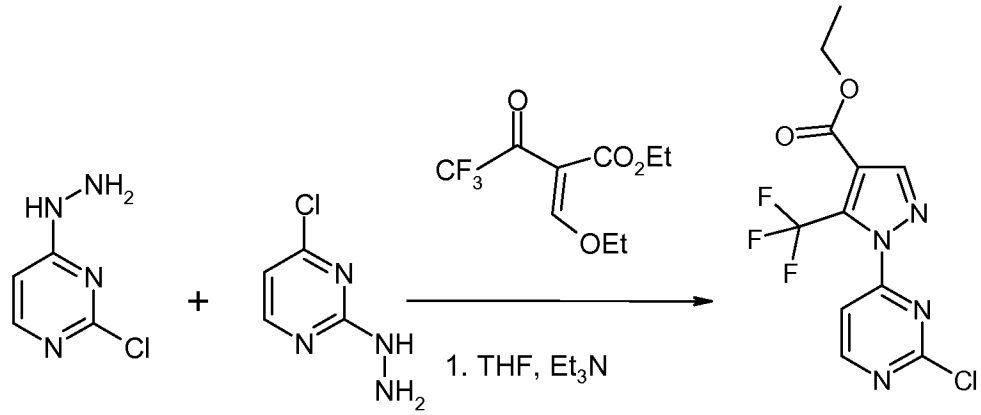
To a solution of ethyl 1-(6-chloropyridin-2-yl)-piperidine-4-carboxylate (D12, 0.5g, 1.86mmol) in DME (20ml) and water (2ml) were added $Pd(PPh_3)_4$ (0.215g, 0.186mmol), then 3,4-dichlorophenylboronic acid (0.355g, 1.86mmol) and Cs_2CO_3 (0.606g, 1.86 mmol) and the mixture was heated at 100°C for 18 hours . 3,4-dichlorophenylboronic acid (0.177g, 0.93mmol) and $Pd(PhP_3)_4$ (0.215g, 0.186mmol) were added and the mixture was heated at 100°C for 18 hours. After cooling, the mixture was poured into water. After extraction with CH_2Cl_2, the organic phase was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient CH_2Cl_2/cHex, 3/7 to CH_2Cl_2 100%) to give the titled compound as a colorless gum (0.14g, 19.8%). LC/MS (method B) Rt= 4.37 min; MH^+ 379.1. H^1 NMR (300MHz, $CDCl_3$, ppm): 8.05 (s, 1H), 7.75 (d, 1H), 7.45 (d, 1H), 7.4 (t, 1H), 6.95 (d, 1H), 6.6 (d, 1H), 4.25 (ld, 2H), 4.05 (q, 2H), 2.95 (t, 2H), 2.5 (m, 1H), 1.95 (m, 2H), 1.75 (m, 2H), 1.25 (t, 3H)

Description 16: 2-Chloro-4-hydrazinopyrimidine (D16A) and 4-chloro-2-hydrazinopyrimidine (D16B)



2,4-Dichloropyrimidine (Aldrich, 4.47g, 30mmol), triethylamine (6.06g,60mmol, 8.34ml) and hydrazine monohydrate (1.507g, 30mmol, 1.46ml) were stirred in ethanol (60ml) at room temperature for 24 hours. The mixture was poured into water and portioned with dichloromethane. The organic extracts were evaporated to give a mixture of the title compounds (986mg) as a colourless solid. LCMS (method A): Single peak, Rt = 0.56 mins; MH^+ 145.

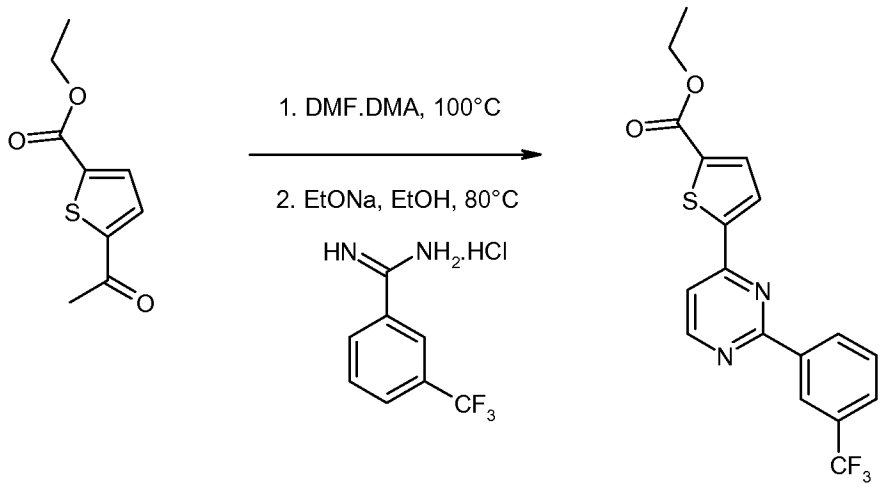
Description 17: Ethyl 1-(2-chloro-4-pyrimidinyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (D17)



A mixture of 2-chloro-4-hydrazinopyrimidine and 4-chloro-2-hydrazinopyrimidine (D16A and D16B, 2.8g, 0.02mol) was stirred in anhydrous tetrahydrofuran (80ml). Triethylamine (0.022mol, 3ml) was added, followed by the dropwise addition of a solution of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutyrate (Aldrich, 5g, 0.021mol). The mixture was stirred at room temperature for 30minutes and the solution hydrolysed with water. The oragic phase was extracted with dichloromethane, dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on silica gel eluting with (CH_2Cl_2 / cHex, 8:2 then CH_2Cl_2 100%) to give the title compound as an oil which crystallizes (2.9g, 45.2%).

