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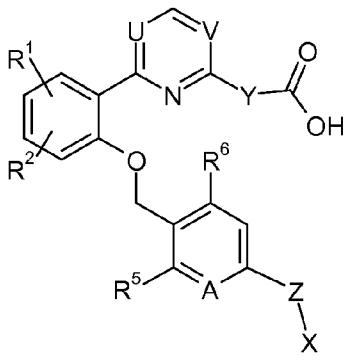
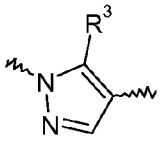
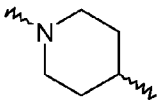
(54) Title: PYRIMIDINE DERIVATIVES AS ACTIVATORS OF SOLUBLE GUANYLATE CYCLASE



(I)



(a)



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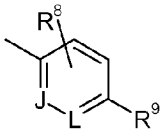

(c)

(57) Abstract: Disclosed are compounds of formula (I) and or salts thereof which activate soluble guanylate cyclase (sGC), pharmaceutical compositions containing them, their use in the manufacture of a medicament for teating cardiovascular diseases, and processes for their preparation.

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PYRIMIDINE DERIVATIVES AS ACTIVATORS OF SOLUBLE GUANYLATE CYCLASE

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.

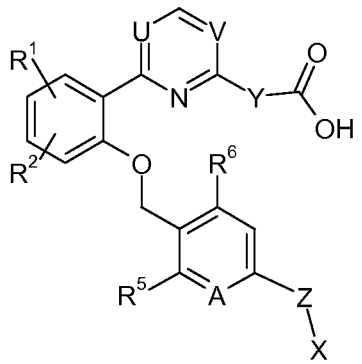
The novel compounds of the invention are activators of sGC and consequently may have application in the treatment of one or more diseases or conditions, which include: cardiovascular diseases and conditions, such as angina (including stable and unstable angina pectoris), low cardiac output, cerebral 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 compounds of the invention 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 compounds of the invention may be useful is congestive heart failure. Another particular disease or condition for which the compounds of the invention may be useful is peripheral vascular disease. Another particular disease or condition for which the compounds of the invention may be useful is arterial hypertension (also known as systemic hypertension). Another particular disease or condition for which the compounds of the invention may be useful is pulmonary arterial hypertension. Another particular disease or condition for which the compounds of the invention may be useful is angina.

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



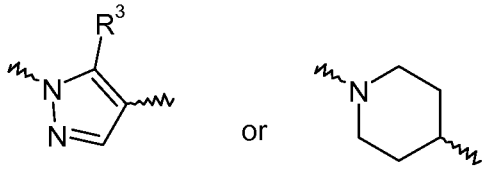
(I)

or a salt thereof;
wherein

R^1 and R^2 are independently selected from hydrogen, halo, CF_3 and C_{1-4}alkyl;

one of U and V represents N and the other represents CH;

—Y— represents



wherein R^3 represents CF_3 or C_{1-4} alkyl;

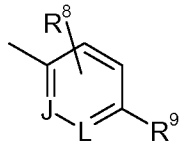
Z is absent or represents O;

A represents CH or N;

when A represents CH, R^5 is selected from hydrogen, methyl, C_{1-4}alkoxy, methoxyC_{2-3}alkoxy, chloro and fluoro and R^6 represents hydrogen;

when A represents N, R^5 and R^6 each represent hydrogen or one of R^5 and R^6 represents hydrogen and the other represents methyl; and

X represents



wherein: J and L both represent CH, or one represents N and the other represents CH, provided that only one of A, J and L represents N;

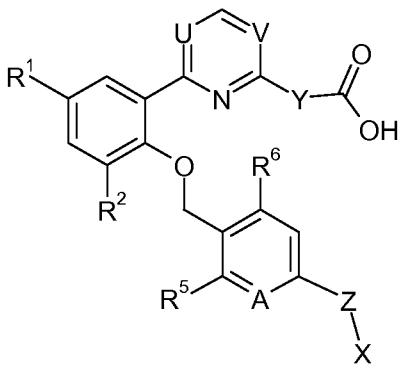
when both J and L represent CH, R^8 represents hydrogen or chloro, fluoro, CF_3, C_{1-4}alkyl or C_{1-4}alkoxy in a meta or ortho position relative to the R^9 substituent;

when one of J and L represents N, R^8 represents hydrogen or halo in a meta or ortho position relative to the R^9 substituent; and

R^9 represents hydrogen, halo, CF_3, OCF_3, C_{1-4}-alkyl, C_{1-4}-alkoxy, CN, $CONR^{10}R^{11}$, CO_2H or N_3, wherein R^{10} and R^{11} are independently selected from hydrogen and C_{1-4}-alkyl;

with the exception of 1-[4-(2-(4-(4-chlorophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid and 1-[4-(2-((4-phenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid.

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



(I)

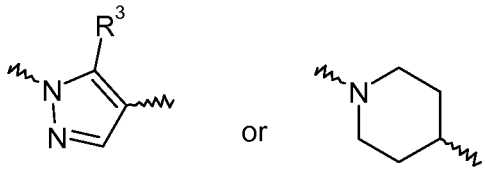
or a salt thereof;

wherein

R^1 and R^2 are independently selected from hydrogen, halo, CF_3 or C_{1-4}alkyl;

one of U and V represents N and the other represents CH;

—Y— represents

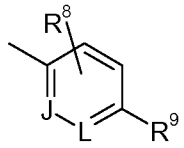


wherein R^3 represents CF_3 or C_{1-4} alkyl;

Z is absent or represents O;

A, J and L each represent CH; or one of A, J and L represents N and the other two each represents CH;
and when A represents CH, R^5 is selected from hydrogen, methyl, C_{1-4}alkoxy, methoxyC_{2-3}alkoxy, chloro and fluoro and R^6 represents hydrogen; or when A represents N, R^5 and R^6 each represent hydrogen or one of R^5 and R^6 represents hydrogen and the other represents methyl;

X represents



wherein when both J and L represent CH, R^8 represents hydrogen or chloro, fluoro, CF_3, C_{1-4}alkyl or C_{1-4}alkoxy in a meta or ortho position relative to the R^9 substituent; or when one of J and L represents N, R^8 represents hydrogen or halo in a meta or ortho position relative to the R^9 substituent; and R^9 represents hydrogen, halo, CF_3, OCF_3, C_{1-4}-alkyl, C_{1-4}-alkoxy, CN, $CONR^{10}R^{11}$, CO_2H or N_3, wherein R^{10} and R^{11} are independently selected from hydrogen and C_{1-4}-alkyl;

with the exception of 1-[4-(2-(4-(4-chlorophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid and 1-[4-(2-((4-phenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid.

As used herein, the term “alkyl” refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C_{1-4}alkyl means a straight or branched alkyl containing at least 1, and at most 4, carbon atoms. Examples of “alkyl” as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, isobutyl, isopropyl, and t-butyl.

As used herein, the term “alkoxy” refers to a straight or branched alkoxy group containing the specified number of carbon atoms. For example, C_{1-4}alkoxy means a straight or branched

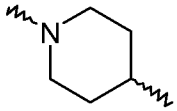
alkoxy group containing at least 1, and at most 4, carbon atoms. Examples of "alkoxy" as used herein include, but are not limited to, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, or 2-methylprop-2-oxy.

As used herein, the term "halo" refers to the elements fluorine, chlorine, bromine and iodine. In an embodiment halo represents bromine, fluorine and chlorine. In a further embodiment halo represents fluorine and chlorine.

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

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

In an embodiment —Y— represents



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In an embodiment R^1 is in a para position relative to the $-OCH_2-$ linker. In a further embodiment R^2 is in an ortho position relative to the $-OCH_2-$ linker. In a further embodiment R^1 is in a para position relative to the $-OCH_2-$ linker and R^2 is in an ortho position relative to the $-OCH_2-$ linker.

In a further embodiment R^1 is in an ortho position relative to the bond linking to the pyridine ring. In a further embodiment R^2 is in a meta position relative to the $-OCH_2-$ linker.

In an embodiment R^1 and R^2 do not both represent C_{2-4}alkyl.

In an embodiment, where one of R^1 and R^2 represents C_{1-4}alkyl, the other represents hydrogen.

In an embodiment R^1 represents C_{1-4}alkyl, CF_3 or halo, in a further embodiment with R^1 in a para position relative to the $-OCH_2-$ linker. In an embodiment R^1 represents methyl, CF_3, fluoro or chloro, in a further embodiment with R^1 in a para position relative to the $-OCH_2-$ linker.

In an embodiment R^2 represents hydrogen.

In an embodiment R^1 represents chloro or fluoro and R^2 represents hydrogen, in a further embodiment with R^1 in an ortho position relative to the bond linking to the pyridine ring.

In an embodiment, R^2 represents chloro or fluoro and R^1 represents hydrogen, in a further embodiment with R^2 in a meta position relative to the $-OCH_2-$ linker.

In an embodiment U represents CH and V represents N.

In an embodiment R^1 and R^2 each represent hydrogen. In an embodiment R^1 represents chloro or fluoro and R^2 represents hydrogen. In an embodiment R^1 represents C_{1-4}alkyl and R^2 represents hydrogen. In an embodiment R^1 represents methyl and R^2 represents hydrogen. In an embodiment R^1 represents CF_3 and R^2 represents hydrogen.

In an embodiment R^3 represents methyl or CF_3. In a further embodiment R^3 represents CF_3.

In an embodiment Z is absent. In an embodiment Z represents O.

In an embodiment A represents CH.

In an embodiment R^6 represents hydrogen.

In an embodiment R^5 represents hydrogen, methyl, methoxy, propyloxy, isopropyloxy, isobutyloxy, methoxyethoxy, fluoro or chloro. In an embodiment, R^5 represents hydrogen, methyl, methoxy or propyloxy.

In an embodiment J and L both represent CH. In a further embodiment J represents N and L represents CH. In a further embodiment J represents CH and L represents N.

In an embodiment R^8 represents hydrogen or chloro, CF_3, methyl or methoxy in a meta or ortho position relative to the R^9 substituent. In an embodiment R^8 represents hydrogen or chloro, CF_3, methyl or methoxy in a meta position relative to the R^9 substituent.

In an embodiment J and L both represent CH and R^8 represents hydrogen or chloro, CF_3, methyl or methoxy in a meta position relative to the R^9 substituent. In an embodiment J represents N and L represents CH and R^8 represents hydrogen, or chloro in a meta position relative to the R^9 substituent. In an embodiment J represents CH and L represents N and R^8 represents hydrogen.

In an embodiment R^9 represents hydrogen, halo, CF_3, OCF_3, C_{1-4}alkyl, C_{1-4}alkoxy or CN. In a further embodiment R^9 represents halo, CF_3, OCF_3, C_{1-4}alkoxy or CN. In a further embodiment R^9 represents chloro, fluoro, CF_3, OCF_3, methoxy or CN.

In an embodiment R^8 represents hydrogen and R^9 represents methoxy, CN, CF_3, OCF_3 or fluoro. In an embodiment R^8 represents methyl and R^9 represents CN, methoxy or CF_3, with R^8 being in a meta position relative to the R^9 substituent. In an embodiment R^8 represents

CF_3, and R^9 represents CN, methoxy or chloro, with R^8 being in a meta position relative to the R^9 substituent. In an embodiment R^8 represents chloro, and R^9 represents CF_3, CN or methoxy, with R^8 being in a meta position relative to the R^9 substituent.

For the avoidance of doubt, the term "independently" means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

In an embodiment there is provided a compound of formula (I) as defined above selected from:
1-[4-(2-(4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid;
1-[4-(5-chloro-2-(4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid
1-[4-(2-(4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid;
1-[4-(2-(4-(4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid;
1-[4-(2-(2-methyl-4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid;
1-[4-(2-(2-methyl-4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid;
1-[4-(2-(2-methyl-4-(4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid;
1-[4-(5-chloro-2-(2-methyl-4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid;
1-[4-(2-(4-(4-cyanophenyloxy)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid;
1-[4-(5-chloro-2-(4-(4-cyanophenyloxy)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid;
1-[4-(5-methyl-2-(4-(3-chloro-5-trifluoromethylpyridin-2-yloxy)phenylmethyloxy)phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methoxy-4-(3-chloro-5-trifluoromethylpyridin-2-yloxy)phenylmethyloxy)phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(3-chloro-5-trifluoromethylpyridin-2-yloxy)phenylmethyloxy)phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid;
1-[2-(2-(4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-4-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid;
1-[2-(2-(4-(4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-4-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid; and
1-[2-(2-(4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-4-yl]-5-trifluoromethyl-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-[4-(5-methyl-2-(2-methyl-4-(4-cyano-2-methylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(4-methoxy-2-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(2-(2-methyl-4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(2-(2-methyl-4-(2,4-dimethoxy-phenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(2-(2-methyl-4-(4-methoxy-2-methyl-phenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(2-(2-methyl-4-(4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(2-(2-methoxy-4-(4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(2-(2-methyl-4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-fluoro-2-(2-methyl-4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-fluoro-2-(2-methyl-4-(4-fluorophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-fluoro-2-(2-methyl-4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-fluoro-2-(4-(4-cyanophenyloxy)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-fluoro-2-(4-(5-trifluoromethylpyridin-2-yloxy)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(4-trifluoromethoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(2-methyl-4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(2-chloro-4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-propyloxy-4-(4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-propyloxy-4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;

1-[4-(5-methyl-2-(2-propyloxy-4-(2-chloro-4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-propyloxy-4-(4-methoxy-2-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-propyloxy-4-(4-chloro-2-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(6-methoxypyridin-3-yl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(5-trifluoromethylpyridin-2-yl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(3-chloro-5-trifluoromethylpyridin-2-yloxy)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-trifluoromethyl-2-(2-methyl-4-(4-chloro-2-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(2-chloro-4-cyanophenoxy)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid; and
1-[4-(5-trifluoromethyl-2-(2-methyl-4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-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:
1-[4-(5-methyl-2-(2-methyl-4-(3-chloro-5-trifluoromethylpyridin-2-yl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid; and
1-[4-(5-trifluoromethyl-2-(2-methyl-4-(3-chloro-5-trifluoromethylpyridin-2-yl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-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.

Separation of the individual enantiomers of the relevant compounds (e.g. from racemic mixtures produced) may be carried out by standard methods well-known to the person skilled in the art, for example by chiral chromatography.

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 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. 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 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, 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 compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as “prodrugs”. All such prodrugs of compounds of the invention 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). 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 the invention.

Hereinafter, compounds of formula (I) (whether in solvated or unsolvated form) or their pharmaceutically acceptable salts (whether in solvated or unsolvated form) are referred to as "compounds of the invention".

Also included within the scope of the invention are polymorphs of a compound of the invention.

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 compounds of the invention, as activators 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 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 the use of a compound of the invention for the manufacture of a medicament for treating a disease or condition mediated by sGC activity.

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

According to a further aspect, the invention provides a pharmaceutical composition comprising a compound of the invention, in association with one or more pharmaceutically acceptable carrier(s), diluents(s) and/or excipient(s). The carrier, diluent and/or excipient must 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 the invention provides a method of treatment of a disease or condition which is mediated by the activity of sGC such as one or more of the diseases described above, for example arterial hypertension, pulmonary arterial hypertension, angina, cardiac ischemia, myocardial infarction, congestive heart failure, acute coronary syndrome, atherosclerosis, peripheral vascular disease 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 comprising a compound of the invention.

According to a further aspect the invention provides a method of treatment of cardiorenal syndrome or hepatorenal syndrome 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.

The compounds 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. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian.

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 "treatment" extend to prophylaxis, prevention of recurrence and 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. Where the compositions comprise dosage units, each unit will typically contain from 5-1000 mg of the active ingredient.

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 particular mammal being treated, 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.

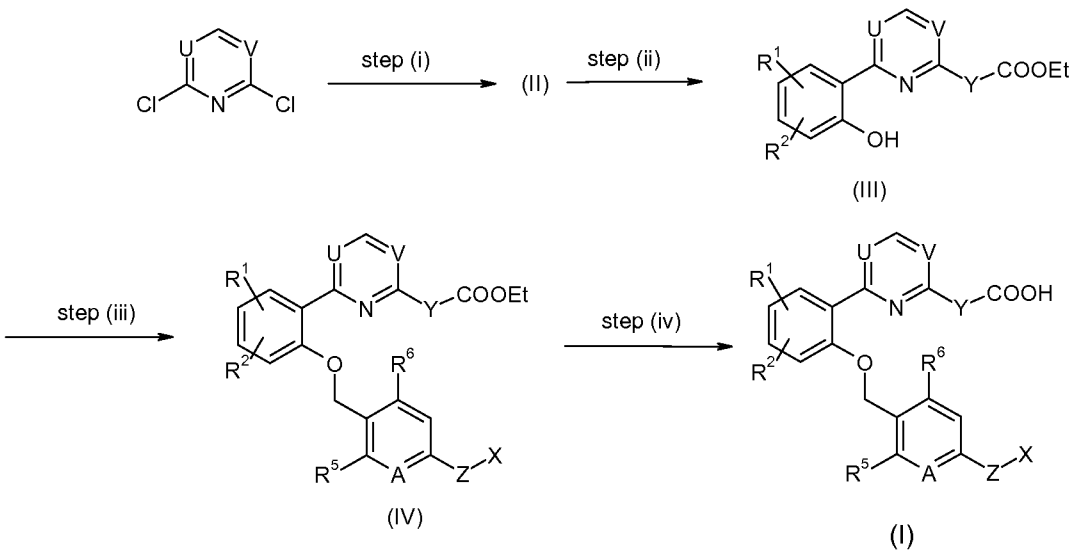
Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each suitably provided in substantially pure form, for example at least 60% pure, for example at least 75% pure, for example at least 85%, for example at least 98% pure (% 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.

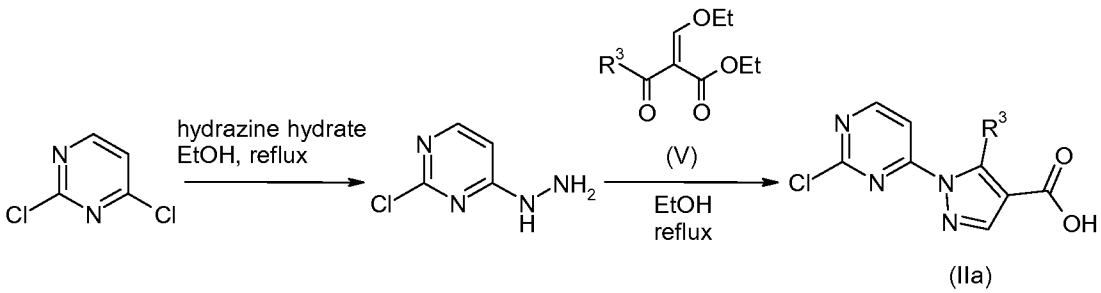
Compounds of formula (I) can be prepared according to the following general synthetic process (Scheme 1):

Scheme 1



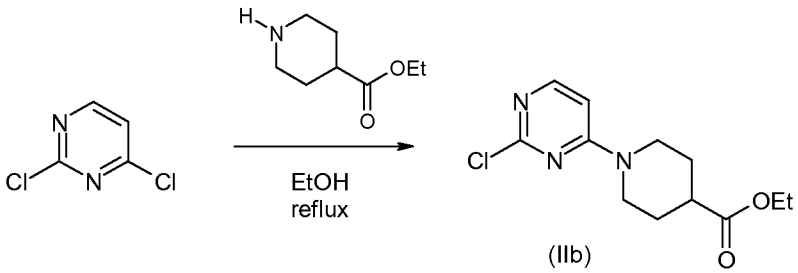
Where U represents N and V represents CH, in respect of step (i) the intermediate compounds of formula (II) can be prepared according to the processes set out in Schemes 2 and 3.

Scheme 2: pyrazole compounds of formula (IIa)



2,4-dichloropyrimidine is commercially available from Aldrich. The compounds of formula (V) wherein R^3 represents CF_3 or CH_3 are commercially available (from Aldrich and Orphachem respectively). The compounds of formula (V) wherein R^3 represents C_{2-4} alkyl can be prepared according to the process described in US2005096353 (see Scheme 6 at page 17 and the Examples).

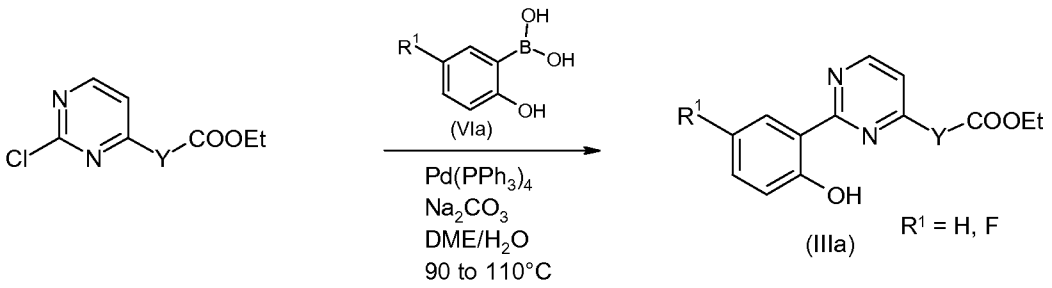
Scheme 3: piperidine compound of formula (IIb)



Ethyl isonipecotate is commercially available (from Aldrich). The compound of formula (IIb) can also be prepared in a solvent such as acetone, CH_3CN or THF in the presence of a base such as Na_2CO_3, K_2CO_3 or Cs_2CO_3, under reflux.

Where U represents N and V represents CH, in respect of step (ii) the intermediate compounds of formula (III) can be prepared according to the processes set out in Schemes 4, 5 and 6.

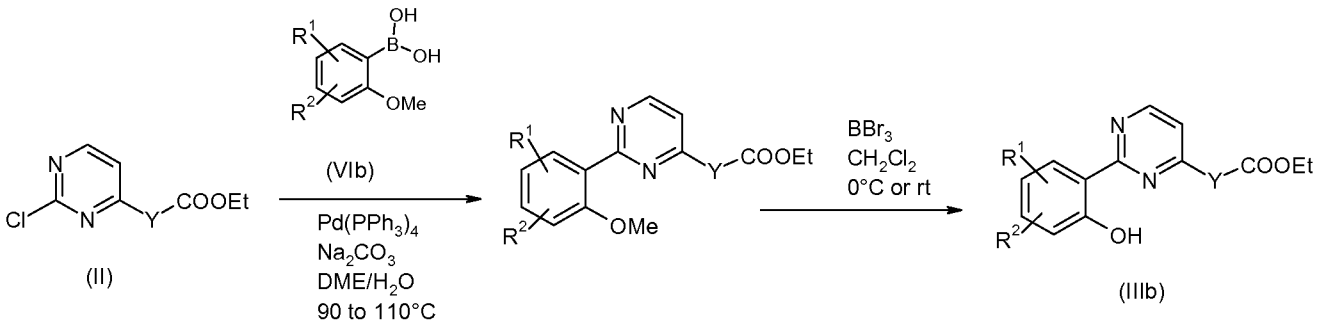
Scheme 4



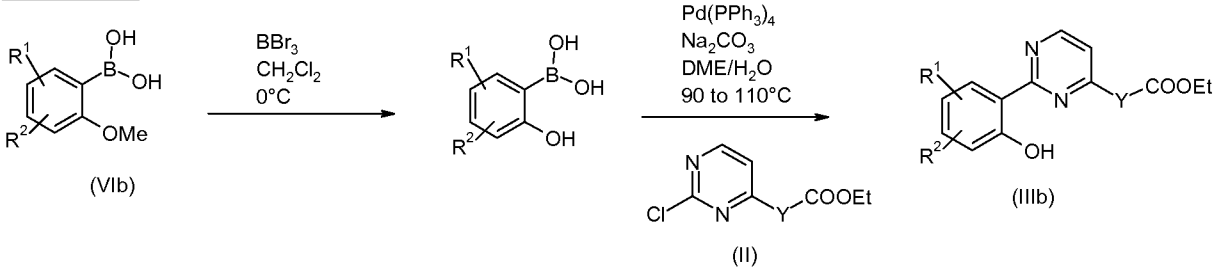
2-hydroxyphenyl boronic acid is commercially available (from Aldrich) as is 5-fluoro-2-hydroxyphenyl boronic acid (from Apollo or Combi Blocks).

Scheme 5

The compounds of formula (IIIb) can be prepared from the boronic acids of formula (VIb); these are either commercially available or can be prepared by standard methods well-known to the person skilled in the art.



Scheme 6



Suitable, for example, for:
R^1 = Cl and R^2 =H
R^1 = R^2 = F
R^1 = CH_3 and R^2 = H
R^1 = CF_3 and R^2 = H

The compound of formula (VIb) where R^1 is ethyl and R^2 is hydrogen may be prepared as described in WO2005019151.

Certain compounds of formula (VIb) are commercially available, for example where R^1 is in a para position relative to the $-OCH_2-$ linker and R^2 is in an ortho position relative to the $-OCH_2-$ linker:

R^1	R^2	available from

methyl	H	Aldrich
isopropyl	H	Aldrich or Alfa Aesar
t-butyl	H	Alfa Aesar
CF_3	H	Combi-Blocks
H	methyl	Chempacific
H	CF_3	Chempacific

Compounds of formula (VIb) where R^1 is propyl in a para position relative to the $–OCH_2–$ linker and R^2 is hydrogen may be prepared from the corresponding 4-propyl anisole by (i) bromination in the position ortho to the methoxy group and (ii) conversion of the bromine to a boronic acid group by standard methods.

Analogous processes may be used to prepare other compounds of formula (VIb) where R^1 is C_{1-4}alkyl and R^2 is as defined above. For example, 2-bromo-4,6-dimethyl phenol is commercially available from Bionet.

Compounds of formula (VIb) where R^1 is H and R^2 is ethyl, isopropyl or t-butyl in an ortho position relative to the $–OCH_2–$ linker may be prepared from the corresponding 2-ethyl-anisole, 2-isopropyl-anisole or 2-t-butyl-anisole, by

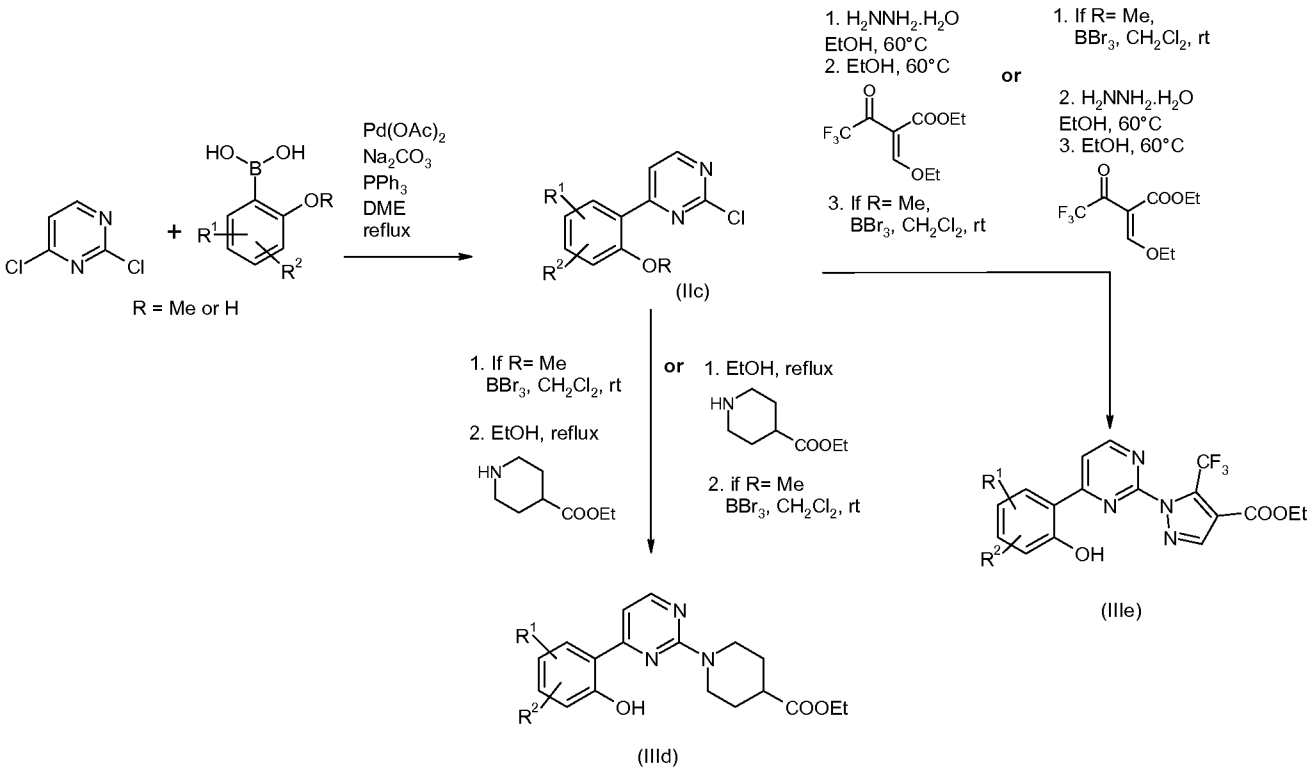
(i) bromination in the position ortho to the methoxy group using NBS and diisopropylethylamine (by a method as described in US2004235852, page 29, compound (0231)), and

(ii) conversion of the bromine to a boronic acid group by standard methods.