LCMS (method B): single peak, Rt = 3.27 min; MH^+ 321

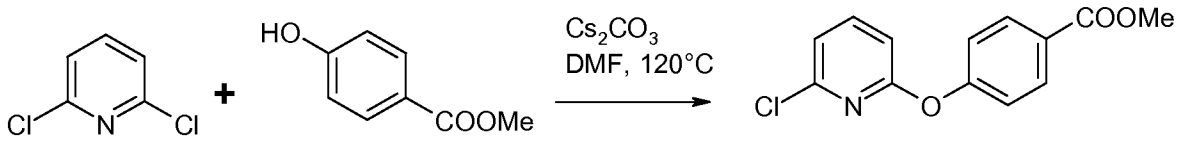
Description 18: Ethyl-5-(2-(3-trifluoromethylphenyl)-pyrimidin-4-yl)-thiophene-2-carboxylate (D18)



A solution of ethyl 5-acetyl-thiophene-2-carboxylate (0.5g, 2.52mmol) in DMF.DMA (2ml) was heated at 100°C for I hour, then cooled and concentrated under reduced pressure. The solid residue was dissolved in EtOH (20ml). Then 3-trifluoromethylbenzamidine.HCl (Interchim, 0.567g, 2.52mmol) and EtONa (0.206g, 3.03mmol) were added and the mixture

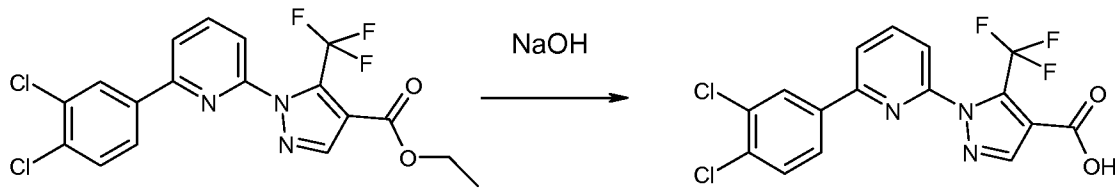
was heated at 80°C for 16 hours and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2). The title compound was obtained as a white solid (0.69g, yield= 72%). LC/MS (method B): Rt= 4.35mins; MH^+ 379.1; H^1 NMR (300MHz, $CDCl_3$, ppm): 8.86 (d, 1H), 8.82 (s, 1H), 8.76 (d, 1H), 7.85 (d, 1H), 7.8 (m, 2H), 7.67 (t, 1H), 7.55 (d, 1H), 4.42 (q, 2H), 1.45 (t, 3H).

Description 19: Ethyl 4-(6-chloropyridin-2-yloxy)-benzoate (D19)



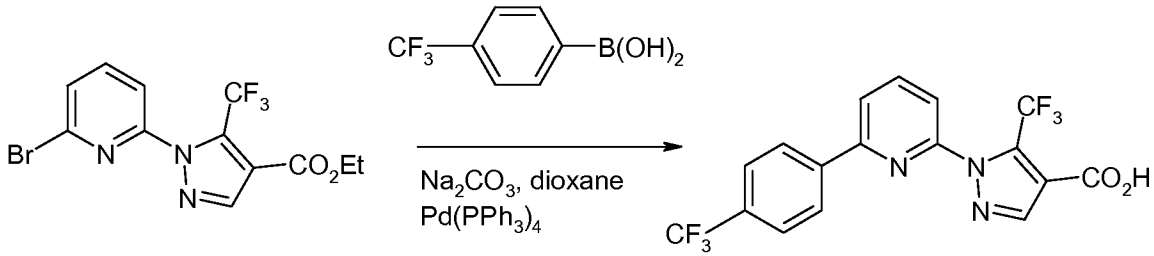
To a solution of methyl 4-hydroxybenzoate (Aldrich, 1.13g, 7.43mmol) in DMF (30ml) was added Cs_2CO_3 (2.64g, 8.11mmol) and the mixture was stirred at room temperature for 10 minutes. Then 2,6-dichloropyridine (1g, 6.76mmol) was added and the mixture was heated at 120°C for 3 hours and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried (Na_2SO_4), and concentrated under reduce pressure. The residue was purified by flash chromatography (CH_2Cl_2/cHex, 3/2) to give the title compound as a colorless oil (1.2g, 67.4%). LC/MS (method B): Rt= 3.24mins; MH^+ 264.15 ; H^1 NMR (300MHz, $CDCl_3$, ppm): 8.1 (d, 2H), 7.7 (t, 1H), 7.2 (d, 2H), 7.15 (d, 1H), 6.9 (d, 1H), 3.95 (s, 3H).

Example 1: 1-[6-(3,4-dichlorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid



A mixture of ethyl 1-[6-(3,4-dichlorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (D7, 0.36g, 0.000837mol) and sodium hydroxide (0.067g, 0.00168 mol) in dioxan (2ml) and water (2ml) was stirred at room temperature for 18 hours. The solution was evaporated and the residue was dissolved in DMSO-Water (1:1; 4ml). The solution was applied in 6 runs to mass directed auto preparation. Appropriate fractions were combined and evaporated to give a white solid. Crystallisation from acetonitrile gave the product as a white powder (0.204g, 61%). LCMS (method A): single Peak, Rt = 4.04 mins; MH^+ 402, 404, 406. ^1H NMR (d_6-DMSO) δ (ppm) 7.8-7.9 (2H,m), 8.1 (1H, dd), 8.25-8.37 (4H, m), 11.7 (1H, broad s).

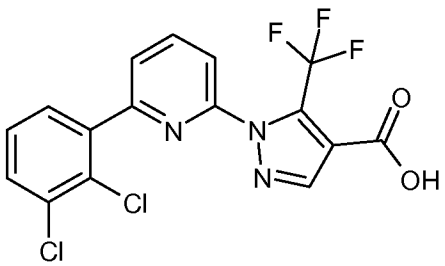
Example 2: 1-{6-[4-(trifluoromethyl)phenyl]-2-pyridinyl}-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid



Ethyl 1-(6-bromo-2-pyridinyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (D6, 100mg, 0.275mmol) and 4-(trifluoromethyl)phenylboronic acid (Aldrich, 52mg, 0.275mmol) were stirred in dioxan (1.5ml). A solution of sodium carbonate (58mg, 0.549mmol) in water (1.5ml) was added and the solution degassed with nitrogen. Tetrakis(triphenylphosphine)palladium (0) (20mg) was added and the mixture stirred and heated at 100°C for 18 hours, under nitrogen. The mixture was cooled to room temperature, filtered and blown dry under nitrogen. The residue was portioned between chloroform and water and the pH adjusted to pH4 with 2M hydrochloric acid. The organic phase was separated and blown down under nitrogen. The residue was purified by mass directed autopreparation and appropriate filtrates were evaporated to give the title compound (46.5mg). LCMS (method A): single peak, Rt = 3.77mins; MH^+ 402.

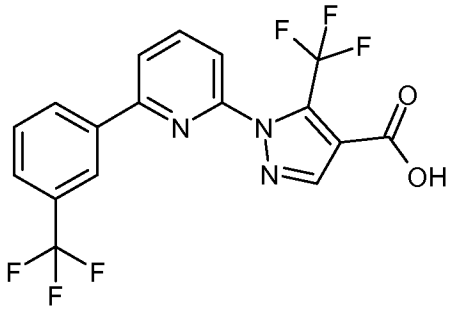
Using a similar procedure to that of Example 2, using the appropriately substituted phenylboronic acid (all available from Aldrich with the exception of 4-bromo-3-fluorophenyl boronic acid which is available from Lancaster Synthesis Ltd), the following Examples 3 to 9 were prepared.

Example 3: 1-[6-(2,3-dichlorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid



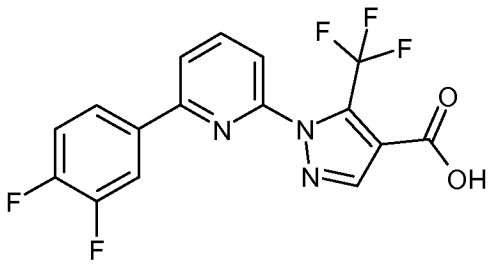
LCMS (method A): single peak, Rt = 3.67mins; MH^+ 402, 404.

Example 4: 1-{6-[3-(trifluoromethyl)phenyl]-2-pyridinyl}-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid



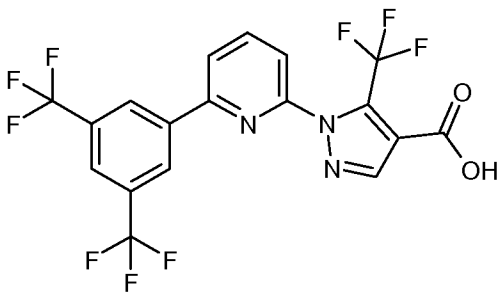
LCMS (method A): single peak, Rt = 3.73mins; MH^+ 402.

Example 5: 1-[6-(3,4-difluorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid



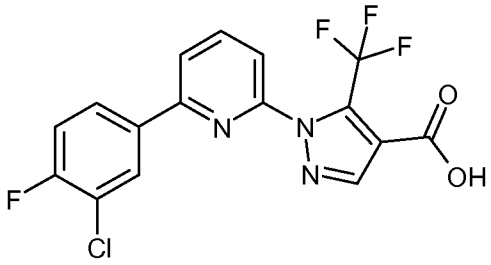
LCMS (method A): single peak, Rt = 3.61mins; MH^+ 370.

Example 6: 1-{6-[3,5-bis(trifluoromethyl)phenyl]-2-pyridinyl}-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid



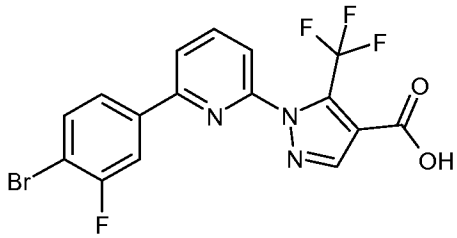
LCMS (method A): Single peak, Rt = 3.97mins, MH^+ 470.

Example 7: 1-[6-(3-chloro-4-fluorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid



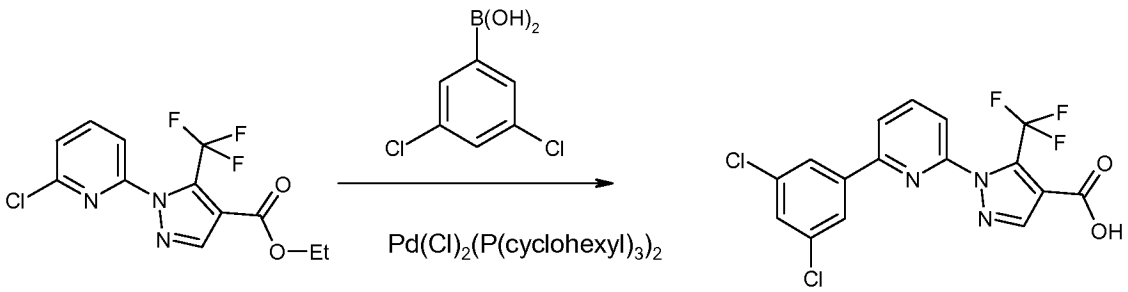
LCMS (method A): single peak, Rt = 3.82mins; MH^+ 386.