Analogous processes may be used to prepare other compounds of formula (VIb) where R^2 is C_{1-4}alkyl and R^1 is as defined above.

Where U represents CH and V represents N, in respect of steps (i) and (ii) the intermediate compounds of formula (II) and (III) can be prepared according to the processes set out in Scheme 7.

Scheme 7

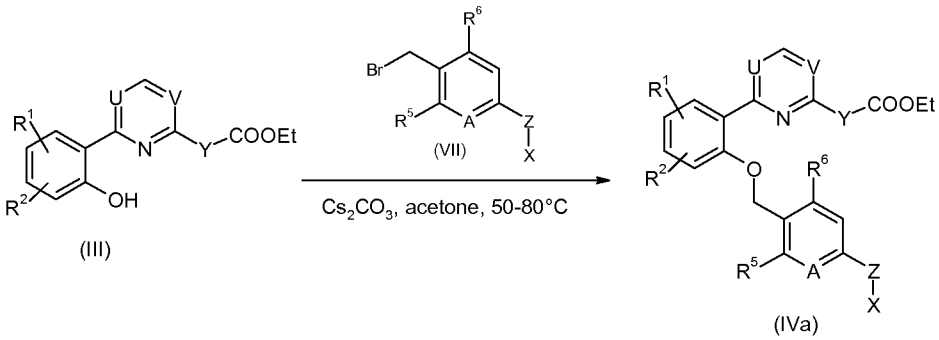


2-hydroxy-phenylboronic acid and 5-methyl-2-methoxy-phenylboronic acid are commercially available from Aldrich. 5-chloro-2-hydroxy-phenylboronic acid, 5-fluoro-2-hydroxy-phenylboronic acid and 5-trifluoromethyl-2-methoxy-phenylboronic acid are commercially available from Combi-blocks.

In respect of step (iii), the following general synthetic schemes can be used (Schemes 8, 9 and 10).

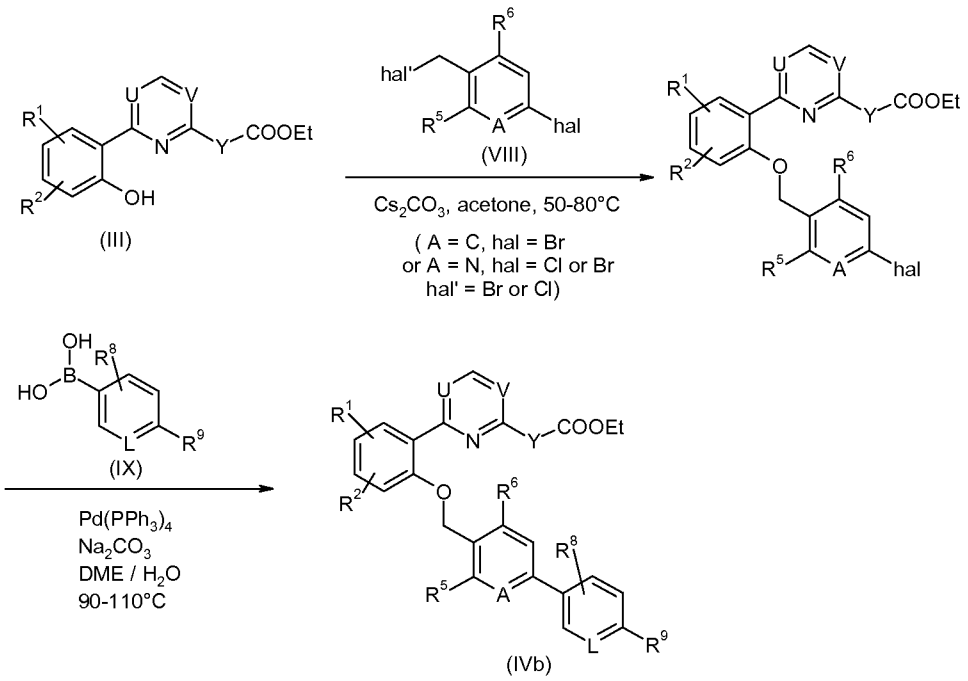
The synthesis described in Scheme 8 is particularly suitable for compounds wherein either A, J or L represents N or Z represents O (although it can also be used wherein Z is absent).

Scheme 8



Scheme 9

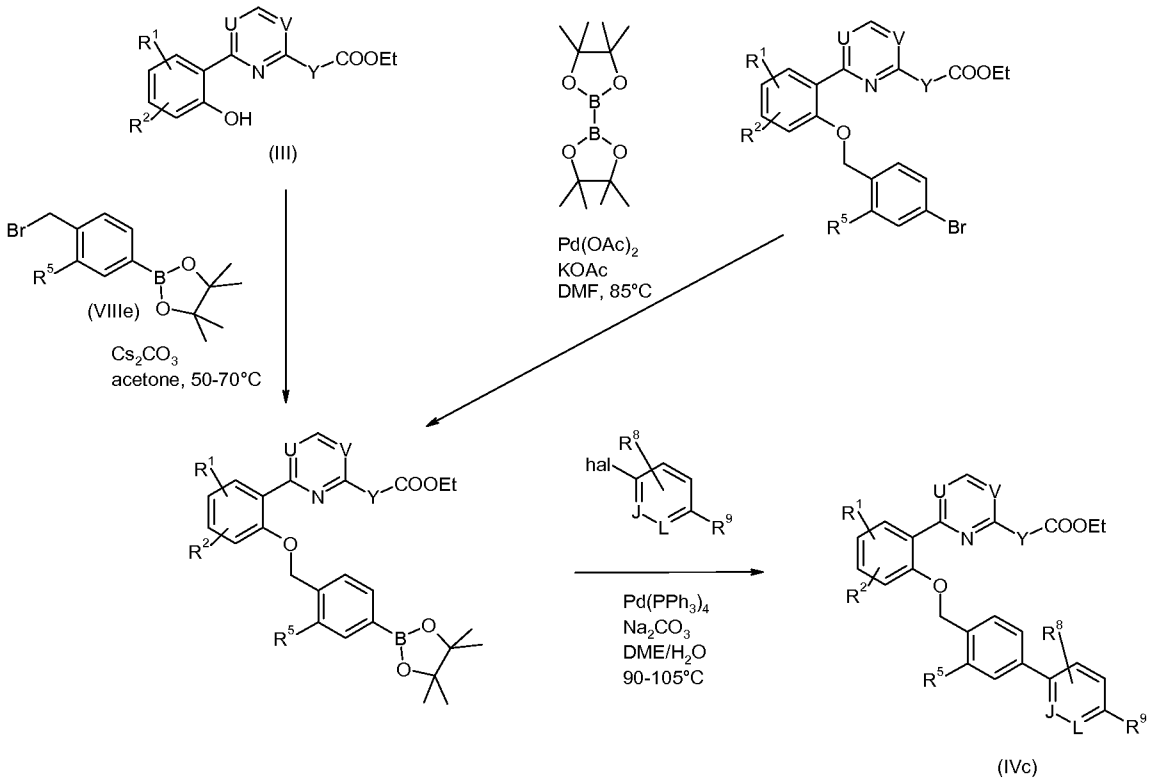
The synthesis described in Scheme 9 relates to compounds wherein Z is absent and both J and L represent CH or J represents CH and L represents N and is particularly suitable for compounds wherein R^5 represents F or Cl.



Compounds of formula (IX) are either commercially available or can be prepared by standard methods well-known to the person skilled in the art.

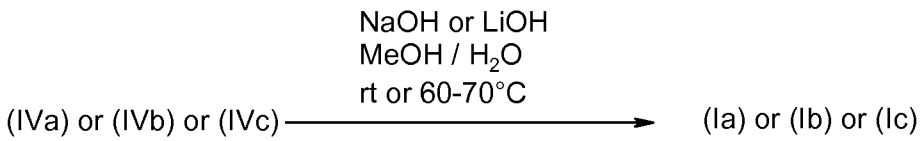
Compounds of formula (IVc) wherein A represents CH and Z is absent and/or J or L represent N may be prepared by the following method (Scheme 10) - as an alternative to using Scheme 8 or 9 above.

Scheme 10



The subsequent step (iv) may be carried out according to Scheme 11a.

Scheme 11a

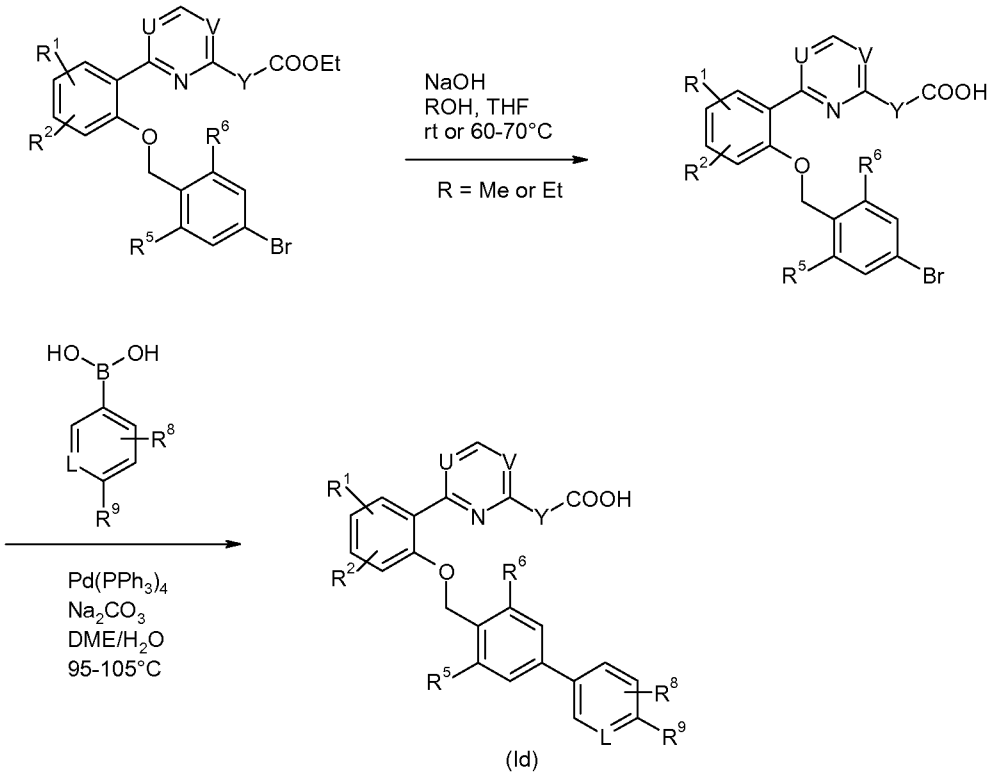


The temperature used in this ester hydrolysis reaction will depend on the nature of the compound and the length of time for which the reaction is performed; this will be well appreciated by the person skilled in the art.

Where R^9 represents CN, the ester hydrolysis reaction is instead suitably carried out using LiOH at room temperature to avoid hydrolysis of the cyano group to an amide group.

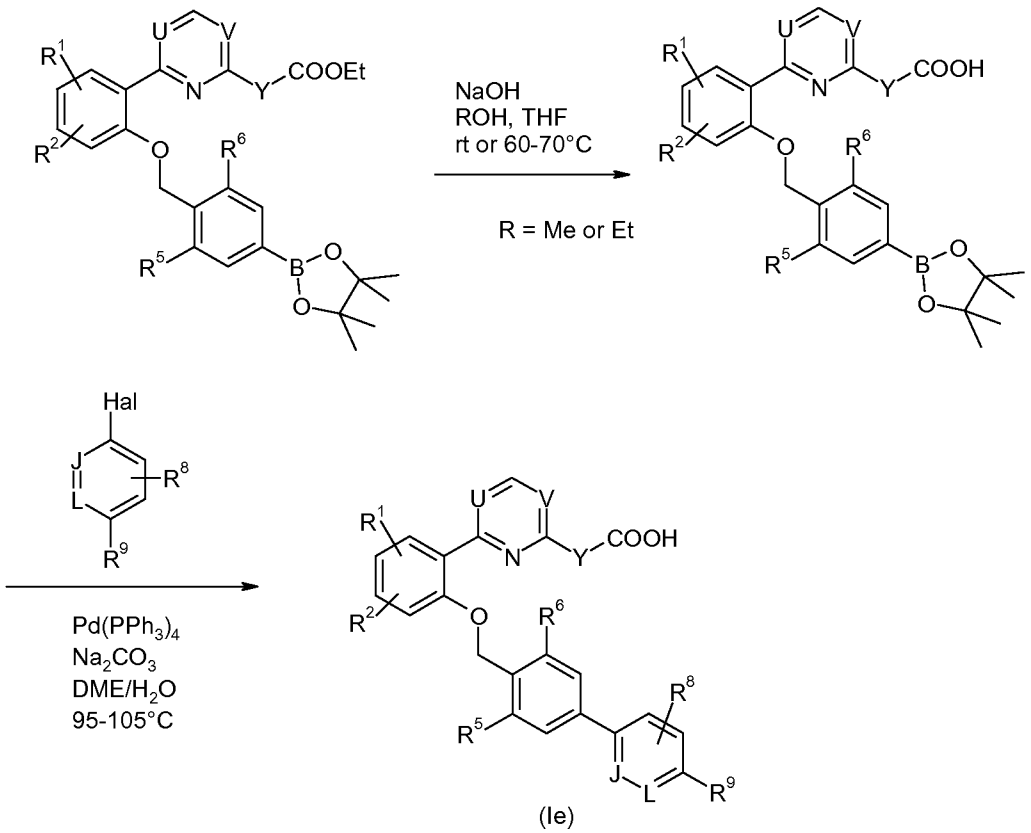
As an alternative, where R^9 represents CN or CO_2R^{12} (R^{12} represents C_{1-4}-alkyl) Schemes 11b and 11c may suitably be used to prepare compounds of formula (I):

Scheme 11b


NaOH
ROH, THF
rt or 60-70°C
R = Me or Et
Pd(PPh3)4
Na2CO3
DME/H2O
95-105°C

(Id)

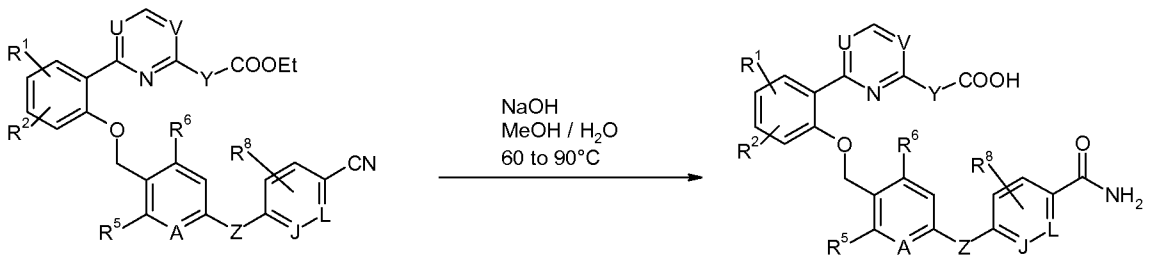
Scheme 11c



(Ie)

Certain compounds of formula (I) wherein R^9 represents $CONH_2$ may also be prepared by the following scheme (Scheme 12) from the corresponding nitrile derivatives (of formula (IVa) or (IVb) or (IVc)) wherein R^9 represents CN synthesised as described in Schemes 8, 9 or 10 above).

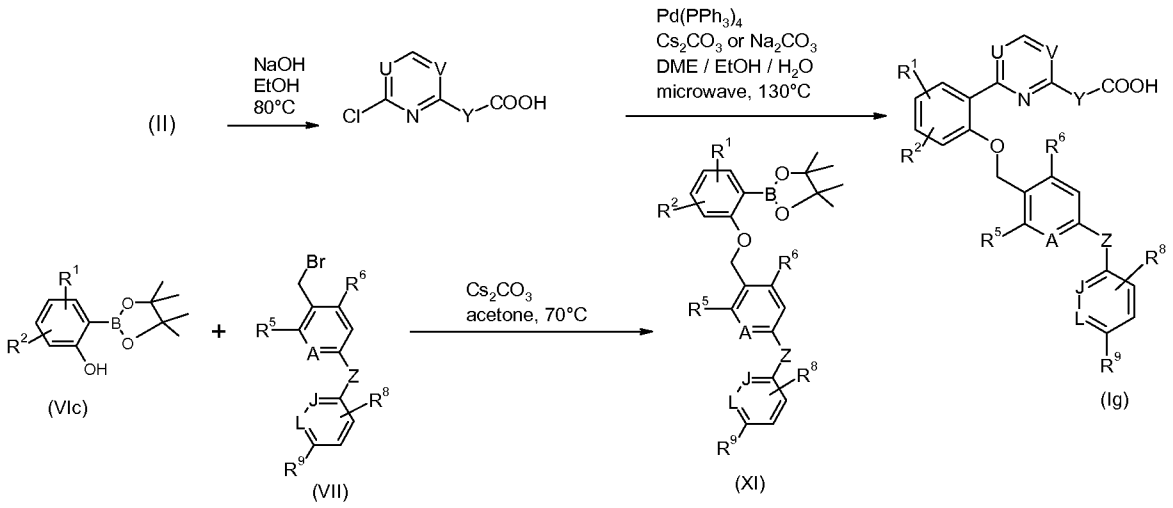
Scheme 12



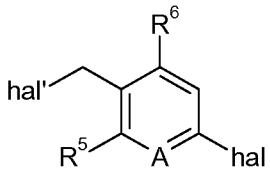
(IVa to IVe) (If)

Scheme 13

Scheme 13 is particularly suitable to prepare compounds wherein R^9 represents CN, Z is absent or Z represents O.



In respect of the compounds of formula (VIII):

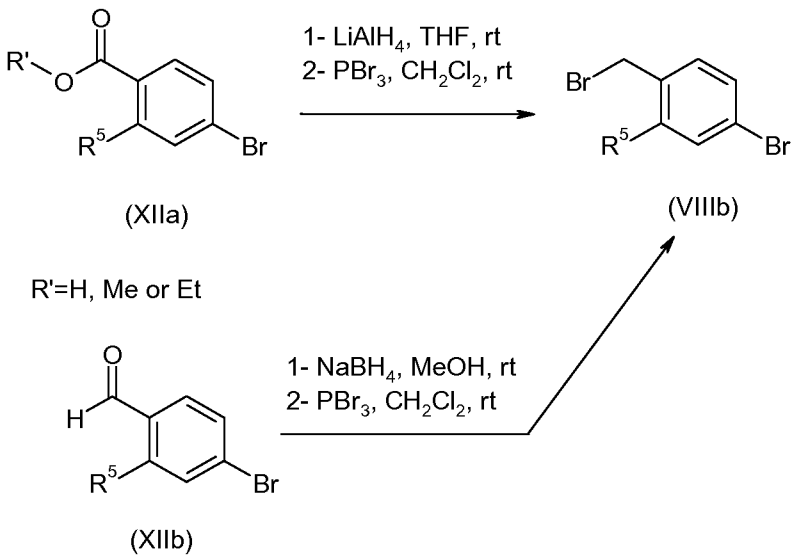


(VIII)

hal' is chloro or bromo if such compounds are commercially available. If not, then the corresponding compound wherein hal' is bromo may be used and may be prepared by standard methods. 2-chloro-5-chloromethylpyridine and 4-bromo-2-fluoro-benzyl bromide are both commercially available (from Aldrich). Other compounds of formula (VIII) may generally be prepared by the following methods (Schemes 14, 15 and 16) or by other standard methods well-known to the person skilled in the art.

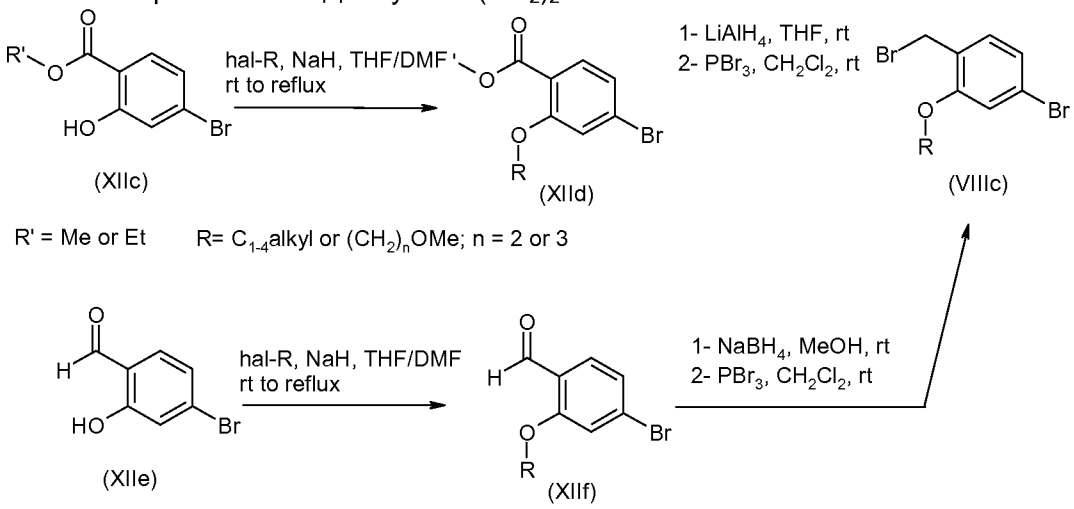
Scheme 14

When R^5 represents Me, OMe or Cl:



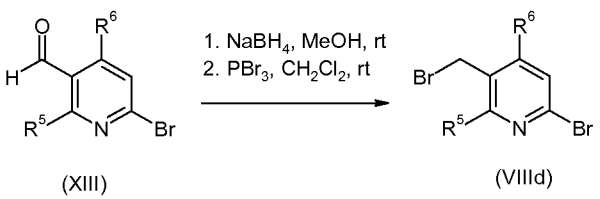
Scheme 15

When R^5 represents OC_{1-4} alkyl or $O(CH_2)_2OMe$:



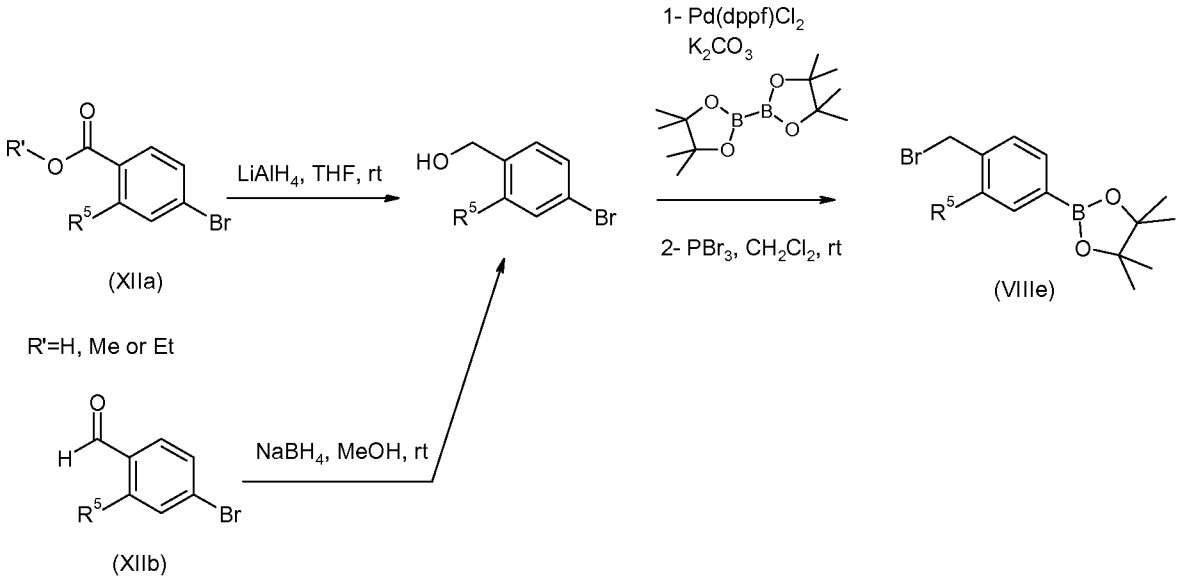
Compounds of formula (XIIa), (XIIb), (XIIc) and (XIId) are commercially available: 4-bromo-2-methylbenzoic acid, 4-bromo-2-chlorobenzoic acid, methyl 4-bromo-2-methoxybenzoate (from Aldrich) or 4-bromo-2-hydroxybenzoic acid (from Apin) and 4-bromo-2-hydroxybenzaldehyde (from Apin); or may be prepared by standard methods well-known to the person skilled in the art.

Scheme 16a



Certain compounds of formula (XIII) are commercially available, for example wherein R^5 represents H and R^6 represents Me or R^5 represents Me and R^6 represents H (from Asymchem). Other compounds of formula (XIII) may be prepared by standard methods well-known to the person skilled in the art.

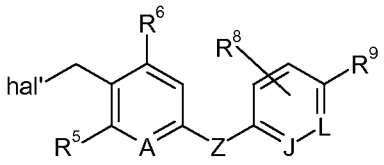
Scheme 16b



(XIIa) (VIIIe)

(XIIb)

Preparation of compounds of formula (VII)



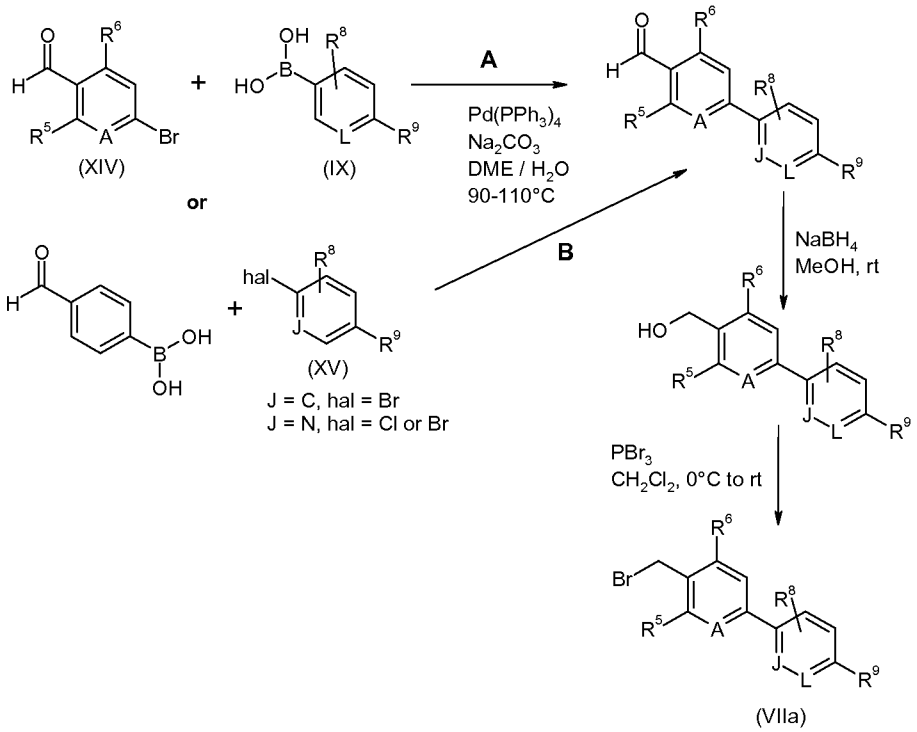
(VII)

may be carried out according to the following Schemes 17 to 21.

Synthesis of biphenyl compounds of formula (VII) wherein Z is absent can be carried out according to Schemes 17 or 18.

Scheme 17

Scheme 17 is particularly suitable for compounds wherein one of A, J or L represents N.