Example 8: 1-[6-(4-bromo-3-fluorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid



LCMS (method A): single peak, Rt = 3.89min; MH^+ 430, 433.

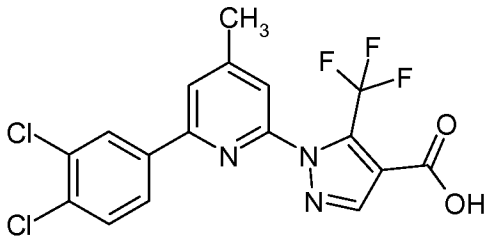
Example 9: 1-[6-(3,5-dichlorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid



A mixture of ethyl 1-(6-chloro-2-pyridinyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (D8, 0.16g, 0.0005 mol), 3,5-dichlorobenzene boronic acid (Aldrich, 0.105g, 0.00055 mol), sodium carbonate (0.053g, 0.0005 mol) and the palladium catalyst (0.037g, 0.00005 mol) in degassed dioxan (10 ml) and water (5 ml) was heated under reflux for 2 hours. To the cooled solution was added 2M sodium hydroxide solution (0.75 ml) and the suspension was stirred for 1 hour. The suspension was filtered and the filtrate was evaporated. The residue was purified by mass directed auto preparation and appropriate filtrates were evaporated.

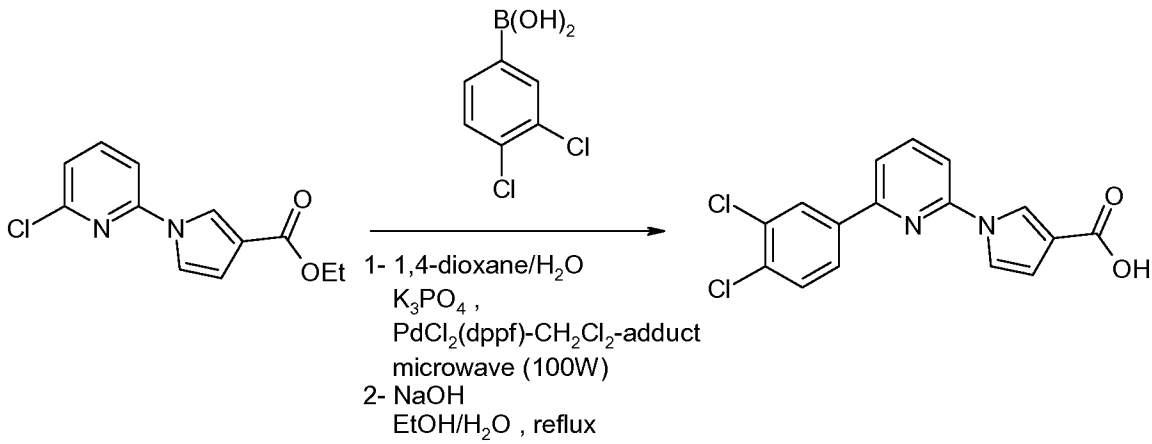
Crystallisation from acetonitrile gave the title compound as an off-white powder (0.018g, 9%). LCMS (method A): single peak, Rt = 4.18mins; MH^+ 402, 404, 406.

Example 10: 1-[6-(3,4-dichlorophenyl)-4-methyl-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid



Ethyl 1-(6-bromo-4-methyl-2-pyridinyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (D9, 1.221g, 3.229mmol) and 3,4-dichlorophenylboronic acid (Aldrich, 0.616g, 3.229mmol) were stirred in dioxan (25ml). A solution of sodium carbonate (0.684g, 6.458mmol) in water (20ml) was added and the solution degassed with nitrogen. Tetrakis(triphenylphosphine)palladium (0) (0.2g) was added and the mixture stirred and heated at 100°C, under nitrogen, for 18 hours. The mixture was cooled to room temperature, poured into brine and extracted with ethyl acetate. The mixture was filtered and the organic phase was separated, dried ($MgSO_4$) and evaporated to give a light brown solid (0.924g). A portion (0.09g) of this solid was purified by mass directed autopreparation to give the title compound (0.029g) as a pale brown solid. LCMS (method A): single peak, Rt = 4.26mins, MH^+ 416, 418.

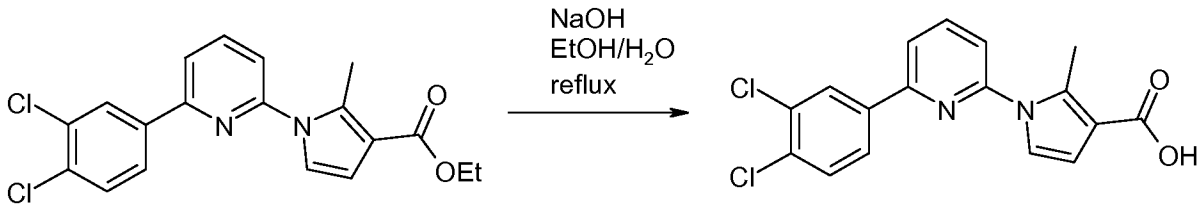
Example 11: 1-(6-(3,4-dichlorophenyl)-pyridin-2-yl)-pyrrole-3-carboxylic acid



To a solution of ethyl 1-(6-chloro-2-pyridinyl)-1*H*-pyrrole-3-carboxylate (D11, 0.3g, 1.2mmol) in 1,4-dioxane (10ml), were added 3,4-dichlorophenylboronic acid (0.23g, 1.2mmol), potassium phosphate tribasic (0.511g, 2.41mmol) in water (2ml) and $PdCl_2(dppf)$-CH_2Cl_2-adduct (0.098g, 0.12mmol). The mixture was heated under microwave (100W) for 40 minutes. The mixture was then filtered over celite, and the filtrate was extracted with AcOEt/H_2O, the organic phase was dried (Na_2SO_4) and concentrated under reduced

pressure. The residue was purified by chromatography on silicagel (CH_2Cl_2). The resulting solid was dissolved in EtOH (30ml). A solution 1N of NaOH (3.2ml) and the mixture was heated under reflux for 18 hours. EtOH was evaporated under reduced pressure and the aqueous phase was acidified to pH=6 with a solution 1N of HCl. The resulting precipitate was filtered, washed with water , then iPr_2O then with hot CH_3CN.The title compound was obtained as an off-white powder (0.08g, yield = 31%). H^1 NMR (DMSO *d6*, ppm): 8.4 (s, 1H), 8.2 (d, 1H), 7.95 (m, 3H), 7.8 (m, 2H), 7.7 (s, 1H), 6.55 (s, 1H); LC-HRMS: Target Mass calculated for $C_{16}H_{10}Cl_2N_2O_2$:331.0041 (M-H), Found: 331.0056 (M-H), Rt= 2.50 mins.

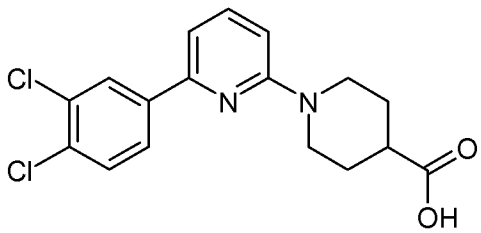
Example 12: 1-(6-(3,4-dichlorophenyl)-pyridin-2-yl)-2-methyl-pyrrole-3-carboxylic acid



To a solution of ethyl 1-[6-(3,4-dichlorophenyl)-2-pyridinyl]-2-methyl-1H-pyrrole-3-carboxylate (D14, 0.19g, 0.506mmol) in EtOH (10ml) was added NaOH (2.53ml of a solution 1N, 2.53mmol) and the mixture was heated under reflux for 18 hours. The EtOH was evaporated under reduced pressure and tha aquous residue was acidified to pH=6 with a solution 1N of HCl, then extracted with AcOEt. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The title compound was obtained as an off-white powder (0.055g, yield= 31.3%). H^1 NMR ($CDCl_3$, ppm): 8.2 (s, 1H), 7.95 (m, 2H), 7.8 (d, 1H), 7.6 (d, 1H), 7.35 (d, 1H), 7.1 (d, 1H), 6.85 (d, 1H), 2.8 (s, 3H); LC-HRMS: Target Mass calculated for $C_{17}H_{12}Cl_2N_2O_2$:345.0198 (M-H), Found: 345.0213 (M-H), Rt= 2.90 mins.

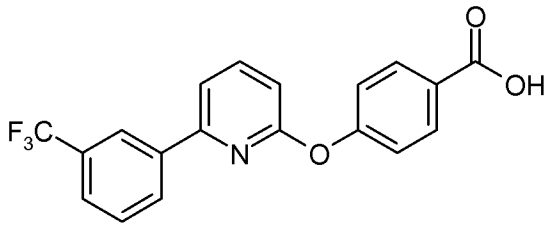
The following Examples were prepared by a similar method as described for Example 12 using the appropriate starting materials:

Example 13 : 1-(6-(3,4-dichlorophenyl)-pyridin-2-yl)-piperidine-4-carboxylic acid



H^1 NMR ($CDCl_3$, ppm): 8.15 (s, 1H), 7.85 (d, 1H), 7.6 (t, 1H), 7.55 (d, 1H), 7.05 (d, 1H), 6.7 (d, 1H), 4.4 (ld, 2H), 3.1 (t, 2H), 2.65 (m, 1H), 2.1 (m, 2H), 1.85 (m, 2H)
LC-HRMS: Target Mass calculated for $C_{17}H_{16}Cl_2N_2O_2$:351.0667 (M+H), Found: 351.0682 (M+H), Rt= 2.61 mins.

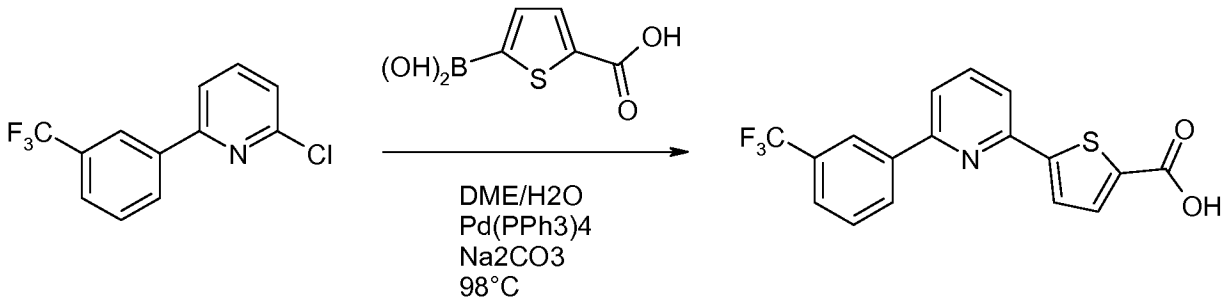
Example 14: 4-(6-(3-trifluoromethylphenyl)-pyridin-2-yloxy)-benzoic acid



H^1 NMR (DMSO *d6*, ppm): 8.2 (m, 2H), 8.05 (m, 3H), 7.95 (d, 1H), 7.8 (d, 1H), 7.7 (t, 1H), 7.35 (d, 2H), 7.15 (d, 1H)