Pathway A is thus typically used where A represents N or L represents N; and pathway B is typically used where J represents N. In respect of the compounds of formula (IX), 2-methoxypyridine-5-boronic acid is available from Aldrich and 2-cyanopyridine-5-boronic acid and 2-trifluoromethylpyridine-5-boronic acid are available from Frontier; other compounds of formula (IX) not commercially available may be prepared by standard methods well-known to the person skilled in the art.

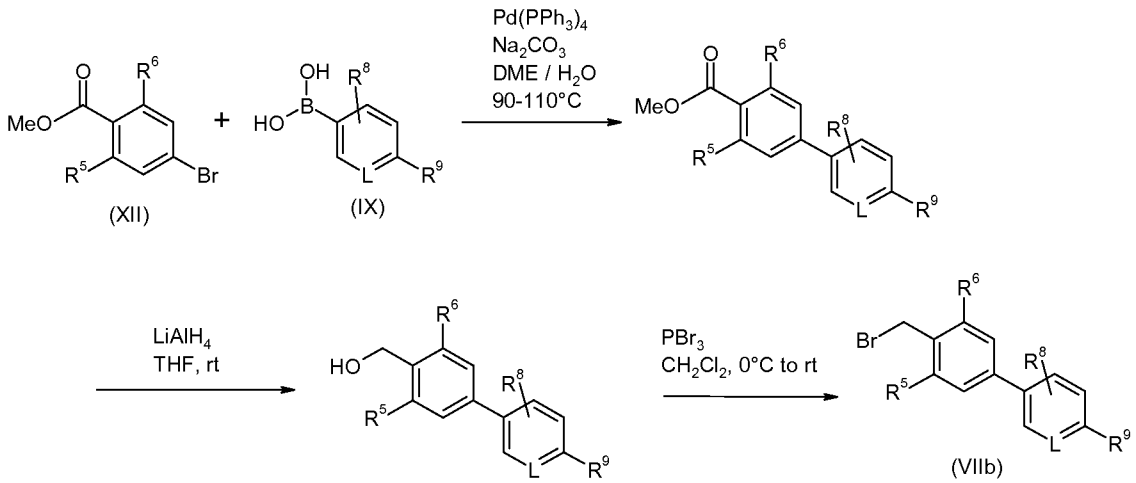
Certain compounds of formula (XIV) are commercially available, for example: where A represents CH and R^5 represents Me (Betapharma); A represents CH and R^5 represents OMe (Aldrich); A represents CH and R^5 represents F (Aldrich). Where A represents N, note the earlier reference to compounds of formula (XIII) in Scheme 16. Other compounds of formula (XIV) may be prepared by standard methods well-known to the person skilled in the art.

Certain compounds of formula (XV) are commercially available, for example: wherein J represents N, R^8 represents H and R^9 represents CN, CF_3, COOR, Cl or OMe (Aldrich, Fluka or Acros); wherein J represents N, R^8 represents Cl and R^9 represents CF_3 (Aldrich). Other compounds of formula (XV) may be prepared by standard methods well-known to the person skilled in the art.

Pathway B is also typically used where J and L both represent CH where hal represents Br.

Scheme 18a

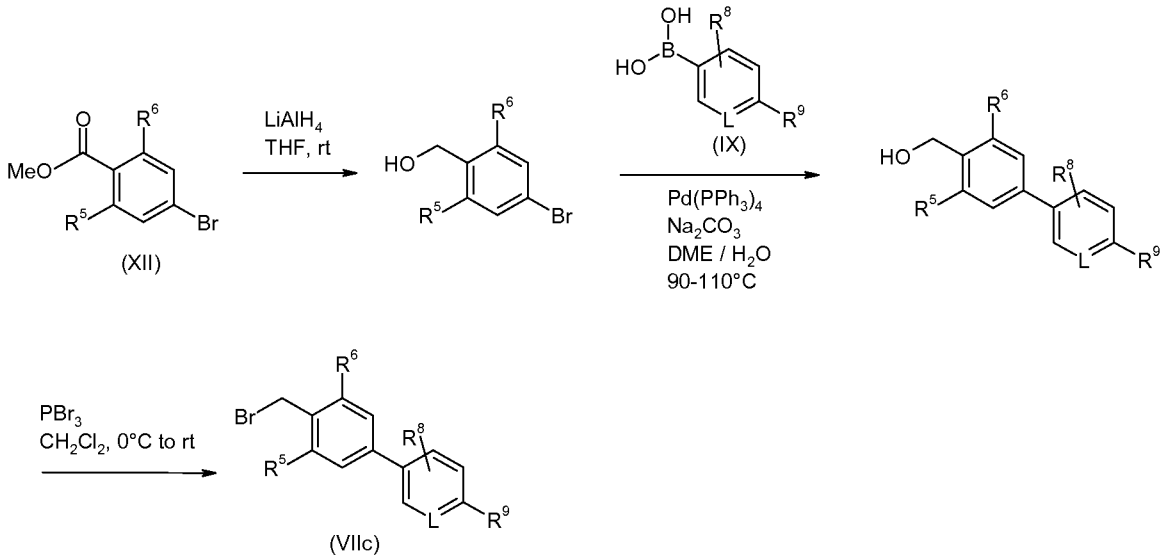
When R^9 is other than CN or CO_2R^{12} (R^{12} represents C_{1-4}alkyl) and A and J each represent CH and R^5/R^6 is other than halogen, Scheme 18a is particularly suitable.



(XII) (IX) (VIIb)

Scheme 18b

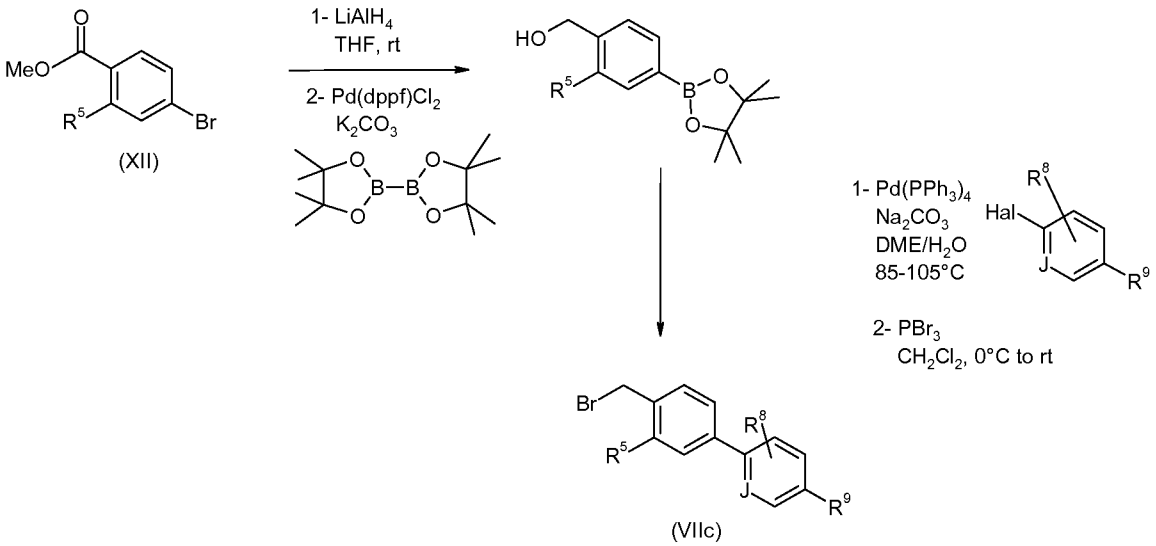
When R^9 is CN or CO_2R^{12} (R^{12} represents C_{1-4}alkyl) and A and J each represent CH and/or R^5/R^6 is halogen, Scheme 18b is particularly suitable.



(XII) (VIIc)

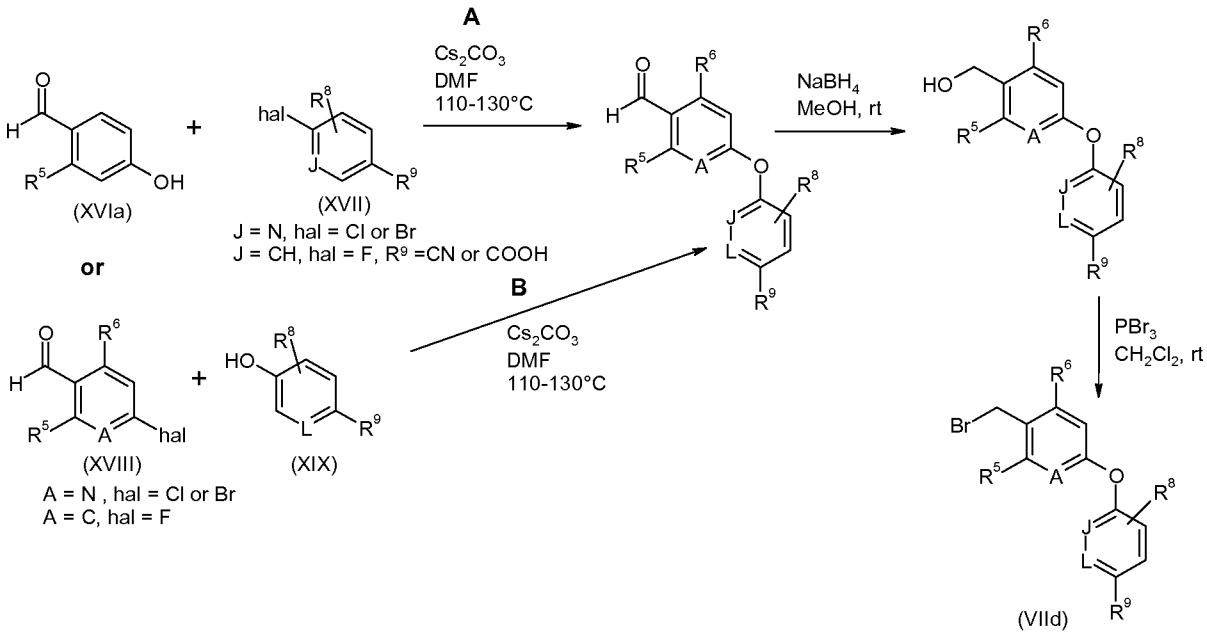
Scheme 18c

When R^9 is CN or CO_2R^{12} (R^{12} represents C_{1-4}alkyl) and A represents CH, and J represents N and/or R^5/R^6 is halogen, Scheme 18c is particularly suitable.



Synthesis of compounds of formula (VII) with Z representing O, can be carried out according to Schemes 19, 20 or 21.

Scheme 19



Pathway A is thus typically used for J represents N and/or R^9 represents CN, COOR and/or R^5 represents H, Me, OMe. Pathway B is thus typically used for A represents N or for A represents CH and hal represents F and R^5 represents H, Me, or OMe.

Compounds of formula (XVIa) are commercially available, for example: 4-hydroxy-2-methylbenzaldehyde (Interchim), 4-hydroxy-2-methoxybenzaldehyde (Fluka or Acros), and 4-hydroxybenzaldehyde (Aldrich).

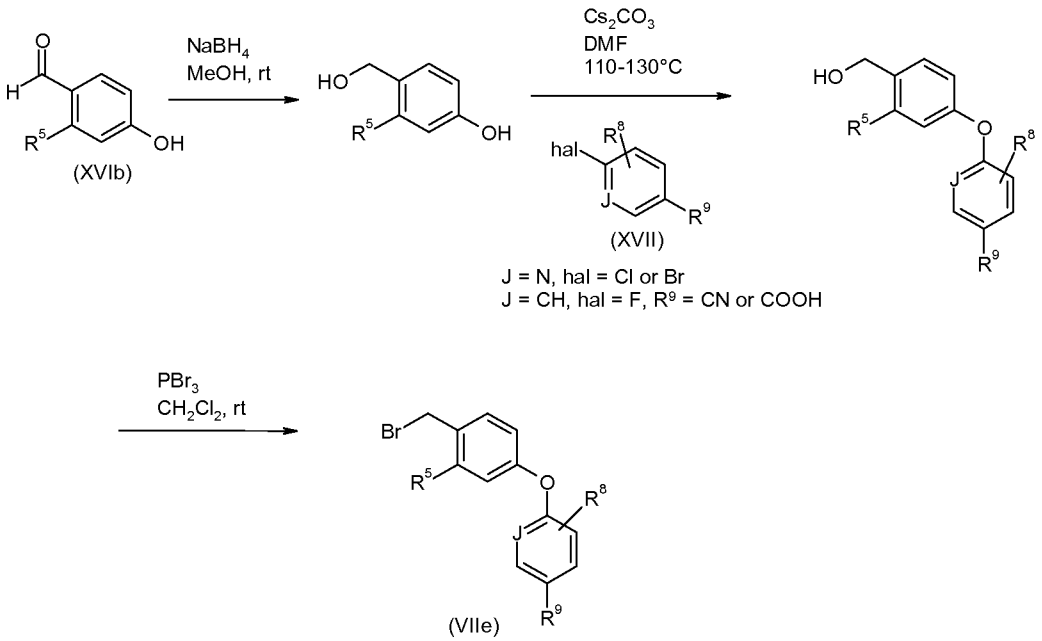
In respect of the compounds of formula (XVIII), note the earlier reference to compounds of formula (XIII) in Scheme 16a. Certain compounds of formula (XVIII) are commercially

available, for example: wherein A represents CH and R^5 represents H, Me or OMe (Aldrich, Apollo or Apin); or wherein A represents N and R^5 and R^6 each represents H (Aldrich). Other compounds of formula (XVIII) may be prepared by standard methods well-known to the person skilled in the art.

Phenol derivatives of formula (XIX) are commercially available or may be prepared by standard methods well-known to the person skilled in the art.

Scheme 20

Where R^5 represents Cl or F:

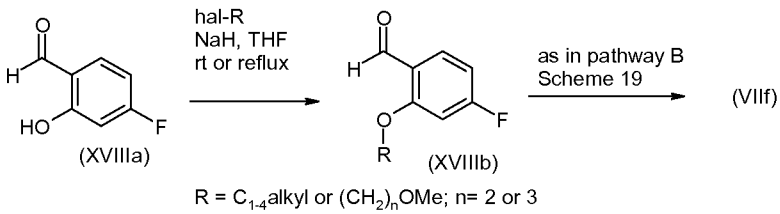


Compounds of formula (XVIb) are commercially available, for example from Aldrich for R^5 represents Cl and from Apin for R^5 represents F.

Certain compounds of formula (XVII) are commercially available, for example: wherein hal represents Br or Cl, J represents N, R^8 represents H, and R^9 represents CN, CF_3, COOR, Cl or OMe (Aldrich, Fluka or Acros); wherein hal represents Cl, J represents N, R^8 represents Cl, and R^9 represents CF_3 (Aldrich); wherein J represents CH, hal represents F, R^8 represents H, F, Cl, OMe, Me, or CF_3, and R^9 represents CN or COOR (Aldrich, Acros, Apin). Other compounds of formula (XVII) may be prepared by standard methods well-known to the person skilled in the art.

Scheme 21

Where R^5 represents OC_{1-4}alkyl or $O(CH_2)_2OMe$:



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 minor variation, 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).

In the reporting of Proton Magnetic Resonance (^{1}H NMR) spectral data, 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
TLC	thin layer chromatography
AcOH	acetic acid
AIBN	azo bis-isobutyronitrile
BBr_3	boron tribromide
tBuOH	tert-butanol
tBuONO	tert-butyl nitrite
Cs_2CO_3	cesium carbonate
CCl_4	carbon tetrachloride
CH_2Cl_2	dichloromethane
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol

i-Pr_2O	di-isopropyl ether
CH_3CN	acetonitrile
cHex	cyclohexane
MeOH	methanol
THF	tetrahydrofuran
RT or rt	room temperature
Rt	retention time
DIEA	*N*,*N*-diisopropylethylamine
EtOAc	ethyl acetate
$NaBH_4$	sodium borohydride
LC/MS	liquid chromatography mass spectroscopy
LC-HRMS	liquid chromatography high resolution mass spectroscopy
$LiAlH_4$	lithium aluminium hydride
LiOH	lithium hydroxyde
K_2CO_3	potassium carbonate
$NaBH_4$	sodium borohydride
Na_2CO_3	sodium carbonate
$NaHCO_3$	sodium bicarbonate
NaN_3	sodium azide
NaOH	sodium hydroxide
Na_2SO_4	sodium sulfate
PBr_3	phosphorus tribromide
$POCl_3$	Phosphorus (III) oxychloride
Pd/C	Palladium on carbon
$Pd(Ph_3P)_4$	Palladium tetrakis(triphenylphosphine)
$CDCl_3$	deuterated chloroform
DMSO d6	deuterated dimethylsulfoxide

Analytical method LC-MS

Analytical HPLC was conducted on a X-terra MS C18 column (2,5 µm 3*30 mm id) eluting with 0.01M ammonium acetate in water (solvent A) and 100% acetonitrile (solvent B) using the following elution gradient: 0 ➔ 4 minutes, 5%B ➔ 100%B; 4 ➔ 5 minutes, 100%B at a flowrate of 1.1 mL/min with a temperature of 40°C. 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.

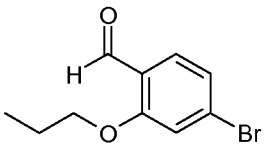
Analytical LC-HRMS

Methods:

(a) Analytical HPLC was conducted on a LUNA 3u C18 column (2,5 µm 30*3 mm id) 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%B ➔ 100%B; 3.5 ➔ 4 minutes, 100%B; 4 ➔ 4.5 minutes, 100%B ➔ 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.

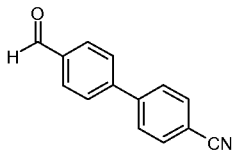
(b) Analytical HPLC was conducted on a X-Bridge C18 column (2,5 µm 30*3 mm id) eluting with 0.01M ammonium acetate in water (solvent A) and 100% acetonitrile (solvent B) using the following elution gradient: 0 ➔ 0.5 minutes, 5%B; 0.5 ➔ 3.5 minutes, 5%B ➔ 100%B; 3.5 ➔ 4 minutes, 100%B; 4 ➔ 4.5 minutes, 100%B ➔ 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.

Description 1: 4-bromo-2-propyloxy-benzaldehyde (D1)



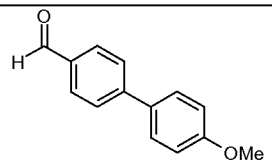
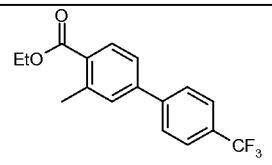
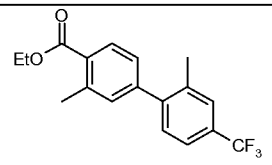
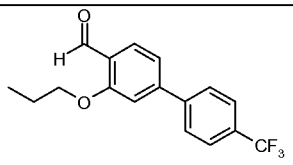
To a solution of 4-bromo-2-hydroxybenzaldehyde (Apin, 5g, 24.87mmol) in DMF (80ml) was added portionwise NaH (60% in mineral oil, 1.19g, 29.85mmol) and the mixture was stirred at room temperature for 30 minutes. Then 1-bromopropane (2.71ml, 29.85mmol) was added and the mixture was heated at 50°C for 4 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 triturated with cHex, and the resulting precipitate was filtered and dried . The title compound was obtained as a cream powder (3.7g, yield= 61.2%). LC/MS: 245 (M+H), Rt= 3.43min. ^1H NMR (300MHz, $CDCl_3$, ppm): 7.7 (d, 1H), 7.2 (d + s, 2H), 4.05 (t, 2H), 1.9 (m, 2H), 1.1 (t, 3H).

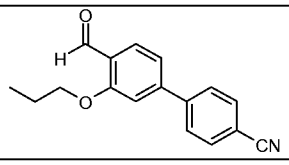
Description 2a: 4-(4-cyanophenyl)-benzaldehyde (D2a)



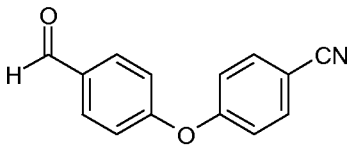
To a solution of 4-bromobenzaldehyde (Aldrich, 3g, 16.2mmol) in DME (80ml) and H_2O (10ml) were added $Pd(PhP_3)_4$ (0.937g, 0.81mmol), 4-cyanophenylboronic acid (Aldrich, 2.86g, 19.46mmol) and Na_2CO_3 (4.29g, 40.53mmol). The mixture was heated at 90°C for 3 hours, cooled and poured into water. After extraction with CH_2Cl_2, the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. After purification by chromatography on silicagel (CH_2Cl_2 / cHex, 4/1), the title compound was obtained as a cream solide (3g, yield: 89.4%). H^1 NMR (300MHz, $CDCl_3$, ppm): 10 (s, 1H), 8.05 (d, 2H), 7.8 (m, 6H).

Prepared by a similar method as described for D2a:

Description No.	Structure	Prepared from	Analytical data
D2b		4-bromobenzaldehyde and 4-methoxyphenyl boronic acid	As white crystals (yield= 84.1%). LC/MS: 213.2 (M+H) , Rt= 3.14min
D2c		Ethyl 4-bromo-2-methyl benzoate and 4-trifluoromethyl phenyl boronic acid	As red oil (yield= 97%) ^1H NMR (300MHz, $CDCl_3$, ppm): 8.04 (d, 1H), 7.73 (bs, 4H), 7.49 (m, 2H), 4.41 (q, 2H), 2.7 (s, 3H), 1.44 (t, 3H)
D2d		Ethyl 4-bromo-2-methyl benzoate and 2-methyl-4-trifluoromethyl phenyl boronic acid	
D2e		D1 and 4-trifluoromethyl phenyl boronic acid	As yellow solid (yield= 96.2%). LC/MS: 309.1 (M+H), Rt= 3.96min. ^1H NMR (300MHz, $CDCl_3$, ppm): 7.95 (d, 1H), 7.75 (s, 4H), 7.25 (dd, 1H), 7.2 (sd, 1H), 4.15 (t, 2H), 1.95 (m, 2H), 1.15 (t, 3H)

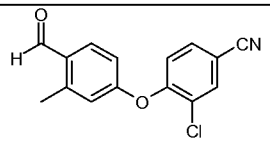
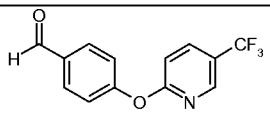
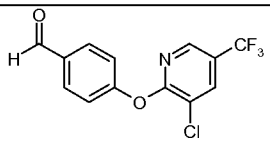
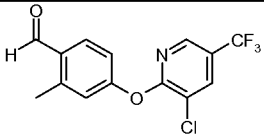
D2f		D1 and 4-cyanophenyl boronic acid	As white solid (yield= 86%). LC/MS: 266.1 (M+H), Rt= 3.50min

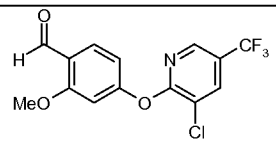
Description 3a: 4-(4-cyanophenoxy)-benzaldehyde (D3a)



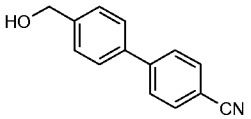
To a solution of 4-hydroxybenzaldehyde (Aldrich, 5.04g, 41.28mmol), in DMF(50ml) was added portionwise Cs_2CO_3 (14.79g, 45.41mmol) and the mixture was stirred at room temperature for 10 minutes. Then 4-fluorobenzonitrile (Aldrich, 5g, 41.28mmol) was added and the mixture was heated at 110°C for 2 hours, 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. After purification by chromatography on silicagel (CH2Cl2 / cHex, 3/2, then 4/1), the title compound was obtained as a white solid(5.25g, yield: 57.0%). LC/MS: 224.1 (M+H) , Rt= 3.07min.

Prepared by a similar method as described for D3a:

Description No.	Structure	Prepared from	Analytical data
D3b		4-hydroxy-2-methyl-benzaldehyde and 3-chloro-4-fluoro-benzonitrile	As a white solid (4.2g, yield= 80%). LC/MS: 272.1 (M+H), Rt= 3.31min
D3c		4-hydroxy benzaldehyde and 2-chloro-5-trifluoromethyl pyridine	As colorless oil which crystallised (yield= 65.5%). LC/MS: 268.1 (M+H) , Rt= 3.18min
D3d		4-hydroxy benzaldehyde and 2,3-di-chloro-5-trifluoromethyl pyridine	As yellow oil (quantitative yield). LC/MS: 302.0 (M+H), Rt= 3.44min
D3e		4-hydroxy-2-methyl benzaldehyde and 2,3-di-chloro-5-trifluoromethyl pyridine	As pale yellow oil (yield= 99%). LC/MS: 316.0 (M+H), Rt= 3.63min

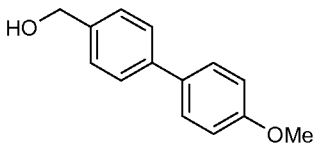
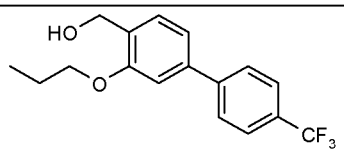
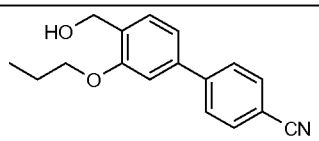
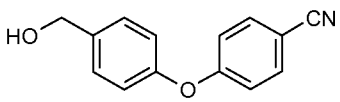
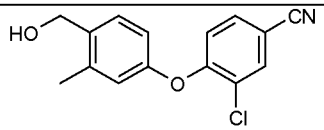
D3f		4-hydroxy-2-methoxy benzaldehyde and 2,3-di-chloro-5-trifluoromethyl pyridine	As cream powder (yield= 70.4%). LC/MS: 332.0 (M+H), Rt= 3.50min

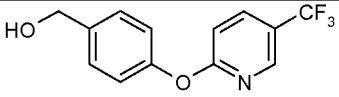
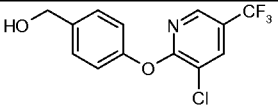
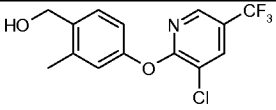
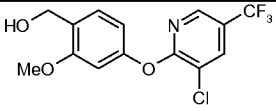
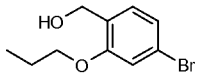
Description 4a: 4-(4-cyanophenyl)-benzyl alcohol (D4a)



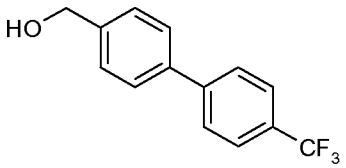
To a solution of 4-(4-cyanophenyl)-benzaldehyde (D2a, 1.5g, 7.25mmol) in MeOH (50ml) was added portionwise $NaBH_4$ (0.303g, 7.97mmol). The mixture was stirred at room temperature for 30 minutes and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The title compound was obtained as a cream solid (1.49g, yield: 98.4%). H^1 NMR (300MHz, $CDCl_3$, ppm): 7.65 (q, 4H), 7.55 (d, 2H), 7.45 (d, 2H), 4.7 (s, 2H).

Prepared by a similar method as described for D4a:

Description No.	Structure	Prepared from	Analytical data
D4b		D2b	As a white solid (92.8%). H^1 NMR (300MHz, $CDCl_3$, ppm): 7.55 (t, 4H), 7.45 (d, 2H), 7 (d, 2H), 4.75 (s, 2H), 3.9 (s, 3H)
D4c		D2e	As a cream solid (yield= 98.24%) LC/MS: Rt= 3.64min. ^1H NMR (300MHz, $CDCl_3$, ppm): 7.65 (s, 4H), 7.35 (d, 1H), 7.15 (dd, 1H), 7.05 (sd, 1H), 4.7 (s, 2H), 4 (t, 2H), 1.85 (m, 2H), 1 (t, 3H)
D4d		D2f	As a white solid (yield= 97%). LC/MS: 266.1 (M-H), Rt= 3.16min
D4e		D3a	As a colorless oil which crystallised (5.13g, yield: 97.8%). LC/MS: 224.1 (M-H) , Rt=2.82min
D4f		D3b	As a colorless oil which crystallised (yield= 98%). LC/MS: 272.1 (M+H), Rt= 3.02min
D4g		D3c	As a colorless oil (yield= 98.6%). LC/MS: 270.1 (M+H) , Rt= 2.85min

			
D4h		D3d	As a yellow oil ((quantitative yield) LC/MS: 304.0 (M+H), Rt= 3.13min
D4i		D3e	As a yellow oil (yield= 97%) LC/MS: 318.0 (M+H), Rt= 3.30min
D4j		D3f	As a yellow oil (yield= 96.1%) ^{1}H NMR ($CDCl_3$, ppm): 8.2 (bs, 1H), 7.92 (bs, 1H), 7.28 (d, 1H), 6.67 (dd, 1H), 6.65 (bs, 1H), 4.63 (bs, 2H), 3.78 (s, 3H)
D4k		D1	As a yellow oil (yield= 99%) LC/MS: Rt= 3.06min

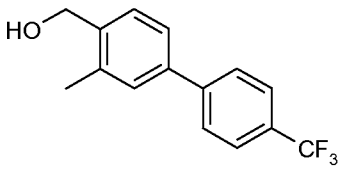
Description 5a: 4-(4-trifluoromethylphenyl)-benzyl alcohol (D5a)



To a solution of 4-(4-trifluoromethylphenyl)-benzoic acid (Apollo, 3g, 11.27mmol) in THF (100ml) was added dropwise a solution of $LiAlH_4$ 1M in THF (11.3ml, 11.27mmol) and the mixture was stirred at room temperature for 30 minutes. Water (50ml) was then added dropwise. The insoluble material was filtered on a Celite pad and washed with CH_2Cl_2. The filtrate was washed with CH_2Cl_2 and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The title compound was obtained as a white solid (1.9g, yield= 66.8%). H^1 NMR (300MHz, DMSO d6, ppm): 7.9 (d, 2H), 7.85 (d, 2H), 7.7 (d, 2H), 7.45 (d, 2H), 5.3 (t, 1H), 4.55 (d, 2H).

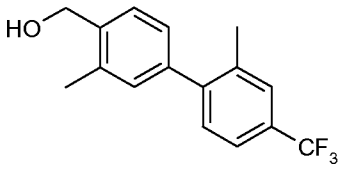
Prepared by a similar method as described for D5a:

Description 5b: 2-methyl-4-(4-trifluoromethylphenyl)-benzyl alcohol



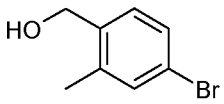
From ethyl 2-methyl-4-(4-trifluoromethylphenyl)-benzoate (D2c) as a grey powder (yield = 78%). ^{1}H NMR (300MHz, $CDCl_3$, ppm): 7.71 (bs, 4H), 7.49 (m, 2H), 7.44 (bs, 1H), 4.79 (s, 2H), 2.46 (s, 3H).

Description 5c: 2-methyl-4-(2-methyl-4-trifluoromethylphenyl)-benzyl alcohol (D5c)



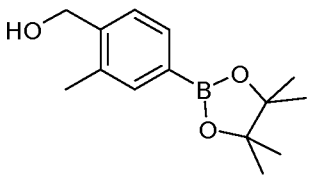
From ethyl 2-methyl-4-(2-methyl-4-trifluoromethylphenyl)-benzoate (D2d).

Description 5d: 4-bromo-2-methyl-benzyl alcohol (D5d)



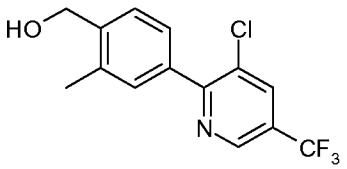
From 4-bromo-2-methylbenzoic acid (Aldrich) as a white powder (yield= 59.9%). LC/MS: Rt= 2.59min

Description 5e : [2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (D5e)



4-bromo-2-methyl-benzyl alcohol (D5d, 30 g, 150 mmol), bis(pinacolato)diboron (40 g, 156 mmol), $Pd(dppf)Cl_2$(II) (8 g, 10 mmol), and potassium acetate (44 g, 448 mmol) were dissolved in 1,4-dioxane (600 mL), and the reaction mixture was heated to reflux under N_2 for 4 h. After cooling, the reaction mixture was filtered, and the filtrate was concentrated. Purification by column chromatography (silica gel; petroleum ether: ethyl acetate = 5:1) afforded the title compound as a red oil (34 g, yield: 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50-7.38 (m, 3H), 5.14 (t, 1H), 4.51 (d, 2H), 2.22 (s, 3H), 1.28 (s, 12H).

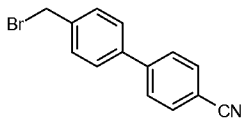
Description 5f : 2-methyl-4-(3-chloro-5-trifluoromethylpyridin-2-yl)-benzyl alcool (D5f)



To a solution of [2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (D5e, 5g, 20.2mmol) in dioxane (50ml) and H_2O (50ml) were added 2,3-dichloro-5-trifluoromethylpyridine (5.2g, 24mmol), $Pd(PPh_3)_4$ (0.69g, 0.6mmol) and K_2CO_3 (8.3g, 60.5mmol) and the mixture was heated at 100°C overnight. Dioxane was removed under reduced pressure and AcOEt and water were added. The organic phase was washed with brine, then water, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by

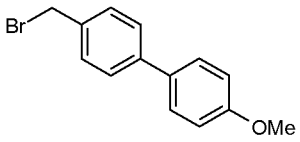
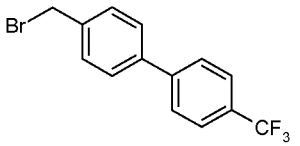
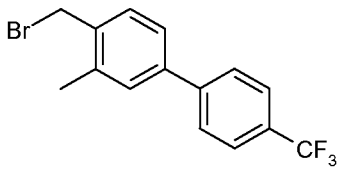
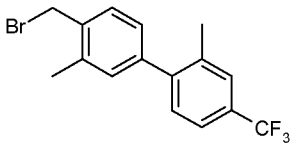
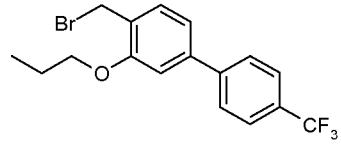
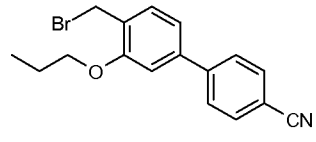
chromatography on Silicagel (petroleum ether/AcOEt, 5/1) afforded the title compound (4 g, yield: 65.9%). LC/MS: 301.7 (M+H), Rt= 1.7min

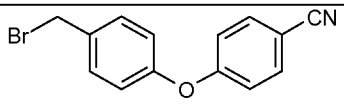
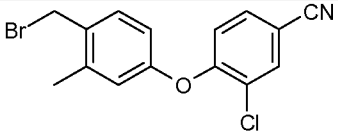
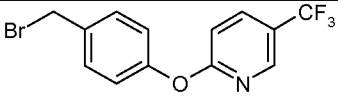
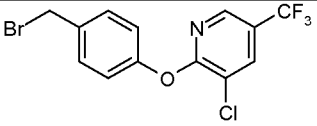
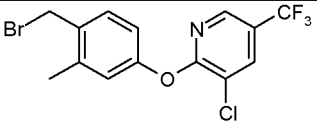
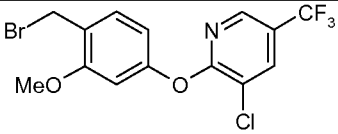
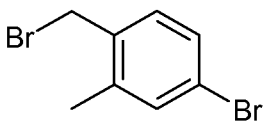
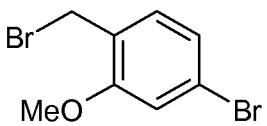
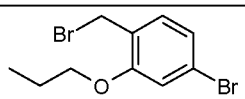
Description 6a: 4-(4-cyanophenyl)-benzyl bromide (D6a)

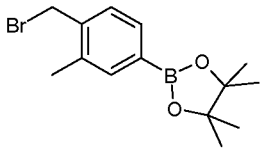
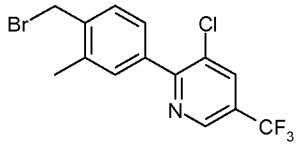


To a solution of 4-(4-cyanophenyl)-benzyl alcohol (D4a, 1.49g, 7.13mmol) in CH_2Cl_2 (40ml) cooled in a ice bath, was added dropwise PBr_3 (solution 1M/CH_2Cl_2, 3.56ml, 3.56mmol). The mixture was stirred at 0°C for 30 minutes, then at room temperature for 1 hour and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The title compound was obtained as a cream solid(1.8g, yield: 92.8%). LC/MS: Rt= 3.53min.

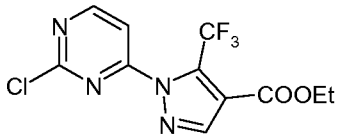
Prepared by a similar method as described for D6a:

Description No.	Structure	Prepared from	Analytical data
D6b		D4b	As a white solid (yield= 99.9%) H^1 NMR (300MHz, $CDCl_3$, ppm): 7.55 (2d, 4H), 7.45 (d, 2H), 7 (d, 2H), 4.6 (s, 2H), 3.9 (s, 3H)
D6c		D5a	As an orange solid (yield= 71.6%) H^1 NMR (300MHz, $CDCl_3$, ppm): 7.6 (s, 4H), 7.5 (d, 2H), 7.4 (d, 2H), 4.45 (s, 2H)
D6d		D5b	As a colorless oil which crystallised (yield= 94%). NMR (300MHz, $CDCl_3$, ppm): 7.7 (bs, 4H), 7.43 (m, 3H), 4.59 (s, 2H), 2.52 (s, 3H)
D6e		D5c	
D6f		D4c	As a cream solid (yield= 100%) LC/MS: Rt= 4.31min
D6g		D4d	As white solid (yield= 92%). LC/MS: Rt= 3.91min. ^1H NMR (300MHz, $CDCl_3$, ppm): 7.65 (d, 2H), 7.58 (d, 2H), 7.36 (d, 1H),

			7.05 (dd, 1H), 6.96 (sd, 1H), 4.54 (s, 2H), 4.01 (t, 2H), 1.84 (m, 2H), 1.05 (t, 3H)
D6h		D4e	As a colorless oil which crystallised (1.15g, yield: 99.8%) H^1 NMR (300MHz, $CDCl_3$, ppm): 7.65 (d, 2H), 7.45 (d, 2H), 7.1 (d, 2H), 7 (d, 2H), 4.55 (s, 2H)
D6i		D4f	As a colorless oil which crystallised (1.6g, yield: 93%). ^1H NMR ($CDCl_3$, ppm): 7.69 (sd, 1H), 7.41 (dd, 1H), 7.27 (d, 1H), 6.85 (d, 1H), 6.81 (bs, 1H), 6.77 (dd, 1H), 4.45 (s, 2H), 2.35 (s, 3H)
D6j		D4g	As a yellow oil which crystallised (yield= 97.1%). LC/MS: 318.0 (M+H) , Rt= 3.74min
D6k		D4h	As a colorless oil (yield= 91.1%) LC/MS: 367.9 (M+H), Rt= 3.89min
D6l		D4i	As pale yellow oil (yield= 95%) LC/MS: 381.8 (M+H), Rt= 4.05min
D6m		D4j	As a colorless oil which crystallised (yield= 92.5%) LC/MS: 397.8 (M+H), Rt= 3.92min
D6n		D5d	As a cream oil which solidified (yield= 96.1%). ^1H NMR (300MHz, $CDCl_3$, ppm): 7.37 (bs, 1H), 7.32 (d, 1H), 7.19 (d, 1H), 4.47 (s, 2H), 2.41 (s, 3H)
D6o		4-bromo-2-methoxy benzyl alcohol (Aldrich)	As a white solid (yield= 98% yield). ^1H NMR ($CDCl_3$): 7.25 (d, 1H), 7.15-7.0 (m, 2H), 4.5 (s, 2H), 3.95 (s, 3H). LC: Rt= 3.47 min.
D6p		D4k	As a cream oil (yield= 98%) LC/MS: Rt= 3.88min

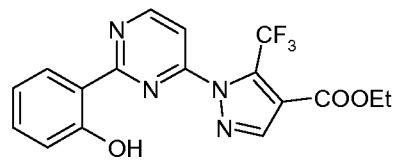
D6q		D5e	As a white solid (yield= 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ:7.62 (d, 1H), 7.31 (d, 1H), 7.26 (d, 1H), 4.51 (s, 2H), 2.42 (s, 3H), 1.34 (s, 12H). LC-MS: 311 (M+H).
D6r		D5f	As white crystals (yield= 47.3%) ^{1}H NMR (300MHz, $CDCl_3$, ppm): 8.83 (s, 1H), 8.04 (s, 1H), 7.58 (m, 2H), 7.43 (d, 1H), 4.56 (s, 2H), 2.5 (s, 3H)

Description 7: ethyl 1-(2-chloro-pyrimidin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (D7)



A solution of 2,4-dichloropyrimidine (2g, 13.42mmol) in THF (50ml) was added dropwise to a solution of hydrazine in THF (1M/THF, 100ml, 100mmol). The mixture was stirred at room temperature for 1 hour and then poured into water. After extraction with AcOEt, the organic phase was dried (Na_2SO_4), and concentrated under reduced pressure. The solid residue was dissolved in EtOH (50ml) and ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutyrate (Aldrich, 3.22g, 13.4mmol) was added. The reaction mixture was stirred at room temperature for 18 hours and then concentrated under reduced pressure. The residue was purified by chromatography on silicagel (cHex/AcOEt, 95/5 to 8/2). The title compound was obtained as solid (1.5g, yield= 34.9%). LC/MS: 320.9 (M+H), Rt= 3.31min. ^{1}H NMR (DMSO d6, ppm): 9.06 (d, 1H), 8.48 (s, 1H), 8.03 (d, 1H), 4.34 (q, 2H), 1.30 (t, 3H).

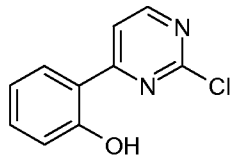
Description 8: ethyl 1-[2-(2-hydroxyphenyl)pyrimidin-4-yl]-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (D8)



To a solution of ethyl 1-(2-chloro-pyrimidin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (D7, 1.5g, 4.68mmol) in DME (100ml) were added $Pd(PPh_3)_4$ (0.541g, 0.468mmol), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (Aldrich, 1.08g, 4.91mmol) and Na_2CO_3 (0.744g, 7.02mmol) in water (15ml). The mixture was heated at 110°C for 4 hours and poured into water. After extraction with AcOEt, 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 a pale yellow

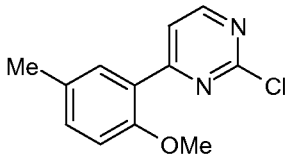
solid (1.4g, yield= 79%). ^{1}H NMR (DMSO d6, ppm): 12.87 (s, OH), 9.16 (d, 1H), 8.49 (s, 1H), 8.29 (dd, 1H), 7.96 (d, 1H), 7.47 (t, 1H), 7.01 (d, 1H), 7 (t, 1H), 4.35 (q, 2H), 1.33 (t, 3H).

Description 9: 2-chloro-4-(2-hydroxyphenyl)pyrimidine (D9)



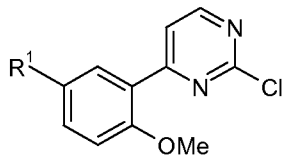
To a solution of 2,4-dichloropyrimidine (Aldrich, 5g, 33.56mmol) in DME (80ml) and H_2O (8ml), were added 2-hydroxyphenylboronic acid (4.86g, 35.23mmol), Na_2CO_3 (5.34g, 50.34mmol), $Pd(OAc)_2$ (0.188g, 0.84mmol) and triphenylphosphine (0.44g, 1.68mmol), and then the mixture was heated at 90°C overnight, 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. After crystallisation from CH_3CN, the title compound was obtained as yellow crystals (4.5g, yield= 64.9%). LC/MS: 207.1 (M+H), Rt= 2.93min. ^{1}H NMR ($CDCl_3$, ppm) : 8.7 (d, 1H), 7.8 (d, 1H), 7.75 (d, 1H), 7.45 (t, 1H), 7.1 (d, 1H), 7 (t, 1H).

Description 10a: 2-chloro-4-(2-methoxy-5-methylphenyl)pyrimidine (D10a)



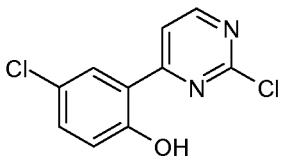
To a solution of 2,4-dichloropyrimidine (Aldrich, 5g, 33.56mmol) in DME (80ml) and H_2O (8ml), were added 2-methoxy-5-methylphenylboronic acid (Aldrich, 5.85g, 35.23mmol), Na_2CO_3 (5.34g, 50.34mmol), $Pd(OAc)_2$ (0.188g, 0.84mmol) and triphenylphosphine (0.44g, 1.68mmol), and then the mixture was heated at 90°C overnight, 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 chromatography on silicagel (CH_2Cl_2/Chex, 3/2 then 4/1). The title compound was obtained as a colorless oil which crystallised (3.25g, yield= 41.3%). LC/MS: 235.1 (M+H), Rt= 3.27min. ^{1}H NMR ($CDCl_3$, ppm) : 8.58 (d, 1H), 7.98 (d, 1H), 7.89 (sd, 1H), 7.28 (dd, 1H), 6.93 (d, 1H), 3.90 (s, 3H), 2.38 (s, 3H).

Prepared by a similar method as described for D10a:



Description No.	R^1	Prepared from	Analytical data
D10b	F	2,4-dichloropyrimidine and, 5-fluoro-2-methoxyphenyl boronic acid	As white solid (yield= 55%) LC/MS: 239.1 (M+H), Rt= 3.09min
D10c	Cl	2,4-dichloropyrimidine and, 5-chloro-2-methoxyphenyl boronic acid	As cream solid (yield= 70%) ^{1}H NMR ($CDCl_3$, ppm): 8.6 (d, 1H), 8.08 (sd, 1H), 7.97 (d, 1H), 7.42 (dd, 1H), 6.96 (d, 1H), 3.93 (s, 3H)
D10d	CF3	2,4-dichloropyrimidine and, 5-trifluoromethyl-2-methoxyphenyl boronic acid	As yellow solid (yield = 59.5%) LC/MS: 289.0 (M+H), Rt= 3.38min

Description 11a: 2-chloro-4-(2-hydroxy-5-chlorophenyl)pyrimidine (D11a)

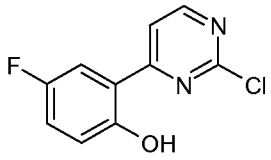


To a solution of 2-chloro-4-(2-methoxy-5-chlorophenyl)pyrimidine (D10c) (0.2g, 0.784mmol) in anhydrous CH_2Cl_2 (ml) cooled in an ice bath was added dropwise BBr_3 (1.56ml of a solution 1M in CH_2Cl_2, 1.56mmol)and the mixture was stirred at 0°C for 30 minutes then at room temperature overnight. The reaction mixture was neutralised with a saturated solution of $NaHCO_3$ in water, then extracted with CH_2Cl_2; The organic phase was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The title compound was obtained as (0.185g, yield= 100%)

^{1}H NMR ($CDCl_3$, ppm) 12.41 (s, OH), 8.73 (d, 1H), 7.75 (sd, 1H), 7.71 (d, 1H), 7.4 (dd, 1H), 7.05 (d, 1H)

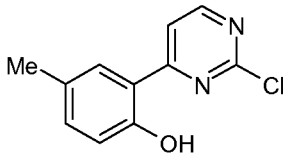
Prepared by a similar method as described for D11a:

Description 11b: 2-chloro-4-(2-hydroxy-5-fluorophenyl)pyrimidine (D11b)



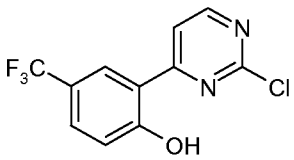
From 2-chloro-4-(2-methoxy-5-fluorophenyl)pyrimidine (D10b). ^{1}H NMR ($CDCl_3$, ppm): 12.21 (s, OH), 8.73 (d, 1H), 7.66 (d, 1H), 7.46 (m, 1H), 7.2 (m, 1H), 7.06 (m, 1H).

Description 12: 2-chloro-4-(2-hydroxy-5-methylphenyl)pyrimidine (D12)



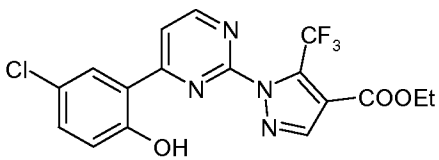
To a solution of 2-chloro-4-(2-methoxy-5-methylphenyl)pyrimidine (D10a, 7g, 29.85mmol) in anhydrous CH_2Cl_2 (100ml) cooled in an ice bath was added dropwise BBr_3 (59.7ml of a solution 1M in CH_2Cl_2, 59.7mmol) and the mixture was stirred at 0°C for 30 minutes then at room temperature overnight, and then poured into water. After extraction with CH_2Cl_2, the organic phase was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The title compound was obtained as a yellow powder (6.3g, yield= 95.7%). LC/MS: 221.1 (M+H), Rt= 3.13min.

Description 13: 2-chloro-4-(2-hydroxy-5-trifluoromethylphenyl)pyrimidine (D13)



From 2-chloro-4-(2-methoxy-5-trifluoromethylphenyl)pyrimidine (D10d) as a yellow solid (yield=). LC/MS: 275.0 (M+H), Rt= 3.32min.

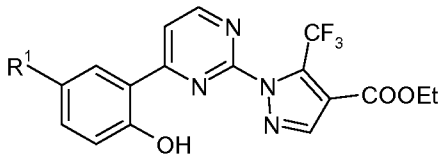
Description 14a: Ethyl 1-(4-(5-chloro-2-hydroxyphenyl)pyrimidin-2-yl)-5-trifluoromethyl-pyrazole-4-carboxylate (D14a)



To a solution of 2-chloro-4-(2-hydroxy-5-chlorophenyl)pyrimidine (D11a, 0.185g, 0.784mmol) in EtOH (ml) was added hydrazine hydrate (0.38ml, 7.84mmol) and the mixture was heated at 60°C for 2 hours and then cooled. After dilution with water (10ml), the precipitate was filtered, washed with water, then CH_2Cl_2 and then with iPr_2O. The resulting yellow solid was

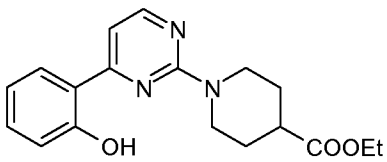
dissolved in EtOH (20ml), and ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutyrate (Aldrich, 0.22g, 0.913mmol) was added. The reaction mixture was heated at 60°C for 2 hours and then concentrated under reduced pressure. The residue was triturated with iPr_2O and the resulting precipitate was filtered, washed with iPr_2O and dried. The title compound was obtained as a cream powder (0.25g, yield= 80%). ^1H NMR ($CDCl_3$, ppm) : 12.39 (s, OH), 8.93 (d, 1H), 8.22 (s, 1H), 7.86 (d, 1H), 7.83 (sd, 1H), 7.42 (dd, 1H), 7.06 (d, 1H), 4.41 (q, 2H), 1.42 (t, 3H).

Prepared by a similar method as described for D14a:



Description No.	R^1	Prepared from	Analytical data
D14b	H	D9	As cream solid (yield= 55%) LC/MS: 379.2 (M+H), Rt= 3.52min
D14c	F	D10b	As cream solid (yield= 78%) LC/MS: 397.2 (M+H) , Rt= 3.57min

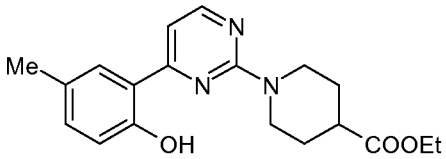
Description 15: Ethyl 1-(4-(2-hydroxyphenyl)pyrimidin-2-yl)piperidine-4-carboxylate (D15)



To a solution of 2-chloro-4-(2-hydroxyphenyl)pyrimidine (D9, 3.6g, 17.43mmol) in EtOH (50ml), was added ethyl isonipecotate (Aldrich, 6.72ml, 43.58mmol) and the mixture was heated under reflux for 3hours 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 silicagel (CH_2Cl_2 then CH_2Cl_2/MeOH, 99/1). The title compound was obtained as a yellow oil which crystallised (5.6g, yield= 98.23%)
LC/MS: 328.1 (M+H), Rt= 3.55min. ^1H NMR ($CDCl_3$, ppm) : 8.45 (d, 1H), 7.75 (d, 1H), 7.4 (t, 1H), 7.05 (2d, 2H), 6.95 (t, 1H), 4.55 (ld, 2H), 4.2 (q, 2H), 3.2 (t, 2H), 2.65 (m, 1H), 2.05 (m, 2H), 1.8 (m, 2H), 1.3 (t, 3H).

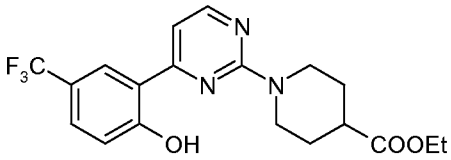
Prepared by a similar method as described for D15:

Description 16: Ethyl 1-(4-(2-hydroxy-5-methylphenyl)pyrimidin-2-yl)piperidine-4-carboxylate (D16)



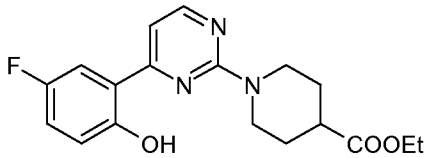
From 2-chloro-4-(2-hydroxy-5-methylphenyl)pyrimidine (D12) as a pale yellow oil (2.7g, yield= 63.4%). LC/MS: 342.1 (M+H), Rt= 3.72min. ^{1}H NMR ($CDCl_3$, ppm) : 13.75 (s, OH), 8.41 (d, 1H), 7.54 (sd, 1H), 7.18 (dd, 1H), 7.01 (d, 1H), 6.90 (d, 1H), 4.51 (ld, 2H), 4.17 (q, 2H), 3.18 (m, 2H), 2.62 (m, 1H), 2.34 (s, 3H), 2.05 (m, 2H), 1.80 (m, 2H), 1.28 (t, 3H).

Description 17: Ethyl 1-(4-(2-hydroxy-5-trifluoromethylphenyl)pyrimidin-2-yl)piperidine-4-carboxylate (D17)



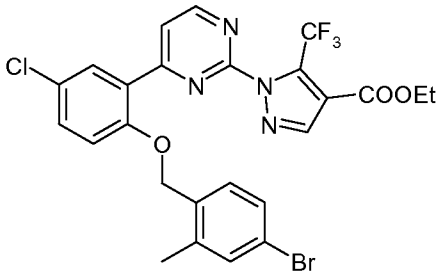
From 2-chloro-4-(2-hydroxy-5-trifluoromethylphenyl)pyrimidine (D13) as a pale yellow oil which crystallised (yield= 82%). LC/MS: 396.0 (M+H), Rt= 3.93min. ^{1}H NMR ($CDCl_3$, ppm) :8.39 (d, 1H), 7.92 (s, 1H), 7.5 (d, 1H), 6.98 (d, 1H), 6.95 (d, 1H), 4.41 (ld, 2H), 4.09 (q, 2H), 3.13 (m, 2H), 2.55 (m, 1H), 1.98 (m, 2H), 1.73 (m, 2H), 1.2 (t, 3H).

Description 18: Ethyl 1-(4-(5-fluoro-2-hydroxyphenyl)pyrimidin-2-yl)piperidine-4-carboxylate (D18)



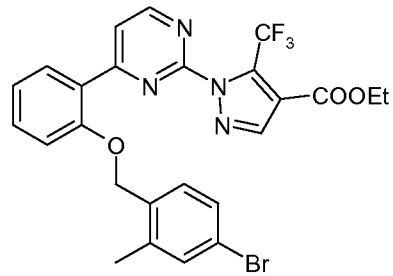
To a solution of 2-chloro-4-(2-hydroxy-5-fluorophenyl)pyrimidine (D11b, 2g, 8.9mmol) in DMF (ml), were added ethyl isonipecotate (Aldrich, 2.8g, 17.8mmol) and triethylamine (6.19ml, 44.5mmol) and the mixture was heated at 100°C for 2hours and then concentrated under reduced pressure. The residue was triturated with iPr_2O and the resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure. After chromatography on silicagel (CH_2Cl_2/cHex), the title compound was obtained as an ocre powder (2.15g, yield= 70%). ^{1}H NMR ($CDCl_3$, ppm) : 8.45 (d, 1H), 7.43 (dd, 1H), 7.11 (m, 1H), 6.95 (m, 2H), 4.51 (ld, 2H), 4.18 (q, 2H), 3.23 (t, 2H), 2.64 (m, 1H), 2.05 (m, 2H), 1.8 (m, 2H), 1.29 (t, 3H).