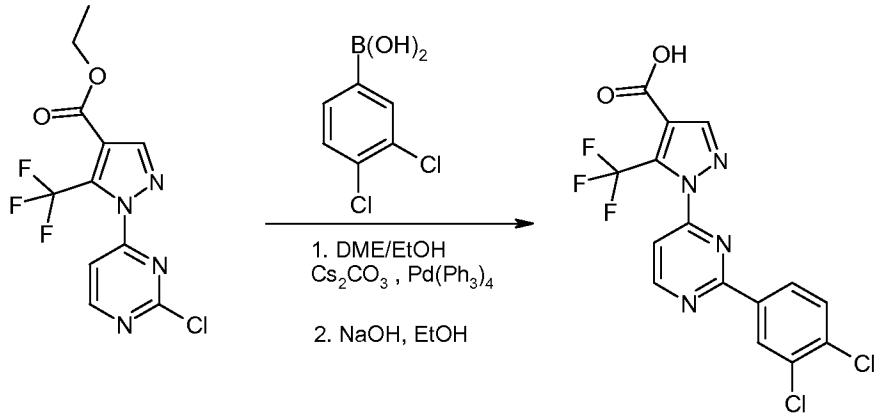
LC-HRMS: Target Mass calculated for $C_{19}H_{12}F_3N_1O_3$: 360.0847 (M+H), Found: 360.0861 (M+H), Rt= 2.41mins.

Example 15: 5-(6-(3-trifluoromethylphenyl)-pyridin-2-yl)-thiophene-2-carboxylic acid



To a solution of 6-chloro-2-(3-trifluoromethylphenyl)-pyridine (D13,1.31g, 5mmol) in DME (20ml) were added $Pd(PPh_3)_4$ (0.59g, 0.5mmol), 5-carboxy-thiophene-2-boronic acid (1.3g, 7.6mmol) and Na_2CO_3 (5.09ml of a solution 2N, 10mmol) and the mixture was heated at 98°C for 48 hours and then poured into water. The aquous phase was washed with CH_2Cl_2 and then acidified to pH 5 with a solution of HCl 1N. After extraction with CH_2Cl_2, the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure.The title compound was obtained as a cream solid (0.21g, 12%). ^1H NMR (300MHz, DMSO d6, ppm): 13.3 (s, 1H), 8.5 (ls, 2H), 8.07 (m, 3H), 7.93 (d, 1H), 7.85 (t, 1H), 7.78 (m, 2H); LC-HRMS: Target Mass calculated for $C_{17}H_{10}F_3N_1O_2S_1$: 350.0462 (M+H), Found: 350.0456 (M+H), Rt= 2.25 mins.

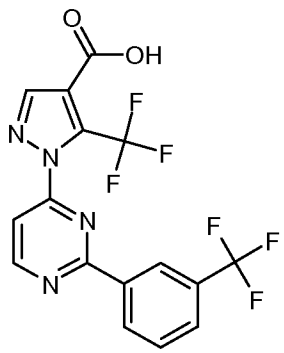
Example 16: 1-[2-(3,4-dichlorophenyl)-4-pyrimidinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid



To a solution of ethyl 1-(2-chloro-4-pyrimidinyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (D17, 0.32g, 1mmol) in a mixture of DME (10ml) and EtOH (2ml), were added 3,4-dichlorophenylboronic acid (Aldrich, 1.1mmol), $Pd(PPh_3)_4$ (0.035g, 0.03mmol) and a solution of cesium carbonate (0.392g, 1.2mmol) in water (2ml). The reaction mixture was stirred at 70°C for 1 hour. The solvent was evaporated to dryness and the residue was portioned between dichloromethane and water, the organic phase was separated and dried over Na_2SO_4. The resulting residue was treated with sodium hydroxide (solution 1N, 5ml) in EtOH (10ml) at 70°C for 12hours. The solvent was evaporated and the residue was acidified with a solution of HCl N to pH 4-5 to give after filtration the title compound as a beige powder (180mg, 45%). ^{1}H NMR (300MHz, DMSO *d6*, ppm): 9.2 (d, 1H), 8.5 (s, 1H), 8.45 (s, 1H), 8.3 (d, 1H), 8.00 (d, 1H), 7.85 (d, 1H).; LC-HRMS: Target Mass calculated for $C_{15}H_7Cl_2F_3N_4O_2$: 369.0366 (M+H), Found: 369.0300 (M+H), Rt= 2.36 mins.

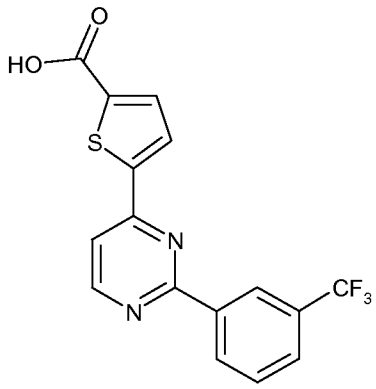
The following Examples were prepared by a similar method as described for Example 16, using the appropriate starting materials:

Example 17: 5-(trifluoromethyl)-1-{2-[3-(trifluoromethyl)phenyl]-4-pyrimidinyl}-1*H*-pyrazole-4-carboxylic acid



H1 NMR (DMSO *d6*, ppm): 9.25 (d, 1H), 8.70 (m, 2H), 8.45 (s, 1H), 8.0 (m,2H), 7.85 (m, 1H). LC-HRMS Target Mass calculated for $C_{16}H_8F_6N_4O_2$: 403.0629 (M+H), Found: 403.0611 (M+H), Rt= 2.29 mins; LC/MS (method B): Rt=2.77 mins; MH^+ 403

Example 18: 5-(2-(3-trifluoromethylphenyl)-pyrimidin-4-yl)-thiophene-2-carboxylic acid



1H NMR (300MHz, DMSO d6, ppm): 8.9 (d, 1H), 8.72 (m, 2H), 8 (d, 1H), 7.93 (m, 2H), 7.83 (t, 1H), 7.36 (d, 1H); LC-HRMS Target Mass calculated for $C_{16}H_9F_3N_2O_2S_1$: 351.0415 (M+H), Found: 351.0441 (M+H), Rt= 2.19 mins.

Biological Assay

The activity of soluble guanylate cyclase (sGC) can be tested in an assay based on measuring the fluorescence polarisation (FP) signal of fluorescently labelled cGMP. FP of this fluorescent molecule increases on interaction with an anti-cGMP antibody as the mobility of the molecule is reduced. Newly produced cGMP displaces this interaction giving rise to a decrease in polarisation and FP signal which can be equated to enzyme activity.

Compounds are incubated with human sGC, anti-cGMP antibody, the GTP substrate and fluorescently labelled cGMP. After a period of one hour the assay is stopped with the addition of EDTA and after a further hour the assay is read.

Assay procedure

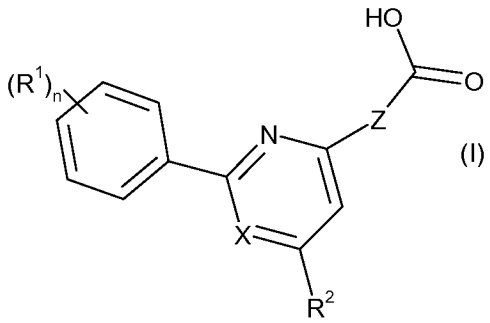
Human sGC is thawed and resuspended in assay buffer (100mM TRIS, 10mM $MgCl_2$, 0.2mM Tween 20, pH7.4, containing 1:100 dilution of sheep anti-cGMP) to give a final concentration of 1nM in the well. A substrate solution is prepared containing GTP and 8-fluo-cGMP in de-ionized water to a final concentration of 25µM and 50nM respectively. Assay plates containing 5µL of various test compounds and of a standard agonist (50µM - 50nM) in 1% DMSO as 6 point, four fold dilutions across a 96 well plate are used in the assay. The plate also contains 6 wells of DMSO (1%) to produce high control and a cGMP standard curve (14nM to 10µM) to convert FP data to cGMP concentration. 25µL of enzyme mix and 20µl of substrate mix described above are added to each well of the plate. Samples are mixed on an orbital shaker and then incubated at room temperature for 1 hour. After this incubation period 5µl of 0.5M EDTA is added to all wells and the plates are incubated for a further hour at room temperature prior to reading the FP signal in an appropriate reader. For data handling FP data are converted to cGMP concentrations and then fitted using ActivityBase software. The activity of a test compound is determined as the pEC500 value which is the concentration able to increase by 5-fold basal cGMP.

The compounds of Examples 1 to 18 gave pEC500 values of greater than 5. In an embodiment the compounds of the invention give a pEC500 value of ≥ 5.5 when tested in this assay. In an embodiment the compounds of the invention give a pEC500 value of ≥ 6 when tested in this assay.

The following compounds were also prepared by similar methods to those described above: 1-[6-(2,4-dichlorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid; and 1-[2-(4-chlorophenyl)-4-pyrimidinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid. When tested in the assay described above both of these compounds gave pEC500 values of < 5 i.e. below the detectable limit of the assay.

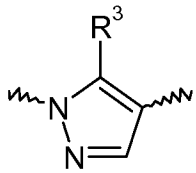
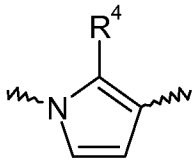
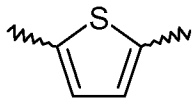
Claims

1. A compound of formula (I)



(I)

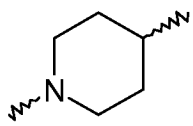
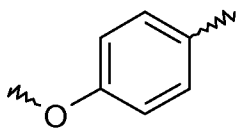
or a salt thereof;
wherein
n represents 1 or 2;
each R^1 independently represents halo or trifluoromethyl; wherein halo represents fluoro, chloro or bromo;
R^2 represents hydrogen or C_{1-3}alkyl;
X represents N or CH;
wherein –Z– represents a group selected from:


,

or

;

wherein R^3 represents trifluoromethyl or C_{1-3}alkyl; and R^4 represents hydrogen, trifluoromethyl or C_{1-3}alkyl;

with the proviso that where Z represents a thiophene group and X represents N, R^2 cannot represent C_{1-3}alkyl;

and when X represents CH, –Z– can additionally represent a group selected from:


or

.

2. A compound of formula (I) as defined in claim 1 or a salt thereof wherein n represents 2 and both R^1 groups independently represent halo.

3. A compound of formula (I) as defined in claim 1 or a salt thereof wherein each R^1 independently represents trifluoromethyl.

4. A compound of formula (I) as defined in any one of claims 1 to 3 or a salt thereof wherein X represents CH and R^2 represents hydrogen or methyl.

5. A compound of formula (I) as defined in any one of claims 1 to 3 or a salt thereof wherein X represents N and R^2 represents hydrogen.

6. A compound of formula (I) as defined in any one of claims 1 to 5 or a salt thereof wherein R^3 represents trifluoromethyl.

7. A compound of formula (I) as defined in any one of claims 1 to 5 or a salt thereof wherein R^4 represents hydrogen or methyl.

8. A compound of formula (I) as defined in claim 1 selected from:
1-[6-(3,4-Dichlorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-{6-[4-(Trifluoromethyl)phenyl]-2-pyridinyl}-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-[6-(2,3-Dichlorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-{6-[3-(Trifluoromethyl)phenyl]-2-pyridinyl}-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-[6-(3,4-Difluorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-{6-[3,5-bis(Trifluoromethyl)phenyl]-2-pyridinyl}-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-[6-(3-Chloro-4-fluorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-[6-(4-Bromo-3-fluorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-[6-(3,5-Dichlorophenyl)-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
1-[6-(3,4-Dichlorophenyl)-4-methyl-2-pyridinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
or a pharmaceutically acceptable salt thereof.