Description 19: Ethyl 1-(4-(5-chloro-2-(4-bromo-2-methylbenzyloxy)-phenyl)pyrimidin-2-yl)-5-trifluoromethyl-pyrazole-4-carboxylate (D19)



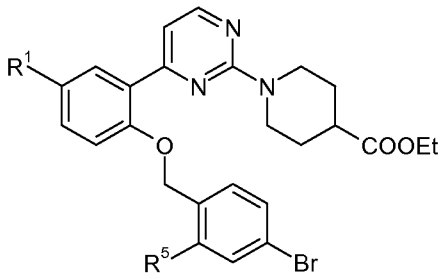
To a solution of ethyl 1-(4-(5-chloro-2-hydroxyphenyl)pyrimidin-2-yl)-5-trifluoromethyl-pyrazole-4-carboxylate (D14a, 1g, 2.42mmol) in acetone (80ml), was added Cs_2CO_3 (1.18g, 3.63mmol) and the mixture was stirred at room temperature for 15 minutes. Intermediate x (0.64g, 2.42mmol) was then added and the mixture was heated under reflux overnight, then cooled and the salts were filtered off. The filtrate was concentrated under reduced pressure and the residue was triturated with iPr_2O. The resulting precipitate was filtered and dried. The title compound was obtained as a white powder (0.95g, yield= 66%). LC/MS: 597.2 (M+H), Rt= 4.48min. ^1H NMR ($CDCl_3$, ppm) : 8.8 (d, 1H), 8.21 (bs, 2H), 8.08 (d, 1H), 7.47 to 7.36 (m, 3H), 7.22 (d, 1H), 7.06 (d, 1H), 5.12 (s, 2H), 4.42 (q, 2H), 2.31 (s, 3H), 1.43 (t, 3H).

Description 20: Ethyl 1-(4-(2-(4-bromo-2-methylbenzyloxy)-phenyl)pyrimidin-2-yl)-5-trifluoromethyl-pyrazole-4-carboxylate (D20)

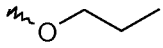
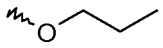


To a solution of 2-chloro-4-(2-hydroxyphenyl)pyrimidine (D9, 2g, 5.29mmol) in acetone (80ml), was added Cs_2CO_3 (2.59g, 7.94mmol) and the mixture was stirred at room temperature for 15 minutes. 4-bromo-2-methyl-benzyl bromide (D6n, 1.54g, 5.82mmol) was then added and the mixture was heated under reflux overnight 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 chromatography on silicagel (CH_2Cl_2 then CH_2Cl_2/MeOH, 99/1). The title compound was obtained as a yellow oil (2.9g, yield= 97.7%). LC/MS: 562.8 (M+H), Rt= 4.26min. ^1H NMR ($CDCl_3$, ppm) : 8.8 (d, 1H), 8.25 (s+d, 2H), 8.1 (d, 1H), 7.55 (t, 1H), 7.4 (m, 2H), 7.25 (d, 1H), 7.2 (t, 1H), 7.15 (d, 1H), 5.15 (s, 2H), 4.4 (q, 2H), 2.35 (s, 3H), 1.4 (t, 3H).

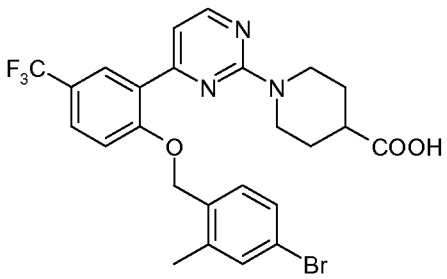
Prepared by a similar method as described for D20:



Description No.	R^1	R^5	Prepared from	Analytical data
D21	H	CH_3	D15 and D6n	As a colorless oil (yield= 96.17%) LC/MS: 511.9 (M+H), Rt= 4.39min ^{1}H NMR ($CDCl_3$, ppm): 8.3 (d, 1H), 8 (d, 1H), 7.45 (t, 1H), 7.35 (d, 1H), 7.3 (d, 1H), 7.15 to 7.05 (m, 4H), 5.1 (s, 2H), 4.8 (ld, 2H), 4.2 (q, 2H), 3.1 (t, 2H), 2.6 (m, 1H), 2.35 (s, 3H), 2 (m, 2H), 1.75 (m, 2H), 1.3 (t, 3H)
D22	H	OCH_3	D15 and D6o	As yellow oil (yield= 99.5%) LC/MS: 527.9 (M+H), Rt= 4.33min ^{1}H NMR ($CDCl_3$, ppm): 8.3 (d, 1H), 7.95 (d, 1H), 7.4 (t, 1H), 7.3 (d, 1H), 7.2 (d, 1H), 7.15 to 7.05 (m, 4H), 5.15 (s, 2H), 4.8 (ld, 2H), 4.2 (q, 2H), 3.85 (s, 3H), 3.1 (t, 2H), 2.6 (m, 1H), 2 (m, 2H), 1.75 (m, 2H), 1.3 (t, 3H)
D23	F	CH_3	D18 and D6n	As a colorless gum (yield= 68%) ^{1}H NMR ($CDCl_3$, ppm): 8.28 (d, 1H), 7.75 (dd, 1H), 7.37 (s, 1H), 7.34 (dd, 1H), 7.23 (d, 1H), 7.14 (d, 1H), 7.10 (m, 1H), 7.0 (dd, 1H), 5.02 (s, 2H), 4.75 (m, 2H), 4.18 (q, 2H), 3.12 (t, 2H), 2.61 (m, 1H), 2.3 (s, 3H), 2.03 (m, 2H), 1.76 (m, 2H), 1.29 (t, 3H)
D24	CH_3	CH_3	D16 and D6n	As colorless oil (yield= 78.1%) LC/MS: 525.9 (M+H), Rt= 4.54min ^{1}H NMR ($CDCl_3$, ppm): 8.17 (d, 1H), 7.63 (sd, 1H), 7.26 (bs, 1H), 7.23 (dd, 1H), 7.16 (d, 1H), 7.11 (d, 1H), 6.97 (d, 1H), 6.84 (d, 1H), 4.92 (s, 2H), 4.68 (ld, 2H), 4.08 (q, 2H), 2.99 (m, 2H), 2.50

				(m, 1H), 2.29 (s, 3H), 2.20 (s, 3H), 1.92 (m, 2H), 1.67 (m, 2H), 1.19 (t, 3H)
D25	CH_3		D16 and D6p	As colorless oil (yield= 95%) LC/MS: 570.0 (M+H), Rt= 4.71min ^{1}H NMR ($CDCl_3$, ppm): 8.2 (d, 1H), 7.62 (bs, 1H), 7.17 (d, 1H), 7.07 (m, 2H), 6.96 (d, 1H), 6.92 (bs, 1H), 6.84 (d, 1H), 5.01 (s, 2H), 4.69 (ld, 2H), 4.08 (q, 2H), 3.86 (t, 2H), 3.0 (m, 2H), 2.5 (m, 1H), 2.28 (s, 3H), 1.93 (m, 2H), 1.73 (m, 2H), 1.69 (m, 2H), 1.19 (t, 3H), 0.95 (t, 3H)
D26	CF_3	CH_3	D17 and D6n	As a yellow solid (yield= 99%) LC/MS: 579.9 (M+H), Rt= 4.54min ^{1}H NMR ($CDCl_3$, ppm): 8.29 (d, 1H), 8.24 (s, 1H), 7.66 (d, 1H), 7.39 (s, 1H), 7.35 (d, 1H), 7.26 (d, 1H), 7.12 (d, 1H), 7.05 (d, 1H), 5.12 (s, 2H), 4.75 (ld, 2H), 4.18 (q, 2H), 3.10 (m, 2H), 2.6 (m, 1H), 2.32 (s, 3H), 2.02 (m, 2H), 1.77 (m, 2H), 1.29 (t, 3H)
D27	CF_3		D17 and D6p	As a pale yellow oil (yield= %) LC/MS: 624.0 (M+H), Rt= 4.75min ^{1}H NMR ($CDCl_3$, ppm): 8.32 (d, 1H), 8.22 (bs, 1H), 7.63 (dd, 1H), 7.24 (d, 1H), 7.15 (d, 2H), 7.1 (bs, 1H), 7.06 (m, 1H), 5.2 (s, 2H), 4.77 (m, 2H), 4.18 (q, 2H), 3.98 (t, 2H), 3.11 (m, 2H), 2.6 (m, 1H), 2.03 (m, 2H), 1.83 (m, 2H), 1.76 (m, 2H), 1.29 (t, 3H), 1.04 (t, 3H)

Description 28: 1-(4-(5-trifluoromethyl-2-(2-methyl-4-bromo-benzyloxy)-phenyl)pyrimidin-2-yl)-piperidine-4-carboxylic acid (D28)

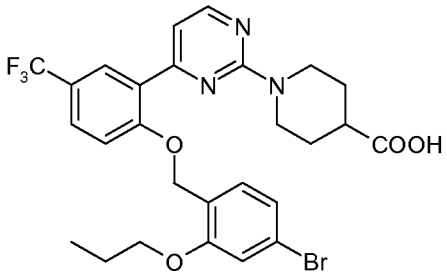


To a solution of ethyl 1-(4-(5-trifluoromethyl-2-(2-methyl-4-bromo-benzyloxy)-phenyl)pyrimidin-2-yl)-piperidine-4-carboxylate (D26, 0.7g, 1.210 mmol) in MeOH (10 ml)

and THF (10ml) was added sodium hydroxyde (6.05 ml of a solution 1N, 6.05 mmol), and the mixture was heated at 60°C for 1 hour and then neutralised with a solution 1N of HCl. After evaporation under reduced pressure of MeOH and THF, the resulting precipitate was filtered, washed with water, then pentane and dried. The product was obtained as pale yellow solid powder (0.65g, yield= 98%). LC/MS: 551.9 (M+H), Rt= 3.36min

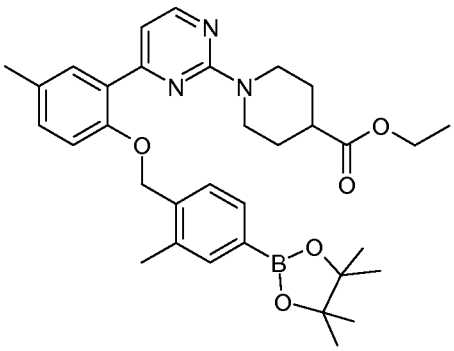
Prepared by a similar method as described for D28:

Description 29: 1-(4-(5-trifluoromethyl-2-(2-propyloxy-4-bromo-benzyloxy)-phenyl)pyrimidin-2-yl)-piperidine-4-carboxylic acid (D29)



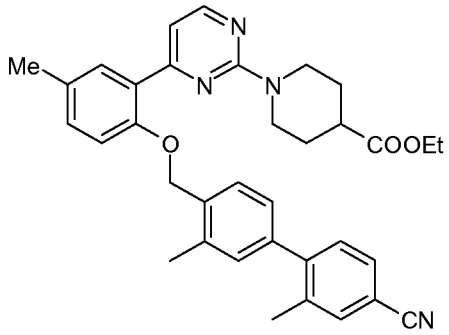
From ethyl 1-(4-(5-trifluoromethyl-2-(2-propyloxy-4-bromo-benzyloxy)-phenyl)pyrimidin-2-yl)-piperidine-4-carboxylate (D27) as pale yellow oil (yield = 99%). LC/MS : 595.9 (M+H), Rt= 3.64min.

Description 30: ethyl 1-{4-[5-methyl-2-({[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl}oxy)phenyl]-2-pyrimidinyl}-4-piperidinecarboxylate



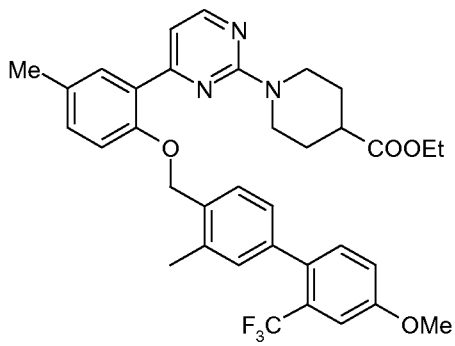
To a solution of ethyl 1-(4-(2-hydroxy-5-methylphenyl)pyrimidin-2-yl)piperidine-4-carboxylate (D16, 2g, 5.86 mmol) in acetone (50 ml) was added Cs_2CO_3 (2.86 g, 8.79 mmol) and the mixture was stirred at room temperature for 30 minutes. Then 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl bromide (D6q, 2.004 g, 6.44 mmol) was added and the mixture was heated at 65°C overnight. The reaction mixture was concentrated *in vacuo* and diluted with CH_2Cl_2. The organic phase was washed with H_2O, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silicagel (cHex/AcOEt 100/0 to 80/20). The title compound was obtained as a colorless oil (3.3g, yield= 99%). LC/MS: 572.2 (M+H), Rt= 4.66min.

Description 31: Ethyl 1-(4-(5-methyl-2-(2-methyl-4-(4-cyano-2-methylphenyl)benzyloxy)-phenyl)pyrimidin-2-yl)-piperidine-4-carboxylate (D 31)



To a solution of ethyl 1-(4-(5-methyl-2-(2-methyl-4-bromo-benzyloxy)-phenyl)pyrimidin-2-yl)-piperidine-4-carboxylate (D24, 0.4g, 0.763 mmol) in DME (50ml) and water (5ml) were added $Pd(PPh_3)_4$ (0.044 g, 0.038 mmol), (4-cyano-2-methylphenyl)boronic acid (0.184 g, 1.144 mmol) and Na_2CO_3 (0.202 g, 1.907 mmol). The reaction was heated at 105°C overnight 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 silicagel (CH_2Cl_2 / MeOH, 99/1). The title compound was obtained as a colorless oil (0.37g, yield= 87%). LC/MS: 561.1 (M+H), Rt= 4.55min. ^1H NMR ($CDCl_3$, ppm): 8.27 (d, 1H), 7.75 (s, 1H), 7.58 (s, 1H), 7.54 (d, 1H), 7.49 (d, 1H), 7.33 (d, 1H), 7.24 (d, 1H), 7.14 (m, 3H), 7.02 (d, 1H), 5.14 (s, 2H), 4.79 (ld, 2H), 4.17 (q, 2H), 3.09 (t, 2H), 2.60 (m, 1H), 2.4 (s, 3H), 2.38 (s, 3H), 2.32 (s, 3H), 2.02 (m, 2H), 1.76 (m, 2H), 1.28 (t, 3H).

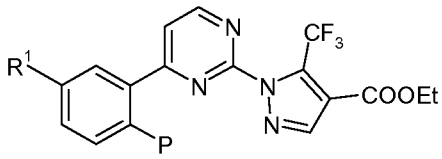
Description 32: Ethyl 1-(4-(5-methyl-2-(2-methyl-4-(4-methoxy-2-trifluoromethylphenyl)benzyloxy)-phenyl)pyrimidin-2-yl)-piperidine-4-carboxylate (D32)

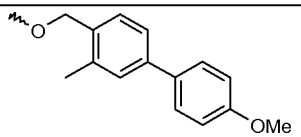
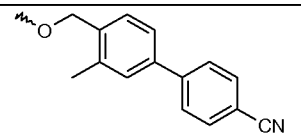
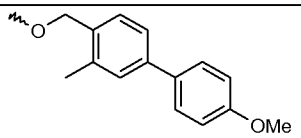


To a solution of ethyl 1-(4-(5-methyl-2-(2-methyl-4-bromo-benzyloxy)-phenyl)pyrimidin-2-yl)-piperidine-4-carboxylate (D24, 0.42 g, 0.801 mmol) in 1,2-Dimethoxyethane (DME) (50 mL) and water (5 mL) were added $Pd(PPh_3)_4$ (0.046 g, 0.040 mmol), [4-(methyloxy)-2-(trifluoromethyl)phenyl]boronic acid (0.264 g, 1.201 mmol) and sodium carbonate (0.212 g, 2.002 mmol) and the reaction mixture was heated at 95°C overnight and then poured into water. After extraction with CH_2Cl_2, the organic phase was dried (Na_2SO_4) and concentrated

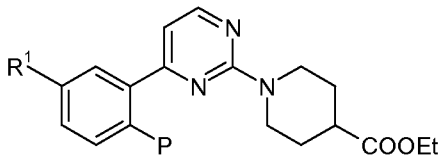
under reduced pressure. The residue was purified by chromatography on silicagel (CH_2Cl_2, 99/1). The product was obtained as a colorless oil (0.44g, yield= 89%). LC/MS: 620.1 (M+H), Rt= 4.67min. ^{1}H NMR ($CDCl_3$, ppm): 8.27 (d, 1H), 7.76 (bs, 1H), 7.42 (d, 1H), 7.25 (m, 3H), 7.15 (m, 3H), 7.09 (dd, 1H), 7.02 (d, 1H), 5.13 (s, 2H), 4.79 (ld, 2H), 4.17 (q, 2H), 3.91 (s, 3H), 3.09 (m, 2H), 2.59 (m, 1H), 2.4 (s, 3H), 2.36 (s, 3H), 2.02 (m, 2H), 1.78 (m, 2H), 1.28 (t, 3H).

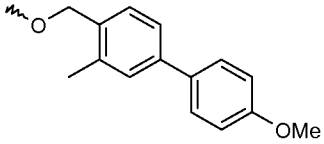
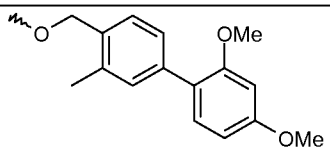
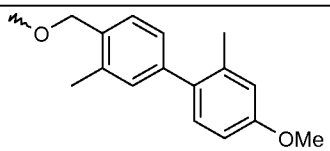
Prepared by a similar method as described for D31:

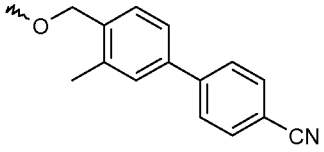
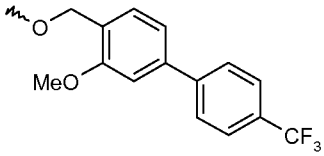
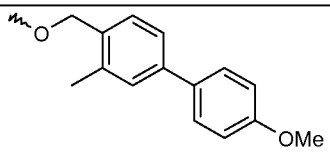


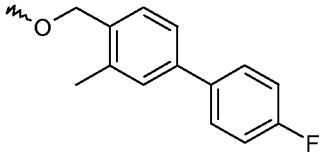
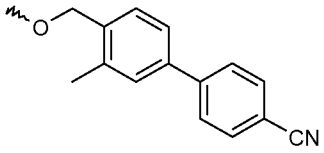
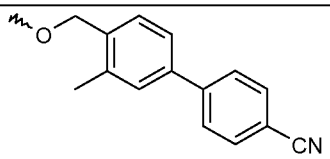
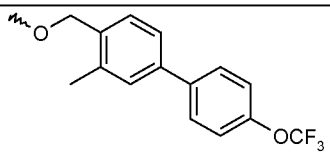
Description No.	R^1	P	Prepared from	Analytical data
D33	H		D20	As a colorless oil (yield= 14.3%). LC/MS: 589.1 (M+H), Rt= 4.56min
D34	H		D20	As a colorless oil (yield= 61.6%). LC/MS: 584.0 (M+H), Rt= 4.23min. ^{1}H NMR ($CDCl_3$, ppm): 8.68 (d, 1H), 8.12 (d, 1H), 8.10 (s, 1H), 8.06 (d, 1H), 7.64 (q, 4H), 7.44 (m, 2H), 7.38 (bs, 2H), 7.10 (t, 2H), 5.17 (s, 2H), 4.32 (q, 2H), 2.33 (s, 3H), 1.33 (t, 3H)
D35	Cl		D19	As a powder (0.12g, yield= 38%). LC/MS: 623.3 (M+H), Rt= 4.58min. ^{1}H NMR ($CDCl_3$, ppm): 8.79 (d, 1H), 8.25 (sd, 1H), 8.2 (s, 1H), 8.17 (d, 1H), 7.56 (d, 2H), 7.48 to 7.40 (m, 4H), 7.13 (d, 1H), 7.0 (d, 2H), 5.22 (s, 2H), 4.42 (q, 2H), 3.88 (s, 3H), 2.39 (s, 3H), 1.42 (t, 3H)

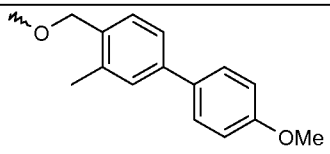
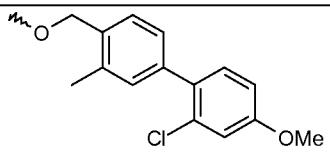
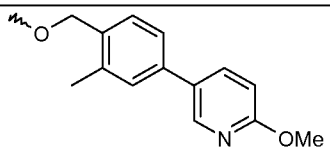
Prepared by a similar method as described for D31:

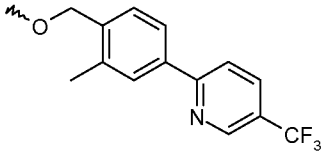
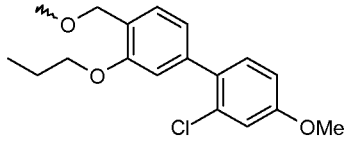
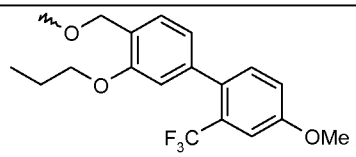


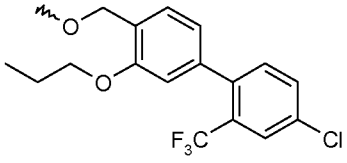
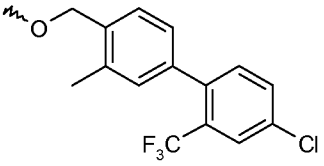
Description No.	R^1	P	Prepared from	Analytical data
D36	H		D21	As a colorless oil (yield= 77.88%). LC/MS: 538.1 (M+H), Rt= 4.55min. ^{1}H NMR ($CDCl_3$, ppm): 8.3 (d, 1H), 8 (d, 1H), 7.55 (d, 2H), 7.45 (m, 4H), 7.2 (d, 1H), 7.15 (t, 1H), 7 (d, 2H), 6.8 (m, 1H), 5.15 (s, 2H), 4.8 (ld, 2H), 4.15 (q, 2H), 3.9 (s, 3H), 3.1 (t, 2H), 2.6 (m, 1H), 2.4 (s, 3H), 2 (m, 2H), 1.8 (m, 2H), 1.3 (t, 3H)
D37	H		D21	As a pale yellow oil (yield= 84.55%). LC/MS: 568.2 (M+H), Rt= 4.50min ^{1}H NMR ($CDCl_3$, ppm): 8.25 (d, 1H), 8 (d, 1H), 7.4 (t, 2H), 7.3 (m, 2H), 7.2 (m, 2H), 7.1 (m, 2H), 6.55 (m, 2H), 5.1 (s, 2H), 4.75 (ld, 2H), 4.1 (q, 2H), 3.85 (s, 3H), 3.8 (s, 3H), 3.05 (t, 2H), 2.55 (m, 1H), 2.35 (s, 3H), 1.95 (m, 2H), 1.75 (m, 2H), 1.2 (t, 3H)
D38	H		D21	As a yellow oil (yield= 77.75%). LC/MS: 552.1 (M+H), Rt= 4.57min ^{1}H NMR ($CDCl_3$, ppm): 8.25 (d, 1H), 8 (d, 1H), 7.4 (m, 2H), 7.1 (m, 6H), 6.75 (m, 2H), 5.15 (s, 2H), 4.75 (ld, 2H), 4.1 (q, 2H), 3.8 (s, 3H), 3.05 (t, 2H), 2.55 (m, 1H),

				2.35 (s, 3H), 2.25 (s, 3H), 2 (m, 2H), 1.75 (m, 2H), 1.25 (t, 3H)
D39	H		D21	As a colorless oil (yield= 78.6%). LC/MS: 533.1 (M+H), Rt= 4.36min. ^{1}H NMR ($CDCl_3$, ppm): 8.19 (d, 1H), 7.89 (dd, 1H), 7.63 (q, 4H), 7.44 (d, 1H), 7.35 (m, 3H), 7.03 (m, 3H), 5.09 (s, 2H), 4.69 (m, 2H), 4.07 (q, 2H), 2.99 (m, 2H), 2.5 (m, 1H), 2.33 (s, 3H), 1.91 (m, 2H), 1.68 (m, 2H), 1.19 (t, 3H)
D40	H		D22	As a colorless oil (yield= 95.67%). LC/MS: 592.1 (M+H), Rt= 4.65min. ^{1}H NMR ($CDCl_3$, ppm): 8.3 (d, 1H), 7.95 (d, 1H), 7.7 (s, 4H), 7.5 (d, 1H), 7.35 (t, 1H), 7.25 (d, 1H), 7.15 (d, 1H), 7.1 (m, 3H), 5.2 (s, 2H), 4.75 (ld, 2H), 4.1 (q, 2H), 3.9 (s, 3H), 3.05 (t, 2H), 2.55 (m, 1H), 1.95 (m, 2H), 1.75 (m, 2H), 1.25 (t, 3H)
D41	F		D23	As a white powder (yield= 37%). LC/MS: 556.2 (M+H), Rt= 4.51min. ^{1}H NMR ($CDCl_3$, ppm): 8.29 (d, 1H), 7.77 (dd, 1H), 7.55 (d, 2H), 7.41 (bs, 3H), 7.22 (d, 1H), 7.12 to 7.04 (m, 2H), 6.99 (d, 2H), 5.12 (s, 2H), 4.77 (ld, 2H), 4.17 (q, 2H), 3.88 (s, 3H), 3.10 (t, 2H), 2.6 (m, 1H), 2.39 (s, 3H), 2.02 (m, 2H), 1.77 (m, 2H), 1.28 (t, 3H)

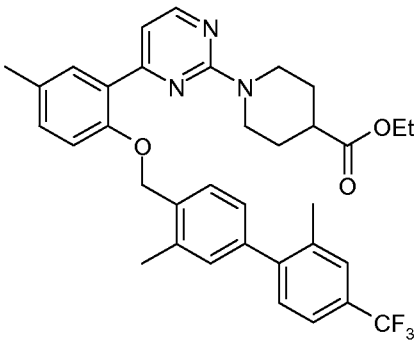
D42	F		D23	As a white powder (yield= 62%). LC/MS: 544.2 (M+H), Rt= 4.55min. ^{1}H NMR ($CDCl_3$, ppm): 8.29 (d, 1H), 7.77 (dd, 1H), 7.56 (m, 2H), 7.44 (m, 1H), 7.40 (m, 2H), 7.21 (d, 1H), 7.15 (m, 3H), 7.06 (m, 1H), 5.12 (s, 2H), 4.77 (ld, 2H), 4.17 (q, 2H), 3.09 (t, 2H), 2.6 (m, 1H), 2.40 (s, 3H), 2.02 (m, 2H), 1.77 (m, 2H), 1.28 (t, 3H)
D43	F		D23	As a white powder (yield= 48%). LC/MS: 551.2 (M+H), Rt= 4.37min. ^{1}H NMR ($CDCl_3$, ppm): 8.29 (d, 1H), 7.77 (dd, 1H), 7.73 (q, 4H), 7.50 (d, 1H), 7.45 (bs, 1H), 7.43 (d, 1H), 7.18 (d, 1H), 7.11 (m, 1H), 7.03 (dd, 1H), 5.14 (s, 2H), 4.77 (ld, 2H), 4.17 (q, 2H), 3.09 (m, 2H), 2.60 (m, 1H), 2.41 (s, 3H), 2.02 (m, 2H), 1.77 (m, 2H), 1.28 (t, 3H)
D44	CH_3		D24	As a colorless oil (yield= 76.8%). LC/MS: 547.1 (M+H), Rt= 4.49min. ^{1}H NMR ($CDCl_3$, ppm): 8.27 (d, 1H), 7.72 (m, 5H), 7.53 (m, 1H), 7.43 (m, 2H), 7.22 (dd, 1H), 7.13 (d, 1H), 6.99 (d, 1H), 5.13 (s, 2H), 4.78 (ld, 2H), 4.17 (q, 2H), 3.08 (m, 2H), 2.59 (m, 1H), 2.41 (s, 3H), 2.39 (s, 3H), 2.01 (m, 1H), 1.77 (m, 2H), 1.28 (t, 3H)
D45	CH_3		D24	As a colorless oil (yield= 67.6%). LC/MS: 606.0 (M+H), Rt= 4.90min. ^{1}H NMR ($CDCl_3$, ppm): 8.18 (d, 1H), 7.65 (s, 1H), 7.52 (d,

				2H), 7.39 (d, 1H), 7.3 (m, 1H), 7.2 (m, 3H), 7.13 (d, 1H), 7.04 (d, 1H), 6.91 (d, 1H), 5.03 (s, 2H), 4.69 (ld, 2H), 4.07 (q, 2H), 2.99 (t, 2H), 2.49 (m, 1H), 2.3 (s, 6H), 1.92 (m, 2H), 1.68 (m, 2H), 1.18 (t, 3H)
D46	CH_3		D24	As a colorless oil (yield= 95%). LC/MS: 552.0 (M+H), Rt= 4.56min. ^{1}H NMR ($CDCl_3$, ppm): 8.27 (d, 1H), 7.76 (s, 1H), 7.55 (d, 2H), 7.42 (m, 3H), 7.23 (d, 1H), 7.17 (d, 1H), 7.01 (m, 3H), 5.12 (s, 2H), 4.79 (d, 2H), 4.17 (q, 2H), 3.88 (s, 3H), 3.09 (t, 2H), 2.59 (m, 1H), 2.4 (bs, 6H), 2.02 (m, 2H), 1.77 (m, 2H), 1.29 (t, 3H)
D47	CH_3		D24	As a colorless oil (yield= 89%). LC/MS: 586.0 (M+H), Rt= 4.65min. ^{1}H NMR ($CDCl_3$, ppm): 8.28 (d, 1H), 7.76 (s, 1H), 7.46 (d, 1H), 7.26 (m, 4H), 7.17 (d, 1H), 7.02 (s+d), 2H), 6.89 (dd, 1H), 5.13 (s, 2H), 4.79 (ld, 2H), 4.17 (q, 2H), 3.86 (s, 3H), 3.09 (t, 2H), 2.59 (m, 1H), 2.4 (s, 3H), 2.38 (s, 3H), 2.02 (m, 2H), 1.79 (m, 2H), 1.28 (t, 3H)
D48	CH_3		D24	As a colorless oil (yield= 79.1%). LC/MS: 553.1 (M+H), Rt= 4.44min. ^{1}H NMR ($CDCl_3$, ppm): 8.41 (s, 1H), 8.27 (d, 1H), 7.81 (d, 1H), 7.75 (s, 1H), 7.48 (d, 1H), 7.37 (bs, 2H), 7.22 (d, 1H), 7.15 (d, 1H), 7.01 (d, 1H), 6.84 (d, 1H), 5.13 (s, 2H), 4.79 (ld, 2H), 4.17 (q,

				2H), 4.00 (s, 3H), 3.09 (t, 2H), 2.59 (m, 1H), 2.4 (s, 6H), 2.02 (m, 2H), 1.76 (m, 2H), 1.28 (t, 3H)
D49	CH_3		D30	As a colorless oil (yield= 81%). LC/MS: 591.2 (M+H), Rt= 4.58min ^{1}H NMR ($CDCl_3$, ppm): 8.96 (bs, 1H), 8.28 (d, 1H), 8.00 (dd, 1H), 7.92 (bs, 1H), 7.85 (m, 2H), 7.75 (bs, 1H), 7.55 (d, 1H), 7.22 (dd, 1H), 7.14 (d, 1H), 6.99 (d, 1H), 5.15 (s, 2H), 4.79 (m, 2H), 4.17 (q, 2H), 3.09 (m, 2H), 2.59 (m, 1H), 2.43 (s, 3H), 2.39 (s, 3H), 2.02 (m, 2H), 1.78 (m, 2H), 1.28 (t, 3H)
D50	CH_3		D25	As a colorless oil (yield= 92%). LC/MS: 630.0 (M+H), Rt= 4.84min. ^{1}H NMR ($CDCl_3$, ppm): 8.21 (d, 1H), 7.65 (s, 1H), 7.34 (d, 1H), 7.18 (m, 2H), 7.11 (d, 1H), 6.94 (m, 2H), 6.88 (d, 1H), 6.87 (s, 1H), 6.79 (dd, 1H), 5.13 (s, 2H), 4.71 (ld, 2H), 4.07 (q, 2H), 3.92 (t, 2H), 3.76 (s, 3H), 3.0 (m, 2H), 2.50 (m, 1H), 2.29 (s, 3H), 1.93 (m, 2H), 1.75 (m, 2H), 1.66 (m, 2H), 1.19 (t, 3H), 0.96 (t, 3H)
D51	CH_3		D25	As a pale yellow oil (yield= 79%). LC/MS: 664.1 (M+H), Rt= 4.86min. ^{1}H NMR ($CDCl_3$, ppm): 8.21 (d, 1H), 7.65 (bs, 1H), 7.34 (d, 1H), 7.18 (m, 3H), 7.12 (dd, 1H), 7.00 (dd, 1H), 6.93 (d, 1H), 6.78 (d, 1H), 6.75 (bs, 1H), 5.13 (s, 2H), 4.7 (m, 2H), 4.08 (q, 2H), 3.88 (t, 2H),

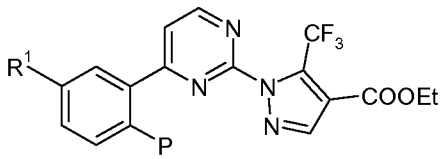
				3.81 (s, 3H), 3.00 (m, 2H), 2.5 (m, 1H), 2.3 (s, 3H), 1.93 (m, 2H), 1.76 to 1.66 (m, 4H), 1.19 (t, 3H), 0.94 (t, 3H)
D52	CH_3		D25	As a pale yellow oil (yield= 96%). LC/MS: 668.1 (M+H), Rt= 4.99min. ^{1}H NMR ($CDCl_3$, ppm): 8.11 (d, 1H), 7.65 (ld, 1H), 7.57 (bs, 1H), 7.44 (m, 2H), 7.33 (d, 1H), 7.21 (d, 1H), 7.16 (m, 1H), 6.93 (d, 1H), 6.77 (d, 1H), 6.74 (s, 1H), 5.13 (s, 2H), 4.6 (ld, 2H), 4.07 (q, 2H), 3.88 (t, 2H), 3.0 (m, 2H), 2.48 (m, 1H), 2.3 (s, 3H), 1.89 (m, 2H), 1.73 (m, 2H), 1.63 (m, 2H), 1.18 (t, 3H), 0.94 (t, 3H)
D53	CF3		D26	As a colorless oil (yield= 90%). LC/MS: 678.0 (M+H), Rt= 4.46min. ^{1}H NMR ($CDCl_3$, ppm): 8.3 (d, 1H), 8.26 (sd, 1H), 7.75 (sd, 1H), 7.68 (dd, 1H), 7.56 (dd, 1H), 7.43 (d, 1H), 7.31 (d, 1H), 7.17 (m, 3H), 7.12 (d, 1H), 5.24 (s, 2H), 4.76 (m, 2H), 4.17 (q, 2H), 3.11 (m, 2H), 2.6 (m, 1H), 2.38 (s, 3H), 2.02 (m, 2H), 1.76 (m, 2H), 1.28 (t, 3H)

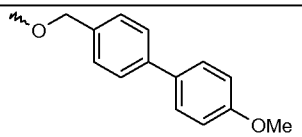
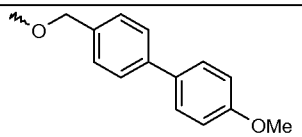
Description 54: Ethyl 1-(4-(5-methyl-2-(2-methyl-4-(2-methyl-4-trifluoromethylphenyl)benzyloxy)-phenyl)pyrimidin-2-yl)-piperidine-4-carboxylate (D54)

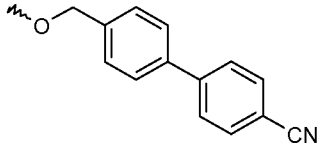
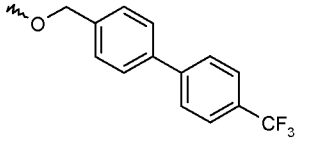
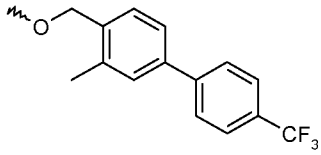
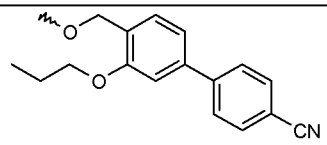
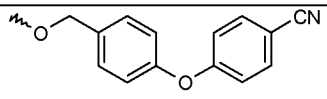
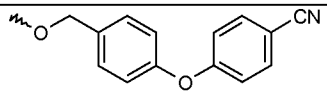


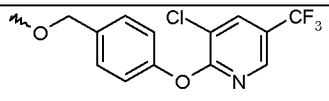
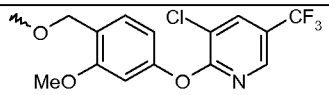
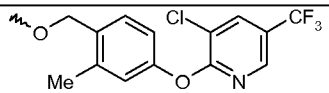
To a solution of ethyl 1-(4-(2-hydroxy-5-methylphenyl)pyrimidin-2-yl)piperidine-4-carboxylate (D16, 0.25g, 0.732 mmol) in acetone (30 ml) was added Cs_2CO_3 (0.358 g, 1.098 mmol), and the mixture was stirred at room temperature for 10 minutes. 2-methyl-4-(2-methyl-4-trifluoromethylphenyl)-benzyl bromide (D6e, 0.264 g, 0.769 mmol) was then added and the mixture was heated at 70°C overnight 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 silicagel (CH_2Cl_2/MeOH, 98/2). The title compound was obtained as a colorless oil (0.4g, yield= 90%). LC/MS: 604.2 (M+H), Rt= 4.82min. ^{1}H NMR ($CDCl_3$, ppm): 8.28 (d, 1H), 7.75 (bs, 1H), 7.5 (m, 3H), 7.34 (d, 1H), 7.24 (dd, 1H), 7.15 (m, 3H), 7.02 (d, 1H), 5.14 (s, 2H), 4.79 (ld, 2H), 4.17 (q, 2H), 3.10 (t, 2H), 2.59 (m, 1H), 2.4 (s, 3H), 2.38 (s, 3H), 2.34 (s, 3H), 2.02 (m, 2H), 1.78 (m, 2H), 1.28 (t, 3H).

Prepared by a similar method as described for D54:

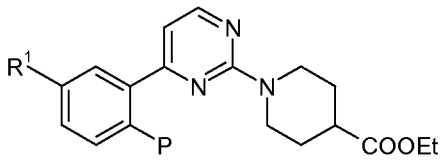


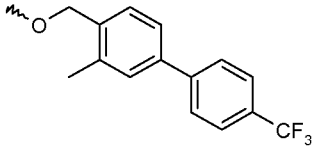
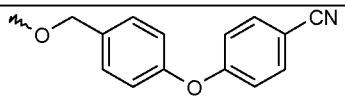
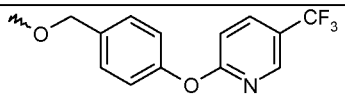
Description No.	R^1	P	Prepared from	Analytical data
D55	H		D14b and D6b	As a yellow powder (yield= 81%). LC/MS: 575.3(M+H), Rt= 4.34min
D56	Cl		D14a and D6b	As a yellow powder (yield= 82%). LC/MS: 609.3 (M+H), Rt= 4.51min

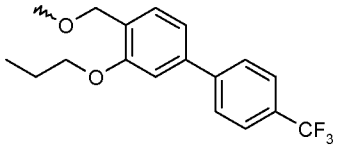
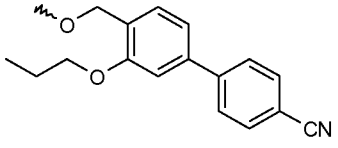
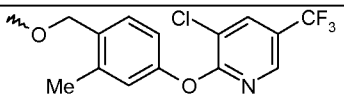
D57	H		D14b and D6a	As a white powder (yield= 77%). ^{1}H NMR ($CDCl_3$, ppm): 8.72 (d, 1H), 8.12 (d+s, 3H), 7.65 (q, 4H), 7.55 (d, 2H), 7.42 (m, 3H), 7.08 (m, 2H), 5.2 (s, 2H), 4.32 (q, 2H), 1.33 (t, 3H)
D58	H		D14b and D6c	As a white powder (yield= 74.1%). ^{1}H NMR ($CDCl_3$, ppm): 8.72 (d, 1H), 8.14 (d, 1H), 8.11 (s, 1H), 7.63 (bs+d, 5H), 7.55 (d, 2H), 7.43 (m, 3H), 7.09 (t, 1H), 7.06 (d, 1H), 5.2 (s, 2H), 4.32 (q, 2H), 1.33 (t, 3H)
D59	H		D14b and D6d	As a pale yellow oil (yield= 94.2%). LC/MS: 626.9 (M+H), Rt= 4.56min. ^{1}H NMR ($CDCl_3$, ppm): 8.75 (d, 1H), 8.15 (m, 3H), 7.7 (s, 4H), 7.5 (t, 1H), 7.45 (m, 3H), 7.15 (m, 2H), 5.2 (s, 2H), 4.35 (q, 2H), 2.4 (s, 3H), 1.4 (t, 3H)
D60	H		D14b and D6g	As a colorless oil (yield= 96 %). LC/MS: 628.0 (M+H), Rt= 4.44min. ^{1}H NMR ($CDCl_3$, ppm): 8.8 (d, 1H), 8.28 (d, 1H), 8.2 (d+s, 2H), 7.75 (d, 2H), 7.69 (d, 2H), 7.51 (m, 1H), 7.45 (d, 1H), 7.17 (m, 3H), 7.11 (bs, 1H), 5.34 (s, 2H), 4.41 (q, 2H), 4.08 (t, 2H), 1.86 (m, 2H), 1.42 (t, 3H), 1.06 (t, 3H)
D61	H		D14b and D6h	^{1}H NMR ($CDCl_3$, ppm): 8.71 (d, 1H), 8.11 (s, 1H), 8.09 (d, 2H), 7.55 (d, 2H), 7.43 (t, 1H), 7.36 (d, 2H), 7.09 (t, 1H), 7.05 (d, 1H), 7.01 (d, 2H), 6.96 (d, 2H), 5.14 (s, 2H), 4.31 (q, 2H), 1.33 (t, 3H)
D62	Cl		D14a and	^{1}H NMR ($CDCl_3$, ppm): 8.81 (d, 1H), 8.19 (m, 3H), 7.64 (d,

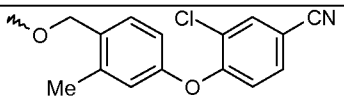
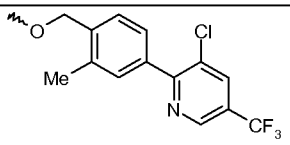
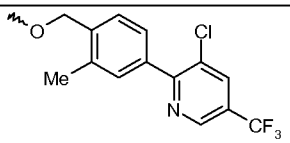
			D6h	2H), 7.45 (m, 1H), 7.44 (d, 2H), 7.10 (d, 2H), 7.05 (d, 3H), 5.22 (s, 2H), 4.42 (q, 2H), 1.42 (t, 3H)
D63	H		D14b and D6k	As a yellow amorphous solid (yield= 81.7%). LC/MS: 663.9 (M+H), Rt= 4.42min. ^{1}H NMR ($CDCl_3$, ppm): 8.81 (d, 1H), 8.3 (bs, 1H), 8.23 (m, 3H), 8.02 (bs, 1H), 7.52 (d+m, 3H), 7.23 (d, 2H), 7.17 (m, 2H), 5.26 (s, 2H), 4.41 (q, 2H), 1.42 (t, 3H)
D64	H		D14b and D6m	As a yellow oil (yield= 81.7%) LC/MS: 693.9 (M+H), Rt= 4.49min. ^{1}H NMR ($CDCl_3$, ppm): 8.7 (d, 1H), 8.22 (bs, 1H), 8.17 (d, 1H), 8.13 (dd, 1H), 8.11 (s, 1H), 7.93 (bs, 1H), 7.42 (t, 1H), 7.34 (d, 1H), 7.07 (m, 2H), 6.7 (m, 2H), 5.18 (s, 2H), 4.32 (q, 2H), 3.78 (s, 3H), 1.33 (t, 3H)
D65	H		D14b and D6l	As a pale yellow oil (yield= 97%). LC/MS: 677.9 (M+H), Rt= 4.56min. ^{1}H NMR ($CDCl_3$, ppm): 8.78 (d, 1H), 8.32 (s, 1H), 8.24 (d, 1H), 8.2 (s, 1H), 8.15 (d, 1H), 8.02 (s, 1H), 7.54 (t, 1H), 7.47 (d, 1H), 7.2 (m, 2H), 7.07 (m, 2H), 5.22 (s, 2H), 4.42 (q, 2H), 2.38 (s, 3H), 1.42 (t, 3H)

Prepared by a similar method as described for D54:

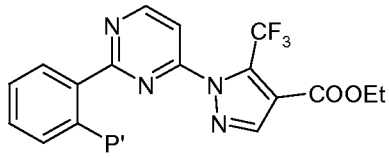


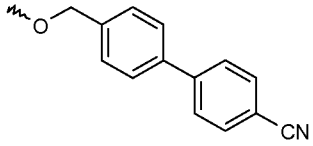
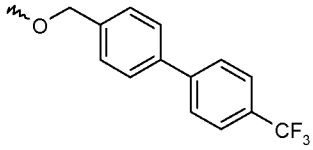
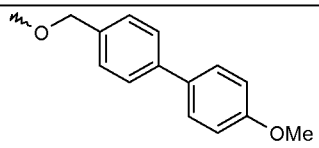
Description No.	R^1	P	Prepared from	Analytical data
D66	H		D15 and D6d	As a yellow oil (yield= 88.71%). LC/MS: 576.0 (M+H), Rt= 4.68min. ^{1}H NMR ($CDCl_3$, ppm): 8.25 (d, 1H), 7.95 (d, 1H), 7.7 (s, 4H), 7.5 (d, 1H), 7.4 (m, 3H), 7.15 (d, 1H), 7.1 (m, 2H), 5.15 (s, 2H), 4.75 (ld, 2H), 4.1 (q, 2H), 3.05 (t, 2H), 2.55 (m, 1H), 2.4 (s, 3H), 1.95 (m, 2H), 1.75 (m, 2H), 1.25 (t, 3H)
D67	F		D18 and D6h	As a white powder (yield= 59%). LC/MS: 553.1 (M+H), Rt= 4.27min. ^{1}H NMR ($CDCl_3$, ppm): 8.32 (d, 1H), 7.75 (dd, 1H), 7.63 (d, 2H), 7.44 (d, 2H), 7.21 (d, 1H), 7.08 (d+m, 3H), 7.03 (d+m, 3H), 5.12 (s, 2H), 4.77 (ld, 2H), 4.17 (q, 2H), 3.10 (t, 2H), 2.61 (m, 1H), 2.02 (m, 2H), 1.75 (m, 2H), 1.29 (t, 3H)
D68	F		D18 and D6j	As a white powder (yield= 77%). LC/MS: 597.1 (M+H), Rt= 4.38min. ^{1}H NMR ($CDCl_3$, ppm): 8.46 (bs, 1H), 8.32 (d, 1H), 7.93 (dd, 1H), 7.76 (dd, 1H), 7.47 (d, 2H), 7.24 (d, 1H), 7.18 (d, 2H), 7.10 (m, 1H), 7.07 to 7 (m, 2H), 5.14 (s, 2H), 4.78 (ld, 2H), 4.17 (q,

				2H), 3.11 (t, 2H), 2.61 (m, 1H), 2.03 (m, 2H), 1.75 (m, 2H), 1.29 (t, 3H)
D69	CH3		D16 and D6f	As a colorless oil (yield= 91%). ^{1}H NMR ($CDCl_3$, ppm): 8.31 (d, 1H), 7.75 (s, 1H), 7.71 (bs, 4H), 7.52 (d, 1H), 7.24 (d, 1H), 7.19 (m, 2H), 7.09 (s, 1H), 7.02 (d, 1H), 5.24 (s, 2H), 4.8 (ld, 2H), 4.18 (q, 2H), 4.08 (t, 2H), 3.10 (t, 2H), 2.6 (m, 1H), 2.39 (s, 3H), 2.03 (m, 2H), 1.88 (m, 2H), 1.77 (m, 2H), 1.29 (t, 3H), 1.09 (t, 3H)
D70	CH3		D16 and D6g	As a colorless oil (yield= 99%). LC/MS: 591.1 (M+H), Rt= 4.66min. ^{1}H NMR ($CDCl_3$, ppm): 8.31 (d, 1H), 7.72 (m, 5H), 7.52 (d, 1H), 7.22 (d, 1H), 7.17 (m, 2H), 7.06 (s, 1H), 7.0 (d, 1H), 5.23 (s, 2H), 4.8 (bd, 2H), 4.17 (q, 2H), 4.07 (t, 2H), 3.1 (m, 2H), 2.6 (m, 1H), 2.39 (s, 3H), 2.02 (m, 2H), 1.88 (m, 2H), 1.76 (m, 2H), 1.28 (t, 3H), 1.08 (t, 3H)
D71	CH3		D16 and D6l	As a colorless oil (yield= 91%). LC/MS: 641.0 (M+H), Rt= 4.77min. ^{1}H NMR ($CDCl_3$, ppm): 8.3 (s, 1H), 8.27 (d, 1H), 8.0 (s, 1H), 7.75 (s, 1H), 7.49 (d, 1H), 7.23 (d, 1H), 7.12 (d, 1H), 7.01 (m, 3H), 5.09 (s, 2H), 4.79 (ld, 2H), 4.18 (q, 2H), 3.10 (t, 2H), 2.60 (m, 1H), 2.4 (s, 3H), 2.36 (s, 3H), 2.02 (m, 2H), 1.77 (m, 2H), 1.29 (t, 3H)

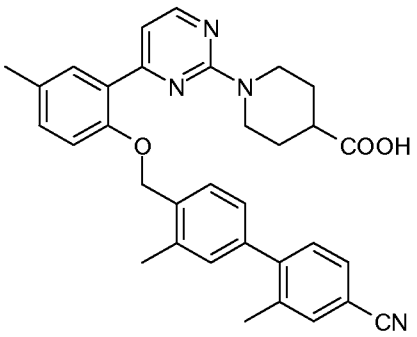
D72	CH3		D16 and D6i	As a colorless oil (yield= 93%). LC/MS: 597.1 (M+H), Rt= 4.52min. ^{1}H NMR ($CDCl_3$, ppm): 8.17 (d, 1H), 7.68 (bs, 1H), 7.63 (bs, 1H), 7.39 (dd, 1H), 7.34 (d, 1H), 7.13 (dd, 1H), 7.0 (d, 1H), 6.89 (d, 1H), 6.8 (m, 3H), 4.98 (s, 2H), 4.69 (ld, 2H), 4.08 (q, 2H), 3.0 (m, 2H), 2.5 (m, 1H), 2.3 (s, 3H), 2.24 (s, 3H), 1.92 (m, 2H), 1.68 (m, 2H), 1.19 (t, 3H)
D73	CH3		D16 and D6r	As a white gum (yield= 87%). LC/MS: 625.1(M+H), Rt= 6.97min; ^{1}H NMR (DMSO d6, ppm):9.03 (s, 1H), 8.58 (s, 1H), 8.31 (d, 1H), 7.56 (m, 4H), 7.28 (d, 1H), 7.21 (d, 1H), 7.07 (d, 1H), 5.24 (s, 2H), 4.6 (ld, 2H), 4.05 (q, 2H), 3.05 (m, 2H), 2.62 (m, 1H), 2.36 (s, 3H), 2.32 (s, 3H), 1.89 (m, 2H), 1.5 (m, 2H), 1.17 (t, 3H)
D74	CF3		D17 and D6r	As a white powder (yield= 64.6%). LC/MS: 679.0 (M+H), Rt= 7.04min; ^{1}H NMR (DMSO d6, ppm): 9.03 (s, 1H), 8.59 (s, 1H), 8.40 (d, 1H), 8.09 (s, 1H), 7.87 (d, 1H), 7.57 (m, 4H), 7.12 (d, 1H), 5.42 (s, 2H), 4.58 (ld, 2H), 4.05 (q, 2H), 3.07 (t, 2H), 2.63 (m, 1H), 2.39 (s, 3H), 1.90 (m, 2H), 1.51 (m, 2H), 1.17 (t, 3H)

Prepared by a similar method as described for D54:



Description No.	P'	Prepared from	Analytical data
D75		D8 and D6a	As a white powder (yield= 44.3%) ^{1}H NMR ($CDCl_3$, ppm): 9.08 (d, 1H), 8.15 (s, 1H), 7.91 (dd, 1H), 7.73 (d, 2H), 7.68 (m, 3H), 7.52 (bs, 4H), 7.47 (m, 1H), 7.14 (m, 2H), 5.28 (s, 2H), 4.39 (q, 2H), 1.39 (t, 3H)
D76		D8 and D6c	As a white powder (yield= 43.2%) ^{1}H NMR ($CDCl_3$, ppm): 9.08 (d, 1H), 8.15 (s, 1H), 7.92 (d, 1H), 7.69 (m, 5H), 7.54 (d, 2H), 7.48 (m, 3H), 7.15 (t, 2H), 5.28 (s, 2H), 4.38 (q, 2H), 1.39 (t, 3H)
D77		D8 and D6b	As a white powder (yield= 74.6%) ^{1}H NMR ($CDCl_3$, ppm): 9.08 (d, 1H), 8.16 (s, 1H), 7.91 (dd, 1H), 7.67 (d, 1H), 7.54 to 7.44 (m, 7H), 7.15 (m, 2H), 6.98 (d, 2H), 5.25 (s, 2H), 4.39 (q, 2H), 3.87 (s, 3H), 1.40 (t, 3H)

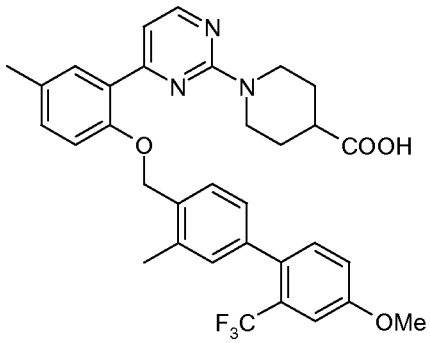
Example 1: 1-(4-(5-methyl-2-(2-methyl-4-(4-cyano-2-methylphenyl)benzyloxy)-phenyl)pyrimidin-2-yl)-piperidine-4-carboxylic acid



To a solution of ethyl 1-(4-(5-methyl-2-(2-methyl-4-(4-cyano-2-methylphenyl)benzyloxy)-phenyl)pyrimidin-2-yl)-piperidine-4-carboxylate (D31, 0.37 g, 0.660 mmol) in THF (10ml) and

MeOH (10ml) was added lithium hydroxyde (3.30 ml of a solution 1N, 3.30 mmol). The reaction mixture was stirred at room temperature overnight and then neutralised with a solution of HCl 1N. After evaporation of MeOH and THF, the resulting precipitate was filtered, washed with water, then pentane and dried. The title compound was obtained as a white solid (0.22g, yield= 62.6%). LC-HRMS (a): $C_{33}H_{32}N_4O_3$, Rt= 3.08min. Calc: 531.2396 (M-H). Found: 531.2374 (M-H). ^{1}H NMR (DMSO d6, ppm): 8.31 (d, 1H), 7.8 (s, 1H), 7.71 (d, 1H), 7.59 (s, 1H), 7.48 (d, 1H), 7.39 (d, 1H), 7.28 (d, 1H), 7.23 (s, 1H), 7.2 (d, 2H), 7.05 (d, 1H), 5.22 (s, 2H), 4.59 (ld, 2H), 3.04 (t, 2H), 2.51 (m, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 2.27 (s, 3H), 1.88 (m, 2H), 1.49 (m, 2H).