9. A compound of formula (I) as defined in claim 1 selected from:
1-(6-(3,4-dichlorophenyl)-pyridin-2-yl)-pyrrole-3-carboxylic acid;
1-(6-(3,4-dichlorophenyl)-pyridin-2-yl)-2-methyl-pyrrole-3-carboxylic acid;
or a pharmaceutically acceptable salt thereof.

10. A compound of formula (I) as defined in claim 1 selected from:
1-(6-(3,4-dichlorophenyl)-pyridin-2-yl)-piperidine-4-carboxylic acid;
4-(6-(3-trifluoromethylphenyl)-pyridin-2-yloxy)-benzoic acid;
5-(6-(3-trifluoromethylphenyl)-pyridin-2-yl)-thiophene-2-carboxylic acid;
or a pharmaceutically acceptable salt thereof.

11. A compound of formula (I) as defined in claim 1 selected from:
5-(2-(3-trifluoromethylphenyl)-pyrimidin-4-yl)-thiophene-2-carboxylic acid;
1-[2-(3,4-dichlorophenyl)-4-pyrimidinyl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid;
5-(trifluoromethyl)-1-{2-[3-(trifluoromethyl)phenyl]-4-pyrimidinyl}-1H-pyrazole-4-carboxylic acid;
or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carrier(s), diluents(s) and/or excipient(s).

13. A compound of formula (I) as defined in any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof for use in therapy.

14. A pharmaceutical composition as claimed in claim 12 for use in therapy.

15. A compound of formula (I) as defined in any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined in claim 12, for use in the treatment of a disease or condition mediated by the activity of sGC.

16. A compound of formula (I) as defined in any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined in claim 12, for use in the treatment of arterial hypertension, pulmonary arterial hypertension, angina, cardiac ischemia, myocardial infarction, congestive heart failure, cardiac hypertrophy, acute coronary syndrome, atherosclerosis, peripheral vascular disease, cardiorenal syndrome, hepatorenal syndrome or restenosis.

17. A compound of formula (I) as defined in any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined in claim 12, for use in the treatment of arterial hypertension, pulmonary arterial hypertension, angina, congestive heart failure or peripheral vascular disease.

18. Use of a compound of formula (I) as defined in any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of a disease or condition mediated by the activity of sGC.

19. Use of a compound of formula (I) as defined in any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of arterial hypertension, pulmonary arterial hypertension, angina, cardiac ischemia, myocardial infarction, congestive heart failure, cardiac hypertrophy, acute coronary syndrome, atherosclerosis, peripheral vascular disease, cardiorenal syndrome, hepatorenal syndrome or restenosis.

20. Use of a compound of formula (I) as defined in any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of arterial hypertension, pulmonary arterial hypertension, angina, congestive heart failure or peripheral vascular disease.

21. A method of treatment of a disease or condition mediated by the activity of sGC comprising administration to a human subject in need of such treatment of a therapeutically effective amount of a compound of formula (I) as defined in any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition as claimed in claim 12.

22. A method of treatment of arterial hypertension, pulmonary arterial hypertension, angina, cardiac ischemia, myocardial infarction, congestive heart failure, cardiac hypertrophy, acute coronary syndrome, atherosclerosis, peripheral vascular disease, cardiorenal syndrome, hepatorenal syndrome or restenosis comprising administration to a human subject in need of such treatment of a therapeutically effective amount of a compound of formula (I) as defined in any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof or of a pharmaceutical composition as claimed in claim 12.

23. A method of treatment of arterial hypertension, pulmonary arterial hypertension, angina, congestive heart failure, or peripheral vascular disease comprising administration to a human subject in need of such treatment of a therapeutically effective amount of a compound of formula (I) as defined in any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof or of a pharmaceutical composition as claimed in claim 12.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/066444

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D403/04 C07D409/04 A61K31/4436 A61K31/4439
C07D213/643

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 198 36 697 A1 (HOECHST MARION ROUSSEL DE GMBH [DE]) 17 February 2000 (2000-02-17) page 1, paragraph 2 claim 1	1,5,12, 13,18,21
A	WO 00/27394 A (UNIV LONDON [GB]; SELWOOD DAVID [GB]; GLEN ROBERT [GB]; LIU QIAN [US];) 18 May 2000 (2000-05-18) page 1, paragraph 1 page 5, line 14 - line 30 claim 1	1,4,12, 13,18,21

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 April 2009	16/04/2009

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claim 21-23 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.

Continuation of Box II.1

Claims Nos.: -

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2008/066444

Box No. 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. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

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 No. 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:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers 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 and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3(part), 5, 6-7(part), 11, 12-23(part)

Compounds of formula I for which X is N

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2. claims: 1-3(part), 4, 6-7(part), 8-10, 12-23(part)

Compounds of formula I for which X is CH

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/066444

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19836697 A1	17-02-2000	AT 240315 T	15-05-2003
		AU 760988 B2	29-05-2003
		AU 5730799 A	06-03-2000
		BR 9913003 A	08-05-2001
		CA 2340405 A1	24-02-2000
		DK 1112266 T3	15-09-2003
		WO 0009496 A1	24-02-2000
		EP 1112266 A1	04-07-2001
		ES 2196849 T3	16-12-2003
		JP 2002522536 T	23-07-2002
		PT 1112266 E	30-09-2003
		US 6844347 B1	18-01-2005
WO 0027394 A	18-05-2000	AU 6481699 A	29-05-2000