Example 2: 1-(4-(5-methyl-2-(2-methyl-4-(4-methoxy-2-trifluoromethylphenyl)benzyloxy)-phenyl)pyrimidin-2-yl)-piperidine-4-carboxylic acid

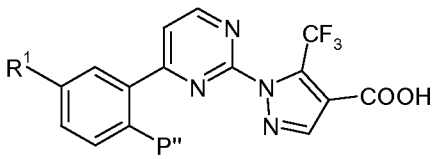


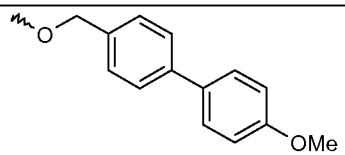
To a solution of ethyl 1-(4-(5-methyl-2-(2-methyl-4-(4-methoxy-2-trifluoromethylphenyl)benzyloxy)-phenyl)pyrimidin-2-yl)-piperidine-4-carboxylate (D32, 0.42 g, 0.678 mmol) in MeOH (10 ml) and THF (10ml) was added NaOH (3.39 ml of a solution 1N, 3.39 mmol), and the mixture was heated at 50°C for 2 hours and then neutralised with a solution 1N of HCl. After evaporation of MeOH and THF under reduced pressure, the resulting precipitate was filtered, washed with water, then pentane and dried. The title compound was obtained as pale yellow powder (0.31g, yield= 77%). LC-HRMS (a): $C_{33}H_{32}F_3N_3O_4$, Rt= 3.40min, Calc: 592.2423 (M+H), Found: 592.2453 (M+H). ^{1}H NMR (DMSO d6, ppm): 8.3 (d, 1H), 7.59 (bs, 1H), 7.42 (d, 1H), 7.29 (m, 4H), 7.21 (m, 1H), 7.11 (m, 2H), 7.06 (d, 1H), 5.2 (s, 2H), 4.59 (ld, 2H), 3.87 (s, 3H), 3.04 (t, 2H), 2.55 (m, 1H), 2.32 (bs, 6H), 1.88 (m, 2H), 1.49 (m, 2H).

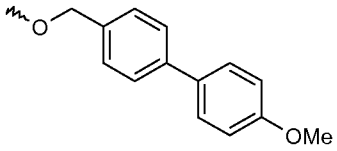
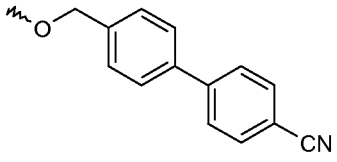
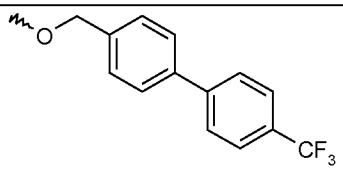
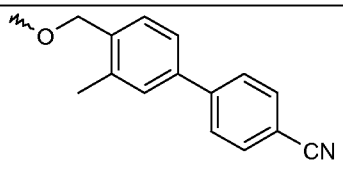
Prepared by a similar method as described for Example 1 for R^9 = CN and by a similar method as described for Example 2 for $R^9 \neq$ CN:

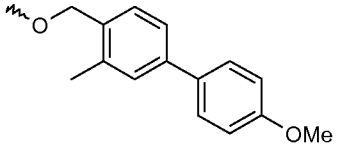
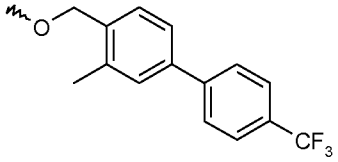
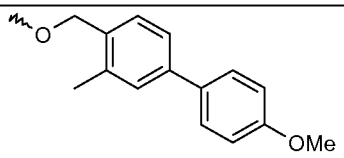
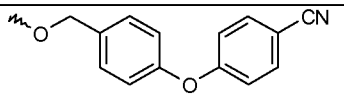
Example No.	Name
3	1-[4-(2-(4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid
4	1-[4-(5-chloro-2-(4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid
5	1-[4-(2-(4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid

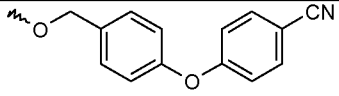
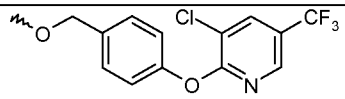
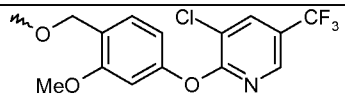
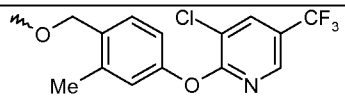
Example No.	Name
6	1-[4-(2-(4-(4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid
7	1-[4-(2-(2-methyl-4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid
8	1-[4-(2-(2-methyl-4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid
9	1-[4-(2-(2-methyl-4-(4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid
10	1-[4-(5-chloro-2-(2-methyl-4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid
11	1-[4-(2-(4-(4-cyanophenyloxy)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid
12	1-[4-(5-chloro-2-(4-(4-cyanophenyloxy)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid
13	1-[4-(5-methyl-2-(4-(3-chloro-5-trifluoromethylpyridin-2-yloxy)phenylmethyloxy)phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid
14	1-[4-(5-methyl-2-(2-methoxy-4-(3-chloro-5-trifluoromethylpyridin-2-yloxy)phenylmethyloxy)phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid
15	1-[4-(5-methyl-2-(2-methyl-4-(3-chloro-5-trifluoromethylpyridin-2-yloxy)phenylmethyloxy)phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid



Example No.	R^1	R2	Prepared from	Analytical data
3	H		D55	As a light yellow powder (yield= 60%). LC-HRMS (a): $C_{29}H_{21}F_3N_4O_4$, Rt= 2.63min, Calc: 545.1437 (M-H), Found: 545.1647 (M-H). ^{1}H NMR (DMSO d6, ppm): 9.04 (d, 1H), 8.35 (s, 1H), 8.33 (d, 1H), 7.98 (d, 1H), 7.64 (d, 2H), 7.62 (d, 2H), 7.55 (d+m, 3H), 7.38 (d, 1H), 7.17 (t, 1H), 7.02 (d, 2H),

				5.35 (s, 2H), 3.80 (s, 3H)
4	Cl		D56	As a cream powder (yield= 5%). LC-HRMS (a): $C_{29}H_{20}Cl_1F_3N_4O_4$, Rt= 2.72min, Calc: 579.1047 (M-H), Found: 579.1030 (M-H). ^{1}H NMR ($CDCl_3$, ppm): 8.75 (d, 1H), 8.17 (m, 3H), 7.52 (d, 2H), 7.47 (d, 2H), 7.36 (d+m, 3H), 7.02 (d, 1H), 6.92 (d, 2H), 5.16 (s, 2H), 3.79 (s, 3H)
5	H		D57	LC-HRMS (a): $C_{29}H_{18}F_3N_5O_3$, Rt= 2.56min, Calc: 542.1440 (M+H), Found: 542.1412 (M+H). ^{1}H NMR (DMSO d6, ppm): 9.05 (d, 1H), 8.36 (s, 1H), 8.34 (d, 1H), 7.97 (d, 1H), 7.91 (d, 2H), 7.82 (d, 2H), 7.77 (d, 2H), 7.62 (d, 2H), 7.59 (m, 1H), 7.38 (d, 1H), 7.18 (t, 1H), 5.4 (s, 2H)
6	H		D58	LC-HRMS (a): $C_{29}H_{18}F_6N_4O_3$, Rt= 2.85min, Calc: 585.1361 (M+H), Found: 585.1304 (M+H). ^{1}H NMR (DMSO d6, ppm): 9.04 (d, 1H), 8.35 (s, 1H), 8.33 (d, 1H), 7.95 (t, 1H), 7.93 (d, 2H), 7.91 (d, 2H), 7.78 (d, 2H), 7.62 (d, 2H), 7.58 (t, 1H), 7.37 (d, 1H), 7.17 (t, 1H), 5.40 (s, 2H)
7	H		D34	As a white powder (yield= 98.7%). LC-HRMS (a): $C_{30}H_{20}F_3N_5O_3$, Rt= 2.78min, Calc: 556.1596 (M+H), Found: 556.1656 (M+H). ^{1}H NMR (DMSO d6, ppm): 9.02 (d, 1H), 8.34 (s, 1H), 8.21 (d, 1H), 7.92 (m, 5H), 7.64 (bs, 1H), 7.56 (m, 3H), 7.43 (d, 1H), 7.19 (t, 1H), 5.37 (s, 2H), 2.36 (s, 3H)

8	H		D33	As a white powder (yield= 17.4%). LC-HRMS (a): $C_{30}H_{23}F_3N_4O_4$, Rt= 2.70min, Calc: 559.1593 (M-H), Found: 559.1582 (M-H). ^{1}H NMR ($CDCl_3$, ppm): 8.78 (d, 1H), 8.28 (s, 1H), 8.25 (dd, 1H), 8.21 (d, 1H), 7.57 (d, 2H), 7.54 (t, 1H), 7.44 (s+d, 3H), 7.19 (d, 2H), 7.01 (d, 2H), 5.24 (s, 2H), 3.88 (s, 3H), 2.41 (s, 3H)
9	H		D59	As a cream powder (yield= 96.6%). LC-HRMS (a): $C_{30}H_{20}F_6N_4O_3$, Rt= 3.04min, Calc: 599.1518 (M+H), Found: 599.1564 (M+H). ^{1}H NMR(DMSO d6, ppm): 9 (d, 1H), 8.35 (s, 1H), 8.25 (d, 1H), 7.95 (m, 3H), 7.8 (d, 2H), 7.6 (m, 4H), 7.45 (d, 1H), 7.2 (t, 1H), 5.35 (s, 2H), 2.35 (s, 3H)
10	Cl		D35	As a white powder (yield=58.4%). LC-HRMS (a): $C_{30}H_{22}Cl_1F_3N_4O_4$, Rt= 2.82min, Calc: 593.1204 (M-H), Found: 593.1200 (M-H). ^{1}H NMR ($CDCl_3$, ppm): 8.81 (d, 1H), 8.28 (s, 1H), 8.24 (sd, 1H), 8.19 (d, 1H), 7.56 (d, 2H), 7.48 (dd, 1H), 7.45 (s, 1H), 7.42 (m, 2H), 7.13 (d, 1H), 7.00 (d, 2H), 5.22 (s, 2H), 3.88 (s, 3H), 2.40 (s, 3H)
11	H		D61	As a cream powder (yield= 52%). LC-HRMS (a): $C_{29}H_{18}F_3N_5O_4$, Rt= 2.56min, Calc: 556.1233 (M-H), Found: 556.1220 (M-H). ^{1}H NMR ($CDCl_3$, ppm): 8.82 (d, 1H), 8.27 (s, 1H), 8.2 (m, 2H), 7.64 (d, 2H), 7.53 (t, 1H), 7.45 (d, 2H), 7.19 (t, 1H), 7.15 (d, 1H),

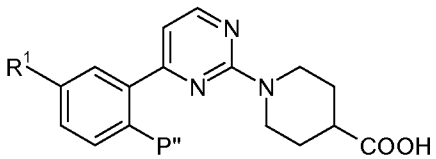
				7.10 (d, 2H), 7.05 (d, 2H), 5.24 (s, 2H)
12	Cl		D62	As a cream powder (yield= 20%). LC-HRMS (a): $C_{29}H_{17}F_3Cl_1N_5O_4$, Rt= 2.65min, Calc: 590.0098 (M-H), Found: 590.0843 (M-H). ^{1}H NMR (DMSO, d6): 9.07 (d, 1H), 8.34 (s, 1H), 8.32 (d, 1H), 7.97 (sd, 1H), 7.85 (d, 2H), 7.66 (dd, 1H), 7.58 (d, 2H), 7.43 (d, 1H), 7.16 (d, 2H), 7.11 (d, 2H), 5.35 (s, 2H)
13	H		D63	As a white powder (yield= 48.6%). LC-HRMS (a): $C_{28}H_{16}F_6Cl_1N_5O_4$, Rt= 2.98min, Calc: 634.0717 (M-H), Found: 634.0700 (M-H). ^{1}H NMR (DMSO, d6): 9.03 (d, 1H), 8.58 (bs, 1H), 8.51 (bs, 1H), 8.34 (s, 1H), 8.33 (d, 1H), 7.97 (d, 1H), 7.59 (ld, 3H), 7.39 (d, 1H), 7.27 (d, 2H), 7.18 (t, 1H), 5.36 (s, 2H)
14	H		D64	As white crystals (yield= 30.1%). LC-HRMS (a): $C_{29}H_{18}F_6Cl_1N_5O_5$, Rt= 3.02min, Calc: 664.0823 (M-H), Found: 664.0843 (M-H). ^{1}H NMR (DMSO, d6): 9.04 (d, 1H), 8.59 (bs, 1H), 8.53 (bs, 1H), 8.34 (s, 1H), 8.32 (d, 1H), 7.98 (dd, 1H), 7.59 (t, 1H), 7.51 (d, 1H), 7.41 (d, 1H), 7.17 (t, 1H), 7.04 (sd, 1H), 6.83 (dd, 1H), 5.29 (s, 2H), 3.83 (s, 3H)
15	H		D65	As a white powder(yield= 68.2%). LC-HRMS (b): $C_{29}H_{18}F_6Cl_1N_5O_4$, Rt= 2.96min, Calc: 650.1030 (M+H), Found: 650.1069 (M+H). ^{1}H NMR (DMSO, d6): 9.02 (d, 1H), 8.58 (s, 1H), 8.52 (s, 1H), 8.33 (s,

				1H), 8.22 (d, 1H), 7.96 (d, 1H), 7.62 (t, 1H), 7.52 (d, 1H), 7.45 (d, 1H), 7.19 (t, 1H), 7.14 (s, 1H), 7.08 (d, 1H), 5.33 (s, 2H), 2.3 (s, 3H)

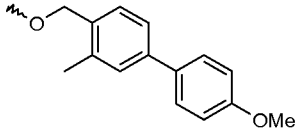
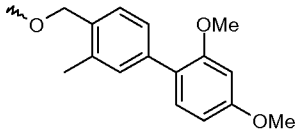
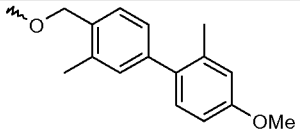
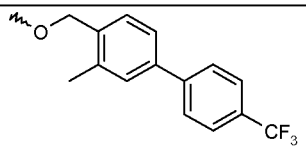
Prepared by a similar method as described for Example 1 for R^9 = CN and by a similar method as described for Example 2 for $R^9 \neq$ CN:

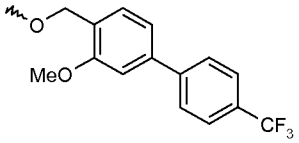
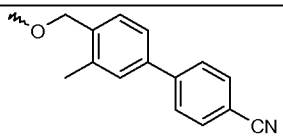
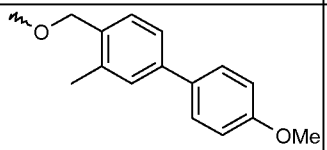
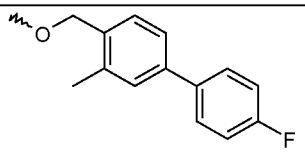
Example No.	Name
16	1-[4-(2-(2-methyl-4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
17	1-[4-(2-(2-methyl-4-(2,4-dimethoxy-phenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
18	1-[4-(2-(2-methyl-4-(4-methoxy-2-methyl-phenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
19	1-[4-(2-(2-methyl-4-(4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
20	1-[4-(2-(2-methoxy-4-(4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
21	1-[4-(2-(2-methyl-4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
22	1-[4-(5-fluoro-2-(2-methyl-4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
23	1-[4-(5-fluoro-2-(2-methyl-4-(4-fluorophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
24	1-[4-(5-fluoro-2-(2-methyl-4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
25	1-[4-(5-fluoro-2-(4-(4-cyanophenyloxy)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
26	1-[4-(5-fluoro-2-(4-(5-trifluoromethylpyridin-2-yloxy)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
27	1-[4-(5-methyl-2-(2-methyl-4-(4-trifluoromethoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
28	1-[4-(5-methyl-2-(2-methyl-4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
29	1-[4-(5-methyl-2-(2-methyl-4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
30	1-[4-(5-methyl-2-(2-methyl-4-(2-methyl-4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid

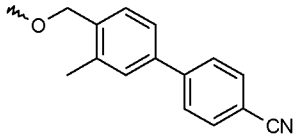
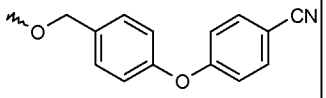
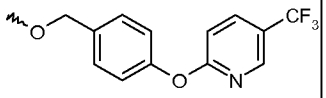
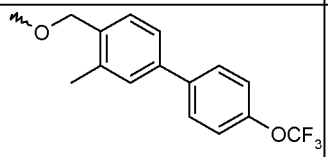
Example No.	Name
31	1-[4-(5-methyl-2-(2-methyl-4-(2-chloro-4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
32	1-[4-(5-methyl-2-(2-propyloxy-4-(4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
33	1-[4-(5-methyl-2-(2-propyloxy-4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
34	1-[4-(5-methyl-2-(2-propyloxy-4-(2-chloro-4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
35	1-[4-(5-methyl-2-(2-propyloxy-4-(4-methoxy-2-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
36	1-[4-(5-methyl-2-(2-propyloxy-4-(4-chloro-2-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
37	1-[4-(5-methyl-2-(2-methyl-4-(6-methoxypyridin-3-yl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
38	1-[4-(5-methyl-2-(2-methyl-4-(5-trifluoromethylpyridin-2-yl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
39	1-[4-(5-methyl-2-(2-methyl-4-(3-chloro-5-trifluoromethylpyridin-2-yl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
40	1-[4-(5-methyl-2-(2-methyl-4-(3-chloro-5-trifluoromethylpyridin-2-yloxy)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
41	1-[4-(5-methyl-2-(2-methyl-4-(2-chloro-4-cyanophenoxy)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
42	1-[4-(5-trifluoromethyl-2-(2-methyl-4-(4-chloro-2-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid
43	1-[4-(5-trifluoromethyl-2-(2-methyl-4-(3-chloro-5-trifluoromethylpyridin-2-yl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid

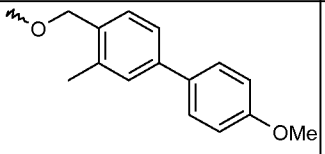
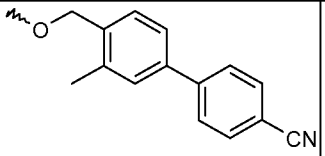
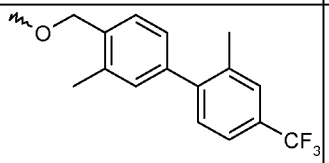
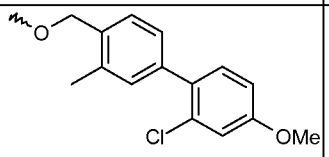


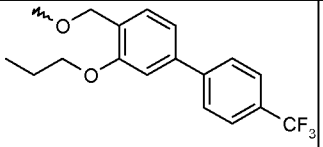
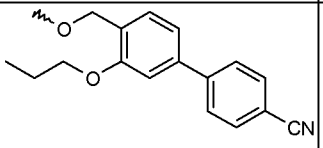
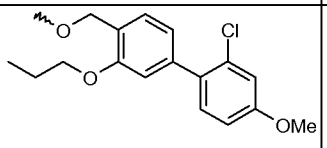
Example No.	R^1	P''	Prepared from	Analytical data

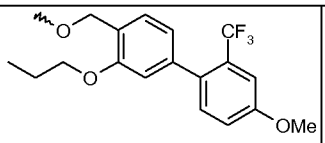
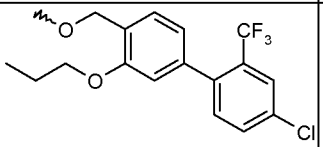
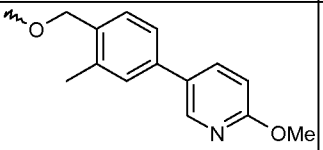
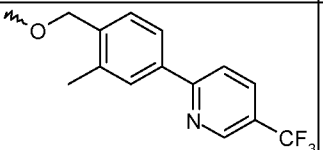
16	H		D36	As a pale yellow powder (yield= 76.4%). LC-HRMS (b): $C_{31}H_{31}N_3O_4$, Rt= 2.94min, Calc: 508.2236 (M-H), Found: 508.2280 (M-H). ^{1}H NMR (DMSO d6, ppm): 8.3 (d, 1H), 7.85 (d, 1H), 7.65 (d, 2H), 7.5 (s, 2H), 7.47 (s, 2H), 7.35 (d, 1H), 7.1 (m, 2H), 7 (d, 2H), 5.25 (s, 2H), 4.6 (ld, 2H), 3.8 (s, 3H), 3.05 (t, 2H), 2.5 (m, 1H), 2.35 (s, 3H), 1.9 (m, 2H), 1.5 (m, 2H)
17	H		D37	As a cream powder (yield= 79.2%) LC-HRMS (b): $C_{32}H_{33}N_3O_5$, Rt= 2.93min, Calc: 538.2342 (M-H), Found: 538.2342 (M-H). ^{1}H NMR (DMSO d6, ppm): 8.35 (d, 1H), 7.85 (d, 1H), 7.5 (t, 1H), 7.4 (d, 1H), 7.35 (d, 1H), 7.3 (s, 1H), 7.25 (m, 2H), 7.1 (m, 2H), 6.65 (s, 1H), 6.6 (d, 1H), 5.25 (s, 2H), 4.6 (ld, 2H), 3.8 (s, 3H), 3.75 (s, 3H), 3.05 (t, 2H), 2.55 (s, 1H), 2.35 (s, 3H), 1.9 (m, 2H), 1.5 (m, 2H)
18	H		D38	As a cream powder (yield= 70.2%) LC-HRMS (b): $C_{32}H_{33}N_3O_4$, Rt= 3.03min, Calc: 522.2393 (M-H), Found: 522.2402 (M-H). ^{1}H NMR (DMSO d6, ppm): 8.35 (d, 1H), 7.85 (d, 1H), 7.45 (m, 2H), 7.35 (d, 1H), 7.15 (m, 5H), 6.8 (m, 2H), 5.25 (s, 2H), 4.6 (ld, 2H), 3.8 (s, 3H), 3.05 (t, 2H), 2.55 (m, 1H), 2.35 (s, 3H), 2.2 (s, 3H), 1.9 (m, 2H), 1.5 (m, 2H)
19	H		D66	As a pale yellow powder (yield= 97%). LC-HRMS (a): $C_{31}H_{28}F_3N_3O_3$, Rt= 3.36min, Calc: 548.2161 (M+H), Found: 548.2134 (M+H). ^{1}H NMR (DMSO d6, ppm): 8.35 (d, 1H), 7.95 (d, 2H), 7.8 (m, 3H), 7.65 (s, 1H), 7.55 (m, 2H), 7.5 (d, 1H), 7.35 (d, 1H), 7.1 (d+t, 2H), 5.25 (s, 2H), 4.55 (ld, 2H), 3.05 (t, 2H), 2.55 (m, 1H), 2.4 (s, 3H), 1.9 (m, 2H),

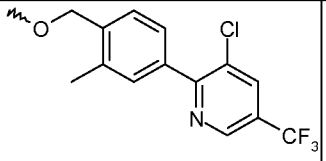
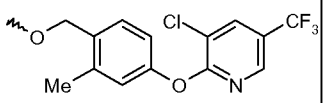
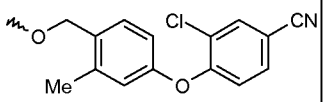
				1.5 (m, 2H)
20	H		D40	As a cream powder (yield= 92.77%) LC-HRMS (a): $C_{31}H_{28}F_3N_3O_4$, Rt= 3.43min, Calc: 562.1954 (M-H), Found: 562.1982 (M-H). ^{1}H NMR (DMSO d6, ppm): 8.35 (d, 1H), 7.95 (d, 2H), 7.85 (m, 3H), 7.55 (d, 1H), 7.5 (t, 1H), 7.4 (s, 1H), 7.35 (d, 1H), 7.25 (d, 1H), 7.2 (d, 1H), 7.1 (t, 1H), 5.25 (s, 2H), 4.6 (ld, 2H), 3.95 (s, 3H), 3.05 (m, 2H), 2.5 (m, 1H), 1.95 (m, 2H), 1.55 (m, 2H)
21	H		D39	As white powder (yield= 64.4%) LC-HRMS (a): $C_{31}H_{28}N_4O_3$, Rt= 3.05min, Calc: 503.2083 (M-H), Found: 503.2137 (M-H). ^{1}H NMR (DMSO d6, ppm): 8.31 (d, 1H), 7.9 (ld, 4H), 7.83 (dd, 1H), 7.63 (s, 1H), 7.58 (m, 1H), 7.53 (d, 1H), 7.47 (m, 1H), 7.31 (d, 1H), 7.11 (t, 1H), 7.07 (d, 1H), 5.26 (s, 2H), 4.57 (ld, 2H), 3.03 (m, 2H), 2.45 (m, 1H), 2.38 (s, 3H), 1.85 (m, 2H), 1.48 (m, 2H)
22	F		D41	As a cream powder (yield= 100%) LC-HRMS (a): $C_{31}H_{30}F_1N_3O_4$, Rt= 3.01min, Calc: 526.2142 (M-H), Found: 526.2117 (M-H). ^{1}H NMR ($CDCl_3$, ppm): 8.3 (d, 1H), 7.77 (dd, 1H), 7.55 (d, 2H), 7.41 (bs, 3H), 7.24 (d, 1H), 7.12 (m, 1H), 7.07 (m, 1H), 6.99 (d, 2H), 5.12 (s, 2H), 4.76 (ld, 2H), 3.87 (s, 3H), 3.13 (t, 2H), 2.66 (m, 1H), 2.39 (s, 3H), 2.06 (m, 2H), 1.80 (m, 2H)
23	F		D42	As a cream powder (yield= 44%) LC-HRMS (a): $C_{30}H_{27}F_2N_3O_3$, Rt= 3.08min, Calc: 514.1942 (M-H), Found: 514.1904 (M-H). ^{1}H NMR ($CDCl_3$, ppm): 8.3 (d, 1H), 7.77 (dd, 1H), 7.56 (m, 2H), 7.41 (m, 3H), 7.22 (d, 1H), 7.14 (m, 3H), 7.06 (m, 1H), 5.12 (s, 2H), 4.77 (ld, 2H), 3.12 (m, 2H), 2.66 (m, 1H), 2.40 (s,

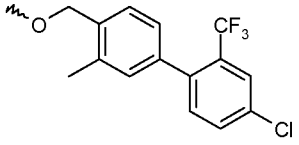
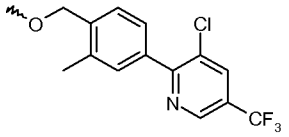
				3H), 2.06 (m, 2H), 1.77 (m, 2H)
24	F		D43	As a cream powder (yield= 81%) LC-HRMS (a): $C_{31}H_{27}F_1N_4O_3$, Rt= 2.89min, Calc: 521.1989 (M-H), Found: 521.1962 (M-H). ^{1}H NMR ($CDCl_3$, ppm): 8.3 (d, 1H), 7.77 (dd, 1H), 7.74 (d, 2H), 7.72 (d, 2H), 7.47 (m, 3H), 7.2 (d, 1H), 7.12 (m, 1H), 7.04 (m, 1H), 5.14 (s, 2H), 4.77 (ld, 2H), 3.12 (m, 2H), 2.67 (m, 1H), 2.41 (s, 3H), 2.06 (m, 2H), 1.77 (m, 2H)
25	F		D67	As a white powder (yield= 83%) LC-HRMS (a): $C_{30}H_{25}F_1N_4O_4$, Rt= 2.83min, Calc: 523.1782 (M-H), Found: 523.1735 (M-H). ^{1}H NMR ($CDCl_3$, ppm): 8.32 (d, 1H), 7.74 (dd, 1H), 7.62 (d, 2H), 7.43 (d, 2H), 7.21 (d, 1H), 7.07 (d+m, 3H), 7.02 (d+m, 3H), 5.11 (s, 2H), 4.77 (ld, 2H), 3.11 (m, 2H), 2.65 (m, 1H), 2.05 (m, 2H), 1.76 (m, 2H)
26	F		D68	As a white powder (yield= 28%) LC-HRMS (a): $C_{29}H_{24}F_4N_4O_4$, Rt= 2.93min, Calc: 567.1655 (M-H), Found: 567.1611 (M-H). ^{1}H NMR ($CDCl_3$, ppm): 8.38 (bs, 1H), 8.25 (d, 1H), 7.85 (dd, 1H), 7.64 (dd, 1H), 7.37 (d, 2H), 7.14 (d, 1H), 7.08 (d, 2H), 7.02 to 6.92 (m, 3H), 5.05 (s, 2H), 4.68 (ld, 2H), 3.04 (t, 2H), 2.58 (m, 1H), 1.96 (m, 2H), 1.69 (m, 2H)
27	CH_3		D45	As white crystals (yield= 53.8%) Mp= 165°C. LC-HRMS (a): $C_{32}H_{30}F_3N_3O_4$, Rt= 3.66min, Calc: 576.2110 (M-H), Found: 576.2119 (M-H). ^{1}H NMR (DMSO d6, ppm): 8.31 (d, 1H), 7.79 (d, 2H), 7.6 (s, 1H), 7.54 (s, 1H), 7.49 (bs, 2H), 7.44 (d, 2H), 7.27 (d, 1H), 7.2 (d, 1H), 7.05 (d, 1H), 5.2 (s, 2H), 4.6 (ld, 2H), 3.05 (t, 2H), 2.53 (m, 1H),

				2.36 (s, 3H), 2.32 (s, 3H), 1.89 (m, 2H), 1.5 (m, 2H)
28	CH_3		D46	As a cream powder (yield= 74.1%) LC-HRMS (a): $C_{32}H_{33}N_3O_4$, Rt= 3.35min, Calc: 524.2549 (M+H), Found: 524.2582 (M+H). ^{1}H NMR (DMSO d6, ppm): 8.29 (d, 1H), 7.61 (m, 3H), 7.47 (bs, 1H), 7.42 (bs, 2H), 7.26 (d, 1H), 7.2 (d, 1H), 7.05 (d, 1H), 7.01 (d, 2H), 5.17 (s, 2H), 4.58 (m, 2H), 3.79 (s, 3H), 3.03 (m, 2H), 2.48 (m, 1H), 2.34 (s, 3H), 2.31 (s, 3H), 1.87 (m, 2H), 1.49 (m, 2H)
29	CH_3		D44	As a cream powder (yield= 65.9%) LC-HRMS (a): $C_{32}H_{30}N_4O_3$, Rt= 3.23min, Calc: 517.2240 (M-H), Found: 517.2208 (M-H). ^{1}H NMR (DMSO d6, ppm): 8.31 (d, 1H), 7.9 (q, 4H), 7.59 (m, 3H), 7.5 (d, 1H), 7.26 (dd, 1H), 7.19 (d, 1H), 7.05 (d, 1H), 5.21 (s, 2H), 4.59 (ld, 2H), 3.04 (t, 2H), 2.54 (m, 1H), 2.36 (s, 3H), 2.31 (s, 3H), 1.88 (m, 2H), 1.48 (m, 2H)
30	CH_3		D54	As a white powder (yield= 77%) LC/MS: 576.1 (M+H), Rt= 3.84min LC-HRMS (a): $C_{33}H_{32}F_3N_3O_3$, Rt= 3.51min, Calc: 576.2474 (M+H), Found: 576.2416 (M+H). ^{1}H NMR (DMSO d6, ppm): 8.31 (d, 1H), 7.67 (bs, 1H), 7.6 (m, 2H), 7.48 (d, 1H), 7.41 (d, 1H), 7.28 (dd, 1H), 7.21 (m, 3H), 7.06 (d, 1H), 5.22 (s, 2H), 4.59 (m, 2H), 3.04 (t, 2H), 2.55 (m, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H), 1.88 (m, 2H), 1.48 (m, 2H)
31	CH_3		D47	As a cream powder (yield= 60.4%) LC/MS: 558.1 (M+H), Rt= 3.63min LC-HRMS (a): $C_{32}H_{32}Cl_1N_3O_4$, Rt= min, Calc: (M-H), Found: (M-H). ^{1}H NMR (DMSO d6, ppm): 8.31 (d, 1H), 7.58 (bs, 1H), 7.44 (d, 1H),

				7.32 (d, 1H), 7.25 (m, 4H), 7.13 (bs, 1H), 7.06 (d, 1H), 6.99 (dd, 1H), 5.2 (s, 2H), 4.59 (ld, 2H), 3.81 (s, 3H), 3.04 (t, 2H), 2.5 (m, 1H), 2.32 (2s, 6H), 1.88 (m, 2H), 1.51 (m, 2H)
32	CH_3		D69	As a white powder (yield= 90%) LC-HRMS (b): $C_{34}H_{34}F_3N_3O_4$, Rt= 3.55min, Calc: 606.2579 (M+H), Found: 606.2537 (M+H). ^{1}H NMR (DMSO d6, ppm): 8.31 (d, 1H), 7.93 (d, 2H), 7.81 (d, 2H), 7.62 (s, 1H), 7.49 (d, 1H), 7.34 (s, 1H), 7.3 (d, 1H), 7.25 (d, 1H), 7.15 (m, 2H), 5.18 (s, 2H), 4.6 (ld, 2H), 4.12 (t, 2H), 3.05 (t, 2H), 2.53 (m, 1H), 2.31 (s, 3H), 1.88 (m, 2H), 1.75 (m, 2H), 1.5 (m, 2H), 0.97 (t, 3H)
33	CH_3		D70	As white crystals (yield= 41.6%) Mp= 155°C. LC-HRMS (a): $C_{34}H_{34}N_4O_4$, Rt= 3.27min, Calc: 563.2658 (M+H), Found: 563.2654 (M+H). ^{1}H NMR (DMSO d6, ppm): 8.29 (d, 1H), 7.92 (bs, 4H), 7.61 (s, 1H), 7.48 (d, 1H), 7.35 (s, 1H), 7.3 (d, 1H), 7.24 (d, 1H), 7.13 (m, 2H), 5.17 (s, 2H), 4.6 (ld, 2H), 4.11 (t, 2H), 3.04 (t, 2H), 2.55 (m, 1H), 2.3 (s, 3H), 1.88 (m, 2H), 1.73 (m, 2H), 1.49 (m, 2H), 0.97 (t, 3H)
34	CH_3		D50	As a white powder (yield= 61.3%) LC-HRMS (a): $C_{34}H_{36}Cl_1N_3O_5$, Rt=3.48 min, Calc: 602.2422 (M+H), Found: 602.2374 (M+H). ^{1}H NMR (DMSO d6, ppm): 8.3 (d, 1H), 7.61 (m, 3H), 7.42 (d, 1H), 7.36 (d, 1H), 7.26 (dd, 1H), 7.15 (m, 2H), 6.99 (m, 2H), 5.17 (s, 2H), 4.6 (ld, 2H), 4.02 (t, 2H), 3.82 (s, 3H), 3.04 (t, 2H), 2.57 (m, 1H), 2.31 (s, 3H), 1.88 (m, 2H), 1.72 (m, 2H), 1.49 (m, 2H), 0.95 (t, 3H)

35	CH_3		D51	As a white powder (yield= 59.3%) LC-HRMS (a): $C_{35}H_{36}F_3N_3O_5$, Rt=3.77 min, Calc: 636.2685 (M+H), Found: 636.2739 (M+H). ^1H NMR (DMSO d6, ppm):8.27 (d, 1H), 7.61 (bs, 1H), 7.41 (d, 1H), 7.37 (d, 1H), 7.27 (m, 3H), 7.14 (m, 2H), 6.92 (s, 1H), 6.85 (d, 1H), 5.17 (s, 2H), 4.6 (ld, 2H), 3.97 (t, 2H), 3.87 (s, 3H), 3.04 (m, 2H), 2.55 (m, 1H), 2.31 (s, 3H), 1.88 (m, 2H), 1.69 (m, 2H), 1.48 (m, 2H), 0.93 (t, 3H)
36	CH_3		D52	As a white powder (yield= 51%) LC-HRMS (a): $C_{34}H_{33}Cl_1F_3N_3O_4$, Rt= 3.75min, Calc: 640.2190 (M+H), Found: 640.2136 (M+H). ^1H NMR (DMSO d6, ppm): 8.27 (d, 1H), 7.9 (bs, 1H), 7.81 (dd, 1H), 7.61 (bs, 1H), 7.48 (d, 1H), 7.44 (d, 1H), 7.26 (dd, 1H), 7.13 (m, 2H), 6.96 (bs, 1H), 6.88 (d, 1H), 5.18 (s, 2H), 4.6 (ld, 2H), 3.98 (t, 2H), 3.04 (t, 2H), 2.55 (m, 1H), 2.31 (s, 3H), 1.88 (m, 2H), 1.69 (m, 2H), 1.49 (m, 2H), 0.93 (t, 3H)
37	CH_3		D48	As a white powder (yield= 96.9%) LC-HRMS (a): $C_{31}H_{32}N_4O_4$, Rt= 3.14min, Calc: 525.2502 (M+H), Found: 525.2485 (M+H). ^1H NMR (DMSO d6, ppm): 8.48 (s, 1H), 8.31 (d, 1H), 8.01 (d, 1H), 7.6 (s, 1H), 7.52 (s, 1H), 7.47 (bs, 2H), 7.27 (d, 1H), 7.2 (d, 1H), 7.05 (d, 1H), 6.9 (d, 1H), 5.19 (s, 2H), 4.59 (ld, 2H), 3.89 (s, 3H), 3.05 (t, 2H), 2.53 (m, 1H), 2.35 (s, 3H), 2.31 (s, 3H), 1.89 (m, 2H), 1.50 (m, 2H)
38	CH_3		D49	As pale orange crystals (yield= 60%). LC-HRMS (a): $C_{31}H_{29}F_3N_4O_3$, Rt= 3.18min, Calc: 563.2270 (M+H), Found: 563.2207 (M+H). ^1H NMR (DMSO d6, ppm): 9.09 (bs,

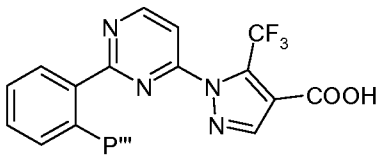
				1H), 8.36 (m, 2H), 8.25 (d, 1H), 8.1 (s, 1H), 8.04 (d, 1H), 7.66 (s, 1H), 7.6 (d, 1H), 7.33 (d, 1H), 7.25 (d, 1H), 7.12 (d, 1H), 5.29 (s, 2H), 4.65 (ld, 2H), 3.10 (t, 2H), 2.55 (m, 1H), 2.45 (s, 3H), 2.37 (s, 3H), 1.95 (m, 2H), 1.57 (m, 2H)
39	CH_3		D73	As a white powder (yield= 62.2%) LC-HRMS (a): $C_{31}H_{28}Cl_1F_3N_4O_3$, Rt= 3.2min, Calc: 597.1880 (M+H), Found: 597.1803 (M+H); ^{1}H NMR (DMSO d6, ppm): 9.03 (s, 1H), 8.58 (s, 1H), 8.33 (d, 1H), 7.56 (m, 4H), 7.28 (d, 1H), 7.21 (d, 1H), 7.07 (d, 1H), 5.25 (s, 2H), 4.6 (ld, 2H), 3.05 (m, 2H), 2.56 (m, 1H), 2.37 (s, 3H), 2.32 (s, 3H), 1.89 (m, 2H), 1.5 (m, 2H)
40	CH_3		D71	As a white powder (yield= 62.7%) LC-HRMS (b): $C_{31}H_{28}Cl_1F_3N_4O_4$, Rt= 3.25min, Calc: 613.1829 (M+H), Found: 613.1852 (M+H). ^{1}H NMR (DMSO d6, ppm): 8.75 (s, 1H), 8.51 (s, 1H), 8.31 (d, 1H), 7.6 (s, 1H), 7.47 (d, 1H), 7.28 (d, 1H), 7.22 (d, 1H), 7.11 (s, 1H), 7.05 (m, 2H), 5.18 (s, 2H), 4.59 (ld, 2H), 3.05 (t, 2H), 2.56 (m, 1H), 2.32 (s, 3H), 2.3 (s, 3H), 1.88 (m, 2H), 1.50 (m, 2H)
41	CH_3		D72	As white crystals (yield= 18.2%) Mp= 143°C. LC-HRMS (a): $C_{32}H_{29}Cl_1N_4O_4$, Rt= 3.11min, Calc: 569.1956 (M+H), Found: 569.1968 (M+H). ^{1}H NMR (DMSO d6, ppm): 8.3 (d, 1H), 8.22 (bs, 1H), 7.79 (dd, 1H), 7.59 (bs, 1H), 7.47 (d, 1H), 7.27 (dd, 1H), 7.2 (d, 1H), 7.02 (m, 3H), 6.94 (dd, 1H), 5.15 (s, 2H), 4.58 (ld, 2H), 3.04 (t, 2H), 2.55 (m, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 1.88 (m, 2H), 1.5 (m, 2H)

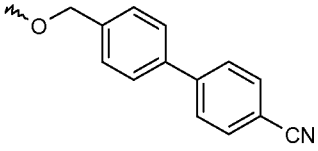
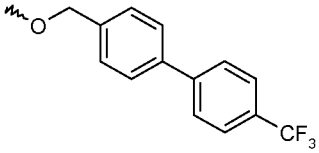
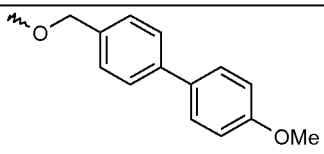
42	CF_3		D53	As a white powder (yield= 42.2%) LC-HRMS (a): $C_{32}H_{26}Cl_1F_6N_3O_3$, Rt= min, Calc: 650.1645 (M+H), Found: 650.1637 (M+H). ^{1}H NMR (DMSO d6, ppm): 8.36 (d, 1H), 8.08 (s, 1H), 7.88 (m, 2H), 7.8 (d, 1H), 7.55 (d, 1H), 7.48 (d, 1H), 7.44 (d, 1H), 7.17 (m, 2H), 7.09 (d, 1H), 5.39 (s, 2H), 4.57 (m, 2H), 3.06 (m, 2H), 2.55 (m, 1H), 2.35 (s, 3H), 1.89 (m, 2H), 1.5 (m, 2H)
43	CF_3		D74	As a white powder (yield= 27%). LC-HRMS (a): $C_{31}H_{25}Cl_1F_6N_4O_3$, Rt= 3.31min, Calc: 651.1597 (M+H), Found: 651.1597 (M+H); ^{1}H NMR (DMSO d6, ppm): 9.03 (s, 1H), 8.59 (s, 1H), 8.39 (d, 1H), 8.09 (s, 1H), 7.86 (d, 1H), 7.58 (m, 4H), 7.12 (d, 1H), 5.42 (s, 2H), 4.57 (ld, 2H), 3.07 (m, 2H), 2.5 (m, 1H), 2.39 (s, 3H), 1.89 (m, 2H), 1.5 (m, 2H)

Prepared by a similar method as described for Example 1 for R^9 = CN and by a similar method as described for Example 2 for $R^9 \neq$ CN:

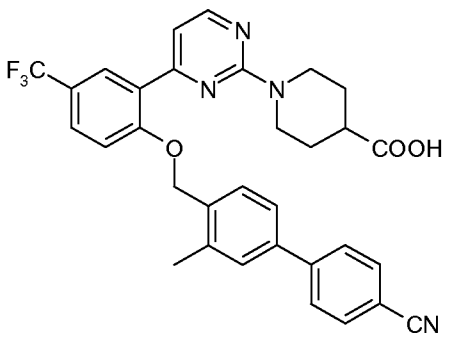
Example No.	Name
44	1-[2-(2-(4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-4-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid
45	1-[2-(2-(4-(4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-4-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid
46	1-[2-(2-(4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-4-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid

5



Example No.	P'''	Prepared from	Analytical data
44		D73	As a white powder (yield= 31.6%) LC-HRMS (a): $C_{29}H_{18}F_3N_5O_3$, Rt= 2.49min, Calc: 542.1440 (M+H), Found: 542.1535 (M+H). ^{1}H NMR ($CDCl_3$, ppm): 9.15 (d, 1H), 8.21 (s, 1H), 7.91 (dd, 1H), 7.71 (m, 3H), 7.66 (d, 2H), 7.52 (bs, 4H), 7.49 (m, 1H), 7.15 (m, 2H), 5.28 (s, 2H)
45		D74	As a white powder (yield= 35%) LC-HRMS (a): $C_{29}H_{18}F_6N_4O_3$, Rt= 2.78min, Calc: 585.1361 (M+H), Found: 585.1353 (M+H). ^{1}H NMR (DMSO d6, ppm): 9.25 (d, 1H), 8.45 (s, 1H), 7.91 (d, 1H), 7.85 (d, 2H), 7.8 (d, 2H), 7.74 (d, 1H), 7.62 (d, 2H), 7.51 (m, 3H), 7.28 (d, 1H), 7.14 (t, 1H), 5.28 (s, 2H)
46		D75	As a white powder (yield= 46.4%) LC-HRMS (a): $C_{29}H_{21}F_3N_4O_4$, Rt= 2.53min, Calc: 545.1437 (M-H), Found: 545.1455 (M-H). ^{1}H NMR (DMSO d6, ppm): 9.24 (d, 1H), 8.42 (s, 1H), 7.9 (d, 1H), 7.72 (dd, 1H), 7.56 (d+m, 3H), 7.5 (d, 2H), 7.42 (d, 2H), 7.28 (d, 1H), 7.13 (t, 1H), 7.01 (d, 2H), 5.23 (s, 2H), 3.79 (s, 3H)

Example 47: 1-(4-(5-trifluoromethyl-2-(2-methyl-4-(4-cyanophenyl)benzyloxy)-phenyl)pyrimidin-2-yl)-piperidine-4-carboxylic acid



To a solution of 1-(4-(5-trifluoromethyl-2-(2-methyl-4-bromo-benzyloxy)-phenyl)pyrimidin-2-yl)-piperidine-4-carboxylic acid (D28, 0.6 g, 1.090 mmol) in DME (50 mL) and water (5 mL) were added $Pd(PPh_3)_4$ (0.063 g, 0.055 mmol), (4-cyanophenyl)boronic acid (0.240 g, 1.635 mmol) and sodium carbonate (0.347 g, 3.27 mmol) and the reaction mixture was heated at 95°C overnight and then poured into water. After neutralisation with a solution of HCl 1N, and then 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 silicagel (CH_2Cl_2/MeOH, 99/1). After crystallisation from CH_3CN, the product was obtained as white crystals (0.262 g, yield= 42%). mp= 180°C. LC-HRMS (a): $C_{32}H_{27}F_3N_4O_3$, Rt= 3.07min, Calc: 573.2114 (M+H), Found: 573.2051 (M+H). ^{1}H NMR (DMSO d6, ppm): 8.38 (d, 1H), 8.08 (bs, 1H), 7.91 (bs, 4H), 7.85 (d, 1H), 7.65 (s, 1H), 7.6 (d, 1H), 7.53 (m, 2H), 7.10 (d, 1H), 5.83 (s, 2H), 4.57 (ld, 2H), 3.06 (t, 2H), 2.54 (m, 1H), 2.39 (s, 3H), 1.89 (m, 2H), 1.49 (m, 2H).

Biological Assay

The activity of soluble guanylate cyclase (sGC) can be tested in an assay based on measuring the fluorescent polarisation (FP) signal of fluorescently labelled cGMP. FP increases on interaction with an anti-cGMP antibody as the motility of the molecule is reduced. Newly produced cGMP displaces the 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.

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 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.

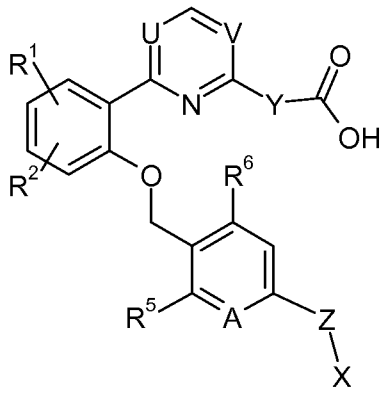
The compounds of Examples 1 to 47 were tested in the assay described above and gave pEC500 values of greater than 5.0. In an embodiment the compounds of the invention give

a pEC500 value of ≥6.0 when tested in this assay. In a further embodiment the compounds of the invention give a pEC500 value of ≥7.0 when tested in this assay.

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

Claims

1. A compound of formula (I)



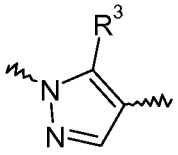
(I)

or a salt thereof;
wherein

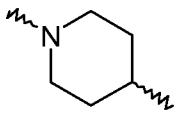
R^1 and R^2 are independently selected from hydrogen, halo, CF_3 and C_{1-4}alkyl;

one of U and V represents N and the other represents CH;

—Y— represents



or



wherein R^3 represents CF_3 or C_{1-4} alkyl;

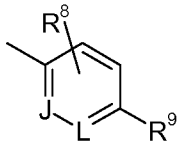
Z is absent or represents O;

A represents CH or N;

when A represents CH, R^5 is selected from hydrogen, methyl, C_{1-4}alkoxy, methoxyC_{2-3}alkoxy, chloro and fluoro and R^6 represents hydrogen;

when A represents N, R^5 and R^6 each represent hydrogen or one of R^5 and R^6 represents hydrogen and the other represents methyl; and

X represents



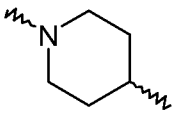
wherein: J and L both represent CH, or one represents N and the other represents CH, provided that only one of A, J and L represents N;

when both J and L represent CH, R^8 represents hydrogen or chloro, fluoro, CF_3, C_{1-4}alkyl or C_{1-4}alkoxy in a meta or ortho position relative to the R^9 substituent;

when one of J and L represents N, R^8 represents hydrogen or halo in a meta or ortho position relative to the R^9 substituent; and

R^9 represents hydrogen, halo, CF_3, OCF_3, C_{1-4}-alkyl, C_{1-4}-alkoxy, CN, $CONR^{10}R^{11}$, CO_2H or N_3, wherein R^{10} and R^{11} are independently selected from hydrogen and C_{1-4}-alkyl;

with the exception of 1-[4-(2-(4-(4-chlorophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid and 1-[4-(2-((4-phenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-5-trifluoromethyl-pyrazole-4-carboxylic acid.

2. A compound of formula (I) or a salt thereof as claimed in claim 1 wherein —Y— represents  .

3. A compound of formula (I) or a salt thereof as claimed in claim 2 wherein R^1 represents C_{1-4}alkyl, CF_3 or halo in a para position relative to the $–OCH_2–$ linker and R^2 represents hydrogen.

4. A compound of formula (I) or a salt thereof as claimed in claim 3 wherein R^1 represents methyl, CF_3, fluoro or chloro.

5. A compound of formula (I) or a salt thereof as claimed in claim 4 wherein R^1 represents methyl or CF_3.

6. A compound of formula (I) or a salt thereof as claimed in any one of claims 2 to 5 wherein U represents CH and V represents N.

7. A compound of formula (I) or a salt thereof as claimed in any one of claims 2 to 6 wherein Z is absent.

8. A compound of formula (I) or a salt thereof as claimed in any one of claims 2 to 7 wherein A represents CH.

9. A compound of formula (I) or a salt thereof as claimed in any one of claims 2 to 8 wherein R^6 represents hydrogen.

10. A compound of formula (I) or a salt thereof as claimed in any one of claims 2 to 9 wherein R^5 represents hydrogen, methyl, methoxy or propyloxy.

11. A compound of formula (I) or a salt thereof as claimed in any one of claims 2 to 10 wherein J and L both represent CH; or wherein J represents N and L represents CH.

12. A compound of formula (I) or a salt thereof as claimed in any one of claims 2 to 11 wherein R^8 represents hydrogen or R^8 represents chloro, CF_3, methyl or methoxy in a meta position relative to the R^9 substituent.

13. A compound of formula (I) or a salt thereof as claimed in claim 11 or claim 12 wherein: J and L both represent CH and R^8 represents hydrogen or R^8 represents chloro, CF_3, methyl or methoxy in a meta position relative to the R^9 substituent; or J represents N and L represents CH, R^8 represents hydrogen, or R^8 represents chloro in a meta position relative to the R^9 substituent.

14. A compound of formula (I) or a salt thereof as claimed in any one of claims 2 to 13 wherein R^9 represents chloro, fluoro, CF_3, OCF_3, methoxy or CN.

15. A compound of formula (I) or a salt thereof as claimed in any one of claims 2 to 14 wherein: R^8 represents hydrogen and R^9 represents methoxy, CN, CF_3, OCF_3 or fluoro; or R^8 represents CF_3 and R^9 represents CN, methoxy or chloro, with R^8 being in a meta position relative to the R^9 substituent; or R^8 represents chloro and R^9 represents CF_3, CN or methoxy, with R^8 being in a meta position relative to the R^9 substituent.

16. A compound of formula (I) as claimed in claim 2 selected from:
1-[4-(5-methyl-2-(2-methyl-4-(4-cyano-2-methylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(4-methoxy-2-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(2-(2-methyl-4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;

1-[4-(2-(2-methyl-4-(2,4-dimethoxy-phenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(2-(2-methyl-4-(4-methoxy-2-methyl-phenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(2-(2-methyl-4-(4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(2-(2-methoxy-4-(4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(2-(2-methyl-4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-fluoro-2-(2-methyl-4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-fluoro-2-(2-methyl-4-(4-fluorophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-fluoro-2-(2-methyl-4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-fluoro-2-(4-(4-cyanophenyloxy)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-fluoro-2-(4-(5-trifluoromethylpyridin-2-yloxy)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(4-trifluoromethoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(2-methyl-4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(2-chloro-4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-propyloxy-4-(4-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-propyloxy-4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-propyloxy-4-(2-chloro-4-methoxyphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-propyloxy-4-(4-methoxy-2-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-propyloxy-4-(4-chloro-2-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(6-methoxypyridin-3-yl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;

1-[4-(5-methyl-2-(2-methyl-4-(5-trifluoromethylpyridin-2-yl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(3-chloro-5-trifluoromethylpyridin-2-yloxy)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(2-chloro-4-cyanophenoxy)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-trifluoromethyl-2-(2-methyl-4-(4-chloro-2-trifluoromethylphenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-trifluoromethyl-2-(2-methyl-4-(4-cyanophenyl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
1-[4-(5-methyl-2-(2-methyl-4-(3-chloro-5-trifluoromethylpyridin-2-yl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid; and
1-[4-(5-trifluoromethyl-2-(2-methyl-4-(3-chloro-5-trifluoromethylpyridin-2-yl)phenylmethyloxy)-phenyl)pyrimidin-2-yl]-piperidine-4-carboxylic acid;
or a salt thereof.

17. A pharmaceutical composition comprising a compound of formula (I) as claimed in any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carrier(s), diluents(s) and/or excipient(s).

18. A compound of formula (I) as claimed in any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as claimed in claim 17, for use in therapy.

19. A compound of formula (I) as claimed in any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as claimed in claim 17, for use in the treatment of a disease or condition mediated by the activity of sGC.

20. A compound of formula (I) as claimed in any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as claimed in claim 17, for use in the treatment of arterial hypertension, pulmonary arterial hypertension, angina, cardiac ischemia, myocardial infarction, congestive heart failure, acute coronary syndrome, atherosclerosis, peripheral vascular disease, cardiorenal syndrome, hepatorenal syndrome or restenosis.

21. Use of a compound of formula (I) as claimed in any one of claims 1 to 16, 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.

22. Use of a compound of formula (I) as claimed in any one of claims 1 to 16, 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, acute coronary syndrome, atherosclerosis, peripheral vascular disease, cardiorenal syndrome, hepatorenal syndrome or restenosis.

23. 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 claimed in any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition as claimed in claim 17.

24. A method of treatment of arterial hypertension, pulmonary arterial hypertension, angina, cardiac ischemia, myocardial infarction, congestive heart failure, 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 claimed in any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition as claimed in claim 17.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/060146

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D401/14 C07D403/04 A61K31/506 A61P9/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN 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.
P,Y	WO 2009/068652 A (SMITHKLINE BEECHAM CORP [US]; BOYER THIERRY [FR]; DODIC NERINA [FR]; E) 4 June 2009 (2009-06-04) page 1, lines 3-7 claims 1-23	1-24
P,X	WO 2009/032249 A (MERCK & CO INC [US]; BITTNER AMY R [US]; SINZ CHRISTOPHER JOSEPH [US];) 12 March 2009 (2009-03-12) claims 1-24 page 3, lines 3-13	1-24
P,Y	WO 2009/071504 A (SMITHKLINE BEECHAM CORP [US]; BOUILLOT ANNE MARIE JEANNE [FR]; DODIC N) 11 June 2009 (2009-06-11) page 1, lines 3-7 claims 1-42	1-24

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[X] Further documents are listed in the continuation of Box C.

[X] 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

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

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

"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 October 2009	16/10/2009

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/060146

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/27394 A (UNIV LONDON [GB]; SELWOOD DAVID [GB]; GLEN ROBERT [GB]; LIU QIAN [US];) 18 May 2000 (2000-05-18) claims 1-19	1-24

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/060146

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009068652 A	04-06-2009	NONE	
WO 2009032249 A	12-03-2009	US 2009209556 A1	20-08-2009
WO 2009071504 A	11-06-2009	UY 31507 A1	17-07-2009
WO 0027394 A	18-05-2000	AU 6481699 A	29-05-2000